A Case Report

Optic Nerve Head Granuloma, Retinal Vasculitis and Elevated Levels of Angiotensin-converting Enzyme: Dilemma of Forme Fruste Ocular Sarcoidosis

Ravi Bypareddy, MD; Brijesh Takkar, MD; Shorya Vardhan Azad, MS; Rohan Chawla, MD Pradeep Venkatesh, MD

Retina and Uvea Services, Dr R P Centre for Ophthalmic Sciences, All India Institute of Medical Sciences, Ansari Nagar, New Delhi, India

ORCID:
Ravi Bypareddy: https://orcid.org/0000-0002-4550-7441
Brijesh Takkar: https://orcid.org/0000-0001-5779-7645
Shorya Vardhan Azad: https://orcid.org/0000-0002-8050-5812
Rohan Chawla: https://orcid.org/0000-0002-6791-4435

Abstract

Purpose: To report 2 cases of optic nerve head (ONH) granuloma, with raised serum angiotensin-converting enzyme (ACE) levels not fitting into the existing criteria for ocular sarcoidosis (OS).
Case Report: Fundus photography, ultrasonography, fluorescein angiography, and optical coherence tomography were performed for both patients. Systemic workup was performed for granulomatous disorders, including sarcoidosis, tuberculosis, and syphilis. Both patients had ONH granulomas and elevated ACE levels, with one of the patients also presenting retinal vasculitis. No other focus of systemic sarcoidosis was localized. Both patients were treated with oral steroids, following which they showed a marked, rapid clinical improvement. Both patients remained stable for at least one year.
Conclusion: The current accepted criterion for diagnosis of OS may need changes to include such borderline cases due to lack of correlation between clinical and investigative findings.

Keywords: Ocular Sarcoidosis; Optic Nerve Head Granuloma; Sarcoidosis; Serum Angiotensin-converting Enzyme Level; Uveitis

J Ophthalmic Vis Res 2019; 14 (1): 105-108

INTRODUCTION

Sarcoidosis is an inflammatory disorder having variable presentations and involving multiple systems. Uveitis, though not extremely common, is a very important clinical clue for the diagnosis of sarcoidosis and may be an isolated initial presentation leading to the diagnosis. Ocular sarcoidosis (OS) without systemic involvement is rare. In the past decade, classification systems have been suggested and diagnostic criteria were set for OS, including presumptive disease.[1] We discuss 2 cases that,

Correspondence to:
Brijesh Takkar, MD. Senior Research Associate;
Dr R P Centre for Ophthalmic Sciences, All India Institute of Medical Sciences, New Delhi 110029, India.
E-mail: britak.aiims@gmail.com

Received: 06-04-2017 Accepted: 19-08-2018

Access this article online

Quick Response Code:

Website: www.jovr.org

DOI: 10.4103/jovr.jovr_74_17

How to cite this article: Bypareddy R, Takkar B, Azad SV, Chawla R, Venkatesh P. Optic nerve head granuloma, retinal vasculitis and elevated levels of angiotensin-converting enzyme: Dilemma of forme fruste ocular sarcoidosis. J Ophthalmic Vis Res 2019;14:105-8.

from the clinical perspective, appear to fall within the spectrum of OS, but do not fit in any category proposed by the current diagnostic systems.[1,2]

CASE REPORT

Case 1: A 17-year-old boy presented with a complaint of acute and painless diminution of vision in his left eye (LE) for one week. Best corrected visual acuity (BCVA) was 6/6 in right eye (RE) and 6/60 in the LE. There were no signs of anterior uveitis in either eye, and the retrolental space and vitreous were devoid of cells. While RE fundus was normal, evaluation of the LE revealed granulomatous optic nerve head (ONH) swelling with engorged veins in the superior quadrant, flame-shaped hemorrhages, and peri-papillary serous retinal detachment extending temporally to involve the fovea [Figure 1a]. The clinical suspicion of ONH granuloma was confirmed with ultrasonography, which showed a significantly raised lesion over the optic disc [Figure 1b]. Fundus fluorescein angiography (FFA) showed early diffuse leak in the peripapillary region along with microaneurysms [Figure 1c], and optical coherence tomography (OCT) revealed the presence of serous retinal detachment. The patient was found to be clinically normal on general physical examination and on examination of the chest, heart, abdomen, and neurological systems.

Case 2: An 18-year-old boy presented with sudden, painless vision loss in RE that started 15 days prior. BCVA was 6/60 in the RE and 6/6 in the LE. The anterior chamber, retrolental space, and anterior vitreous were unremarkable in both eyes and did not contain cells. RE fundus examination revealed optic disc edema (more marked in its upper half), hyperemia, and small haemorrhages over the optic disc, along with engorged veins and extensive perivascular exudation (phlebitis; superior retina >> inferior retina). The posterior vitreous had localized inflammation around the regions of vasculitis and near the optic disc. Loss of foveal reflex, macular edema, and serous macular detachment were also found in the RE [Figure 2a]. LE fundus was unremarkable. FFA confirmed the clinical findings and did not reveal any new vessels. OCT revealed increased macular thickness of nearly 992 microns in addition to serous retinal detachment. The patient was clinically normal on systemic examination, as in Case 1.

Complete blood count, peripheral blood smear, liver function tests, and serum globulin level measurement of both patients yielded normal results. Mantoux test reading was 10 mm in case 1 and 8 mm in case 2. Ultrasonography of the abdomen, chest radiography, high resolution contrast enhanced computerized tomography of the chest, and magnetic resonance imaging of the brain (for ruling out CNS granulomas/optic nerve lesions) revealed no anomaly. Serum angiotensin-converting enzyme (ACE) level was elevated in both patients (Case 1: 55 µg/L, Normal range: 9-39 µg/L; case 2: 68.3 µg/L; normal range 8.0-52 µg/L). Serum of both patients was non-reactive to treponemal antibodies and viral markers, including HIV -1 and 2, and Hepatitis B and Hepatitis C viruses. Toxoplasmosis and cat scratch disease were ruled out on the basis of serology results.

Both patients were prescribed oral prednisolone (1 mg/kg) with slow tapering over 3 months. Case 1 showed a drastic response in ONH swelling and his vision recovered to 6/24 at 3 weeks, 6/12 at 9 weeks, and 6/6 at 12 weeks after start of treatment [Figure 1d]. In the second case, visual acuity recovered to 6/9 in

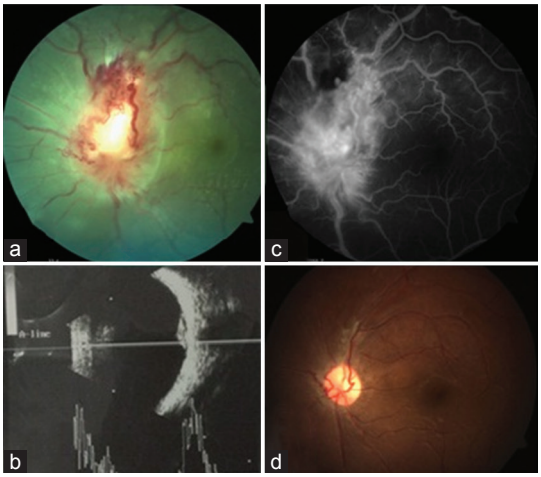

Figure 1. (a) Fundus photo of the LE of case 1, showing the optic nerve head granuloma and serous retinal detachment. (b) Ultrasonography of the LE of case 1, showing significantly raised lesion over the optic disc. (c) FFA of the LE of case 1, showing severe leakage of dye at the optic disc along with microaneurysms. (d) Fundus photo of the LE of case 1, at 3 months of follow-up, showing resolution of the granuloma and the retinal edema.

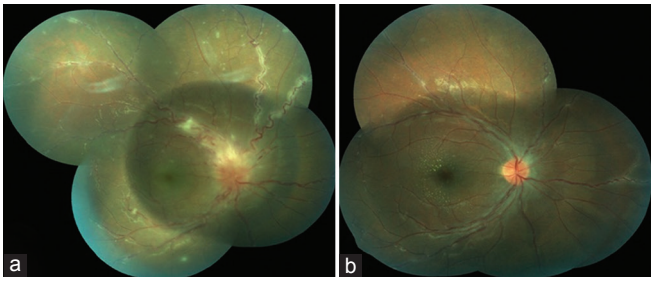

Figure 2. (a) Fundus photo montage of RE of case 2, depicting granuloma at the superior margin of the optic disc, serous retinal detachment of the macula, and retinal phlebitis with "candle wax drippings" seen superiorly. (b) Fundus photo montage of the RE of case 2, at 3 months of follow-up. Granuloma has resolved and cuffing has been replaced with sheathing. Hard exudates can be seen in the macula after resolution of the subretinal fluid.

right eye at day 4 after the start of the treatment and disc edema and vasculitis resolved gradually [Figure 2b]. OCT imaging was performed during follow-up in both cases to document macular changes [Figure 3]. While sub retinal fluid resolved within 15 days of therapy in case 1, macular thickness decreased to 580 microns at day 4 and to 330 microns at week 3 of follow up in case 2. Case 1 has been followed up for 2 years and Case 2 has been followed up for over a year. Both patients are stable, with no recurrence of uveitis or any sign of systemic sarcoidosis/granulomatous disease or steroid toxicity. In both cases, consulting pulmonary specialists advised against a lung biopsy.

DISCUSSION

ONH granulomas are described as solitary and as an initial clinical manifestation of systemic sarcoidosis.[3] These are characterised by raised lesions near the ONH, hemorrhages, swelling, and severe leakage of the dye on FFA. These characteristics are typically seen in cases of OS and tuberculosis. Distinguishing features of active intraocular tuberculosis include large tuberculomas, sub retinal abscess, and serpigenous-like chorioretinopoathy. Leukemia may mimic retinal vasculitis and have optic disc infiltrates, but the presence of Roth spots with abnormal peripheral smear is typical. Other clinical settings include acquired immune deficiency syndrome and infections such as syphilis and cat scratch disease, which may cause peripapillary granulomas. In the two cases presented here, the investigations mentioned earlier and the systemic examination were not indicative of any of these conditions. A recent study of ACE levels in patients with ocular involvement by inflammatory conditions (such as OS and Behcet's disease) and infectious disorders (such as tuberculosis and syphilis), found a very strong association between elevated ACE levels and presumed OS in comparison to other disorders.[4] The sensitivity, specificity, and positive and negative predictive values of serum ACE levels for diagnosis of systemic sarcoidosis have been found to be 58.1%, 83.8%, 83.8%, and 58.1%, respectively. The sensitivity increased to 92% in the presence of clinically active disease.[5] False positive rates were 2% in normal controls and 9% in patients of tuberculosis.[5] Another study on patients with OS and uveitis found the sensitivity of the test to be 84%, the specificity to be 95%, and the predictive value to be 47%.[6] However, the precise role of serum ACE levels in the diagnosis of OS, especially with the new diagnostic criteria, remains to be elucidated. Serum ACE is produced by cells in the granuloma, and has been used to monitor disease activity.[7]

In 2009, the International Workshop on Ocular Sarcoidosis (IWOS) gave 4 levels of certainty, depending on biopsy results, clinical signs, and investigative results, for diagnosing OS [Table 1].[1] While they identified tissue

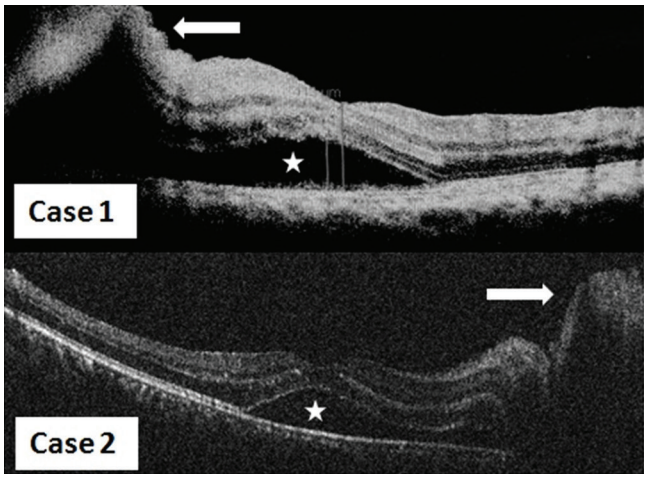

Figure 3. Optical coherence tomographic images of the 2 cases during treatment. Subretinal fluid can be seen (stars) along with a raised lesion at the optic disc (arrows), suggesting granuloma, in both cases.

Table 1. Diagnostic criteria suggested by International workshop on ocular sarcoidosis[1]

Definite OS	Biopsy positive with compatible uveitis
Presumed OS	Biopsy not done, presence of BHL with compatible uveitis
Probable OS	Biopsy not done and BHL absent, presence of 3 ocular signs and 2 positive investigations
Possible OS	Biopsy negative, presence of 4 ocular signs and 2 positive investigations

Signs: mutton-fat KPs/iris nodules, tent shaped peripheral anterior synechia/trabecular nodules, snow balls, multiple chorioretinal lesions, periphlebitis/macroaneurysm, disc/choroidal granuloma, bilaterality Investigations: negative Mantoux reaction, raised serum ACE/lysozyme, BHL on x-ray, abnormal liver enzymes, Chest CT findings in presence of negative x-ray. OS, ocular sarcoidosis; BHL, bilateral hilar lymphadenopathy

diagnosis and bilateral hilar lymphadenopathy to be highly suggestive of sarcoidosis, they also identified 7 clinical signs and 5 investigative modalities favouring a diagnosis of OS. For the cases where biopsy was not performed and hilar lymphadenopathy was absent, the term "Probable OS" was suggested in the presence of at least 3 clinical signs and 2 positive investigative tests.[1] Similarly, Japanese criteria,[2] described a few years earlier, suggested "strong suspicion" for OS if 3 of the 6 described clinical signs were present in addition to 3 of the 6 investigative tests described.[2]

In both our cases, only 2 investigative tests were positive: a negative tuberculin test and elevated ACE activity levels. The first case had a single positive clinical sign of ONH granuloma, while the second case had the additional sign of retinal vasculitis (candle-wax dripping). Hence, these cases do not fit in the diagnosis of OS as per either the IWOS or the Japanese criteria. In both our patients, ACE levels remained above the normal limits at 6 months of follow-up. The high ACE

levels at 6 months in our patients may be explained by the fact that we treated the cases as OS for 3 months, and that either the therapy was not enough for an underlying systemic disease, or that the disease relapsed systemically after cessation of therapy without ocular signs. It has been noted before, in cases of systemic sarcoidosis that ACE levels can increase again after stopping steroid therapy without any clinical or imaging signs of relapse.[8] In view of reports of steroid responsive optic nerve head granulomas in cases of sarcoidosis, we have been monitoring these patients for systemic signs of sarcoidosis, and we plan to perform an annual repeat chest radiographic examination, along with regular pulmonology consultations. We assume that these cases may represent "Forme Fruste OS", and systemic signs may manifest in the coming years.

Such cases of ONH granulomas without anterior signs of uveitis or signs of systemic sarcoidosis have been encountered before and managed successfully as OS.[3] In that series, the authors described 4 cases where ONH granuloma was the presenting feature of sarcoidosis. In 2/4 cases, chest imaging was negative; in 1 case, subcortical vasculitis was noted on head imaging, while in all the 4 cases, ACE levels were elevated. Typically, these patients are female with unilateral disease and are responsive to therapy.[3] It should be noted that tissue diagnosis cannot be performed in every case[3] and common adaptations of the set criteria are likely to rely more on clinical and investigative evidence. In the context of biopsy, inclusion of less invasive investigations such as bronchoalveolar lavage and pulmonary function tests in the diagnostic criteria should also be considered. Perhaps, a new category may be suitable for including such borderline "Forme Fruste" cases. This report is limited by the non-usage of indocyanine green angiography and laser flare photometry to ascertain sub-clinical bilateral disease, which is a separate clinical sign. Furthermore, these patients had borderline Mantoux reactions (between 5-10 may be considered positive in patients infected with HIV, patients with healed scars on chest radiography, and those who had been in close contact with TB patients). These 2 cases did not satisfy the criteria given by Gupta and Gupta for diagnosing presumed ocular TB as demonstrated by negative imaging investigations, no signs of extrapulmonary TB, and good response to treatment with steroids without anti-tubercular therapy.[9]

In conclusion, the current accepted criteria for diagnosis of OS may be incomplete and may need changes to include/exclude such borderline cases. There may not always be a clinical and investigative correlation between the manifestations of OS, which can lead to diagnostic dilemma despite best efforts.

Declaration of Patient Consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial Support and Sponsorship

Nil.

Conflicts of Interest

There are no conflicts of interest.

REFERENCES

1. Herbort CP, Rao NA, Mochizuki M, members of Scientific Committee of First International Workshop on Ocular Sarcoidosis. International criteria for the diagnosis of ocular sarcoidosis: Results of the first International Workshop On Ocular Sarcoidosis (IWOS). *Ocul Immunol Inflamm* 2009;17:160-169.
2. Kawaguchi T, Hanada A, Horie S, Sugamoto Y, Sugita S, Mochizuki M. Evaluation of characteristic ocular signs and systemic investigations in ocular sarcoidosis. *Jpn J Ophthalmol* 2007;51:121-126.
3. Ganesh SK, Kaduskar AV. Optic nerve head granuloma as a primary manifestation of ocular sarcoidosis - A tertiary uveitis clinic experience. *Oman J Ophthalmol* 2015;8:157-161.
4. Sahin O, Ziaei A, Karaismailoğlu E, Taheri N. The serum angiotensin converting enzyme and lysozyme levels in patients with ocular involvement of autoimmune and infectious diseases. *BMC Ophthalmol* 2016;16:19.
5. Ainslie GM, Benatar SR. Serum angiotensin converting enzyme in sarcoidosis: Sensitivity and specificity in diagnosis: Correlations with disease activity, duration, extra-thoracic involvement, radiographic type and therapy. *Q J Med* 1985;55:253-270.
6. Baarsma GS, La Hey E, Glasius E, de Vries J, Kijlstra A. The predictive value of serum angiotensin converting enzyme and lysozyme levels in the diagnosis of ocular sarcoidosis. *Am J Ophthalmol* 1987;104:211-217.
7. Rohatgi PK, Ryan JW, Lindeman P. Value of serial measurement of serum angiotensin converting enzyme in the management of sarcoidosis. *Am J Med* 1981;70:44-50.
8. Yotsumoto H. Longitudinal observations of serum angiotensin-converting enzyme activity in sarcoidosis with and without treatment. *Chest* 1982;82:556-559.
9. Gupta A, Gupta V. Tubercular posterior uveitis. *Int Ophthalmol Clin* 2005;45:71-88.