

Patterns of ocular sarcoidosis at a tertiary eye center in Nepal

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ABSTRACT



Background: Sarcoidosis has been identified as a chronic granulomatous disease involving multiple organ systems, including the eye. Having an unknown incidence and prevalence and closely mimicking tuberculosis which has high prevalence, this disease is often misdiagnosed. This study has been undertaken to assess the patterns of presentation of sarcoid uveitis in a tertiary level eye hospital in Nepal.

Methods: This was a retrospective observational study based on Electronic Medical Recording (EMR). 35 patients fulfilling International Workshop on Ocular sarcoidosis (IWOS) criteria for ocular sarcoidosis were included in the study and clinical signs and symptoms were studied. Ethical clearance was attained from institutional review board of Tilganga Institute of Ophthalmology (Ref. no 16/2020) Associations were sought regarding the type of uveitis, either granulomatous or non-granulomatous and demographic parameters of age and gender and other characteristics like IWOS group and presence of an increased Angiotensin Converting enzyme (ACE) and involvement of anterior segment or not. Chi-square test was used to find the level of significance and p value of <0.05 was considered statistically significant.

Results: The most common pattern of occurrence of ocular sarcoidosis was bilateral disease (82.8%) with panuveitis (39%) being the most common anatomical involvement followed by anterior with intermediate uveitis (29%), isolated anterior uveitis (23%) and posterior uveitis (7%). There was no disparity regarding age, gender, caste or habitat in the occurrence of ocular sarcoidosis. Granulomatous inflammation (62.85%) was more common than non-granulomatous (31.42%) and was significantly more common in people >40 years old (p=0.036).

Conclusion: Sarcoidosis should be considered in the differential diagnosis of any uveitis as sarcoidosis has no known prevalence and yet extremely variable ocular presentation.

Keywords: ocular, pattern, sarcoidosis, tuberculosis, uveitis.

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INTRODUCTION

Sarcoidosis is a multisystem granulomatous disorder of unknown etiology characterized by intra-thoracic involvement. Its intra-thoracic involvement is known to closely mimic tuberculosis, which has high incidence and prevalence in Nepal.¹ Even though it was described as early as 1869 by Hutchinson, its various manifestations and varied clinical course still cause it to be a diagnostic as well as therapeutic challenge. Hence various criteria have been laid down by different study groups to describe the clinical manifestations of sarcoidosis. However no single specific clinical feature has been a sine-qua-non in the diagnosis of sarcoidosis. Ocular manifestations have been found to occur in 20-70% of patients with sarcoidosis with posterior segment being involved in up to 28% of all patients with ocular sarcoid.²⁻⁵

Sarcoidosis is worldwide in distribution.²⁻⁵ However, it has not been elaborately studied in Nepal. There is very little literature regarding sarcoidosis in Nepal and none states the incidence and prevalence. Also, as it is a chronic granulomatous disease most commonly affecting the lungs and closely mimicking tuberculosis, which has high incidence and prevalence in Nepal, there is a large chance of being either underdiagnosed or misdiagnosed as tuberculosis. Considering that one hundred and seventeen thousand, 117,000 (88,000 – 145,000) people with TB disease are living in Nepal today.¹ Considering major lung involvement in both diseases and similar symptomatology, it is highly possible that a number of patients are under empirical treatment for tuberculosis who are actually suffering from sarcoidosis. Sarcoidosis involves the eye in 20-50% cases. Uveitis is the most common manifestation in the eye, anterior segment being involved in upto 70% of cases and posterior segment in 33%.²⁻⁵ Three different studies regarding the etiology of

uveitis done at tertiary eye centers in Nepal stated that sarcoidosis was found as the cause in only 1.2-1.7% of cases⁶⁻⁸. In the earlier study done at TUTH only 5 cases were attributed to sarcoidosis and all cases presented with panuveitis.⁶ However, a latter study noted different clinical presentations of ocular sarcoidosis, even though panuveitis was still the most common presenting diagnosis.⁸ In the meantime, a study regarding the epidemiology of systemic sarcoidosis in Nepal stated that sarcoidosis is common in Nepal.⁹ The present study attempts to fill the gap in knowledge regarding the different presentation patterns of sarcoid uveitis in Nepal.

MATERIALS AND METHODS

Retrospective study done at Tilganga Institute of Ophthalmology, uveitis out-patient department (OPD). This site was selected based on convenience and the presence of uveitis specialists with experience in diagnosis and treatment of sarcoid uveitis. Ethical approval for the study was attained from the institutional review board (IRB) of Tilganga Institute of Ophthalmology (TIO). The study was done by convenient sampling technique on consecutive patients visiting the department and their findings and investigation reports listed in the Electronic Medical Recording (EMR) which was started in Dec 2017. The total duration of study was 2.5 years-from Dec 2017 to March 2020. The classification of uveitis was done according to the Standardization of Uveitis Nomenclature system (SUN classification).¹⁰ Inclusion criteria were all patients of suspected sarcoid uveitis fulfilling IWOS criteria of definite, presumed, probable or possible ocular sarcoidosis. A total of 35 patients were found to fulfill these criteria and were classified according to IWOS criteria.¹¹

In order to further differentiate between HRCT findings suggestive of sarcoidosis or tuberculosis, a study done in India was taken into consideration. In the study, the radiologist made a diagnosis of 'normal'; 'sarcoid/ likely

sarcoid'; 'tuberculosis/likely tuberculosis'; sarcoid/tuberculosis', based on the HRCT findings.¹²

As sarcoidosis is typically described as a cause for granulomatous uveitis more than non-granulomatous, association was sought between the occurrence of type of uveitis (granulomatous or non-granulomatous) and age, gender, presence of raised ACE, IWOS criteria and presence or absence of anterior uveitis.

Results

A total of 35 patients were included in this study which included patients which fulfilled the IWOS criteria for definite, presumed, probable or possible ocular sarcoidosis. In this study, it was found that by gender there was a slight female predominance with 21 females (60%) and 14 males (40%) (Table 1). 17 patients belonged to a rural background and 18 to a rural background. By caste, there were 10 Newars, 8 Brahmin, 9 Chhetri, 7 Madhesi, 6 Janajati and 1 Dalit patients. (Table 2). Hence, there was no specific predilection for sarcoid uveitis on the basis of these factors.

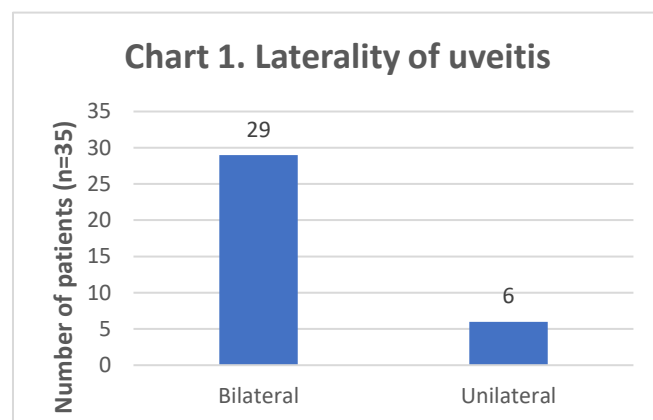
Sex	Number of patients	Percent
Female	21	60.0
Male	14	40.0

Caste	Number of patients	Percent
Brahmin	8	22.9
Chhetri	3	8.6
Dalit	1	2.9
Janajati	6	17.1
Madhesi	7	20.0
Newar	10	28.6

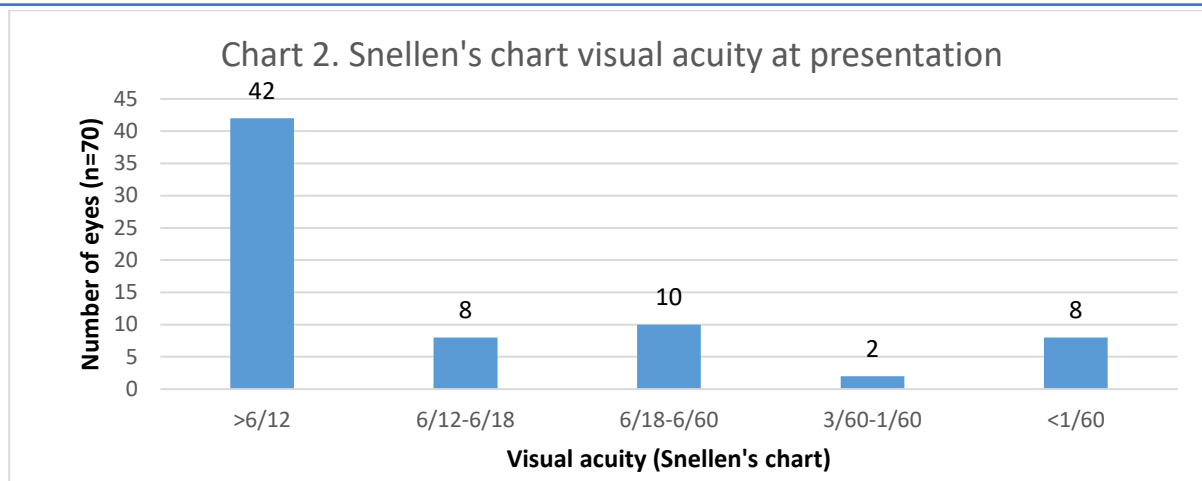
Age distribution revealed 4 patients (11.4%) to be less than 20 years of age at diagnosis, 21(60%) patients between 20-40 years of age and 10 patients (28.5%) were of 40-60 years age group. There were no patients above 60 years of age in this study (Table 3).

Age	Number of patients	Percent
<20	4	11.4
20-40	21	60.0
40-60	10	28.6

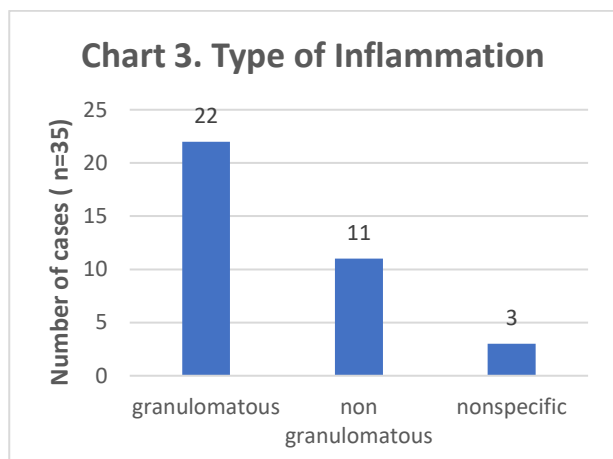
The ocular symptoms were bilateral in 29 (82.8%) cases and unilateral in only 6 (17.1%) (Figure 1).



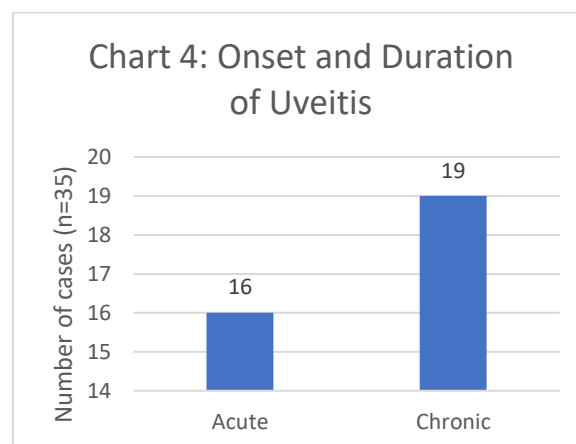
By visual acuity, of total 70 eyes of 35 patients included in the study, 42 eyes (60%) had Snellen's visual acuity of better than 6/12, 8 eyes had visual acuity of 6/12-6/18, 10 eyes had visual acuity of 6/18 -6/60, no eyes had visual acuity in the range 6-60 -3/60 (hence omitted), 2 eyes had visual acuity of 3/60-1/60 and 8 eyes had visual acuity of worse than 1/60 (Figure 2).



Of total 35 patients, 22 patients (62.85%) had granulomatous ocular inflammation and 11(31.42%) patients had non granulomatous ocular inflammation (Chart 3).

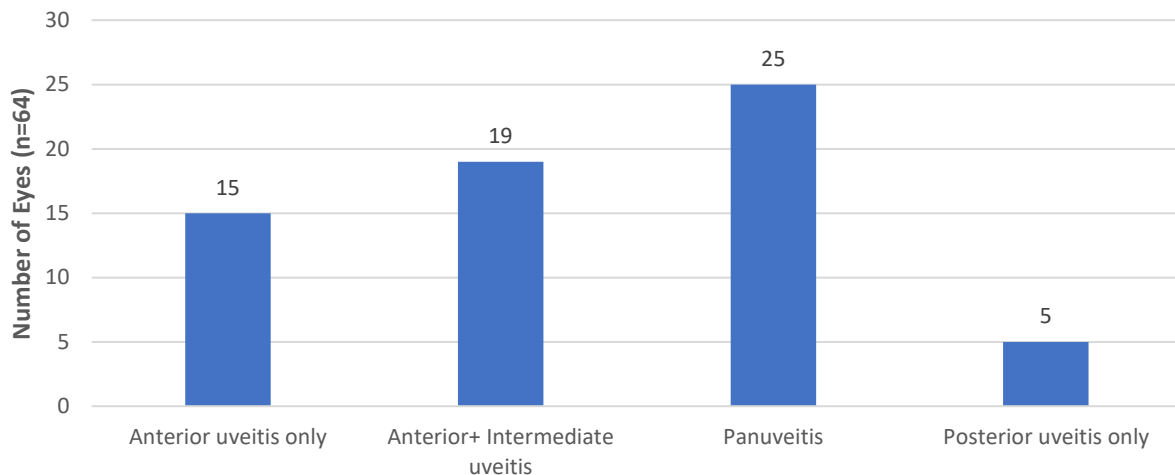


As regards onset and duration of illness, going by standard SUN classification of duration of uveitis,¹¹ 16 patients (45.7%) had acute uveitis, 19 (54.2%) had chronic uveitis in association with sarcoidosis. 14 had recurrent episodes of uveitis.(Chart 4)



Of the total 70 eyes of 35 patients, ocular involvement in the form of Sarcoid uveitis occurred in 64 eyes. 15 (23.4%) eyes had isolated anterior uveitis only, whereas 19 (29.6%) eyes had anterior and intermediate uveitis. 5 (7.8%) eyes had isolated posterior uveitis in the form of active or healed choroidal granulomas or retinal vasculitis. Panuveitis was seen in 25 eyes (39%) and no patient had isolated intermediate uveitis. (Chart 5)

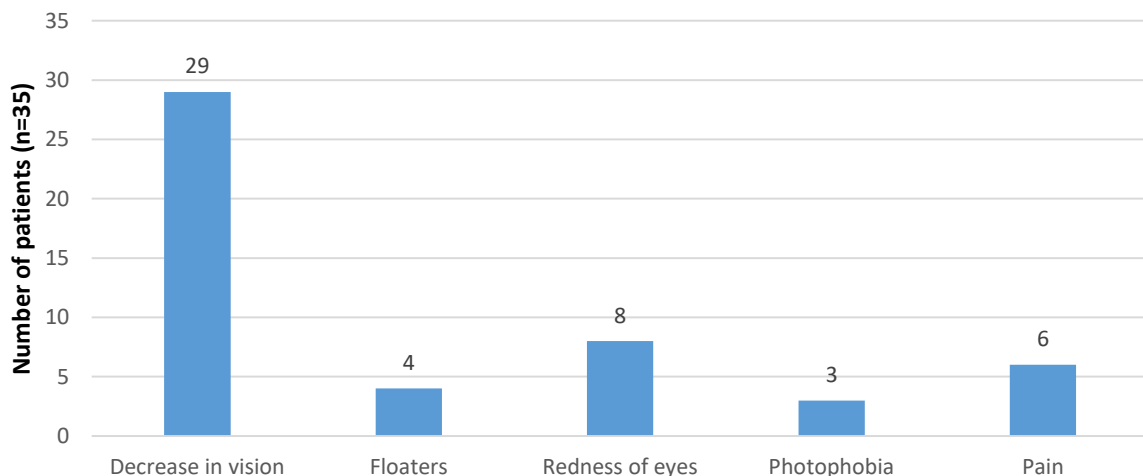
Chart 5. Site of involvement in Sarcoid uveitis



The most frequent symptomatic presentation was of diminution of vision-29 of total 35

patients (82.9%). other complaints were- floaters- 4(11.4%), redness of eyes -8(22.9%), photophobia-3 (8.6%) and pain 6 (17.1%). (Chart 6)

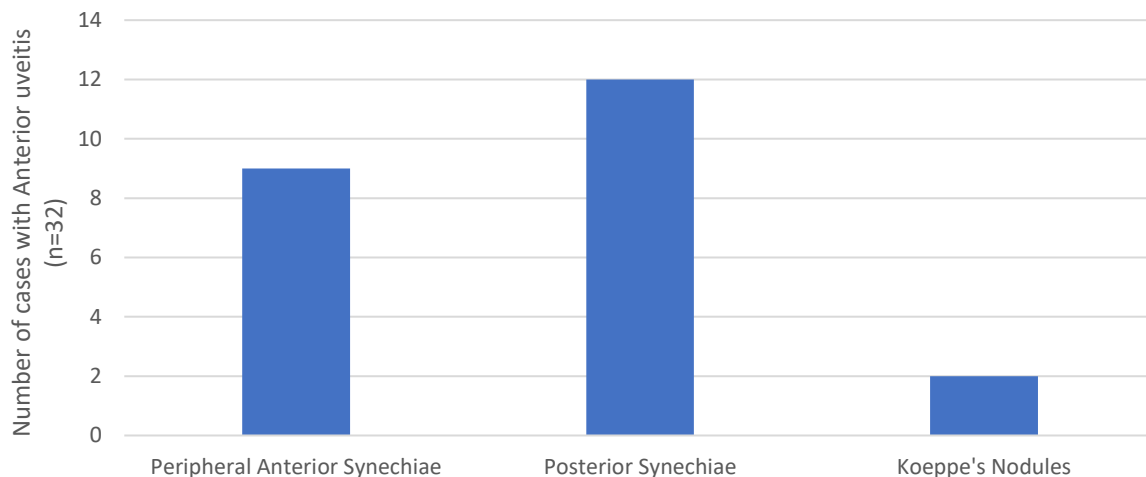
Chart 6. Symptomatology of Ocular Sarcoidosis



Only one patient had external ocular inflammation in the form of episcleritis.

As regards the clinical signs typical of sarcoid uveitis, 9 (25.7%) patients had peripheral anterior synechiae, 12(34.28%) had posterior synechiae and 2 (5.7%) had Koeppel's nodules. (Chart 7)

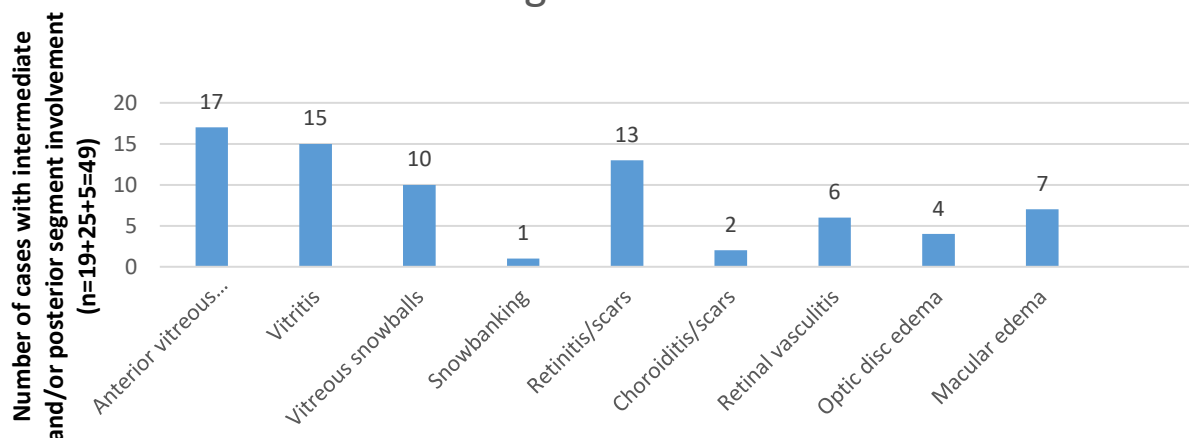
Chart 7. Signs of ocular sarcoidosis in Anterior segment



In the posterior segment findings, 17 patients had anterior vitreous cells and vitritis per se was seen in 15 patients. In 10 patients, vitreous snowballs were seen and snowbanking was observed in only one patient. Retinitis or scars suggestive of previous retinitis was seen in 13

patients and choroiditis scars were seen in 2 patients. No active choroiditis lesions were seen in any patients in this study. As regards retinal vasculitis, active vasculitis was seen in 6 patients and old sheathing was seen in 4 patients. Optic disc edema was seen in 4 patients and macular edema in 7 patients. (Chart 8)

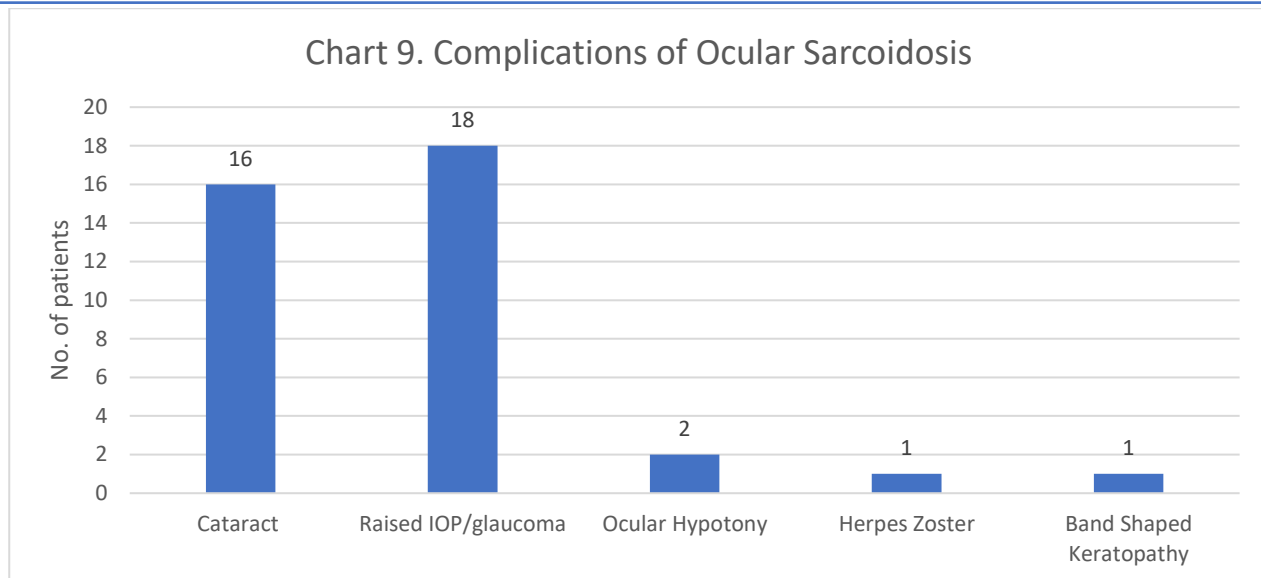
Chart 8. Signs of ocular sarcoidosis: Posterior segment



The complications of Ocular Sarcoidosis (disease or treatment-related) noted in this study included Cataract in 16 patients(45.7%), raised IOP or diagnosed glaucoma in 18

patients (51.4%), ocular hypotony in 2 patients (5.7%) and band shaped keratopathy and herpes zoster in 1 patient each. (Chart 9)

Chart 9. Complications of Ocular Sarcoidosis



On the basis of the findings of this study, associations were sought between the type of uveitis (granulomatous or non-granulomatous) of ocular sarcoidosis depending on age, gender, presence of an increased ACE, IWOS category, and anterior uveitis using the Chi-square test. An association was found linking

age of presentation (<40 or >40 years) with occurrence of granulomatous or non-granulomatous uveitis as there was significantly more granulomatous inflammation in patients over the age of 40 years, with a 5% level of significance. (Table 4)

Table 4. Correlation between Age, Gender, increase in ACE, IWOS category, and presence or absence of anterior uveitis with type of uveitis (granulomatous vs. non granulomatous)

Characteristics	Non Granulomatous n(%)	Granulomatous n(%)	Chi-Square	P-value
Age				
<40 years	12(48)	13(52)	4.41	0.036*
>40 years	1(10)	9(90)		
Gender				
Female	7(33.3)	14(66.7)	0.32	0.56
Male	6(42.9)	8(57.1)		
ACE				
Yes	6(54.5)	5(45.5)	2.081	0.149
No	7(29.2)	17(70.8)		
IWOS				
Definitive	5(50)	5(50)		
Presumed	5(31.3)	11(68.8)	1.002	0.606
Probable	3(33.3)	6(66.7)		
Anterior uveitis				
No	11(42.3)	15(57.7)	1.15	0.282
Yes	2(22.2)	7(77.8)		

*Statistically significant at 5% level of significance.

Beyond the ocular findings, lungs were found to be definitely involved in 10 patients (by HRCT chest and biopsy in the related cases)

and skin in 2 patients. In one other patient, bone marrow, spleen and liver were found to be involved actively in the disease process.

Discussion

Ocular involvement in Sarcoidosis was noted early in the 1900s, and more elaborately described in the mid-1900s. The frequency of ocular involvement in sarcoidosis has been reported variously from 13-79%. Ocular involvement is the presenting feature of sarcoidosis in 20-30% cases. Uveitis has been the most common ocular feature, occurring in 20-70% of cases diagnosed with systemic sarcoidosis.²⁻⁵

It has been stated that no singular extraocular manifestation of sarcoidosis was predictive of the development of ocular involvement or uveitis.^{13,14} In this study too, no such specific systemic manifestation was seen preceding the onset of ocular sarcoidosis.

Two peaks of incidence were reported for ocular sarcoidosis, the first at ages 20–30 years and the second at ages 50–60 years.¹⁴ However, typically, literature states that sarcoidosis is a disease of the young adults, with three-fourths occurring in those younger than 40 years of age. Children were noted to be affected uncommonly and even though both males and females were affected, females were found to be affected more frequently at a 60:40 ratio.^{2-4, 15-19} In a study of 83 patients with biopsy proven sarcoid uveitis, a median age at onset of 52 (37–62) years and an unbalanced gender ratio (women 77.1%) was noted.²⁰ Similarly, in this study, the peak incidence was in the age group 20-40 years. Also, findings seemed to be consistent in terms of gender predilection with a somewhat female predominance (M: F=2:3).

Considering the chronology or sequence of occurrence of ocular features in a diagnosed case of systemic sarcoidosis, it is to be noted that there is no specific course of ocular

involvement in sarcoidosis as the eye may be involved at any time in a patient with systemic sarcoidosis. In a previous study, 37.3% had systemic sarcoidosis in addition to ocular localization, whereas 62.6% initially presented with isolated uveitis and were later diagnosed to have systemic sarcoidosis. Among the latter, 7.7% (n=4) developed an extraocular disease after a median follow-up duration of 60 (44–110) months.²⁰

Various studies have been done in the past in various geographical regions of the world in an attempt to establish a definite cause for uveitis. In a study done in Tokyo, among 695 patients with uveitis, a definite diagnosis was made in 431 (62.0%). The most common specific diagnosis of uveitis was Sarcoidosis (8.1%).²¹ In another study done in New Zealand, among 1148 patients, sarcoidosis was established as amongst the most common diagnoses, particularly in cases of panuveitis.²² In the previous studies done in Nepal, the number of uveitis patients included were 1113, 308 and 4359 and sarcoidosis was found to be the cause for 1.22-1.7% of total uveitis.⁶⁻⁸

Bilaterality has been a consistent feature in all studies throughout the world. Bilaterality has been reported to occur from 86-93%. In certain studies, bilaterality was the only clinical feature suggestive of ocular sarcoidosis in diagnosed cases of systemic sarcoidosis with no alternative diagnosis.^{23, 24} In the present study too, bilaterality was found to be the most common clinical feature, occurring in 77.14% cases.

In an attempt to study the ocular manifestations of systemic sarcoidosis, a retrospective study was done involving 345 cases of systemic sarcoidosis in USA. In the study, only 40 eyes of 23 patients had ocular involvement. Anterior uveitis was the most common feature (71%) followed by intermediate uveitis (21%), posterior uveitis (7%) and panuveitis (7%). One patient had anterior uveitis and intermediate uveitis.²³ In

another study done in New Zealand, the most common presentation was Panuveitis.²² In an international cohort of 884 patients suffering from uveitis from 19 uveitis clinics in 12 countries, 264 patients were suspected to have sarcoid uveitis. Of the total uveitis cases, the most common type of uveitis was panuveitis (39%) followed by anterior uveitis (37%), posterior uveitis (17%), intermediate uveitis (4%), and anterior with intermediate uveitis (2%).²⁴ In another retrospective study done in Italy, charts of 44 patients with biopsy proven sarcoidosis and bilateral uveitis were studied. In that study too, the majority of patients presented with panuveitis (52%).²⁵ In the study done in India too, the most common presentation was panuveitis.¹² In Nepal, out of three studies on patterns of uveitis in Nepal, in two, all sarcoid uveitis patients presented with panuveitis.^{6,7} Whereas in the third study, although sarcoidosis accounted for only 1.22% of the total uveitis cases, there was a variation in the anatomical involvement with 9.4% anterior uveitis, 16.9% intermediate uveitis, 24.5% posterior uveitis and 49% panuveitis.⁸ Thus, in all the previous studies in Nepal, there was a definite majority of panuveitis being the presenting pattern. In the present study too, we found that the most common single diagnosis on the basis of anatomical location was Panuveitis (39%). However, 92% cases had some form of anterior uveitis (with or without posterior involvement). Hence, the ocular involvement in sarcoidosis seems to be grossly uniform throughout geographical barriers. It is important to note from these findings that that all cases of anterior uveitis should have proper posterior segment evaluation and ocular sarcoidosis as a differential.

In the study done at USA, the visual acuity (VA) of patients with uveitis was generally good at diagnosis with the majority of eyes having VA of 6/6 to 6/7.5 (20/20 to 20/25) in each eye.²³ In the study in Italy too, visual acuity was not severely decreased. The median best-corrected visual acuity in the worst-seeing

eye at presentation and at end of follow-up was respectively 6/15-6/9.5 (LogMAR 0.4 with interquartile range [IQR] 0.26–0.80 and 0.63 with IQR 0.36–1.00)²⁵ In the present study too, majority of patients had good visual acuity at presentation (60% had > 6/12 Snellen's acuity).

In the study done in an international cohort of patients over 12 countries, the most common ocular signs were: bilaterality (86%); trabecular meshwork nodules, tent-shaped peripheral anterior synechiae (PAS), or both (51%); snowballs or strings of pearls (50%); and mutton-fat KPs, iris nodules, or both (44%). Sixty-two of 98 patients (63%) had 3 or more clinical signs, and 39 (40%) had 4 or more clinical signs. Five biopsy-positive patients (5%) showed no clinical signs, and 5 (5%) had bilaterality as the only sign. The least common ocular signs were optic disc nodules or granulomas, solitary choroidal nodules, or both (7%).²⁴ In the study in USA, all but one case was bilateral (93%).²³ In the study including 44 patients in Italy, most patients had granulomatous inflammation (61%) and most had posterior synechiae (62%).²⁵ In the study done in India comparing features of ocular tuberculosis with ocular sarcoidosis, although broad based posterior synechiae was found in both groups, it was found that candle-wax type perivasculitis and depigmented chorioretinal lesions were significantly suggestive of ocular sarcoidosis.($p=0.001$)¹² Bilaterality was a prominent feature in this study too (82.8%). However other features were not similar as there was PAS in only 25%, iris nodules in 5.7%, focal choroiditis/ retinitis was found in 42.8% and none with optic disc granulomas or nodules.

Ocular complications associated with inflammation and/or treatment included 50% posterior synechiae, 43% cataract, 36% glaucoma/ocular hypertension, and 36% macular edema.²³ In the study done in Italy, the most frequent vision-threatening

complications were cystoid macular edema (56%) and cataract (56%).²⁵ In the present study, the complications associated with inflammation and/or treatment included cataract (45.7%) and raised IOP/ documented glaucoma (51.4%) but there was a significantly lower occurrence of macular edema (2%). Other complications noted were ocular hypotony (5.7%), and herpes zoster infection and band shaped keratopathy (2.8%) each.

Conclusion

Sarcoidosis should be considered in the diagnosis of all uveitic entities in Nepal as it can present in any form, acute, chronic or granulomatous or non-granulomatous. Though it was found to be the cause of only panuveitis in previous studies, this study found it to cause anterior, intermediate and posterior uveitis as well, even though panuveitis was still the most common clinical presentation. However the most common suggestive features of ocular sarcoidosis found in this study were bilaterality and anterior uveitis (isolated or in combination) in all age groups and granulomatous uveitis in patients over 40 years of age.

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