SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2015; 32; 237-245

Ocular and systemic features of sarcoidosis and correlation with the International Workshop for Ocular Sarcoidosis diagnostic criteria

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Abstract. *Purpose:* To describe the ocular and systemic features in biopsy proven (definite) and non-biopsy proven (clinical) ocular sarcoidosis and to compare the ocular features with those proposed by the International Workshop for Ocular Sarcoidosis (IWOS). *Methods:* Retrospective chart review of 83 patients who attended a tertiary referral uveitis clinic and were diagnosed with sarcoidosis. Patients were divided into two groups based on the type of diagnosis: those who had tissue biopsy confirmed diagnosis 'definite sarcoidosis' (n= 42; 50.60%) and those who had 'clinical sarcoidosis' (n= 41; 49.40%). Ocular and systemic manifestations, including lung function tests and bronchoalveolar lavage findings were compared in the two groups. The ocular features were also compared with the categories laid down by the International Workshop on Ocular Sarcoidosis (IWOS). *Results:* The mean age at presentation was 38.75 years (SD=12.33), 55.42% patients were female and mean follow-up was 24.35 months (SD=18.35). Trabecular meshwork nodules and/or tent-shaped PAS (category II of IWOS) were observed more frequently in patients with biopsy proven sarcoidosis (26.19 % v/s 9.76%; p=0.08). After logistic regression analysis, the predictor coefficient curve showed area under curve of 0.7262. Lymphocytosis (38.61% and 28.02%, p=0.93) and monocytosis (55.11% and 53.83%, p=0.56) on bronchoalveolar lavage analysis was present in both the groups, highlighting presence of granulomatous disease. *Conclusion:* This study suggests high reliability for the clinical diagnosis of ocular sarcoidosis in patients with signs recommended by IWOS and that our diagnostic criteria are consistent with that of the IWOS. *(Sarcoidosis Vasc Diffuse Lung Dis 2015; 32: 237-245)*

Key words: ocular sarcoidosis, lung function test, biopsy, systemic sarcoidosis, IWOS

Introduction

Sarcoidosis is a multi-system, chronic, inflammatory condition of uncertain etiology that was first described in 1877 by Jonathan Hutchison (1). Histologically, it is characterised by granulomatous inflammation without caseation (2, 3). While 25% to 60% of patients with systemic sarcoidosis develop ocular involvement at some stage during the course of the disease (4-8). Ocular involvement can precede systemic sarcoidosis in up to 30% (9) of cases, making the diagnosis quite difficult in the absence of any systemic manifestations. The disease can affect many organs throughout the body including lung, lymph nodes, skin, heart, liver, muscles, and the eye (2).

Early recognition of the ocular features and establishing the diagnosis of systemic sarcoidosis has significant implications for treatment and for the patient systemic and visual prognosis.

Received: 5 October 2014
Accepted after revision: 26 Janurary 2015
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The presence of non-caseating granulomata on tissue biopsy is the gold standard for the diagnosis of sarcoidosis (3). Due to the invasive nature of tissue biopsy, this test has limited indications in the eye and diagnosis of ocular sarcoidosis becomes mostly clinical, supported by ancillary investigations. In 1990, Diffuse Pulmonary Disease Research Committee of Japan published the guidelines for diagnosis of ocular sarcoidosis. These were further revised by Asukata et al in 2006 (10) and later validated and shown to have a high sensitivity and specificity (11). These diagnostic criteria were hence adapted by the International Workshop on Ocular Sarcoidosis (IWOS) in 2009 (12) (Table 1). IWOS recommended seven clinical categories of ocular signs which are suggestive of ocular or possible systemic sarcoidosis.

The main objective of this study was to compare ocular and systemic features of sarcoidosis in a cohort of biopsy proven to those with clinically suspected ocular sarcoidosis. Secondary objectives were to test the criteria described by IWOS using ROC curve in our setting, and determine how useful they can be in establishing the diagnosis and also how bronchoalveolar lavage findings and pulmonary function tests can be used to assist in the diagnosis of patients presenting primarily with ocular manifestations.

Methodology

This was a retrospective study of a cohort of 83 consecutive patients who were seen at a tertiary referral eye care center in the UK and had the diagnosis of sarcoidosis related uveitis. Institutional Board review and ethics committee approval was obtained for the study. This study was performed in adherence to the tenets of the Declaration of Helsinki. All patients with biopsy proven sarcoidosis and with clinical signs suggestive of ocular sarcoidosis were included in the study group. Patients with any other established diagnosis that explained their uveitis were excluded from the study. All the patients were referred to or were concurrently under the care of an internist for pulmonary or other systemic sarcoidosis.

The data were collected from the patients' clinical records and entered in a computerized database. Based on the mode of confirmatory diagnosis, the study population was divided into two groups: 1-Definite sarcoidosis group – biopsy proven sarcoidosis, and 2-Clinical sarcoidosis group – diagnosis based on clinical features and other ancillary investigations. As group 2 did not had any of the set diagnostic criteria laid down by IWOS for probable, possible or presumed sarcoidosis, it was referred to as "clinical sarcoidosis" group.

Table 1. International Workshop on Ocular Sarcoidosis (IWOS) guidelines for diagnosis of Ocular sarcoidosis (7)

1A: Clinical signs suggestive of ocular sarcoidosis	
I	Mutton-fat KPs and/or iris nodules at pupillary margin or in stroma
II	Trabecular meshwork nodules and/or tent-shaped PAS
III	Snowballs/ string of pearls vitreous opacities
IV	Multiple chorioretinal peripheral lesions (active and atrophic)
V	Nodular and/or segmental periphlebitis and/or macroaneursym
VI	Optic disc nodule/ granuloma and/or solitary choroidal nodule
VII	Bilaterality on clinical examination or on investigation
1B: Laboratory investigations in suspected ocular sarcoidosis	
1	Negative tuberculin test in BCG vaccinated patient
2	Elevated Serum ACE and/or elevated serum lysozyme
3	Chest X-ray – presence of Bilateral hilar lymphadenopathy (BHL)
4	Abnormal liver enzyme tests (any two)
5	Chest CT scan in patients with negative chest X-ray
1C: Diagnostic criteria for ocular sarcoidosis	
Definite	Biopsy supported diagnosis with a compatible uveitis
Presumed	Biopsy not done, presence of BHL with a compatible uveitis
Probable	Biopsy not done, BHL negative, presence of three clinical signs and two positive investigational tests.
Possible	Biopsy negative, four of the suggestive intraocular signs and two of the investigations are positive

The data collected included demographic features (e.g. age, gender and ethnic origin), ocular manifestations (anterior segment and posterior segment features), associated systemic findings, details about biopsy, pulmonary function tests and bronchoalveolar lavage (BAL) findings. Out of total of 42 cases of biopsy proven sarcoidosis, the source of tissue biopsy included lungs in 33 (78.57%) patients, lymph node in 4 (9.52%), skin in 4 (9.52%) and conjunctiva in 1 (2.38%). Based on chest physician decision, BAL was done in 26 patients with biopsy proven sarcoidosis patients and in 18 patients in the clinical sarcoidosis group. The BAL fluid was examined for monocytosis, lymphocytosis, neutrophils and eosinophils. Pulmonary function tests were performed in 39/42 patients in the definite sarcoidosis group and in 37/41 patients in the clinical sarcoidosis group; based on clinical involvement of the lung , it was performed in 43 patients with pulmonary involvement and 33 patients without obvious clinical lung involvement. Comparison of ophthalmic manifestations was done with IWOS criteria (12) Stata 13.0 (Stata Corp, College Station, TX) for Windows was used for the statistical analysis of the data.

Qualitative variables were expressed as percentages. Quantitative variables were expressed as mean values ± standard deviation (SD) if they followed a normal distribution or as median values (range) if they did not. Association was tested with chi-square test or with Fisher's exact test when necessary. The strength of associations was measured by odds ratio (OR), or by Haldane's odds ratio estimator for small samples (13) Differences between 2 means were tested with the independent samples t-test, when normality and homoscedasticity conditions allowed it. When this was not possible, the Mann–Whitney test for 2 independent samples was performed.

Multivariate logistic regression model was constructed, including all 7 diagnostic categories, and using the biopsy result as the gold standard for the diagnosis. A ROC (Receiver Operating Characteristics) curve was created using the predicted probabilities from the multivariate logistic regression model, and the area under the curve (C-index) was calculated for all the diangostic signs. Results were considered statistically significant when $p < 0.05$. We used an online confidence interval calculator tool (www.pedro.org.au/english/downloads/confidence-interval-calculator) to calculate specificity, sensitivity, positive and negative likelihood ratio and diagnostic odds ratio for each of the seven clinical signs.

Results

Detailed demographic profile is presented in Table 2 for both groups. There was a similar distribution between the two groups for age, gender distribution, ethnicity and smoking history. Both groups had a very strong positive history of smoking (either current smokers or ex-smokers).

Total mean follow up was 24.35 months (18.35, 4-105 months). There was no statistically significant difference between the two groups with regards to demographics, ocular involvement and systemic involvement. The ocular findings according to the IWOS categories are listed in Table 3A for both groups. No statistically significant differences between the two groups for any of the clinical signs

Table 2. Demographics of patients with clinical and definite sarcoidosis

	Definite Sarcoidosis (n=42)	Clinical Sarcoidosis (n=41)	Effect size (95% CI)	p value
Age (SD, IQR)	37.33 (12.22, 21-71)	40.21 (12.42, 25-72)		
Gender (Female)	24 (57.14%)	22 (53.66%)	-0.23 (-0.67 to 0.20)	0.289
Ethnicity		0.151		
Caucasians	9 (21.43%)	14 (34.15%)		
Indians	5 (11.90%)	10 (24.39%)	0.77 (0.19 to 3.09)	0.720
Afro-Caribbean	25 (59.52%)	11 (26.83%)	3.53 (1.10 to11.27)	0.022
Semitic	3 (7.14%)	6 (14.63%)	0.77 (0.14 to 4.03)	0.568
Smoking history	39 (95.03%)	36 (90.00%)	1.64 (0.65 to 4.14)	0.287
Bilaterality	18 (42.85%)	16 (39.02%)	0.93 (0.37 to 2.31)	0.881

p value calculated by Chi Square and Fischer's exact test

were observed. Although it did not reach statistical significance, trabecular meshwork nodules and/or tent-shaped PAS were observed more frequently in patients with biopsy proven sarcoidosis (26.19 in biopsy proven vs 9.76% in clinical sarcoidosis). The number of positive clinical signs as per IWOS in both groups is described in Table 3B. Mann Whitney U test did not show any statistical significance between the two groups based on number of clinical signs. In addition to the classical signs recommended by IWOS, we also categorized other ocular features in both groups (Table 3C).

Systemic findings in both the groups are presented in Table 4. Lungs (57.14% in definite group and 48.78% in clinical group) followed by skin (16.67% in definite group and 14.63% in clinical group) were predominantly involved in both groups as compare to other involved sites. Bronchoalveolar lavage findings are presented in Table 5. Thirty-seven out of a total of 44 patients (84.09%) had lymphocytosis of more than 15% with definite sarcoidosis group having average lymphocytosis of 38.61% and clinical sarcoidosis group having average lymphocytosis of 28.02%. In non-smokers, average lymphocytosis count was 26.06% (SD=17.23) whereas in smokers average lymphocytosis count was 34.69% (SD=24.33). There was marked monocytosis on BAL analysis though it did not reach statistical significance. (55.11% in definite sarcoidosis group v/s 53.83% in probable sarcoidosis group, p =0.56)

The results of the pulmonary function tests are presented in Table 6. There were no statistically significant differences between the lung function tests between the two groups. We also performed subgroup analysis of pulmonary function test for patients with and without lung involvement and there was no statistically significant difference noted between those two subgroups.

Table 3. Clinical signs in both the cohort of definite and clinical sarcoidosis group

3A IWOS criteria for sarcoidosis (7)

IWOS clinical criteria	Definite Sarcoidosis	Clinical Sarcoidosis	OR (95%CI)	p value
I	20 (47.62%)	24 (58.54%)	0.98 (0.26-1.54)	0.322
II	11 (26.19%)	4 (9.76%)	3.28 (0.91-11.76)	0.085
III	29 (69.05%)	33 (80.49%)	0.54 (0.19-1.51)	0.233
IV	18 (42.86%)	20 (48.78%)	0.78 (0.32-1.88)	0.590
V	16 (38.10%)	22 (53.66%)	0.53 (0.21-1.29)	0.157
VI	9 (21.43%)	10 (24.39%)	0.84 (0.30-2.37)	0.749
VII	27 (64.29%)	27 (65.85%)	0.93 (0.37-2.31)	0.88

p value calculated by Chi Square and Fischer's exact test

3B: Number of positive ocular signs in biopsy proven and non-biopsy proven ocular sarcoidosis (p=0.153)

Number of positive ocular signs	Definite sarcoidosis group- number of patients	Clinical Sarcoidosis group – number of patients
1	2 (4.76%)	0
2	8 (19.05%)	0
3	18 (42.86%)	27 (65.85%)
4	11 (26.19%)	11 (26.83%)
5	3 (7.14%)	3 (7.32%)
6	0	0
7	0	0

3C: Additional ocular findings (not listed under IWOS)

	Definite Sarcoidosis (n=42)	Clinical Sarcoidosis (n=41)	OR (95%CI)	P value
Initial Ocular presentation	23 (54.76%)	33 (80.49%)	0.69 (0.40-1.18)	0.012
Dry Eyes	1 (2.38%)	3 (7.32%)	0.33 (0.03-3.20)	0.296
Scleritis	1 (2.38%)	1 (2.44%)	0.97 (0.05-16.41)	0.986
Conjunctival nodule	4 (9.52%)	3 (7.32%)	1.33 (0.27-6.43)	1.000
Disc oedema	4 (9.52%)	7 (17.07%)	0.57 (0.16-1.95)	1.000
Macular involvement (CMO)	7 (16.67%)	7 (17.07%)	1.00 (0.35-2.85)	0.960

Table 4. Associated Systemic findings

	Definite Sarcoidosis (n=42)	Probable Sarcoidosis (n=41)	OR (95%CI)	p value
Lungs	24 (57.14%)	20 (48.78%)	1.40 (0.58-3.35	0.448
Skin	7 (16.67%)	6 (14.63%)	1.16 (0.35-3.85)	0.800
Brain	2 (4.76%)	4 (9.76%)	0.46 (0.07-2.72)	0.433
Joints	4 (9.52%)	2 (4.88%)	2.05 (0.34-12.08)	0.676
Liver	5 (11.90%)	1 (2.44%)	5.40 (0.57-50.98)	0.202
Spleen	1 (2.38%)	0 (0.00%)	3 (0.12-75.80)	1.000
kidney	0	1 (2.44%)	0.32 (0.01-8.03)	0.494
Epididymis	0	1 (2.44%)	0.32 (0.01-8.03)	0.494
Bronchus	1 (2.38%)	0	3 (0.12-75.80)	1.000
Nodes	2 (4.76%)	0	5.12 (0.24-110.05)	0.494
Heart	1 (2.38%)	1 (2.44%)	0.97 (0.05-16.41)	0.986
Glands	4 (9.52%)	3 (7.32%)	1.33 (0.276-6.433)	0.719
Pituitary	0	1 (2.44%)	0.32 (0.01-8.03)	0.494
Parotid	1 (2.38%)	0	3 (0.12-75.80)	1.000
Laryngeal	1 (2.38%)	0	3 (0.12-75.80)	1.000

p value calculated by Chi Square and Fischer's exact test

Table 5. Bronchoalveloar lavage (BAL) findings in patients with pulmonary involvement

	Definite Sarcoidosis (n=26)	Probable Sarcoidosis (n=18)	Effect size estimate	P value
Monocytosis	55.11 (24.31, 0-92)	53.83 (31.38, 0-93.3)	-0.04 (-0.63 to 0.53)	0.562
Lymphocytosis	38.61 (22.81, 0-87.32)	28.02 (23.02, 0-83)	-0.46 (-1.05 to 0.13)	0.936
Neutrophils	0.91 (0.90, 0-2.7)	0.7 (0.98, 0-3)	-0.22 (-0.80 to -0.36)	0.772
Eosinophils	1.09 (1.63, 0-5.4)	0.11 (0.26, 0-1)	-0.73 (-1.34to -0.12)	0.990

Cohen's D effect size estimate used; p value- calculated using t test

Table 6. Pulmonary function test

	Definite Sarcoidosis (n=39)	Probable Sarcoidosis (n=37)	Effect size	p value
FEV1	91.64(17.98, 50-130)	98.24(14.76, 73-143)	0.40(-0.05 to 0.85)	0.957
FVC	98(17.26, 56-143)	102.97(15.21, 79-147)	0.30(-0.14 to 0.75)	0.906
TLC	94.42 (14.41, 61-124)	97.56(14.47, 74-153)	0.21(-0.23 to 0.67)	0.825
TLCO	69.43(16.52, 38-95)	79.62(14.83, 55-115)	0.64(0.18-1.10)	0.996
KCO	84.56(19.08, 45-125)	88.97(16.18, 57-125)	0.24(-0.20 to 0.69)	0.858

Pulmonary function tests by lungs involvement clinically

	Lungs involved (n=43)	Lungs not involved (n=33)		
FEV1	94.16 (16.84, 50-138)	95.75(16.77, 62-143)	0.09(-0.35 to 0.54)	0.658
FVC	98.97 (16.24, 56-144)	102.30(16.61, 75-147)	0.20(-0.25 to 0.65)	0.808
TLC	95.19(13.56, 61-120)	96.96 (15.62, 71-153)	0.12(-0.33 to 0.57)	0.700
TLCO	72.86(18.33, 38-115)	76.39(13.59, 46-103)	0.21(-0.24to 0.66)	0.821
KCO	85.95(19.39, 45-125)	87.69(15.59, 59-125)	0.09(-0.35 to 0.55)	0.662

Ref values (18):
FEV1 (Forced expiratory volume at one second): 80-120; FVC (Forced vital capacity): 80-120;
TLC (Total lung capacity): 80-120
TLCO or DLCO (Total diffusing capacity of lung for carbon monoxide): 75-120
KCO or DLCOc (diffusion capacity of lung per unit volume-transfer coefficient): 80-120
Cohen's D effect size estimate used, P value- calculated using t test.

Table 7. Multivariate Regression model for IWOS clinical signs and number of clinical signs as predictors of a positive biopsy for sarcoidosis

Variable	β	SE of β	OR	p
IWOS Cat I	-0.948	0.555	**0.387**	0.087
IWOS Cat II	1.010	0.736	**2.745**	0.170
IWOS Cat III	-0.653	0.591	**0.520**	0.269
IWOS Cat IV	-0.491	0.557	**0.612**	0.378
IWOS Cat V	-1.207	0.546	**0.299**	0.027
IWOS Cat VI	-0.627	0.605	**0.534**	0.300
IWOS Cat VII	0.038	0.522	**1.039**	0.942

Diagnostic probability of IWOS criteria: Results of the logistic regression model predicting the probability of a positive biopsy based on the IWOS diagnostic categories is shown in Table 7.

Figure 1 shows the ROC curve for the predicted probabilities. Individual ROC curves were calculated for the individual categories (Fig. 1). ROC plot did not show an area under the curve above the reference range (0.500) for any of the individual clinical signs except category II of IWOS (presence of trabecular meshwork nodules or tent shaped PAS). Also, the area under the curve for the ROC plot for number of positive clinical signs in non-biopsy proven cases was <0.500. We performed logistic regression analysis for all the seven clinical criteria and using the outcome from that analysis, ROC curve was plotted and concordance index (C-index) was calculated.

The predictor coefficient ROC curve has an area under the curve (C-index) of 0.7262. Using online confidence interval calculator tool (www.pedro.org.au/english/downloads/confidence-interval-calculator) we calculated sensitivity, specificity, positive and negative likelihood ratio and diagnostic odds ratio for each of the seven clinical signs (Table 8). None of the diagnostic categories showed a statistically significant OR by bivariate analysis. Logistic regression analysis showed that the presence of category V (Nodular and/or segmental periphlebitis in our case series) significantly decreased the probability of a positive biopsy (Table 8).

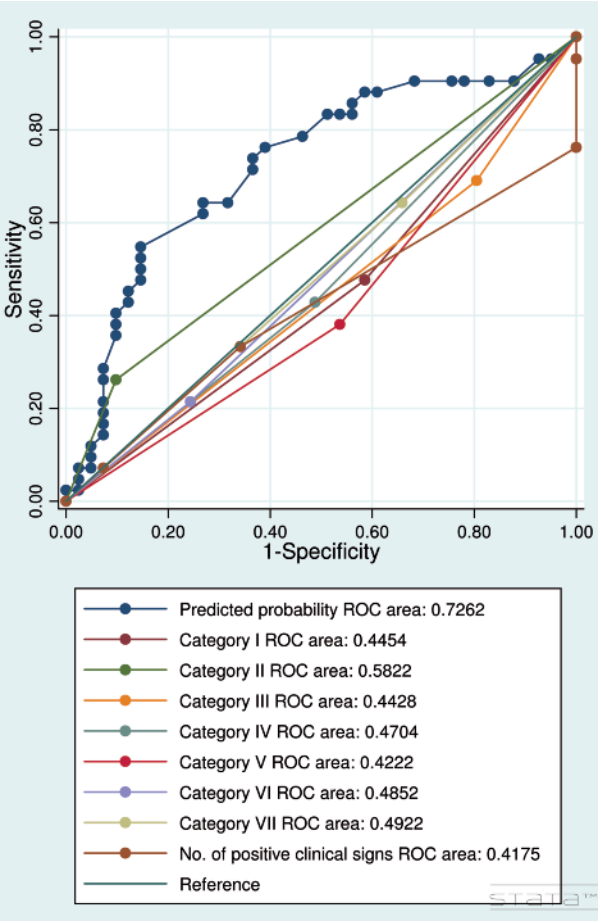

Fig. 1. Receiver Operating characteristics (ROC) plot showing Area under curve (AUC) for different clinical categories of ocular sarcoidosis as per IWOS criteria based on reference of biopsy proven sarcoidosis

Discussion

Sarcoidosis is characterized by its heterogeneous clinical expression with overlapping clinical findings as well as the silent nature and non-specificity of many of its clinical findings (14). Intraocular inflammation is a frequent and early feature in sarcoidosis (14) and it can be the presenting manifestation in 30% of patients with sarcoidosis (15).

Approximately 80% of the patients with sarcoidosis can have ocular involvement within one year of the systemic disease (9). Without tissue biopsy we are, however, still faced with the dilemma of establishing the clinical diagnosis when confronted with the signs of granulomatous uveitis, retinal vasculitis, intermediate uveitis or choroiditis.

Based on the international criteria for the diagnosis of ocular sarcoidosis proposed by the First International Workshop on Ocular Sarcoidosis (IWOS), 2009, the diagnosis of ocular sarcoidosis requires seven clinical ophthalmic signs (Table 1A)

Table 8. Calculation of sensitivity and specificity of different categories of clinical signs in ocular sarcoidosis

IWOS Category (95% CI)	I	II	III	IV	V	VI	VII
Sensitivity (%)	0.47 (0.33-0.62)	0.26 (0.15-0.41)	0.69 (0.53-0.80)	0.42 (0.29-0.57)	0.38 (0.25-0.53)	0.21 (0.11-0.35)	0.64 (0.49-0.77)
Specificity (%)	0.52 (0.39-0.65)	**0.90 (0.77-0.96)**	0.19 (0.10-0.34)	0.51 (0.36-0.65)	0.46 (0.32-0.61)	0.80 (0.67-0.88)	0.34 (0.21-0.49)
Likelihood ratio for a positive test result	1.01 (0.65-1.55)	2.68 (0.66-1.00)	0.85 (0.66-1.10)	0.87 (0.54-1.40)	0.71 (0.44-1.14)	1.09 (0.49-2.43)	0.97 (0.71-1.33)
Likelihood ratio for a negative test result	0.98 (0.67-1.45)	0.81 (0.66-1.00)	1.58 (0.73-3.42)	1.11 (0.75-1.66)	1.33 (0.89-2.00)	0.97 (0.79-1.20)	1.04 (0.58-1.88)
Diagnostic Odds ratio	1.02 (0.45-2.31)	**3.28 (0.95-11.35)**	0.54 (0.19-1.48)	0.78 (0.33-1.87)	0.53 (0.22-1.27)	1.11 (0.40-3.07)	0.93 (0.37-2.30)

and five ancillary investigations (Table 1B) (12) .Further, based on the clinical signs and investigations, four categories of ocular sarcoidosis (Definite, Presumed, Probable and Possible) are described by IWOS (Table 1C) (12).

Asukata et al validated the diagnostic signs proposed by the original and revised Japanese guidelines (10, 11). They computed the sensitivity, specificity, positive predictive value and negative predictive value for each of the seven categories which are currently adapted by IWOS (11). However, in this paper the authors compared the ocular signs predictive of ocular sarcoidosis with the ocular signs not at all suggestive of sarcoidosis (VKH, Acute retinal necrosis etc.) (10, 11). In current clinical settings, physicians including specialists are challenged with the diagnostic conundrum due to this overlapping clinical signs.

We attempted to correlate our clinical findings for both biopsy proven and non-biopsy proven ocular sarcoidosis group (Table 3). Our non-biopsy proven cases had clinical signs very closely suggestive of sarcoidosis. As our non –biopsy group were not meeting the criteria laid down by IWOS, we grouped them under a category of clinically suspect sarcoidosis (clinical group) In both biopsy proven (definite) and non-biopsy proven (clinical) ocular sarcoidosis, there were significant proportion of patients (31/42 in biopsy proven sarcoidosis and 37/41 in non-biopsy proven ocular sarcoidosis) with 3 or 4 positive ocular signs (Table 3C) implying the usefulness of international criteria for the diagnosis of ocular sarcoidosis (12). We further attempted to investigate sensitivity and specificity of each of the clinical signs of IWOS but we did not find any of the individual signs to have a good predictive value for a positive biopsy. Diagnostic odds ratio was also computed for each of the seven categories and it did not seem to show any statistical association. Also, using the number of positive clinical signs suggestive of ocular sarcoidosis, we compared the proportion between two groups using Mann Whitney U test; which was not found to be statistically significant. This further supports our impression regarding the usefulness of the clinical signs in establishing the diagnosis of sarcoidosis in patients who did not have confirmatory tissue biopsy.

Literature review reported similar clinical signs in patients with biopsy proven cases of sarcoidosis from different parts of the world. Ganesh et al reported nine patients with biopsy proven (Definite) sarcoidosis from India (16). Sarcoidosis is relatively less prevalent and less commonly diagnosed in India than in Western population. Presumed ocular tuberculosis is a more common differential diagnosis for granulomatous intraocular inflammation in Asian population. They reported intermediate uveitis and granulomatous anterior uveitis as the most common manifestation in biopsy proven ocular sarcoidosis in their series (16). Another study of 34 biopsy proven systemic sarcoidosis from India by Das et al, reported only 3/34 (8.8%) patients with ocular involvement (17). Babu et al presented a series of patients with ocular sarcoidosis with systemic findings (18).

The authors reported posterior synechiae, granulomatous keratic precipitates, increased anterior chamber reaction, and cystoid macular edema were significantly more common in those presenting initially to an ophthalmologist (18). Systemically they reported involvement of lungs, skin, joints, lymph nodes with predominant involvement of lungs in their case series. We also had pulmonary involvement as the most common systemic sign in our cohort with ocular sarcoidosis.

Birnbaum et al reported case series of 63 patients with biopsy proven sarcoid uveitis in African-American patient population (19). The authors concluded that granulomatous anterior uveitis was the most common clinical association with biopsy proven sarcoidosis cases.[19] Our case series also showed a significant number of patients with granulomatous anterior segment inflammation in non-biopsy proven as well as biopsy proven cases with ocular sarcoidosis.

A similar study of biopsy proven sarcoidosis in Greek population was reported by Pefkianaki et al in 2011 (20). From fifty patients with transbronchial lung biopsy proven sarcoidosis, periphlebitis, periarteritis and episcleritis was reported in 8 patients (16%) each; iris nodules were noted in 9 patients (8%) and cataract was found in 16 patients (38%) (20). The findings in our series of biopsy proven sarcoidosis are similar to those reported by these authors.

Sungur et al reported 47 patients with biopsy proven ocular sarcoidosis in Turkey (21). They performed subgroup analysis comparing patients with or without uveitis. They demonstrated involvement of lungs, eye, peripheral lymph nodes, skin, joint, liver and spleen in decreasing order of frequency. The most frequent types of uveitis reported by the authors was intermediate uveitis (46.2%), followed by panuveitis (38.4%) an anterior uveitis (15.3%) (21).

Atmaca et al reported 12.9% ocular involvement in 139 Turkish patients with biopsy proven systemic sarcoidosis. The ocular findings reported by the authors in the series of 139 patients included 39% patients with both anterior and posterior segment involvement (22).

Bronchoalveolar lavage can be a very useful analysis in patients with pulmonary involvement. Fluid sample obtained from this technique can be subjected to cytology to assess for lymphocytosis or monocytosis (23). Based on the previous reports, lymphocytosis of more than 15% is supposed to be a predictor of granulomatous disease (24). In smokers, the risk of obtaining a false positive result increases.[23] Likewise, presence of monocytosis in peripheral blood has been shown to be a marker of chronic inflammatory disease (23). Our study revealed monocytosis and lymphocytosis in these patients, and this may be further explored in the future, as it may be an important parameter that can help with the diagnosis of sarcoidosis.

We also presented the results of pulmonary function test in patients with ocular sarcoidosis. As expected, pulmonary function test performed in our study subset showed impaired total diffusing capacity of lung for carbon monoxide in patients with biopsy proven ocular sarcoidosis as against non-biopsy proven ocular sarcoidosis although the results did not reach statistical significant, probably due to the limited sample size.

To the best of our knowledge, this study is the first ever case series of ocular sarcoidosis comparing biopsy proven with non-biopsy proven clinical cases of ocular sarcoidosis with clinical signs suggestive of ocular sarcoidosis. In this series we established a correlation with IWOS categories (clinical) for diagnosis of ocular sarcoidosis using ROC curve and specificity and sensitivity test along with diagnostic odds ratio. Obtaining a biopsy sample from cases with features of ocular sarcoidosis and suspicion of systemic involvement may not be a very practical approach in all cases and, more often than not, the clinician may have to rely on clinical signs to arrive at appropriate diagnosis. Bui et al reported less than 50% positivity with conjunctival biopsy in a series of eight cases with presumed ocular sarcoidosis and hence the yield of biopsy may not be optimal to arrive at diagnosis in all the suspect cases (25). Blaise et al reported utility of minor salivary gland biopsy for assessing the diagnosis of sarcoidosis in patients with clinical features suggestive of ocular sarcoidosis. The authors reported positive sarcoid granuloma in 7 out of 230 (3.04%) patients with uveitis on the biopsy from minor salivary gland (26).

In conclusion, ocular and systemic findings in patients with clinical sarcoidosis and biopsy proven sarcoidosis are similar. IWOS criteria (12) are helpful for diagnosing ocular sarcoidosis, even in the absence of a positive biopsy. Pulmonary function tests

were more affected in patients with biopsy proven sarcoidosis than in patients with clinical ocular sarcoidosis. Bronchoalveolar lavage may be helpful when a positive biopsy cannot be taken.

Acknowledgements

"This work was supported by the National Institute for Health Research (NIHR) Biomedical Research Centre based at Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health."

Authors' contribution

RA had written the first draft of the manuscript and was involved in data analysis and intellectual inputs. JG has edited the draft, did literature review, data analysis and were involved in intellectual inputs. FM was involved in data collection. CP was directly involved in patient care and edited the draft and intellectual inputs.

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