Clinical and multimodal imaging clues in differentiating between tuberculomas and sarcoid choroidal granulomas

Aniruddha Agarwal , Kanika Aggarwal , Francesco Pichi , Tian Meng , Marion R. Munk , Krinjeela Bazgain , Reema Bansal , Rupesh Agrawal , Vishali Gupta

PII: S0002-9394(21)00046-5
DOI: https://doi.org/10.1016/j.ajo.2021.01.025
Reference: AJOPHT 11714

To appear in: *American Journal of Ophthalmology*

Received date: August 18, 2020
Revised date: January 26, 2021
Accepted date: January 26, 2021

Please cite this article as: Aniruddha Agarwal , Kanika Aggarwal , Francesco Pichi , Tian Meng , Marion R. Munk , Krinjeela Bazgain , Reema Bansal , Rupesh Agrawal , Vishali Gupta , Clinical and multimodal imaging clues in differentiating between tuberculomas and sarcoid choroidal granulomas, *American Journal of Ophthalmology* (2021), doi: https://doi.org/10.1016/j.ajo.2021.01.025

Title: Clinical and multimodal imaging clues in differentiating between tuberculomas and sarcoid choroidal granulomas

Authors: Aniruddha Agarwal, MD,[1] Kanika Aggarwal, MS,[1] Francesco Pichi, MD,[2,3] Tian Meng, MD,[4] Marion R. Munk, MD, PhD,[4] Krinjeela Bazgain, MS,[1] Reema Bansal, MS,[1] Rupesh Agrawal, FRCS,[5-11] Vishali Gupta, MS[1]

Affiliation:
[1:] Advanced Eye Center, Post Graduate Institute of Medical Education and Research, Sector 12, Chandigarh, India – 160012
[2:] Eye Institute, Cleveland Clinic Abu Dhabi, Al Maryah Island, Abu Dhabi, United Arab Emirates
[3:] Cleveland Clinic Lerner College of Medicine, Case Western Reserve University, Cleveland, OH, USA
[4:] Department of Ophthalmology, Inselspital, University Hospital, University of Bern, Bern, Switzerland
[5:] National Healthcare Group Eye Institute, Tan Tock Seng Hospital, Singapore
[6:] Singapore Eye Research Institute, Singapore
[7:] Moorfields Eye Hospital, NHS Foundation Trust, London, UK
[8:] Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore
[9:] Duke NUS Medical School, Singapore
[10:] Yong Loo Linn School of Medicine, National University of Singapore, Singapore
[11:] School of Material Science and Engineering, Nanyang Technological University, Singapore

Short Title: Differentiating tubercular and sarcoid choroidal granulomas

Corresponding author:
Aniruddha Agarwal, MS
Advanced Eye Centre,
Postgraduate Institute of Medical Education and Research (PGIMER),
Chandigarh, 160012,
India
Tel: +911722756111
Fax: +911722756111

Email: aniruddha9@gmail.com

Word count: 3754

Keywords: Tuberculosis; choroidal granuloma; sarcoidosis; tuberculoma; optical coherence tomography; fluorescein angiography

ABSTRACT

PURPOSE: To compare the differences between clinical, demographic, and multimodal imaging features of choroidal granulomas associated with tuberculosis and sarcoidosis.

DESIGN: Retrospective comparative case series.

METHODS: Clinical features and fundus imaging including fluorescein and indocyanine green angiography, and optical coherence tomography of patients with tuberculomas and sarcoid choroidal granulomas seen at three tertiary care centers were reviewed. The differences between clinical appearance including morphology of the lesions (size, shape, extent), vascularity, and multimodal imaging features were compared. Repeated measures logistic regression with a multi-level random effects model was used to assess characteristics of individual granulomas that could predict the underlying etiology.

RESULTS: The study included 47 eyes of 38 patients (22 with tuberculomas and 16 with sarcoid granulomas; total of 138 granulomas). Patients with tuberculoma were significantly younger (33.8±10.1 versus 48.6±14.3 years; p=0.002), but no gender differences were observed. In comparison with sarcoid granulomas, tuberculomas were solitary (p<0.001), intense yellow, lobulated, full thickness and located in the perivascular region (all p<0.001), larger in size (16.01±9.7mm^2 versus 2.7±4.5mm^2; p<0.001), and were vascularized (p<0.001). Sarcoid granulomas were associated with retinal vasculitis (p=0.003) and disc hyperfluorescence (p<0.001). Logistic regression showed that multiple granulomas were associated with sarcoidosis (odds ratio – OR: 3.5; 95%CI: 1.8-6.9; p<0.001). Granulomas larger than 6.45mm^2 had the highest area under the ROC (0.94) for differentiating tuberculomas from sarcoid granulomas.

CONCLUSIONS: Tuberculomas and sarcoid choroidal granulomas have various clinical and imaging features that help differentiate the two entities with high predictability, and can supplement immunological and radiological tests in making a diagnosis.

In this retrospective study, clinical and imaging features on color fundus photography, fluorescein and indocyanine green angiography and optical coherence tomography were compared between tuberculomas and sarcoid choroidal granulomas. Tuberculomas were usually solitary, larger in size, full thickness, intense yellow in color, lobulated in shape, associated with pre-retinal hemorrhages and vascularity, differentiating them from sarcoid granulomas.

Introduction

Systemic granulomatous diseases are known to cause granuloma formation in the vascular structures of the eye especially the choroid. Tuberculosis (TB) and sarcoidosis are two important systemic granulomatous diseases with ocular manifestations ranging from anterior and intermediate uveitis to posterior and panuveitis.[1–4] As per the Collaborative Ocular Tuberculosis Study (COTS-1) study results, among cases of TB posterior uveitis, 13.5% cases consist of choroidal granulomas, termed as tuberculoma.[5–7] Similarly, among patients with posterior segment involvement due to sarcoid uveitis, the incidence of choroidal granulomas has been reported to be nearly 12%.[2,8,9]

Choroidal granulomas can result in significant visual morbidity, and can present as a diagnostic and therapeutic challenge.[1,3] The treatment of choroidal granuloma depends on the underlying etiology. Often, in clinical practice, patients present with only ocular manifestations with no histopathologic evidence of the underlying etiology that can guide the treating physician. In such cases, the ophthalmologist has to rely mainly upon immunologic tests such as interferon release assays and tuberculin skin test, and laboratory tests such as serum angiotensin converting enzyme (ACE) levels.[10–14] Radiological tests such as computerized chest tomography for detection of features including Ghon's complex in TB,[15] and bilateral hilar lymphadenopathy (BHL) in sarcoidosis also have a diagnostic role.[16,17] Based on the consensus guidelines of COTS, for a case of a suspected tuberculoma, positive results from even 1 immunologic test is considered sufficient to recommend treatment with anti-tubercular therapy (ATT) in addition to oral corticosteroids.[18] On the other hand, a case of sarcoid granuloma is usually treated with corticosteroids with or without addition of long-term immunosuppressive therapy.[2,8,9]

However, the criteria for a positive immunologic test may vary from region to region depending on the endemicity and immunization status of the population.[19] Hence, immunological and laboratory tests may have certain limitations in distinguishing a tuberculoma from a sarcoid choroidal granuloma. In addition, radiological tests have limitations and the findings are not pathognomic of either TB or sarcoidosis.[16,17] In this study, we aim to identify key clinical and chorioretinal imaging markers that may aid in differentiation between tuberculoma and sarcoid choroidal granuloma in order to institute prompt and appropriate therapy.

Materials and Methods

Study Subjects

A retrospective analysis of patient clinical records and images was done for all cases of choroidal granulomas due to TB and sarcoidosis as the underlying etiology from January 2015 to January 2020 across three tertiary care centers namely Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India; Cleveland Clinic Abu Dhabi, Abu Dhabi, UAE; University Hospital Bern, Bern, Switzerland. Institutional ethics committee approval was obtained from the Institute Review Board (IRB) of all the three institutes and the study adhered to the tenets of declaration of Helsinki. The study adhered to the rules laid down by Health Insurance

Portability and Accountability Act (HIPAA) of 1996. Since the study was a retrospective analysis, waiver of informed consent was obtained.

Choroidal granuloma was defined as a yellowish subretinal lesion with indistinct borders with or without surrounding exudative fluid, and presence of round/oval hyporeflective lesions in the choroidal stroma on OCT,[20,21] early hypofluorescence and late hyperfluorescence on FA and early and late iso-/hypofluorescence on ICGA.[22,23] These lesions may be located in the posterior pole or mid-periphery and may be single or multiple. The criteria for classifying these lesions as tuberculoma or sarcoid choroidal granuloma were as follows:

Tuberculoma: The diagnosis of tuberculoma was based diagnostic criteria adopted by COTS.[5,6] Briefly, patients fulfilling criteria 1 and 2 with at least one out of 3 and 4 were classified as tuberculomas:

1. Clinical signs suggestive of granulomatous posterior uveitis
2. Exclusion of other infectious and non-infectious uveitic entities
3. Investigations documenting the mycobacteria or its genome such as microscopic demonstration of acid-fast bacilli (AFB) or culture of *Mycobacterium tuberculosis* from ocular fluid; positive polymerase chain reaction from ocular fluid, confirmed extra-pulmonary TB (by microscopic examination or culture of a tissue sample from the affected tissue)
4. Corroborative investigations including: positive tuberculin skin test (induration >10mm × 10mm after 48-72 hours); positive interferon gamma release assay (IGRA) such as QuantiFERON TB Gold®; evidence of healed or active TB on chest radiography or computerized tomography.

Sarcoid granuloma: The diagnosis of sarcoidosis was based on the recent International Workshop of Ocular Sarcoidosis (IWOS).[24] These include intraocular clinical signs compatible with ocular sarcoidosis supported by radiologic signs such as BHL and other systemic investigations such as elevated serum angiotensin converting enzyme (ACE) with or without positive biopsy results.

Patients diagnosed with active tuberculoma or sarcoid choroidal granulomas in at least one eye were required to fulfil the following criteria for enrolment in the study: complete clinical records, fundus fluorescein angiography (FA) and indocyanine green angiography (ICGA) (central 55 degrees with peripheral sweeps), and enhanced-depth imaging optical coherence tomography (EDI-OCT) (dense raster line scans passing through the lesion). A minimum follow-up of at least 6 months was required to be included in the study. The demographic and clinical details of slit lamp examination findings, documented as cellular reaction in the anterior chamber and/or vitreous, as well as keratic precipitates were noted.

Subjects with poor media clarity and/or poor quality of images were excluded from the study. In addition, subjects with other chorioretinal disorders and concomitant disease such as diabetic retinopathy, age-related macular degeneration, and retinal dystrophies, among others were excluded from the analysis.

Image Analyses

Two independent observers (A.A. and K.A.; both fellowship trained uveitis specialists) graded the colored fundus photographs and compared clinical characteristics such as number of lesions, color, and shape of the lesions. In case of any disagreement, the opinion of a senior grader (V.G.) was taken. The color fundus photographs were performed on Carl Zeiss Visupac FF450, Zeiss Meditech, Germany. FA, ICGA and EDI-OCT scans were obtained on Spectralis®, Heidelberg, Germany for all the subjects. The lesions in the central 30 degrees were chosen for image analysis. The color of the lesions was classified either as (Figure 1):

Intense yellow: yellow opacification within the lesion with retinal edema/elevation that is readily distinguished from the surrounding normal retina;

Dull yellow: faint yellow-white lesion with relatively ill-defined borders; not readily distinguishable from the surrounding normal retina.

The number of the lesions was counted on the color fundus photographs and confirmed on ICGA imaging. Based on the location, granulomas were classified as macular, perivascular, optic disc granulomas, or diffusely distributed. Other features assessed on fundus photography included presence of dilated tortuous vessels over the granuloma, and pre-retinal hemorrhages.

On FA, features such as associated retinal vasculitis, presence of surrounding pin-point retinal pigment epithelium (RPE) leaks, cystoid macular edema (CME), and optic nerve head hyperfluorescence were noted. In the presence of intense retinal vascular leakage, presence of pre-retinal hemorrhages, dilated and tortuous retinal vessels over the granuloma, and surrounding exudative fluid, the granulomas were classified as *vascularized choroidal granulomas.*[25–28] The shape of the lesions was also confirmed on ICGA imaging (either oval or lobulated). ICGA images were analyzed to detect presence of hot-spots within the granuloma suggestive of retinal angiomatous proliferation (RAP).[29] Both the graders independently measured the area of the choroidal granulomas on ICGA using the area measurement tool on Heyex software (Spectralis® v6.0). The average of the two graders' readings was taken for the analysis. Any lesion that measured less than 0.1 mm^2 in area and appeared as a small pin-point hypofluorescent lesion on ICGA was not considered for analysis.

EDI-OCT scans passing through the lesions were analyzed to note the internal reflectivity and homogeneity of the choroidal granulomas. Signal transmission through the granulomas was noted. In addition, the anteroposterior extent of the granulomas (i.e. full thickness versus partial thickness) was confirmed on OCT by identifying the posterior sclerochoroidal junction.[20,21] Presence of subretinal fluid was also noted. Outer retinal hyper-reflectivity, and disruption of the retinal pigment epithelium (RPE)-Bruch's membrane complex were noted.

Study Treatments

Patients diagnosed with tuberculoma received standard treatment with systemic corticosteroids (prednisolone 1 mg/kg/day with gradual tapering off over 1 to 2 months based on the healing of the lesions) and anti-tubercular therapy (ATT). ATT consisted of four-drug chemotherapy, including 2 months with isoniazid,

rifampicin, ethambutol, and pyrazinamide. Thereafter, patients continued rifampicin and isoniazid for additional 7 months. Adjuvant anti-vascular endothelial growth factor (anti-VEGF) injections were given based on the discretion of the treating ophthalmologist. Subjects with sarcoid granulomas received systemic corticosteroids and immunosuppression/biological therapy that was introduced at clinician discretion if the patients required steroid-sparing therapy.

Statistical Analysis

All continuous variables were presented as means with standard deviation or median with interquartile range while categorical variables were presented as proportions (n, %). Group differences between continuous variables were assessed using the student t test or the Wilcoxon rank sum test for non-parametric distributions while differences in categorical variables were assessed using the chi square or Fischer's exact test.

The agreement between the two graders in assessing the area of the lesion on ICGA was analysed using the inter-class correlation coefficient and on account of a very high agreement, we calculated the mean of the two readings and used it for analysis. To assess characteristics of individual granulomas that could predict the underlying etiology (tubercular versus sarcoid), we performed repeated measures logistic regression with a multi-level random effects model that accounted for inclusion of both eyes and the correlation between different granulomas from the same eye. Receiver operating curves (ROC) were set up to separately identify the predictive accuracy of the area of the granuloma on ICGA to detect tubercular compared to sarcoid etiology and presented as area under the ROC (AUROC) along with its standard error and 95% CI. The Youden index was used to identify the best cut off value from the predicted AUROC to differentiate etiologies and sensitivity and specificity for identifying the area of the granuloma at the best cut off points were reported.

All data was entered in Microsoft Excel and statistical analyses was performed using Stata software, version 12.1 I/c (Stata Corp, Fort Worth, Texas). All p values <0.05 were considered statistically significant.

Results

We enrolled 47 eyes of 38 patients with a mean age of 40.1 ± 13.9 years in the study. Nineteen patients (50%) were male. In the cohort, 22 patients had tuberculomas, all of which were unilateral (n=22 eyes, 100%) and 16 patients had sarcoid granulomas, 7 of which were unilateral (44%) while the remaining 9 had bilateral disease (n=18 eyes) (p<0.001 in comparison with tuberculoma; Chi square test). Patients with tuberculomas were significantly younger (mean age: 33.8 ± 10.1 years) compared to those with sarcoid granulomas (48.6 ± 14.3 years) (p=0.002, student-t test, uncorrected), while there were no gender differences [13 men (59.1%) in tuberculomas versus 6 (37.5%) men in the sarcoid group, p=0.19, Chi square test]. Slit-lamp assessment revealed anterior chamber cells in 5 eyes (22.7%) diagnosed with tuberculoma, compared to 14 eyes (56%) with sarcoidosis (p=0.03, Chi square test). Similarly, significantly higher number of eyes with sarcoidosis had vitreous cells compared to eyes with tuberculoma [20 eyes (80%) versus 11 eyes

(50%), p=0.04, Chi square test]. The demographic and clinical details of the subjects are listed in Table 1.

A total of 138 granulomas were identified amongst this study cohort and analyzed. A comparison between clinical and OCT characteristics between tubercular and sarcoid granulomas is shown in Table 2. Tuberculomas were solitary in 20 out of the 22 eyes (90.9%) whereas sarcoid granulomas were solitary in 12 out of 25 eyes (48%) (p<0.001, Chi square test). There were significantly greater number of granulomas per eye in the sarcoid group compared to the tubercular group. The number of granulomas per eye ranged from 1-24 in the sarcoid group whereas tubercular granulomas were either solitary or a maximum of two per eye. One patient in the sarcoid group had 18 granulomas in his right eye and 24 granulomas in his left eye.

In addition to being mostly solitary, tuberculomas were mostly lobulated, located in the perivascular region and had a central yellow core on fundus photographs. In contrast, sarcoid granulomas were commonly multiple, oval, distributed in a diffuse manner over the posterior pole, and had a dull yellow colour which helped differentiate them from tuberculomas with statistical significance (Table 2; Figure 1).

In terms of structural OCT features (Table 2), all lesions showed a hyporeflective internal pattern and homogeneity, irrespective of the etiology. In addition, all the granulomas demonstrated increased signal transmission. A significantly higher number of tuberculomas' had subretinal fluid and outer retinal hyper-reflectivity on OCT (Figure 2 and 3). A majority of tuberculomas had full thickness choroidal involvement as opposed to sarcoid granulomas which were significantly smaller and involved partial thickness choroid (Table 2). On FA (Table 3), significantly more sarcoid granulomas were associated with accompanying retinal vasculitis and had CME (Figure 4). In tuberculomas, lesions showed intense leakage and vascularity on FA (Figure 5). On ICGA (Table 3), tuberculomas were significantly larger, had higher proportion of RAP lesions associated with granulomas, and had no RAP associated with them (Figure 6). The interclass correlation coefficient between the two graders for the area of the granuloma on ICGA was 0.94 and the mean area was 5.8 ± 8.2mm^2 (median=1.64mm^2, IQR=0.6–5.4mm, range=0.17-44.3mm^2) (all granulomas taken together). Based on intense FA leakage, presence of dilated and tortuous vessels over the lesion, pre-retinal hemorrhages, and subretinal fluid, significantly higher proportion of tuberculomas were classified as *vascularized* granulomas (Figure 2 and 5).

On logistic regression with random mixed effects modelling (Table 4), we observed that having multiple granulomas increased the likelihood of sarcoid etiology by more than three times, after adjusting for the size of the granulomas. Therefore, in cases with multiple granulomas, an increment of 1 granuloma significantly increased the likelihood of sarcoidosis as the underlying etiology. The other variables studied such as color, shape, pre-retinal hemorrhages, and OCT characteristics (summarized in Tables 2 and 3) were found to be exclusive to the etiologies. Hence, odds ratio were not calculated for these variables (Table 4). An area of granuloma on ICGA at a cut off value of 6.45 mm^2 had the highest AUROC (0.94) and showed a

very high sensitivity (91.8%) and specificity (87.5%) for differentiating tubercular from sarcoid granulomas.

Discussion

Inflammation of the choroidal stroma in granulomatous uveitides such as TB and sarcoidosis manifests as choroidal granulomas. Choroidal granulomas are a distinctive phenotype of granulomatous inflammatory condition that can present as a diagnostic challenge, often mimicking intraocular tumors. Tubercular choroidal granulomas have been described more than a century ago by Friedenwald[30] in a young girl, as a large, solitary, elevated lesion with overlying pinpoint hemorrhages. However, the lesion was mistaken as a tumor (likely sarcoma) and the patient was subjected to enucleation and histopathology, which revealed lymphocytes, endothelial leucocytes, plasma cells, central necrosis and caseation, revealing the diagnosis of tuberculoma. No acid-fast bacilli were detected. The patient also had a negative tuberculin skin test, and no systemic focus of active TB.[30] Sarcoid choroidal granulomas are composed of inflammatory aggregates of bone marrow-derived monocytes, plasma cells, necrosis and non-caseating granulomas.[31,32]

After more than a century since the initial descriptions, choroidal granulomas are still known to present as a diagnostic challenge, often mimicking other conditions such as tumors.[33,34] In addition, since ophthalmologists rely upon immunological tests and radiological evaluation to distinguish between granulomatous inflammatory etiologies (such as TB and sarcoidosis), there can be diagnostic dilemmas if the tests are falsely negative or positive. The interpretation of the immunological tests including tuberculin skin test and interferon gamma release assay is influenced by ethnicity, endemicity, geographical origin, and immigrant status of the patient. Radiological tests are often non-specific, and cannot be used as a gold standard in establishing a diagnosis.[5,6,19] Since choroidal tissue biopsy cannot be performed in these cases, diagnosis and treatment is mostly presumptive relying on supportive laboratory/radiological investigations.[6,18] It is recommended that all patients with choroidal granulomas should undergo testing for TB (by performing interferon gamma release assay/tuberculin skin test), and sarcoidosis (by performing chest imaging by either radiography of computerized tomography, and total leucocyte counts to rule out lymphopenia). In the present time, due to lack of specificity and suboptimal diagnostic value, tests such as angiotensin converting enzyme (ACE) levels, and serum lysozyme assays are no longer recommended for the diagnosis of sarcoidosis. Soluble interleukin 2 receptor (sIL-2R) may be a better marker for diagnosing sarcoidosis compared to ACE levels.[35]

Apart from TB and sarcoidosis, various other entities can have a similar presentation and must be included in the differential diagnosis during the evaluation of these patients. Multifocal choroidal lesions can represent “white dot syndromes” such as birdshot chorioretinopathy.[36,37] Due to its multifocality and associated retinal vasculitis, sarcoidosis often mimics birdshot chorioretinopathy.[38] However, unlike sarcoidosis, birdshot chorioretinopathy is characterized by typical “birdshot” lesions (creamy, irregular and elongated lesions inferior and nasal to the disc), diffuse retinal vasculitis, and HLA-A29 positivity.[36] Other multifocal choroidal pathologies include multifocal choroiditis (MFC), punctate inner choroidopathy (PIC), and acute posterior multifocal placoid pigment epitheliopathy (APMPPE), all of which affect the

choriocapillaris (unlike sarcoid granulomas that affect the choroidal stroma). These entities are differentiated based on their clinical appearance and multimodal imaging features.[37] Choroidal tubercles are also multifocal lesions seen in patients with disseminated or miliary TB and differentiated from tuberculomas because they are small (0.5-disc diameter) grey lesions with a peripheral active zone and a central core.[7] Occasionally, uveal melanomas can mimic multifocal choroiditis leading to diagnostic dilemmas.[39] Solitary idiopathic choroiditis (SIC), previously known as unifocal helioid choroiditis, presents as a single, nummular, yellow-white choroidal mass (>1 disc diameter). A characteristic sign of SIC is the presence of red-orange halo surrounding the lesion. Since these lesions can also have associated exudation, retinal vessel dilation, and hemorrhages, SIC can mimic tuberculomas. However, adequate laboratory evaluation can exclude these entities.[40] Occasionally, tumors such as amelanotic melanoma, choroidal nevus, osteoma and metastasis can mimic solitary choroidal lesions and must be kept in the differential diagnosis.

Our study demonstrates that using certain clinical features and imaging clues, it may be possible to distinguish between choroidal granulomas associated with TB or sarcoidosis. We observed that tuberculomas were more often unilateral, solitary (as opposed to multiple in sarcoidosis), much larger (typically >6.5mm^2), lobulated in shape, and located in the perivascular region. On the other hand, sarcoid granulomas were more likely to be multiple, small in size, oval in shape, distributed in a diffuse manner, and have associated retinal vascular leakage, disc hyperfluorescence/leakage, and CME (Figure 1, 4 and 5). In comparison with sarcoid granulomas which appear dull yellow in color, tuberculomas were more intensely yellow. These morphological features can be easily identified using color fundus photography, FA and ICGA that are routinely performed in the clinical evaluation of these entities (Figures 1, 5 and 6). In tuberculoma, high local antigenic load may be responsible for higher levels of inflammation resulting in the lesion appearing more yellow and opaque.[41] Such focal intense inflammation may also result in development of larger, solitary granulomas with surrounding subretinal fluid. On the other hand, sarcoid granulomas may be caused by a more diffuse choroidal inflammation and therefore, appear dull yellow in color, besides being multiple and bilateral (Table 2). Our findings agree with published literature that fundus lesions in TB choroiditis are more extensive and confluent compared to sarcoidosis.[22,42]

In our study, we observed that tuberculomas were significantly associated with overlying pre-retinal hemorrhages, dilated and tortuous retinal vessels, exudative detachment with subretinal fluid accumulation, and other complications such as development of RAP lesions (Figure 5).[29,43] Previously published clinicopathological studies on tuberculomas have also revealed high vascularity in tuberculomas. In the report by Friedenwald,[30] the author observed striking hemorrhages on the surface of the choroidal granuloma. Similarly, Lyon et al in their clinicopathological study of a young patient with tuberculoma observed dilated retinal vessels over the choroidal lesion, with intense leakage on FA.[44] In the literature, tuberculoma has been described to present as a *vascularized* choroidal granuloma.[25,27,28] Recent evidences from zebrafish model of ocular TB have highlighted the chorioretinal ischemia and higher levels of VEGF in the local milieu, which may be responsible for this abnormal vascularization.[45,46] Only one patient in our series had a vascularized sarcoid granuloma (Table 3), indicating that this may be an important feature of ocular TB.

Previous studies by our group have shown that EDI-OCT is a useful tool in detecting and monitoring choroidal granulomas due to various etiologies.[20,21,47] On OCT, choroidal granulomas appear as hyporeflective deep choroidal lesions with internal homogeneity and compression of the choriocapillaris. EDI-OCT is also useful in determining the extent of the lesion, i.e. whether they are full thickness or partial thickness, by identifying the sclerochoroidal junction. Serial follow-up on OCT aids in demonstrating the healing of the granulomas, which tend to first decrease in the anteroposterior extent, followed by lateral extent.[20,21,47] In our series, we observed that sarcoid granulomas were mostly small and partial thickness (68%). However, large sarcoid granulomas tended to be full thickness (32%). On the other hand, tuberculomas were mostly larger in size and full thickness (83%) (Table 3). Tuberculomas also had outer retinal hyper-reflectivity in 46% lesions along with elevation of the RPE, and disruption of the ellipsoid zone and interdigitation zone. These changes were observed in <1% of sarcoid granulomas (Figure 2 and 3).

In the literature, the imaging features of TB and sarcoid granulomas on ICGA have been shown to have a considerable overlap. In both the entities, ICGA imaging shows hypofluorescent spots in the early and intermediate phase, which become isofluorescent or hyperfluorescent in the late phase. In addition, fuzziness of the choroidal vessels may be seen in the intermediate phase.[22,42] Our observations suggest that it may not be necessary to perform all the imaging modalities in every case, namely FA, ICGA and OCT. By combining clinical evaluation with FA and OCT, one can readily distinguish between TB and sarcoidosis. This is relevant because ICGA may not be widely available, and other challenges with ICGA include the high cost of the dye. These clinical and imaging assessments may aid the clinician in arriving at the diagnosis by combining them with the results of laboratory assays and radiological tests.

FA imaging revealed additional features that enable differentiation between TB and sarcoidosis. We observed that 32% eyes with sarcoidosis had concomitant retinal vasculitis. Inflammation of retinal vessels is a hallmark of ocular sarcoidosis, and is classically described as ‘candle-wax drippings’ on clinical examination due to exuberant sheathing.[2,24] Retinal vasculitis due to TB is usually occlusive,[1,48] and appears to be a separate phenotype of the disease that may be rarely present with tuberculomas in the same eye simultaneously. Eyes with tuberculomas also revealed pin-point RPE leaks surrounding the main granuloma in 18% eyes of the cohort, which appeared as multifocal dot-like areas of hyperfluorescence. These could represent focal disruption/inflammation of the RPE leading to dye extravasation. Optic disc hyperfluorescence/leakage appears to be a hallmark of sarcoidosis as it was present in all eyes, compared to only 13% eyes with TB. CME, although more common in sarcoidosis, was not significantly different between the two groups (Table 3)

Our study has a number of limitations that need to be addressed. Both tubercular and sarcoid granulomas are known to affect the optic nerve head, posterior pole and retinal periphery. In our cohort, there were no cases of TB optic nerve head granulomas due to rarity of the disease, though they have been reported in the literature.[49] Thus, in our analysis, we were unable to distinguish between optic nerve head granulomas caused by TB and sarcoidosis. In addition, we did not

analyze granulomas affecting the peripheral retina, and those not amenable to OCT imaging. Associated findings such as vasculitis could have been missed since we did not include peripheral retinal images in our study. Since ours is a retrospective study, there is a potential bias due to possible inaccuracies in the documentation and collection of information from clinic charts. Since the images were collected from different centers, it is possible that there may be variations in the images obtained. However, we ensured that the same type of camera was used to capture the images (capturing the central 55 degrees), and adequate quality was ensured prior to the analysis. In addition, we analyzed only lesions in the central macular region for uniformity. We used a simple two-step scale to evaluate the color of the choroidal granulomas. However, we believe that this may be a straightforward and more practical approach that can be used in the clinics to classify the lesions. The study may have excluded patients with poor media clarity, suboptimal fundus imaging, and unavailability of certain imaging (for instance, if an ICGA was not performed). This may be a source of selection bias in our study. Another possible source of bias is that patients with TB presenting from India, where the disease is endemic, may have presented late (from the time of initial onset), resulting in larger lesions visible on fundus evaluation. Other limitations include subjective image assessment and possible errors in manual calculations. The investigators of this study are leading the international multicenter COTS, which plans prospective imaging studies that can help distinguish TB from other uveitic entities, which can help overcome the various limitations of the index study.

In conclusion, our study reveals a number of differences between TB and sarcoid-related granulomas detectable on color fundus photography, FA, ICGA and OCT. Tuberculomas tend to be solitary, intense yellow in color, larger in size, full thickness, lobulated, and associated with significant vascularity, hemorrhage and exudation. Sarcoid granulomas are diffuse, bilateral, multiple, small and partial thickness, dull yellow in color, rounded, and not associated with increased vascularity. Other differences include presence of optic nerve head and retinal vascular inflammation in a higher proportion of patients with sarcoidosis. In the future, prospective studies that validate the results of this study, and correlate fundus lesions with laboratory parameters may help in the development of a revised diagnostic criteria and improving our understanding of the exact pathophysiology of this disease.

Acknowledgments:
a. Funding/Support: None.
b. Financial Disclosures: None.
c. Other Acknowledgments: None.

References

1. Gupta V, Gupta A, Rao NA. Intraocular tuberculosis--an update. *Surv Ophthalmol*. 2007;52(6):561-587. doi:10.1016/j.survophthal.2007.08.015

2. Liu D, Birnbaum AD. Update on sarcoidosis. *Curr Opin Ophthalmol*. 2015;26(6):512-516. doi:10.1097/ICU.0000000000000207

3. Gupta V, Shoughy SS, Mahajan S, et al. Clinics of ocular tuberculosis. *Ocul Immunol Inflamm*. 2015;23(1):14-24. doi:10.3109/09273948.2014.986582

4. Mehta H, Sim DA, Keane PA, et al. Structural changes of the choroid in sarcoid- and tuberculosis-related granulomatous uveitis. *Eye (Lond)*. 2015;29(8):1060-1068. doi:10.1038/eye.2015.65

5. Agrawal R, Gunasekeran DV, Agarwal A, et al. The Collaborative Ocular Tuberculosis Study (COTS)-1: A Multinational Description of the Spectrum of Choroidal Involvement in 245 Patients with Tubercular Uveitis. *Ocul Immunol Inflamm*. Published online August 29, 2018:1-11. doi:10.1080/09273948.2018.1489061

6. Agrawal R, Gunasekeran DV, Grant R, et al. Clinical Features and Outcomes of Patients With Tubercular Uveitis Treated With Antitubercular Therapy in the Collaborative Ocular Tuberculosis Study (COTS)-1. *JAMA Ophthalmol*. 2017;135(12):1318-1327. doi:10.1001/jamaophthalmol.2017.4485

7. Agrawal R, Agarwal A, Jabs DA, et al. Standardization of Nomenclature for Ocular Tuberculosis - Results of Collaborative Ocular Tuberculosis Study (COTS) Workshop. *Ocul Immunol Inflamm*. Published online December 10, 2019:1-11. doi:10.1080/09273948.2019.1653933

8. Jones NP. Sarcoidosis. *Curr Opin Ophthalmol*. 2002;13(6):393-396. doi:10.1097/00055735-200212000-00009

9. Yang SJ, Salek S, Rosenbaum JT. Ocular sarcoidosis: new diagnostic modalities and treatment. *Curr Opin Pulm Med*. 2017;23(5):458-467. doi:10.1097/MCP.0000000000000409

10. Agrawal R, Kee AR, Ang L, et al. Tuberculosis or sarcoidosis: Opposite ends of the same disease spectrum? *Tuberculosis (Edinb)*. 2016;98:21-26. doi:10.1016/j.tube.2016.01.003

11. Morimura Y, Okada AA, Kawahara S, et al. Tuberculin skin testing in uveitis patients and treatment of presumed intraocular tuberculosis in Japan. *Ophthalmology*. 2002;109(5):851-857. doi:10.1016/s0161-6420(02)00973-9

12. Sudharshan S, Ganesh SK, Balu G, et al. Utility of QuantiFERON®-TB Gold test in diagnosis and management of suspected tubercular uveitis in India. *Int Ophthalmol*. 2012;32(3):217-223. doi:10.1007/s10792-012-9554-0

13. Vasconcelos-Santos DV, Rao PK, Davies JB, Sohn EH, Rao NA. Clinical features of tuberculous serpiginouslike choroiditis in contrast to classic

serpiginous choroiditis. *Arch Ophthalmol*. 2010;128(7):853-858. doi:10.1001/archophthalmol.2010.116

14. Gundlach E, Hoffmann MM, Prasse A, Heinzelmann S, Ness T. Interleukin-2 Receptor and Angiotensin-Converting Enzyme as Markers for Ocular Sarcoidosis. *PLoS ONE*. 2016;11(1):e0147258. doi:10.1371/journal.pone.0147258

15. Bansal R, Gupta A, Agarwal R, et al. Role of CT Chest and Cytology in Differentiating Tuberculosis from Presumed Sarcoidosis in Uveitis. *Ocul Immunol Inflamm*. 2019;27(7):1041-1048. doi:10.1080/09273948.2018.1425460

16. Criado E, Sánchez M, Ramírez J, et al. Pulmonary sarcoidosis: typical and atypical manifestations at high-resolution CT with pathologic correlation. *Radiographics*. 2010;30(6):1567-1586. doi:10.1148/rg.306105512

17. Wessendorf TE, Bonella F, Costabel U. Diagnosis of Sarcoidosis. *Clin Rev Allergy Immunol*. 2015;49(1):54-62. doi:10.1007/s12016-015-8475-x

18. Agrawal R, Testi I, Mahajan S, et al. Collaborative Ocular Tuberculosis Study Consensus Guidelines on the Management of Tubercular Uveitis-Report 1: Guidelines for Initiating Antitubercular Therapy in Tubercular Choroiditis. *Ophthalmology*. Published online January 11, 2020. doi:10.1016/j.ophtha.2020.01.008

19. Agrawal R, Gunasekeran DV, Raje D, et al. Global Variations and Challenges With Tubercular Uveitis in the Collaborative Ocular Tuberculosis Study. *Invest Ophthalmol Vis Sci*. 2018;59(10):4162-4171. doi:10.1167/iovs.18-24102

20. Invernizzi A, Mapelli C, Viola F, et al. Choroidal granulomas visualized by enhanced depth imaging optical coherence tomography. *Retina (Philadelphia, Pa)*. 2015;35(3):525-531. doi:10.1097/IAE.0000000000000312

21. Invernizzi A, Agarwal A, Mapelli C, Nguyen QD, Staurenghi G, Viola F. LONGITUDINAL FOLLOW-UP OF CHOROIDAL GRANULOMAS USING ENHANCED DEPTH IMAGING OPTICAL COHERENCE TOMOGRAPHY. *Retina (Philadelphia, Pa)*. 2017;37(1):144-153. doi:10.1097/IAE.0000000000001128

22. Wolfensberger TJ, Herbort CP. Indocyanine green angiographic features in ocular sarcoidosis. *Ophthalmology*. 1999;106(2):285-289. doi:10.1016/S0161-6420(99)90067-2

23. Bouchenaki N, Herbort CP. The contribution of indocyanine green angiography to the appraisal and management of Vogt-Koyanagi-Harada disease. *Ophthalmology*. 2001;108(1):54-64.

24. Mochizuki M, Smith JR, Takase H, et al. Revised criteria of International Workshop on Ocular Sarcoidosis (IWOS) for the diagnosis of ocular sarcoidosis. *Br J Ophthalmol*. 2019;103(10):1418-1422. doi:10.1136/bjophthalmol-2018-313356

25. Jain S, Agarwal A, Gupta V. Resolution of Large Choroidal Tuberculoma following Monotherapy with Intravitreal Ranibizumab. *Ocul Immunol Inflamm*. 2020;28(3):494-497. doi:10.1080/09273948.2019.1582786

26. Pichi F. VASCULARIZED SARCOID GRANULOMA COMPLICATED BY PLACOID DISEASE IN A PEDIATRIC PATIENT. *Retin Cases Brief Rep*. Published online July 24, 2018. doi:10.1097/ICB.0000000000000806

27. Bansal R, Beke N, Sharma A, Gupta A. Intravitreal bevacizumab as an adjunct in the management of a vascular choroidal granuloma. *BMJ Case Rep*. 2013;2013. doi:10.1136/bcr-2013-200255

28. Babu K, Murthy PR, Murthy KR. Intravitreal bevacizumab as an adjunct in a patient with presumed vascularised choroidal tubercular granuloma. *Eye (Lond)*. 2010;24(2):397-399. doi:10.1038/eye.2009.83

29. Sharma K, Gautam N, Sharma M, et al. Ocular mycobacteriosis-dual infection of M. tuberculosis complex with M. fortuitum and M. bovis. *J Ophthalmic Inflamm Infect*. 2017;7(1):2. doi:10.1186/s12348-016-0121-0

30. Friedenwald H. Ophthalmoscopic Conditions Simulating Sarcoma of the Choroid: (a) Granuloma of the Choroid. (b) Tumor Formation Associated with Retinitis with Massive Exudation. *Trans Am Ophthalmol Soc*. 1918;16:208-219.

31. Chan CC, BenEzra D, Hsu SM, Palestine AG, Nussenblatt RB. Granulomas in sympathetic ophthalmia and sarcoidosis. Immunohistochemical study. *Arch Ophthalmol*. 1985;103(2):198-202. doi:10.1001/archopht.1985.01050020050017

32. Marcus DF, Bovino JA, Burton TC. Sarcoid granuloma of the choroid. *Ophthalmology*. 1982;89(12):1326-1330. doi:10.1016/s0161-6420(82)34627-8

33. Alaraj AM, Al-Dhibi H, Al-Mezaine HS, Abu El-Asrar AM. Solitary presumed choroidal tuberculomas masquerading as choroidal tumors. *Saudi Med J*. 2013;34(1):86-90.

34. Turkoglu EB, Lally SE, Shields CL. CHOROIDAL SARCOID GRANULOMA SIMULATING PROSTATE CARCINOMA METASTASIS. *Retin Cases Brief Rep*. 2017;11 Suppl 1:S226-S228. doi:10.1097/ICB.0000000000000468

35. Groen-Hakan F, Eurelings L, ten Berge JC, et al. Diagnostic Value of Serum-Soluble Interleukin 2 Receptor Levels vs Angiotensin-Converting Enzyme in Patients With Sarcoidosis-Associated Uveitis. *JAMA Ophthalmol*. 2017;135(12):1352-1358. doi:10.1001/jamaophthalmol.2017.4771

36. Rothova A, Berendschot TTJM, Probst K, van Kooij B, Baarsma GS. Birdshot chorioretinopathy: long-term manifestations and visual prognosis. *Ophthalmology*. 2004;111(5):954-959. doi:10.1016/j.ophtha.2003.09.031

37. Quillen DA, Davis JB, Gottlieb JL, et al. The white dot syndromes. *Am J Ophthalmol*. 2004;137(3):538-550. doi:10.1016/j.ajo.2004.01.053

38. Khurana RN, Parikh JG, Rao NA. Sarcoid choroiditis simulating birdshot chorioretinopathy. *Retin Cases Brief Rep*. 2008;2(4):301-303. doi:10.1097/ICB.0b013e31809ed9a2

39. Echegaray JJ, Medina CA, Biscotti CV, Plesec T, Singh AD. Multifocal Primary Uveal Melanoma: Clinical and Molecular Characteristics. *Ocul Oncol Pathol*. 2019;5(1):8-12. doi:10.1159/000487891

40. Shields JA, Shields CL, Demirci H, Hanovar S. Solitary idiopathic choroiditis: the Richard B. Weaver lecture. *Arch Ophthalmol*. 2002;120(3):311-319. doi:10.1001/archopht.120.3.311

41. Agarwal A, Marchese A, Rabiolo A, Agrawal R, Bansal R, Gupta V. Clinical and imaging factors associated with the outcomes of tubercular serpiginous-like choroiditis. *Am J Ophthalmol*. Published online July 22, 2020. doi:10.1016/j.ajo.2020.07.024

42. Wolfensberger TJ, Piguet B, Herbort CP. Indocyanine green angiographic features in tuberculous chorioretinitis. *Am J Ophthalmol*. 1999;127(3):350-353. doi:10.1016/s0002-9394(98)00325-0

43. Agarwal A, Aggarwal K, Handa S, Markan A, Gupta V. Subretinal hemorrhage complicating retinal angiomatous proliferation in tubercular retinal vasculitis. *Ocular Immunology and Inflammation*. Ahead of Print.

44. Lyon CE, Grimson BS, Peiffer RL, Merritt JC. Clinicopathological correlation of a solitary choroidal tuberculoma. *Ophthalmology*. 1985;92(6):845-850. doi:10.1016/s0161-6420(85)33964-7

45. Takaki K, Ramakrishnan L, Basu S. A zebrafish model for ocular tuberculosis. *PLoS ONE*. 2018;13(3):e0194982. doi:10.1371/journal.pone.0194982

46. Basu S, Rao N, Elkington P. Animal Models of Ocular Tuberculosis: Implications for Diagnosis and Treatment. *Ocul Immunol Inflamm*. Published online May 14, 2020:1-7. doi:10.1080/09273948.2020.1746358

47. Pichi F, Smith SD, Neri P, et al. CHOROIDAL GRANULOMAS VISUALIZED BY SWEPT-SOURCE OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY. *Retina (Philadelphia, Pa)*. Published online May 27, 2020. doi:10.1097/IAE.0000000000002864

48. Agarwal A, Afridi R, Agrawal R, Do DV, Gupta V, Nguyen QD. Multimodal Imaging in Retinal Vasculitis. *Ocul Immunol Inflamm*. 2017;25(3):424-433. doi:10.1080/09273948.2017.1319494

49. Invernizzi A, Franzetti F, Viola F, Meroni L, Staurenghi G. Optic nerve head tubercular granuloma successfully treated with anti-VEGF intravitreal injections in addition to systemic therapy. *Eur J Ophthalmol*. 2015;25(3):270-272. doi:10.5301/ejo.5000528

Aniruddha Agarwal is currently working as Faculty (Assistant Professor in Vitreoretina and Uveitis) at the Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India. He has completed his Clinical Research Fellowship at the Stanley M. Truhlsen Eye Institute, Omaha, Nebraska, USA (2014-2016) and Surgical Vitreoretina Fellowship at PGIMER, India (2016-2019). In 2014, he was awarded the Kataria Memorial Gold Medal Award by Prime Minister of India Sh. Narendra Modi. He has authored more than 200 publications and 40 book chapters. His areas of interest include ocular imaging, retinal diseases and uveitis.

Kanika Aggarwal is a Vitreoretina and Uveitis Specialist at the Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India. She has completed her residency and training in Vitreoretina and Uveitis from PGIMER. In addition, she has worked as a Clinical Observer at the Stanley M. Truhlsen Eye Institute, Omaha, Nebraska, USA. She is also a Fellow of the Royal College of Surgeons (FRCS), UK. Dr. Aggarwal has more than 70 peer-reviewed publications, and her areas of interest include diabetic retinopathy, uveitis and surgical retina.

Figure 1: Two-point scale for grading of the color of choroidal granulomas included in the study. (Top row) Examples of tuberculomas are shown which demonstrate intense yellow color of the lesions along with retinal edema/elevation. These lesions can be easily differentiated from the surrounding retina. (Bottom row) Three eyes with sarcoid choroidal granulomas are shown. These lesions are dull yellow and not readily differentiated from surrounding normal retina.

Figure 2: Enhanced-depth optical coherence tomography (EDI-OCT) of two patients with tuberculomas. (Top left) EDI-OCT horizontal line scan of a patient showing a large choroidal granuloma (yellow asterisk) leading to retinal elevation, outer retinal hyper-reflectivity, retinal pigment epithelial disruption (dashed square), and subretinal fluid. (Top right) EDI-OCT of the same patient from a different location shows outer retinal hyper-reflectivity (white arrowhead). (Bottom left) EDI-OCT scan of another patient shows a large tuberculoma (yellow asterisk) along with outer retinal hyper-reflectivity (white arrowheads). (Bottom right) EDI-OCT scan of patient 2 shows the large choroidal granuloma along with streak of subretinal fluid.

Figure 3: Enhanced-depth optical coherence tomography (EDI-OCT) of three patients with sarcoid choroidal granulomas. (Top left) EDI-OCT scan passing through one of the lesion shows a choroidal granuloma (white arrows). Note the normal reflectivity patterns of the outer retinal layers. (Middle row) EDI-OCT scan of another patient shows a deep choroidal stromal granuloma (white arrows) without any subretinal fluid. (Bottom row) EDI-OCT scan of another patient shows a larger-sized choroidal granuloma (white arrows) due to sarcoidosis along with subretinal fluid accumulation.

Figure 4: Fundus photography, fluorescein angiography (FA), and indocyanine green angiography (ICGA) features of a patient with sarcoidosis. (Left) Fundus photograph of a patient with sarcoidosis revealed multiple deep choroidal yellow lesions in the posterior pole with a dull yellow color. (Middle) The peak phase of FA shows presence of optic disc leakage (white arrowhead) along with multiple hyperfluorescent areas of leakage in the posterior pole suggestive of sarcoid granulomas. There was a subtle central foveal leakage indicating cystoid macular

edema (yellow asterisk). There were focal areas of vasculitis (white arrows). (Right) ICGA imaging of the patient shows multiple hypofluorescent lesions suggestive of sarcoid granulomas.

Figure 5: Fundus photography and fluorescein angiography (FA) features of tuberculomas in three eyes. (Top row) Patient #1: Fundus photograph shows an intense yellow choroidal granuloma located near the inferior arcade with surrounding exudation and pre-retinal hemorrhages. The lesion shows intense leakage on FA. There is blocked fluorescence in the superior part of the lesion due to pre-retinal hemorrhage. (Middle row) Patient #2: Fundus photograph shows a tuberculoma with multiple surrounding pre-retinal hemorrhages (white arrowheads). The lesion also shows hyperfluorescence in the late phase of the FA. (Bottom row) Patient #3: Fundus photograph shows a large tuberculoma involving the entire macula, along with optic nerve head edema, and dilated, tortuous retinal vessels overlying the lesion (white arrows). The early phase FA shows the intense vascularity of the lesion and venous looping (yellow arrows).

Figure 6: Comparison between indocyanine green angiography (ICGA) features of tubercular and sarcoid-related choroidal granulomas. (Top row) Patient #1 (tuberculoma): Fundus photograph shows a yellow lobulated choroidal lesion with surrounding exudation, which is hypofluorescent on ICGA. The Spectralis® Heyex software has been used to measure the lesion outline using the area measurement tool. (Bottom row) Patient #2 (sarcoid-related granuloma): Fundus photograph shows few dull yellow deep choroidal lesions that are not readily differentiated from the surrounding retina. ICGA shows these granulomas clearly, and using the Heyex tool, area of these lesions was calculated.

Table 1. Baseline demographic and clinical features of patients with tubercular and sarcoid choroidal granulomas included in the study

Variable		**Tuberculoma**	**Sarcoid Granuloma**
Total number included	Patients (eyes) [lesions]	22 (22) [24]	16 (25) [114]
Location of the subjects	India	22	4
	Switzerland	0	4
	United Arab Emirates	0	8
Age	(years, standard deviation)	33.8 ± 10.1	48.6 ± 14.3
Gender			
	Male (n, %)	13 (59.1)	6 (37.5)
	Female (n, %)	9 (40.9)	10 (62.5)

Laterality			
	Unilateral (n, %)	22 (100)	7 (43.7)
	Bilateral (n, %)	0 (0)	9 (56.3)
Slit-lamp findings	Anterior chamber cells (eyes, %)	5 (22.7)	14 (56)
	Keratic precipitates (eyes, %)	3 (13.6)	8 (32)
	Posterior synechiae (eyes, %)	13 (59.1)	19 (76)
	Vitreous cells (eyes, %)	11 (50)	20 (80)
Laboratory assessments			
	Positive tuberculin skin test[a] (n, %)	19 (86.4)	0 (0)
	Positive interferon gamma release assay (n, %)	16 (72.7)	0 (0)
	Positive radiological features[b] (n, %)	9 (40.9)	15 (93.7)
	Elevated serum ACE levels (n, %)	-	6 (37.5)
	Positive biopsy[c] (n, %)	0 (0)	10 (62.5)
Treatments			
	Systemic corticosteroids (n, %)	22 (100)	10 (62.5)
	Systemic immunosuppressive therapy (n, %)	0 (0)	9 (56.3)
	Biological agents (n, %)	0 (0)	2 (12.5)
	Anti-tubercular therapy (n, %)	22 (100)	0 (0)
	Intravitreal ranibizumab (eyes, n, %)	6 (27.3)	0 (0)
	Intravitreal/periocular corticosteroids (eyes, n, %)	0 (0)	2 (12.5)

[a]Indicates induration ≥ 10 mm × 10 mm by tuberculin skin test after 48-72 hours
[b]Indicates evidence of healed or active tuberculosis on chest radiography (in case of tuberculoma), or bilateral hilar lymphadenopathy (BHL) in case of sarcoidosis

[c]Indicates biopsy from lung/lymph nodes, or minor salivary glands
IQR: interquartile range

Table 2: Comparison of clinical and enhanced-depth imaging optical coherence tomography-based parameters between tubercular and sarcoid granulomas

Variable	**Tuberculoma (n=24)**	**Sarcoid granuloma (n=114)**	**p value**
Median number of granulomas per eye (IQR)	1 (1)	3 ± (1-6)	0.006
Shape of granulomas[a]			
Oval (%)	3 (13)	94 (85)	<0.001
Lobulated (%)	21 (87)	16 (15)	
Location of granulomas			
Macular (%)	7 (29)	20 (17)	<0.001
Perivascular (%)	17 (71)	0	
Optic disc (%)	0	4 (4)	
Diffuse (%)	0	90 (79)	
Color of granulomas[a]			
Intense yellow (%)	21 (87)	1 (1)	<0.001
Dull yellow (%)	3 (13)	109 (99)	
Pre-retinal hemorrhage over granuloma (%)	15 (63)	1 (<1)	<0.001
Optical coherence tomography parameters			
Presence of subretinal fluid (%)	20 (83)	4 (4)	<0.001
Outer retinal hyper-reflectivity (%)	11 (46)	1 (<1)	<0.001
Partial thickness involvement	4 (17%)	78 (68%)	<0.001

Full thickness involvement	20 (83%)	36 (32%)	

[a]4 eyes with sarcoidosis could not be graded since they had optic nerve head granulomas

Table 3: Comparison on fluorescein (FA) and indocyanine green angiography (ICGA) parameters between tubercular and sarcoid granulomas

Variable	**TB granulomas (22 eyes; n=24)**	**Sarcoid granuloma (25 eyes; n=114)**	**P value**
FA Characteristics			
Retinal vasculitis	0	8 (32%)	**0.003**
Surrounding RPE leaks	4 (18%)	0	**0.05**
Cystoid macular edema	1 (5%)	4 (17%)	0.06
Disc hyperfluorescence	3 (13%)	25 (100%)	**<0.001**
Vascularized granulomas	15 (63%)	1 (<1%)	**<0.001**
ICGA Characteristics			
RAP	4 (18.2%)	0	**<0.001**
Mean area of granuloma (mm^2)	16.01 ± 9.7	2.7 ± 4.5	**<0.001**

RAP – Retinal angiomatous proliferation

RPE – retinal pigment epithelium

Table 4: Univariate and multivariable logistic regression analysis with multi-level random effects modelling to predict sarcoid granulomas

Variable[a]	Interval	Univariate Analysis		Multivariable analysis		
		OR	95% CI	OR	95% CI	P value
Number of granulomas	Every 1 increment	2.98	1.6 – 5.3	3.5	1.8 – 6.9	<0.001
Area of granuloma on ICGA	1 mm^2 increment	0.78	0.6 – 0.9	0.96	0.9 – 1.05	0.38

[a]Colour, location, shape, pre-retinal hemorrhages, and OCT characteristics were omitted due to collinearity

CI: confidence interval

ICGA: indocyanine green angiography

OR: Odds ratio