

Comparison of wide-field swept source optical coherence tomography angiography and fundus autofluorescence in tubercular serpiginous-like choroiditis

Manpreet Brar¹, Mansi Sharma¹, S P S Grewal¹, Dilraj S Grewal^{1,2}

Purpose: To evaluate the potential clinical utility of wide-field swept source optical coherence tomography angiography (SS-OCTA) using a prototype device compared to a wide-field fundus autofluorescence (FAF) for analysis of the disease activity in eyes with tubercular serpiginous-like choroiditis (TBSLC). **Methods:** Using a prototype SS-OCTA device (PLEX Elite, Carl Zeiss Meditec, Dublin, CA), 17 eyes of 12 consecutive patients with TBSLC were imaged and multiple 12 mm × 12 mm OCTA scans were captured, which were montaged to create wide-field montage OCTA images scans. A wide- FAF (Eidon, CenterVue, Padova, Italy) was performed in the same sitting. Two masked graders independently analyzed OCTA and FAF images for the presence of choroidal lesions, recorded the number of lesions identifiable, and provided a subjective grading for the activity of individual lesion, which were then compared. **Results:** The total number of lesions identified on FAF were 282 (posterior pole lesions, $n = 129$ and peripheral lesions $n = 153$) and on wide-field SS-OCTA were 230 (posterior pole lesions, $n = 108$ and peripheral lesions $n = 122$). Active choroidal lesions were comparable on the two machines ($n = 28$ on FAF and $n = 28$ on SS-OCTA, respectively); whereas numerous healed lesions were identified on FAF ($n = 219$) as compared to SS-OCTA ($n = 170$). There was good correlation among the devices for healed lesions (Pearson correlation, $r = 0.82$) and active lesions ($r = 0.88$). **Conclusion:** There was good correlation between FAF and wide-field SS-OCTA for detection of disease activity in TBSLC; however, FAF depicted greater number of healed lesions compared to wide-field SS-OCTA.

Key words: Fundus autofluorescence, tubercular choroiditis, wide-field swept source optical coherence tomography angiography

Optical coherence tomography angiography (OCTA) has emerged as a noninvasive imaging method to detect the presence or absence of blood flow signal in the retina.^[1,2] Currently available OCTA devices use spectral domain (SD) OCT technology, which may make diseases of the choroid and choriocapillaris difficult to study because of retina pigment epithelium (RPE) attenuation of the 840 nm central wavelength.^[3] Despite this limitation, SD-OCTA has identified flow voids in the choroid of patients with placoid chorioretinal diseases, such as acute posterior multifocal placoid pigment epitheliopathy.^[4]

Swept source OCTA (SS-OCTA) uses a longer central wavelength (1050 nm) that provides improved signal penetration through the RPE and produces high-resolution images of the choriocapillaris and choroidal vessels.^[5,6] The SS-OCTA has the potential to provide the benefits of noninvasive vascular imaging to identify and monitor diseases that are believed to originate in the choriocapillaris. Further advancement in the technology has now led to the emergence of wide-field SS-OCTA, and its ability to detect capillary nonperfusion has been evaluated in diabetic retinopathy and retinal vasculitis.^[7-9]

In this study, we sought to examine the usefulness of wide-field SS-OCTA to detect the involvement of choriocapillaris in patients with tubercular serpiginous-like choroiditis (TBSLC) as compared to fundus autofluorescence (FAF) to characterize active and quiescent chorioretinal lesions.

Methods

This was a retrospective cross-sectional case series of patients with diagnosis of TBSLC examined at the Retina and Uveitis clinic, Grewal Eye Institute, Chandigarh, India between March 2018 and October 2018. All patients underwent both, the FAF and OCT-angiography at the same sitting. All patients recruited in the study had complete ophthalmic examination, and the diagnosis of intraocular tuberculosis (TB) was made based on the ocular findings, strongly positive to the tuberculin skin test results (≥ 15 mm area of induration/necrosis), radiological evidence of healed or active tubercular lesions in the chest, or evidence of confirmed active extra-pulmonary TB either

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¹Department of Retina, Grewal Eye Institute, Chandigarh, India, ²Department of Ophthalmology, Duke University, Durham, North Carolina, USA

Correspondence to: Dr. Manpreet Brar, Grewal Eye Institute, SCO: 168-169, Sector 9C, Chandigarh - 160 009, India. E-mail: dr.manpreetbrar@gmail.com

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by microscopic examination or by culture from affected tissues.^[10,11]

Demographic data were gathered from medical records. Information collected included age, sex, and lab test results (complete blood count [CBC], erythrocyte sedimentation rate [ESR], serum angiotensin converting enzyme [ACE] levels, treponema pallidum immunoglobulin (Ig) G and M for syphilis, an interferon- γ release assay for TB [QuantIFERON-TB Gold, Qiagen, Hilden, Germany], a chest radiograph and mantoux skin test). All patients had received antitubercular treatment in the past or were receiving it at the time of inclusion.

Clinical disease activity was based on a slit lamp and fundus examination. We classified our patients into two distinct patterns of TBSLC—multifocal (discrete choroidal lesions that were initially noncontiguous and later progressed to form diffuse lesions with an active edge resembling serpiginous choroiditis) and solitary (diffuse plaque-like lesion with an amoeboid extension).

Individuals with media opacities that precluded imaging were excluded. Also, individuals with high myopia or hyperopia (spherical equivalent > 6 diopters [D]), age-related macular degeneration, or diabetic retinopathy were excluded from the original cohort as these conditions have been associated with choroidal abnormalities.^[2,12] The study was approved by the institutional review board and a written informed consent was obtained from each study participant. The study adhered to the tenets of the Declaration of Helsinki for research involving human subjects.

SS-OCTA imaging

SS-OCTA imaging was performed using the PLEX Elite 9000 (Carl Zeiss Meditec, Dublin, California). Patients were imaged using a wide-field montage SS-OCTA scan, consisting

of five 12×12 mm scans, covering about 80° to 90° of the posterior pole, one centered on the fovea, the others centered on the temporal-superior, temporal-inferior, nasal-superior, and nasal-inferior quadrants, directed by changes in visual fixation. This platform uses a swept-source, tunable laser centered at 1060 nm and operating at a scan speed of 100,000 A scans per second with an axial resolution of $6.3 \mu\text{m}$. The software utilizes optical microangiography complex (OMAGc) algorithms to visualize microvasculature using the wider 12×12 mm OCTA scan protocols. The individual 12×12 mm scans were reviewed for the presence of alignment errors and artifacts due to floaters and manually corrected if present. After quality check (QC) the 12×12 images were montaged using the automatic montage export function available on the device [Fig. 1]. SS-OCTA images of the choriocapillaris slab (measured from 15 to 35 microns below the RPE best-fit line) were studied. Lesions were determined manually by two expert graders with fellowship training in both medical retina and uveitis (M.B and M.S.) and were graded according to the level of inflammatory activity as described previously^[13] into three different groups. Type 1: hypo areas of flow void (active); Type 2: hypo areas admixed with few areas of visible choroidal vessels—stippled hyper area with hypo border (healing); and Type 3: discrete hyper areas with underlying prominent medium to large choroidal vessels visible (healed) [Fig. 2]. In case of any discrepancy between the two graders, images were reviewed again by the third reviewer (D.G.) and these were included in the analysis.

FAF imaging

FAF was acquired with a standardized protocol using the confocal 450 nm blue-light FAF device (450-FAF) (Eidon; CenterVue, Padua, Italy). The 450 nm FAF images were obtained with a confocal fundus imaging system (Eidon; CenterVue), which has an emission spectrum detection of 500

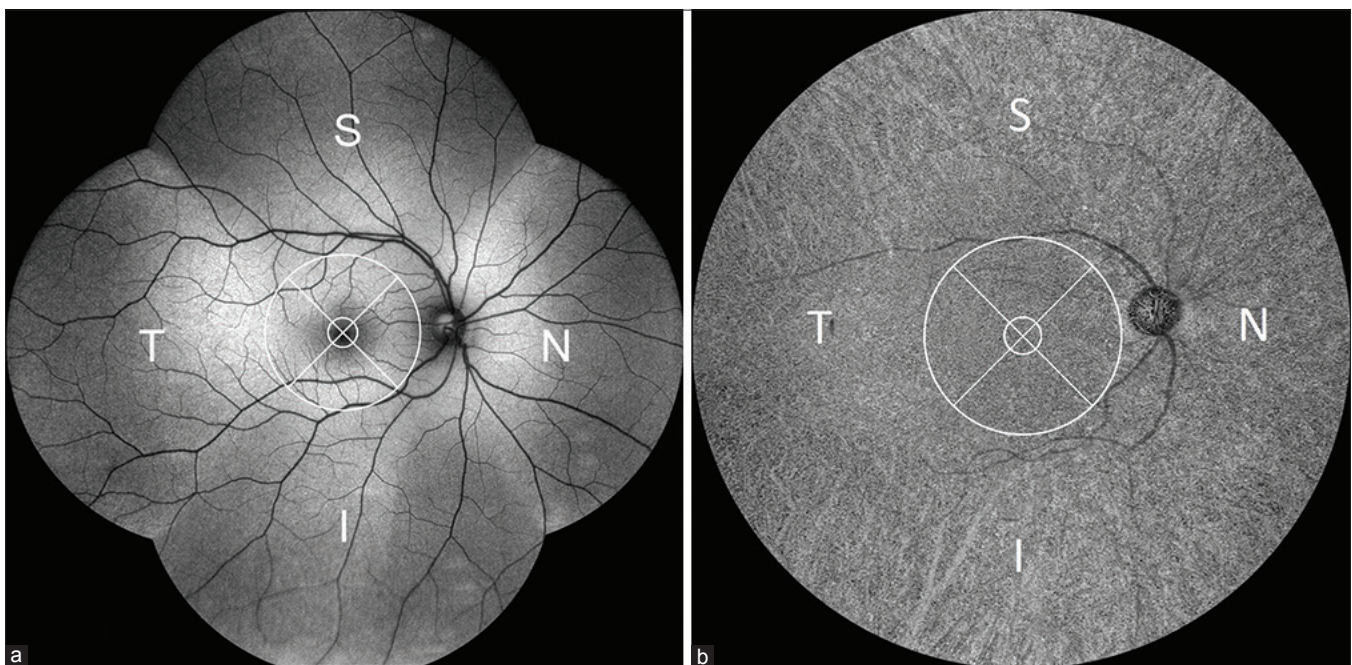


Figure 1: Normal wide-field FAF (a) Wide-field OCTA (b) Images (choriocapillaris slab) showing protocol settings. A fovea-centered images shows areas of analysis in ETDRS ring pattern-macular region that includes the foveal region (central inner circle) and pericentral macular ring. Extramacular area (outside the outer circle) is divided into superior (S)/nasal (N)/inferior (I)/temporal (T)

to 750 nm. The device automatically aligns the patient in a way that the optics and light path are centered in the pupil and an autofocus procedure is then performed to compensate for the eye's spherical defect. A grayscale FAF image with a frame size of 60(h) × 55(w) degrees and a resolution of 4608 × 3288 pixels was acquired with a single exposure. A montage of FAF images was created to obtain a 110° FAF image. A trained retina and uveitis specialist (MB), masked to clinical data, graded the

presence of autofluorescence (AF) abnormalities.^[14,15] Active inflammation was characterized by ill-defined predominantly hyperautofluorescent lesions (type 1). Later in the disease process, the lesions appeared more defined with a stippled mixture of hypo AF and hyper AF (type 2). When the lesion evolved, inactive inflammation was characterized by FAF images of lesions that were dark, i.e., hypoautofluorescent revealing complete loss of fluorophores, with very sharp

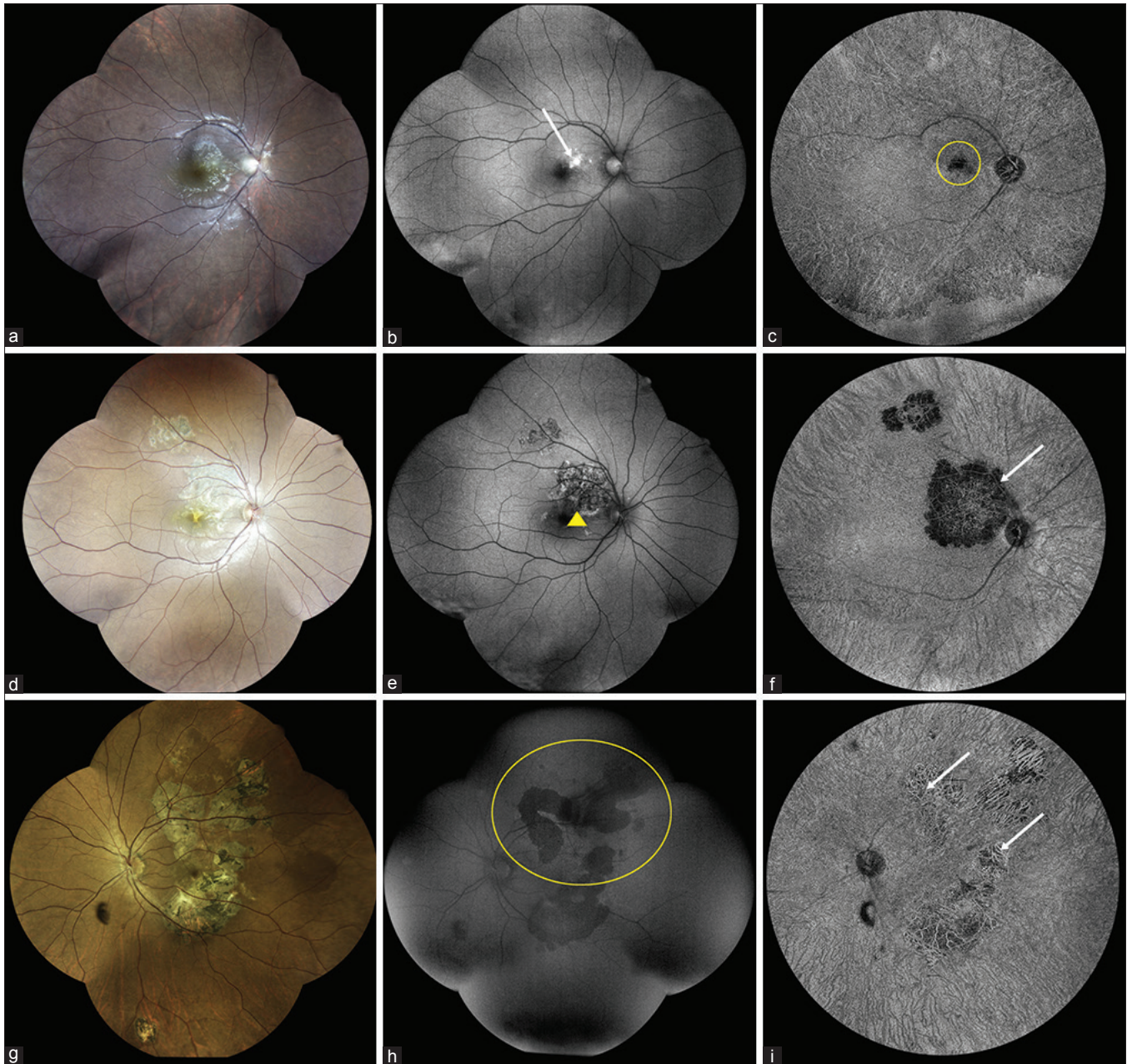


Figure 2: Fundus photographs, FAF and OCTA images showing various patterns of lesion activity in eyes with Tubercular choroiditis Fundus photograph shows a creamy white active patch of choroiditis superior to the fovea (a). Corresponding FAF shows characteristic pattern of hyperautofluorescence within the lesion (b). OCTA image shows presence of flow void areas at the level of the choriocapillaris just superior to the fovea (yellow oval) (c). Color fundus photograph shows two different patches of healing choroiditis in the superior macula with discrete edges and increased pigmentation. (d). Corresponding FAF image shows a mixed stippled pattern of hypo and hyperautofluorescence (yellow triangle) (e) OCTA image shows dark flow void areas at the edge of the lesion whereas the center of the lesion has islands of preserved choriocapillaris (white arrow) (f). Fundus photograph showing well-demarcated pigmentary lesion in the healed stage of choroiditis involving the macula and superior mid periphery (g). FAF image depicts complete hypoautofluorescence corresponding to the fundus lesion (h). OCTA image shows medium sized choroidal vessels and preserved choriocapillaris (i)

Table 1: Wide-field FAF and wide-field OCTA findings in eyes with tubercular choroiditis

	Pattern and number of lesions (n) identified on FAF			Pattern and number of lesions (n) identified on OCTA		
	Type 1 (Active)*	Type 2 (Healing)**	Type 3 (Healed)***	Type 1 (Active)*	Type 2 (Healing)**	Type 3 (Healed)***
Macula [†]	15	21	93	15	20	73
Extramacula [‡]	13	14	126	13	12	97
Total	28	35	229	29	32	180

Type 1 (Active)*: Hypo areas of flow void, Type 2 (Healing)**: Hypo areas admixed with few areas of visible choroidal vessels stippled hyper area with hypo border, Type 3 (Healed)***: Discrete hyper areas with underlying prominent medium to large choroidal vessels visible, [†]The macular region included the area within 6 mm from the geometric center of the fovea (central circle and pericentral macular ring on the fovea-centered FAF image). [‡]The extramacular region included the area captured peripheral to the pericentral macular ring (greater than 6 mm from the geometric center of the fovea) on the fovea-centered FAF image and the area captured on the disc-centered FAF image. FAF=Fundus autofluorescence, OCTA=Optical coherence tomography angiography

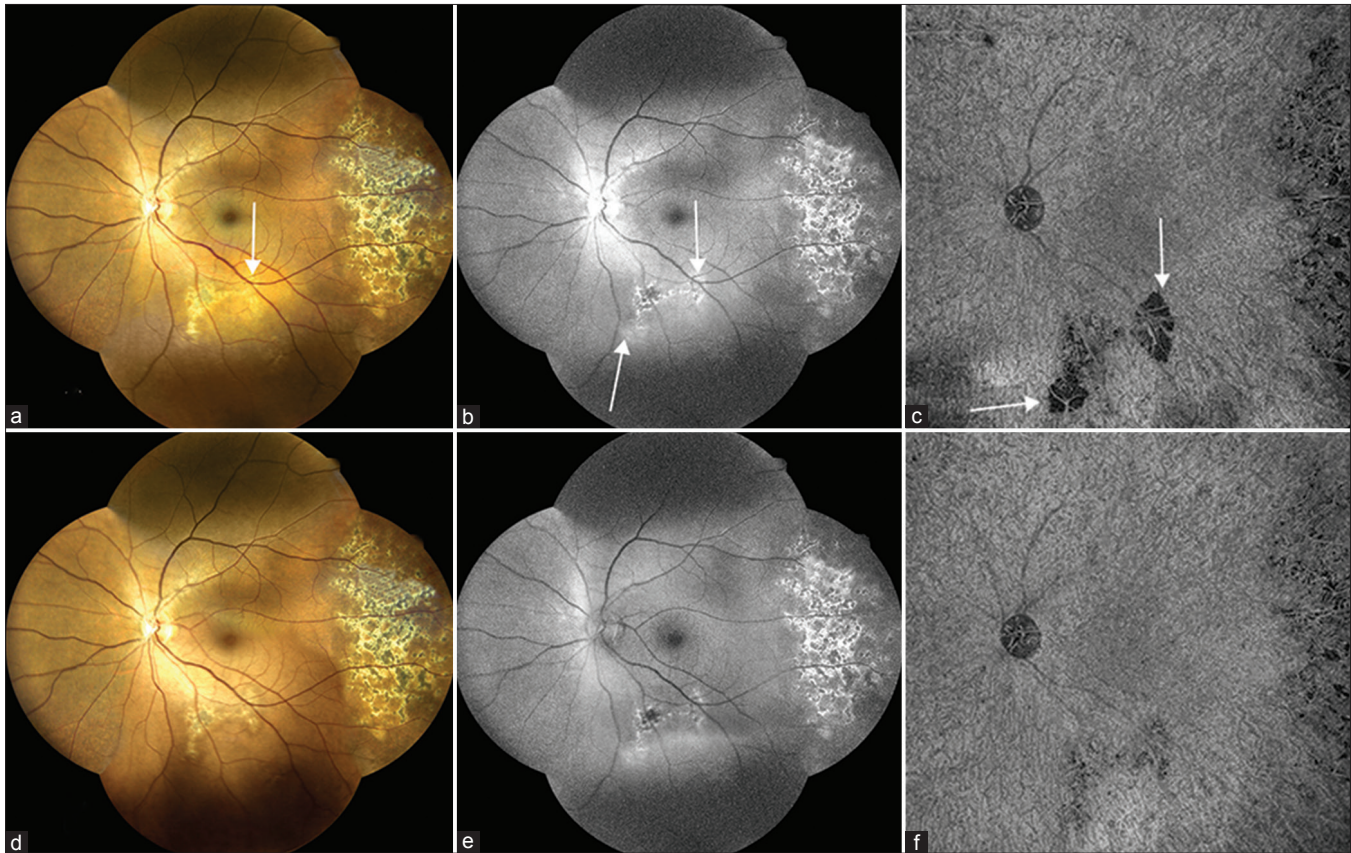


Figure 3: Case of tubercular choroiditis: Color fundus photograph (a) at baseline depicts the creamy-white active lesions (white arrow) and multiple pigmented discrete healed choroidal lesions in the temporal periphery. FAF shows mixed pattern of autofluorescence with increased autofluorescence at the edge of the lesions (b). Corresponding OCTA (c) image shows areas of flow void at the level of the choriocapillaris corresponding to the active patch of choroiditis, (white arrow) whereas the center of the lesion has islands of preserved choriocapillaris. After 3 weeks of treatment the lesions become pigmented on fundus photography (d). FAF image shows mixed pattern of autofluorescence (e) However, the OCTA image shows regression of the lesion with decrease in the area of choriocapillaris flow void suggestive of remarkable improvement compared to baseline (f)

borders (type 3) [Fig. 2]. Isolated FAF abnormalities smaller than 0.5 mm in diameter were not clinically relevant and recorded.

During evaluation of the FAF and OCTA, fovea-centered image, the early treatment diabetic retinopathy study (ETDRS) macular grid was used to identify these areas—within the central 1-mm circle (termed central circle), between the 1- and 6-mm circle (termed pericentral macular ring, superior, nasal, inferior, and temporal) and extramacular (outside the 6-mm circle—superior, nasal, inferior, and temporal) were

identified and recorded as per each quadrant [Fig. 1]. The wide-field FAF images of each studied eye were evaluated and compared with wide-field OCTA images. In case of large serpiginous lesions, score was given to all the areas where it extended.

Results: Included in the study were 17 affected eyes of 12 individuals with tubercular choroiditis. Twelve eyes had multifocal type choroiditis and 5 had serpiginous type. Median age of participants was 38.95 years (Range 17–61 years); 9 (52.9%) were females and 8 (47.1%) were

males. Clinical diagnosis of active tubercular choroiditis was present in eight eyes and nine eyes had inactive tubercular choroiditis.

FAF findings: Ninety-three abnormal well-demarcated hypoautofluorescent lesions (type 3) identified at the posterior pole, 21 lesions were at the healing stage (type 2), and 15 were classified as active choroidal lesions (type 1). Table 1 summarizes FAF findings by pattern and region. In the retinal periphery, i.e., outside 6 mm ETDRS circle, 126 type 3 lesions, 14 type 2 and 13 type 1 lesions were identifiable.

OCTA montage findings: Fifteen abnormal hypo flow void lesions (type 1) were identified at the posterior pole, 20 lesions were type 2 (healing), and 73 were classified into type 3 (inactive). Table 1 summarizes OCTA findings by pattern and region. In the retinal periphery, i.e., outside 6 mm ETDRS circle 13 type 1, 12 type 2, and 97 type 3 lesions were identifiable.

In total, number of lesions identified on FAF were 282 (posterior pole lesions, $n = 129$ and peripheral lesions $n = 153$) and on wide-field OCT angiography were 230 (posterior pole lesions, $n = 108$ and peripheral lesions $n = 122$). Active choroidal lesions were comparable on two machines ($n = 28$, $n = 28$ on FAF and OCTA respectively); whereas healed lesions were better identified on FAF as compared to OCTA ($n = 219$, $n = 170$ on FAF and OCTA respectively). Pearson correlation test value was 0.82 for healed lesions and 0.88 for active lesions. 95% confidence interval and a 5% level of significance were utilized; therefore, results with P value less than or equal to 0.05 were considered significant.

Discussion

Tubercular choroiditis is a disease mainly affecting the choriocapillaris; thus, the monitoring of the disease activity is obtained with indocyanin green angiography (ICGA). However this being an invasive test, alternatively, FAF has been described as a useful entity in tubercular choroiditis^[16,17] FAF imaging has also been extensively used to study a variety of inflammatory eye diseases, including multifocal choroiditis and panuveitis syndrome, punctate inner choroidopathy, serpiginous choroiditis, multiple evanescent white dot syndrome, and Vogt-Koyanagi-Harada disease^[12,18-20] In many conditions, FAF imaging reveals areas of disease activity that are more widespread than would be suspected by other imaging techniques or by clinical investigation, suggesting its potential value in the clinical assessment of patients with these disorders. Reznicek *et al.* compared wide-field FAF images with wide field color fundus photographs and observed in 42.3% of the studied eyes a higher number or larger involvement of chorioretinal abnormalities with clearer demarcation lines seen on FAF images.^[21] Chorioretinal infiltrates or scars affect the RPE layer and result in RPE alterations, including RPE atrophy or hyperpigmentation, changes that cannot always be seen to such an extent in fundus ophthalmoscopy or composite color fundus imaging and hence established wide-field FAF as a better noninvasive tool to confirm disease activity. Hence, in our present study, we have used FAF wide-field images to study the disease activity in tubercular choroiditis, and we further compared it with wide-field OCTA images. Our study suggested that OCTA could also pick up choroidal lesion activity in a similar manner as FAF does; hence, with the advantage of wider

field of view possible with the use of 12 mm × 12 mm OCTA montage, the use of invasive testing like FFA and ICGA is not absolutely necessary in each and every case. We defined three different stage of clinical activity as studied on both FAF and OCTA images [Fig. 2]. Our results on the use of OCTA agreed with a recent small study of six eyes on SS-OCTA in serpiginous choroiditis.^[22] However, this report suggests that FAF imaging may not be as sensitive of a noninvasive imaging marker of acute disease as OCTA. In our study, we demonstrated that FAF and OCTA images were comparable to detect active lesions; rather on FAF, healed inactive lesions were better delineated and easily identified. The most significant strength of FAF (FAF) imaging is the capability to assess the integrity of the RPE/photo-receptor complex.^[23] One of the most important roles of the RPE is to digest, by lysosomal action, the tips of the outer segments of the photo-receptors that are phagocytosed on a daily diurnal basis. A fraction of these phagocytosed outer segments is chemically incompatible for degradation; therefore, it accumulates in lysosomes of the RPE as lipofuscin. Accumulation of fluorescent material in the RPE reflects the level of metabolic activity, which is largely determined by the quantity of photo-receptor outer segment turnover. Abnormally high levels of FAF in an active inflammatory lesions may be the result of an abnormal metabolic load that cannot be properly processed by the RPE. As the lesions heal, the RPE is sequentially affected following the death of photo-receptor cells, may lead to unmasking of the underlying normal RPE AF; thus, it may make the healed lesions appear hypoautofluorescent.^[24,25]

Even if OCTA does not possess the capability to detect disruption of the RPE, secondary to active inflammation, it may provide other meaningful information. Our findings in choroiditis implicate the choriocapillaris as the primary site of pathological features. Our data suggest that lesions seen on the choriocapillaris slab represent flow voids rather than blockage because of the consistent signal penetration to deeper structures in regions and the absence of shadowing on the B scans used to generate the en face slabs. These findings, in conjunction with delayed damage identified on FAF to overlying RPE, suggest an ischemic event at the level of the choriocapillaris rather than inflammatory infiltrate, which would block light signal at deeper levels. However, slow blood flow beyond detection limits could not be differentiated from complete lack of flow with current technology used in this study. Despite this, our data also suggest that the most acute lesions appear as flow voids on OCTA and may have the potential for rapid and complete resolution when treatment is instituted promptly. However, when outer retinal changes develop and, particularly, when RPE damage causes FAF changes, permanent scars may be more likely to develop [Fig. 3]. Our patient had tubercular choroiditis [Fig. 3], and there were two active lesions identifiable on both FAF and OCTA. Following treatment with steroids, there was rapid healing, but FAF showed hypofluorescent lesion suggestive of RPE damage as a result of healing. We also demonstrated that the lesion started to heal from the center as seen on FAF as hypo spot in the center and hyperactive edge, as well as on OCT-A active edge still appears flow void as compared to the central area [Fig. 2].

Limitations of this study include the small number of patients and limited comparison of OCTA imaging with the traditional standard of FFA and ICGA imaging. It is likely that ICGA would detect some or all of the lesions found on

SS-OCTA^[26,27]; however, because of the risks associated with an invasive test, it was not performed when the treating clinician at our institution believed that management would not change. Future studies should seek to validate SS-OCTA against traditional ICGA with a prospective study design. Artifacts have been identified in previous studies using SD-OCTA^[22] and have the potential to influence imaging and quantification of the deeper choroidal structures. Shadowing from overlying retinal structures could lead to false attribution of choroidal flow voids.

Conclusion

To summarize, our study validates the use of wide-wield OCTA as another nondiagnostic tool to identify the disease activity in tubercular choroiditis. By comparing findings on OCTA with data obtained from traditional FAF, we are gaining essential information on the pathogenesis of various inflammatory conditions; developing more optimal and reliable follow-up protocols in a noninvasive way; and more accurately and objectively assessing the response to treatment in uveitis.

Declaration of patient consent

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

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Conflicts of interest

There are no conflicts of interest.

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