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Title: Imaging in posterior uveitis due to ocular tuberculosis: Current concepts

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Short Title: Imaging in OTB

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Abstract

Purpose: Ocular tuberculosis has protean clinical manifestations. Because of its varied clinical presentation, multimodal imaging is essential to characterize the disease activity, presence of inflammation, determining therapeutic response, and detection of complications.

Methods: Narrative review

Results: In this review, various imaging modalities employed in the management of ocular tuberculosis including fluorescein angiography (FA), indocyanine green angiography (ICGA), optical coherence tomography (OCT), and optical coherence tomography angiography (OCTA) have been reviewed. Not only do these imaging tools complement each other in providing a comprehensive assessment of the pathology, they also help in gaining valuable insights regarding the evolution of the disease.

Conclusions: Fundus imaging plays a vital role in the diagnosis and management of patients with posterior uveitis due to tuberculosis. Fundus imaging may have a useful role in defining clinical endpoints for ocular tuberculosis in the future.

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

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1. Prologue: Relevance of imaging in posterior uveitis due to tuberculosis

Posterior segment involvement in ocular tuberculosis (OTB) is characterized by different underlying pathological mechanisms that give rise to heterogeneous clinical phenotypes.[1–4] In the context of a disease with protean clinical manifestations, multimodal imaging not only has significantly contributed to a better understanding of morphology and pathophysiology of OTB, but also helped identify the suggestive clinical phenotype, which is essential for achieving a presumptive diagnosis of the disease.[5] Characterization of morphological aspects of lesions possibly secondary to either active infection or inflammatory response is crucial in the diagnostic pathway and assessment of disease activity. Inflammatory sequelae and ocular complications of the disease are often diagnosed with the help of digital images. In addition, in a disease characterized by long-course therapeutic management and slow response to treatment, multimodal imaging represents an essential tool in guiding treatment decision-making and monitoring response to therapy.[2,5,6]

Recent advances in technology have further contributed in affirming the role of multimodal imaging in the diagnosis and management of OTB. Modalities, including fluorescein angiography (FA), indocyanine green angiography (ICGA), and optical coherence tomography (OCT), together with novel imaging techniques, namely fundus autofluorescence (FAF), ultra-wide field (UWF) imaging, and different OCT technologies, such as enhanced-depth imaging (EDI-OCT), swept-source and OCT angiography (OCTA), complement each other and provide extremely useful information on phenotypic expression and tissue involvement, assessing disease activity, treatment response and potential complications.[5,6]

This review focuses on conventional and novel imaging techniques for tubercular choroiditis, highlighting the relevance of multimodal imaging in clinical application.

2. Tubercular choroiditis

The most characteristic presentation of choroidal involvement in OTB that is nearly diagnostic especially in a patient from an endemic country is serpiginous-like choroiditis (SLC).[7] In the COTS, choroidal involvement was seen in 245 patients (from a database of 945 patients; 25.93%). TB SLC was observed to be the most common phenotypic presentation of TB choroiditis in 113 out of 245 eyes (46.1%).[1] However, it is important to note that TB choroiditis can have other phenotypic presentations such as multifocal choroiditis, ampiginous choroiditis, and other rare phenotypes such as acute posterior multifocal placoid pigment epitheliopathy (APMPPE).[1,8] Thus, it is important to understand the fundus appearance of these lesions and their features on dye and non-dye based angiographies of the retina, OCT and other imaging tools.

2.1. Fundus Photography and Autofluorescence

Fundus photography is important to document the appearance of the choroiditis lesions and determine their morphological features such as shape, extent, borders, and

associated changes such as fibrosis, scarring and pigmentation. Fundus photography greatly aids in providing an objective assessment of change in the lesions over an extended period of time. Serial fundus photography (from acute stage to the stage of healing) is very useful in the assessment of evolution of choroiditis lesions. Careful analysis of fundus photographs may also help in the detection of complications such as development of choroidal neovascular membranes (CNV) which may appear clinically as subtle hemorrhages adjacent to previous scars.[2,5,6,9,10]

2.1.1. Morphological Classification of Serpiginous-like Choroiditis

The lesions of TB SLC can be classified into three phenotypes based on the location of the lesions, their multifocality and their progression. The classification commonly used in reported literature includes (Figure 1):[11,12]

a. **Multifocal SLC:** consists of multifocal discreet lesions that are yellowish-white in color, measuring up to one disc diameter in size with well-defined margins and slightly raised edges. These lesions have a tendency to become confluent.

b. **Placoid SLC:** consists of large plaque-like lesion and an active serpentine edge.[13] The edges are yellowish and elevated whereas the center of the lesion is less elevated with pigmentary changes. This pattern suggests healing process in the center of the lesion with activity in the periphery of the lesion. Choriocapillaris atrophy is commonly seen in the center of the lesion with visible underlying choroidal vessels.[6,12]

c. **Mixed Pattern of SLC:** consists of overlapping features of multifocal and placoid variety.

2.1.2. Healing Pattern on Fundus Autofluorescence

Apart from fundus photography, fundus autofluorescence (FAF) imaging is a very useful non-invasive imaging modality that helps in determining the therapeutic response to anti-tubercular therapy and corticosteroids from the acute stage to the stage of healing.[11,14–16] On FAF imaging, active lesions demonstrate ill-defined hyper-autofluorescence throughout the extent of the lesions. Thus, the lesions have a diffuse, amorphous appearance (Stage 1). In the stage of early healing (Stage 2), a thin rim of hypo-autofluorescence is seen surrounding the lesion which remains predominantly hyper-autofluorescent with a stippled pattern. With further healing, the lesion becomes predominantly hypo-autofluorescent (Stage 3) on FAF imaging. When the lesions have healed completely, they become uniformly hypo-autofluorescent without hyper-autofluorescent areas (Stage 4).[11]

A case report by Gupta and Biswas in 2014[16] defined a sequential pattern of FAF during the entire course of TB SLC, i.e. *evolution, progression, and healing.* In the evolution phase, they showed that the lesions were hyper-autofluorescent. They also noticed faint hyperautofluorescence extending over a large area that was predictive of

future extent of the lesion. The authors defined progression when the advancing edge showed more hyperautofluorescence. During healing, there was sharpening of hyper-autofluorescent borders, and few specks of hyperautofluorescence were seen within the hypo-autofluorescent lesion.[16] The lesions of TB SLC have been classified by other authors as well. Piccolino et al also described similar FAF features; however, they suggested that even early active lesions of TB SLC may have hypo-autofluorescence within the lesion.[14] Carreno et al have described a similar pattern of FAF findings in TB SLC: *active inflammation, transitional, and inactive inflammation* characterized by increasing hypo-autofluorescence as the lesions begin to heal.[15] In general, as the lesions heal, there is increasing hypo-autofluorescence within the lesion.

In a study by Khanamiri and Rao, during the active stage, the authors have stated that there may be no FAF abnormalities in the first 1-2 days after clinical presentation. Subsequently, acute lesions show hyper- and hypo-autofluorescence patches with sharp margins. After 2 weeks, the lesions show granular/speckled pattern of autofluorescence. Healed lesions appear uniform hypo-autofluorescent.[17]

Kawali et al[18] have recently studied the FAF features of 33 eyes with TB SLC and determined the features of FAF in predicting treatment response and relapses. The authors identified three patterns on FAF, which included: dendritic FAF (lesions with thin body and elongated borders), advanced dendritic form (larger lesions more than 2 disc diameters with elongated borders, and placoid form (rounded borders and thick body). The authors noted different outcomes in these groups, with placoid form having the worst prognosis especially once the fovea was involved. Dendritic lesions tended to be bilateral.[18]

2.2. Ultrawide-Field and Montage Photography

Ultra-wide field (UWF) fundus imaging is valuable in the assessment of TB SLC. Compared to conventional imaging (fundus photography and FA), UWF imaging systems aid in detection of additional features such as perivascular choroiditis, vitreous haze, retinal vasculitis and retinal neovascularization in the context of OTB.[5,19–21] The technology of UWF imaging has been applied in studying the lesions of TB SLC. Confocal UWF devices that are commercially available can be used to obtain 450 nm blue-light FAF images. Using these devices, it is also possible to obtain montage of FAF images.[22–25]

In addition, ultra-wide field imaging may be superior to conventional imaging in identifying changes such as *peripheral paradoxical worsening* (worsening of the primary disease upon initiation of anti-TB therapy due to possible release of antigens from the mycobacteria; Ocular *Jarisch-Herxheimer reaction*) which may be otherwise missed on conventional imaging. Aggarwal et al examined 44 eyes with TB SLC using UWF imaging in detection of paradoxical worsening. In their study, the authors defined paradoxical worsening either as central (located within the 75º circle), peripheral (located outside the 75º circle) or both central and peripheral paradoxical worsening. The authors observed a much higher rate of paradoxical worsening (approximately

36%)[26] after initiation of anti-tubercular therapy compared to previously reported rate of 14%.[27] Using UWF imaging, the authors noted that 18.7% eyes showed only peripheral paradoxical worsening, while 62.5% eyes showed both central and peripheral paradoxical worsening. Management was altered in 37.9% based on UWF imaging (Figure 2 and 3).[26]

In a study by Brar et al,[28] the authors have classified FAF patterns on UWF imaging as follows: Type 1: active inflammation characterized by ill-defined predominantly hyper-autofluorescent lesions; Type 2: better defined lesions with a stippled mixture of hypo-autofluorescent and hyper-autofluorescent; Type 3: inactive inflammation characterized by hypo-autofluorescent FAF images revealing complete loss of fluorophores, with very sharp borders.[28]

2.3. Dye-Based Angiographies

2.3.1. Fluorescein Angiography

FA is a useful modality in the management of patients with TB SLC.[2,3,5,6,9,10] At the time of baseline evaluation of active TB SLC lesions, FA is an important imaging modality that can be performed along with other evaluations such as FAF and OCT. The active lesions of TB SLC appear hypofluorescent in the early phase and hyperfluorescent with fuzzy edges in the late phase. Without treatment, these lesions tend to progress and become confluent, and the advancing edge shows early hypofluorescence with late hyperfluorescence. If the lesions are large and placoid, there may be central RPE damage and choriocapillaris atrophy, and in these areas the choroiditis lesions have already healed. Such areas of healing may demonstrate window defects on FA due to RPE damage (Figure 4).[5,17] Combining FA with FAF imaging is thus, useful in demonstrating the activity of the lesions of TB SLC. In addition, complications of the disease such as inflammatory CNV may be detected using FA, though it may be very challenging in the absence of high index of suspicion.[10,29,30] In such situations, it is important to obtain an OCTA and compare the two imaging modalities to be certain regarding the diagnosis of a CNV.

UWF FA has been shown to be useful in the management of OTB. In comparison with conventional FA, UWF imaging can reveal additional information such as peripheral capillary non-perfusion areas, retinal neovascularization, and retinal vascular leakage. Such findings may alter treatment decisions such as the need for scatter laser photocoagulation.[9] In TB SLC, peripheral choroiditis lesions can be documented using UWF FA. In the recent times, UWF FA is being increasingly used in the management of TB SLC.

2.3.2. Indocyanine Green Angiography

The proper evaluation of TB SLC is incomplete without performing an ICGA. During the initial evaluation, combined FA and ICGA are very useful in the evaluation of patients with TB SLC.[5,13,31,32] The active lesions of TB SLC appear hypofluorescent in

the early and late phase of ICGA. As the lesions heal, the late phase ICGA shows a well-demarcated area of hypofluorescence and visible underlying choroidal vasculature which suggests choriocapillaris atrophy. Thus, ICGA can greatly aid in the detection of choriocapillaris hypoperfusion among patients with TB SLC. Other changes observed on ICGA in TB posterior uveitis include presence of numerous hyperfluorescent spots, fuzzy appearance of choroidal vessels in the intermediate phase and late choroidal hyperfluorescence due to dye leakage which tends to regress after completion of treatment with anti-tubercular therapy and corticosteroids (Figure 4).[13,17,31]

Longitudinal follow-up of TB SLC lesions on ICGA help in the monitoring of the healing patterns of the lesions and recovery of the choriocapillaris and the RPE. The recovery of choriocapillaris may have a direct impact on the visual function, especially in cases where the choroiditis lesions involve the macula. ICGA changes can be reversible and useful in monitoring the response to therapy.[13,33,34] The lesions of TB SLC may heal and result in development of choriocapillaris atrophy, which presents with early hypofluorescence followed by iso-/hypofluorescence in the late phase.

2.4. Optical Coherence Tomography

Various OCT technologies such as spectral-domain, enhanced-depth and swept-source OCT provide high-resolution near-histological images of the retinochoroid, and provide numerous insights into the pathogenesis of TB SLC. In the current era, OCT is an indispensable tool in the management of TB SLC. With the help of OCT, various retinochoroidal changes in active and healed disease can be evaluated non-invasively.[35,36]

2.4.1. Changes in outer retina and retinal pigment epithelium

The OCT features of active TB SLC lesions include disruption of the photoreceptor and other outer retinal layers, thinning of the RPE, mild cystic changes, subretinal fibrosis in area of old CNV, and marked attenuation of the interdigitation zone in the outer retina.[14,15] In addition, the lesions of TB SLC may also result in alteration of the ellipsoid and the myoid zones in the outer retina. These changes may be accompanied by alterations of the choriocapillaris which are explained in the subsequent section. In the acute stage of TB SLC, active edges of the lesions show localized, fuzzy areas of hyper-reflectivity in the outer retinal layers involving the RPE, photoreceptor outer segment tips, external limiting membrane, and the outer nuclear layer without increased backscattering from the inner choroid. The involvement of the RPE and photoreceptors in active TB SLC correlates well with the changes on other imaging tools such as FAF imaging (Figure 5).[11,37–42]

Wang et al gave demonstrated similar features including hyper-reflective spots in the vitreous, hyper-reflectivity of the outer nuclear layers, sub-RPE drusenoid changes, and outer retinal tabulations.[37]

Konana et al[43] have recently described a ‘double-layer sign’ in TB SLC, characterized by a separation between Bruch’s membrane and the hyperreflective RPE at the area of activity. The authors evaluated 5 eyes, all of which had this sign present. The double-layer sign showed resolution when the lesions began healing. The authors speculate that this sign signifies choroidal infiltration, extracellular fluid accumulation, and cellular infiltration in the outer retina due to the inflammation caused by TB SLC.[43] Further studies are needed to understand the relevance and mechanisms behind this finding (Figure 6).

2.4.2. Pathological changes in the choroid

EDI-OCT and swept-source OCT help in detection of deeper choroidal involvement in various vitreoretinal conditions including TB SLC.[22,44] Using these tools, choroidal infiltration, elevation of the RPE-Bruch’s membrane complex, and focal increase in choroidal thickness have been observed along lesions of TB SLC. During the active stage of the disease, imaging of the choriocapillaris is vital in TB SLC, as it probably reflects the site of the primary pathology. Careful evaluation of the choriocapillaris layer in TB SLC reveals the most characteristic alterations on OCT, which is the development of choriocapillaris ischemia that morphologically appears as a thickening of the choriocapillaris layer along with loss of the normal dotted pattern seen just below the RPE-Bruch’s complex (Figure 5).[11,33,37,40]

Rifkin et al[45] demonstrated elevation of the RPE, choroidal infiltration and increase in thickness in a patient with active TB SLC on EDI-OCT. Similar findings were obtained in a larger sample by Moharana et al.[46] In their series, Moharana et al have demonstrated an increase in the mean subfoveal choroidal thickness in eyes with TB SLC, which decreases in the follow-up period after initiation of therapy. In addition, they observed a localized area of mixed reflectivity (with a central hyperreflectivity surrounded by a zone of hyporeflectivity) in the region of thickened choroid beneath the active lesion. In these areas, thinning and fibrosis of the choroid was observed as the lesions healed. Focal loss was also seen involving the ellipsoid zone, myoid zone and the RPE-Bruch’s complex (Figure 5 and 6).[46]

Further, changes in the choroidal vascularity can be evaluated using indices such as choroidal vascularity index (CVI), and other imaging tool such as OCTA which have been detailed in the subsequent sections.

2.4.3. Features of healed disease

Using OCT imaging, it is possible to study the changes in the outer retina, RPE and the choroid once the lesions heal. As the lesions begin to heal from the center, the hyper-reflective fuzzy areas begin to disappear and are replaced by irregular, hyper-reflective knobbly elevations of the outer retinal layers. There is an increased reflectance from the choroidal layers due to attenuation of the RPE-photoreceptor complex. As the lesions continue to heal further, there is loss of RPE and outer retinal

layers, and persistent increased reflectance from the choroid on OCT (Figure 5 and 6).[11,16,37,46]

2.4.4. Choroidal vascularity index

CVI has been described as a novel objective proxy measure of choroidal vascular perfusion in both non-inflammatory retinal disease such as age-related macular degeneration and diabetic retinopathy, and inflammatory pathologies such as Vogt-Koyanagi-Harada Syndrome, posterior uveitis, among others.[47–50] CVI is calculated on OCT images in terms of total choroidal area, luminal area and stromal area, which provide an indirect measure of the vascularity of the choroid. CVI has also been applied in eyes with TB SLC to understand the effect of the ocular inflammatory process on choroidal vasculature. The analysis of TB SLC images showed that during the active stage of the disease, the total choroidal area is higher in inflamed eyes compared to the normal population. This is in line with the finding that patients with active TB SLC have an increased choroidal thickness. Eyes with TB SLC have a much increased luminal and stromal areas indicating increase in the volume of both vascular as well as stromal/interstitial component of the choroid. However, when analyzed keeping in mind the total choroidal area, it was observed that subjects with active disease had a decrease in CVI due to a relative ischemia of the choroid. As the lesions of TB SLC heal, the CVI improved suggesting a normalization of the perfusion of the choroid compared to the active stage of the disease.[51] Thus, CVI can serve as a useful clinical biomarker in the assessment of the health of the choroid in TB SLC.

2.5. Optical Coherence Tomography Angiography

OCTA is a recently introduced, non-invasive imaging modality to visualize the retinal and choroidal circulation without use of an injectable dye. It provides segmented en-face images of blood flow in the superficial, intermediate and deep retinal capillary plexuses, the outer retina, the choriocapillaris and other areas of interest. In the context of OTB, OCTA has revolutionized our thinking and understanding of the pathophysiology of chorioretinal vascular involvement in this condition. OCTA is being increasingly used in the management of TB uveitis to provide further insights into the natural history of the disease and detection of early complications such as CNV.[5,22,39,52–56]

2.5.1. Flow deficit areas in choroiditis

The utility of OCTA in TB SLC was demonstrated initially by Mandadi et al[57] who described 18 eyes of 18 subjects with TB SLC. The authors obtained OCTA for all the eyes with active disease, and imaging with FA and ICGA. The lesions of TB SLC resulted in hyporeflective flow deficit areas in the choriocapillaris slab during the active stage. These flow deficit areas exactly co-localized and agreed with the ICGA imaging. The areas of flow deficit appeared better defined on OCTA compared to ICGA. In addition, areas of preserved choriocapillaris were observed within the lesions. Other features included vascular tufts and tangled vessels among lesions of TB SLC in

advanced stages of healing (Figure 7). Thus, non-invasive tools such as OCTA may enable detailed evaluation of the retinochoroidal vasculature among patients with TB SLC.[57]

Further insights into the healing patterns of choroiditis lesions (especially TB placoid choroiditis) were provided by Klufas et al.[58] The authors evaluated 24 eyes of 15 patients (including patients with placoid type of TB SLC) using OCTA. In the study, areas of choriocapillaris flow deficit correlated closely with ischemic lesions seen with FA and ICGA but were more extensive with OCTA. During follow-up, these lesions significantly improved with treatment.[58]

Subsequently, several authors have demonstrated flow deficit areas corresponding to active lesions in TB SLC. Pakzad-Vaezi et al[52] performed a prospective study evaluating the use of a prototype swept-source OCTA in imaging the choroid in subjects with TB SLC. The authors observed flow deficit areas in the choriocapillaris slab whose shape and size correlated well with ICGA. The area of flow deficit increased if the lesions increased in size, and did not change if there was scarring of the lesions. With the availability of UWF swept-source OCTA commercially, Brar et al[28] have studied the utility of this tool in 17 eyes of 12 subjects with TB SLC. The authors used 12 × 12 mm OCTA scans to create a montage, and compared the images to FAF imaging. The authors observed a good correlation between the two imaging tools in detection of active lesions (Figure 8). Similarly, Nagpal et al[59] have utilized panoramic OCTA in evaluating eyes with TB SLC, and observed flow deficit areas which correlated with hypofluorescent areas on ICGA. During the healing stage, the authors observed residual unmasked choriocapillaris that corresponded to reduced hypofluorescence on ICGA.

2.5.2. Insights in paradoxical worsening

The technique of OCTA has potential advantages of detecting subclinical pathological changes in the retinochoroid in various conditions including posterior uveitis. In TB SLC, one major challenge in the management is development of paradoxical worsening of the disease which can result in significant visual morbidity. Using OCTA, development of paradoxical worsening can be evaluated by detection of persistent hyporeflective dark flow deficit areas in the area of the active edge of the lesion, corresponding to the hyper-autofluorescent edge of the lesion on FAF imaging. Thus, OCTA can be helpful additional tool in the evaluation of subjects with TB SLC to demonstrate the underlying choriocapillaris changes in paradoxical worsening of the disease.[60]

2.5.3. Detection of choroidal neovascularization

CNV is a rare but sight-threatening complication of TB SLC. CNV lesions are known to occur in the healed, scarred stage of the disease where there is significant damage to the RPE, and a heightened neovascular drive due to the choriocapillaris atrophy-related ischemia.[10,29,30] Detection of CNV can be a challenge in these situations

because of the significant background retinal scarring and pigmentation. Often, conventional dye-based angiographies may be inconclusive in detection of such lesions, especially small neovascularization harboring beneath/adjacent to a scar. Yee et al[56] have demonstrated the role of OCTA in detection of CNV lesions in TB SLC.

More recently, Aggarwal et al[61] evaluated 9 eyes with TB SLC with low-lying pigment epithelial detachments on EDI-OCT. None of the patients had clinically detectable intraretinal fluid on OCT imaging. However, OCTA imaging detected type 1 CNV lesions in all eyes which appeared as a fine anastomotic network of vessels, some of which had a hairpin loop configuration. These branching anastomosis decreased with anti-vascular endothelial growth factor (anti-VEGF) injections.

Thus, further advances in OCTA may enhance our knowledge of pathogenesis choroidal involvement and development of CNV in TB SLC.[22,62]

3. Tubercular choroidal granuloma (Tuberculoma)

Choroidal granulomas are characteristic pathological finding in ocular tuberculosis involving the posterior segment of the eye. Unlike the lesions of TB SLC, and other forms of choriocapillaritis (such as APMPPE), choroidal granulomas affect the *stroma* of the choroid, with secondary changes involving the choriocapillaris. Histopathological examination have shown that granulomas consist of nodular collection of immune cells, usually macrophages and epithelioid cells with surrounding lymphocytes. Granuloma is a host immune reaction to contain the pathogen.[2,3] Choroid being the most vascular tissue of the eye is the site for granuloma formation. Choroidal granulomas due to tuberculosis have been termed as tuberculoma by the COTS group. The COTS proposed that the term “choroidal granuloma” is incorrect since a granuloma is a histological term, and preferred using “tuberculoma” instead.[7]

Tuberculomas can involve the following regions of the fundus:[2]

a. **Macula:** involvement of the posterior pole is commonly seen in tuberculoma. The lesions may involve perivascular retina and result in early visual loss due to subretinal fluid accumulation (Figure 9).

b. **Optic nerve head:** tuberculomas may appear on the optic nerve head and result in disc elevation, peripapillary fluid accumulation, hemorrhages and exudates, and can be classically seen on OCT as choroidal elevations.

c. **Periphery:** occasionally, the tuberculoma can involve the peripheral retina and appear as a vasoproliferative tumor involving the peripheral retina. These lesions can be associated with retinal neovascularization leading to intermittent vitreous hemorrhage.

It is relevant to understand the differences between tuberculomas and choroidal tubercles. Tubercles are typically found in individuals with disseminated or miliary TB.

These lesions could be either unilateral or bilateral and usually multiple (but may be single). Their size is generally less than 0.5 disc diameter, and are discreet grayish-white lesions with a central core and surrounding rim of inflammation (Figure 10). In the healed stage, the lesions appear oval/rounded scars with variable pigmentation and resolution.[63] Choroidal tubercles result from hematogenous spread of the bacilli.[64–66] They are also associated with tubercular meningitis.[67] Eyes with choroidal tubercles usually do not have anterior segment inflammation or vitritis.[68]

Tuberculomas are usually larger (up to 14 mm) and solitary lesions.[69] They are commonly seen in foveal and perifoveal region. Tuberculomas appear as subretinal, round-shaped, yellowish lesions with overlying exudative detachment.[70,71] Rarely, a tuberculoma may be the presenting sign in a patient with no evidence of systemic disease.[72] Rapid multiplication of the bacilli can occur within a tuberculoma, causing tissue destruction through liquefactive necrosis, thus forming subretinal abscess.[73] These lesions are predisposed to develop retinal angiomatous proliferation (type 3 choroidal neovascularization).[74] These lesions may respond well to anti-tubercular therapy and heal with pigmentation, thus forming an atrophic scar.

3.1. Fundus imaging in tuberculoma

Color fundus photography helps in documenting the size, extent and distribution of choroidal tubercles or granulomas. It also helps to differentiate between active and healed lesions. Active lesions tend to have irregular margins, are lobulated with perilesional edema, whereas healed lesions are more discrete and rounded. Serial fundus imaging is done to look for progression of the disease, appearance of new lesions and healing of active lesions in response to treatment. Multicolor imaging (MCI) is a recently introduced imaging modality which is based on confocal scanning ophthalmoscopy. MCI can detect associated superficial retinal pathologies associated with choroidal granulomas. Other advantages of MCI include imaging through small pupil, simultaneous optical coherence tomography imaging, control of eye movement artifact, and lack of backscatter that may decrease quality of color images.[75]

3.2. Fluorescein and Indocyanine Green Angiography

3.2.1. Interpretation of FA and ICGA

FA helps to characterize the retinal, choroidal, and optic disc involvement in OTB; helps in differentiating between active and healed lesions; and is useful for detection of any complications such as development of CNV; and finally, in monitoring the response to treatment.

Active tuberculomas show an early hypofluorescence with late hyperfluorescence, while inactive healed tubercles show transmission hyperfluorescence.[76,77] Large tuberculomas with subretinal fluid accumulation may show early hyperfluorescence with a dilated capillary bed, progressive increase in hyperfluorescence, and late pooling of dye in the subretinal space (Figure 9).[2,5] FA is

also useful in detecting CNV lesions in patients with tuberculomas. Chung et al first of all reported a case of CNV in a patient who had TB meningitis and had multiple choroidal tubercles and disciform maculopathy.[78] The increased vascular endothelial growth factor (VEGF) levels and hypoxia within the tuberculoma have been shown to play a role in CNV formation in such cases.[79] CNV secondary to posterior segment inflammation may occur either due to a defect in Bruch's membrane-RPE complex secondary to degeneration following inflammation or from the inflammation mediated angiogenesis itself.[80]

Indocyanine green (ICG) dye has a high protein binding capacity (98%), and does not leak from the choriocapillaris. This dye is slow to clear from choroidal veins and arteries. It impregnates into the choroidal stroma and slowly washes out of the stromal tissue. These properties of the ICG dye helps to delineate the choroidal pathology. Tuberculomas show different ICG patterns depending upon the amount of choroidal tissue involved.[81] Partial thickness choroidal granuloma appear oval or round hypocyanescent lesions during early phase and become isofluorescent during the late phases. On the other hand, full thickness choroidal granuloma remains hypofluorescence both in early and late phases.[34,82] Choroidal lesions detected on ICGA are larger and more in number than seen clinically or on FA. Hypofluorescence of the choroidal granulomas decreases with treatment and ICGA can be used to monitor treatment response and resolution of the disease. This prevents premature cessation of treatment for these granulomas.[83]

ICGA is useful in detecting complications such as CNV that can develop during the active or inactive stage of the disease. While these CNV lesions may be better visible on techniques such as OCTA, ICGA helps in detecting any subclinical tuberculomas that may not be appreciable clinically. In addition, ICGA is helpful in detecting retinal angiomatous proliferation (RAP) lesions (type 3 CNV) that frequently develop in active tuberculomas.[74]

3.2.2. Vascularization in tubercular choroidal granuloma

Several studies evaluating choroidal granulomas have described tuberculomas to be *vascularized* granulomas.[84–86] A choroidal granuloma has been termed vascularized in the presence of dilated, tortuous vessels overlying the granuloma associated with significant exudation and leakage on FA, and presence of subretinal fluid on OCT. Tuberculomas may be predisposed to develop vascularization due to the same mechanisms thought to be responsible for development of CNV, i.e. elevated levels of VEGF in the local milieu leading to hyperpermeability and an increased angiogenic drive.

Apart from *vascularization,* RAP lesions (type 3 CNV) has been noted in eyes with tuberculomas. In one such published case, choroidal granuloma was determined to be caused by a dual infection of M. tuberculosis complex with M. fortuitum and M. bovis.[74] The patient presented with a large subretinal lesion with overlying exudative retinal detachment. Lesion revealed early blocked fluorescence, network of retinal

vessels forming RAP lesions with late pooling of dye on FA. It is believed that subretinal abscess due to TB usually presents with overlying retinal hemorrhage and has a tendency to develop RAP over time.

3.3. Optical Coherence Tomography

3.3.1. Choroidal stromal alterations

Choroidal granulomas result in inflammation primarily affecting the choroidal stroma. Hence, fundus imaging that provides high quality choroidal imaging is vital in the assessment of pathological alterations caused by choroidal granulomas. Therefore, enhanced-depth imaging OCT (EDI-OCT) is ideal in evaluating such lesions. On EDI-OCT, tuberculomas appear homogenously hyporeflective lesions involving the choroidal stroma. There is an appreciable loss of normal vascular architecture in the choroid.[86,87] Invernizzi et al has shown 100% detection of choroidal granulomas on EDI-OCT.[86] In their study, authors included eyes diagnosed with tuberculomas and showed that EDI-OCT has a moderate agreement with ICGA in detecting the extension of the granuloma, i.e. whether the lesion is partial thickness or full thickness. Another important observation from their study was that the authors observed tuberculomas to be mostly lobulated in shape, with a non-homogenous pattern and ill-defined. This was in contrast to sarcoid granulomas which were rounded, with a homogenous pattern, and were well defined. The variable internal reflectivity pattern of the tuberculoma was attributed to absence of any definite orientation in the structure or organization of the inflammatory cells within the granuloma that could reflect the EDI-OCT signal. Choroidal granulomas irrespective of their size have shown to exhibit increased signal transmission. This feature helps to differentiate granulomas from large choroidal vessels (Figure 11).[86]

Subsequently, Invernizzi et al[88] have published a longitudinal follow-up of eyes with choroidal granulomas imaged using EDI-OCT. In their study, the authors evaluated 16 eyes with tuberculomas on EDI-OCT. Using EDI-OCT, the authors observed a significant decrease in the size of the granulomas compared to ICGA, and observed that the granulomas initially reduced in their antero-posterior extent, followed by reduction in their lateral extent. Thus, EDI-OCT is a very valuable tool that can non-invasively help in the analysis of choroidal granulomas. Swept-source OCT is new technology that promises better imaging of the choroidal vasculature, and may have certain advantages in imaging the choroidal granulomas over EDI-OCT; however, there is no literature in this regard yet. In summary, OCT is a useful non-invasive tool for detection and serial evaluation of choroidal granulomas as a supplement to ICGA.

3.3.2. Outer retinal changes

OCT is helpful in detecting outer retinal changes in tuberculoma such as detection of subretinal fluid due to exudation from the granuloma (Figure 11). This subretinal fluid accumulation can result in rapid deterioration of visual acuity, and reduction of subretinal fluid can be demonstrated after initiating therapies such as anti-

VEGF injections, systemic corticosteroids, and anti-tubercular therapy. OCT can be used to demonstrate the improvement in outer retinal layer integrity in such cases.[74,85]

In addition, accumulation of subretinal fluid may be accompanied by fluid accumulation within the photoreceptor layer by a split involving the myoid zone (MZ) of the photoreceptors. This has been termed recently as bacillary layer detachment (BLD), which refers to a split at the level of MZ due to shedding of an entire layer of inner photoreceptor segments. Occurrence of BLD was initially described by Mehta et al[89] in a case of toxoplasma chorioretinitis and pachychoroid disease. Authors believed that intense chorioretinal inflammation can cause a split of the photoreceptors.

Subretinal fluid accumulation in a tuberculoma can be rarely associated with a splitting BLD (unpublished data) though this phenomenon has not been described in a large series of patients.

3.4. Optical Coherence Tomography Angiography

3.4.1. Choriocapillaris changes in stromal granulomas

OCTA has been recently employed to study the pathological alterations of the choroid due to tuberculomas by Pichi et al.[90] In their study, the authors included 23 eyes with choroidal granulomas (of which 8 eyes were affected by tuberculomas). Imaging was performed on a swept-source platform. The authors additionally obtained FA, ICGA and EDI-OCT for the choroidal granulomas included in their cohort. Of the choroidal lesions detected on ICGA, 94% were well visualized by the authors on OCTA. Moreover, the authors observed additional lesions on OCTA which they identified as granulomas. Thus, a higher proportion of granulomas (including tuberculomas) were visualized on OCTA compared to ICGA. Tuberculomas appear as mass occupying lesions in the choroidal stroma, thus causing mechanical compression of surrounding choroidal vasculature. This impairs the choroidal blood flow and appears as areas of flow void on OCTA.[90,91] Aksoy et al have shown that not only these stromal granulomas cause choriocapillaris compression leading to flow voids, but also cause decreased vascular density in deep capillary plexus and increase in foveal avascular zone in the retina.[92]

Thus, OCTA is very useful in detecting choriocapillaris and deeper choroidal changes in eyes with tuberculomas. Further studies comparing OCTA with ICGA and other imaging techniques are needed to better understand the utility of this tool in clinical practice.

3.4.2. New vessels on OCTA

OCTA is helpful in detecting presence of CNV lesions accompanying tuberculomas. Although CNV lesions associated with choroidal granulomas (specifically with TB) are rarely reported, imaging with OCTA is very helpful in their evaluation. This is because presence of intra- or subretinal fluid with a choroidal granuloma can be

misdiagnosed as an active *vascularized* tuberculoma, and the detection of CNV may be missed on clinical examination and conventional imaging techniques (which would demonstrate leakage that is likely to be misinterpreted).[93] In such cases, OCTA can provide high quality images of the underlying CNV. Following treatment, the regression of the CNV lesion and the branching patterns can be helpful in assessing the response to anti-VEGF therapy.

4. Conclusions

There has been rapid improvement in the available technologies for imaging the retina and the choroid in the recent years. Application of novel imaging modalities such as EDI-OCT, swept-source imaging, and UWF imaging has greatly aided in improving our understanding of retinochoroidal alterations in TB uveitis. Most studies in the literature have correlated newer imaging technologies with available conventional tools such as FA and ICGA, thereby providing advanced information in the context of available knowledge. There has been a considerable improvement in the understanding of the primary pathological site of involvement by TB choroiditis (i.e. inner choroid/RPE and choroidal stroma), and the extent to which damage can occur to these structures if timely therapy is not initiated. Reversibility of certain changes such as regression of CNV lesions, improvements in the outer retinal integrity, and normalization of choroidal anatomy can be observed using multimodal imaging. Therefore, multimodal imaging has the capability of providing a comprehensive evaluation of subjects with OTB. The investigators of the COTS realize the importance of incorporating fundus imaging in the management of patients with OTB, and have planned future prospective clinical studies incorporating imaging biomarkers in the diagnosis as well as endpoints in treatment.

Figure Legends

Figure 1: Figure shows two commonly encountered phenotypes of tubercular serpiginous-like choroiditis (TB SLC) in the clinics. (A) The fundus photograph demonstrates classic form of multifocal serpiginous choroiditis with an active serpentine edge. On fundus autofluorescence (FAF) (B), the activity is denoted by hyper-autofluorescent signal (yellow asterisk). The placoid phenotype (B) is characterized by a large placoid lesion often involving the posterior pole. Extensive retinal pigment epithelial damage and disease activity is demonstrated by FAF imaging (yellow asterisk) (D).

Figure 2: The figure depicts development of a paradoxical worsening involving the posterior pole in a patient with serpiginous-like choroiditis who was initiated on anti-tubercular therapy. At baseline (A), there is an active placoid lesion involving the posterior pole. After 3 weeks of initiating therapy (B), the lesion has expanded and reached the major vascular arcades. Further, at 4 weeks (C), the lesion has progressed and is seen to extend beyond the major vascular arcades.

Figure 3: The figure depicts role of ultra-wide field imaging in the detection of peripheral paradoxical worsening. At baseline (A), the serpiginous-like lesions are seen to involve the central macula and the retinal periphery (both superior and inferiorly). The yellow circle drawn with the macula in the center denotes the area imaged using conventional fundus photography. At 4 weeks follow-up (B), the image shows peripheral paradoxical worsening (white arrowheads) that lie outside the yellow circle, indicating that these could be potentially missed on conventional imaging.

Figure 4: Conventional dye-based angiographies in a patient with tubercular serpiginous-like choroiditis (TB SLC) is shown. The fundus photograph at baseline shows the characteristic appearance of the TB SLC lesion (A). The patient has complete healing with retinal pigment epithelial atrophy at 3 months follow-up (B). The combined fluorescein angiography (FA) and indocyanine green angiography (ICGA) at baseline is shown in C and D. The early frame (C) FA shows lesions near the superior arcade which have hyperfluorescence at the edges (blue arrowhead). The lesions in the inferior macula and arcade are hypofluorescent. The hypofluorescent lesions are better appreciated on ICGA (yellow arrows). The late phase FA (D) shows fuzzy hyperfluorescence of the active lesions (blue arrowhead), and the lesions continue to remain hypofluorescent on ICGA (yellow arrows).

Figure 5: Serial enhanced-depth imaging optical coherence tomography (EDI-OCT) imaging of an active lesion of tubercular serpiginous-like choroiditis (TB SLC) is shown. At baseline (A), the lesion shows irregularity and disruption of the external limiting membrane, ellipsoid and myoid zones, and outer nuclear layer involvement (white arrows). This is better seen in the magnified OCT image (area denoted by yellow dashed square). At 6 weeks follow-up (B), there is pigment clumping at the level of the retinal pigment epithelium and interval recovery of the photoreceptors (white arrow). At

3 months follow-up (C), the lesions have completely healed, with residual pigment clumping (white arrow) (knobbly elevations).

Figure 6: Serial enhanced-depth imaging optical coherence tomography (EDI-OCT) imaging of an active lesion of tubercular serpiginous-like choroiditis (TB SLC) shows presence of a double-layer sign (DLS). At baseline, the active lesion shows elevation of the retinal pigment epithelium (RPE) from the underlying Bruch's membrane (white arrowheads). At 6 weeks, the DLS has resolved and the RPE elevation has subsided. However, a small area of photoreceptor loss (denoted by focal hyporeflectivity) is noted (white arrowhead). At 3 months follow-up, the DLS has resolved, and there is no change in the OCT appearance of the lesions (white arrowhead).

Figure 7: Serial optical coherence tomography angiography (OCTA) imaging of an active lesion of tubercular serpiginous-like choroiditis (TB SLC) is shown. During the initial visit (A), the TB SLC lesions are seen to involve the posterior pole of the left eye. The lesions show healing at 6 weeks (B), and have completely resolved at 12 weeks (C) follow-up visit. The OCTA scan corresponding to the baseline visit (D) shows hyporeflectivity involving the choriocapillaris slab suggestive of flow deficit areas. These flow deficit areas can be gradually seen to reduce in size at 6 weeks (E), and nearly resolve at 12 weeks (F).

Figure 8: The figure shows indocyanine green angiography (ICGA) and ultrawide field (UWF) optical coherence tomography angiography (OCTA) imaging of a patient with tubercular serpiginous-like choroiditis (TB SLC). The peripheral sweeps of the ICGA, and the macula centered image shows significant hypofluorescence suggestive of choriocapillaris ischemia (A-D). These changes can be appreciated on the UWF OCTA (E) which exactly corresponds to the ICGA images and shows extensive choriocapillaris ischemia.

Figure 9: Fundus photograph and fluorescein angiography (FA) of a patient with choroidal granuloma due to tuberculosis (tuberculoma) is depicted. The fundus photograph shows a large yellow elevated lesion involving the posterior pole wit surrounding subretinal fluid (white arrowhead) (A). The FA image shows early hyperfluorescence along with surrounding pin-point leaks (white arrow) (B). The late phase FA shows intense leakage from the tuberculoma suggestive of a *vascularized* choroidal granuloma (C and D).

Figure 10: Fundus photograph and fluorescein angiography (FA) of a patient with choroidal tubercles in a setting of tubercular meningitis is shown. The fundus photograph (A) shows a deep, well-demarcated, yellow lesion measuring less than 1 disc diameter in size. The tubercle shows mild hyperfluorescence on FA in the early phase (B) which does not show much increase in the late phase (C).

Figure 11: Swept-source optical coherence tomography (SS-OCT) at baseline and follow-up of a patient with choroidal granuloma is shown. At baseline, there is a large oval, lobulated, hyporeflective lesion seen in the deep choroidal stroma (yellow dashes)

suggestive of a granuloma. There is a streak accumulation of subretinal fluid (white arrows), and outer retinal hyper-reflectivity (white arrowheads) (A). At follow-up 3 weeks later (after a single intravitreal ranibizumab injection, and initiation of high-dose oral corticosteroids and anti-tubercular therapy), the granuloma has completely resolved on the SS-OCT scan, and the choroidal stroma and the outer retinal layers appear normal (B).

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