Imaging in tuberculosis-associated uveitis

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Intraocular tuberculosis (TB) can have several clinical presentations, affecting nearly every tissue of the eye. These clinical signs have specific imaging characteristics which help in associating them with tuberculous etiology. This review enumerates the conventional and emerging imaging techniques for intraocular TB and highlights their clinical application for diagnosis and management of specific clinical presentations.

Key words: Imaging, multimodal imaging, optical coherence tomography angiography, tuberculosis, uveitis

Intraocular tuberculosis (TB) is increasingly being recognized as a common cause of uveitis in endemic as well as nonendemic countries.¹ ² The disease has several manifestations involving different segments of the eye. These include choroidal lesions such as focal, multifocal, or multifocal serpiginoid choroiditis (MSC), retinal lesions such as retinal vasculitis, optic nerve lesions such as optic disc granuloma or optic neuritis, and intermediate and anterior uveitis.³ Not surprisingly, a variety of imaging tools is required for diagnosis and management of intraocular TB.

Imaging techniques have special significance in intraocular TB for two reasons. First, they are important in identifying the disease pattern which is crucial for making a presumptive diagnosis of TB-associated uveitis. This is especially important since microbiological evidence of Mycobacterium tuberculosis is nearly always lacking in these patients. Second, intraocular TB often results in chronic inflammation that responds slowly to treatment. In such situations, imaging tools are helpful in measuring disease activity and guiding the course of therapy. In addition, imaging is required for diagnosing various sequelae and complications of intraocular TB. In this review, we will discuss the basic principles of each imaging technique and their different applications in intraocular TB.

Fundus Photography and Fluorescein Angiography

Fundus photography provides an accurate method of documenting clinical signs in the posterior segment, in intermediate, posterior, or panuveitis. Serial fundus photographs help in identifying new lesions or resolution of active lesions [Fig. 1a]. Digital images may also allow grading of vitreous haze. Wide-field or ultra-wide-field cameras offer an additional advantage of rapidly acquiring images of the nearly entire posterior segment, besides providing additional information on peripheral lesions that are otherwise missed by conventional imaging [Fig. 1b].⁴ ⁵

Fluorescein angiography (FA) has applications in diagnosis of several types of intraocular TB. In MSC or choroidal granuloma, it can help delineate active lesions, which show early hypofluorescence and late hyper-fluorescence. It can help differentiate tubercular retinal vasculitis from other forms of retinal vasculitis, by revealing extensive capillary nonperfusion [Fig. 1c]. Subtle hyperfluorescence of the optic disc can be used to detect early disc edema. Besides these diagnostic applications, FA is also useful for detecting uveitis complications such as cystoid macular edema (CME) [Fig. 1d] or choroidal neovascularization (CNVM).

Wide-field FA is now being increasingly used for demonstrating peripheral and posterior pole pathologies.

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Ultra-wide-field angiography reveals the active multifocal serpiginoid choroiditis involving the macula, (b) wide-field photograph of the right eye showing inferior extension of multifocal serpiginoid choroiditis lesions, (c) fundus fluorescein angiogram of the left eye with tuberculous-retinal vasculitis showing large area of capillary nonperfusion and laser marks in inferonasal quadrant, (d) fundus fluorescein angiogram of the right eye with intermediate uveitis showing petalloid pattern hyperfluorescence at macula suggestive of cystoid macular edema. Disc leakage is also seen simultaneously.\[^{14-16}\] Ultra-wide-field angiography reveals additional information on the extent of retinal vasculitis, retinal ischemia, and choroiditis lesions that can influence or change treatment options.

## Indocyanine Green Angiography

Indocyanine green angiography (ICGA) is most useful for studying primary disorders of the choroid. Unlike FA, indocyanine green (ICG) dye, most of which is protein bound, does not leak from the choroidal arteries or veins though it leaks slowly from the choriocapillaris, impregnating the choroidal stroma.\[^{7-9}\] It fluoresces in the infrared light and is not blocked by pigment or blood.

**Intraocular TB commonly affects either the choriocapillaris - outer retina complex as in MSC, or as single or multiple choroidal granulomas that occupy either partial or full thickness of the choroid. In MSC, inflammation leads to multifocal areas of occlusion of the choriocapillaris. These areas do not fill with the ICG dye and appear hypofluorescent in the initial frames and remain so even in the late frames taken at 20–30 min after injection of the dye. Unlike fundus fluorescein angiogram that shows initial hypofluorescence with late staining of the active edges of the MSC lesions, ICG remains hypofluorescent throughout indicating permanent occlusion of the choriocapillaris in the MSC lesions [Fig. 2a-d]. In patients with partial thickness tubercular granulomas, the ICG demonstrates mass effect. These are seen as regular-shaped, hypofluorescent lesions in the initial frames that become isofluorescent in the late frames. Full-thickness granulomas would be seen as regular-shaped hypofluorescent lesions that remain hypofluorescent even in the late frames.

ICG is also useful in detecting the Type 2 CNVM that may complicate the healed lesions of MSC or the Type 3 CNVM (retinal angiomatous proliferation) that frequently develop in active tubercular granulomas.

## Fundus Autofluorescence

Fundus autofluorescence (FAF) is a noninvasive fundus imaging modality emanating primarily from lipofuscin accumulation in the retinal pigment epithelium (RPE) cytosol that has been in use to delineate choriotinal changes in posterior and panuveitis. In experimental uveitis models, before infiltration of inflammatory cells in the retina/choroid, the early phase of uveitis reveals enhanced autofluorescence from mitochondrial oxidative damage of photoreceptors (PRs) lipid-rich cell membranes.\[^{10}\] Such experimental results suggest that in humans, mild hyperautofluorescence changes observed during the early phase of posterior uveitis could be earliest pathologic process affecting PRs before inflammatory cell infiltration.

FAF imaging has greatly enhanced in clinical detection of early pathologic event of acute stage of posterior uveitis, particularly in patients presenting with MSC.\[^{11-13}\] Various patterns of autofluorescence changes observed in MSC include hypofluorescence, hyperfluorescence, and punctate hyperautofluorescence dots in the previously noted foci of hypofluorescence.\[^{11}\] All these autofluorescence changes represent various stages of choroiditis; the acute stage reveals hyperautofluorescent lesions whereas the healed lesions display hypofluorescence.\[^{12,13}\] The hypofluorescence is from degeneration of PRs with loss of RPE and chorioretinal adhesions, reflecting irreversible damage of outer retina and RPE. In the acute stage, the lesions reveal an advancing edge of hypofluorescence which is replaced by hyperautofluorescence within a week. As the inflammation begins to subside, these hyperautofluorescence foci show breakdown resulting in multiple punctuate hyperautofluorescence dots surrounded by hypofluorescence. These punctate hyperautofluorescence patterns include hypoautofluorescence, hyperautofluorescence, and multiple punctuate hyperautofluorescence dots surrounded by hypofluorescence.
changes are also seen during chronic stage of the choroiditis lasting over 3 months. Thus, the patients presenting with tuberculous MSC usually display the choroidal lesions of various stages in the form of hypo, hyper, and punctate hyper-autofluorescence changes [Fig. 3a]. These changes are crucial not only for identification of active lesions but also for documenting response to treatment and planning future course of therapy. A unique application of autofluorescence in intraocular TB is the detection of paradoxical worsening of inflammation after initiation of anti-TB therapy. It is diagnosed by advancing areas of hyperautofluorescence beyond those noted at baseline [Fig. 3b and c]. Typically, escalation of corticosteroid therapy results in a gradual transition to hypoaurofluorescence as noted during resolution of lesions.

**Optical Coherence Tomography and Multimodal Imaging**

Multimodal imaging by the spectralis HRA + optical coherence tomography (OCT) (Heidelberg Engineering, Heidelberg, Germany) allows simultaneous recordings of topographic and tomographic images of the retina and choroid, using scanning laser ophthalmoscopy and OCT.[14,15] It includes confocal angiograms, FAF images, and other imaging modes with the high-resolution spectral domain (SD)-OCT scans. Simultaneous imaging with FAF and OCT has emerged as sensitive and reliable imaging tool in the evaluation of chorioretinal disorders.[12,14‑16] In tubercular MSC, acute lesions (diffusely hyperautofluorescent) correspond to hyperreflective areas on SD-OCT involving the RPE, PR outer segment tips, inner segment–outer segment junction, external limiting membrane (ELM), and outer nuclear layer with a minimal distortion of inner retinal layers. During healing, there is atrophy of the outer retinal layers in the areas corresponding to increasing hypoautofluorescence [Fig. 4a-d].[15] In a few eyes, following an initial insult of acute MSC, the ELM, and PR layers exhibit anatomical restoration once the lesions heal. The underlying choroid, in these eyes, regains normal thickness and does not show atrophy, indicating that the choroidal atrophy may predispose to RPE-PR atrophy [Fig. 5a-f], also see next section. Investigating *in vivo* choroidal changes in tubercular uveitis by SD-OCT and enhanced depth imaging (EDI)-OCT imaging may provide a useful insight into the debate on the primary site of inflammation (whether RPE or choroid) in MSC. It appears that primary stromal choroiditis is unlikely in tubercular MSC as the compartments are not respected (as is evident by diffuse choroidal swelling despite choroiditis lesions being localized), and the outer retinal layers show significant involvement along with disorganization of inner retinal layers.

**Enhanced Depth Imaging**

EDI-OCT is a noninvasive imaging technique that provides *in vivo* quasihistological images of the eye, allowing good visualization of deeper structures, such as the choroid and the inner sclera, in healthy participants and in many eye diseases including posterior uveitis.[17]

When the posterior segment is involved in intraocular TB, the choroid plays an important role in the disease development, either being the primary site of infection (and therefore granuloma formation) or being contiguous to other sites of infection (RPE, retinal vasculature). EDI-OCT could, therefore, be a useful tool for assessing disease activity in the choroid as well as for anatomical characterization of TB-related lesions.

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**Figure 3:** (a) Fundus autofluorescence image of right eye showing bright hyperautofluorescence (arrowhead) in areas of active lesions, punctate hyperautofluorescence (arrow) in healing lesions, and dark hypoaurofluorescence (notched arrow) in healed lesions, (b) fundus autofluorescence image of right eye showing multifocal serpiginoid choroiditis at presentation, and (c) expansion of active margins of lesions (paradoxical worsening) after initiation of anti-tuberculosis therapy

**Figure 4:** Multimodal imaging - Simultaneous fundus autofluorescence and enhanced depth imaging-optical coherence tomography imaging through active lesion showing diffuse choroidal thickening at presentation (a), decreasing choroidal thickness at 17 days (b), and 28 days (c) after starting therapy, and localized choroidal atrophy at 12 weeks in the region of hypoaurofluorescence lesion (delineated by red arrows) as compared to uninvolved area (delineated by green arrows) (d)
However, this technique has recently been reported to be more sensitive than ICGA in eyes with TB retinal vasculitis. In addition, OCT-A can also be useful in detecting other vascular abnormalities such as nonvascular tufts and tangled vessels, as well as choroidal neovascular membranes. However, this technique has important limitations. It cannot delineate disruption of blood-retinal barriers as shown by dye leakage on FA. Furthermore, it can only identify vascular networks with rapid blood flow and has low sensitivity for sluggish circulations such as choroidal neovascularization.

Anterior Segment Imaging

Although isolated involvement of the anterior segment is relatively uncommon in intraocular TB, anterior segment imaging is occasionally required to make an accurate diagnosis and decide a plan of management. Slit-lamp photography is useful for documentation of scleritis, keratitis, or anterior segment granuloma. High-frequency ultrasound biomicroscopy is required in patients with intermediate uveitis and complicated cataracts to distinguish between ciliary body membranes or atrophy of ciliary processes as the cause for hypotony. The findings would influence the surgical management plans for such patients.

Chest and Other Systemic Imaging

Pathologies of both primary and postprimary TB may be well detected by chest radiography. Radiologic features representing primary disease include lymphadenopathy, parenchymal disease, pleural effusion, and atelectasis, both segmental

Optical Coherence Tomography Angiography

OCT angiography (OCT-A) is a recently introduced noninvasive imaging tool for mapping different vascular networks in the retina and choroid. OCT-A is most useful in MSC, in which en face images of the choriocapillaris mirror the changes seen on FAF. Active disease shows areas of flow void (representing choriocapillaris hypoperfusion, as seen on ICGA) corresponding to areas of hyperautofluorescence [Fig. 7a and b]. As the lesions heal, the flow void areas become more and more irregular, till an intertwined meshwork of vessels is left at the site of flow voids [Fig. 7c and d]. OCT-A can also be useful in demonstrating retinal capillary nonperfusion in eyes with TB retinal vasculitis. In addition, OCT-A can also help in detection of other vascular abnormalities such as nonvascular tufts and tangled vessels, as well as choroidal neovascular membranes. However, this technique has important limitations. It cannot delineate disruption of blood-retinal barriers as shown by dye leakage on FA. Furthermore, it can only identify vascular networks with rapid blood flow and has low sensitivity for sluggish circulations such as choroidal neovascularization.

It has recently been shown that EDI-OCT-based assessment of choroidal thickness could help in the management of patients affected by TB-related uveitis, with choroidal thickness being significantly increased during the active phases of the disease [Fig. 6a and b]. In the same study, a structural analysis of the choroidal layers has shown that EDI-OCT could also be useful in differentiating sarcoid from TB-related uveitis since the first one is often characterized by an enlarged Sattler’s layer, not detectable in TB. In another report describing TB-MSC, EDI-OCT showed choroidal infiltration with elevation of the RPE corresponding to active areas of the disease.

Tubercular focal lesions in the choroid are mainly represented by granulomas. These lesions are clearly visible on EDI-OCT as hypo- or isoreflective areas of increased homogeneity within the choroid, caused by the loss of the typical vascular pattern [Fig. 6c and d]. Granulomatous lesions usually cause an increase transmission effect on the OCT signal, a useful sign to differentiate granulomas from large choroidal vessels that could present with similar characteristics on EDI-OCT. The EDI-OCT features of the granulomas could also help in the differential diagnosis of granulomatous uveitis since TB-related lesions are usually lobulated in shape and less homogeneous in internal pattern as compared to sarcoid and Vogt–Koyanagi–Harada syndrome. Finally, EDI-OCT has recently been reported to be more sensitive than ICGA in early decrease in granuloma size in response to treatment, thus becoming a useful tool in follow-up of these lesions.

Figure 5: Fundus photograph of left eye of a 36-year-old male with tubercular multifocal serpiginoid choroiditis showing active lesions (a), with corresponding fundus autofluorescence-enhanced depth imaging-optical coherence tomography scans showing diffuse choroidal thickening and disruption of outer retinal layers (b). At 3 weeks, the lesions started to heal (c), with decreasing choroidal thickness (d). At 14 weeks, the lesions are healed (e), and the choroid shows normal thickness all over, with anatomical restoration of external limiting membrane and near normal photoreceptor layer (f).

Figure 6: (a) Fundus autofluorescence of left eye multifocal serpiginoid choroiditis, and (b) corresponding (inset) optical coherence tomography-angiogram of choriocapillaris layer, showing flow void areas (arrowheads) representing active inflammation, which show varying degrees of irregularity (arrow), during resolution. (c) Fundus autofluorescence of healed multifocal serpiginoid choroiditis showing uniform hypautofluorescence, and (d) corresponding (inset) optical coherence tomography-angiogram of choriocapillaris showing an intertwined meshwork of vessels (notched arrow) in the healed regions.
Commonly used chest imaging techniques used for diagnosis of lung TB-related lesions include X-rays and computerized tomography (CT). Lymphadenopathy is most commonly seen in children, unilateral in 70% cases, and located in the hilum or the paratracheal region [Fig. 8a]. The lesion resolves slowly over 6 months leaving nodal calcification. It may be associated with parenchymal consolidation and atelectasis.

The earliest radiologic finding in postprimary TB is the development of patchy, ill-defined segmental consolidation with a predilection for the apical or posterior segment of the upper lobes or the superior segment of the lower lobes [Fig. 8b]. Tuberculous cavitation most commonly occurs within areas of consolidation and indicates a high likelihood of activity. Cavities are often multiple and demonstrate thick, irregular walls. Presentation commonly consists of two or more involved segments, typically bilateral upper lobe disease. Chest X-ray (CXR) provides good sensitivity but poor specificity, with high negative predictive value for the presence of active TB. Diagnosis of active disease can be reliable on the basis of temporal changes. Chest CT scan with contrast enhancement helps to distinguish active from inactive disease and is considered complementary to CXR in screening to detect the past and latent TB. A recent study from South India has shown that high-resolution CT scan of thorax may be more useful than CXR in revealing active or healed pulmonary signs in patients with granulomatous uveitis.

Positron emission tomography CT scan (PET-CT) is occasionally used for the diagnosis of TB. It is most commonly used to differentiate benign from malignant focal pulmonary lesion. Elevated uptake is typically found in cancer cells, yet increased uptake is not cancer specific and may be found in pulmonary TB as well. Double phase acquisition 18-fluorodeoxyglucose PET-CT may help identify active granuloma in lungs, lymph nodes, or elsewhere in the body [Fig. 8c].

Besides chest imaging, CT, PET-CT, and magnetic resonance imaging (MRI) scans have applications in imaging of other organ systems that are involved in TB. MRI is preferred for TB of the spine, whereas CT imaging is sufficient for abdominal and hepatobiliary TB. Since metabolic changes precede morphological ones, PET-CT scans are likely to find greater applications in extrapulmonary TB in the future.

Ophthalmologists, pulmonologists, and infectious disease experts tend to seek at least one remote sign of TB to make the diagnosis. Does chest imaging help us make the diagnosis of IOTB? It does have an adjunct value. However,
since extrapolummary spread occurs very early in primary TB and primary TB may leave no radiologic sign, the lack of radiographic sings of TB is not surprising and is not a prerequisite to make the diagnosis of intraocular TB.

Can Imaging Tools Help in Understanding Pathogenesis of Intraocular Tuberculosis?

The pathogenesis of intraocular TB is poorly understood, primarily due to a lack of clinical material for histological evaluation of the disease process. Currently, available imaging tools can provide an opportunity to overcome this limitation and gain insights into pathogenesis of intraocular TB. As described above, imaging can be either based on intrinsic properties of ocular tissues, as in fundus photography, autofluorescence or OCT, or on physical properties of extrinsically administered compounds as in FA or ICGA. Evaluation of these intrinsic or extrinsic characteristics can help determine both structural and functional changes in the disease process. For example, SD-OCT and EDI-OCT can create quasihistological sections of diseased ocular tissue, based on changes in optical properties of incident light. They can help distinguish primary choroidal from outer retinal disease. FA, on the other hand, reveals functional alterations in the RPE during inflammation, through accumulations of lipofuscin. FA can reveal changes in the inner and outer blood-retinal barriers besides delineating areas of capillary perfusion. OCT-A, combined with ICGA, gives us a unique insight into the local hypoxia in the choriocapillaris in MSC, previously demonstrated in guinea pig model of intraocular TB,[13] and its recovery as the lesions heal. Taken together, serial documentation of various imaging modalities can help recreate a pathogenesis model of intraocular TB that can guide decision-making in diagnosis and management.

Conclusions

Intraocular TB can involve various tissues in the eye that can be targeted by one or more imaging modalities. These can be used individually or in combination to identify disease pattern, activity, response to treatment, sequelae, and complications and also to understand the pathogenesis of intraocular TB.

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Conflicts of interest

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