

Yellow Sub-Retinal Pigment Epithelium (YSRPE) Deposits: A Novel Sign in Ocular Tuberculosis

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SUMMARY STATEMENT

In this series of 3 challenging cases with tubercular panuveitis, deep yellow chorioretinal lesions were observed that involved peripheral and mid-peripheral retina. These lesions appear as irregular retinal pigment epithelium elevations and are different morphologically from similar lesions such as Dalen Fuchs nodules and deposits in vitreoretinal lymphoma.

Abstract

Purpose: To describe a novel clinical and imaging finding in patients with tubercular posterior uveitis.

Methods: A retrospective review of 3 cases presented at a tertiary referral eye centre in North India between June 2016 to March 2019 was performed. All the patients had received an initial diagnosis of non-infective etiologies (sympathetic ophthalmia, necrotizing scleritis and lymphoma). Fundus photography, fluorescein angiography (FA), fundus autofluorescence (FAF), and enhanced-depth imaging optical coherence tomography (EDI-OCT) were reviewed.

Results: Three patients (all Asian Indian females: aged 18, 49 and 52 years) diagnosed with panuveitis were investigated for various etiologies based on the initial clinical suspicion. During the course of therapy, all the patients developed peripheral yellow sub-retinal pigment epithelium (RPE) deposits (YSRPE) which appeared hypo-autofluorescent on FAF, and initially hypofluorescent with late hyperfluorescence on FA. The patients were subjected to detailed systemic evaluation and laboratory tests. All the patients showed acid fast bacilli on invasive tissue biopsies. After initiation of anti-tubercular therapy, the lesions resolved in all eyes.

Conclusions: YSRPE deposits represent a novel and important diagnostic sign of tubercular posterior uveitis.

Keywords: Tuberculosis; OTB; subretinal deposits; uveitis; choroiditis; optical coherence tomography

Introduction

The management of ocular tuberculosis (OTB) is often challenging due to difficulties in the diagnosis caused by protean manifestations of the disease. Because of the difficulty in isolating *Mycobacterium tuberculosis* from ocular tissues, and availability of only indirect evidences to support the diagnosis, the role of clinical and/or imaging biomarkers is extremely important.¹⁻³

With the advances in fundus imaging and optical coherence tomography (OCT), the assessment of posterior segment pathology in OTB has become easier. The involvement of the outer retina, retinal pigment epithelium (RPE), and choroid can be evaluated in detail.^{3,4} We have described three difficult cases of posterior uveitis where there was a diagnostic dilemma, and a novel feature on clinical examination and OCT led to the diagnosis of OTB.

Material and Methods

This study was conducted at the Advanced Eye Center, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India. In this study, three cases of posterior uveitis with exudative retinal detachment, which were initially treated with systemic corticosteroids (and immunosuppressive therapy in 2 patients) and later diagnosed with OTB are included. All the patients in the study were evaluated extensively using both ultra-wide field (UWF) and conventional fundus imaging, fundus autofluorescence (FAF), fluorescein angiography (FA), and swept-source OCT (DRI Triton, Topcon®, Tokyo, Japan). In all the cases, diagnosis of OTB was established conclusively from tissue biopsies (either enucleation specimen or invasive biopsies from other remote sites).

Results

Three patients (Asian Indian females) (mean age: 44.33 years; range: 18-66 years) were included. During the initial course of therapy, all the patients developed yellow sub-RPE (YSPRE) deposits that were mostly localized to the peripheral retina. These deposits were differentiated from subretinal deposits seen in other entities (such as Dalen-Fuchs nodules and lymphoma) based on clinical examination and multimodal imaging. Once the diagnosis of OTB was established, four-drug anti-tubercular therapy (ATT) (isoniazid, rifampin, ethambutol and pyrazinamide) was initiated with resolution of uveitis in all patients.

Patient 1: A 52-year-old Asian Indian female presented 2 years after blunt trauma to the left eye (OS) with sudden progressive decreased vision in right eye (OD) for the past one month. BCVA in OD was 20/20 and no perception of light in OS. Examination of OD revealed 1+ cells and flare, and granulomatous keratic precipitates (KPs). Posterior segment examination showed presence of vitritis, but no chorioretinal lesions were visible. OCT showed serous macular detachment. A working diagnosis of sympathetic ophthalmia (SO) was made and baseline investigations including chest radiography were performed, which were within normal limits. The patient was initiated on intravenous methylprednisolone (1 gm/day for three days) followed by oral corticosteroids (1 mg/kg prednisone). The patient demonstrated interval improvement at one week with decrease in peripapillary fluid and vitritis. Therapy with oral azathioprine (2 mg/kg) was considered. However, at 12 weeks, fundus examination revealed multiple yellow outer retinal lesions in the peripheral retina with mild vitritis (Figure 1). These lesions appeared hypofluorescent in the early and hyperfluorescent in the late phase of FA. On FAF, the lesions were hypo-autofluorescent. Peripheral OCT scans passing through these lesions showed that these yellow sub-RPE (YSRPE) deposits differed from Dalen-Fuch's nodules seen in SO (Table 1) (Figure 1). Thus, SO was considered unlikely, and additional investigations were performed. Her tuberculin skin test (18×18 mm) and QuantiFERON TB Gold® were positive. Contrast-enhanced computerized tomography (CECT) chest did not reveal any abnormalities. Finally, a diagnostic enucleation of the non-seeing eye (OS) was performed. Histopathology of OS revealed multiple choroidal granulomas with caseous necrosis. Polymerase chain reaction (PCR) for TB was positive from the vitreous fluid

sample and Ziehl-Neelsen staining of the specimen showed numerous AFB. The patient was started on ATT and within four weeks, there was decrease in the vitritis and improvement in BCVA to 20/60. At 1 year follow-up, her BCVA is 20/20 and OD is quiescent.

Patient 2: A 49-year old Asian Indian female presented with painful decrease in vision in OS for the past one month. There was no history of trauma or past ocular surgery. BCVA in OS was 20/60. Examination revealed a large area of necrotizing scleritis with scleral thinning and congestion in the temporal aspect of OS (Figure 2). The scleral swabs were negative for bacteria and fungi. CECT chest revealed a large cavity in the right middle lobe, with thickened and irregular cavity wall. Possibility of granulomatosis with polyangiitis (GPA) was kept, and the patient was started on oral corticosteroids (prednisolone 60 mg/day). Enzyme immunoassay for antineutrophil cytoplasmic antibody (ANCA against PR-3) was strongly positive in serum. In consultation with the rheumatology team, the patient received a single dose of intravenous cyclophosphamide 15 mg/kg. One week later, the patient noted increased blurriness and deterioration of vision in OS. Fundus examination revealed vitritis, exudative retinal detachment along with YSRPE deposits. Peripheral OCT scans passing through these deposits were similar to patient #1 (Figure 2). Tuberculin skin test was positive (25×30 mm). Since there was a diagnostic dilemma between GPA and OTB, CT-guided fine needle aspiration was performed from the cavity wall which revealed necrotizing granulomatous inflammation and *M. tuberculosis* was detected in the aspirate by polymerase chain reaction. The patient was started on ATT and the exudative detachment resolved within 8 weeks of therapy. At 3-month follow-up, scleral inflammation reduced, and BCVA improved to 20/50.

Patient 3: An 18-year-old Asian Indian girl presented with a temporal scotoma in OD. Examination revealed BCVA of 20/20 in both the eyes. Anterior segment of OD showed 0.5+ cells, and faint flare. Fundus examination revealed a large, yellow, superonasal elevated lesion with surrounding mild exudative fluid. Ultrasonography revealed retinochoroidal elevation with heterogeneous echogenicity. FA revealed intense hyperfluorescence in the late phase with mild pooling of the dye. Physical examination revealed normal vitals, however, there was significant cervical lymphadenopathy. Tuberculin skin test was 8×8 mm, and other tests for infectious etiologies were negative. Lymphoma was considered a strong possibility, and magnetic resonance imaging (MRI) of the brain and whole-body positron emission tomography (PET) scan was performed, which were normal. The patient developed YSRPE deposits in the peripheral retina similar to the previous cases. OCT through these deposits did not show features of intraocular lymphoma (Table 1). She underwent cervical lymph node biopsy, which revealed acid fast bacilli in a background of caseous necrosis. She was started on ATT and corticosteroids, and showed near complete healing at 3 months follow-up.

Discussion

M. tuberculosis can result in several pathological alterations in the retina and the choroid. Commonly, posterior uveitis in OTB presents with either choroiditis (inner

choroid/choriocapillaris/RPE inflammation) or choroidal granulomas (choroidal stromal inflammation).^{5,6}

In our patients, we observed a distinct and novel sign – YSRPE deposits, involving the peripheral retina. These deposits appeared different in distribution, size, morphology, location and on imaging compared to other yellow deposits such as hard exudates, Dalen Fuchs nodules and subretinal deposits of lymphoma (Table 1) (Figure 3). The atypical appearance of these lesions triggered further detailed evaluation in all the cases. These YSRPE deposits appeared hypo-autofluorescent on FAF imaging. These deposits could represent infectious infiltrate due to mycobacterial involvement, or accumulation of inflammatory cells. It is unlikely that these deposits could be lipofuscin because they should appear hyper-autofluorescent. Direct mycobacterial infiltration may also be another possibility since the YSRPE deposits appeared after initiation of steroids/immunosuppressive therapies in two cases. However, there are no previous histopathological studies in the literature that have isolated acid fast bacilli from the sub-RPE layer. The second possibility is that YSRPE deposits could represent accumulation of inflammatory material leading to irregular knob-like RPE elevations (seen on the OCT scans), accompanied by disruption of the RPE over central large deposits. A recent histopathological study by Kawali et al⁷ in a patient with tubercular serpiginous-like choroiditis also showed granulomatous inflammation with necrosis involving the inner choroid with disruption of the RPE and photoreceptors. Without a direct histopathological correlation, the true nature of these deposits is unknown. After appropriate therapy (ATT and corticosteroids), these inflammatory deposits resolved, with residual RPE changes.

Thus, to conclude, YSRPE deposits may represent an important diagnostic sign of OTB. When such deposits are observed, emphasis must be laid on establishing an accurate microbiological and histopathological diagnosis so that appropriate therapy can be initiated. Further studies may aid in characterizing the true nature of these deposits.

Figure Legends

Figure 1: Fundus photographs of the patient (case #1) (A-E) shows presence of mild media haze due to vitritis. Photographs of the retinal periphery shows presence of multiple yellow sub-retinal pigment epithelial (RPE) lesions in all the quadrants. Some of the yellow deposits have coalesced to form larger aggregates. Fundus autofluorescence (FAF) imaging (F) demonstrates that the lesions are hypo-autofluorescent, with sharp, well-defined hyper-autofluorescent borders. Peripheral optical coherence tomography (OCT) scans (G-I) at different locations (defined by the *en face* image in the inset) shows that the lesions are characterized by irregular knobbly RPE elevations with an intact underlying Bruch's membrane, RPE loss at the apices/central part of the elevation, and focal choroidal thickening (black arrowheads).

Figure 2: Anterior segment photograph of a patient (case #2) shows presence of a large temporal area of necrotizing scleritis with deep scleral congestion, dilated episcleral and conjunctival vessels, and visible underlying uveal tissue (A). Fundus photograph showing temporal retinal periphery shows an area of exudative retinal detachment with yellow sub-retinal pigment epithelial (RPE) lesions of variable sizes and shapes. There is media haze due to overlying vitritis (B). Fluorescein angiography of the temporal periphery shows early iso- to hypofluorescence and late staining of the lesions, and pooling of dye in the area of exudative detachment (C and D). Optical coherence tomography (OCT) scan through the temporal periphery (E) shows multiple nodular RPE elevations with an intact underlying Bruch's membrane and relatively preserved outer retina (similar to case #1).

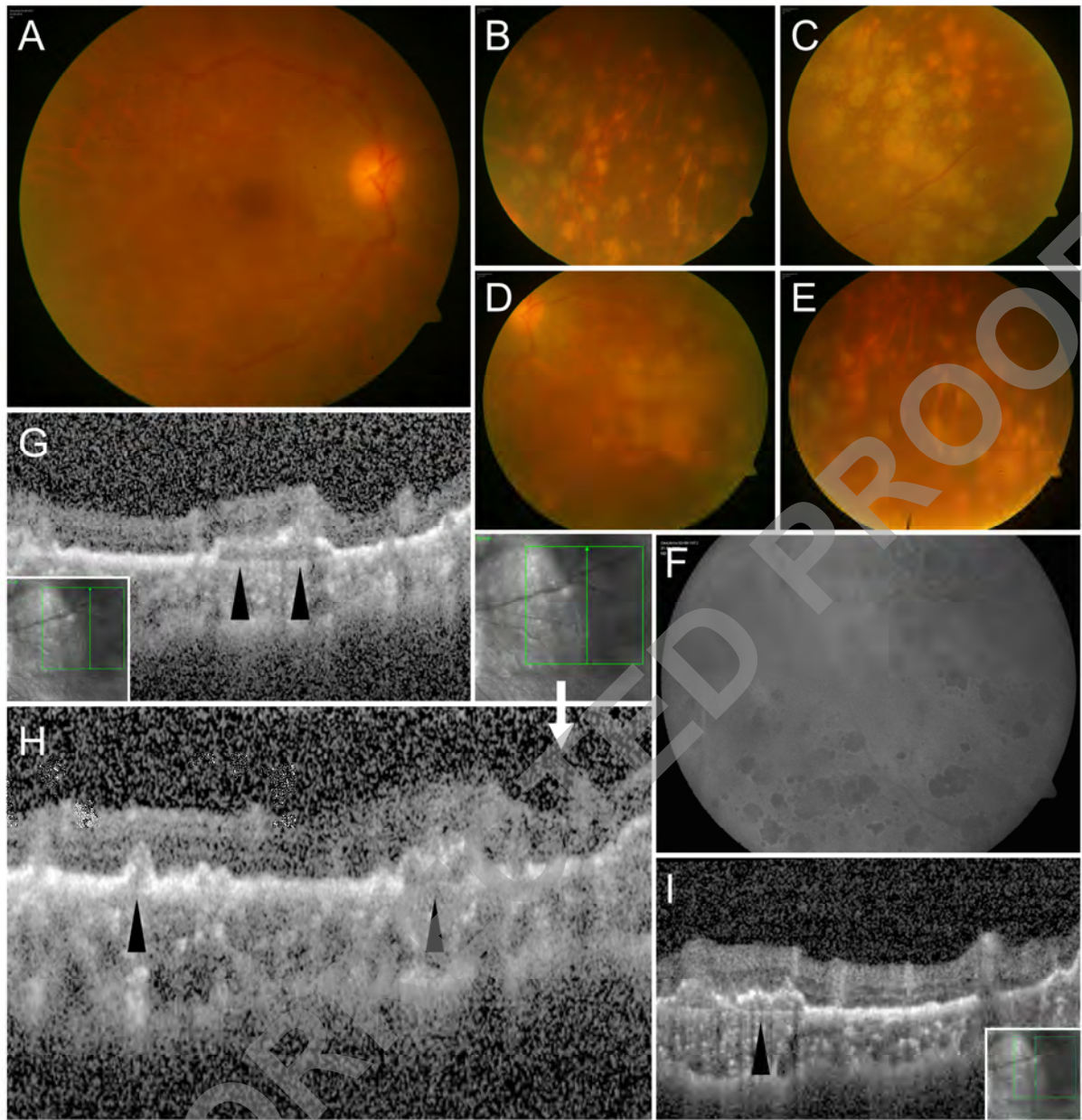
Figure 3: Figure 3 shows a comparison of spectral-domain optical coherence tomography (SD-OCT) findings in yellow sub-retinal pigment epithelial (YSRPE) deposits in tuberculosis (A), Dalen Fuchs nodule in sympathetic ophthalmia (B), intraocular lymphoma (C and D) and hard exudates in a patient with resolving exudative retinal detachment (E). The YSRPE deposits are characterized by irregular knob-like RPE elevations (black arrows), with central RPE disruption (white arrowhead) over large deposits. This morphology may be responsible for central hypo-autofluorescence with surrounding hyper-autofluorescence on fundus autofluorescence imaging. The Bruch's membrane appears intact (white arrow). There are no retinal infiltrates (A). On the other hand, Dalen Fuchs nodules show RPE disruption (white arrowhead) and Bruch's membrane loss (white arrow). There is outer retinal hyper-reflectivity (yellow asterisk) (B). Panel (C) shows two OCT scans of a patient with intraocular lymphoma showing irregular RPE elevation with sub-RPE deposits and outer retinal sheath-like diffuse hyper-reflectivity suggestive of malignant infiltrates. The right image shows large RPE humps with massive sub-RPE deposits. Hard exudates appear as outer retinal hyper-reflective foci with back-shadowing with normal RPE and Bruch's membrane (D).

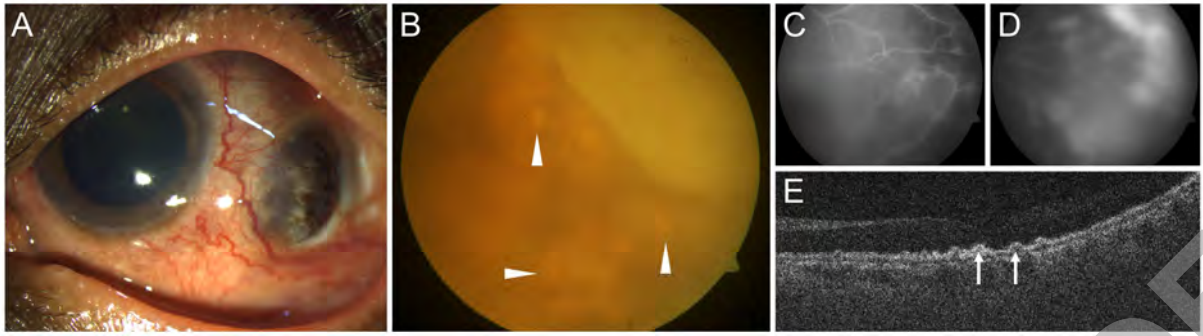
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Table 1: Differentiating features between yellow sub-retinal pigment epithelium (YSRPE) deposits in ocular tuberculosis with other entities				
Feature	YSRPE Deposits	Dalen Fuchs Nodules	Deposits in VRL	Hard Exudates
Associated Condition	Ocular tuberculosis	Sympathetic Ophthalmia	Vitreoretinal lymphoma	Exudative retinal detachment
Color	Dull yellow	Creamy-white/yellow	Yellow-white	Bright yellow
Size	Small (1/4th DD) to large coalesced lesions	Less than 1 DD	Variable; typically large irregular clumps	Variable (small pin-head size to large accumulations)
Morphology	Irregular, round-to-oval, nodular aggregates	Small subretinal, nodular, hemispherical aggregates ⁷	Typical: subretinal aggregates with overlying vitritis and vasculitis ^{8,9} Atypical: peripheral lesions mimicking acute retinal necrosis ^{10,11}	Bright, discreet, irregular spots or collection of lipid
Distribution	Retinal periphery and mid-equator	Posterior pole or mid-equator ¹²	Posterior pole or periphery	Posterior pole or peripapillary region
Associated features	Active inflammation; choroidal thickening	Sunset glow fundus	Masquerade uveitis syndrome	Subretinal fluid; subretinal migration; fibrosis
FAF imaging	Hypo-autofluorescence with hyper-autofluorescent borders	Hypo-fluorescent spots ¹³	Granular hyper-/hypo-autofluorescence; blocked FAF in subretinal lesions; nodular hyper-autofluorescent spots ^{14,15}	Blocked FAF signal on imaging
Fluorescein angiography	Early hypofluorescence with late staining	Early hypofluorescence with late staining (variable; based on the evolution of the nodule) ¹⁶⁻¹⁸	Leopard spot pattern; vascular leakage; hyperfluorescence due to subretinal lesions, and hypofluorescence in sub-RPE lesions ^{15,19,20}	Blocked fluorescence due to signal attenuation
OCT	Irregular, multiple,	Hyper-reflective round	Hyper-reflective	Hyper-reflective

features	knob-like RPE elevations with intact underlying Bruch's membrane, central RPE disruption; no outer retinal hyper-reflectivity	nodular elevation with disruption of RPE and Bruch's membrane, outer retinal disruption (upto inner nuclear layer), and photoreceptor loss. ^{13,17,21,22}	inner retinal or subretinal infiltrates (usually multiple); RPE undulation with large sub-RPE deposits; PEDs; inner retinal vertical hyper-reflective lesions ²³⁻²⁵	deposits involving various retinal layers (esp outer nuclear layer with back-shadowing, relative sparing of the retinal layers; subretinal fibrosis in the late stage of organization. ²⁶⁻²⁸
DD: disc diameter; FAF: fundus autofluorescence; OCT: optical coherence tomography; PED: pigment epithelial detachment; RPE: retinal pigment epithelium; VRL: vitreoretinal lymphoma; YSRPE: yellow sub-retinal pigment epithelium				





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