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REVIEW ARTICLE

Infectious uveitis: an Asian perspective

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Abstract
Several intraocular infections can present with protean manifestations posing major diagnostic and management challenges. Infections such as tuberculosis, dengue and chikungunya fever have continued to remain major endemic diseases that are associated with uveitis in the Asia Pacific region. These entities often require a high index of clinical suspicion and laboratory analysis including assays of ocular fluids and/or tissues for confirmation of the diagnosis. Infectious uveitis caused by tuberculosis, dengue and chikungunya can present with characteristic clinical features and imaging findings on ancillary investigations; that may provide clue to the early diagnosis. Use of modern imaging modalities such as enhanced-depth imaging optical coherence tomography, optical coherence tomography angiography and ultra-wide field fundus photography greatly aid in the evaluation of these conditions. In the current review, we have discussed the epidemiology, clinical phenotypes, imaging characteristics, diagnosis and management of uveitis caused by tuberculosis, dengue and chikungunya.

Introduction

A number of infectious agents, including a host of bacteria, viruses, fungi, and parasites lead to ocular inflammation with development of various chorioretinal manifestations. These infections are especially common in Asia Pacific countries and other developing countries of the world, unlike western countries where autoimmune uveitis is the most common form [1–3]. An early diagnosis is imperative for the initiation of specific therapy that would help in preventing the severe visual loss.

Since several decades, tuberculosis (TB) has remained endemic in Asian countries with India, with a large population size, accounting for nearly 20% of the global tuberculosis burden. TB is also common in other countries of the Pacific region (Singapore, Malaysia, Bangladesh, and Nepal, among others), and Island countries such as Fiji [4–7]. Currently, the diagnosis of TB uveitis is a conundrum because the only way to determine tubercular etiology is using a conglomerate of clinical signs, radiologic findings, and immunologic tests.

Certain viral infections such as dengue and chikungunya are highly endemic in the Asia Pacific countries. This may be attributed to the conducive weather and abundance of the arthropod vectors in this part of the world [8–11]. Due to various contributory factors such as overcrowding, lack of hygiene, excessive rainfall, and poor outreach measures, frequent outbreaks of dengue and chikungunya fevers are common especially in the monsoons. The most common clinical presentation of these viral illnesses is development of high-grade fevers, rash, arthralgia, low platelets, and muscle/bone pain. However, both dengue and chikungunya may result in severe sight-threatening ocular inflammation that may lead to permanent visual disability.

In this index review, infectious uveitis (namely TB, dengue, and chikungunya) that continue to plague Asian countries have been described. A brief update on the epidemiological patterns of these conditions, along with their clinical features, imaging characteristics, and management has been provided. Illustrative case examples have been provided to give the reader insights into the challenges encountered while managing these patients.

Intraocular tuberculosis

TB is a leading infectious cause of morbidity and mortality and Asian countries such as India and China contribute significantly toward the global disease burden. TB has been

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declared as a global emergency by the World Health Organization (WHO). Nearly one-third of the world's population is infected by *Mycobacterium tuberculosis* [5–7]. Intraocular TB (IOTB) represents an extrapulmonary form of the disease. Therefore, though rare, IOTB is an important cause of uveitis in both developed and developing countries.

An update on epidemiology of tuberculosis in Asia

TB is highly prevalent in Asian countries. Estimates by the WHO suggest that 4.9 million prevalent cases (one-third of the world's burden of TB) are found in the South-East Asia Region. High number of cases, including extensively drug-resistant TB have been reported from Bangladesh, India, Indonesia, Myanmar, and Thailand [12]. The WHO statistics for India for 2016 give an estimated incidence of 2.79 million cases of TB. India also has more than a million "missing" cases every year that are not notified and most remain either undiagnosed or unaccountably and inadequately diagnosed and treated in the private sector [13].

Based on the diagnostic criteria used, the incidence of IOTB in India has varied from 0.6% of all uveitis patients in South India (1995) [14] to 10.1% in North India (2004) [15]. In 2017, a report from a major tertiary care center in North India reported that 23% cases of infectious uveitis were attributed to TB [16]. This finding was supported by a study from South India in the same year [17]. Similarly, in Sri Lanka, IOTB was responsible for significant number of patients with posterior uveitis (11%), intermediate uveitis (8%), and panuveitis (11%) [18]. In Philippines (2017), IOTB accounts for more than 25% cases of infectious uveitis, more common than toxoplasmosis. Taiwan reported TB as the most common cause of infectious uveitis (9%) [19]. A study from Singapore also reported that TB was the most common cause of panuveitis, especially among Malays and Indians [20].

TB also forms an important cause of infectious uveitis in children. In a study on pediatric uveitis from North India, TB was identified in 15% cases of infectious uveitis [21]. Out of 20 children diagnosed with intermediate uveitis from South India, 9 were diagnosed with TB in 2017 [22].

Clinical presentation of intraocular tuberculosis

The choroid is the most commonly affected structure in IOTB. Posterior uveitis is the most common form of involvement in IOTB [4, 23, 24]. It is well known that IOTB can have protean clinical manifestations leading to a diagnostic challenge. It can have varied presentations such as granulomatous uveitis and may mimic several inflammatory and non-inflammatory conditions such as tumors, macular degeneration, as well as non-infectious autoimmune uveitic entities [13]. Moderate to severe visual impairment can occur in 42% patients with IOTB, especially in cases of posterior and panuveitis. Therefore, it is relevant to understand the common clinical presentations of the disease.

Selected observations from the COTS-1: The Collaborative Ocular Tuberculosis Study-1 (COTS-1) is a recently completed multicenter retrospective collaborative study between 30 uveitis centers across the world with participation of more than 40 uveitis experts around the world. COTS-1 was a big data analysis that studied the current practice of IOTB worldwide. The study consisted of 962 patients most of whom were of Asian ethnicity (74.4%) [11]. The broad aims of the study were as follows: to determine the global epidemiological profile of IOTB; how do experts diagnose and manage IOTB; what are the treatment outcomes of IOTB.

A total of 945 patients (1485 eyes) diagnosed with IOTB from 2004 to 2014 were included in this study. The COTS-1 showed that individuals with Asian ethnicity (both native and immigrants) are at a high risk of developing features of IOTB. Based on the anatomical location of uveitis, COTS-1 report showed that TB serpiginous-like choroiditis (which represents one of the most characteristic manifestation of the disease) was the most prevalent phenotype in the Asia Pacific region, whereas it was much less prevalent in the West [25]. The common phenotypic variants reported with IOTB included SLC (46.1%), choroidal tuberculomas (13.5%), and multifocal choroiditis (9.4%) [25]. Presumed TB retinal vasculitis was seen in 251 out of 945 patients, most commonly Asians (71%) [26].

The following section summarizes the various forms of IOTB and highlights their clinical and imaging features.

Choroidal tubercles

Choroidal tubercles are the most common clinical manifestations among patients with systemic TB [23, 27]. Choroidal tubercles form as a result of hematogenous dissemination of the bacilli from pulmonary and other extrapulmonary sites. These tubercles may be unilateral or bilateral, solitary, or multiple (but usually ≤5 in number), discreet grayish-white to yellowish subretinal lesions with indistinct borders. Choroidal tubercles are usually located in the posterior pole or mid-periphery [27].

On fluorescein angiography (FA), choroidal tubercles are hypofluorescent in the dye transit and become hyperfluorescent in the late frames. Optical coherence tomography (OCT) is useful in confirming the presence of a choroidal tubercle.

Choroidal granulomas/subretinal abscess

Solitary large choroidal granuloma may present as an elevated yellowish subretinal mass lesion with exudative
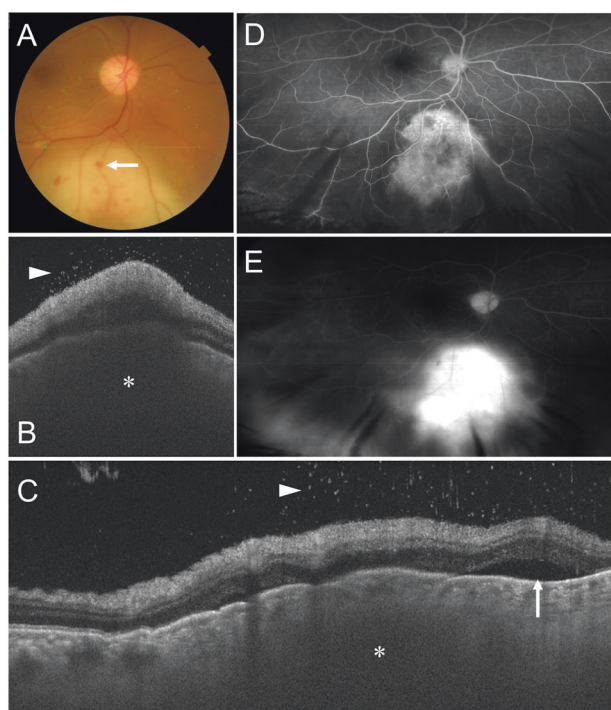
Fig. 1 Figure shows multimodal imaging of a 55-year-old female who presented with diminution of vision in the left eye. There was presence of a large subretinal lesion with overlying hemorrhages (white arrows) and exudative fluid (**a**). Swept-source optical coherence tomography (SS-OCT) (**b**) B-scan passing through the lesion showed a large choroidal granuloma (asterisk), retinal edema, as well as vitritis (arrowhead). Another OCT B-scan shows presence of retinal pigment epithelial elevation due to choroidal granuloma (asterisk), vitreous cells (arrowhead), and subretinal fluid (white arrow) (**c**). Fluorescein angiography (FA) in the early phase showed early hyperfluorescence with areas of blocked fluorescence due to overlying hemorrhages (**d**). In the late phase, FA showed intense hyperfluorescence with peripheral leakage suggestive of an inflammatory choroidal lesion (**e**). The patient was diagnosed with tubercular choroidal granuloma due to positive laboratory tests

retinal detachment and fluid (Fig. 1). A choroidal granuloma may clinically resemble non-inflammatory conditions such as central serous chorioretinopathy, choroidal metastases, melanoma of the choroid, and other non-uveitic entities such as age-related macular degeneration [4, 23, 27, 28]. The subretinal abscesses are more yellowish in color than a small choroidal granuloma and may have overlying retinal hemorrhages [29].

On FA, the lesions show early hypofluorescence and late hyperfluorescence. There may be blocked fluorescence due to the overlying hemorrhages. On ICGA, subretinal abscesses appear hypofluorescent throughout the early as well as late phase [30–32]. OCT is useful in detecting exudative retinal detachment associated with choroidal granulomas [28, 33]. Enhanced-depth imaging OCT (EDI-OCT) shows choroidal changes that correlate well with the findings on indocyanine green angiography

(ICGA). A recent study showed that all choroidal granuloma lesions generated an increased transmission of the OCT signal towards the sclera [34]. Compared with small lesions, large granulomas were more likely to be full-thickness, round-shaped, with defined margins, lower reflective than the surrounding structures, and with a homogenous internal pattern. Granulomas in patients affected by TB-related uveitis were more likely to have a lobulated shape and non-homogeneous internal pattern [34, 35].

Serpiginous-like choroiditis

Tubercular serpiginous-like choroiditis (TB SLC) is a characteristic entity which is very common among young to middle-aged adults from TB-endemic areas in the Asia Pacific region [23, 36, 37]. TB SLC was first described by Gupta et al. in 2003 in 11 eyes of 7 patients. All the patients in the series had strongly positive tuberculin skin test and lesions on chest radiography. For the first time, the authors concluded that these lesions showed a good response to anti-tubercular therapy [38]. Following this report, there were several reports from different parts of the world that associated SLC with TB [39–41]. In a recently published report, *Mycobacterium tuberculosis* DNA was isolated in an Asian Indian male with SLC lesions on vitreous biopsy. Chorioretinal biopsy sample showed granulomatous inflammation with central choroidal necrosis and disruption of the outer retina/retinal pigment epithelium [42].

TB SLC can be distinguished from autoimmune garden variety of choroiditis by its subtle differences. Unlike autoimmune serpiginous choroiditis, TB SLC occurs at a younger age, can be associated with mild vitritis and is commonly bilateral. It may have different morphological patterns:

1. *Multifocal pattern*: This pattern is characterized by the presence of multifocal discreet lesions that are yellowish-white in color, measuring a maximum of one disc diameter in size with well-defined margins and slightly raised edges [36]. These progress over a few weeks and gradually become confluent (Figs. 2 and 3) [36, 43].
2. *Placoid pattern*: The diffuse placoid pattern of TB SLC presents with a large plaque-like lesion and an active serpentine edge [44]. 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 [36, 43].
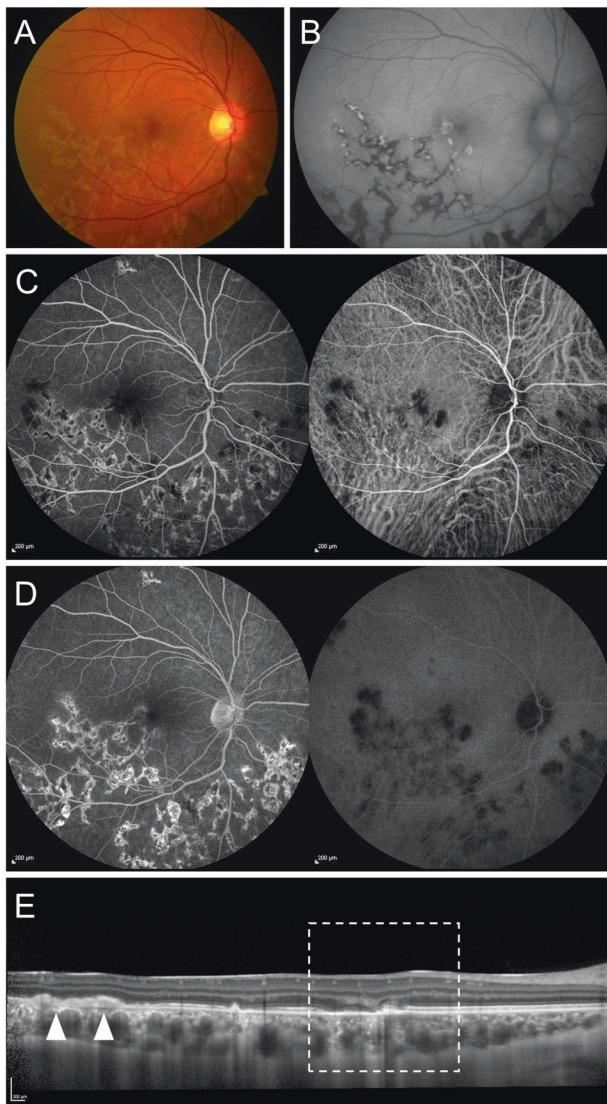
Fig. 2 Fundus photograph of a patient with tubercular serpiginous-like choroiditis (TB SLC) shows presence of yellowish serpentine choroiditis lesions in the posterior pole with fuzzy edges and ill-defined margins (**a**). The autofluorescence imaging shows mixed hyper-autofluorescent (within the lesion) and hypo-autofluorescence of the lesions suggestive of activity (**b**). Early phase of the combined fluorescein angiography (FA) and indocyanine green angiography (ICGA) shows hypofluorescence of the active lesions (**c**), and in the late phase (**d**), the lesions are hyperfluorescent on FA and continue to remain hypofluorescent in the ICGA. The optical coherence tomography (dense scan) passing through the choroiditis lesions show outer retinal disruption (white arrowheads), choriocapillaris ischemia, and disruption of the photoreceptor layer (white dashed square) (**e**)

3. *Mixed pattern*: This pattern of TB SLC presents with overlapping features in opposite eyes.

Imaging features of TB SLC

Fluorescein angiography and indocyanine green angiography: There is a uniform agreement in the literature on the appearance of active and inactive lesions of TB SLC on FA and ICGA. Multifocal TB SLC lesions are hypofluorescent in the early phase with late hyperfluorescence on FA. The advancing edge of the lesions may show early hypofluorescence with late hyperfluorescence. On the other hand, in placoid TB SLC lesions, the center of the lesion shows mixed hyperfluorescence while the advancing edge shows early hypofluorescence with late hyperfluorescence on FA. On ICGA, both the lesions remain hypofluorescence from early to late phase during the active stage [36, 43, 45, 46].

Fundus autofluorescence (FAF) features of TB SLC: FAF features of TB SLC are relevant in the understanding of the healing patterns of the disease. Based on the FAF appearance of the lesions, our group has shown that in the early active disease, the lesions appear predominantly hyper-autofluorescent on FAF (stage 1). With progressive healing, FAF shows a combination of hypo- and hyper-autofluorescence signals, where the distinct hypo-autofluorescent (inactive) rim surrounds the hyper-autofluorescent (active) center (stage 2). As the healing process continues, there is a progressive increase in the hypo-autofluorescence of the lesion with an intermixed hyper-autofluorescent stippled pattern (stage 3). A resolved fully resolved/healed lesion shows uniform hypo-autofluorescence (stage 4) [45, 47, 48].

A case report by Gupta and Biswas in 2014 [49] 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 hyper-autofluorescence. During healing, there was sharpening of hyper-autofluorescent borders, and few specks of hyper-autofluorescence were seen within the hypo-autofluorescent lesion [49]. 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 [50]. 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 [51].

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 hypoautofluorescence patches with sharp margins. After 2 weeks, the lesions show granular/speckled pattern of autofluorescence. Healed lesions appear uniform hypo-autofluorescent [46].

Ultra-wide field imaging of TB SLC: The relatively new ultra-wide field (UWF) imaging technique allows 200
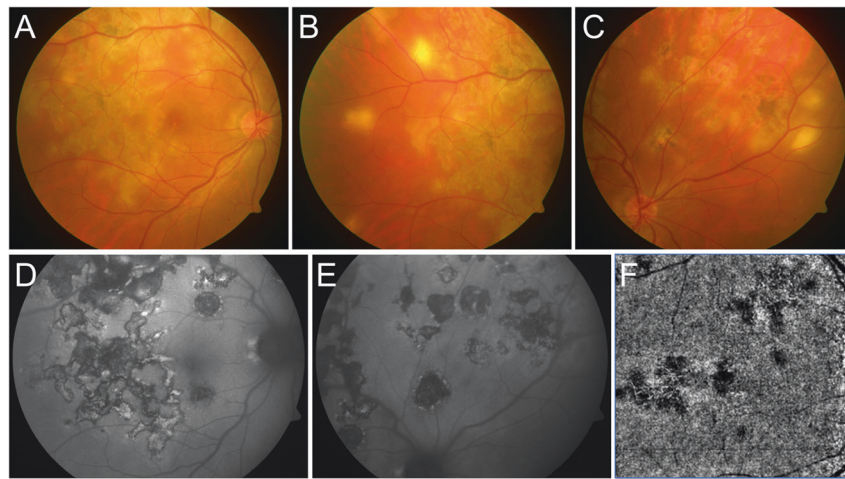
Fig. 3 Figure shows fundus imaging of a 35-year-old Asian Indian male who presented with characteristic choroidal lesions in the right eye. Fundus photographs (**a–c**) shows presence of multiple yellowish-white multifocal choroiditis lesions with fuzzy appearance, ill-defined margins and early pigmentary changes suggestive of active serpiginous-like choroiditis. The patient had a necrotic tuberculin skin test and few subcentimetric lymph nodes in his chest. Fundus autofluorescence imaging (**d, e**) shows hyper-autofluorescence within the lesions along with hypo-autofluorescence of the superior lesions. Optical coherence tomography angiography en face scan passing through the choriocapillaris slab (**f**) shows presence of dark flow deficit areas suggestive of choriocapillaris hypoperfusion, which is seen in active tubercular choroiditis

degrees of the retina to be captured in a single image thereby allowing simultaneous capture of all retinal lesions in a single frame. As shown by Aggarwal et al., UWF imaging is a very useful tool in the management of IOTB as it helps to capture peripheral areas of retinal non-perfusion, active retinal vasculitis, neovascularization, and choroiditis lesions which would otherwise be missed on conventional fundus imaging [52–54]. UWF imaging revealed additional TB SLC lesions in 39 out of 44 eyes (88.6%) compared to conventional imaging. It has been shown to provide additional information in 90.9% of the eyes with TB posterior uveitis and affected management decisions in over 45% of the eyes [52].

OCT features of TB SLC: Various studies have shown the role of OCT in detecting retinochoroidal changes in TB SLC. In the active stage of the disease, OCT B-scans passing the active edge of TB SLC lesion show a localized, fuzzy area of hyperreflectivity in the outer retinal layers involving the RPE, ellipsoid and myoid zone, external limiting membrane (ELM), and the outer nuclear layer (ONL) with no increased backscattering from the inner choroid. As the lesions heal, there is disappearance of the hyperreflective fuzzy areas which are replaced by irregular, hyperreflective knobbly elevations of the outer retinal layers. The RPE, ellipsoid and myoid zones, and the ELM cannot be distinguished at this stage [24, 43, 45, 55].

Rifkin et al. have shown that EDI-OCT is very useful in detecting active choroidal infiltration with RPE elevation in patients with TB SLC. The authors proposed that this finding may be useful in distinguishing TB SLC from the autoimmune garden variety of serpiginous choroiditis [56].

OCT angiography in TB choroiditis: The novel technique of OCT angiography has recently shown novel findings that greatly aid in understanding the pathology and sequelae of chorioretinal changes in TB SLC. OCT angiography provides high-resolution imaging of the choriocapillaris in different stages of this disease. In the acute stage, Mandadi et al. have shown alterations in choriocapillaris flow (flow deficit) that may progress to atrophy during the inactive stage (Fig. 3). Morphologic information obtained from OCT angiography images correlates well with and supplements other imaging techniques such as ICGA and EDI-OCT [57].

Recently, OCT angiography has also been shown to be useful in detecting novel type 1 choroidal neovascular (CNV) lesions among patients with TB SLC. Aggarwal et al. demonstrate that type 1 CNV can lead to significant visual loss even in the healed stages of the disease. OCT angiography is useful even in cases where conventional multimodal imaging, including FA and OCT, fail to make a definitive diagnosis [58].

Presumed tubercular retinal vasculitis

Presumed TB retinal vasculitis is characterized by peripheral occlusive retinal periphlebitis with inflamed retinal vessels and features of distal retinal ischemia such as cotton-wool spots or lack of blood flow on fundus imaging. TB vasculitis can present with sequelae such as peripheral retinal neovascularisation and recurrent vitreous hemorrhage leading to tractional retinal detachment and/or macular scarring. This condition may mimic other causes of retinal vasculitis such as other infective causes

(toxoplasmosis, viral retinitis, syphilis, toxocariasis, among others) and non-infective causes such as birdshot chorioretinopathy, systemic vasculitides, among others [26, 59, 60].

Eales' disease is a condition characterized by occlusive vasculitis and development of retinal neovascularization. Biswas et al. have been instrumental in providing an update on the current understanding and etiopathogenesis of this condition [61, 62]. Eales' disease is presently thought to be due to hypersensitivity reaction to tubercular proteins. In a study, significant number of patients operated for epiretinal membrane were positive for Mycobacteria when tested by polymerase chain reaction (PCR) [63]. Verma et al. have shown presence of *Mycobacterium tuberculosis* DNA in an enucleated eyeball using nested PCR technique [64]. More recently, our group has shown that *Mycobacterium tuberculosis* genome was present in more than 50% vitreous fluid samples of patients with Eales' disease with a significant bacillary load [65]. Therefore, there is increasing evidence that Eales' disease could indeed represent TB vasculitis especially in endemic Asian countries, and these patients must be thoroughly investigated for evidence of TB infection in the body [61].

There is no definitive method of establishing TB as the etiology of retinal vasculitis. Therefore, these cases are considered to be *presumed* tubercular in nature. Usually, the diagnosis of TB retinal vasculitis is suspected by the treating uveitis experts by considering various clinical, immunological, and radiological criteria, and excluding other infectious and non-infectious known etiologies [26, 66, 67]. Among individuals with Asian ethnicity, majority of the patients with TB retinal vasculitis will present with an occlusive disease. It is pertinent to note that most Caucasian patients may not have an occlusive disease [26]. Such differences may be related to the genetic differences (e.g., HLA) between these ethnicities of patients.

While there is a lack of consensus on the diagnostic criteria and management of TB retinal vasculitis, this condition has shown good anatomic and visual response with prompt ATT and/or steroid therapy in smaller studies [59, 68].

Unusual clinical phenotypes

Rarely, in endemic countries, IOTB may present with uncommon phenotypes such as panophthalmitis and endophthalmitis, which may mimic as ocular tumors [69, 70]. Tuberculous optic neuropathy is also uncommon, and may manifest as papillitis, neuroretinitis, and optic nerve tubercle [71–73]. Optic nerve head tubercle may present as an elevation at the optic nerve head with surrounding exudation and fluid. Choroidal involvement in IOTB may also have rare phenotypic presentations. In the COTS-1, IOTB

was diagnosed in patients with ampiginous choroiditis, acute posterior multifocal placoid pigment epitheliopathy (APMPPE), and other types of choroiditis that did not fit into any of the classical descriptions [25]. Such forms of choroidal involvement in IOTB has not been previously reported.

TB panuveitis may be confused with other forms of granulomatous panuveitis. Many patients may require extensive clinical, laboratory, and imaging workup, including invasive microbiological and histopathological evidence in order to establish a diagnosis. In a case report published by our group in 2016, we describe a monocular Asian Indian female who presented with significant panuveitis which was misdiagnosed as sympathetic ophthalmia. The correct diagnosis could be established only when the non-seeing phthisical fellow eye was enucleated and careful histopathological examination revealed presence of acid-fast bacilli (AFB) on Ziehl–Neelsen staining, tubercular granulomas, and the sample tested positive for TB on PCR [74].

It must be kept in mind that in rare phenotypic presentations, the diagnosis of TB may be presumptive, based on a constellation of clinical, radiological, and laboratory findings. It must be emphasized that in a lot of patients, unequivocal evidence of the infection is often unavailable.

Diagnosis of intraocular tuberculosis

The diagnosis of IOTB is indeed challenging. Till date, there are no randomized controlled trials that have defined the diagnosis of IOTB. Furthermore, there are no consensus guidelines amongst the uveitis experts world over regarding the diagnosis of IOTB. The criteria that have been applied for diagnosing IOTB by various studies include [4, 23, 45, 75]:

1. Clinical signs suggestive of IOTB including:

    a. *Anterior uveitis*: Granulomatous or non-granulomatous, iris nodules, ciliary body granuloma.
    b. *Intermediate uveitis*: Granulomatous or non-granulomatous with exudates in the pars plana or peripheral uvea, with/without snow balls.
    c. *Posterior and Panuveitis*: choroidal tubercle, choroidal granuloma, subretinal abscess, serpiginous-like choroiditis.
    d. Other features such as retinal vasculitis, neuroretinitis, optic neuritis, endophthalmitis, panophthalmitis, scleritis.

2. Exclusion of other uveitic entities based on clinical manifestations of disease and regional epidemiology.

3. Investigations documenting the mycobacteria or its genome:

   a. Demonstration of AFB by microscopy or culture of *Mycobacterium tuberculosis* from ocular fluid
   b. Positive polymerase chain reaction from ocular fluid for IS 6110 or other conserved sequences in mycobacterial genome
   c. Evidence of confirmed active extra-pulmonary TB (by microscopic examination or culture of a tissue sample from the affected tissue)

4. Corroborative investigations such as:

   a. Positive Mantoux test
   b. Interferon Gamma Release Assay (IGRA) such as QuantiFERON TB Gold
   c. Evidence of healed or active TB on chest radiography

There is no single gold standard test available for diagnosing IOTB. Tests such as Mantoux test and interferon gamma release assays may be highly positive in some centers (especially in Asian countries) due to endemicity of TB in the region. Therefore, it is necessary to develop a prospectively derived clinical risk score that will help to improve the diagnosis and management of IOTB.

Therapies for intraocular tuberculosis

Standard therapy for intraocular tuberculosis

Anti-tubercular therapy (ATT) consists of a combination of four drugs namely isoniazid, rifampin, ethambutol, and pyrazinamide. These four agents constitute the first-line agents and are started empirically in patients with systemic TB. The four agents are given in the following doses: isoniazid (5 mg/kg/day), rifampicin (10 mg/kg/day), ethambutol (15 mg/kg/day), and pyrazinamide (20–25 mg/kg/day) along with pyridoxine (vitamin B6) (10 mg/day).

In 2008, Bansal et al. reviewed the role of ATT in the treatment of active TB uveitis in a large retrospective interventional series ($n = 360$). In this study, the authors observed that among the 216 patients who received ATT, the recurrences of uveitis substantially decreased compared to 144 patients who did not receive ATT (15.74% versus 46.53%; $p < 0.001$). Therefore, the authors speculated that since the disease occurs due to a hypersensitivity reaction, ATT may have an important role in treating latent TB infection in the body, eliminating future recurrences of IOTB [76]. While the study by Bansal et al. was performed in a highly endemic region of world for TB, i.e. India,

Agrawal et al. published a retrospective study highlighting the role of ATT in a low endemic country (UK) in 2015. In this study, patients who received long-term treatment with ATT showed reduced recurrence of the disease [77].

In 2016, a major review and systematic analysis of 28 studies (a total of 1917 patients) published by Kee et al. reviewed the role of ATT for IOTB. The study results showed that among patients who received ATT, the non-recurrence of inflammation was observed in pooled estimate of 84%. While the study results showed benefit of ATT in reducing recurrences, there were limitations due to lack of a control group and non-standard recruitment and treatment criteria [78].

The standard therapy for IOTB as per the recommended guidelines consists of four drug regimen mentioned above. Ethambutol and pyrazinamide are stopped after a period of 2 months. There is regular monitoring of liver function tests when a patient is started on ATT.

Thus far, there is no definite guideline on the duration of ATT in patients with IOTB. Agrawal et al. have shown beneficial results in patients who receive ATT for ≥9 months [77]. In a study from Singapore by Ang et al., 186 patients with IOTB were included, of whom 46 received more than 6 months of ATT. The authors showed that patients who completed >9 months ATT were less likely to develop recurrences compared with those not treated with ATT ($p = 0.027$) [79]. Till date, however, there is no common consensus among uveitis experts regarding the regimen and duration of ATT, as shown in the COTS-1 study [25].

Managing inflammation in intraocular tuberculosis—oral corticosteroids

There is no uniform recommendation regarding the use of concomitant corticosteroids along with ATT in IOTB. Corticosteroids are employed to reduce the intraocular inflammation since IOTB is hypothesized to occur due to type IV hypersensitivity reaction to tubercular proteins. Oral corticosteroids may also play a role in reducing inflammatory macular edema [80]. However, unlike in the case of meningeal and pericardial TB where there are clear guidelines supporting the use of systemic corticosteroids, their use in IOTB is considered to be controversial by certain authors [81].

Various series have reported the use of oral corticosteroids along with ATT as a combination (oral prednisolone 1 mg/kg/day) for IOTB with favorable control of inflammation [23, 36, 37, 68, 76, 77, 82]. Corticosteroids can be tapered over the next 6–12 weeks depending upon the severity of inflammation and occurrence of paradoxical worsening of the disease [83]. Certain authors favor the use of corticosteroids only when the lesions are involving or threatening the macula in order to decrease macular scarring [84].

Paradoxical worsening

One of the most clinically intriguing features of TB SLC is the paradoxical worsening of the disease after initiation of anti-tubercular therapy (ATT). The worsening of these lesions occurs due to a combination of factors including enhanced delayed hypersensitivity of the host, decreased suppressor mechanisms, and increased exposure to the mycobacterial antigens or a response to mycobacterial antigens such as tubercular proteins [37, 85, 86]. Cheung and Chee have described a case of a 77-year-old woman with biopsy-proven TB cervical lymphadenitis who developed choroiditis in one eye after initiation of ATT. The authors identified mycobacterial DNA from the vitreous tap using polymerase chain reaction, and a diagnosis of paradoxical worsening following ATT was made [87]. In a case series by Basu et al., 4 patients with IOTB (including 1 patient with intermediate uveitis; 1 patient with TB granuloma, and 2 patients with TB SLC) who were started on ATT developed paradoxical worsening (appearance of new lesions or worsening of existing lesions). Therefore, paradoxical worsening is a major challenge in the management of IOTB [82].

With the recent introduction of ultra-wide field (UWF) retinal imaging, the detection rates of paradoxical worsening have significantly increased. Using conventional imaging, paradoxical worsening was reported in 14% patients after 2 to 6 weeks of initiation of ATT [37]. With UWF imaging, paradoxical worsening may be observed in over 36% patients after initiation of ATT [52, 88, 89]. In a series by Agarwal et al., OCT angiography was shown to be very useful in the detection of choriocapillaris alterations in patients of TB SLC developing paradoxical worsening [88]. Patients who develop paradoxical worsening may require increase in the dosage of corticosteroids, or addition of intravenous methylprednisolone pulses. Topical steroids may be employed in cases with anterior segment inflammation. Systemic immunosuppressants and steroid sparing agents such as azathioprine may be added as and when required depending on the discretion of the treating uveitis specialist.

Novel local and systemic therapies

In order to improve the outcomes of IOTB by reducing the systemic corticosteroid-related adverse effects in severe or long-standing inflammation, and address various challenges such as paradoxical worsening of the disease, a number of alternative therapeutic strategies have been tried. Intravitreal injection of depot steroid (dexamethasone implant, Ozurdex ®) has been employed in the management of TB multifocal serpiginoid choroiditis [90, 91]. In a case report by Fonollosa et al., Ozurdex implant was shown to be useful in continuous progression of the lesions despite ATT and oral corticosteroids [90]. Similarly, Jain et al. showed that Ozurdex implant is useful in cases where the disease continues to progress, or there is intolerance to oral corticosteroids [91]. In a larger series by Agarwal et al., 19 eyes of 17 patients with IOTB (including intermediate uveitis, retinal vasculitis, and TB SLC) received Ozurdex implant with favorable resolution of inflammation, and improvement in visual acuity [92].

Intravitreal methotrexate has also been employed in the management of IOTB. In a series by Julian et al., 3 eyes of 2 patients with active presumed TB choroiditis received intravitreal methotrexate due to progressive macular threatening disease. In all 3 eyes, healing of choroidal lesions without any adverse event occurred within 1 month of the injections [93]. Sahin et al. published a similar favorable experience with intravitreal methotrexate in 2 cases of IOTB [94].

Interferons (IFN) are a group of low molecular weight polypeptides secreted by activated immune cells and possess high activity and various functions. IFNs alpha/beta signaling by the retinal pigment epithelium has been linked to high *Mycobacterium tuberculosis* disease activity in patients with active disease, leading to inhibition of the outgrowth of intracellular mycobacteria [95]. In a series of 12 eyes (6 patients) by Invernizzi et al., IFN-alpha 2a was employed in the management of presumed chronic TB uveitis patients in whom the uveitis was recurrent upon tapering of corticosteroids below 7.5 mg/day. The use of subcutaneous IFN-alpha 2a showed good results in all the eyes with resolution of inflammatory signs (vitritis and vasculitis), decrease in retinal thickening, and improvement in visual acuity without any major complications [96]. IFN-alpha 2a has also been used by Oray et al. in 5 patients with presumed IOTB for recurrent cystoid macular edema after completion of ATT. IFN-alpha 2a were shown to be safe and effective in managing macular edema in this series [97].

The challenge in the management of intraocular tuberculosis

Till date, there are no uniform guidelines in the management of IOTB. There are several regional variations in treatment practices for IOTB including the regime, duration of ATT, concomitant use of corticosteroids and immunosuppressive agents (both systemic and local). The treatment in a majority of IOTB cases is directed in consultation with the attending pulmonologist/internist based on guidelines that vary depending on the region of their practice. In the COTS-1 [25], analyses revealed variation in outcomes between different ethnic groups and geographical regions. For instance, the proportion of patients that received treatment with both ATT and corticosteroids was highly variable

between Asia (80.4%), Australia (60.0%), and the West (62.9%). Thus, Asian patients are most likely to receive a combination of ATT and steroids compared to the Western countries. In addition, treatment outcomes on survival analysis were superior in patients of Asian ethnicity.

Dengue fever-associated uveitis

Dengue fever is a mosquito-borne viral illness caused by a flavivirus which has four serotypes. The most common arthropod vector for this condition is *Aedes aegypti*, which is common in tropical and subtropical regions. The mortality and morbidity due to dengue fever has tremendously increased in the tropical and sub-tropical zones of the world. Dengue fever can present with various vitreoretinal manifestations, where inflammation and ischemia are the hallmark features of the disease.

Epidemiology of dengue fever and recent outbreaks in Asia

Dengue is endemic world over in areas such as United States, Southeast Asia, and the Western Pacific. This arthropod borne disease is endemic in more than 100 countries, and is regarded as the most common mosquito-borne disease in humans [98–100]. The first case of dengue fever-related posterior uveitis was in 1979 amongst tourists who returned from dengue-endemic countries. More than 50 million dengue infections are estimated to occur annually throughout the world. Since the beginning of the 21st century, most cases have been reported from the South East Asian countries. There are four serotypes of the dengue virus. In countries such as Singapore, the number of cases have been steadily rising over the last few years [101]. Dengue and related uveitis have been reported from Singapore, Sri Lanka, Thailand, Taiwan, India, Mexico, and Brazil [102–107]. In Malaysia, a total of 101,357 dengue cases and 237 deaths were reported in 2016 [108]. Frequent outbreaks are also reported from Taiwan. From 2007 to 2011, a total of 3,322 confirmed dengue cases were noted in Taiwan, particularly from Kaohsiung city [109]. In 2017, the data from the National Vector Borne Disease Control Program (NVBDCP), India showed the highest number of cases and deaths due to dengue fever [110].

Chorioretinal manifestations of dengue fever

Ocular involvement in dengue may be unilateral or bilateral. Anterior segment features of dengue infection include subconjunctival hemorrhage, keratitis, anterior uveitis, and angle closure glaucoma. Most common posterior segment manifestations of dengue fever include macular edema, hemorrhages, foveolitis, cotton wool spots, and micro-aneurysms [111–113].

1. *Dengue maculopathy*: Dengue maculopathy is a common posterior segment condition and its incidence may correlate with the severity of systemic disease. Patients with dengue maculopathy may complain of visual symptoms such as blurring or scotomas due to outer retinal involvement [114, 115]. Fundus examination of this condition reveals arteriolar sheathing, cotton-wool spots, micro-aneurysms, intraretinal cystoid spaces, and macular edema (Fig. 4), perifoveal telangiectasia and intraretinal hemorrhages. There may be presence of well-defined yellowish subretinal lesions in the macular along with retinal striae radiating around the fovea (*foveolitis*). These lesions may represent disruption of photoreceptors (Fig. 5) [116–120].

Acute macular neuroretinopathy: It is notable that acute macular neuroretinopathy (AMN) has been recently reported to be an unusual manifestation of dengue maculopathy [121, 122]. AMN presents with hyper-reflectivity of the outer retina (outer plexiform layer and outer nuclear layer), and disruption of ellipsoid zone, external limiting membrane (ELM) and inter-digitation zone.

2. *Dengue vasculopathy*: Dengue-related uveitis has been reported to present with retinal vasculitis. Vasculitis may be associated with retinal ischemia, intraretinal hemorrhages, and other manifestations such as branch retinal arteriolar occlusion. Capillary endothelial dysfunction or occlusion of precapillary arterioles due to immune complex deposition may be the likely underlying mechanism of retinal vasculitis in dengue fever [112, 113, 120].

3. *Dengue chorioretinitis*: One of the possible manifestations of dengue posterior uveitis includes chorioretinal involvement presenting with severe vitreous inflammation and exudative retinal detachment. Chorioretinitis may present with single or multiple multifocal lesions involving the macula along with retinal pigment epithelium disturbances. Chorioretinitis may evolve into atrophic perifoveal pigmentary scars (nummular scars). There may be associated
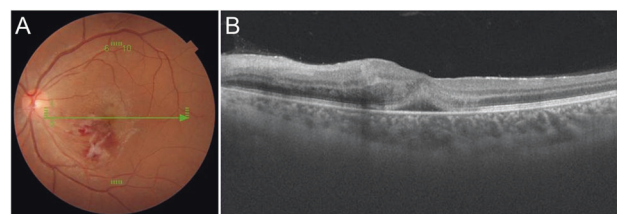

Fig. 4 Fundus photograph of a 23-year-old male who presented with low vision in the left eye 15 days after a severe febrile illness is shown (**a**). The patient was diagnosed with dengue fever based on NS1 antigen test positivity. The platelet nadir was 20,000/mm³. There was an altered foveal reflex with whitish retinal opacification along with retinal edema and hemorrhages. Optical coherence tomography B-scan shows presence of serous subretinal fluid, retinal thickening, and intraretinal cystoid spaces suggestive of dengue maculopathy (**b**)
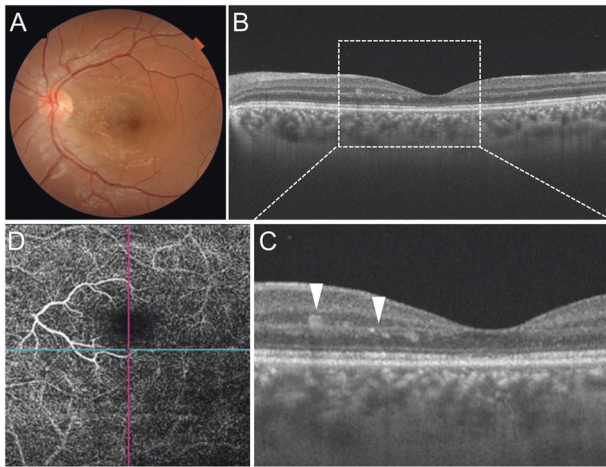
Fig. 5 Multimodal imaging of a patient (32-year-old female) with dengue maculopathy is shown here. The patient complained of scotoma in front of both her eyes 2 weeks after subsidence of dengue fever (tested positive for NS1 antigen). Fundus photograph revealed mild optic nerve hyperemia, and an altered red foveal reflex with yellow spots in the nasal macula (**a**). Optical coherence tomography B-scan (**b**) shows no evidence of retinal thickening; however, careful examination (**c**) revealed hyper-reflective spots in the outer nuclear layer (arrowheads). The deep retinal capillary plexus on optical coherence tomography angiography (**d**) showed evidence of capillary flow deficit suggestive of retinal vascular micro-occlusion

choroidal thickening and evidence of neuroretinitis or papillitis [118, 119].

Imaging features of dengue-related uveitis: FA is a useful imaging modality to determine the extent and severity of retinal manifestations such as maculopathy and retinal vasculitis. Foveolitis appears as retinal pigment epithelial hyperfluorescence that appears in the early phase and persists till the late phase. There may be presence of macular periphlebitis and occlusion. Common findings include arteriolar leakage, macular edema, and disc leakage. ICGA may show presence of hypofluorescent spots suggestive of involvement of choriocapillaris and the retinal pigment epithelium [122–124].

OCT imaging is useful to diagnose presence of macular edema as well as other changes such as foveolitis. The OCT classification consisting of three patterns of dengue maculopathy as proposed by Teoh et al. [125] is as follows:

Type 1: diffuse retinal thickening: Type 1 maculopathy included patients with diffuse retinal edema with an increase in central and paracentral retinal thickness and loss of the normal foveal dimple. Patients with type 1 maculopathy were described to carry the best visual prognosis.

Type 2: cystoid macular edema: Type 2 maculopathy was characterized by large intraretinal cystoid spaces extending through the level of photoreceptors with reflective septae separating the cystoid cavities.

Type 3: foveolitis: Type 3 maculopathy was characterized by an area of thickening and high reflectivity in the outer retina at the foveal region. There may or may not be associated retinal edema.

The most common feature of OCT in dengue maculopathy is diffuse retinal thickening. Disruption of external limiting membrane, ellipsoid zone, and inter-digitation zone may also be noted in these patients [120, 125–127].

Dengue-induced inflammatory, ischemic foveolitis and outer maculopathy (DIII-FOM): In a recent outbreak of dengue virus fever in North India (2017), a number of patients presented with a unique set of posterior segment features such as mild posterior vitritis, disruption of outer retinal layers, conical retinal elevations, and retinal capillary flow deficits on OCT angiography. In these patients, both ischemia and inflammation appear to be the central mechanisms of visual loss due to dengue fever. Therefore, based on their clinical phenotype and fundus imaging characteristics, we have coined a new term for this entity, DIII-FOM (Fig. 6).

Management of dengue-associated uveitis

There are no available guidelines regarding management of dengue-related maculopathy. Dengue maculopathy may be self-limiting in nature. In the presence of significant inflammation, topical, periocular, and systemic steroids may be used. Patients with AMN associated with dengue fever may also benefit from initiation of corticosteroids. However, there are no prospective trials assessing the efficacy of therapy till date. Thus, there is no clear evidence supporting the role of either steroids or intravenous immunoglobulin for the treatment of dengue retinochoroiditis or vasculitis [116, 120].

Chikungunya-associated uveitis

Chikungunya fever is a common arthropod-borne viral illness that commonly affects Asian countries and Pacific islands. Epidemics of chikungunya have been reported from several Asian countries such as India in the recent past. Chikungunya is caused by an *Alphavirus* which belongs to the family *Togaviridae*, a single-stranded RNA virus. The arthropod vector for chikungunya is the *Aedes aegypti* mosquito.

Epidemiology of chikungunya

Chikungunya fever can affect all ages and both sexes equally. This condition is endemic in Asia and Africa. The chikungunya virus was first isolated in Tanzania in 1953. More than 266,000 people were infected during the 2007 outbreak in Réunion and 1,400,000 cases were reported in India in 2006 [128]. Several outbreaks of chikungunya have
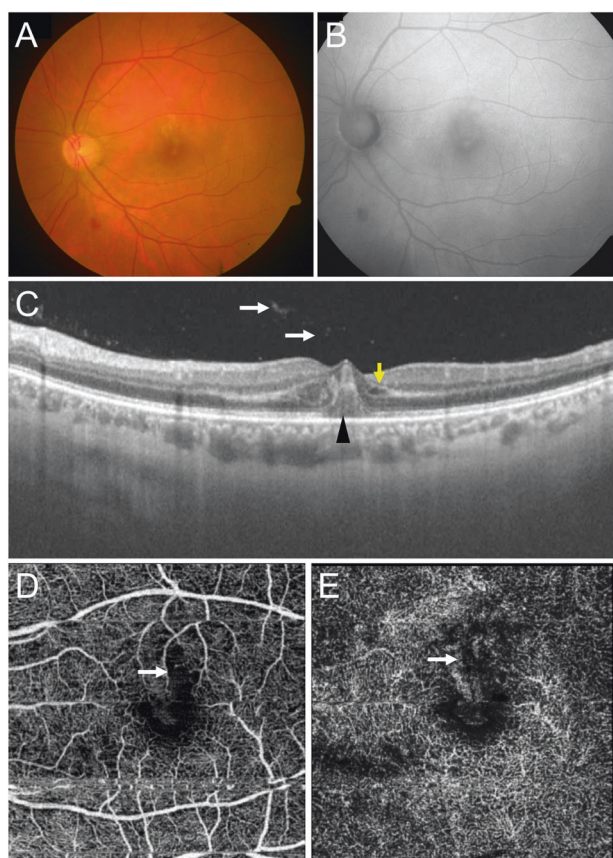
Fig. 6 A patient with dengue-induced ischemic inflammatory foveolitis and outer maculopathy (DIII-FOM) shows retinal hemorrhages in the macula with greyish white parafoveal lesions (**a**). Autofluorescence imaging shows hypo-autofluorescence in the macular region (**b**). The optical coherence tomography (OCT) scan shows vitreous cells (white arrows), hyper-reflectivity of the outer plexiform (OPL) and outer nuclear layers, and hyper-reflective "conical foveal elevation" involving all retinal layers (black arrowhead) (**c**). There are cystoid spaces in the left eye (yellow arrow). OCT angiography shows an area of flow deficit (white arrow) in the perifoveal region in the superficial (**d**) and deep plexus (**e**)

been reported between 1957 and 1974. The disease is also endemic in Seychelles, Madagascar, Comoro Islands, Mauritius, and Mayotte. Other countries that are affected include Sri Lanka, Maldives, Malaysia and Indonesia [129–132]. Viral mutations may lead to newer genotypes of the Chikungunya virus (such as A226V) which have increased virulence and infectivity. Due to the lack of herd immunity and increased travel/globalization, even visitors who hail from Europe, Canada, United States, and Australia are susceptible to chikungunya fever [129, 133].

Chikungunya virus-associated uveitis

Chikungunya fever may have ocular manifestations which may be unilateral or bilateral. Ocular inflammation associated with chikungunya may present with symptoms such

as redness, pain, diplopia, and retro-orbital heaviness. Anterior uveitis is the most common feature of this condition. There may be concomitant corneal involvement with dendritic pattern of keratic precipitates. Other features include raised intraocular pressure, episcleritis, and lagophthalmos [111, 134, 135].

Posterior segment manifestations of chikungunya infection include choroiditis, retinitis, optic neuritis, neuroretinitis, and panuveitis. The most common posterior segment features are retinitis with surrounding retinal edema and opacification. Retinal lesions may be associated with mild vitritis and disc edema. Severe inflammation may result in exudative retinal detachment, retinal vasculitis, and intraretinal hemorrhages. Published reports suggest that long-term implications of chikungunya-related posterior segment manifestations are poorly understood [117, 136–139].

Imaging features of chikungunya-related uveitis: Imaging tools such as FA and OCT are very useful in the evaluation and management of patients with chikungunya uveitis. FA reveals presence of early hypofluorescence followed by late hyperfluorescence corresponding to the area of retinitis. Similar to choroiditis associated with other etiologies, Chikungunya choroiditis shows early hypofluorescence followed by late leakage of dye on FA. On OCT, macular edema and retinal thickening may be observed (Fig. 7). OCT may also reveal presence of AMN in patients with chikungunya [135–138]. Features of AMN include hyper-reflectivity of the outer plexiform layer, outer nuclear layer, and disruption of ellipsoid zone, ELM and inter-digitation zone [140].

Management of chikungunya-related uveitis

There is no specific anti-viral therapy against Chikungunya virus. Therefore, the treatment of chikungunya is largely symptomatic including management of fever, intravenous fluid therapy, and symptomatic pain relief. Ocular inflammation can be treated with topical steroids and cycloplegic agents. Majority of patients with chikungunya posterior uveitis recover well with good visual outcome. In the presence of significant inflammation, including manifestations such as vision-threatening retinitis and AMN, systemic corticosteroids can be initiated to control the tissue damage [135, 136, 140].

Summary and conclusions

In the Asia Pacific region, TB, dengue and Chikungunya remain the major infections that continue to remain endemic and affect a large number of individuals. All the three entities are associated with potentially severe vision
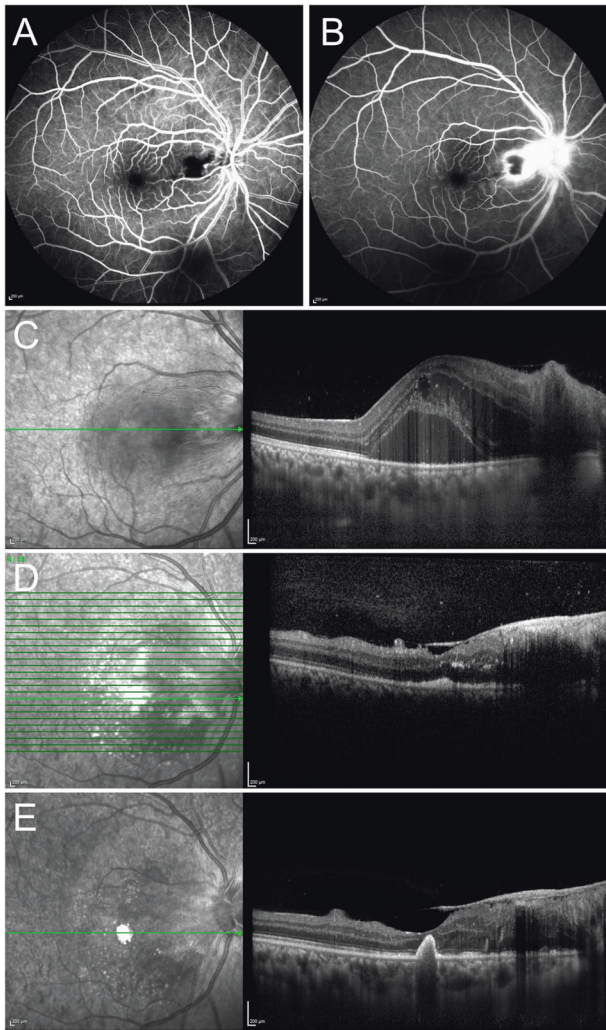
Fig. 7 Fluorescein angiography (FA) and optical coherence tomography (OCT) of a 34-year-old male with retinitis. The patient tested IgM positive for chikungunya virus infection. FA imaging in the early phase shows hypofluorescence (**a**) followed by intense leakage in the late phase (**b**) suggestive of retinitis. OCT scan at presentation (**c**) shows retinal edema, intraretinal fluid, serous retinal detachment, and disruption of retinal layers. The patient was treated with oral corticosteroids and he also received an injection of posterior subtenon triamcinolone acetonide. At 3 months, there was significant resolution of retinal edema and serous retinal detachment (**d**). At 7-month follow-up, retinal thickening and retinitis lesions have resolved, and a thick epiretinal membrane is seen on OCT (**e**). (Image courtesy: Dr. Ankush Kawali, MS, Consultant, Uveitis Department, Narayana Nethralaya, Bangalore, India)

threatening uveitis. Entities such as TB may have protean clinical manifestations and may present with diagnostic challenges, especially because they can cause myriad conditions, including choroiditis, vasculitis, panuveitis, optic neuritis, endophthalmitis, and scleritis, among others. For establishing a proper diagnosis of IOTB, it is necessary to consider various factors such as endemicity, geographical location, ethnicity, and immigration status, as well as

clinical and imaging features. Similarly, dengue and Chikungunya present with retinitis and/or vasculitis of varying severity. While there is no definitive therapy for these viral entities, supportive therapy corticosteroids may help to reduce the inflammatory damage. In summary, with the recent increase in the outbreaks and epidemics of dengue and Chikungunya fever, it is important to recognize the potentially vision-threatening posterior segment manifestations of these conditions.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest

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