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Multimodal imaging in dengue fever associated maculopathy

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Introduction

Dengue fever is a significant cause of morbidity in tropical climates worldwide.^{1,2} Dengue endemic countries have an estimated total population of 2.5 billion, and while the World Health Organization estimates 50 million dengue infections occur annually, cartographic estimates suggest a rate of 96 million clinical dengue infections per year.^{1,2} In light of the growing public health implications of dengue fever, ocular complications are important to understand and recognize. Dengue-related eye disease has more commonly been reported from endemic countries, such as Singapore (88.3%), and India (9.8%).³ These reports describe a wide variety of phenotypic characteristics ranging from subconjunctival and petechial hemorrhages to anterior uveitis. There have been some observations of dengue-associated foveolitis,^{4–6} and a few reports characterize dengue associated acute macular neuroretinopathy (AMN),^{7,8} however we present a case that has features from both entities, suggesting that dengue associated maculopathy is a wider spectrum than previously reported. The term foveolitis suggests inflammation as the cause for the anatomic changes seen in the macula, however, we prefer using the term dengue associated maculopathy, due to the multifactorial nature of this condition.

Materials and Methods

A retrospective chart review of a case with serologic evidence of dengue fever seen at the Uveitis Clinic at the National Eye Institute, Bethesda, MD was performed. The history was elucidated. Comprehensive multimodal imaging including color fundus photography, fluorescein angiogram (FA), fundus autofluorescence (FAF), optical coherence tomography (OCT), indocyanine green angiography (ICG-A), and visual field testing was evaluated.

Results

A 43-year-old woman reported “blind spots” in both eyes after contracting dengue fever on a trip to Mexico. Her past ocular history was significant for dry eye disease and bilateral laser-assisted in situ keratomileusis (LASIK).

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Declaration of interest:

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Her initial symptoms included fever and diarrhea. She was treated with ciprofloxacin after testing negative for probable infectious causes including *Shigella*, *Salmonella*, *Escherichia coli* and *Yersinia*. Around the same time, she noticed dark colored scotomas, first in the left eye, shortly followed by the right eye. Her laboratory results were significant for thrombocytopenia of 98×10^3 cells/uL, noted four days after the scotomas began. Further, serologic IgG and IgM testing confirmed the diagnosis of acute dengue fever. She was switched to azithromycin for better efficacy, but unfortunately developed an allergic reaction, requiring oral prednisone 1mg/kg, followed by a taper over several weeks. She was seen by a retina specialist who noted early disruption of the outer retinal layer on macular OCT, but no other clinical or angiographic features to explain her symptoms (Figures 1 and 2).

She presented to our clinic 6 weeks following the start of her dengue symptoms, on a tapered dose of 5mg oral prednisone daily. At this time, she reported mild improvement of the scotomas bilaterally. Her best-corrected visual acuity (BCVA) was 20/16 in both eyes. Intraocular pressure (IOP) was measured at 12 and 14 mmHg in the right and left eyes, respectively. Goldmann visual fields demonstrated central scotomas in both eyes corresponding to the symptoms described by the patient. The anterior chambers were quiet in both eyes, with no evidence of inflammation. Fundoscopic examination of both eyes showed no clinically apparent abnormalities, however infrared imaging and FAF revealed hypoautofluorescent spots in the perifoveal area. These lesions were not associated with leakage on fluorescein angiography but showed hypocyancescence on late frames of ICG-A (Figure 3 and 4). High resolution macular OCT through those lesions showed focal swelling of the outer plexiform and outer nuclear layers and discontinuity in the underlying ellipsoid zone, with an intact retinal pigment epithelium.

Given the patient's subjective improvement in visual complaints, a decision was made to observe her on the current prednisone taper with no additional therapy. A month later, she reported the scotomas were lighter, but she still had localized metamorphopsiae centrally. Her BCVA continued to remain 20/16 in both eyes. Macular OCT showed partial reconstitution of the ellipsoid zone with resolution of the swelling in the outer nuclear layer of both eyes (Figure 5 and 6).

Discussion

Our patient with dengue fever presented with macular lesions that were best seen on infrared imaging, with disruptions of the outer retinal layers, and demonstrated anatomic improvement on OCT. These imaging findings and her clinical course are consistent with dengue associated maculopathy.

Up to 10% of patients with dengue fever may have associated maculopathy.^{7,9} OCT studies of dengue eye disease have classified three types of dengue maculopathy: Type 1 with diffuse retinal thickening centered around the fovea, Type 2 with cystoid macular edema occurring within the retina and disrupting the photoreceptor layers, and Type 3 with foveolitis characterized by thickening at the subfoveal outer retina.¹⁰

About 28 – 34% of patients with dengue maculopathy have yellow-orange lesions seen on funduscopy corresponding to the outer retinal changes seen on OCT.⁶ Characteristic lesions of AMN occurred in 55.6% of dengue maculopathy cases seen at one center,⁷ which are best visualized on near-infrared reflectance.^{8,11} OCT findings include hyperreflectivity of the outer nuclear layer (ONL) and outer plexiform layer (OPL) in the acute phase, followed by irreversible outer segment disruption and outer nuclear layer thinning that persist long term with scotomas even after visual recovery.^{9–11} Our patient did not show the yellow lesions, but demonstrated these OCT findings, with resolution of the outer nuclear and outer plexiform layer swelling after 4 weeks.

A proposed theory for the disrupted ellipsoid zone is that the thickening of the inner retina blocks OCT signal leading to poor visualization of the ellipsoid zone, which then re-appears when the inner retinal edema has resolved.¹² Another important aspect to consider in this patient is that the typically described symptoms of dengue-related eye disease such as intraretinal hemorrhages, vasculitis, or cotton wool spots were not seen. Possible explanation for the absence of these findings may include her delayed presentation after the acute stage of her illness or her use of oral steroid and its mediation of the inflammatory component of dengue associated ocular complications.^{13,14} Some authors have questioned the association between certain serological strains of dengue causing retinal hemorrhages, however, classically in dengue eye disease, visual symptoms and pathological signs peak as platelet levels reach their nadir.^{3,8,13–15} The co-occurrence of thrombocytopenia with ocular findings suggests the possibility of dengue maculopathy occurring due to endothelial dysfunction, immune complex deposition, or retinal capillary ischemia.^{3,8,13–15} Visual recovery has been noted to improve with improving platelet levels.^{8,16,17}

Regardless of disease manifestations, treatment has remained conservative, with spontaneous resolution of visual complaints.^{3,7,14} A large case series from Singapore showed that 12 of 13 patients had visual recovery over 6 days to 3 months and nine patients achieved a best corrected visual acuity of 20/25 or better at a mean of 4.0 weeks.¹⁶ Testing with multifocal electroretinography (mfERG) in dengue maculopathy, shows retinal dysfunction corresponding to the scotoma up to a year after diagnosis,¹⁸ likely due to loss of the photoreceptors or bipolar cells.^{11,18} A recent case study demonstrated an irregularly enlarged foveal avascular zone with persistent loss of internal and external retinal plexus capillaries on OCT angiography, suggesting a vascular mechanism for the neural loss and persistence of scotoma.¹⁹ Multimodal imaging is thus necessary to better understand the extent of macular involvement in dengue-associated maculopathy.

There are very limited reports on the natural history and long term follow-up of dengue associated maculopathy and even fewer examples of resolution of the ellipsoid zone on OCT. We show that multimodal imaging can characterize the lesions and allow for close monitoring of visual changes during convalescence.

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FIGURE 1.

Multimodal imaging of the right eye three weeks following onset of symptoms. A) Color fundus photograph shows mottling of fovea without hemorrhage. B) Wide-angle infrared photograph. C) Fluorescein angiogram was normal with no leakage or blockage of dye. D) ICG was normal. E) OCT showing discontinuities in the ellipsoid zone, with intact RPE.

FIGURE 2.

Multimodal imaging of the left eye three weeks following onset of symptoms. A) Color fundus photograph shows mottling of fovea without hemorrhage. B) Wide-angle infrared imaging shows an early lesion superior to the fovea (white arrow). C) Fluorescein angiogram was normal with no leakage or blockage of dye. D) ICG was normal. E) OCT showing multiple discontinuities in the ellipsoid zone, with intact RPE.

FIGURE 3.

Multimodal imaging of the right eye seven weeks following onset of symptoms. A) Color fundus photograph shows mottling of the fovea with a yellow colored lesion (black arrow). B) Infrared imaging shows the discrete lesion superior to the fovea (white arrow). C) Fluorescein angiogram was normal with no leakage or blockage of dye. D) Goldmann visual fields showed central scotoma. E) ICG showed hypocyanescence corresponding to the lesions at 30 minutes (white arrow). F) Humphrey visual fields showed no abnormalities in the right eye. G) OCT showing discontinuities in the ellipsoid zone, with intact RPE.

FIGURE 4.

Multimodal imaging of the left eye seven weeks following onset of symptoms. A) Color fundus photograph shows mottling of the fovea with yellow colored lesion (black arrow). B) Infrared imaging shows the discrete lesion superior to the fovea (white arrow). C) Fluorescein angiogram was normal with no leakage or blockage of dye. D) Goldmann visual fields showed central scotoma. E) ICG showed hypocyanescence corresponding to the lesions at 30 minutes (white arrow). F) Humphrey visual fields showed no abnormalities in the left eye. G) OCT showing multiple discontinuities in the ellipsoid zone, with intact RPE.

FIGURE 5.

High resolution macular OCT of the right eye across all visits. A) Mild disruption of the ellipsoid zone and minimal swelling of the outer retina (white arrow). B) Four weeks later, the same area shows edema in the inner layers (dashed white arrow), and increased disruption and swelling are evident in the outer retina (solid white arrow). C) Eight weeks after the initial visit, there is partial restitution of the ellipsoid zone and the swelling of the outer retina has greatly improved.

FIGURE 6.

High resolution macular OCT of the left eye across all visits. A) Retinal edema (white dashed arrow) is present alongside multiple disruptions of the ellipsoid zone with corresponding swelling of the outer retina (solid white arrows). B) Four weeks later, the same area shows increased edema (dashed white arrow), disruption and swelling (solid white arrows). C) Eight weeks after the initial visit, there is partial restitution of the ellipsoid zone and the swelling of the outer retina has improved.