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Acute macular neuroretinopathy in dengue virus serotype 1

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ABSTRACT

Purpose: To report a case of acute macular neuroretinopathy (AMN) associated with dengue virus serotype 1 infection.
Observation: An 18-year-old Puerto Rican female was evaluated due to painless paracentral scotomas in each eye that developed after being hospitalized for dengue fever a week before. Clinical examination and multimodal imaging revealed bilateral hypopigmented macular lesions, hyperreflectivity at the outer nuclear and photoreceptor layer, and reduced flow signal in the deep capillary plexus. Additionally, hypoautofluorescent parafoveal lesions were found in the left eye. AMN was diagnosed. Two-month follow-up after the initial evaluation showed resolution of symptoms but persistence of some findings on optical coherence tomography.
Conclusions and importance: Patients with dengue virus serotype 1 may develop paracentral scotomas with classic AMN findings and obtain complete symptomatic recovery without treatment.

1. Introduction

Dengue fever is a human arboviral disease transmitted by the *Aedes aegypti* mosquito bite, which is present in many tropical and subtropical countries. Symptoms include fever, headache, vomiting, muscle/joint pains, and papulomacular rash.[1] Ocular complications, although uncommon, may lead to permanent visual impairment.[2,3]

Dengue maculopathy consists of a spectrum of retinal vascular manifestations that develop during or immediately after the symptomatic phase of dengue fever and may be characterized by macular hemorrhage, retinal edema, and foveolitis.[1,3–5] There is an overlap between the clinical findings of dengue maculopathy and those of acute macular neuroretinopathy (AMN), which was first described in 1975 by Bos and Deutman in four young women (ages 24–35) using oral contraceptives.[2,6,7] In the present manuscript, we report a young woman with Dengue type 1 confirmed by real-time reverse transcription-polymerase chain reaction (rRT-PCR) who developed AMN with spontaneous recovery.

2. Case report

An 18-year-old Puerto Rican female with primary dysmenorrhea (treated with oral contraceptives) was consulted due to painless paracentral scotomas in each eye (OU) that developed during a dengue fever hospitalization a week before. At the time, the patient experienced symptoms such as myalgias, headache, nausea, vomiting, generalized maculopapular rash, and fever. Visual acuity was 20/20 OU, and the clinical examination appeared normal. Color fundus photography (Optos, Inc.) showed subtle hypopigmented macular lesions OU (Fig. 1a, Fig. 1b). Fundus autofluorescence showed a subtle hypoautofluorescence parafoveal lesion in the left eye (OS) (Fig. 1d). Fluorescein angiography was unremarkable. Spectral-domain optical coherence tomography (SD-OCT) (Heidelberg Engineering, Inc.) was remarkable for bilateral focal hyperreflectivity at the outer nuclear and photoreceptor layers within the lesion (Fig. 2). At the initial evaluation, OCT angiography (Heidelberg Engineering, Inc.) showed a reduced flow signal in the deep capillary plexus OU (Fig. 3a, Fig. 3c). The patient was subsequently diagnosed with AMN, and oral contraceptive therapy was discontinued.

Two weeks after the initial evaluation, her symptoms, examination, and OCT findings were stable. Follow-up two months after the first assessment was remarkable for the resolution of symptoms. Centers for Disease Control and Prevention Dengue virus 1–4 (rRT-PCR) and Trioplex (Trioplex Real-Time RT-PCR) acquired during the hospitalization

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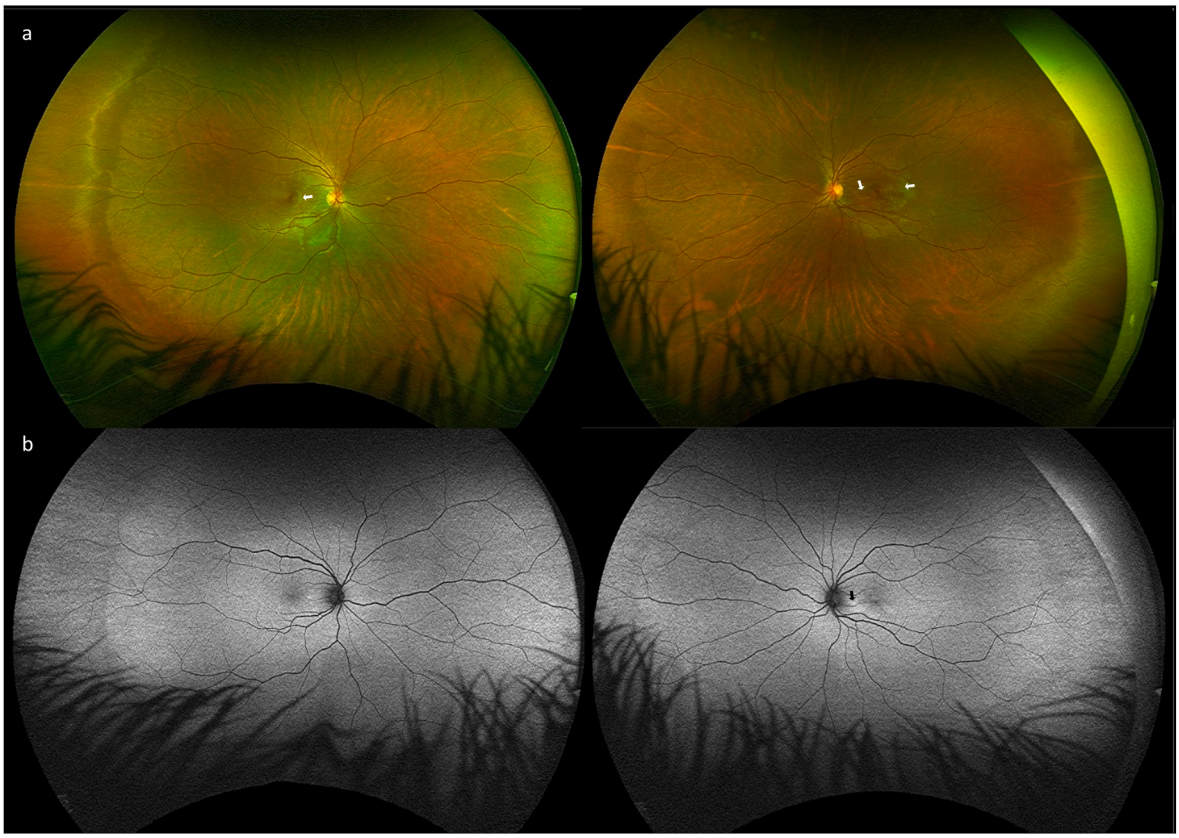

Fig. 1. Color fundus photography and autofluorescence. A. Right eye, subtle hypopigmented macular lesions (white arrow). B. Left eye, subtle hypopigmented macular lesions (white arrows). C. Right eye, normal findings. D. Left eye, hypo-autofluorescence surrounding the fovea (black arrow). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

returned positive for dengue virus serotype 1. SD-OCT showed outer nuclear layer thinning and photoreceptor attenuation in the affected areas OU (Fig. 2c, d, Fig. 2e, f). OCT angiography showed areas of decreased flow in the deep capillary plexus OU (Fig. 3b and d). Discontinuation of oral contraceptive was advised.

3. Discussion

Dengue maculopathy has a broad clinical spectrum that typically develops one week after fever onset and may include intraretinal hemorrhages, macular edema, optic disc swelling, and foveolitis.[3,4] A cross-sectional study of 160 seropositive patients hospitalized for dengue fever during an epidemic in Singapore estimated that the prevalence of dengue maculopathy was 10%.[1] The most common clinical findings included macular edema, small yellow dots, and intraretinal hemorrhages.1 Additionally, in a case series of 9 patients with dengue maculopathy during a dengue outbreak in South China, 5 patients (55.6%) developed AMN.[2]

In 2010 Teoh et al.[5] described 3 patterns of dengue maculopathy based on time-domain OCT: type I (diffuse retinal thickening), type II (cystoid macular edema), and type III (foveolitis). However, with the advent of SD-OCT, prior reports of type III dengue maculopathy may represent AMN.[2] It seems that SD-OCT may improve the specificity in dengue maculopathy.[4]

The pathophysiologic mechanism behind dengue maculopathy is unknown.[4] It has been hypothesized that the typical one-week delay between the onset of fever and the onset of visual symptoms represents a pathological inflammatory response rather than the infection itself.[1,2,4,5] Anecdotal reports of visual improvement following treatment with systemic corticosteroids or immunoglobulin therapy further supports this view.[3,4,8] However, since ocular manifestations are mostly self-limited and treatment is usually reserved for severe cases, it is unrecognized whether the disease's natural progression or medical intervention is responsible for visual recovery.[2] In our report, the patient had resolution of symptoms despite persistent disruption in the normal macular outer retinal structure as seen on SD-OCT.

AMN is a rare maculopathy characterized by the onset of sudden paracentral scotoma with wedge-shaped dark reddish-brown macular lesions.[1] AMN is more common in young women and has been reported associated with viral illness, oral contraceptives, trauma, nocturnal hypotension, caffeine use, injected adrenaline, and norepinephrine use.[9–13] Of note, the current patient was taking oral contraceptives prior to her hospitalization for dengue fever, but the timing of her AMN symptoms suggests that the dengue fever, rather than the contraceptives, was responsible.

Ooi et al.[14] described an adult male with hematologically confirmed dengue fever who presented with paracentral scotomas OU that fully resolved after topical treatment with steroids and cycloplegia. SD-OCT of AMN is characterized by hyperreflective lesions of the outer retinal layers during the acute phase.[15] Disruption of the ellipsoid zone, external limiting membrane, and interdigitation zone with outer plexiform layer and outer nuclear layer hyperreflectivity are typical features.[16–19] Immune complex deposition leading to defective capillary endothelium or blockage at the level of the collecting venule, resulting in ischemia of the choriocapillaris, has been suggested as the most likely underlying pathophysiological mechanism.[20]

The outer retinal SD-OCT abnormalities along with normal angiographic findings initially suggested that the primary insult in AMN was ischemia of the deep capillary plexus.[15] However, Lee et al.[15] stated that deep capillary plexus ischemia results in paracentral acute middle maculopathy (PAMM), previously considered a variant of AMN, as documented in several studies using OCT angiography.[21–24] Most

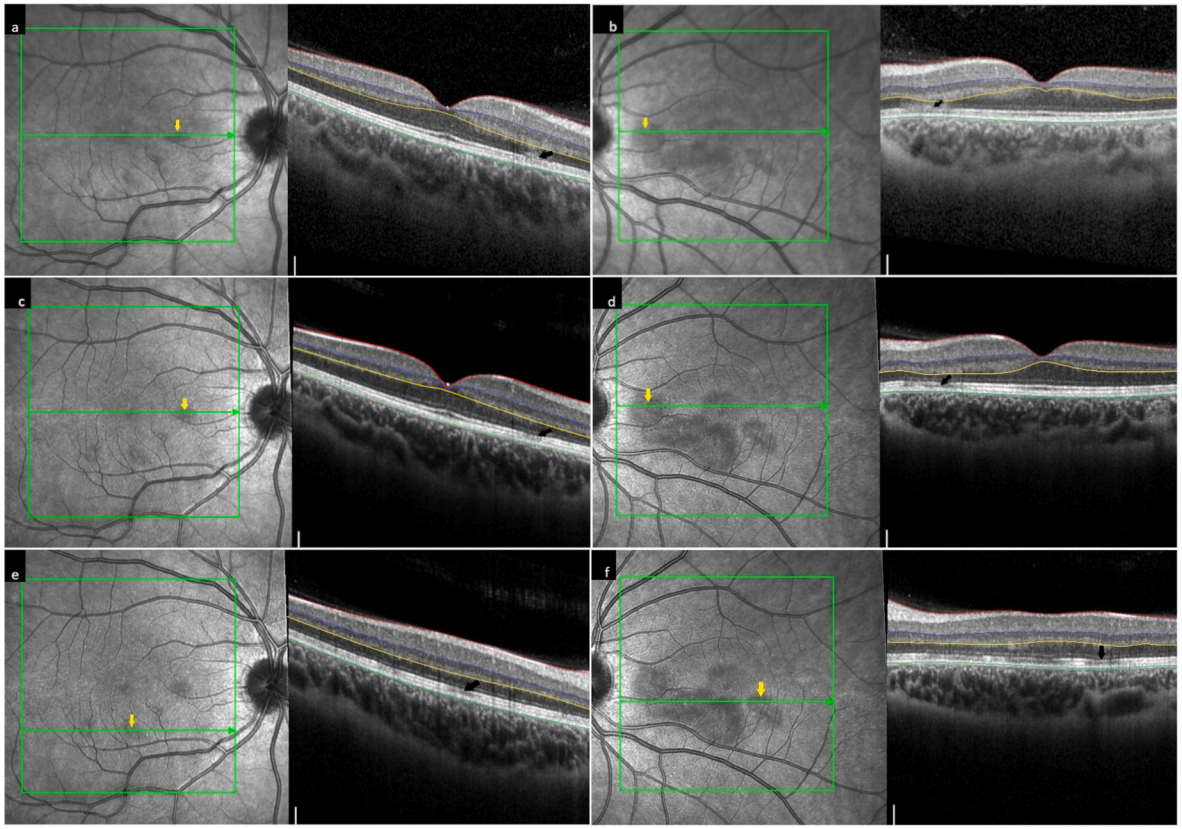

Fig. 2. Macular spectral-domain optical coherence tomography. Segmentation lines are delineated with red, blue, yellow, and green solid lines, respectively, the internal limiting membrane, internal plexiform layer, outer plexiform layer, and basement membrane. A. Right eye, initial evaluation showing hyperreflective changes surrounding the fovea (yellow arrow) and hyperreflectivity at the level of the outer plexiform layer (black arrow) with disruption of the inner and outer photoreceptor segment junction, external limiting membrane, and interdigitation zone. B. Left eye, initial evaluation showing hyporeflective placoid lesions (yellow arrow) involving the fovea and extending inferonasally. Transverse raster scan shows hyperreflective lesion at the level of the outer nuclear layer (black arrow) with disruption of the inner and outer photoreceptor segment junction, external limiting membrane, and interdigitation zone. C. Right eye, 2 months after the initial evaluation showing decreased reflective changes surrounding the fovea (yellow arrow) and decreased reflectivity at the level of the outer plexiform layer (black arrow) with disruption of the inner and outer photoreceptor segment junction, external limiting membrane, and interdigitation zone. D. Left eye, 2 months after the initial evaluation showing decreased reflective changes surrounding the fovea (yellow arrow) and decreased reflectivity at the level of the outer plexiform layer (black arrow) with disruption of the inner and outer photoreceptor segment junction, external limiting membrane, and interdigitation zone. E. Right eye, 2 months after the initial evaluation showing similar changes as C in other affected regions. F. Left eye, 2 months after initial evaluation showing similar changes as D in other affected regions. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

recently, Aggarwal et al.[18] reported on a 39-year-old female with dengue fever and AMN disrupting the superficial and deep capillary plexus on OCT angiography. Our case had diminished flow signal in the deep capillary plexus and choriocapillaris layers on OCT angiography. This implies that the pathophysiology leading to AMN may involve processes beyond ischemia. An exaggerated inflammatory response leading to apoptosis and tissue damage has been proposed as an alternative mechanism.[25]

4. Conclusion

In conclusion, patients with dengue virus serotype 1 may develop paracentral scotomas with classic AMN retinal findings and obtain complete symptomatic recovery after two months without treatment.

Patient consent

Consent to publish this case was not obtained from the patient. The case report does not contain any identifying information.

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Intellectual property

We confirm that we have given due consideration to the protection of intellectual property associated with this work. There are no impediments to publication, including the timing of publication, concerning intellectual property. In so doing, we confirm that we have followed the regulations of our institutions concerning intellectual property.

Research ethics

We further confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

Authorship

All listed authors meet the ICMJE criteria.

We attest that all authors contributed significantly to the creation of this manuscript, each having fulfilled the criteria as established by the ICMJE.

We confirm that all named authors have read and approved the manuscript.

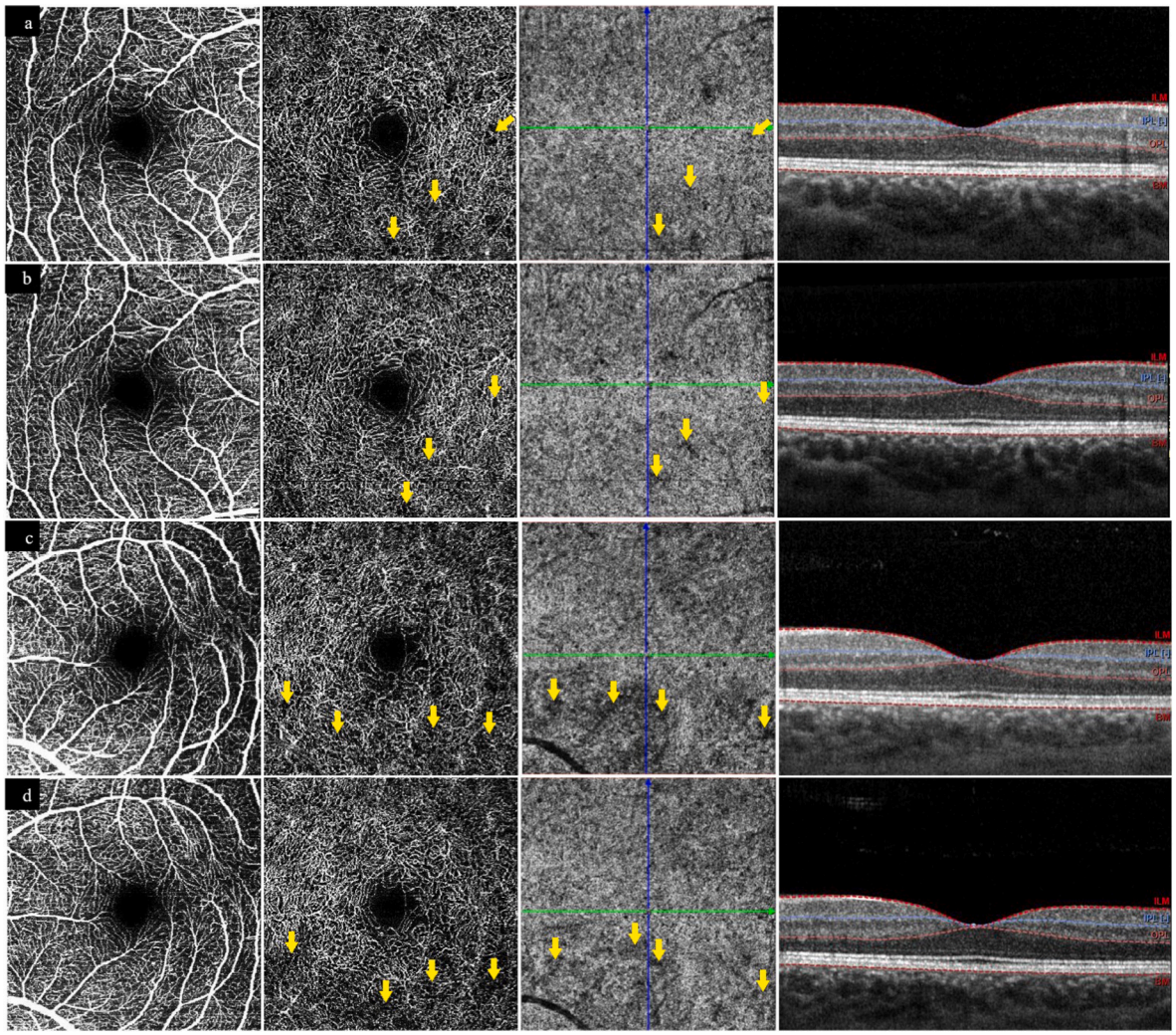

Fig. 3. Macular optical coherence tomography angiography *en face*. Segmentation lines are delineated and labeled as internal limiting membrane (ILM), internal plexiform layer (IPL), outer plexiform layer (OPL) and basement membrane (BM). A. Right eye, superficial capillary plexus, deep capillary plexus, choriocapillaris, and transverse raster scan during the initial evaluation. The deep capillary plexus and choriocapillaris shows some areas of decreased flow (yellow arrows). B. Right eye, superficial capillary plexus, deep capillary plexus, choriocapillaris, and transverse raster scan 2 months after the initial evaluation. The deep capillary plexus and choriocapillaris shows some areas of decreased flow (yellow arrows). C. Left eye, superficial capillary plexus, deep capillary plexus, choriocapillaris, and transverse raster scan during the initial evaluation. The deep capillary plexus and choriocapillaris shows some areas of decreased flow (yellow arrows). D. Left eye, superficial capillary plexus, deep capillary plexus, choriocapillaris, and transverse raster scan 2 months after the initial evaluation. The deep capillary plexus and choriocapillaris shows some areas of decreased flow (yellow arrows). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

We confirm that all named authors have approved the order of authors listed in the manuscript.

Contact with the editorial office

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Declaration of competing interest

No conflict of interest exists.

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