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Evidence of dengue virus in eviscerated specimens of panophthalmitis secondary to dengue fever: A possible cause-effect phenomenon

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Purpose: To report a retrospective series of three cases of infectious panophthalmitis post-dengue fever with *ex vivo* confirmation of dengue virus ribonucleic acid (RNA) in the tissues of the eye. **Methods:** Four eyes of three patients, who were diagnosed with panophthalmitis following dengue fever and who underwent evisceration, were included. All demographic and clinical data were recorded. The eviscerated samples were subjected to direct microscopy, culture for bacteria, fungi, and parasites, and molecular virology (dengue virus [DENV] NS1-specific reverse transcription loop-mediated isothermal amplification (RT-LAMP) assay). **Results:** The time from the development of dengue fever to the occurrence of ocular symptoms was 4.33 ± 1.15 (median 5) days. DENV NS1 RNA, suggestive of the presence of the dengue virus, was confirmed in all evisceration specimens (uveal tissue, cornea). All the patients recovered completely from dengue fever and on follow-up had healthy eviscerated sockets. **Conclusion:** Demonstration of the DENV RNA in the eviscerated specimens of panophthalmitis following dengue fever implicates the DENV in the pathophysiology of the ocular infection.

Key words: DENV NS1, dengue fever, panophthalmitis, pathophysiology, RT-LAMP assay

Dengue fever is a virus-borne (flavivirus) infection endemic in South East Asia, Central America, and South America caused by the dengue virus (DENV). It is characterized by fever, headache, arthralgia, and rash.[1,2] While largely known for its systemic manifestations, dengue fever also causes ocular morbidity. The anterior segment manifestations include periorbital ecchymosis, subconjunctival hemorrhage, bilateral punctate corneal erosions, and anterior uveitis while the posterior segment involvement which is commoner can present as intermediate uveitis, maculopathy (foveolitis), retinal vasculitis, retrobulbar hemorrhage, isolated peripheral hemorrhage, vitreous hemorrhage, sub-hyaloid hemorrhage, and Roth spots.[3,4] A plethora of studies on the host–virus interactions to understand the systemic pathogenesis in humans has been published, however, the literature is bereft of publications on DENV and its role in ocular diseases.[5] Similarly, cellular and molecular mechanisms to understand systemic dengue have been extensively studied, but on the literature search, no publications of DENV *in vitro* or *in vivo* to understand the disease pathology, risk factors for eye disease, and preventive measures could be found. The precise pathogenesis of dengue ophthalmic complications is not well understood. Many studies have alluded to the possibility of an immune-mediated process as a likely mechanism.[4,6,7] Keeping this gap in the literature in mind, in the current communication, we sought to report

the clinical presentation, virology, and management of three cases of panophthalmitis in dengue fever; and demonstrate the presence of DENV RNA coding for non-structural protein 1 (NS1 DENV RNA) in the uveal and other tissues using NS1 DENV-specific reverse transcription loop-mediated isothermal amplification (RT-LAMP) assay. We also hypothesize and discuss the uvea to be the seat of initiation of the infection and inflammation in cases of intraocular involvement by the DENV.

This was a retrospective consecutive, interventional case series. The study was approved by the institutional review board and adhered to the tenets of the Declaration of Helsinki. All the patients provided written informed consent for use of data and photographs for academic purposes. The study included cases presenting to the clinic with panophthalmitis and having a systemic diagnosis of dengue infection based on typical clinical features and positive serology for antibody to NS1 within 3 months of ocular involvement. Demographic details such as age, gender, details of systemic comorbidities, duration between the onset of systemic to ocular symptoms, records of systemic and prior ocular treatment, laterality of ocular involvement, ocular symptoms and signs including visual acuity, anterior segment, posterior segment, and adnexal involvement were noted. The details of the intraoperative findings of ocular

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and periocular tissues, medical and surgical treatment, ocular and body fluid investigations, and hemogram parameters were recorded. The data of the microbiological investigations including direct microscopy, culture for bacteria, fungi, or parasites, and molecular virology were collated and analyzed.

Case Reports

Case 1

A 34-year-old man, with a history of dengue hemorrhagic fever and under treatment for 5 days presented to us with a sudden-onset loss of vision, watering, and photophobia since 1 day in the left eye. He had a history of five transfusions of the platelets in the previous week. On examination, the vision in the left eye was an inaccurate projection of the rays. The clinical examination revealed intense conjunctival chemosis, microcystic corneal edema, hyphema, and raised intraocular pressure [Fig. 1a]. There was a poor view of the fundus and the B-scan ultrasonography revealed choroidal thickening and subtenons fluid. He was started on topical and oral antiglaucoma management (oral acetazolamide 250 mg three times a day (TID), topical brimonidine tartrate 0.15%, timolol maleate 0.5% eye drops) for the control of intraocular pressure (IOP), and an urgent referral was made to an internist in view of the shortness of breath with a systolic blood pressure of 70 mmHg. The following day, he was brought to the clinic with complaints of progressive proptosis [Fig. 1b]. He was in dengue shock syndrome at the time of presentation to the eye clinic. On examination, the right eye vision and ocular examination were normal [Fig. 1b]. The vision in the left eye was an inaccurate perception of light. There was abaxial proptosis with complete exposure of the left ocular surface, chemosis with dense subconjunctival hemorrhage, hyphema, and no view of

Figure 1: Case 1. (a) Slit-lamp photograph under diffuse illumination suggestive of left eye conjunctival congestion, corneal edema, and hyphema, (b) standard photograph suggestive of left eye severe proptosis and chemosis, (c) standard photograph suggestive of bilateral ocular involvement, (d) high magnification photograph of the left eye suggestive of corneal melt, (e) CT scan of the orbit in the axial view suggestive of bilateral disorganized globes with left severe proptosis and diffuse orbital involvement, (f) standard photo of both eyes following evisceration.

the fundus [Fig. 1b]. He was advised of an urgent computed tomography (CT) scan, however, in view of the unstable systemic status, the patient could not come back for a follow-up eye examination over the next 3 weeks. Three weeks later, the patient was systemically stable but complained of loss of vision in the right eye as well [Fig. 1c]. Blood culture done for the patient elsewhere was suggestive of systemic *Klebsiella* infection and he was on systemic imipenem for the same. The right eye had developed a corneal melt [Fig. 1d] and the left eye had severe proptosis with disorganized globes in both eyes. A B-scan of both the eyes was suggestive of panophthalmitis with corneal melt. The CT scan of the orbit revealed a disorganized right eyeball. There was left orbit proptosis, ill-defined iso-dense shadows, and a disorganized eyeball [Fig. 1e]. In view of bilateral corneal melt and panophthalmitis with nil visual prognosis, both eyes were taken up for evisceration.

Part of the eviscerated material from both eyes was submitted for histopathological study and complete microbiological evaluation and cultured for bacteria and fungi. This was subsequently reported to be sterile after 7 days of incubation. Of the remaining material, the tissue from each layer (conjunctiva, cornea, sclera, uveal tissue) from both eyes was submitted in saline along with the vitreous and the patient's blood samples and were sent for molecular virology testing. The viral RNA was extracted from the samples by using the QIAamp viral RNA mini kit (Qiagen, Germany). The RNA was eluted from the QIA spin columns in a final volume of 50 µL of the elution buffer and screened. Initially, all the samples were screened for NS1 DENV RNA using NS1 DENV-specific reverse transcription loop-mediated isothermal amplification (RT-LAMP) assay.[8] All the DENV RNA-amplified products were further assayed to identify the specific serotype involved. Using 95% consensus sequence, primer sets had been generated that were directed against the serotype-specific regions of the NS1 gene for all four serotypes of DENV (1-4). An RT-LAMP DENV-positive serum sample was used as a positive control for the assay. An NS1 DENV negative serum sample and a no template control (NTC) were used as a negative control to validate the assay runs. The DENV NS1 serotype RNA was found in the uveal tissue from the right eye while none of the other samples were positive. The left eye samples did not show DENV NS1 RNA. Fig. 2 shows the results of RT-LAMP DENV assay. The histopathology showed necrosis, chronic inflammation, and exudative debris in the uveal tissue. Gram, Gomori methenamine silver, and Ziehl–Neelsen stain were negative for the organisms. The patient was systemically stable after the evisceration and the socket was healthy [Fig. 1f].

Case 2

A twenty-one-year-old man presented with complaints of sudden decrease of vision in the left eye 3 days after he was diagnosed with dengue hemorrhagic fever. It was associated with pain, watering, swelling, and redness. He gave a history of platelet transfusion 1 week ago in view of the dengue hemorrhagic fever. He was also reported to have respiratory acidosis. At presentation, the platelet count was 60,000 per microliter of blood. On examination, the right eye vision and ocular examination were within normal limits. The left eye had no perception of light. There was the presence of a left eye tense proptosis [Fig. 3a] with mechanical ptosis, conjunctival chemosis, and frozen globe [Fig. 3b].

The fundus was not visible and the B-scan was suggestive of moderate echospike reflectivity in the vitreous cavity with thickened choroid and subretinal hemorrhage [Fig. 3c]. The CT scan of the orbit was suggestive of left eye proptosis with a disfigured globe, thickened ocular coats, and diffuse orbital fat stranding [Fig. 3d]. There was no evidence of retrobulbar hemorrhage. He was diagnosed to have dengue panophthalmitis with orbital cellulitis. He was started on intravenous injection augmentin in a dose of 1.2 g bd and topical antibiotics and after 48 h intravenous steroids were initiated. While on treatment, the inflammation subsided but he developed a progressive nasal scleral abscess with melt [Fig. 3e and f]. He eventually underwent evisceration with an implant for the left eye [Fig. 3g]. The conjunctiva, cornea, sclera, uveal tissue, vitreous, and the patient's blood sample were sent for molecular virology for the detection of DENV NS1 RNA as described for case 1. While all other samples were negative, the DENV NS1 RNA was detected in the uveal tissue. He was systemically stable after evisceration and the eye socket was healthy. He was dispensed with a custom ocular prosthesis [Fig. 3h].

Case 3

A 48-year-old farmer complained of pain, swelling, and sudden loss of vision in the right eye of 1-day duration. He was diagnosed with dengue hemorrhagic fever 5 days ago. He was admitted and was on intensive care for 4 days following which the eye symptoms developed and an urgent referral to the ophthalmology services was made. On examination, his vision in the right eye was a perception of light with an inaccurate projection of rays. He had right-sided conjunctival congestion, chemosis, limited extraocular movements, corneal stromal edema with raised IOP, and no view of the fundus. The B-scan revealed minimal vitreous echoes with thickened choroid and a "T" sign. A diagnosis of panophthalmitis secondary to endogenous endophthalmitis with dengue hemorrhagic fever was made. A vitreous biopsy with intraocular injection of prophylactic vancomycin and dexamethasone was performed and he was continued on the systemic antibiotics and steroids. The calcofluor white mount of the vitreous sample in direct fluorescence microscopy was negative while the Gram stain showed thick, beaded gram-positive bacilli [Fig. 4a] suggestive of *Bacillus* sp. The culture showed heavy growth of the *Bacillus* species on all media including blood agar [Fig. 4b]. The isolate

was susceptible to chloramphenicol, ofloxacin, amikacin, gatifloxacin, moxifloxacin, and vancomycin by the Kirby Bauer disk diffusion method of antibiotic susceptibility testing. He underwent multiple intraocular antibiotic injections and the panophthalmitis resolved but he had a painful blind eye with scleral necrosis in the inferotemporal quadrant [Fig. 4c and d].

He underwent an uneventful evisceration with the implant. Similar to case 1, each layer of the eye was sent in formalin for histopathology and in saline for molecular virology to look for the presence of the DENV in the ocular structures and diagnostic microscopy and culture. The histopathological findings were similar to case 1. There were no organisms seen on microscopy but the culture showed significant growth of *Staphylococcus epidermidis*. The dengue molecular assay with loop-mediated isothermal amplification for DENV NS1 RNA was positive in the corneal and the uveal tissue. The other samples were negative for the DENV NS1 RNA. He was systemically stable after the evisceration and a custom prosthesis was dispensed [Fig. 4e and f]. The clinical and microbiological profiles of all three patients are given in Table 1.
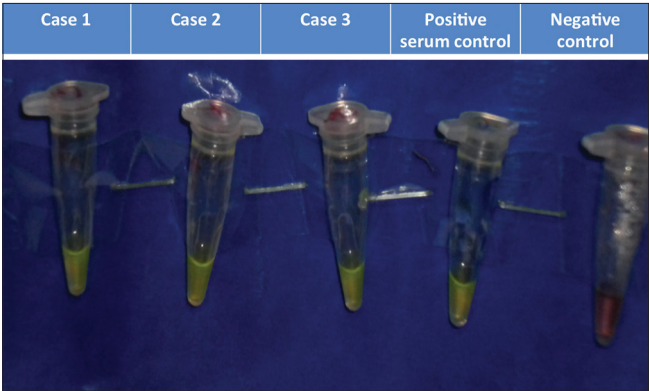

Figure 2: Standard photograph of microcentrifuge tubes showing the result of LAMP assay with uveal tissue extracts from all three cases along with positive and negative controls. The green fluorescence indicates a positive reaction and the orange color indicates a negative reaction.
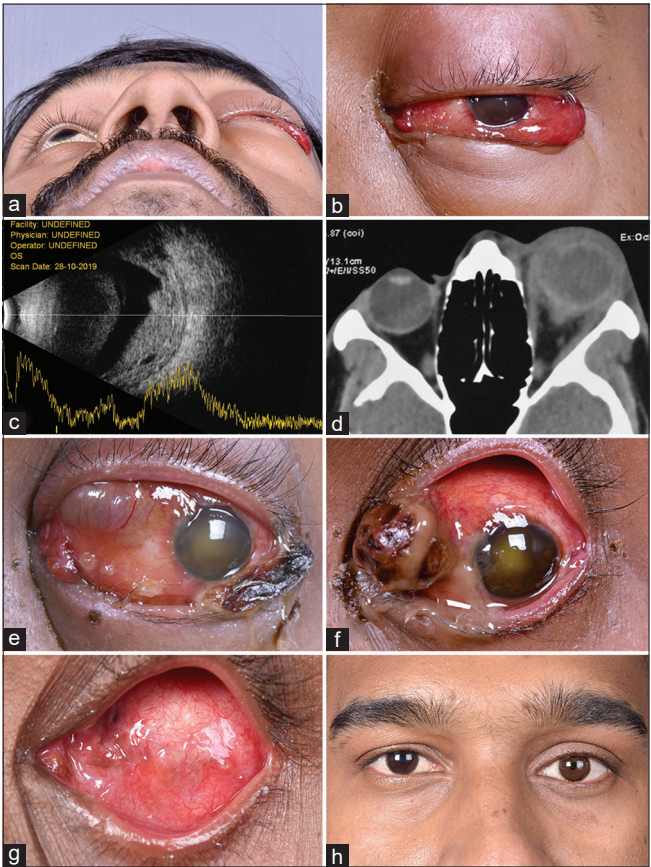

Figure 3: Case 2 (a) Standard photograph in worm's view suggestive of left severe proptosis, (b) high magnification photograph suggestive of left severe proptosis and chemosis, (c) B-scan of the left eye suggestive of moderate echospike reflectivity in the vitreous cavity with thickened choroid and subretinal hemorrhage, (d) CT scan of the orbit in the axial view suggestive of left severe proptosis with isodense echoes around the globe, (e and f) high magnification photos of the left eye suggestive of progressive nasal scleral necrosis and melt, (g) high magnification photograph of the socket post-evisceration, (h) standard photograph following dispension of left ocular prosthesis.

Discussion

The current series reports four eyes of three patients with dengue fever-related panophthalmitis. All eyes were managed surgically with evisceration as per the standard of care. The dengue molecular assay with loop-mediated isothermal amplification for DENV NS1 RNA was positive in three of the four uveal samples and one corneal sample. The first and second cases had severe thrombocytopenia and presented with proptosis due to hemorrhagic complications. The subsequent worsening was probably due to the superadded infection, as patient 1 had septicemia due to the *Klebsiella* species. In the second case, we could not detect any infectious agent apart from the DENV itself.
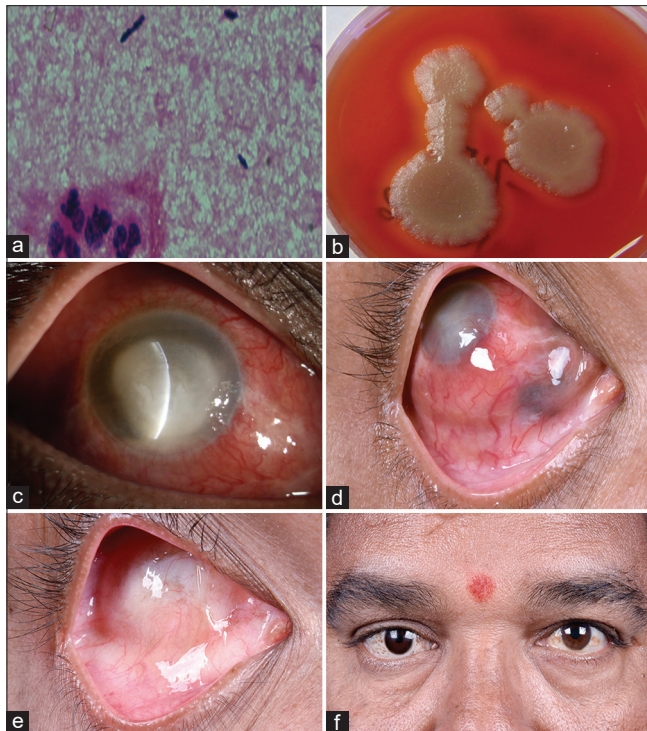

Figure 4: Case 3 (a) Direct microscopy of vitreous biopsy showing thick, beaded gram-positive bacilli and inflammatory cells (X1000), (b) vitreous biopsy culture on blood agar shows heavy growth of yellowish, dry colonies that were identified as Bacillus species, (c) slit-lamp photograph suggestive of the right eye conjunctival congestion, corneal edema, and exudates in the anterior chamber, (d) high magnification photograph suggestive of left inferonasal scleral necrosis, (e) high magnification photograph following evisceration, (f) standard photograph following dispension of the right ocular prosthesis.

The third case showed the *Bacillus* species in the vitreous biopsy and the subsequent cultures of the eviscerated specimens grew *Staphylococcus epidermidis*. The presence of a live virus in these cases may have contributed to the relentless worsening that we noted. A variety of ocular complications have been reported in dengue fever and are mostly attributed to thrombocytopenia and the associated bleeding diathesis. Panophthalmitis, though uncommon, is a known posterior segment complication of ocular involvement secondary to dengue fever.[9]

Saranappa *et al.*[9] have reported a case of proptosis secondary to panophthalmitis in a 6-year-old child diagnosed with dengue fever. The child initially presented with angle-closure glaucoma but subsequently progressed to develop exudates in the vitreous cavity. The ultrasound imaging showed inflammatory thickening of the retinochoroidal and orbital tissues. The authors hypothesized the panophthalmitis to be a part of the inflammatory or immune response to the DENV infection. Arya *et al.*[10] described a case of a 22-year-old male having dengue fever, who presented with pain, redness, swelling, and loss of vision in his right eye. He was diagnosed with panophthalmitis with subretinal hemorrhage. In their case, the Tenon's capsule and sclera showed necrosis and extensive areas of scleral melt with the fragmentation of the sclera. The eviscerated ocular specimen along with scleral biopsy underwent histopathology and microbiological examination. The microbiological examination revealed no growth on any culture media. The histopathological examination of the scleral tissue was similar to our cases and showed severe nonspecific inflammatory infiltration with areas of necrosis. The authors proposed immune-mediated vasculitis as a cause of possible manifestations in their cases.

Kamal *et al.*[11] reported a culture-positive case of panophthalmitis caused by *Bacillus cereus* in a patient with serology-positive dengue hemorrhagic fever. They postulated that the disintegration of the endothelial cells caused by the antibodies against the NS 1 protein facilitated the direct entry of the bacteria into the uveal and retinal circulation causing septic focus and secondary endophthalmitis. In our series too, the vitreous from one of the four eyes grew the *Bacillus* species. Kumar *et al.*[12] reported a case of panophthalmitis in a patient with dengue fever who subsequently developed intracranial abscesses. The authors postulated that the condition occurred due to a dysregulated immunological response which could have targeted the eye antigens and led to the inflammation of all layers of the eyeball. This inflammation compromised the local immunity of the eyeball and led to the invasion of secondary infection by conjunctival flora, *Staphylococcus epidermidis*. Although in all of the previously existing scant literature on dengue-related panophthalmitis, the inflammatory or immunological role of the dengue virus is postulated, only one other report[13] suggests the

Table 1: The clinical and microbiological profile of all the three patients

Case no., Eye	Clinical profile	Ocular presentation	Microbiology: body fluids	Microbiology: ocular	DENV-NS1 RNA
Case 1 LE	35 years, male, 5-day history	Proptosis, corneal melt, disorganized globe, panophthalmitis	*Klebsiella* sp. (blood)	No growth	Negative
Case 1 RE	35 years, male, 3 weeks history	Proptosis, corneal melt, panophthalmitis	*Klebsiella* sp. (blood)	No growth	DENSV NSI from uveal tissue
Case 2 LE	21 years, male, 3 days history	Proptosis, disfigured globe, panophthalmitis, orbital cellulitis	Not available	No growth	DENSV NSI from uveal tissue
Case 3 RE	48 years, male, 1 day history	Panopthalmitis, endogenous endophthalmitis	Not available	*Bacillus* sp., *Staphylococcus epidermidis*	DENSV NSI from uveal tissue, cornea

presence of DENV detected in the RNA extracted from the donor corneoscleral rim excised from a cadaver with a history of viral hemorrhagic fever. The current series shows the presence of the DENV from the intraocular tissues.

Gupta *et al*.,[14] in their article on uveitis in dengue fever, suggest immune-mediated pathogenesis due to the low complement C3 and C4 in the dengue patients. They proposed the possibility of specific autoantibodies being produced in such cases against the retina, retinal pigment epithelium, and the choroid. Dengue fever-associated acute angle-closure glaucoma was reported previously.[15,16] They postulated that this syndrome causes ciliary body edema, which triggers acute angle-closure. Though no attempts were made to isolate the DENV from the eye, these reports indirectly incriminate the uveal tissue as the site of pathology.

Studies have been performed to assess the localization of the DENV in the naturally infected human tissues.[17,18] They reveal that macrophages, peripheral blood monocytes, reactive splenic lymphoid cells, and peripheral lymphocytes may be the major target cells of the dengue viral replication in natural human infections. The liver is commonly involved in the DENV infections in the humans and mouse models where it is known to cause hepatocyte apoptosis and necrosis.[19,20] The DENV also shows tropism for the vascular endothelial cells where it increases vascular permeability and a tendency to activate complement and set up a cascade of inflammation in the surrounding tissue.[21,22] In the current study, the DENV RNA was demonstrated in the uveal tissue in all the cases. It is plausible that, in these cases, the virus from the uveal tissue caused intraocular cellular necrosis, increased vascular permeability with subsequent in-flow of inflammatory cells, and profuse inflammation due to the activation of the complement. All of this manifested clinically as panophthalmitis. A limitation of the present study is that the mere detection of the viral RNA may not indicate the presence of an infectious virus or that dengue is the causative agent for ocular manifestations. Since one of the cases isolated bacteria from intraocular tissues, it is highly possible that the DENV may have enabled the breakdown of the blood-retinal barrier, making way for bacterial infection of the ocular tissues causing panophthalmitis. The presence of DENV RNA may be incidental due to its presence in the blood and traveling to the intraocular tissues after the breakdown of the blood-ocular barrier.

Conclusion

In conclusion, panophthalmitis is a rare but known ocular adverse event following systemic dengue fever. The conclusive presence of the DENV RNA in the current case series in the background of the known pathophysiology of systemic dengue suggests a direct role of the DENV on the intraocular tissues leading to rapid progression of ocular infection to panophthalmitis.

Conflicts of interest

There are no conflicts of interest.

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