case report

Dengue retinochoroiditis

Khalid Tabbara

From the Department of Ophthalmology, The Eye Center and The Eye Foundation for Research in Ophthalmology, Riyadh, Saudi Arabia

Correspondence: Khalid Tabbara, MD · The Eye Center and The Eye Foundation for Research in Ophthalmology, 241 Makkah Road (Takhassussi East), PO Box 55307, Riyadh 11534, Saudi Arabia · T: +966-1-4649614 F: +966-1-462-9675 · k.tabbara@nesma.net.sa

Ann Saudi Med 2012; 32(5): 530-533

DOI: 10.5144/0256-4947.2012.30.4.1105

Dengue is a mosquito-borne infection caused by a flavivirus. I describe the ocular findings observed in two patients infected with dengue virus who presented with acute onset of loss of vision preceded by febrile illness, malaise, generalized fatigue headache, and maculopapular rash. Ophthalmologic evaluation in each patient revealed a normal anterior segment. Vitreous cells were noted in one patient. Ophthalmoscopy revealed multiple foci of retinochoroiditis, vasculitis, cotton-wool spots, and retinal hemorrhages. The healing of the lesion showed discrete atrophic and pigmented retinochoroiditic scars. Fluorescein angiography displayed early hypofluorescence and late hyperfluorescence suggestive of leakage. The healed scars showed late staining. The serologic testing showed elevated IgG antibodies, and one had high IgM antibodies to dengue virus. Ocular findings of dengue fever consist of multifocal areas of retinochoroiditis and may lead to loss of vision. In Saudi Arabia, dengue fever should be considered in the differential diagnosis of multifocal chorioretinal lesions and retinal vasculitis.

Dengue fever is a vector-borne infection caused by a flavivirus. The disease is endemic in tropical regions of the world. In recent years, there has been an increase in number of cases reported in Saudi Arabia.[1-4] It is estimated that 100 million people are infected with dengue viruses each year worldwide.[5,6] The disease is characterized by an influenza-like syndrome with sudden onset. Patients develop fever, cough, malaise, generalized fatigue, and headache. The disease is characterized by severe pains in the muscles and joints and may develop enlargement of the lymph nodes. Maculopapular rash and leukopenia are common. The disease has a spontaneous recovery with regression of the findings except for weakness that may persists for several weeks. Dengue fever is regarded as a mild self-limited disease. However, 10% of dengue patients may develop potentially fatal complications of dengue hemorrhagic fever. Patients may have the same initial symptoms of dengue fever followed by hemorrhage and shock. The hemorrhage may occur in the mucosal surfaces and the skin. It is believed that the hemorrhagic-shock syndrome is due to the production of a large amount of cross-reacting antibodies in addition to a previous exposure to dengue virus. Following recovery from a classic dengue fever by 1 of the 4 known serotypes, antibodies against the dengue virus serotypes are produced.

Dengue virus is transmitted by the mosquito *Aedes aegypti*. This is the same vector as that of the yellow fever virus. Humans are a known reservoir of dengue virus. The diagnosis is made by an elevated IgM antibody level against one of the four known serotypes of dengue virus or a 4-fold increase in the IgG antibody titer in acute and convalescent sera. No treatment or vaccination is available for dengue fever. Recent climate changes may have increased the burden of vector-borne diseases.[7,8] It is estimated that half of the world's population is at risk of infection and as many as 100 million cases occur annually.[6] Visitors to dengue endemic countries may come back to western Europe and the United States with symptoms of dengue fever.

Ocular involvement in dengue fever has been previously reported.[9-13] Acute retinitis and maculopathy may occur in 10% of the cases who are hospitalized with dengue fever.[14] Patients with dengue fever may develop retinal hemorrhages.[13] Anterior uveitis may occur, but is usually mild. The ocular symptoms may range from mild blurring of vision to blindness.[15-18] Patients may present with a sudden decrease in visual acuity and central scotoma or vitreous floaters.[19-22] The disease is bilateral in 73% of cases.[11] This report describes two cases of multifocal chorioretinitis following dengue fever.

CASE 1

A-32-year-old male from Jeddah, Saudi Arabia, pre-

sented with a history of seeing floaters and a decrease in vision in both eyes of a 5-day duration. The ocular findings were preceded by symptoms of fever, malaise, headache, arthralgias, and skin rash 1 week earlier. On eye examination, the patient was found to have a visual acuity of 20/100 in the right eye and 20/40 in the left eye. Biomicroscopy of both eyes revealed no cells and no flare. The pupils were regular and reactive and the lens in each eye was clear. The vitreous showed minimal cells in both eyes. Ophthalmoscopy of the right eye revealed multifocal areas of chorioretinitis with retinal vasculitis, cotton-wool spots, and flame-shaped hemorrhages. The left eye showed similar findings of foci of multifocal chorioretinitis with retinal hemorrhages and retinal vasculitis (**Figures 1a and 1b**). The fundus fluorescein angiography showed areas of early blockage of the dye and late leakage. Laboratory investigations for syphilis, toxoplasma, rubella, brucella, rickettsia, and herpes were all made. The purified protein derivative (PPD) test was negative and chest x-ray was also negative. Renal and liver function tests were normal. The patient had leukopenia and thrombocytopenia. Serologic antibody titers for dengue virus showed high titers of IgM antibodies to dengue virus. The diagnosis of dengue chorioretinitis was made, and the patient was given oral nonsteroidal anti-inflammatory drugs for his joint pain. The patient had a complete resolution of his ocular lesions and showed areas of pigmented scars that were nummular in shape, and his visual acuity 6 weeks after the onset of disease was 20/50 in the right eye and 20/25 in the left eye.

CASE 2

A 43-year-old male from Jeddah, Saudi Arabia, pre-

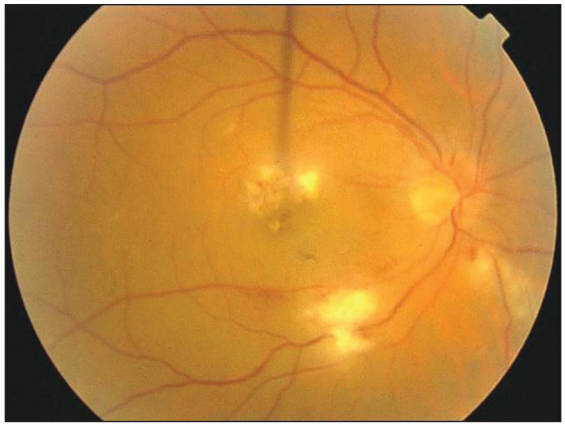

Figure 1a. A 32-year-old male with history of blurring of vision in both eyes one week following febrile illness showing multifocal areas of retinochoroiditis, with cotton-wool spots and retinal hemorrhages in the right eye.

Figure 2a. A 43-year-old male with multifocal nummular pigmented retinochoroiditic scars in the right eye. Photo taken four months after onset of dengue fever.

Figure 1b. The left eye of the patient in Figure 1 showing areas of active retinochoroiditis.

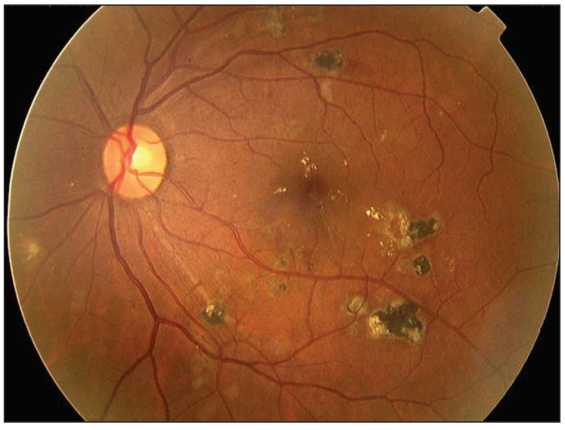

Figure 2b. The left eye of patient in Figure 3 showing multifocal retinochoroiditic scars taken four months after onset of dengue fever.

sented with a history of blurring of vision of both eyes of 1-week duration. The patient gave a history of fever, malaise, generalized fatigue, and joints pain of a 2-week duration. The onset of his ocular findings occurred 1 week after the fever. On eye examination, the patient was found to have a visual acuity of 20/30 in the right eye and 20/40 in the left eye. Tension was 15 mm Hg in the right eye and 18 mm Hg in the left eye. Biomicroscopy of both eyes revealed normal eyelids and conjunctiva. The cornea was clear with no keratic precipitates. The anterior chamber showed no cells or flare. The pupils were regular and reactive, and the lens was clear in each eye. Ophthalmoscopy of both eyes showed no vitreous cells. Both eyes showed multiple foci of nummular retinochoroiditis with healed vasculitis and cystoid macular edema in the left eye. Laboratory investigations showed a normal complete blood cell count (CBC) differential and sedimentation rate. The quantiferon test was negative (4 IU/mL). The PPD was negative, and the chest x-ray and CT scan of the chest were within normal limits. Antinuclear antibodies , angiotensin converting enzyme, and rapid plasma reagin were all negative. Dengue virus IgG antibodies showed a 4-fold increase in the titer, and IgM antibodies to dengue virus were negative. The patient had thrombocycopenia. No treatment was rendered and the patient had spontaneous resolution of the retinochoroiditis with residual nummular retinochoroiditic scars in both eyes (**Figures 2a and 2b**). The patient's visual acuity 2 months later was 20/20 in the right eye and 20/30 in the left eye.

DISCUSSION

Flaviviruses are icosahedral nucleocapsids surrounded by an envelope and a single-stranded, positive-polarity RNA genome. The virus measures 40 to 50 nm in diameter. There are 4 serotypes of dengue virus that cause a wide spectrum of clinical disease ranging from asymptomatic infection to dengue hemorrhagic fever. The most common clinical manifestation is dengue fever, while dengue hemorrhagic fever occurs in a minority of patients and is characterized by the leakage of plasma from blood vessels and hypotensive shock. Plasma leakage is the most serious complication of dengue Infection.[23] Dengue virus appears to infect the endothelial cells of the blood vessels and lead to change in vascular permeability.[24,25] Dengue fever is endemic in the western region of Saudi Arabia. Most of the cases occur in the summer months of June, July, and August. Fever is the most common feature of the disease followed by generalized muscle aches, headaches, and vomiting. The main neurologic abnormalities are thrombocytopenia and leukopenia.

A new viral hemorrhagic form was described in Saudi Arabia.[5] The flavivirus is referred as "Alkhumra" virus. Infection with Alkhumra virus is characterized by hepatitis with hemorrhagic manifestations and encephalitis. Twenty-five percent of patients infected with Alkhumra virus die. The disease seems to be transmitted from sheep or goats by mosquito bites or direct contact with animals.[5] Dengue fever is caused by the same group of viruses that cause West Nile infection. The typical ocular feature of our two cases with dengue fever chorioretinitis was characterized by foci of multifocal choroiditis with retinal vasculitis involving the small vessels. The clinical findings occurred 1 week after the onset of fever just as the fever was decreasing and the platelet count was increasing. Both patients had a sudden onset of decrease in vision, and the disease was bilateral. The main clinical findings were retinal hemorrhages, sheathing of the veins, cotton-wool spots, and multiple areas of retinochoroiditis with macular edema. Vitreous cells were observed in 1 patient. Previous reports emphasized the involvement of the macula and fovea in patients with dengue fever retinitis.[13]

Dengue fever is endemic in tropical regions. Infected humans have high blood levels of virus and can infect the vector mosquitoes. The mosquito *A aegypti* harbors the virus in the salivary glands where it multiplies, and the virus can be transmitted to another person. Climate change may have enormous implications on the burden of vector-borne diseases such as dengue fever.[7,8] In Jeddah, there were severe climate events that led to floods and more stagnated water. Rising temperatures and changing rainfall patterns are expected to have a substantial effect on insect vectors. *A aegypti* is more active at higher temperatures and thrives in aquatic habitats where they lay their eggs in water-filled and stagnant containers. Epidemics of mosquito-borne infections can also occur during times of drought.

The macular chorioretinitis that occurred in one of our patients led to a marked decrease in vision because of scarring. Spontaneous resolution of the chorioretinitis occurred in both patients. The retinal hemorrhages that were observed may have been due to the dengue virus infection of endothelial cells of retinal blood vessels. In addition, patients may develop plasma leakage and hemorrhages. The FasL/Fas pathway is believed to be involved in dengue virus-induced apoptosis of vascular endothelial cells.[26-28] This may lead to microvascular occlusions and cotton-wool spots in the inner layers of the retina. The spread of dengue virus in Jeddah was studied by Zaki and associates.[2] They found that 3 of the 4 dengue serotypes (DENV-1, DENV-2,

DENV-3) were causative agents in Saudi Arabia. More than one dengue virus serotype was detected in each outbreak. In summer of 2004, all three serotypes were isolated, and the DENV-1 serotype was the cause of the outbreak in the summer of 2005 through early 2006. Khan and co-workers[3] documented the occurrence of dengue virus infection in Makkah, Saudi Arabia. In Saudi Arabia, the clinician should consider dengue fever in the differential diagnosis of multifocal chorioretinal lesions and retinal vasculitis.

REFERENCES

1. Kheir SM, Alahmed AM, Al Kurji MA, Al Zubyani SF. Distribution and seasonal activity of mosquitoes in al Madinah AlMunwwrah, Saudi Arabia. J Egypt Soc Parasitol 2010;40:215-27.
2. Zaki A, Perera D, Jahan SS, Cardosa MJ. Phylogeny of dengue viruses circulating in Jeddah, Saudi Arabia:1994 to 2006. Trop Med Int Health 2008;13:584-92.
3. Khan NA, Azhar EI, El-Fiky S, Madani HH, Abuljadial MA. Clinical profile and outcome of hospitalized patients during first outbreak of dengue in Makkah, Saudi Arabia. Acta Trop 2008;105:39-44.
4. Ayyub M, Khazindar AM, Lubbad EH, Barlas S, Alfi AY, Al-Ukayli S. Characteristics of dengue fever in a large public hospital, Jeddah, Saudi Arabia. J Ayub Med Coll Abbottabad 2006;18:9-13.
5. Madani TA. Alkhumra virus infection, a new viral hemorrhagic fever in Saudi Arabia. J Infect 2005;51:91-7.
6. Monath TP. Dengue and Yellow Fever – challenges for the development and use of vaccines. N Engl J Med 2007;357:2222-5.
7. Shuman EK. Global climate change and infectious diseases. N Engl J Med 2010;362:1061-3.
8. Lafferty KD. The ecology of climate change and infectious diseases. Ecology 2009;90:888-900.
9. Haritoglou C, Scholtz F, Bialaslewicz A, Klauss V. Ocular manifestations in dengue fever. Ophthalmologe 2000;97:433-6.
10. Haritoglou C, Dotse SD, Rudolph G, Stephan CM, Thurau SR, Klauss V. A tourist with dengue fever and visual loss. Lancet 2002;360:1070.
11. Lim WK, Mathur R, Koh A, Yeoh R, Chee SP. Ocular manifestations of dengue fever. Ophthalmology 2004;111:2057-64.
12. Chlebicki MP, Ang B, Barkham T, Laude A. Retinal haemorrhages in a 4 patients with dengue fever. Emerg Infect Dis (Serial on the Internet). http://www.cdc.gov/ncidod/EID/vol11/n005/04-0992.htm
13. Chlebicki MP, Ang B, Barkham T, Laude A. Retinal hemorrhages in 4 patients with Dengue fever. Emerg Infect Dis 2005;11:770-2.
14. Bacsal KE, Chee SP, Cheng CL, Flores JV. Dengue-associated maculopathy. Arch Ophthalmol 2007;125:501-10.
15. Cruz-Villegas V, Berrocal AM, Davis JL. Bilateral choroidal effusions associated with dengue fever. Retina 2003:23:576-8.
16. Siqueira RC, Vitral NP, Campos WR, Oréfice F, de Moraes Figueiredo LT. Ocular manifestations in dengue fever. Ocul Immunol Inflamm 2004;12:323-7
17. Su DH, Bacsal K, Chee SP, Flores JV, Lim WK, Cheng BC, Jap AH. Dengue Maculopathy Study Group. Prevalence of dengue maculopathy in patients hospitalized for dengue fever. Ophthalmology 2007;114:1743-7.
18. Mehta S. Ocular lesions in severe dengue hemorrhagic fever (DHF). J Assoc Phys India 2005;53:656-7.
19. Chang PE, Cheng CL, Asok K, Fong KY, Chee SP, Tan CK. Visual disturbances in dengue fever: an answer at last? Singapore Med J 2007;48:e71-3.
20. Kapoor HK, Bhai S, John M, Xavier J. Ocular manifestations of dengue fever in an East Indian epidemic. Can J Ophthalmol 2006;41:741-6.
21. Chan DP, Teoh SC, Tan CS, Nah GK, Rajagopalan R, Prabhakaragupta MK, et al.,
Eye Institute Dengue-Related Ophthalmic Complications Workgroup. Ophthalmic complications of dengue. Emerg Infect Dis 2006;12:285-9.
22. Tan CS, Teoh SC, Chan DP, Wong IB, Lim TH. Dengue retinopathy manifesting with bilateral vasculitis and macular oedema. Eye 2007;21:875-7.
23. Srikiatkhachom A. Plasma leakage in dengue haemorrhagic fever. Thromb Haemost 2009;102:1042-9.
24. Kanlaya R, Pattanakitsakul SN, Sinchaikul S, Chen ST, Thongboonkerd V. The ubiquitin-proteasome pathway is important for dengue virus infection in primary human endothelial cells. J Proteome Res 2010;9:4960-71.
25. Chen LC, Yeh TM, Lin YY, Wang YF, Su SJ, Chen CY, et al. The envelope glycoprotein domain III of Dengue virus type 2 induced the expression of anticoagulant molecules in endothelial cells. Mol Cell Biochem 2010;342:215-21.
26. Liao H, Xu J, Huang J. FasL/Fas pathway is involved in dengue virus induced apoptosis of the vascular endothelial cells. J Med Virol 2010;82:1392-9.
27. Wang Z, Shi Q, Li S, Du J, Liu J, Dai K. Hyperthermia induces platelet apoptosis and glycoprotein Ibalpha ectodomain shedding. Platelets 2010;21:229-37.
28. Teyssou R. Dengue fever: from disease to vaccination. Med Trop 2009;69:333-4.