Ebola and the Ophthalmologist

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The recent Ebola virus disease (EVD) epidemic in West Africa has captured the world’s attention. Ebola virus disease is a multisystem hemorrhagic fever with remarkably high mortality. Patients typically present with high fever and flu-like symptoms, progressing to diarrhea, vomiting, and disseminated hemorrhage with multisystem organ failure. Overall mortality is greater than 40%, with most patients dying within 1 month of contracting the virus. As of August 2015, there have been more than 27 000 reported cases worldwide resulting in more than 11 000 deaths, with more than 10 000 of these cases occurring during the 2014 to 2015 epidemic. Because the virus is spread by contact with infected fluids, the potential for a sustained epidemic is high. Fruit bats serve as a natural reservoir for the virus, making prospects for eradication unlikely. International concern has been heightened as cases have been confirmed in North America and Europe during the past year. Now, with the recent publication of a remarkable case report in The New England Journal of Medicine by Varkey et al, demonstrating the presence of apparently infectious virus in the ocular fluids of a patient with EVD and uveitis in the United States, months after clearance of the virus from the blood, ophthalmologists will need to become familiar with this potentially fatal virus.

Ebola virus disease was first recognized in 1976 after a series of hemorrhagic fever cases arising near the Ebola river in Zaire. Subsequently, 5 viruses of the Ebola virus genus, all members of the Filovirus family of single-stranded RNA viruses, have been found to be capable of producing similar illness (reviewed by Beeching et al). Hemorrhagic conjunctivitis has long been recognized as a presenting sign of infection, reportedly occurring in 58% of patients. In 1999, Kibadi et al described the first uveitic manifestations of Ebola virus. The group studied survivors of a 1995 outbreak of EVD near the city of Kikwit in the Democratic Republic of the Congo affecting 316 patients. Subsequent to this epidemic, 4 surviving patients noted blurred vision during their recovery. Three of these subjects were identified by virtue of enrollment in a follow-up study of late complications of EVD and represented 15% of this cohort. The fourth case presented independently. In each case, the patient presented between 42 and 72 days post-Ebola diagnosis with symptoms of unilateral pain, redness, photophobia, and tearing, and was found to have anterior or panuveitis on ophthalmoscopy. Treatment was topical corticosteroid and cyclopia in each case, and by report all cases resolved (although visual acuities and late sequelae were not reported). In 1 patient, viral RNA was detected by polymerase chain reaction (PCR) from conjunctiva, even after blood testing was negative for viral antigen. The authors of this work argued that the uveitis in this patient represented late-onset delayed hypersensitivity to viral antigen.

The recent report by Varkey et al challenges this assumption. This group describes the clinical course of 1 of the 4 documented EVD cases identified in the United States in 2014. A 43-year-old physician providing care for patients with EVD in Kenema, Sierra Leone, returned to the United States with flu-like illness. He was diagnosed with EVD by serology and PCR, and treated at the Centers for Disease Control and Prevention (CDC)/Emory University Hospital in a special Ebola isolation unit. He had a very severe and nearly fatal course but eventually recovered and was discharged after 40 days of hospitalization. At discharge, serial blood and urine specimens tested negative for Ebola virus by quantitative reverse transcription PCR (qRT-PCR), although a semen sample obtained before discharge was positive for Ebola virus by both culture and qRT-PCR. During his hospitalization, the patient did not have specific eye symptoms. However, shortly after discharge he had occasional bilateral burning, foreign body sensation, and photophobia, and required an adjustment in the prescription of his reading glasses, consistent with accommodative change.

Ten weeks after discharge, the patient had a complete ophthalmologic examination that revealed excellent corrected visual acuity, quiet anterior chambers, bilateral choriorretinal scars, and 1 small intraretinal hemorrhage. Four weeks later, he presented with acute onset of redness, pain, photophobia, blurred vision, and visual haloes in the left eye. He was found to have mildly decreased vision in this eye, along with scant keratic precipitates, 1+ anterior chamber cell and flare, and an intraocular pressure of 44 mmHg. Posterior segment examination results were unchanged. He was treated with topical corticosteroids and pressure-lowering agents, but had a progressively worsening course. A diagnostic aqueous humor paracentesis was performed that revealed Ebola virus by viral culture and high amounts of Ebola virus RNA by qRT-PCR (indeed, as high as serum levels had been at peak of the disease course). Concurrent serum sampling revealed no infection in the blood, and serial swabs of the conjunctiva were similarly negative for Ebola virus. Five days after the initial diagnosis of iritis, the patient was noted to have

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scleritis and vitritis. He was treated with systemic corticosteroids with improvement of the iritis and scleritis but worsening of the vitritis with vision worsening to 20/400. After a protracted course including treatment with an experimental antiviral (famciclovir) and systemic and regional corticosteroids, the vitritis slowly cleared, and the patient recovered 20/15 vision.

In this case, the patient’s eye harbored Ebola virus, associated with marked inflammation, weeks after clearance of virus from the serum. Similar persistence of Ebola virus was observed in his semen, well after clearance from the blood. It is possible that persistence of Ebola virus in the eye and testes may be due to the immune-privileged status of these tissues, but the actual mechanism is unknown. Other instances of the eye serving as a reservoir for active virus have been reported. For instance, a nearly identical presentation of delayed onset, unilateral severe uveitis with viable intraocular virus has been described for Marburg virus disease, another Filovirus hemorrhagic fever disease found in Africa. Rubella virus also may remain active in the eye for years and is thought to underlie many cases of Fuchs’ heterochromic iridocyclitis. Unlike herpes viruses, however, Ebola is not known to become latent or integrated into the host genome. Thus, the assumption is that the eye remained actively infected in the case described by Varkey et al.

What does this mean for the practicing ophthalmologist? We have long worked with eyes harboring dangerous infectious agents. At the peak of the human immunodeficiency virus epidemic in the 1990s, tens of thousands of procedures were performed on eyes with active human immunodeficiency virus. To date, there are no firm lines of evidence that Ebola is naturally transmitted by aerosol. However, in 1 case report, a Macaque monkey systemically infected with Ebola virus manifested a conjunctivitis and scleritis 18 days after inoculation, which was positive for viral antigen in conjunctiva and sclera at necropsy, suggesting that the acute conjunctivitis could harbor infectious virions. Ophthalmologists working in endemic areas will need to harbor clinical suspicion for infection in patients presenting with hemorrhagic conjunctivitis; specific features of this condition have not been described. It is not yet known whether uveitis also can be a presenting sign of infection, but this possibility must be considered.Suspected infection can be confirmed through enzyme-linked immunosorbent assay antigen testing, *Ebolavirus* immunoglobulin-M testing, or PCR of blood or other body fluids.

Currently, highest level precautions for isolation of patients with active Ebola virus including full body protection with special donning and doffing procedures for providers are recommended by the CDC for treating physicians (http://www.cdc.gov/vhf/ebola/healthcare-us/hospitals/infection-control.html, last update February 12, 2015). The American College of Surgeons has offered recommended protocols for the general surgical approach to the patient with Ebola, which includes Association for the Advancement of Medical Instrumentation Level 4 impervious surgical gowns and drapes, use of leg coverings that have full plastic film coating over the fabric (not just over the foot area), strong consideration of using a surgical helmet with an integrated Association for the Advancement of Medical Instrumentation Level 4 gown to prevent potential face splashes, fluid-resistant surgical mask or N95 masks if aerosols will be generated, double gloves (with the outer layer of gloves being extra long surgical gloves), and capetyle fluid-impervious hoods (https://www.facs.org/surgeons/ebola/surgical-protocol, Version 2, October 19, 2014).

Appropriate indications and optimal protocols for intraocular surgery in this setting remain to be determined. Fluids removed from the eyes of patients who have had Ebola should be considered potentially infectious and treated appropriately (see CDC guidelines, http://www.cdc.gov/vhf/ebola/healthcare-us/cleaning/waste-management.html, August 20, 2015). The operating ophthalmologist and team should assume that the virus remains active in eyes of these patients for months after the initial infection. Consultation with the CDC for up-to-date recommendations is essential for ophthalmologists believing they are treating active or postinfectious Ebola.

The case reported by Varkey et al raises many important questions that will need to be answered by further studies. How long does the virus stay active in the eyes of patients with Ebola disease? Are particular strains more or less likely to cause uveitis? What is the optimal treatment for these patients? Can uveitis occur concomitant with systemic infection? What are the outcomes of patients with this form of uveitis? Although we all hope that this epidemic is limited, eradication of Ebola is unlikely because multiple animals (particularly bats) can serve as reservoirs for the disease. We will need to learn to live with Ebola as ophthalmologists begin to encounter Ebola-related eye disease in their practices.

### References


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Pictures & Perspectives

Papillomatous Compound Nevus
An 8-year-old boy was observed for 5 years for an enlarging, pigmented lesion on his left lower lid (Fig 1). An excisional biopsy was performed and histopathology (H&E) revealed skin with keratinized, stratified squamous epithelium in a papillomatous configuration (Figs 2 and 3). The lesion had nests of densely pigmented melanocytes within the epithelium (black arrows), at the epithelial-stromal junction (white arrows) and within the underlying stroma (asterisks). The history of growth and the junctional location are of much less concern in a juvenile nevus than in an adult nevus.

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