VA BOSTON MEDICAL FORUM

HIV-Positive Veteran With Progressive Visual Changes

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Case Presentation. *This case involves a 49-year-old U.S. Army veteran (service included time in Somalia and Panama) with a history of HIV, diabetes mellitus, and hypertension who presented with progressive visual changes. Three years prior to the current presentation, he was diagnosed with HIV and started highly active antiretroviral therapy (HAART) therapy. About 1 year prior to presentation, he was off therapy for a month. When laboratory results indicated a detectable viral load, HAART was restarted (abacavir, lamivudine, and efavirenz). Four months prior to presentation, he noted a flicker in his left eye, followed 2 months later by a shadow over his left upper visual field along with occasional floaters and blurry vision in his left eye. In the days leading to the presentation, the shadow worsened, prompting evaluation.*

➤ **Lakshmana Swamy, MD, chief medical resident, VA Boston Healthcare System (VABHS) and Boston Medical Center.** Dr. Serrao, when you hear about vision changes in a patient with HIV, what differential diagnosis is generated? What epidemiologic or historical factors can help distinguish these entities?

➤ **Richard Serrao, MD, Infectious Disease Service, VABHS and assistant professor of medicine, Boston University School of Medicine.** The differential diagnoses for vision changes in a patient with HIV is based on the overall immunosuppression of the patient: the lower the patient's CD4 count, the higher the number of etiologies.[1] The portions of the visual pathway as well as the pattern of vision loss are useful in narrowing the differential. For example, monocular visual disturbances with dermatomal vesicles within the ophthalmic division of the trigeminal nerve strongly implicates varicella zoster retinitis or keratitis; abducens nerve palsy could suggest granulomatous basilar meningitis from cryptococcosis. Likewise, ongoing fevers in an advanced AIDS patient with concomitant colitis, hepatitis, and pneumonitis is strongly suspicious for cytomegalovirus (CMV) retinitis with wide dissemination.

Geographic epidemiologic factors can suggest pathogens more prevalent to certain regions of the world, such as histoplasma chorioretinitis in a resident of the central and eastern U.S. or tuberculosis in a returning traveler. Likewise, a cat owner or one who consumes steak tartare increases the likelihood for toxoplasma retinochoroiditis, or syphilis in men who have sex with men (MSM) in the U.S. given that the majority of new cases occur in this patient population. Other clues one should consider include the presence of splinter hemorrhages in the extremities in an intravenous drug user, raising the possibility of embolic endophthalmitis from bacterial or fungal endocarditis. A variety of other diagnoses can certainly occur as a result of drug treatment (uveitis from rifampin, for example), immune reconstitution from HAART, infections with other HIV-associated pathogens, such as *Pneumocystis jiroveci*, and many non-HIV-related ocular diseases.

➤ **Dr. Swamy.** Dr. Butler, what concerns do you have when you hear about an HIV-infected patient with vision loss from the ophthalmology perspective?

Dr. Breu is a hospitalist and the director of resident education at VA Boston Healthcare System and an assistant professor of medicine at Harvard University in Massachusetts. He is the corresponding author and supervises the VA Boston Medical Forum chief resident case conferences. All patients or their surogate decision makers understand and have signed appropriate patient release forms. This article has received an abbreviated peer review.

➤ **Nicholas Butler, MD, Ophthalmology Service, Uveitis and Ocular Immunology, VABHS and assistant professor of ophthalmology, Harvard Medical School.** Of course, patients with HIV suffer from common causes of vision loss—cataract, glaucoma, diabetes, macular degeneration, for instance—just like those without HIV infection. If there is no significant immunodeficiency, then the patient's HIV status would be less relevant, and these more common causes of vision loss should be pursued. My first task would be to determine the patient's most recent CD4 T-cell count.

Assuming an HIV-positive individual is experiencing visual symptoms related to his/her underlying HIV infection (especially in the setting of CD4 counts < 200 cells/mm^3), ocular opportunistic infections (OOI) come to mind first. Despite a reduction in incidence of 75% to 80% in the HAART-era, CMV retinitis remains the most common OOI in patients with AIDS and carries the greatest risk of ocular morbidity.[2] In fact, based on enrollment data for the Longitudinal Study of the Ocular Complications of AIDS (LSOCA), the prevalence of CMV retinitis among patients with AIDS is more than 20-fold higher than all other ocular complications of AIDS (OOIs and ocular neoplastic disease), including Kaposi sarcoma, lymphoma, herpes zoster ophthalmicus, ocular syphilis, ocular toxoplasma, necrotizing herpetic retinitis, cryptococcal choroiditis, and pneumocystis choroiditis.[3] Beyond ocular opportunistic infections, the most common retinal finding in HIV-positive people is HIV retinopathy, nonspecific microvascular findings in the retina affecting nearly 70% of those with advanced HIV disease. Fortunately, HIV retinopathy is generally asymptomatic.[4]

➤ **Dr. Swamy.** Thank you for those explanations. Based on Dr. Serrao's differential, it is worth noting that this patient is MSM. He was evaluated in urgent care with the initial examination showing a temperature of 98.0° F, pulse 83 beats per minute, and blood pressure 110/70 mm Hg. The eye exam showed no injection with normal extraocular movements. Initial laboratory data were notable for a CD4 count of 730 cells/mm^3 with fewer than 20 HIV viral copies/mL. Cytomegalovirus immunoglobulin G (IgG) was positive, and immunoglobulin M (IgM) was negative.

Table 1. Blood Test Analysis

Tests	Reference	Result
White blood cell count (x 10^9/L)	4.5-11.0	5.8
Differential count (%)		
Neutrophils	40-75	62.6
Bands	0-10	0.3
Lymphocytes	10-55	24.5
Monocytes	2-12	9.8
Eosinophils	0-7	2.1
Basophils	0-2	0.7
Hemoglobin (g/dL)	10.3	13.1
Hematocrit (%)	40-52	38
Mean corpuscular volume (fL)	80-98	91.8
Red cell distribution width (%)	11.5-14.5	12.8
Platelets (per mm^3)	130-450	327
Sodium (mmol/L)	135-145	140
Potassium (mmol/L)	3.5-5.0	4.3
Chloride (mmol/L)	100-110	101
Carbon dioxide (mmol/L)	20-30	29
Urea nitrogen (mg/dL)	7-25	20
Creatinine (mg/dL)	0.5-1.5	1.25
Glucose (mmol/L)	65-100	213
Albumin (g/dL)	3.2-5.0	3.6
Total protein (mg/dL)	6.0-8.5	7.1
Alkaline phosphatase (U/L)	40-150	98
Aspartate aminotransferase (U/L)	5-34	24
Alanine aminotransferase (U/L)	7-52	35
Bilirubin, total (mg/dL)	0.2-1.2	0.2
CD4 (cells/mm^3)	410-1,590	730
HIV (copies/mL)	Not detected	< 20
Cytomegalovirus immunoglobulin G (IU/mL)	Negative	Positive
Cytomegalovirus immunoglobulin M (AU/mL)	Negative	Negative
Antineutrophil cytoplasmic antibodies	Negative	Negative
Angiotensin converting enzyme (U/L)	6-67	30
Rapid plasma reagin	Nonreactive	1:32, Reactive
Toxoplasma immunoglobulin G (IU/mL)	Negative	Negative
Toxoplasma immunoglobulin M (AU/mL)	Negative	Negative
Lyme antibody	Not detected	Positive
Lyme immunoglobulin G Western blot	Negative	Negative
Lyme immunoglobulin M	Negative	Negative

Table 2. Cerebrospinal Fluid Analysis

Tests	Reference	Result
Turbidity	Clear	Clear
Color	Colorless	Colorless
Nucleated cells (cells/cumm)	0-5	10
Red blood cells (cells/cumm)	0-10	< 1,000
Lymphocytes (%)		94
Mononucleocytes (%)		6
Protein (mg/dL)	15-45	30.9
Glucose (mg/dL)	40-75	138
Lactate dehydrogenase (U/L)	< 25	33
Lyme polymerase chain reaction	Negative	Negative
Venereal disease	Nonreactive	Nonreactive
Cerebrospinal fluid fluorescent treponemal antibody	Nonreactive	Reactive

A Lyme antibody was positive with negative IgM and IgG by Western blot. Additional tests can be seen in Tables 1 and 2. The patient has good immunologic and virologic control. How does this change your thinking about the case?

➤ **Dr. Serrao.** His CD4 count is well above 350, increasing the likelihood of a relatively uncomplicated course and treatment. Cytomegalovirus antibodies reflect prior infection. As CMV generally does not manifest with disease of any variety (including CMV retinitis) at this high CD4 count, one can presume he does not have CMV retinitis as a cause for his visual changes. CMV retinitis occurs mainly when substantial CD4 depletion has occurred (typically less than 50 cells/mm^3). A positive Lyme antibody screen, not specific to Lyme, can be falsely positive in other treponema diseases (eg, *Treponema pallidum*, the etiologic organism of syphilis) as evidenced by negative confirmatory Western blot IgG and IgM. Antineutrophil cytoplasmic antibodies, lysozyme, angiotensin-converting enzyme, rapid plasma reagin (RPR), herpes simplex virus, toxoplasma are generally included in the workup for the differential of uveitis, retinitis, choroiditis, etc.

➤ **Dr. Swamy.** Based on the visual changes, the patient was referred for urgent ophthalmologic evaluation. Dr. Butler, when should a generalist consider urgent ophthalmology referral?

➤ **Dr. Butler.** In general, all patients with acute (and significant) vision loss should be referred immediately to an ophthalmologist. The challenge for the general practitioner is determining the true extent of the reported vision loss. If possible, some assessment of visual acuity should be obtained, testing each eye independently and with the correct glasses correction (ie, the patient's distance glasses if the test object is 12 feet or more from the patient or their reading glasses if the test object is held inside arm's length). If the general practitioner does not have access to an eye chart or near card, any assessment of vision with an appropriate description will be useful (eg, the patient can quickly count fingers at 15 feet in the unaffected eye, but the eye with reported vision loss cannot reliably count fingers outside of 2 feet). Additional ocular symptoms associated with the vision loss, such as pain, redness, photophobia, new flashes or floaters, increase the urgency of the referral. The threshold for referral for any ocular complaint is lower compared with that of the general population for those with evidence of immunodeficiency, such as for this patient with HIV. Any CD4 count < 200 cells/mm^3 should raise the practitioner's concern for an ocular opportunistic infection, with the greatest concern with CD4 counts < 50 cells/mm^3.

➤ **Dr. Swamy.** The patient underwent further testing in the ophthalmology clinic. Dr. Butler, can you please interpret the funduscopic exam?

➤ **Dr. Butler.** Both eyes demonstrate findings (microaneurysms and small dot-blot hemorrhages) consistent with moderate nonproliferative diabetic retinopathy (Figure 1A, white arrows). HIV-associated retinopathy could produce similar findings, but it is not generally seen with CD4 counts > 200 cells/mm^3. Additionally, in the left eye, there is a diffuse patch of retinal whitening (retinitis) associated with the inferotemporal vascular arcades (Figure 1B, white arrows). The entire area involved is poorly circumscribed and the whitening is subtle in areas. Overlying some areas of deeper, ground-glass whitening there are scattered,

punctate white spots (Figure 1B, green arrows). Wickremasinghe and colleagues described this pattern of retinitis and suggested that it had a high positive-predictive value in the diagnosis of ocular syphilis.[5]

➤ **Dr. Swamy.** The patient then underwent fluorescein angiography and optical coherence tomography (OCT). Dr. Butler, what did the fluorescein angiography show?

➤ **Dr. Butler.** The fluorescein angiogram in both eyes revealed leakage of dye consistent with diabetic retinopathy, with the right eye (OD) worse than the left (OS). Additionally, the areas of active retinitis in the left eye displayed gradual staining with leopard-spot changes, along with late leakage of fluorescein dye, indicating vasculopathy in the infected area (Figure 2, arrows). The patient also underwent OCT in the left eye (images not displayed) demonstrating vitreous cells (vitritis), patches of inner retinal thickening with hyperreflectivity, and hyperreflective nodules at the level of the retinal pigment epithelium with overlying photoreceptor disruption. These OCT findings are fairly stereotypic for syphilitic chorioretinitis.[6]

➤ **Dr. Swamy.** Based on the ophthalmic findings, a diagnosis of ocular syphilis was made. Dr. Serrao, what should internists consider as they evaluate and manage a patient with ocular syphilis?

➤ **Dr. Serrao.** Although isolated ocular involvement from syphilis is possible, the majority of patients (up to 85%) with HIV can present with concomitant central nervous system infection and about 30% present with symptomatic neurosyphilis (a typical late manifestation of this disease) that reflects the aggressiveness, accelerated course and propensity for wide dissemination of syphilis in this patient population.[7] This is more probable in those with a CD4 cell count < 350 cells/mm^3 and high (> 1:128) RPR titer. By definition, ocular syphilis is reflective of symptomatic neurosyphilis and therefore warrants a lumbar puncture to quantitate the inflammatory severity (cerebrospinal fluid [CSF] cell count) and to detect the presence or absence of locally produced antibodies, which are useful to

Case Imaging at Presentation

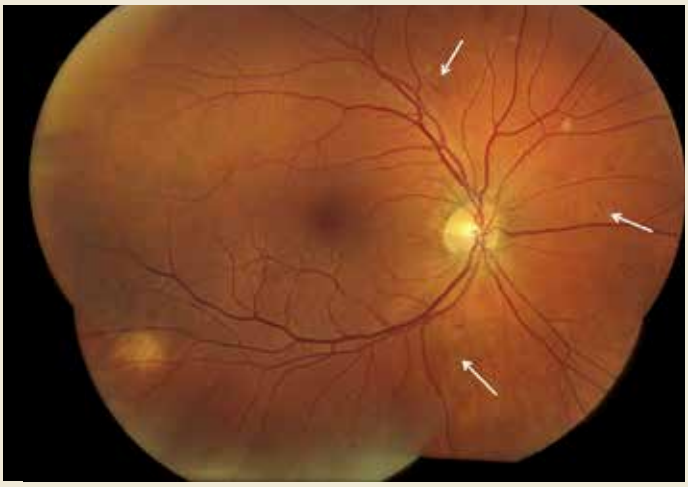

Figure 1A. Fundus photo of right eye.

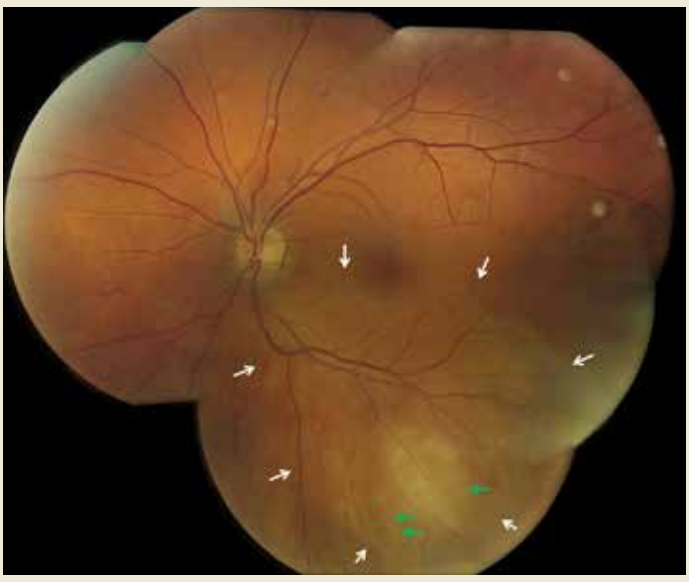

Figure 1B. Fundus photo of left eye.

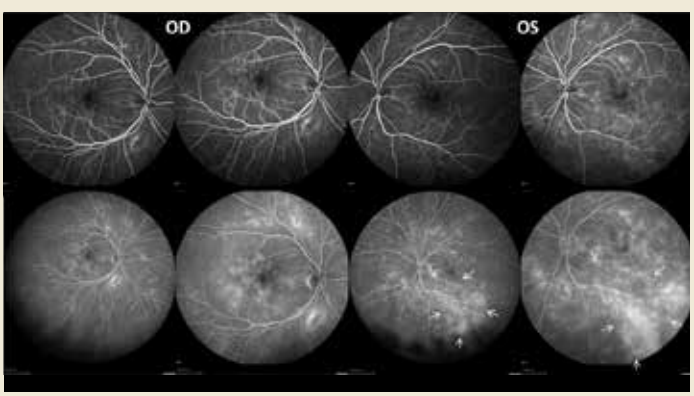

Figure 2. Fluorescein angiogram of right and left eye.

Clinical Takeaways

All patients with acute (and significant) vision loss should be referred immediately to an ophthalmologist.

In patients with HIV common causes of vision loss (cataracts, glaucoma, diabetes, macular degeneration) should be considered first if there is no significant immunodeficiency. Once the CD4 count falls below 50 cells/mm^3, CMV retinitis is the most common OOI and carries the greatest risk of ocular morbidity. The lower the CD4 count, the higher the risk for opportunistic infections or malignancies of the eye and its associated structures.

Ocular syphilis is reflective of symptomatic neurosyphilis and therefore warrants a lumbar puncture to quantitate the inflammatory severity (CSF cell count) and to detect the presence or absence of locally produced antibodies, which are useful to prognosticate and gauge response to treatment.

The presence of concomitant cutaneous rashes should prompt universal precautions because transmission can occur via skin to skin contact. As syphilis is sexually acquired, clinicians should test for coexistent sexually transmitted infections, vaccinate for those that are preventable (eg, hepatitis B), notify sexual partners via assistance from local departments of public health, and assess for coexistent drug use and offer counseling in order to optimize risk reduction.

This case was originally presented as a Medical Forum at the VA Boston Healthcare System.

prognosticate and gauge response to treatment as treatment failures can occur. Since early neurosyphilis is the most common present-day manifestation of syphilis involving the central nervous system, ocular syphilis can occur simultaneously with syphilitic meningitis (headache, meningismus) and cerebral arteritis, which can result in strokes.[8]

The presence of concomitant cutaneous rashes should prompt universal precautions, because transmission can occur via skin to skin contact. Clinicians should watch for the Jarisch-Herxheimer reaction during treatment, a syndrome of fever, myalgias, and headache, which results from circulating cytokines produced because of rapidly dying spirochetes that could mimic a penicillin drug reaction, yet is treated supportively.

As syphilis is sexually acquired, clinicians should test for coexistent sexually transmitted infections, vaccinate for those that are preventable (eg, hepatitis B), notify sexual partners via assistance from local departments of public health, and assess for coexistent drug use and offer counseling in order to optimize risk reduction. Special attention should be paid to virologic control of HIV since some studies have shown an increase in the propensity for breakthrough HIV viremia while on effective ART.[9] This should warrant counseling for ongoing optimal ART adherence and close monitoring in the follow-up visits with a provider specialized in the treatment of syphilis and HIV.

➤ **Dr. Swamy.** A lumbar puncture is performed with the results listed in Table 2. Dr. Serrao, is the CSF consistent with neurosyphilis? What would you do next?

➤ **Dr. Serrao.** The lumbar puncture is inflammatory with a lymphocytic predominance, consistent with active ocular/neurosyphilis. The CSF Venereal Disease Research Laboratory test is specific but not sensitive so a negative value does not rule out the presence of central nervous system infection.[10] The CSF fluorescent treponemal antibody (CSF FTA-ABS) is sensitive but not specific. In this case, the ocular findings, positive serum RPR, CSF lymphocytic predominance, and CSF FTA ABS strongly supports the diagnosis of ocular/early neurosyphilis in a patient with HIV infection in whom early aggressive treatment is warranted to prevent rapid progression/potential loss of vision.[11]

➤ **Dr. Swamy.** Dr. Butler, how does syphilis behave in the eye as compared to other infectious or inflammatory diseases? Do visual symptoms respond well to treatment?

➤ **Dr. Butler.** As opposed to the dramatic reduction in rates and severity of CMV retinitis, HAART has had a negligible effect on ocular syphilis in the setting of HIV coinfection; in fact, rates of syphilis, including ocular syphilis, are currently surging worldwide, and HIV coinfection portends a worse prognosis.[12] This is especially true among gay men. More so, there appears to be no correlation between CD4 count and incidence of developing ocular syphilis, as opposed to CMV retinitis, which occurs far more frequently in those with CD4 counts < 50 cells/mm^3. In

keeping with its epithet as one of the "Great Imitators," syphilis can affect virtually every tissue of the eye—conjunctiva, sclera, cornea, iris, lens, vitreous, retina, choroid, optic nerve—unlike other OOI, such as CMV or toxoplasma, which generally hone to the retina. Nonetheless, various findings and patterns on clinical exam and ancillary testing, such as the more recently described punctate inner retinitis (as seen in our patient) and the more classic acute syphilitic posterior placoid chorioretinitis, carry high specificity for ocular syphilis.[13]

Patients with ocular syphilis should be treated according to neurosyphilis treatment protocols. In general, these patients respond very well to treatment with resolution of the ocular findings and recovery of complete, or nearly so, visual function, as long as an excessive delay between diagnosis and proper treatment does not occur.[14]

➤ **Dr. Swamy.** Following this testing, the patient completed 14 days of IV penicillin with resolution of symptoms. He had no further vision complaints. He was started on Triumeq (abacavir, dolutegravir, and lamivudine) with good adherence to therapy. Dr. Serrao, in 2016 the CDC released a clinical advisory about ocular syphilis. Can you tell us about why this is an important diagnosis to be aware of today?

➤ **Dr. Serrao.** As with any disease, the epidemiologic characteristics of an infection like syphilis allow the clinician to more carefully entertain such a diagnosis in any one individual by improving the index of suspicion for a particular disease. Awareness of an increase in ocular syphilis in HIV positive MSM allows for a more timely assessment and subsequent treatment with the goal of preventing loss of vision.[15] ●

Author disclosures

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