Ocular Syphilis with HIV Co-infection

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Abstract

Background: Syphilis is caused by the spirochete bacterium Treponema pallidum, and manifests in a broad range of ocular clinical presentations. The most common risk factors for syphilis and human immunodeficiency virus (HIV) infection include participating in unprotected sex and having sex with multiple partners. Among the population of men who have sex with men (MSM), syphilis is diagnosed more often in patients who have been previously diagnosed with HIV.

Case Reports: We present 2 case reports of patients presenting to the eye clinic with complaints of foggy vision. Clinical examination revealed keratic precipitates, vitritis and swollen optic nerves. Both patients had a prior diagnosis of HIV and were not currently on treatment with antiretroviral therapy. Additional workup in both cases resulted in a diagnosis of neurosyphilis secondary to optic nerve involvement.

Conclusion: Routine eye screening and treatment in patients diagnosed with HIV and/or syphilis is important in minimizing the likelihood of irreversible vision loss. It is recommended that all patients with syphilis be tested for HIV due to the close association between the two infections, as well as possible progression to neurosyphilis.

Key words: HIV, syphilis, ocular syphilis

Introduction

Syphilis is a sexually transmitted infection caused by the spirochete bacterium Treponema pallidum. It was first identified in Europe over 500 years ago, and is often referred to as the “great masquerader” due to its range of clinical presentations. In the most at risk population, men who have sex with men (MSM), syphilis has been diagnosed at higher rates in patients who have also been diagnosed with HIV infection. Syphilitic infection was reported to be at an all-time low in the early 2000’s, however there has been a significant increase in infection rates since then.

Syphilis is classified into primary, secondary, tertiary and latent stages each with its own characteristics for systemic and ocular involvement. Neurosyphilis, the invasion of the nervous system, and ocular syphilis, the invasion of the ocular structures, may both occur at any stage of the disease. Neurosyphilis is more commonly seen in HIV positive individuals, and particularly in patients who are not on antiretroviral therapy, have low CD4 cell counts, or exhibit high rapid plasma reagin (RPR) titers. This review will mainly focus on the synergistic relationship between HIV and syphilis, highlighting the importance of routine care and prompt treatment.

Case Reports

Case 1. A 43-year-old male new to the eye clinic reported dim and foggy vision in both eyes over the past 2 months that was progressive in nature. He denied any pain but confirmed mild flashes of light and floaters in the left eye over the past month. His medical history was remarkable for HIV, which was diagnosed the year before. He reported reinitiating HIV medication recently and had pending lab work.

Ophthalmic examination revealed best corrected visual acuities of 20/150 OD and 20/100 OS. Pinhole did not improve the visual acuity of either eye. His extraocular muscles were full and smooth. Pupils were round, equal and reactive to light with no afferent pupillary defect (APD). Confrontation fields were full to finger counting in both eyes. Frequency doubling technology (FDT) visual field screening resulted in the patient missing all test points with poor reliability OU.
Figure 2. RNFL OCT depicting ONH involvement with 360 thickening (top image) and post treatment with resolution of ONH findings OD and OS (bottom image).
Slit lamp biomicroscopy revealed multiple old keratic precipitates (KPs) OD>OS and conjunctival papillary reaction OD>OS. In addition, slit lamp biomicroscopy was remarkable for vitreous cells OD>OS. Predilated Goldmann application tonometry showed normotensive intraocular pressures of 10mmHg OD and 12mmHg OS.

Dilated fundus examination revealed indistinct margins of the optic nerve heads in both eyes and difficulty in judging cup to disc ratio. The maculae were flat. Peripheral fundus examination was unremarkable in both eyes to the extent seen due to the active vitritis. (Figure 1)

Retinal nerve fiber layer optical coherence tomography (RNFL OCT) revealed elevated global value of 200um OD and 174um OS with significant RNFL thickening 360 OU. (Figure 2) In addition, macular OCT was obtained revealing multiple elevated, hyper-reflective lesions at the level of the retinal pigmented epithelium (RPE). No macular edema was appreciated OU. (Figure 3) Fundus photos were obtained with resulting hazy quality secondary to the active vitritis in both eyes.

A diagnosis of bilateral swollen optic nerves was made with concern of an infectious etiology, particularly for syphilis given the patient’s HIV diagnosis and history of poor compliance with antiretroviral therapy. A consult was obtained with the retina service, which advised that the macular OCT findings were consistent with a diagnosis of syphilis. Review of prior laboratory testing indicated that both RPR and Quantiferon TB testing were negative 6 months ago. The latest CD4 count from a few days prior to the eye exam was 149 cells/ul. A repeat RPR was ordered based on clinical suspicion for active syphilitic infection, and the infectious disease (ID) service was consulted. ID recommended that the patient be sent to the emergency department for work up including lumbar puncture, MRI with contrast, and lab work including Venereal Disease Research Laboratory (VDRL) and updated CD4 cell counts. The patient was instructed to follow up with ophthalmology in 5 days.

At the 5-day follow up visit, a review of the most recent laboratory testing indicated an extremely low CD4 count of 71 cells/ul, a positive RPR test (1:1024), and positive CSF VDRL (1:80). Following these results, the patient had been admitted and started on IV penicillin. He reported a subjective improvement in visual acuity, although objectively his visual acuities remained reduced in both eyes at 20/100 OD and 20/50 OS. There were no changes in slit lamp biomicroscopy or fundoscopic examination. The optic nerves remained edematous OD>OS, and the vitritis was still present. At this time, the diagnosis of neurosyphilis was confirmed.

The patient presented to the eye clinic 11 days later for a follow up examination, again reporting a notable improvement in vision OS>OD with treatment. Best corrected visual acuities were stable at 20/100 OD and 20/50 OS and no improvement with pinhole. Slit lamp biomicroscopy revealed a notable decrease in vitreous cells OD and no cells were present OS.

Dilated funduscopy revealed resolving optic nerve head edema in both eyes. Fluorescein angiography was obtained at this visit, revealing mild disc leakage with focal areas of blockage corresponding with hyper-autofluorescence parafoveally, and mild capillary nonperfusion/leakage in the temporal periphery in both eyes. At this time, the patient was compliant with antiretroviral HIV therapy.

The patient was lost to follow for the next year. A year after the initial presentation, the patient was correctable to 20/20 in each eye with complete resolution of optic nerve edema, vitritis, and the macular hyper-reflective bodies in both eyes. (Figure 4)

**Case 2.** A 35-year-old male presented to the eye clinic and reported slightly blurry vision in his right eye at distance with his current spectacles over the past 5 months. He also reported having slight discomfort when going from indoors to outdoors. The patient denied any recent illness. His medical history was remarkable for HIV, which was diagnosed 7 years prior with no current or past treatment.

Best corrected visual acuity was 20/20 OD and 20/20 OS. His extraocular muscles were full and smooth. Pupils were round and minimally reactive to light with no APD. Confrontation fields were full to finger counting OD and OS.

Slit lamp biomicroscopy revealed diffuse pigmented granulomatous KPs covering the visual axis OD>OS, posterior synechiae OD>OS and pigment on the anterior lens OU. In addition, slit lamp biomicroscopy was remarkable for cells and flare within the anterior chamber OD>OS and mild vitreous cells OD>OS. Predilated Goldmann application tonometry showed normotensive intraocular pressures of 12mmHg OD and 12mmHg OS. Dilated fundus examination was unremarkable in both eyes to the extent visualized due to hazy views secondary to active vitritis OU.

A diagnosis of bilateral granulomatous uveitis OD>OS with suspicion for infectious etiology was made. Lab work was ordered including complete blood cell count (CBC), TORCH (toxoplasmosis, rubella, cytomegalovirus, herpes 1&2, RPR/PPAT and HLAB27). The patient was started on cyclopentolate 1% and prednisolone acetate 1% and instructed to return for follow up in 1 week. Unfortunately, the patient no showed to multiple appointments over the next 7 months.

The patient presented to ophthalmology 7 months later and reported cloudy vision and floaters in his right eye for the last 6-7 months. Pinhole visual acuity was 20/40-2 OD and 20/30-2 OS. Slit lamp biomicroscopy revealed similar corneal findings to prior examination with an increase in posterior synechiae spanning 270 degrees OD and no synechiae OS. Persistent anterior chamber cells were present OU with pigmented deposits and fibrinous changes on the anterior lens capsule of OD which obscured the visual axis. (Figure 5) The lens OS was clear. Dilated fundoscopical examination of the OD was not able to be completed due to poor dilation. Optic nerve head...
edema and mild vitritis OS were observed. Peripheral retinal examination was unremarkable.

A diagnosis of bilateral granulomatous anterior uveitis with intermediate uveitis OD>OS was made. The lab orders from the prior visit were not completed and new lab orders were placed with the addition of quantiferon gold, angiotensin-converting enzyme (ACE), HIV Viral Load, CD4 count and chest x-ray. The patient was counseled on establishing care with an infectious disease specialist to initiate treatment and was instructed to return to the eye clinic in 1 week to be seen in the uveitis clinic. Unfortunately, the patient was lost to follow up again and presented to the emergency department about 5 months later upon which he was referred back to the ophthalmology for comprehensive care.

The patient reported worsening of vision OU and denied any eye pain. Examination confirmed reduced vision of 20/200 OD and 20/70 OS without improvement with pinhole testing OU. OD pupil was fixed with no reverse afferent pupillary defect (RAPD) and a minimally reactive pupil OS. Slit lamp biomicroscopy revealed diffuse, fresh and old mutton fat KP's on the corneal endothelium OU. Stable posterior synechiae OD and new synechiae OS that was broken post dilation. Persistent anterior
chamber and vitreous cells were present OU, and the lens OD was completely obscured by a white pupillary membrane. Dilation revealed a ring of pigment deposition on the anterior lens capsule OS. Fundoscopic examination of the OS revealed a perfused optic nerve head with mild vitritis OS. No views of fundus OD were obtained due to the pupillary membrane.

A review of the lab work ordered on the prior visit revealed a positive RPR (1:128) and a positive PPAT-TP (2+). Quantiferon TB Gold was negative, and HIV PCR Ultra sensitive revealed 50,200 copies/mL. A recent lumbar puncture was obtained revealing positive VDRL (1:4), prompting IV penicillin treatment for the treatment of neurosyphilis.

At this visit, the patient was diagnosed with bilateral intermediate uveitis OD>OS secondary to active neurosyphilis. The patient was started on prednisolone acetate 1% 1gtt every hour while awake OU and atropine 1% 1gtt TID OD and instructed to follow up with ophthalmology in 5-7 days.

The follow up visit 1 week later revealed an improvement in vision 20/60 OD and 20/50 OS, as well as improvement in the anterior chamber reaction OU. The patient was instructed to begin to taper the steroid drops to q2h from q1h and continue atropine TID OD and follow up in 1 week. The subsequent 3 follow up visits showed improvement in visual acuity and ocular findings. A discussion was conducted with the patient on possible treatment options for improving vision OD including cataract surgery or a trial of 0.5% tropicamide TID OD. A decision was made to start 0.5% tropicamide TID OD and follow up in 6 weeks to evaluate. At the final follow up visit, the patient noted a subjective improvement in vision with use of tropicamide and best corrected visual acuity was 20/25 OD.

**Discussion**

**Epidemiology**

In the early 1990’s the US was dealing with a national epidemic of primary and secondary syphilis. A decade later, there was a stark drop off in syphilis infection rates by 87%12. According to the CDC, by 2000-2001, the national rate of primary and secondary syphilis had reached an all-time low with 2.1 cases per 100,000.10 Unfortunately, the annual rate of contraction has steadily increased since then. In 2013 the number of cases in the United States was 5.5 cases per 100,000 and by 2018, the rate of contraction had doubled to 10.8 cases per 100,000. The number of syphilis cases in 2018 that included co-infection with HIV within the MSM population was 41.6%.10 The high incidence of co-infection of HIV and syphilis has been speculated to be related to the advent of antiretroviral therapy, which may have resulted in individuals being less concerned with contracting HIV, and thus more willing to partake in risky sexual behaviors such as unprotected sex and sex with multiple partners.12 An et al demonstrated that the diagnosis of syphilis was found most commonly in the MSM population who were between 25-29 years old, HIV positive, with 10 or more sexual partners in the previous year, and who had seen a health care provider in the last year.2 Today, syphilis rates are on the rise in the United States, especially among the population of MSM co-infected with HIV.7-13-14 Consistent with other reports, Horberg et al found that 81% of HIV infected men coinfected with syphilis were MSM only or bisexual, as opposed to only 36% of HIV uninfected.14-15 This study examined the link between syphilis diagnosis among the MSM HIV positive individuals.18 A report by the CDC in 2017 provided further support for the relationship between HIV, syphilis and MSM stating that almost half of patients with syphilis were also co-infected with HIV.6 The CDC also reported that the MSM population has an increased risk of acquiring HIV in the future.6 Another study by Majumder et al reported an 86x higher risk of acquiring syphilis in an individual already diagnosed with HIV.7 The features that were consistent in the majority of studies among males co-infected with HIV and neurosyphilis were increased plasma HIV viral load, decreased CD4 cell counts, high RPR titer, and no use of antiretroviral therapy.1,11,14,16-19 Dumaresq et al and Oliver et al found that individuals with CD4 cell count of <500cells/mL had symptomatic neurosyphilis, in contrast to other studies reporting <200-350cells/mL.9,11,14,19-21

Ocular manifestations of syphilis resulting in a new diagnosis of previously undetected HIV is not uncommon.5,14,16,22-24 From 2000-2011, Petermen et al found among the population of MSM, the risk of HIV co-infection was 3.6% within the first year of syphilis diagnosis, and 17.5% at the 10 year mark.23 From 2001-2004, Petermen et al found among the population of MSM, the risk of HIV co-infection was 6.5% within the first year of syphilis diagnosis, and 17.5% at the 10 year mark.23 Taylor et al found that from 2001-2004, 2.1% of the patients with neurosyphilis were HIV positive compared to the 0.6% who were HIV negative.23 Neurosyphilis has been found to have a greater association with HIV positive individuals, with asymptomatic neurosyphilis occurring in 70% of early syphilis cases,14,16,25-30 RPR titer greater than or equal to 1:32 and co-infection of HIV were found to be more closely linked to neurosyphilis.25,28,31
Clinical Characteristics

Stages of Syphilis

The primary stage of syphilis physically manifests as a painless ulcer known as a chancre that can last 3 to 6 weeks at the site of inoculation. The secondary stage of syphilis typically occurs 2 to 12 weeks after inoculation and involves skin rashes and lesions of mucous membranes. The classic skin rash appearance is rough red-brown spots. Fever, malaise, lymphadenopathy, sore throat, patchy hair loss, headache, weight loss, and muscle aches are all symptoms of secondary syphilis. Signs and symptoms of primary and secondary syphilis resolve without treatment, but progression of the disease is possible. When an individual shows no signs or symptoms of syphilis but has a positive serological test results, it is classified as latent syphilis. If left untreated, tertiary syphilis may affect multiple organ systems and can be fatal. Neurosyphilis and ocular syphilis may occur at any point of the disease.

Ocular Syphilis

Syphilis may affect any structure of the eye. (Table 1) The primary stage of ocular syphilis is limited to chances of the eyelid and conjunctiva. Secondary stage may present with uveitis, keratitis, iris nodules, episcleritis, scleritis, vitritis, chorioretinitis, retinitis, and optic neuritis. The most common clinical feature of ocular syphilis is panuveitis, followed by posterior uveitis. Tertiary syphilis includes optic nerve and pupil involvement associated with neurosyphilis. Lee et al reported that co-infection of HIV and syphilis led to a more widespread ocular involvement, such as panuveitis, and increased the prevalence of optic nerve head edema. Tertiary syphilis includes optic nerve and pupil involvement associated with neurosyphilis. Lee et al reported that co-infection of HIV and syphilis led to a more widespread ocular involvement, such as panuveitis, and increased the prevalence of optic nerve head edema.

Neurosyphilis

Clinical presentation of neurosyphilis may include cranial nerve dysfunction, meningitis, acute or chronic alterations of mental status, stroke, and auditory or ophthalmic complications. Argyll-Robertson pupil, defined as the ability to accommodate to near stimuli but not react to light, dysarthria, and tremors are noted to be classic neurological symptoms. Early symptoms of neurosyphilis may include headaches, personality changes, forgetfulness and irritability while late symptoms may include disorientation and delusion, impaired memory, seizures and emotional instability.

A reactive CSF-VDRL confirms the diagnosis of neurosyphilis, however a negative result does not automatically rule out the diagnosis as sensitivity ranges from 30-70%. In asymptomatic cases, LP with CSF analysis is necessary for the diagnosis of neurosyphilis.

Table 1. Ocular and Systemic manifestations of syphilis

<table>
<thead>
<tr>
<th>SYSTEMIC</th>
<th>OCULAR</th>
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<tr>
<td>PRIMARY</td>
<td>Chancre: ulcerated painless lesion</td>
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<tr>
<td>SECONDARY</td>
<td>Lesions on skin or mucous membrane</td>
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<td></td>
<td>Generalized lymphadenopathy</td>
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<td>Symptoms of sore throat or fever</td>
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<td>Meningitis (symptomatic or asymptomatic)</td>
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<td>TERTIARY</td>
<td>Cardiovascular disease</td>
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<td>CNS disease</td>
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<tr>
<td>LATENT</td>
<td>No clinical manifestations</td>
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Differential Diagnosis

Syphilis is known as the “great masquerader” for its ability to present itself like many other ocular diseases. As such, it is important to rule out other possible etiologies of the clinical presentation. While uveitis is the most common finding in syphilis, it is not limited to syphilis. Diagnosis of posterior uveitis can be separated into infectious or non-infectious etiologies, including inflammatory or neoplastic etiologies. Other ocular complications that may present itself like many other ocular diseases. As such, it is important to rule out other possible etiologies of the clinical presentation.

Diagnosis of Syphilis

Early diagnosis and treatment of syphilis and more specifically asymptomatic neurosyphilis among the HIV population remains a significant burden. The diagnosis of ocular syphilis is made with characteristic ocular signs in conjunction with positive serology testing.

Dark field microscopy, polymerase chain reaction (PCR) and immunohistochemistry are direct detection methods known to provide unambiguous diagnosis of syphilis. Dark field microscopy has sensitivity of approximately 90% and specificity of 100% but due to difficult testing method its use is limited. PCR is more widely accepted compared to other direct detection.

Serological testing is the standard for the diagnosis of syphilis due to the difficulty of culturing Treponema pallidum. Serologic testing can be divided into two groups: Nontreponemal tests (NNT) which detect nontreponemal antibodies and Treponemal tests (TT) which detect antibodies against T. Pallidum. (Table 2). NTT include the VDRL test and RPR that analyze the amount of immunoglobulin G (IgG) and immunoglobulin M (IgM) antibodies in response to cardiolipin, which are found to be detectable six days post infection. They are useful in monitoring treatment response and screening for syphilis.
Currently, RPR is used to test serum samples and VDRL is used to analyze CSF. TT includes T. pallidum hemagglutination assay (TPHA), T. pallidum passive particle agglutination assay (TPPA), and fluorescent treponemal antibody-absorption (FTA-abs). The antibodies detected by TT remain reactive post assay (TPPA), and fluorescent treponemal antibody-absorption (TPHA), T. pallidum passive particle agglutination (TPPA). The antibodies detected by TT remain reactive post treatment and cannot be used to determine disease activity or treatment response. TT are used to confirm the diagnosis of syphilis in adjunct to positive NTT screening. The sensitivity and specificity vary depending on the type of test and stage of syphilis.

### Treatment & Prognosis

The treatment of choice recommended by the CDC for any stage of syphilis is Penicillin G administered either intravenously (IV) or intramuscularly (IM). The specific stage of syphilis determines the preparation used, dosing, and duration of treatment. A single dose of IM benzathine penicillin G 2.4 million units is the recommended treatment for adults with primary or secondary syphilis and early latent syphilis. The dosage increases to 7.2 million units total for adults with late latent syphilis and tertiary syphilis. Aqueous crystalline penicillin G 18-24 million units per day for 10-14 days is the recommended treatment for both ocular and neurosyphilis in adults. The recommended treatment does not differ for individuals co-infected with HIV. Prompt ocular diagnosis and treatment has favorable prognosis especially with the advent of antiretroviral medications. However, it has been shown that ocular symptoms lasting greater than 28 days have been associated with poorer prognosis regardless of HIV status. Most cases recover the initial vision lost, but in cases of optic atrophy, there could be irreversible loss. For HIV infected individuals, post treatment results have been shown to take longer to reach resolution. Untreated syphilis or sub-optimal treatment levels can have devastating effects including neurological and cardiovascular complications. With the risk of neurological involvement and treatment failure in individuals co-infected with HIV and syphilis, routine care is highly recommended to ensure proper resolution. CSF analysis should be performed every 6 months if abnormal results are obtained. Evaluating leukocyte count is recommended for monitoring therapy. If the CSF cell count or protein has not normalized by 2 years or decreased in 6 months, re-treatment should be considered.

### References:


