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Ocular Syphilis: a Clinical Review

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Abstract While ocular syphilis is not a new phenomenon, recent increased rates of new diagnoses, especially in human immunodeficiency virus (HIV)-infected persons and men who have sex with men, have sparked a new interest in an old disease. This article will review the clinical presentation, diagnosis, and treatment of ocular syphilis, and provide guidance on management.

Keywords Syphilis · Human immunodeficiency virus (HIV)-related syphilis · Ocular syphilis

Introduction

Syphilis is a spirochetal bacterial sexually transmitted infection caused by *Treponema pallidum*. Incidence of overall syphilis cases in the United States (US) is on the rise [CDC, 2015], especially in men who have sex with men (MSM) and people infected with human immunodeficiency virus (HIV-1) [1]. Ocular syphilis, once thought to be a disease manifestation occurring only in the pre-penicillin era, also appears to be increasing in incidence and prevalence in the USA [2]. In fact, the Centers for Disease Control (CDC) issued a clinical advisory in 2015 [2], and since that time, over 200 cases of ocular syphilis have been reported to the CDC in the USA. While not a new form of the disease, given this surge in reporting of cases, interest in this particular manifestation has increased. This article will describe two related cases of ocular syphilis, as well as review the epidemiology, the clinical syndrome, diagnosis, and treatment of this condition.

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Case Report

The initial experience with ocular syphilis involved two patients who presented in late 2014 to a Seattle-based human immunodeficiency virus (HIV) clinic affiliated with the University of Washington Medical Center and were included in the first MMWR report. Briefly, the first patient was a HIV-infected male who presented with progressive bilateral vision loss for 3 months, floaters, and a unilateral paracentral scotoma. He was not being treated with antiretroviral therapy (ARVs). He had bilateral hand and feet parasthesias and a resolved diffuse rash. His neurologic examination revealed diffuse weakness; his ocular examination revealed chronic, bilateral anterior uveitis, focal tractional retinal detachment bilaterally, and bilateral synechiae. His CD4 count was 64 cells/mm [3], HIV RNA was approximately 1 million copies/mL, and RPR titer was 1:1024. A lumbar puncture (LP) revealed 318 white blood cells (58 % lymphocytes) and protein of 124 mg/dL. His CSF VDRL was 1:4 and CSF-FTA was reactive. The second patient, his sexual partner, was a 35-year-old HIV-positive male, also not on ARVs, also diagnosed with HIV 4 years prior. He presented with bilateral vision loss

for 8 months, floaters, bilateral field cuts, and painless palmar and plantar white nodules. He was found to have bilateral panuveitis, bilateral retinal detachment, left dense cataract, right nuclear sclerosis cataract, and left iris bombe. His CD4 count was 111 cells/mm [3]; his HIV RNA was approximately 35, 000 copies/mL. His RPR titer was 1:2048. A lumbar puncture (LP) revealed 78 white blood cells (90 % lymphocytes) and protein of 58 mg/dL. His CSF VDRL was 1:4 and CSF-FTA was reactive. Both patients were given the diagnosis of secondary syphilis complicated by ocular syphilis and syphilitic meningitis, treated with aqueous crystalline penicillin G, and started on ARVs. Subsequently, both have achieved virologic control of their HIV, improvement of their RPR titers as well as their CSF-VDRL titers, and visual acuity. Between December 2014 and January 2015, a total of four cases of ocular syphilis were identified in King County, WA. An additional 11 cases were identified in San Francisco, CA. Most patients were men who have sex with men (MSM), HIV positive, and not on ARVs [3].

Epidemiology

Overall, reported syphilis diagnoses are on the rise, largely in young MSM in the South and West of the United States (US). In 2014, 63,450 total cases of syphilis were reported, which is a 12.3 % increase from 2013, when 56,482 cases were reported. Since 2000–2001, when the national rate of reported primary and secondary syphilis (P&S) cases was at its lowest (5979 cases, 2.1 cases per 100,000 population) since reporting began in 1941, rates of P&S syphilis have increased yearly. In contrast, in 2014 (the last year with national data available), a total of 19,999 P&S syphilis cases were reported, and the national P&S syphilis rate increased to 6.3 cases per 100,000 population, the highest rate reported since 1994. The rate increase over time during 2000–2014 has been largely attributable to an increase in cases in MSM specifically. Between 2010 and 2014, there was an increase of 47.9 % of cases of P&S syphilis in MSM in the 27 states that report the sex of sex partners. Nationally, during 2013–2014, there was an overall increase of 15.1 % in total primary and secondary syphilis cases. In addition, incidence of P&S cases is the highest in the southern (rate per 100,000: 6.9) and western (rate per 100,000 persons: 7.9) regions of the US. Specifically, the greater Atlanta area had a rate of P&S syphilis of 18.0 per 100,000 population, the New Orleans metropolitan area had a rate of 17.8 per 100,000, and San Francisco had a rate of 17.0 per 100,000. Overall, the rate of reported P&S syphilis cases in the 50 most populous metropolitan statistical areas (MSAs) was 8.7 cases per 100,000 population in 2014, which is an increase of 13.0 % since 2013. In addition, the number of reported cases of early latent disease increased by 14.8 % and the number of late and late latent cases increased by 7.9 % [1].

No national estimates of incidence or prevalence of ocular syphilis exist, likely either due to low incidence or underreporting of disease. Past epidemiologic surveys of a sexually transmitted diseases clinic in the pre-HIV era indicate that ocular involvement occurred in 4.5 % of new diagnoses of early secondary syphilis, 9.3 % of recurrent secondary, and 3.1 % of late syphilitic cases [4]. Among patients with neurosyphilis, ocular involvement was found in 12 % of the cases [5•]. In an HIV clinic, the estimated prevalence of syphilis was 7.3 % (33/453). Of the patients diagnosed with syphilis, 9 % (3/33) had ocular involvement. In this study, the only statistically significant predictor of ocular syphilis (when compared to the entire study population) was male sex [6]. Within Washington State, in 2015, 40 cases of ocular syphilis were reported to the CDC (38 males, 2 females). Seattle and King County had 22 cases [7]. A comparison of recently reported cases to previous years is ongoing.

Clinical Syndrome/Manifestations

Acquired syphilis infection is a sexually transmitted disease caused by the spirochetal bacteria *T. pallidum*. It can affect most organ systems of the human body including the skin, heart, blood vessels, bones, nervous system, and eye [8, 9]. Ocular syphilis is considered to be a type of neurosyphilis. Notably, however, ocular syphilis is not always accompanied by syphilitic meningitis, and the clinician should not be discouraged from considering the diagnosis in the setting of a normal lumbar puncture. In three large studies, a majority of patients with ocular syphilis had posterior uveitis as the primary site of infection and had bilateral involvement, presented with symptoms for over a month, and all had a positive RPR. Approximately 10 % of affected patients had permanent visual impairment [10, 11•, 12, 13]. Nevertheless, the clinical description can be quite varied. Patients may complain of eye pain, vision loss, floaters, flashing lights, eye pressure, or photophobia. Syphilis may affect the eye at both early and late states of syphilis in both HIV- uninfected [14–16] and HIV-infected patients [10, 17, 18]. Syphilis has been documented to affect almost every structure of the eye [10]. Panuveitis and posterior uveitis are the most common type of ocular inflammation documented [10, 11•] though optic neuropathy, interstitial keratitis, anterior uveitis, and retinal vasculitis may all occur. In a review of 143 patients (93 HIV positive and 50 HIV negative), posterior uveitis was reported in 79 (55.2 %), panuveitis in 36 (25.2 %), and anterior/intermediate uveitis in 28 (19.6 %). Lumbar puncture findings were abnormal in 82 patients (57 %); a majority of these patients (76 %) were HIV positive. Most patients regained their sight, though there were 13 (9 %) treatment failures (which was defined as either lack

of clinical improvement or lack of change in serology) which was more likely in HIV-positive patients ($n = 11$), and those with abnormal CSF findings ($n = 8$). Eleven of the 13 treatment failures were initially treated with parenteral penicillin, suggesting that even with optimal therapy, treatment failure is possible [11•].

Ocular syphilis is often, but not always, accompanied with syphilitic meningitis [13], and the absence of lymphocytes or elevated protein in cerebral spinal fluid (CSF) does not eliminate the possibility of the diagnosis. The CDC has defined ocular syphilis as syphilis of any stage in addition to clinical symptoms or signs consistent with ocular disease that include uveitis, panuveitis, diminished visual acuity, blindness, optic neuropathy, interstitial keratitis, anterior uveitis, and retinal vasculitis [2].

Clinical outcomes of patients vary. In one retrospective chart review, incidence of visual impairment was 0.29 per eye-year for HIV-negative patients and 0.21 per eye-year in HIV-positive patients. Incidence of blindness was 0.07 per eye year and 0.06 per eye year in HIV-negative and HIV-positive patients respectively. Longer duration of uveitis prior to diagnosis and chorioretinitis in the macula at presentation were associated with more than two Snellen lines of visual loss ($P < 0.01$) and visual acuity loss to 20/50 or worse ($P = 0.03$) in HIV-negative patients [10].

Patients infected with HIV may have worse outcomes than their HIV-uninfected peers [19], but this observation has not been validated in a randomized controlled trial. However, no correlation between CD4+ cell count and syphilis-related ocular manifestations has been found [20], and it is unknown if patients who are virologically suppressed are protected. HIV-infected patients with ocular syphilis are more likely to have abnormal lumbar punctures.

Diagnosis

The diagnostic criteria for ocular syphilis include having a new diagnosis of syphilis (defined as having serologic evidence of syphilis) and evidence of syphilitic infection in the eye, or documented ocular inflammation related to syphilis on ocular examination. The CDC also recommends that a lumbar puncture be performed as ocular syphilis can be associated with neurosyphilis, even in the absence of clinical neurological findings. However, recognizing the difficulty of obtaining a lumbar puncture, alternative diagnostic criteria for a confirmed case can include (1) serologic evidence of syphilis or physical exam evidence of a chancre plus (2) ocular symptoms plus (3) ophthalmologic examination consistent with syphilis or evidence of syphilis infection in ocular fluid. Presumptive ocular syphilis is defined as any ocular symptoms and serologic evidence of syphilis. Serologic diagnosis of syphilis includes appropriate serologic screening in two forms. First is traditional serologic testing which includes a positive nontreponemal test (such as a rapid plasma reagin (RPR), Venereal Disease Research Laboratory (VDRL), or toluidine red unheated serum test) confirmed by a treponemal specific test. Treponemal specific tests include Fluorescent treponemal antibody absorption, microhemagglutination test for antibodies to *T. pallidum*, *T. pallidum* particle agglutination assay, and *T. pallidum* enzyme immunoassay (TP-EIA). An alternative approach to initial screening is the "reverse screening algorithm," in which a treponemal test is performed first; if positive, the result is confirmed by a nontreponemal test. This strategy is gaining popularity, particularly in high volume laboratories since the initial screening test (TP-EIA) is generally less expensive than an RPR. The 2015 CDC Sexually Transmitted Diseases Treatment Guidelines provide clear diagnostic and screening guidelines for clinicians.

Examples of positive diagnoses include the following:

1. A patient presents with unilateral blurry vision, photophobia, paracentral scotoma. His ocular examination revealed panuveitis in the affected eye. His RPR titer was 1:256. A lumbar puncture was unable to be performed.
2. An HIV-positive man presents with one month of unilateral, intermittent episodes of complete vision loss, eye pain, flashes of light, and photophobia. Ocular exam revealed panuveitis in the affected eye. His RPR titer was 1:512. His lumbar puncture revealed elevated lymphocyte count, glucose and protein but a non-reactive CSF-VDRL. His vitreous PCR was positive for *T. pallidum*.
3. HIV-positive man presents with unknown duration of blurry vision, headache, dizziness, and numbness. His ocular examination revealed bilateral uveitis, his RPR was 1:128, a lumbar puncture was not performed.
4. HIV-positive male presents initially to an emergency room complaining of blurry vision, headache, and eye pain. Initially given eye drops. Represents 1 week later to a different emergency room complaining of severely decreased vision and a palmar rash. Ocular examination was not performed. His RPR was 1:1024; his lumbar puncture showed 8 white blood cells (89 % lymphocytes), CSF VDRL 1:1.

Clinicians should be aware that visual symptoms vary widely and may or may not be accompanied with other symptoms found in syphilis. Finally, ocular syphilis may occur at any stage of syphilis.

Ocular syphilis should be considered in any patient at risk for syphilis, MSM, any patient who is HIV infected, any person with multiple or anonymous sex partners, or any patient at risk for HIV or on HIV post-exposure

prophylaxis (PrEP). Therefore, with a new diagnosis of syphilis, these patient groups should be screened using a standardized review of systems (ROS) that include questions about symptoms related to otosyphilis, ocular syphilis, and neurosyphilis (Fig. 1).

According to the CDC, the following patients should have a lumbar puncture at diagnosis of syphilis: those with neurologic, ophthalmic, or otologic signs or symptoms; evidence of active tertiary syphilic disease; or treatment failure (defined as a sustained fourfold increase in VDRL or RPR or high (>1:32) RPR titer that does not decline 2 titers over 6–12 months in early syphilis or 12–24 months in latent syphilis). While a presumptive diagnosis of ocular syphilis can be made without a lumbar puncture, a lumbar puncture can make the diagnosis clear, rule out other infectious and non-infectious causes of a patient's symptoms and provide guidance to the clinician in the case that the patient's symptoms do not resolve after treatment.

Management of Ocular Syphilis

Patients with suspected ocular syphilis should have an ophthalmologic examination and a lumbar puncture. The CDC recommends that all patients be managed in collaboration with an ophthalmologist. Both evaluations can clearly establish the diagnosis as well as rule in or out additional diagnoses, which is particularly important in HIV-infected individuals who are at risk for opportunistic infections which can cause opththalmologic and neurologic symptoms. Further, both baseline evaluations can provide comparisons for careful, objective monitoring of a patient's progress after treatment, which seems of particular concern given treatment failure may result in blindness. However, delayed treatment can place patients at higher risk for permanent vision loss. Therefore, in a presumed case of ocular syphilis, treatment should not be delayed beyond 24 hours if either spinal fluid analysis or ophthalmologic exam cannot be performed. In addition, it is acknowledged that not all facilities where patients present may be equipped with an ophthalmologist or the resources to provide a lumbar puncture. However, as the clinical course varies widely, and the consequences of treatment failure so great, attempts should be made to provide each patient with both evaluations.

Additionally, all patients with a new diagnosis of ocular syphilis should be tested for HIV infection as well as screening for other common STDs, especially gonorrhea and chlamydia. All patients with a new diagnosis of HIV should be screened for syphilis.

Ocular syphilis should be treated as neurosyphilis. Patients should receive a 10–14-day regimen of either 18–24 million intravenous units of aqueous crystalline penicillin per day or 2.4 million units of intramuscular procaine penicillin per day administered with oral probenecid 500 mg four times daily. Practitioners should be aware that oral penicillin or oral penicillin alternatives have not had demonstrated efficacy in the treatment of ocular syphilis. Additionally, benzathine penicillin has not been shown to cross the blood-brain barrier.

The Jarisch Herxeimer reaction, an acute febrile reaction accompanied by headache, myalgias, rigors, or chills that occurs within 24 h of the initiation of treatment for ocular syphilis, has been reported in case reports [21, 22]. Typically, patients have been described as having a rapid loss of vision after the first adequate dose of penicillin.

Sexual partners of patients with ocular syphilis should be notified as they are at risk. They should be provided treatment if sexual contact was made within 3 months plus the duration of symptoms for patients diagnosed with primary syphilis,

Screening Questions for Neurosyphilis (Including Ocular and Otosyphilis)

Questions		
Symptoms of Otosyphilis		
1) Have you recently had new trouble hearing?	□ Yes – refer to ENT	□ No
2) Do you have ringing in your ears?	□ Yes – refer to ENT	□ No
Symptoms of Ocular syphilis		
3) Have you recently had a change in vision?	□ Yes – refer to ophthalmology	□ No
4) Do you see flashing lights?	□ Yes – refer to ophthalmology	□ No
5) Do you see spots that move or float by in your vision?	□ Yes – refer to ophthalmology	□ No
6) Have you had any blurring of your vision?		
Symptoms of neurosyphilis		
7) Are you having headaches?	□ Yes	□ No
8) Have you recently been confused?	□ Yes	□ No
9) Has your memory recently gotten worse?	□ Yes	□ No
10) Do you have trouble concentrating?	□ Yes	□ No
11) Do you feel that your personality has recently changed?	□ Yes	□ No
12) Are you having a new problem walking?	□ Yes	□ No
13) Do you have weakness or numbness in your legs?	□ Yes	□ No

Fig. 1 Standardized review of systems for patients at high risk for neurosyphilis, ocular syphilis, and otosyphilis. Created by Christina Marra, MD

6 months plus duration of symptoms for those with secondary syphilis, and 1 year for patients with early latent syphilis [23••].

The CDC recommends repeating a lumbar puncture if CSF pleocytosis was present initially (and recommends considering repeating an LP if the CSF-VDRL or CSF protein evaluations were abnormal) every 6 months until the cell count has normalized. If the cell count has not decreased after 6 months, or CSF cell count or protein has not normalized after 6 months, retreatment should be considered.

All patients with ocular syphilis should be seen regularly after treatment to assess visual acuity as well as assessment of quantitative serologic non-treponemal test titers (regardless of whether a patient notes a new sexual partner or new symptoms). No clear recommendation for timeline of clinical follow up exists, but in general, patients should be evaluated every 3 months for the first year after treatment, then 3–6 months depending on the clinical situation thereafter. Additionally, the patient should be followed by an ophthalmologist post-treatment and may need lifelong routine ophthalmologic care.

Treatment Controversies and Concerns

Patients with HIV who are initiating ARVs at the time of treatment of ocular syphilis may theoretically be at risk for immune reconstitution inflammatory syndrome (IRIS), but to our knowledge, this has not been reported. Thus, the CDC recommends concomitant initiation of ARVs, with close follow-up. Another area of controversy is whether topical or systemic steroids can worsen clinical outcomes in ocular syphilis [24]. At this time, no recommendation exists for the use of topical or systemic steroids. Finally, practitioners should be aware that if a patient with ocular syphilis has a penicillin allergy, the patient must be desensitized. If a patient cannot be desensitized, but the patient is deemed safe to be treated with other beta-lactam drugs, ceftriaxone (2 g IV daily for 10–14 days) can be considered. Other oral alternatives such as oral amoxicillin with probenecid or oral doxycycline should not be prescribed as they are not considered to be effective or standard of care by the US Center for Disease Control and Prevention.

Conclusions

Overall, syphilis rates and reported ocular syphilis cases are on the rise. It remains unclear if this increase is a result of increased recognition and reporting bias or a true increase in incidence of disease. Research into specific strains of oculotropic syphilis is ongoing. Clearly, MSM and HIV-positive individuals are at risk for syphilis and ocular syphilis. Although ocular syphilis may presents with a broad spectrum of ocular symptoms and findings, the most common clinical manifestation is vision loss. Examination typically reveals posterior or panuveitis, but almost all structures of the eye are vulnerable to involvement. Ocular syphilis should be treated as neurosyphilis. Practitioners should assess all at-risk populations with a positive RPR for symptoms, and with any ocular symptom in a high-risk person, ocular syphilis should be considered. At this time, an ophthalmologic examination and lumbar puncture are recommended to substantiate the diagnosis. In the future, better epidemiologic data on ocular syphilis rates should be collected, and case definitions may need to be revised to consider presumed cases, particularly given the difficulties of obtaining an ophthalmologic examination or lumbar puncture. Ocular syphilis remains a fascinating clinical syndrome, challenging diagnosis, and potentially devastating infection if untreated.

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Compliance with Ethical Standards

Conflict of Interest Drs Woolston, Dhanireddy, and Marrazzo do not find any conflicts of interest.

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