Case Series

Ocular syphilis: a case series of four patients and a review of the literature

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Background: The incidence of syphilis has been increasing in the United States over the last two decades, with a more recent increase among women. Ocular syphilis is an uncommon but important complication of syphilis, most often presenting as posterior or panuveitis in late or latent syphilis of unknown duration. Untreated ocular syphilis may lead to permanent vision loss, underscoring the importance of appropriate evaluation and treatment of ocular syphilis.

Case Description: In a retrospective, non-contiguous case series, we highlight four patients diagnosed and treated with ocular syphilis at a single institution. Four presentations of ocular syphilis are illustrated: anterior and intermediate uveitis, optic neuritis, posterior uveitis, and panuveitis. All patients initially presented with a decreased visual acuity (VA). One patient had a previous diagnosis of human immunodeficiency virus (HIV). Three patients were treated with intravenous (IV) penicillin and one patient with IV ceftriaxone. All had a return to their baseline VA after their course of treatment.

Conclusions: Syphilis may go undetected without a high index of clinical suspicion due to its nonspecific presentations. All patients with ocular inflammation should have syphilis testing as a part of their infectious workup with both treponemal and non-treponemal testing. Patients diagnosed with syphilis and are not known to be HIV-negative should undergo testing for HIV due to the high rate of co-infection. Early diagnosis and prompt treatment after onset of symptoms may contribute to a more favorable prognosis for ocular syphilis.

Keywords: Ocular syphilis; uveitis; choroiditis; intermediate uveitis; case series

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Introduction

Rates of syphilis are on the rise in the United States. The natural history of syphilis is divided into four stages: primary, secondary, tertiary, and latent syphilis. The primary and secondary stages are the disease's peak infectious periods (1). In 2019, there were 39.7 cases per 100,000 people of all stages of syphilis (2). All stages of syphilis have seen increases in the past 10 years, but late (greater than one year after infection) or latent of unknown duration syphilis contributed the most to the increase (2). Similar trends have been noted in Canada, Europe, and China (3-5). The rise in primary and secondary syphilis is classically associated with men who have sex with men (MSM), with

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more than five times as many cases in men than women in 2019 (6). However, in 2019–2020, the case counts of primary and secondary syphilis in MSM decreased by 2.2% while the rate in women increased by 21% during that same time period (7).

The prevalence of ocular manifestations in patients with syphilis has been reported from 0.6% to 2.6% (8-10). Ocular syphilis can be the only presenting symptom of syphilis in up to 31.7% to 40% of patients (10,11). The range of presentation of ocular syphilis includes, but is not limited to, anterior, intermediate, posterior, or panuveitis, optic neuropathy, retinal vasculitis, and interstitial keratitis (12). Symptoms of ocular syphilis are nonspecific, but may include blurred vision, redness, floaters, and photophobia (13,14). Ocular involvement can occur at any stage in the natural history of syphilis; however, nearly half (49.7%) of cases are diagnosed as late (greater than one year after infection) or latent of unknown duration, with only 2% of cases reported during primary syphilis (8). Early recognition and prompt treatment of ocular syphilis is imperative due to the potential for permanent vision loss. A retrospective study demonstrated a lower visual acuity (VA) at diagnosis and a delay in treatment of more than 12 weeks were associated with a lower VA at 6-month follow-up (15). A case series of six patients detailed two patients with permanent blindness as a result of delayed treatment (16).

This report will discuss four cases with different presentations of ocular syphilis and present a relevant review of the current literature. This case series is a retrospective, single center study of non-consecutive cases from 2014–2022. All patients were seen by a uveitis-trained ophthalmologist (L.M.R.) in private and academic settings. All patients included did not have a diagnosis of syphilis prior to presentation, tested positive for syphilis with treponemal specific testing, and maintained continuity with the ophthalmology clinic during their course of treatment for at least 1 month. We present this article in accordance with the AME Case Series reporting checklist (available at https://aes.amegroups.com/article/view/10.21037/aes-22-80/rc).

Highlight box

Key findings

- Syphilis can affect any ocular structure.
- Prompt diagnosis and treatment of ocular syphilis are key for a favorable prognosis.

What is known and what is new?

- Rates of syphilis are increasing in the United States, especially among women, although the majority of syphilis cases continue to be diagnosed in men.
- We illustrate four presentations of ocular syphilis: anterior and intermediate, posterior, optic neuritis, and panuveitis.

What is the implication, and what should change now?

- All patients with ocular inflammation should have specific syphilis testing.
- Appropriate workup for syphilis must include both treponemal and non-treponemal testing.

Case presentation

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Institutional review board (IRB) approval and informed consent were waived as this was a retrospective and non-interventional collection of case reports from a single physician.

Patient 1: acute posterior placoid chorioretinitis

A 44-year-old white male presented to the ophthalmologist with a 4-day history of sudden vision loss in his right eye (OD). He also reported fatigue, hair loss, and palmar skin lesions. Best-corrected VA (BCVA) was 20/100 in the OD and 20/20 in the left eye (OS). Slit lamp exam was normal in both eyes (OU). Fundoscopic exam and red-free fundus photography OD and optical coherence tomography (OCT) were conducted (*Figures 1,2*). On fundoscopic exam and red-free fundus photography OD, retinal pigment epithelium (RPE) mottling in a circinate pattern was noted (*Figure 1A,1B*). OCT demonstrated outer retinal disruption OD (*Figure 2A*). Ocular syphilis was suspected despite the fact that he had initially presented to rheumatology with a limited workup at that time, including a negative rapid plasma reagin (RPR). Subsequent testing with fluorescent treponemal antibody absorption (FTA-Abs) testing and repeat RPR, one week after initial RPR, resulted positive with an RPR titer of 1:128. Human immunodeficiency virus (HIV) testing was negative. He was diagnosed with syphilitic placoid and referred to infectious disease where he was treated with intravenous (IV) ceftriaxone. Repeat funduscopic exam showed marked improvement in RPE mottling (*Figure 1C,1D*). Repeat OCT OD was normal with reconstitution of normal outer retinal architecture

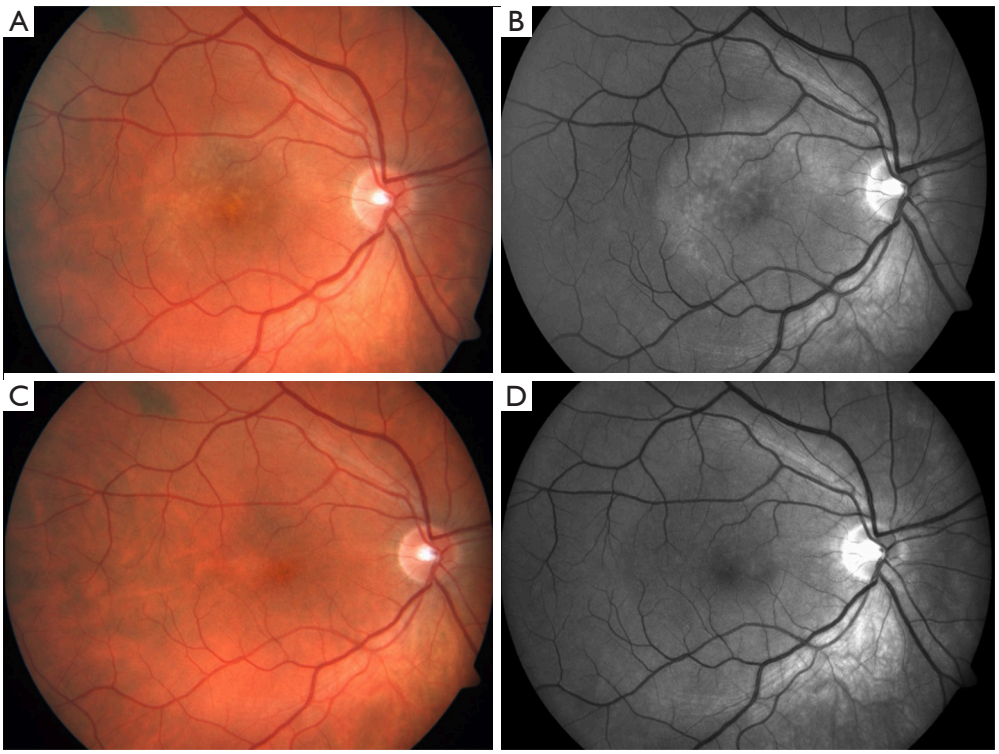

Figure 1 Color fundus photos of both eyes demonstrating acute posterior placoid chorioretinitis. (A) Color fundus photo and (B) red-free fundus photo of the right eye demonstrating RPE mottling/placoid lesion in a circinate pattern. (C) Repeat color fundus photo and (D) red-free fundus photo after treatment with IV ceftriaxone demonstrating improvement in RPE mottling and resolution of placoid lesion. RPE, retinal pigment epithelium; IV, intravenous.

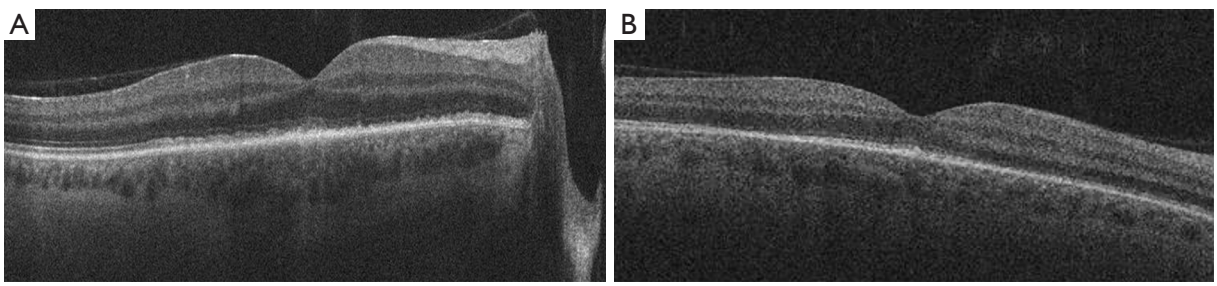

Figure 2 OCT of the right eye demonstrating acute posterior placoid chorioretinitis. (A) OCT of the right eye demonstrating outer retinal disruption typical of syphilis. (B) Repeat OCT normal with reconstitution of photoreceptors after treatment. OCT, optical coherence tomography.

(*Figure 2B*). His BCVA improved to 20/20 in OU. On examination, his anterior chamber remained quiet, and no vitreous cell was noted in OU.

Patient 2: anterior and intermediate uveitis

A 45-year-old white male with a history of well-controlled HIV (700 cells/mm^3; undetectable viral load) presented with redness and pain OS. Review of systems was negative for non-ocular symptoms. He had a BCVA of 20/100 OD and 20/50 OS. Slit lamp examination was notable for conjunctival granulomas in the inferior fornices OU, granulomatous keratic precipitates in Arlt's triangle OU, posterior synechiae OS, and 2+ anterior chamber cell OD

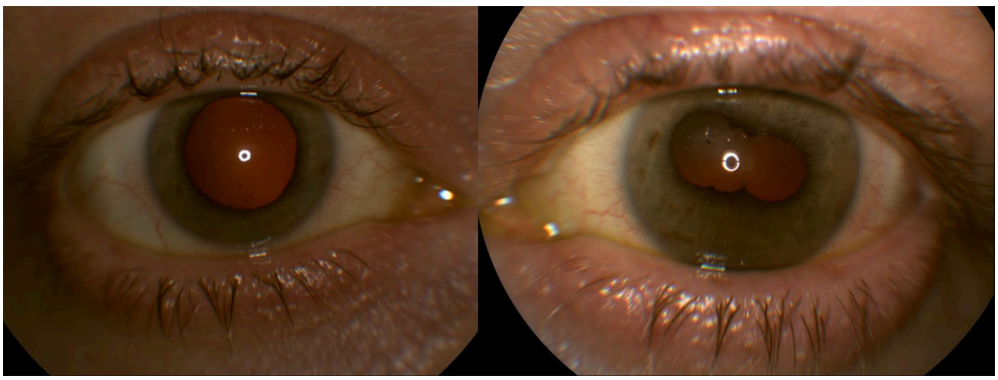

Figure 3 Slit-lamp photos demonstrating mild conjunctival injection in both eyes with posterior synechiae in the left eye.

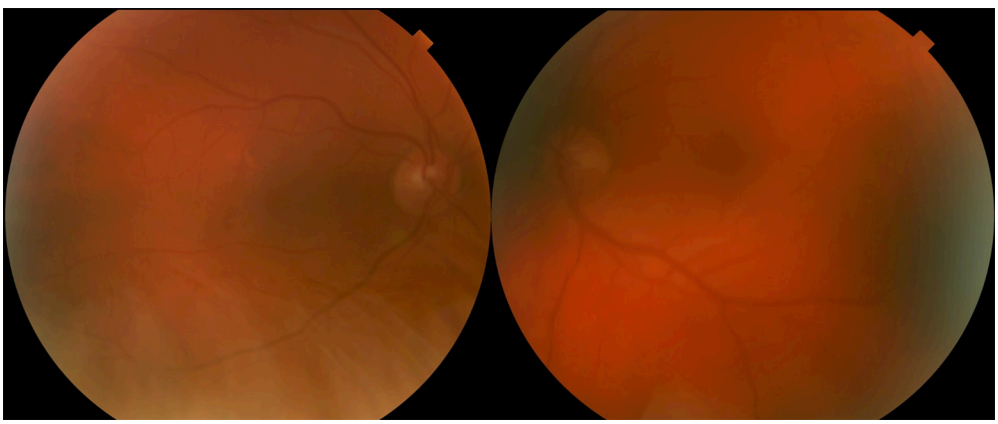

Figure 4 Color fundus photo of both eyes demonstrating haze. No retinitis, choroiditis, or vasculitis noted.

and 3+ anterior chamber cell OS (*Figure 3*). Funduscopic exam demonstrated 1+ AV (anterior vitreous) cell, 1+ haze OD and 2+ AV cell, 2+ haze OS with no retinitis, choroiditis, or vasculitis OU (*Figure 4*). Workup revealed a positive RPR and positive FTA-Abs and was negative for tuberculosis and sarcoidosis. A lumbar puncture was performed, and the venereal disease research laboratory-cerebrospinal fluid (VDRL-CSF) was negative. Of note, FTA-Abs was negative the year prior to presentation. His final diagnosis was anterior and intermediate uveitis secondary to syphilis. He subsequently received treatment with IV penicillin for 14 days. After 2 weeks, his BCVA improved to 20/20 OU with complete resolution of ocular inflammation.

Patient 3: optic neuritis

A 47-year-old white female presented with flashes and a "film" OD. Medical history was non-contributory. She reported stomach pain, lethargy, and unintentional weight loss. On exam, BCVA was 20/30 OD and 20/20 OS. Anterior exam was within normal limits in OU. Funduscopic examination OD demonstrated disc elevation with disc margin obscuration and no disc hemorrhages (*Figure 5A*). Optic nerve OS was normal (*Figure 5B*). Visual field testing OD showed an inferior arcuate defect. Brain magnetic resonance imaging was negative for any demyelinating plaques, compressive lesions, or alternative etiologies for optic neuritis. Serologic testing was obtained, with pertinent negatives results for sarcoidosis, tuberculosis, Lyme disease serology and a normal erythrocyte sedimentation rate and C-reactive protein. Both the RPR and FTA-Abs were positive, and she was diagnosed with syphilitic optic neuritis. Treatment included IV penicillin for 14 days. She reported symptomatic improvement after her treatment. On follow up, BCVA improved to 20/20 OU with funduscopic exam revealing improving disc edema OD.

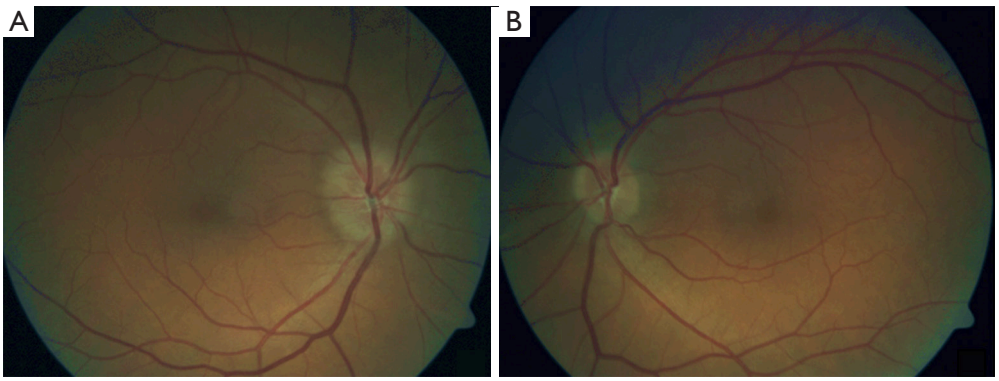

Figure 5 Color fundus photos of both eyes demonstrating syphilis optic neuritis. (A) Color fundus photo of the right eye demonstrating disc elevation with disc margin obscuration and no disc hemorrhages. (B) Color fundus photo of the left eye normal without disc edema. Used with permission from SLACK Incorporated, published originally by Athappilly G & Dajani OAW (2017, August 2). Women referred for acute flashing lights and visual distortion. Healio (https://healio.com/news/ophthalmology/20170724/woman-referred-for-acute-flashing-lights-and-visual-distortion).

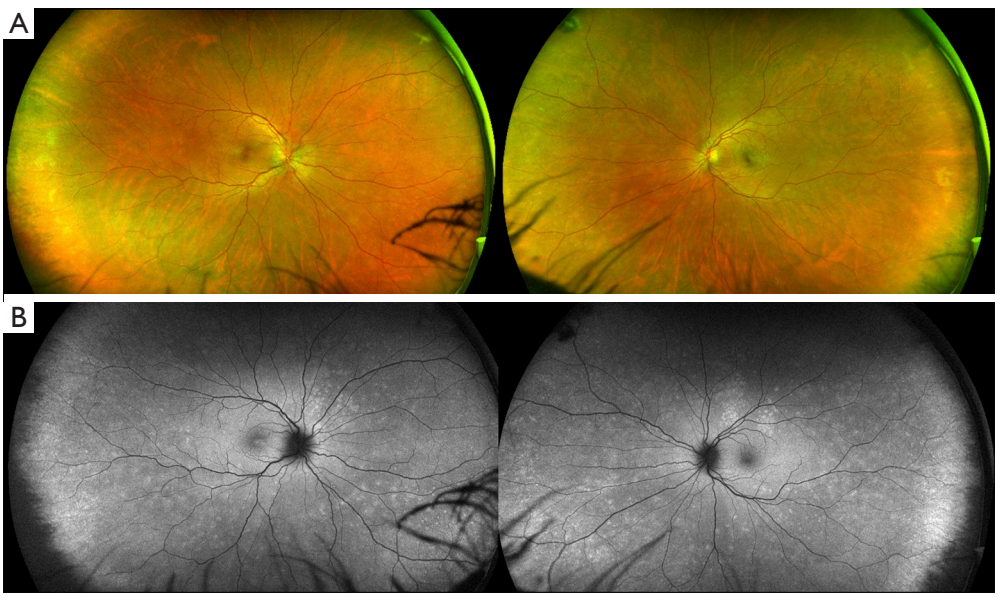

Figure 6 Color fundus and fundus autofluorescence photos of both eyes with panuveitis. (A) Color fundus photo of both eyes demonstrating disc edema and white spots in the periphery. (B) Fundus autofluorescence of both eyes showing distinct small round areas of hyperautofluorescence throughout posterior pole and periphery.

Patient 4: *panuveitis*

A 35-year-old female presented with a 2-month history of eye pain, photophobia, and floaters OU. On review of systems, she also reported a new onset rash and joint pain. She had previously been seen by rheumatology and was undergoing workup for suspected Behçet's syndrome. On exam, BCVA was 20/30 +2 OD and 20/25 –2 OS. Slit lamp examination was notable for 0.5+ cell, 1+ AV cell OD without haze, and 1+ cell, trace AV cell OS without haze. Fundoscopic exam showed disc edema OU with OD worse than OS; RPE mottling OD, and white spots in the periphery OU (*Figure 6A*). OCT macula demonstrated subretinal fluid OD, peripapillary edema OU, and normal inner and outer segment junction OU.

Fundus autofluorescence OU demonstrated small pinpoint hyperautofluorescence throughout, most evident nasally (*Figure 6B*). Subsequent testing resulted in a positive FTA-Abs and a positive RPR at a ratio of 1:32. The patient was diagnosed with panuveitis secondary to syphilis and treated with IV penicillin for 14 days. On follow up, subretinal edema was resolved and BCVA was 20/20 OU. Her systemic symptoms improved dramatically as well, and it was felt that her systemic symptoms were due to syphilis rather than Behçet's.

Discussion

Ocular syphilis, despite its increasing global prevalence, is still a rare disease. A prospective study showed an incidence of 0.3 per million in the adult population over a 2-year period in the United Kingdom between 2009 and 2011 (11). There is a consistent male predominance in ocular syphilis, up to 93% of cases (8). However, demographic distribution may be changing: between 2016–2020, there was a 147.4% increase in cases of primary and secondary syphilis in women in the US in comparison to a 34.2% increase in men (2). An analysis of the 2019 National Notifiable Diseases Surveillance System (NNDSS) data on reported syphilis in the US showed that 1.3% of women with verified, likely, and possible syphilis had ocular manifestations as compared to 1.1% of men (17).

Diagnosis of syphilis consists of both non-treponemal (e.g., VDRL or RPR) and treponemal [e.g., *Treponema pallidum* passive particle agglutination (TP-PA) assay and enzyme immunoassays, FTA-Abs] testing. CSF evaluation is indicated for neurologic or cranial nerve dysfunction but is not necessary for isolated ocular symptoms (1). Testing with VDRL or RPR alone is insufficient to diagnose syphilis due to the risk for false positives in other infections or medical conditions such as pregnancy or recent vaccination as well as the concern for false negatives early in the disease course. A complete workup must include treponemal specific testing such as TP-PA or FTA-Abs.

Syphilis can affect any ocular structure and therefore has varying presentations. For posterior uveitis, the classical presentation is acute posterior placoid chorioretinitis (18). A retrospective study of 20 patients with acute and chronic syphilitic posterior uveitis, 75% had chorioretinitis and 15% had panuveitis (19). Optic neuritis may present as anterior or retrobulbar retinitis, papilledema, or perineuritis (14,20-22). Other potential posterior segment manifestations include necrotizing retinitis, vasculopathy, and retinal detachment (23-31).

The differential diagnosis for ocular syphilis is broad and dependent on the ocular structures that are involved. Anterior uveitis can be unilateral or bilateral and granulomatous or non-granulomatous in nature. Interstitial keratitis is another uncommon complication of syphilis (14,32). Primary syphilis ocular manifestations are limited to chancres on the eyelid and conjunctiva (14). Scleritis, episcleritis, and iridocyclitis are atypical but possible and syphilis should remain on the differential for all ocular inflammation (33).

For posterior uveitis, other infectious etiologies such toxoplasmosis, cytomegalovirus retinitis, ocular tuberculosis, and herpetic retinitis must be considered (34). Non-infectious etiologies include sarcoidosis, systemic lupus erythematosus, acute retinal necrosis, and vasculitides like Behçet's disease may also be evaluated (35).

There is high rate of co-infection of HIV with syphilis with a similar route of transmission for MSM (36,37). In 2010, in Florida, 42% of all patients diagnosed with infectious syphilis were also found to be co-infected with HIV (38). A Centers for Disease Control (CDC) report of 388 patients with ocular syphilis from 2014–2015 found 51% of the patients to HIV positive (8). An analysis of the 2019 NNDSS data of reported syphilis showed an increased proportion of ocular manifestations in HIV-infected persons (1.3%) as compared to HIV-negative persons (1.0%) (17). Furthermore, the prevalence of ocular symptoms was higher in the late stages of syphilis as compared to the early stages of syphilis when stratified by HIV status (17). It remains unclear to what degree HIV influences the development, severity, or prognosis of ocular syphilis with overall low prevalence rates and multiple studies with conflicting reports (8,10,11,15,39). However, it is still recommended that all patients not known to be HIV-negative should be tested for HIV when diagnosed with syphilis.

For treatment of ocular syphilis, the CDC recommends 18–24 million units of IV penicillin for 10–14 days, with limited data to support IV ceftriaxone 1–2 grams for 10–14 days as an alternative therapy for a penicillin allergy (40). It is important to note that a single dose of intramuscular treatment is insufficient for the treatment of ocular syphilis. While ocular syphilis is treated similarly to neurosyphilis, a lumbar puncture is not necessary when no signs of cranial nerve dysfunction are present (40).

This report highlights four of the many presentations of ocular syphilis: anterior, intermediate, posterior uveitis,

optic neuritis, and panuveitis. One patient had co-infection with HIV. Three patients were treated with IV penicillin and one patient was treated with IV ceftriaxone. All four patients had improvement in the BCVA to baseline after treatment without any complications. Of note, one patient's initial workup demonstrated a negative RPR, with no specific treponemal testing done initially, causing a delay in diagnosis.

Limitations of this study include the retrospective nature of this case series and the limited number of patients. The strengths of this case series are the varied presentations of ocular syphilis, appropriate follow-up, and relevant imaging.

Conclusions

Syphilis is a sight-threatening disease if not appropriately diagnosed and promptly treated. The nonspecific and far-ranging presentations of ocular syphilis pose a diagnostic challenge to ophthalmologists. While syphilis can present in any ocular structure, posterior uveitis and panuveitis are the most common manifestations. The rates of primary and secondary syphilis are on the rise in the female population in the US, with the incidence in MSM stable or slightly decreasing, reinforcing the need for wide screening. Physicians should have a high index of suspicion for syphilis and order specific treponemal testing such as TP-PA or FTA-Abs in all cases of ocular inflammation. Non-treponemal testing alone (e.g., RPR, VDRL) is not sufficient to rule out disease. In all cases of diagnosed syphilis except for patients already known to be living with HIV, testing for HIV should be performed due to the high rate of co-infection.

With prompt diagnosis and treatment after onset of symptoms, the prognosis of ocular syphilis may be quite favorable. Continued awareness and recognition of the varied presentations of ocular syphilis are recommended.

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Footnote

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