Ocular Syphilis and Human Immunodeficiency Virus Co-infection: A Case Report

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Abstract

Ocular syphilis is a rare complication of syphilis caused by the spirochete bacterium *Treponema pallidum*. Diagnosing ocular syphilis is a challenge due to its diverse and often non-pathognomonic clinical manifestations. We report a patient with no known history of sexually transmitted infections who presented with sudden-onset reduced vision and bilateral granulomatous uveitis. Serological testing subsequently confirmed syphilis and human immunodeficiency virus (HIV) co-infection. This case highlights the importance of a multidisciplinary approach to ocular syphilis management, especially in the context of HIV co-infection.

KEY WORDS

Ocular syphilis, granulomatous uveitis, case report, HIV/STI, *Treponema pallidum*, vision loss, co-infection

INTRODUCTION

Ocular syphilis can occur at any stage of syphilis and has a broad range of clinical manifestations. Uveitis is the most common ophthalmological presentation of syphilis and more specifically posterior uveitis and panuveitis are more likely to occur in the later stages of syphilis[1,2] Other manifestations of ocular syphilis include anterior uveitis, optic neuropathy, retinal vasculitis, and interstitial keratitis.[2] Even though ocular syphilis accounts for only 1-5% of uveitis cases in the United States (U.S.), it should remain a differential diagnosis when ocular inflammation is present.[3] Furthermore, ocular syphilis may be the only indication of undiagnosed syphilis. Therefore, early detection is imperative to ensure timely treatment to prevent further complications. However, ocular syphilis is a diagnostic challenge, since clinical findings are generally non-specific and non-pathognomonic. A definitive diagnosis involves serological testing and, if neurosyphilis is suspected, an analysis of cerebrospinal fluid (CSF).[2,4,5,6] An estimated 40% of syphilis patients have a human immunodeficiency virus (HIV) co-infection and therefore should be evaluated for both.[5]

We report a patient with no known history of sexually transmitted infections (STIs) who presented with sudden-onset reduced vision and bilateral granulomatous uveitis. Serological testing subsequently confirmed syphilis and human immunodeficiency virus (HIV) co-infection. This case highlights the importance of a multidisciplinary approach to ocular syphilis management, especially in the context of HIV co-infection.

CASE REPORT

A 67-year-old African American male presented for an unscheduled eye exam with a chief complaint of persistent uncorrected blurred vision in both eyes (OU) for two consecutive weeks. The patient did not recall the date of his last eye exam, stating it was a while ago. The patient's personal and family ocular histories were unremarkable for eye disease, injuries, or infections. His medical and social history were significant for prostate cancer, cocaine dependence, tobacco use and lack of housing. Best corrected visual acuity (BCVA) was 20/40 in the right eye (OD) and 20/40 in the left eye (OS). Pupils were equal, round,

and reactive to light (PERRL) with no relative afferent pupillary defect (RAPD). Gross confrontation visual fields (CVF) were full OD/OS and extraocular motilities (EOMs) were unrestricted OU. Slit lamp examination (SLE) revealed bilateral mutton-fat keratic precipitates (KPs) diffusely distributed across the corneal endothelium and mild anterior chamber inflammation with no apparent synechia of the iris or conjunctival hyperemia. Intraocular pressures (IOPs) were 20 mmHg OD and 23 mmHg OS. There were mild nuclear sclerotic cataracts of the lens OU. There was no apparent vitritis, optic nerve or macular involvement, vasculitis or retinitis on dilated fundus examination (DFE) including peri-phlebitis or retinitis. The results of optical coherence tomography (OCT) of the macula and the optic nerve retinal nerve fiber layer (RNFL) were within normal limits (WNL) OU. (Figs. 1 and 2). Since the posterior segment examination was unremarkable, the reduced visual acuity was attributed to the anterior ocular inflammatory response. The patient was initially diagnosed with bilateral anterior uveitis and referred to a uveitis specialist. Since he denied photophobia and ocular discomfort, the initiation of treatment and further work-up were deferred to the specialist.

Figure 1: *Initial OCT of the macula with unremarkable findings and no evidence of central macular edema OD and OS.*

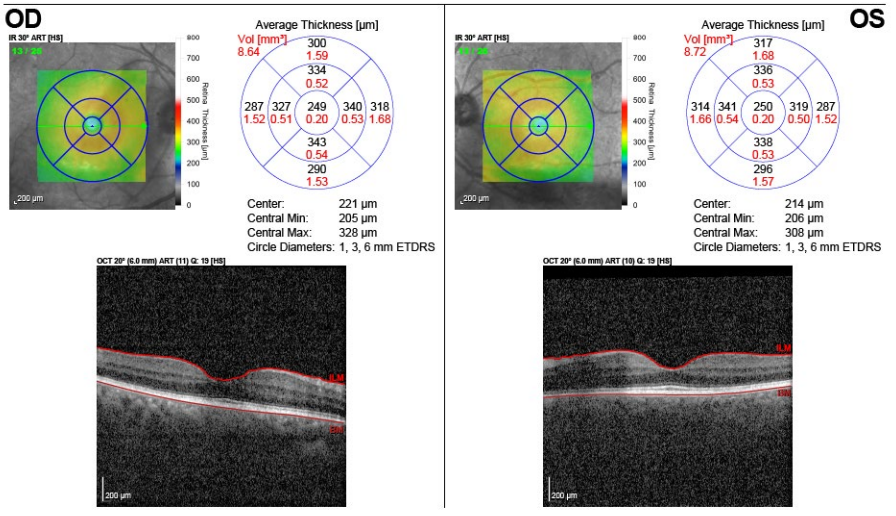
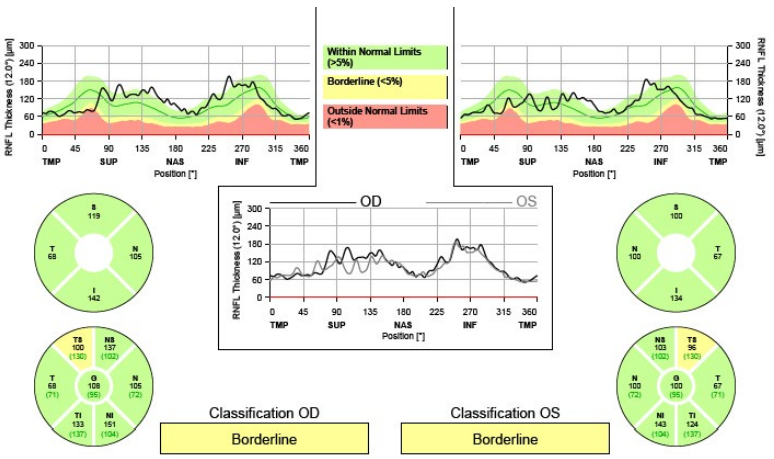


Figure 2: *Initial OCT of the optic nerve showing normal retinal nerve fiber layer (RNFL) thicknes OD and OS.*



First visit with a uveitis specialist

Despite the immediate referral to the specialist, the patient presented two weeks after the initial exam, citing personal scheduling conflicts as the reason for the delay in follow-up. The patient reported stable "cloudy" vision OU and denied eye pain and photophobia. BCVA remained stable and preliminary testing of pupils, CVF, and EOMs showed no abnormalities. SLE revealed small to medium-size granulomatous KPs OU and trace to grade 1+ cell and flare in the anterior chamber OU with spill-over into the vitreous evident on DFE OU. IOPs were measured at 11 mmHg OD and 17 mmHg OS.

Posterior segment remained unremarkable OU. OCT of the macula appeared to be WNL OU. The patient was diagnosed with bilateral granulomatous anterior uveitis, and treatment was initiated with prednisolone acetate 1% ophthalmic suspension administered four times daily (QID) OU. Difluprednate or more frequent dosing of prednisolone acetate 1% (e.g., q2hours) would have been considered if the patient had more moderate inflammation or was symptomatic.

A chest x-ray and uveitis serologic panel (Table 1) were ordered, which included human immunodeficiency virus (HIV) antibodies, complete blood count (CBC), complete metabolic panel (CMP), human leukocyte antigens B27 (HLA-B27), rapid plasma regain (RPR), and microhemagglutination assay for *T. pallidum* (MHA-TP). The patient was scheduled for a 2-week follow-up.

Table 1: *Uveitis laboratory and imaging work-up.*

Serological testing	Purpose
Chest X-ray	Identifies lung granulomas
HIV Ag/Ab test	Identifies HIV antibodies
Complete Blood Count with differentials	Detects any disease or illness in the body
Complete metabolic panel (CMP)	Provides metabolism and balance of chemicals in the body
Human Leukocyte Antigens B27 (HLA-B27)	Identifies protein on the surface of WBC that causes certain autoimmune conditions
Rapid Plasma Reagin (RPR)	Identifies antibodies to syphilis that is currently present in the body
Microhemagglutination assay for *T.pallidum* (MHA-TP)	Qualitative detection of T. palladium antibodies that are currently or were previously present in the body
Lyme AB (not part of the hospital's standard uveitis panel)	Testing for Lyme disease (not performed on our patient due to lack of reported tick exposure)

Second visit with a uveitis specialist; 4 weeks after the initial presentation

The patient did not express any new visual concerns and noted stable reduced vision. However, he did report experiencing bilateral foot pain. He was instilling prednisolone acetate 1% ophthalmic suspension twice a day (BID) OU instead of QID as originally prescribed. BCVA, SLE, DFE and OCT findings remained unchanged. IOPs measured 17 mmHg OD and 21 mmHg OS. No evidence of inflamed preauricular (PA) nodes was detected upon palpation. The patient reported not undergoing the ordered serologic tests and chest X-ray despite being informed of their importance. The patient was instructed to undergo lab testing and chest x-ray on the same day as this visit and was reminded of the importance of compliance with prednisolone acetate ophthalmic suspension QID OU. A follow-up appointment was scheduled in 3 weeks.

Consultation with infectious disease (ID)

Twenty-four hours after his last visit with the uveitis specialist, the patient's lab results showed a reactive RPR and confirmatory MHA-TP at >1:512, and a presumptive positive HIV Ag/Ab test. His risk factor for HIV was unprotected heterosexual contact with multiple partners. Several months prior he had noted a lesion on his penis that "resembled ringworm" that resolved without treatment. He also reported a recent unintentional weight loss of 9 kilograms and occasional night sweats.

An infectious disease (ID) consultation was ordered, and the patient was subsequently admitted for inpatient treatment. The physical exam was positive for bilateral temporal wasting and oral thrush on the posterior tongue. In addition to a baseline comprehensive metabolic and lipid panel, his initial HIV work-up results are delineated in Table 2. A lumbar puncture to evaluate CSF and brain imaging (e.g. computed tomography or magnetic resonance imaging) were not performed since he had no other neurological signs to indicate neurosyphilis such as cranial nerve dysfunction, altered mental status, meningisumus, or evidence of a stroke. He was started on triple antiretroviral therapy (ART) with bictegravir, emtricitabine and tenofovir alafenamide. He had no history of a penicillin allergy and was started on first-line treatment of intravenous aqueous penicillin G, 4 million units every 4 hours for 14 days.

Thrush was treated with mycostatin oral suspension (500,000 units/5ml Q6H). He completed the 14-day treatment for syphilis in the hospital, and his thrush resolved. He was seen by ID 3 weeks after discharge. His CD4 had risen to 563 cells per cubic millimeter (18.2%), and his HIV viral load had decreased to 72 copies.

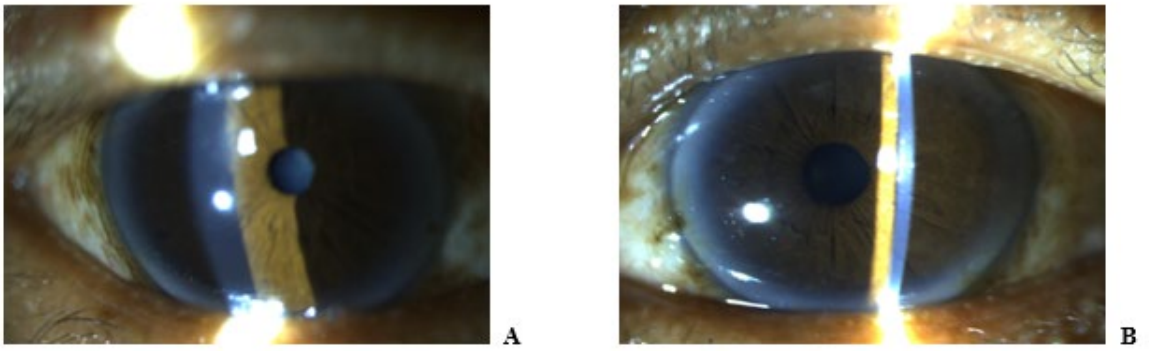
Table 2: *Baseline HIV lab work-up*

Routine Lab Tests	Result	Reference Range	Description
CD4/T cell count	300 (13.6%)	>500 (38-58%)	Measures white blood cells (T (thymus)-cells) that preserve immune function
HIV viral load	49,100 RNA copies	No HIV RNA detected	Measures the amount of HIV circulating in the blood
HIV Genotypic Resistance	Pansensitive	No resistance	Delineates resistance to approved classes of drugs used to treat HIV
QuantiFERON TB Gold	Negative	Negative	Aids in the evaluation of latent or active TB using an interferon-gamma release assay (IGRA)
Gonorrhea/Chlamydia PCR	Not detected	Not detected	Uses a polymerase chain reaction (PCR) to detect the presence of bacterial DNA that could indicate a chlamydia or gonorrhea infection
Quantitative G6PD (Glucose-6-phosphate dehydrogenase)	216 U/10E 12RBC	127 – 427	Measures G6PD enzyme activity in the blood to determine G6PD deficiency
Serum cryptococcal antigen	Negative	Negative	Detects *Cryptococcus neoformans,* an AIDS-defining diagnosis
Toxoplasma IgG antibody	40.3 IU/mL	0.0 – 7.1	Indicates past infection with *Toxoplasma gondi*
Toxoplasma IgM antibody	<0.3 AU/mL	0.0 – 7.9	Detects antibodies produced in response to Toxoplasma infection (recent or acute)
Hepatitis C viral load	Not detected	Not detected	Measures amount of hepatitis C virus in the blood
Hepatitis B serologies HbsAb, quantitative HbsAg HbcAb (total)	 < 3.31 Nonreactive Nonreactive	 – 12.00 Nonreactive Nonreactive	Measures prior exposure to Hep B Screens for Hep B and if positive Hep B is transmissible to others. Measures antibodies against Hep B core antigen

Third visit with a uveitis specialist; 7 weeks after the initial presentation

The patient reported stable vision and compliance with prednisolone acetate 1% ophthalmic suspension QID OU. The patient was on ART for HIV and completed inpatient treatment for tertiary syphilis with intravenous penicillin G. Uncorrected VA improved to 20/25 OD and 20/30 OS. Preliminary testing including EOMS, pupils, and CVF testing remained stable and unremarkable. IOPs were 13mmHg OD and 16mmHg OS. SLE revealed rare KPs OD and small KPs OS (Fig. 3) with no anterior chamber reaction OU. OCT of the macula was WNL OU. Considering the improvement of KPs and the absence of anterior chamber inflammation, a decision was made to begin tapering prednisolone acetate 1% ophthalmic suspension to BID OU. The patient was advised to continue follow-up visits with ID and scheduled in one month for an anterior and posterior segment evaluation.

Figure 3: *Anterior segment photos of rare KPs OD (photo A) and small KPs OS (photo B) with no anterior chamber reaction.*



Fourth visit with a uveitis specialist; 11 weeks after the initial presentation
The patient noted a significant improvement in uncorrected vision, achieving 20/20 OD and 20/20 OS. SLE revealed the absence of KPs and anterior chamber reaction. IOPs measured 16 mmHg OD and 18 mmHg OS. DFE showed no remarkable findings. The patient received instructions to taper prednisolone acetate 1% ophthalmic suspension to once a day OU for the next 2 weeks, followed by complete discontinuation. A 3-month follow-up appointment was scheduled for an anterior segment check and macular OCT.

DISCUSSION

Syphilis, a sexually or congenitally transmitted infection caused by the spirochete bacterium *T. pallidum*, presents a diagnostic challenge due to its diverse and often non-pathognomonic clinical manifestations as exemplified in this case report. Our patient was incidentally diagnosed with syphilis when he sought an eye exam for recent-onset blurred vision in the absence of typical subjective symptoms of uveitis such as photophobia and eye pain. The presence of mutton-fat KPs and anterior chamber reaction prompted further work-up, resulting in a diagnosis of ocular syphilis and an HIV co-infection. Therefore, ocular syphilis, which can occur at any stage of syphilis, should be considered a differential diagnosis in patients with uveitis. [4,7]

Syphilis Resurgence

The Centers for Disease Control's (CDC's) 2022 STI surveillance report showed the highest levels of syphilis cases in the U.S. since 1950. Over the period 2018-2022, there was an estimated 80% increase in syphilis cases, with more than 200,000 cases reported nationwide in 2022. The largest spike occurred during the height of the COVID-19 pandemic between 2020 and 2021.[8,9] There has also been an increase in the number of ocular syphilis cases reported, concurrent with the rise in systemic syphilis. However, the precise statistical increase is difficult to ascertain since ocular syphilis is believed to be underdiagnosed.[4]

Ocular Syphilis

Ocular syphilis can involve any part of the eye (Table 3) and mimic various conditions, making its recognition crucial for appropriate treatment and management.[4,10] Pathophysiology involves *T. pallidum* entering the body via the mucous membrane or abraded skin and eventually crossing the blood-ocular barrier, resulting in an immune response and subsequent inflammation.[4] The primary stage of syphilis causes a chancre which is a painless ulcer at the site of inoculation. Chancres are usually seen on the genitals, perirectal area, or mouth and rarely on the eyelid and conjunctiva. Upon testing positive for syphilis, our patient was evaluated by ID and divulged having had a painless ringworm-shaped lesion on his penis that had subsequently disappeared. This lesion was most likely an ulcer or chancre at the site of inoculation.

Syphilis more frequently affects the eyes in the secondary and tertiary stages.[3] In the secondary stage, the spirochete bacterium spreads through the bloodstream and can cause fever, rash, mucocutaneous lesions, lymphadenopathy, and ocular tissue inflammation of the anterior or posterior segment such as granulomatous or non-granulomatous anterior uveitis, interstitial keratitis, and chorioretinitis (Table 3). If secondary syphilis progresses to the tertiary stage, there is a risk of widespread damage to the cardiovascular system and other tissues, which may manifest in the form of gummas, non-tender granulomatous lesions that can also appear on the eyelids. Neurosyphilis, like ocular syphilis, may occur during any clinical stage and develops when *T. pallidum* invades the central nervous system by crossing the blood-brain barrier. Signs and symptoms of neurosyphilis include meningitis, cranial nerve neuropathies, and Argyll Robertson pupil.[10]

Table 3: *Ocular manifestations.*[3,9]

Ocular Structure	Ocular Manifestations of Syphilis
Eyelid/conjunctiva	Chancres and Gumma lesions Episcleritis
Cornea	Keratouveitis Interstitial keratitis
Anterior Segment	Gummatous Dacryoadenitis Scleritis Granulomatous iridocyclitis (most common) Koeppe and Busacca iris nodules Posterior Synechiae causing uveitic glaucoma Panuveitis
Posterior Segment	Intermediate uveitis Necrotizing and non-necrotizing retinitis Chorioretinitis Placoid chorioretinitis Retinal vasculitis Panuveitis
Optic Nerve	Neuroretinitis causing Argyll Robertson pupil Disc pallor Perineuritis Anterior or retrobulbar optic neuritis and disc edema

HIV and Syphilis Co-infection

Co-infection with HIV has emerged as a significant risk factor for the development of syphilitic ocular manifestations as both diseases have similar routes of transmission and demographic risk factors. Given that syphilis transmission can occur through sexual contact, a significant risk factor includes engaging in sexual activities with an infected individual.[3,4] Transmission rates fluctuate across studies but are generally estimated to be anywhere from 10% to 60% between an infected to non-infected individual. The common demographic characteristics of ocular syphilis patients in the U.S. are males, fifth decade of life, and African American or Caucasian ethnicity. With regard to HIV status, ocular syphilis is more common in HIV-positive men than women. Studies of ocular syphilis-infected subjects have shown that HIV-positive patients are 5-20 years younger than HIV-negative patients.[4] Our patient met these demographic characteristics, except for being older.

Interestingly, ocular syphilis may be the initial manifestation of syphilis before the HIV status is officially determined, as in our patient's case.[3,4] Syphilis patients with HIV were also twice as likely to report ocular syphilis symptoms than patients without HIV.[7] Surveillance data collected by Taylor et al. in four U.S. cities demonstrated that co-infected individuals had an increased prevalence of detectable HIV VL which is associated with an elevated risk of HIV transmission.[11] Some reports have found that HIV may compromise the immune response leading to a predisposition for posterior segment involvement and neurosyphilis compared to HIV-negative patients. Interestingly, multiple studies have shown no association between HIV status and final visual prognosis, however, since an HIV-syphilis co-infection can accelerate systemic complications for both conditions, it is imperative that patients with ocular syphilis be tested for HIV. [4]

Syphilitic Uveitis Differential Diagnoses

Uveitis has a broad range of infectious and non-infectious etiologies, and therefore it is important to distinguish syphilitic uveitis for appropriate systemic management.[3,10] Although our patient lacked a self-reported history of inflammatory ocular or systemic diseases, the unique appearance of bilateral mutton-fat KPs, indicative of chronic granulomatous anterior uveitis, suggested an undiagnosed systemic condition that required further investigation.

Non-infectious etiologies include HLA-B27 seronegative spondyloarthropathies (ankylosing spondylitis, reactive arthritis, psoriatic arthritis, inflammatory bowel disease), sarcoidosis, systemic lupus, Behcet's, Vogt-Koyanagi-Harada Disease, multiple sclerosis, and a lengthy list of less frequent non-infectious causes. The most frequent infectious etiologies other than syphilis include bacterial (*Mycobacterium tuberculosis,* Lyme disease *{Borrelia burgdorferi*), viral (Herpes simplex, Herpes Zoster, Cytomegalovirus), and parasitic (*Toxoplasma gondii*, Toxocariasis, Trematodes) backgrounds.[12,13]Therefore, appropriate laboratory testing (Tables 1, 2), and in cases of suspected neurosyphilis, CSF analysis, is indicated. In the U.S., diagnostic testing for syphilis includes non-treponemal and treponemal tests. The non-treponemal tests, primarily the rapid plasma reagin (RPR) and venereal disease research laboratory (VDRL), are generally used to screen and detect antiphospholipid antibodies. Of note, serum RPR appears to be more sensitive than serum VDRL for detecting non-treponemal antibodies, independent of the syphilis stage, and RPR appears to be more specific than VDRL. Serum RPR and VDRL titers should not be used interchangeably to manage patients as they are not equivalent tests. The toluidine red unheated serum test (TRUST) is also available, but is less commonly used. Treponemal tests detect antibodies that respond to *T. pallidum*-specific antibodies. It is not uncommon for antibodies to persist after treatment, which is reflected by the term serofast. Serofast titers tend to be more predominant in patients with HIV infection.[2,14]

In our patient's case, treatment of uveitis and the serological lab panel were deferred to the uveitis specialist. However, they could have been ordered at the initial eye exam to expedite multidisciplinary co-management with ID. Despite this, the patient received prompt inpatient treatment for syphilis as the entire medical team was within the same hospital setting, which facilitated interdisciplinary communication, and access to serologic test results and electronic medical records. In a setting in which referrals to other facilities may be indicated, delays in treatment and disjointed communication between providers could be an impediment to cohesive management.

Treatment and Management

Current guidelines recommend intravenous penicillin G as the primary treatment for syphilis, as highlighted in this case. The initiation of ART in the presence of concurrent HIV infection is also crucial.[4] Data suggest that ART can decrease the susceptibility to syphilis transmission and expedite the response to syphilis treatment through immunorestoration. [15,16] Corticosteroids and cycloplegic agents, such as prednisolone acetate 1% ophthalmic suspension and cyclopentolate 1%, are often used as adjunctive therapy to manage ocular inflammation and pain.[3,11] Our patient remained asymptomatic for ocular discomfort with no evidence of posterior synechiae. Therefore, cycloplegic agents were not used, however, they would have been considered if uveitis did not improve at subsequent visits.

Ocular syphilis and neurosyphilis treatments are identical and a CSF examination is not necessary prior to starting treatment.[8] Had our patient developed other neurologic signs or symptoms; CSF analysis would have been necessary. A CSF analysis may also be helpful in patients with syphilis who present with ocular symptoms but show no abnormal findings during an eye exam.[10] Typical CSF findings in neurosyphilis include an elevated CSF white blood cell count with increased lymphocyte pleocytosis, increased CSF protein, a positive CSF VDRL or RPR (more specific but less sensitive) or a CSF FTS-ABS or TP-PA (more sensitive but less specific).

Prognosis

The prognosis for ocular syphilis is variable and depends on factors such as the stage of the infection, a timely diagnosis, and adherence to treatment. A patient with uveitis on topical or oral steroids who does not show improvement may be noncompliant, have an untreated active infection or, as in our patient's case, both. Early detection and treatment of syphilis can result in favorable visual acuity outcomes of 20/40 or better in patients with ocular syphilis. Our patient, for instance, demonstrated a rapid improvement in ocular inflammation and visual recovery following intravenous antibiotic therapy with penicillin G.[3,4,10,13,15]

Prevention and patient education

Prompt syphilis detection and medical intervention can mitigate ocular complications, thereby facilitating visual recovery. Routine screening for syphilis in high-risk populations, such as in patients with multiple sexual partners or a history of STIs, as well as patient education on risk factors for STI transmission is imperative.[17] Patient education includes but is not limited to lifestyle modifications such as safe sexual practices, STI testing, awareness of STI signs and symptoms, and treatment as prevention.[18,19]

CONCLUSION

Even though ocular syphilis occurs in less than 5% of syphilis patients, eye care professionals may observe an increase in ocular syphilis cases especially given the resurgence of syphilis in recent years.[3] This case underscores the importance of maintaining a high level of suspicion for ocular syphilis and a potential HIV co-infection in patients presenting with granulomatous uveitis, especially in those with relevant risk factors. Timely diagnosis and appropriate treatment, along with multidisciplinary collaboration, can lead to improved outcomes and preservation of visual function. ●

DISCLOSURES

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