Ocular Syphilis: Clinical Manifestations and Treatment Course

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ABSTRACT

Introduction: We report 3 ocular syphilis cases that highlight the increasing incidence, variable presentation, diagnostic challenges, and treatment considerations of this potentially vision-threatening disease.

Case Series: A 39-year-old woman with diabetes and intravenous (IV) drug use presented with 3 weeks of decreased vision, left-eye photopsia, and rash. A 52-year-old man who has sex with men (MSM), presented with a 1-month history of upper respiratory infection-like symptoms, right-eye scotoma, redness, headache, and muffled hearing. A 24-year-old man with a history of MSM presented with right-eye scotoma and a history of transaminitis, rash, and systemic symptoms months prior.

Discussion: Syphilis rates are increasing. Each patient presented with nonspecific symptoms that, in retrospect, were early signs of infection. Vision recovery depends on the extent of ocular involvement, early recognition, and prompt initiation of appropriate therapy.

Conclusion: Ocular syphilis must be considered in at-risk groups, but systemic signs may precede vision changes. Diagnosis requires a high index of suspicion and treatment with IV penicillin is effective.

INTRODUCTION

Since 2013, syphilis rates have increased two-fold in Wisconsin[1] and nationwide.[2] Syphilis is a sexually transmitted infection (STI) caused by the spirochete Treponema pallidum, and can affect multiple organ systems, becoming a sexually transmitted disease (STD). Ocular syphilis can present at any stage of syphilis with various vision-threatening conditions, most commonly, uveitis.[3] We report 3 cases of ocular syphilis managed at the University of Wisconsin Hospital and Clinics between January 2018 and April 2019 (Table 1).

CASE PRESENTATIONS

Case 1

A 39-year-old woman with a history of poorly controlled type-1 diabetes mellitus and intravenous (IV) drug use presented to the emergency department with gradual, painless vision loss, floaters, and photopsia in the right eye for 3 to 4 weeks followed by vision loss in the left eye for 1 week. She had been seen by 2 optometrists and a primary care provider, who prescribed clindamycin for a painless ulcerative lesion on her upper lip. She reported a full-body rash 1 month prior to her presentation, which resolved without treatment. She had no prior ophthalmic history and denied other recent illnesses, trauma, or travel outside the United States. She is married with no new sexual partners, and her last use of IV drugs was 9 months prior.

The right and left eye visual acuity (VA) was 20/400 and 20/300, respectively. Her pupils were poorly reactive to light with a right afferent pupillary defect. Intraocular pressure (IOP) and ocular motility were normal. Inferior visual field defects were pronounced with mild superior peripheral deficits. Examination showed keratic precipitates with anterior chamber cell and flare in both eyes. In the right eye, a 2+ vitritis with superotemporal white placoid chorioretinal lesions and optic nerve edema was present

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Table 1. Comparison of Clinical Characteristics, Laboratory Results, and Ophthalmological Findings of 3 Cases

	Patient 1	Patient 2	Patient 3
Age of onset	39	52	24
Sex	Female	Male	Male
Presenting symptoms	Photopsia, reduced vision	Scotoma	Scotoma
Presenting visual acuity, right eye and left eye	20/400 and 20/300	20/30 and 20/20	20/20 both eyes
Timing of secondary temic syphilis symptoms	Body rash 1 month prior	URI-like symptoms, headache, muffled hearing 1 month prior	Body rash and sys-symptoms[a] 9 months prior
Serum RPR titer	1:128	1:64	1:64
CSF VDRL	Reactive	Reactive	Non-reactive
CSF WBC (0-5 per µL)	426 (89% lymphocytes)	14 (96% lymphocytes)	4 (no differential)
CSF protein (15 - 40 mg/dL)	1,145	73	25
CSF glucose (40 - 80 mg/dL)	125	63	67
Laterality	Bilateral	Right	Right
Anterior uveitis	Yes	Yes	Yes
Vitritis	Yes	No	No
Chorioretinitis	Yes	Yes	Yes
Subretinal fluid	No	No	Yes
Optic neuritis	Yes	No	No

[a]Systemic symptoms: sore throat, nonproductive cough, nausea, muscle cramps, lymphadenopathy, arthralgia, and strawberry tongue in setting of transaminitis.
Abbreviations: URI, upper respiratory infection; RPR, rapid plasma reagin; CSF, cerebrospinal fluid; VDRL, Venereal Disease Research Laboratory; WBC, white blood cell.

(Figure 1A). In the left eye, there was a 1+ vitritis with optic nerve edema and adjacent macular edema (Figure 1B).

Findings were concerning for syphilis or an endogenous endopthalmitis. A comprehensive laboratory and serology workup revealed negative blood cultures, reactive rapid plasma reagin (RPR) titer of 1:128, reactive serum fluorescent treponemal antibody absorption (FTA-ABS), and nonreactive HIV antigen-antibody testing. A lumbar puncture revealed a cerebrospinal fluid (CSF) white blood cell (WBC) count of 426 cells/mm3 with 89% lymphocytes, glucose 125 mg/dL, protein 1,145 mg/dL, and a reactive CSF Venereal Disease Research Laboratory (VDRL) test. Due to her childhood-reported penicillin allergy, without features of an IgE-mediated or type-4 delayed-type hypersensitivity, she did not undergo skin testing but started a supervised penicillin graded challenge, which was well tolerated. After 2 weeks of IV aqueous crystalline penicillin G 24 million units per day, the patient's right and left eye vision improved to 20/60 and 20/200, respectively. At last follow-up, 2.5-months after presentation, chorioretinal lesions and optic nerve edema improved, but some vitritis remained without further improvement of VA (Figure 1C-D).

Case 2

A 52-year-old man with a history of multiple male sexual partners presented with a 3-day history of a "black spot" in his superonasal right visual field. He also noted a red-eye, 1-month history of upper respiratory tract symptoms, and headache with muffled hearing that developed prior to the new scotoma. The patient denied history of genital ulcers. He was seen initially by his primary care provider, who referred him to ophthalmology.

The right and left eye VA at presentation was 20/30 and 20/20, respectively. Intraocular pressure was normal. A superonasal visual field defect was noted by confrontation in the right eye. Slit lamp examination showed trace anterior chamber cell in the right eye, but was otherwise unremarkable. Retinal exam demonstrated a placoid chorioretinal lesion in the inferotemporal macula (Figure 1E and Figure 2A-D,F-G). The left eye had a normal examination.

A uveitis workup revealed a reactive RPR titer of 1:64, reactive serum FTA-ABS, and nonreactive HIV antigen-antibody testing. Lumbar puncture revealed a CSF WBC of 14 cells/mm3 with 96% lymphocytes, glucose 63 mg/dL, protein 73 mg/dL, and a reactive CSF VDRL. Following treatment with 2 weeks of IV aqueous crystalline penicillin G 24 million units per day, VA improved to 20/25 at the 6-month follow-up and the chorioretinal lesion resolved (Figure 1F and Figure 2E).

Case 3

A 24-year-old man with an ocular history of a right eye retinal hole, treated with cryopexy 3 months prior, was referred to the uveitis service for evaluation of a new right retinal lesion and posterior uveitis. The patient presented with a sudden "black spot" in the periphery of his right visual field 1 week prior. He was seen 9 months prior by his primary care provider with sore throat, nonproductive cough, muscle cramps, cervical lymphadenopathy, arthralgia, strawberry tongue, and transaminitis. He followed up 1 month later with a diffuse maculopapular rash of his trunk, penis, palms, and soles, which was subsequently evaluated by dermatology but had resolved on its own, so no biopsy or additional labs were performed. He denied any genital ulcerations.

At presentation, VA was 20/20 in both eyes. He had a normal pupillary response and intraocular pressure. Despite the black spot, visual fields by confrontation were full in both eyes. Slit lamp examination demonstrated 1-2+ anterior chamber cell and minimal vitreous cell in the right eye. The right temporal retina contained 2 chorioretinal lesions with surrounding subretinal fluid and overlying vitreous clumping (Figure 1G). The left eye was normal.

Laboratory workup for his uveitis revealed a reactive RPR titer of 1:64, reactive serum FTA-ABS, and nonreactive HIV antigen-antibody testing. Lumbar puncture revealed a CSF WBC count

of 4 cells/mm^3 without differential due to low cell count, glucose 67 mg/dL, protein 25 mg/dL, and a nonreactive CSF VDRL. The patient was treated with IV aqueous crystalline penicillin G 24 million units per day for 2 weeks and azithromycin for Chlamydia trachomatis urogenital co-infection. At time of admission, he described having multiple male sexual partners. One month after treatment, the patient's VA remained 20/20 in both eyes and the chorioretinal lesion resolved (Figure 1 H).

DISCUSSION

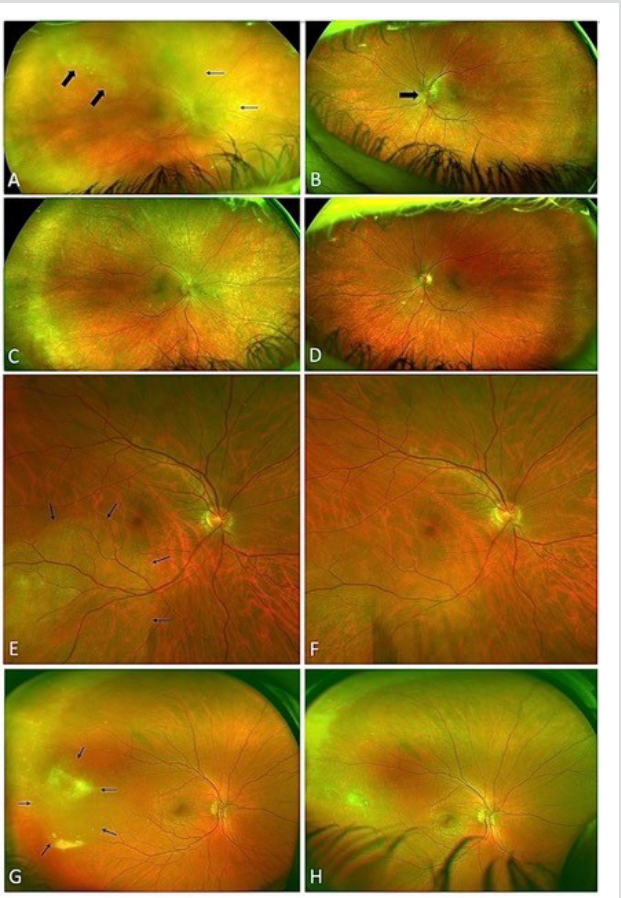
According to the Centers for Disease Control and Prevention (CDC), the number of newly diagnosed syphilis cases in the United States increased 79.9% from 2013 to 2017.[2] Primary and secondary syphilis increased 76.4%. In Wisconsin, a total of 510 syphilis cases were reported in 2018, a 100% increase from 2013.[1] The largest percentage of cases were from Southeastern Wisconsin (53% in 2018).[1]

A review of newly diagnosed syphilis cases from 8 other states in 2014 and 2015 revealed that 0.17% to 3.9% were ocular syphilis.[4] In the largest prospective series to date, the British Ocular Syphilis Study (BOSS) described that ocular syphilis was most common among men, with a mean age at presentation of 48.7 years.[5] Approximately 51% were MSM, and 31% were HIV positive. Our cases fit the profile of the BOSS patients as well, suggesting that younger patients should have a detailed history taken when presenting with vision changes.

Syphilis is divided into multiple stages according to clinical manifestations.[6] Primary syphilis presents approximately 3 weeks (range 10 to 90 days) after exposure with 1 or more cutaneous chancres that resolve spontaneously within days to weeks. Secondary syphilis usually presents from 3 weeks to 3 months after infection with a nonspecific constitutional syndrome of fever, chills, and malaise. It is often mistaken for a "viral" syndrome. Rash is usually macular, nonpruritic, and often covers the entire body, including palms and soles. Other manifestations can include lymphadenopathy, mucosal lesions, patchy alopecia, hepatitis, and bone and renal involvement. Latent syphilis is categorized by positive serology in the absence of clinical manifestations. In some, tertiary syphilis may occur years later with gummas involving multiple organ systems, cardiovascular syphilis, or neurologic manifestations such as tabes dorsalis and general paresis. This is now a very uncommon presentation in the United States. Neurosyphilis and ocular syphilis can present at any stage of syphilis, with early clinical manifestations occurring within months or years after infection. In each of our cases, the patients presented with initial findings of secondary syphilis and had been seen by other care providers. These cases highlight the importance of obtaining a thorough history and having a high index of suspicion for syphilis in patients with risk factors for infection.

Ocular manifestations of syphilis are highly variable and can present at any stage of syphilis.[3] In the BOSS series, mean duration of symptoms prior to presentation was 1 month, and mean VA at presentation was 20/63.[5] The series reported that most patients had bilateral involvement and posterior segment uveitis. Two of our cases had good acuity and all patients had varying presentations of posterior uveitis (Table 1). Case 2 was a typical presentation of acute syphilitic posterior placoid chorioretinitis, which often has mild symptoms and can have full recovery with early treatment. In addition, anterior segment involvement also varies, with some patients demonstrating nonspecific granulomatous anterior uveitis or iris nodules. Often presenting symptoms can be vague, such as reduced vision, eye pain, redness, floaters, photophobia, photopsia, or scotoma.[7] Patients are often diagnosed

Figure 1. Fundus Photos for Each of 3 Cases

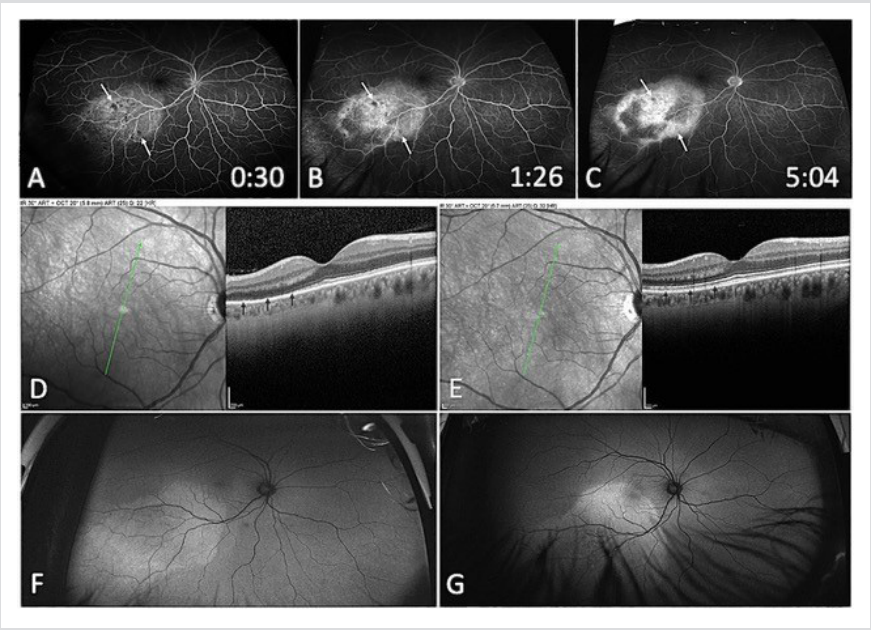


Case 1, A-D: A. Right eye at initial presentation showed multiple yellow-white fluffy vitreous floaters superotemporally (thick arrows), several yellow placoid retinal lesions with overlying vitritis (thin arrows), and mild papillitis. B. Left eye at presentation with severe optic nerve edema with flame hemorrhages (thick arrow), and macular edema. Eight weeks post IV penicillin shows some resolution of vitritis and chorioretinal lesions in right eye (C), as well as resolved optic nerve edema and mild nasal radiating macular exudates in left eye (D).

Case 2, E-F: E. Wedge of retinal whitening around the narrowed inferotemporal arteriole in the right eye at the time of presentation (thin arrows). F**.** Resolution of retinal lesion 4 weeks post treatment.

Case 3, G-H: G. Right temporal retina with raised whitened chorioretinal lesions with overlying vitreous clumping with subretinal fluid (thin arrows). H. The subretinal fluid resolved and there was improvement of the chorioretinal lesions and vitritis after 2 weeks of treatment.

Figure 2. Case 2 Syphilitic Retinal Placoid in the Right Eye



A-C. Fluorescein angiography showed progressive hyperfluorescence of placoid lesion with scattered hypofluorescent spots (white arrows) in the area corresponding to the yellow opacifications seen in Figure 1E.
D. Retinal OCT at day 5 showed outer retinal thinning inferotemporal to the macula (black arrows).
E. OCT at 6 months post treatment with improved inferotemporal outer retina (black arrows).
F. Fundus autofluorescence showed inferotemporal hyperautofluorescence corresponding to the area of the placoid lesion at time of presentation.
G. Progression of lesion toward fovea was seen on fundus autofluorescence at day 5.
Abbreviations: OCT, optical coherence tomography.

because of inflammatory changes on exam and a uveitis workup with laboratory evaluation.

Serology remains the cornerstone of syphilis diagnosis, utilizing a combination of nontreponemal (eg, RPR or VDRL) and treponemal (eg, FTA-ABS, TP-PA, enzyme immunoassay) tests. Two different laboratory approaches can be used, known as the traditional and reverse screening algorithms.[3] The traditional algorithm starts with a screening nontreponemal test followed by a confirmatory treponemal test for reactive samples. The reverse algorithm starts with screening treponemal test followed by a nontreponemal test for reactive tests, and is being utilized by an increasing number of clinical laboratories.[8] A lumbar puncture should be performed in all cases of ocular syphilis, regardless of the severity of ocular disease or stage of presentation.[9] If baseline CSF abnormalities are present, this provides another means of posttreatment follow-up. However, CSF testing can be normal in ocular syphilis and does not rule out ocular disease.[3] All patients diagnosed with ocular syphilis should undergo testing for HIV and other STIs due to high risk of co-infection.

Penicillin G is the gold standard treatment for syphilis, and IV aqueous crystalline penicillin G 18 million to 24 million units per day administered as 3 million to 4 million units every 4 hours or as a continuous infusion for 10 to 14 days is the recommended regimen for ocular syphilis and neurosyphilis.[3] All 3 cases were treated with IV penicillin G. Penicillin allergy warrants evaluation, including potential skin testing and desensitization if there is a history of immediate-type or delayed-type hypersensitivity reaction. In Case 1, the patient was able to be treated with close monitoring and no formal testing. In the BOSS, mean VA improved from 20/63 to 20/40 following antibiotic treatment in over 90% of patients.[5] The addition of corticosteroids may have a role, especially in reducing vitritis; however, steroids should not be started until adequate antibiotic therapy has been initiated.[10] The most common complications of ocular syphilis include cataract, glaucoma, epiretinal membrane, optic nerve atrophy, and retinal detachment. Early identification and treatment are imperative to prevent permanent vision loss.[11] In addition, timely diagnosis significantly lessens the financial burden placed on patients and the health care system as a whole (ie, outpatient clinic visit vs 10- to 14-day hospital admission).

Our cases highlight the importance and difficulties in diagnosing syphilis. The diagnosis requires high suspicion, a careful history, and close follow-up, often with multispecialty care. Follow-up includes ophthalmologic exams, evaluation of systemic syphilis features, posttreatment serology, and reassessment of CSF abnormalities. Nontreponemal antibody titers are used to follow treatment response, with a four-fold change demonstrating significance. The treponemal tests generally remain reactive for life. Syphilis is a reportable communicable disease and all cases should be reported to the local public health department within 72 hours upon recognition of a case.[12] Mandatory reporting is imperative for partner notification as well as disease prevention and control programs.

CONCLUSION

Syphilis rates are on the rise pointing to the need for increased awareness in outpatient clinics, urgent care, and emergency departments. All 3 of our cases presented with vision changes, but in retrospect had other classic syphilis manifestations that predated the ocular complaints and were diagnostically challenging due to the mild symptoms. Ocular syphilis must be considered with groups at risk for syphilis with reduced vision. Diagnosis requires a low threshold for serologic testing. Early recognition and IV penicillin treatment can prevent permanent vision loss.

Financial Disclosures: None declared.

Funding/Support: Funding for this research was provided by NIH Core Grant P30 EY016665 and an Unrestricted Grant from Research to Prevent Blindness, Inc. to the University of Wisconsin Department of Ophthalmology and Visual Sciences.

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