1040-5488/16/9306-0647/0 VOL. 93, NO. 6, PP. 647–651
OPTOMETRY AND VISION SCIENCE

CLINICAL CASE

Nongranulomatous Uveitis as the First Manifestation of Syphilis

Grace L. Tsan*, Pathik Amin†, and Michael Sullivan-Mee*

ABSTRACT

Purpose. The incidence of syphilis appears to be increasing in recent years. Although any structure of the eye can be involved in syphilis, isolated unilateral anterior uveitis as an initial sign of the disease is rare. We report a case of ocular syphilis presenting as a mild unilateral, nongranulomatous, anterior uveitis in an otherwise asymptomatic patient.

Case Report. A 64-year-old white male patient presented with a 3-day history of mildly reduced vision, photophobia, and pain in his left eye. The patient denied prior occurrences, and no contributing ocular or medical history was elicited. Entering corrected distance acuities were 20/25+ in the right eye and 20/20- in the left eye. Slit lamp examination of the left eye revealed a moderate circumlimbal flush, numerous fine keratic precipitates, and mild-to-moderate white blood cells in the anterior chamber. The patient was diagnosed as having acute, idiopathic, nongranulomatous, anterior uveitis, and topical steroid/cycloplegic treatment was initiated. Despite an initially positive, although somewhat sluggish response to treatment, the patient's uveitis suddenly worsened on day 44, exhibiting increased anterior chamber cells, several mutton-fat keratic precipitates, and elevated intraocular pressure. Systemic diagnostic workup led to the diagnosis of neurosyphilis, and the patient subsequently admitted to high-risk sexual behaviors. Treatment with intravenous aqueous penicillin-G 24 million units per day for 14 days led to complete resolution of uveitis. The case was reported to the local health department within 24 h of syphilis diagnosis.

Conclusions. Syphilis, although an uncommon cause of ocular inflammation, is a highly contagious, but curable disease. Given its potentially devastating neurologic consequences, syphilis should be considered in all patients presenting with uveitis. A high index of clinical suspicion and a detailed sexual history are crucial for the accurate and timely diagnosis of ocular syphilis.

(Optom Vis Sci 2016;93:647–651)

Key Words: syphilis, anterior uveitis, nongranulomatous uveitis, granulomatous uveitis, neurosyphilis, inflammatory ocular hypertension syndrome

Syphilis is a sexually transmitted disease caused by the spirochete *Treponema pallidum*, which may affect any organ system of the body, including the eyes.[1,2] The diagnosis of syphilis is based on medical history, clinical findings, and serologic testing. It can be classified into primary, secondary, latent, and tertiary (including neurosyphilis) stages based on the progression of the disease.[3] Ocular syphilis is relatively uncommon, typically presenting in the latent and tertiary phases of the disease. The most common ophthalmic presentations of syphilis are posterior uveitis and panuveitis, but it can also present as anterior uveitis, intermediate uveitis, interstitial keratitis, chorioretinitis, retinal vasculitis, retinitis, perineuritis, papillitis, retrobulbar neuritis, optic atrophy, optic nerve gumma, and various stroke syndromes.[4,5] We report a case of neurosyphilis that presented with unilateral nongranulomatous anterior uveitis that initially improved and then worsened on standard topical uveitis treatment. This case emphasizes the importance of careful history taking, the value of closely monitoring case evolution, and a high index of clinical suspicion for the diagnosis of syphilis.

CASE REPORT

A 64-year-old white male veteran was referred to the Albuquerque VA Medical Center Optometry Clinic by the emergency department with a chief complaint of mildly reduced vision, photophobia, and pain in his left eye for the past 3 days. His medical history included type 2 diabetes mellitus (HbA1c, 6.3%; reference range, 4.0 to 5.6%) controlled by diet and exercise and atrial fibrillation on aspirin 325-mg tablet daily. In addition, the patient reported taking a daily over-the-counter multivitamin and

*OD, FAAO
†OD
New Mexico VA Health Care System, Albuquerque, New Mexico.

prior drug allergies to prochlorperazine and codeine. The patient denied prior episodes of uveitis, joint or back pain, dysuria, dyspnea, rash, gastrointestinal distress, or other recent changes to his general health. Corrected distance visual acuities measured 20/25+ in the right eye and 20/20- in the left eye. Pupils, ocular motility, binocular alignment, and confrontation visual field tests were normal. Although anterior segment examination was unremarkable in the right eye, several abnormal findings were present in the left eye, including moderate circumlimbal injection of the bulbar conjunctiva; scattered, fine, white keratic precipitates (KPs) on the inferior cornea; and mild-to-moderate white blood cells (2+) with mild (1+) flare in the anterior chamber. The irides were flat without neovascularization, mass lesions, nodules, or transillumination, and the anterior chamber angles appeared open. Intraocular pressure (IOP) measured 16 mm Hg in the right eye and 10 mm Hg in the left eye using Goldmann applanation tonometry. Dilated posterior segment examination was unremarkable in each eye, including normal optic nerve appearances (no signs of disc edema, hemorrhage, or pallor with cup/disc ratios of 0.2 round in each eye), and no vitritis, chorioretinitis, phlebitis, scarring, or vitreous/retinal hemorrhage.

The patient was diagnosed as having acute, mild-to-moderate nongranulomatous, idiopathic anterior uveitis in the left eye. Because this was the patient's first reported episode of uveitis and there were no other findings pointing to a specific underlying etiology, systemic diagnostic workup was deferred. Treatment was initiated in the left eye with hourly dosing of topical steroid (prednisolone acetate 1.0%) and daily dosing of topical cycloplegic (atropine sulfate 1.0%). During follow-up evaluations for the next 5 weeks, the anterior chamber reaction steadily improved to trace cell only and the topical steroid was slowly tapered. All other clinical factors remained stable.

The next follow-up, 6 weeks from the initial presentation, was expected to be his last visit. The patient reported he was asymptomatic, vision was stable, and he had completed his topical steroid taper as directed. Best corrected distance acuity measured 20/20 in each eye, and pupils were normal. On slit lamp examination of the left eye, however, we observed new mild diffuse bulbar injection, moderate (2+) anterior chamber cell and flare, moderate KPs including several "mutton-fat"–type KPs, and elevated IOP (20 mm Hg in the right eye and 32 mm Hg in the left eye). Dilated posterior segment examination remained unremarkable without signs of intermediate or posterior uveitis. Considering these findings, the diagnosis was changed to acute, moderate, granulomatous, anterior uveitis of the left eye, and a systemic workup was initiated.

We ordered the following tests: complete blood count (CBC) with differential, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), T-SPOT assay, *Treponema pallidum* particle agglutination (TPPA) assay, rapid plasma reagin (RPR) test, angiotensin-converting enzyme (ACE), and chest X-ray. The patient was instructed to restart his topical steroid and cycloplegic medications. Initiation of ocular hypotensive medication was deferred to determine whether the elevated IOP would respond to anti-inflammatory treatment alone.

Three days later, the patient reported mildly blurry vision in the left eye but no eye pain or photophobia. In addition, he reported good compliance with topical steroid and cycloplegic medications. Corrected distance acuity was stable at 20/20 in each eye while slit lamp examination revealed improved bulbar injection, diminished KPs, reduced anterior chamber cell, and no flare. Intraocular pressure measured 19 mm Hg in the right eye and 22 mm Hg in the left eye. Dilated posterior segment examination of the left eye was again stable without signs of intermediate or posterior uveitis. Topical steroid and cycloplegic treatments were continued.

Systemic workup results subsequently became available (Table 1). The patient's chest X-ray revealed no acute pathology. Laboratory testing results included normal CBC, ACE, and T-SPOT; slightly elevated systemic inflammatory markers (ESR = 41, reference ≤21; CRP = 12.3, reference ≤10); positive TPPA assay (reference = negative); and elevated RPR titer (1:128, reference = negative). As these findings were consistent with a diagnosis of syphilis, we informed the patient about the need for further diagnostic workup to rule out neurosyphilis and for additional treatment decisions. A supplementary more detailed sexual history was also taken at which time the patient reported that he had oral sex with multiple partners during the past 2 years, including an ex-girlfriend who was a known intravenous (IV) drug abuser. We then consulted the patient's primary care physician, Infectious Disease service, and Neurology service, and plans were made to admit the patient to the hospital for further workup and treatment. In addition, the case was reported to the New Mexico State Department of Health. We advised the patient to continue his topical steroid and cycloplegic medications.

TABLE 1.
Initial laboratory and imaging results

Variable	Patient's results	Reference range
Blood		
Red blood cells, million/mm^3	4.63	4.64–6.00
Hemoglobin, g/dl	14.3	14.5–17.7
Hematocrit, %	42.2	42.0–53.0
White blood cells, 1000/mm^3	7.7	4.0–10.6
Platelets, 1000/mm^3	362	150–400
ESR, mm/h	41	≤20
Serum		
CRP, mg/l	12.6	≤10.0
ACE, U/l	26	9–67
TPPA assay	Positive	Negative
RPR	Reactive at 1:128	Nonreactive
HIV antibody	Negative	Negative
Hepatitis C virus antibody	Negative	Negative
Gonorrhea DNA, SDA	Negative	Negative
Chlamydia DNA	Negative	Negative
Chest X-ray	Normal	
CSF		
Appearance	Clear	
Red cell (N/ml)	3	0
Total nucleated cell (N/ml)	75	<5
Neutrophil, %	3	0–6
Lymphocyte, %	91	40–80
Monocyte, %	6	15–45
Protein, mg/dl	61	12–60
VDRL test	Reactive at 1:8	Nonreactive
Bacterial culture	No growth	No growth

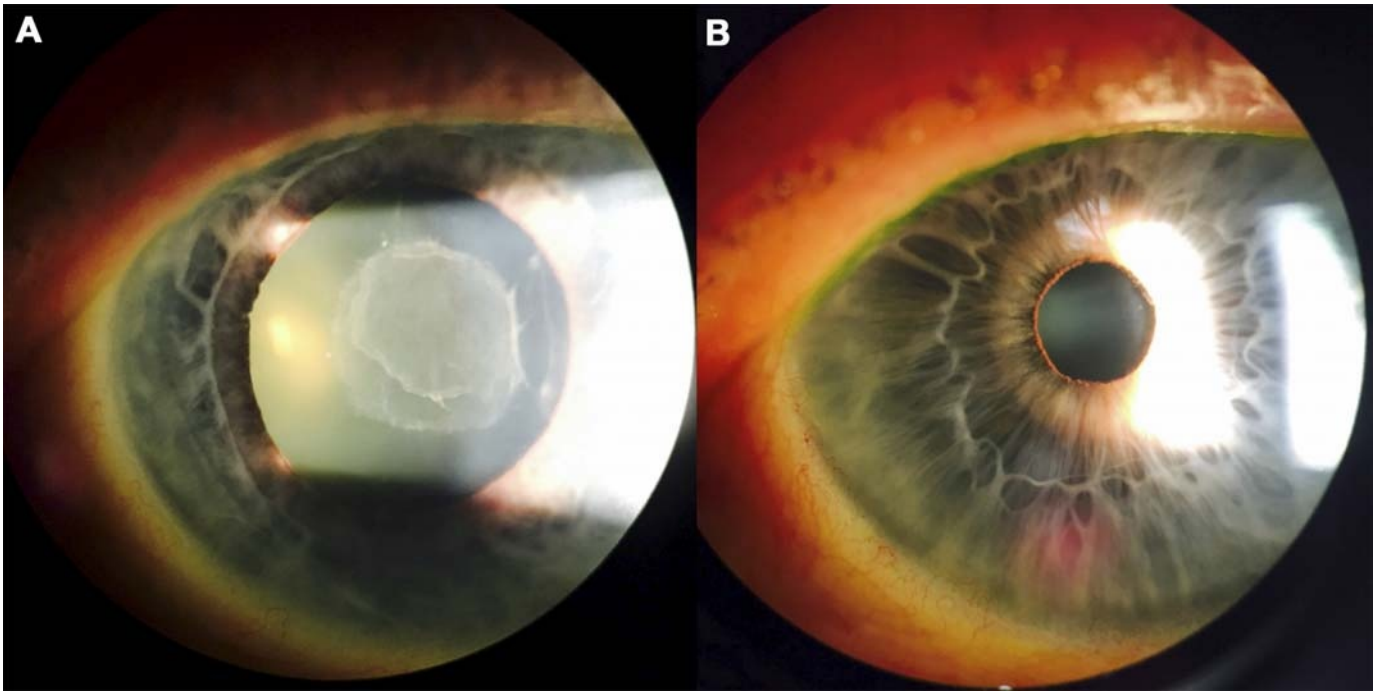

FIGURE 1.
Anterior segment photography in syphilitic uveitis. (A) Initial presentation of fibrin plaque in the left eye. (B) Resolution of fibrin plaque 8 days later.

Because of a hospital bed shortage, the patient could not be immediately admitted to the hospital and the patient unexpectedly returned to our clinic 4 days later. At this visit, he reported new onset of night sweats the preceding night, along with increasing blurry vision in the left eye. Corrected distance acuity measured 20/20 in the right eye and 20/25 in the left eye. Slit lamp examination revealed new anterior chamber cells in the right eye and marked worsening of anterior chamber inflammation in the left eye, along with a new dense fibrin plaque on the anterior lens surface (Fig. 1A). Intraocular pressure measured 22 mm Hg in the right eye and 17 mm Hg in the left eye, and dilated posterior segment examination was stable without signs of intermediate or posterior uveitis. Infectious Disease was notified immediately, and the patient was admitted to the hospital that day. We added topical steroid treatment to the right eye and increased steroid dosing to hourly in the left eye.

On admission, a lumbar puncture was performed to obtain cerebrospinal fluid (CSF) for syphilis testing. A diagnosis of neurosyphilis was made when the patient's CSF sample tested positive for venereal disease research laboratory (VDRL) (1:8, reference = negative). Testing for other sexually transmitted diseases was negative, including human immunodeficiency virus (HIV), hepatitis C virus, gonorrhea, and chlamydial infections. After treatment with 24 million units of IV aqueous penicillin-G per day via continuous infusion for 14 days, along with topical steroid and cycloplegic medications, the patient's bilateral syphilitic uveitis and fibrin plaque on the left crystalline lens gradually resolved without complication or adverse sequela.

Given the patient's good overall response to the IV penicillin-G treatment, the patient was scheduled for a 6-month follow-up in the Infectious Disease clinic to check for normalization of RPR and CSF VDRL titers. Repeat RPR titer reduced from 1:128 to 1:32, which was more than the anticipated fourfold decrease at 6 months after treatment. Similarly, lumbar puncture revealed that the CSF VDRL titer had reduced from 1:8 to 1:2 (Table 2). Therefore, no additional treatment was indicated and would only be considered in the future with worsening CSF pleocytosis on any lumbar puncture, increase in CSF VDRL titer by fourfold, or failure of CSF abnormalities to resolve at 2 years. The Infectious Disease clinic planned to follow up with the patient in another 6 months, with expected normalization by 2 years.

DISCUSSION

Syphilis is relatively uncommon in the United States. However, its incidence appears to have increased in recent years. In 2014, there were 5.3 reported cases of primary and secondary syphilis per 100,000 people as compared with 2.1 cases per 100,000 people in

TABLE 2.
Laboratory results 6 months after IV penicillin-G treatment

Variable	Patient's results	Reference range
Serum		
TPPA assay	Positive	Negative
RPR	Reactive at 1:32	Nonreactive
CSF		
Appearance	Clear	
Red cell (N/ml)	5	0
Total nucleated cell (N/ml)	3	<5
Neutrophil, %	0	0–6
Lymphocyte, %	84	40–80
Monocyte, %	16	15–45
Protein, mg/dl	51	12–60
VDRL test	Reactive at 1:2	Nonreactive
Bacterial culture	No growth	No growth

2000.[6] Ocular syphilis is even more rare. Between December 2014 and April 2015, the Centers for Disease Control and Prevention reported 24 cases of ocular syphilis from the states of California and Washington, with the majority of cases involving HIV-infected men who had sex with other men.[5] Because neurosyphilis can develop if the infection is untreated, potentially leading to severe neurologic compromise, it is important for optometrists and ophthalmologists to be aware of ocular syphilis and screen for signs and symptoms of syphilis in high-risk patient populations.[4,5,7]

Ocular syphilis can be classified into primary, secondary, latent, and tertiary stages. Primary ocular syphilis signs include chancre of the eyelid or conjunctiva.

Secondary ocular syphilis is usually associated with anterior uveitis or chorioretinitis, whereas latent syphilis has no clinical manifestations. Tertiary syphilis can present with some or all of the following: anterior uveitis, intermediate uveitis, interstitial keratitis, chorioretinitis, retinal vasculitis, retinitis, perineuritis, papillitis, retrobulbar neuritis, optic atrophy, optic nerve gumma, and various stroke syndromes. In addition, optic nerve atrophy and Argyll-Robertson pupils have been linked to tertiary syphilis. Considering that syphilis can involve any structure of the eye and is known as ''the great imitator,'' diagnosis and management of syphilis can be challenging.[3]

Studies have shown that the most common ophthalmic presentations of syphilis are posterior uveitis and/or panuveitis.[4,5,7] Conversely, only a very small number of cases have been reported to present with isolated anterior uveitis as the initial sign of syphilis as described in this report. Despite this rarity, however, it is important to consider syphilis in differential diagnosis of isolated anterior uveitis given that syphilis is highly contagious and treatable and is associated with significant morbidity if left untreated.

The patient described in this report presented with a single episode of acute, unilateral, nongranulomatous, anterior uveitis and was otherwise asymptomatic. Table 3 summarizes the differential diagnosis considered for acute anterior uveitis.[3] Given that this was the first documented occurrence and its mild presentation, the condition was treated as an idiopathic case without systemic workup. The patient initially responded well to topical steroids. However, after the topical steroid taper, the uveitis rebounded and began to manifest new mutton-fat KPs and elevated IOP. Although it is relatively well known that mutton-fat KPs are frequently associated with an underlying systemic disease process,[8] it is less recognized that increased IOP has also been associated with syphilitic anterior uveitis.[9] Syphilis, along with other infectious or inflammatory entities such as herpes, toxoplasmosis, and sarcoidosis, all tend to produce an elevated IOP, a condition often referred to as *inflammatory ocular hypertension syndrome*. In a study by Reddy et al., 18% of syphilitic uveitis patients presented with inflammatory ocular hypertension syndrome.[9] The increased IOP is directly related to the anterior chamber inflammation, thus, treating the underlying uveitis should normalize it.[10] Ultimately, the evolution of our case with rebound inflammation, mutton-fat KPs, and elevated IOP prompted a systemic diagnostic workup that led to the diagnosis of syphilis. This sequence of events supports the importance of regular monitoring of patients with uveitis, even in seemingly mild cases.

TABLE 3.
Differential diagnoses of anterior uveitis

Nongranulomatous	Granulomatous
HLA B-27–associated diseases	Syphilis
Fuchs' heterochromic iridocyclitis	Tuberculosis
Glaucomatocyclitic crisis	Sarcoidosis
Juvenile rheumatoid arthritis	Herpes simplex
Masquerade syndrome	Vogt Koyanagi Harada syndrome
Behcet disease	Lyme disease
Uveitis-glaucoma-hyphema syndrome	Phacoanaphylactic
Trauma, drug induced, etc.	Leptospirosis
Pars planitis	Pars planitis Idiopathic

After results of the serologic testing were known, a detailed sexual history revealed that the patient participated in high-risk sexual practices, that is, oral sex, with multiple female partners including a known IV drug abuser. However, the patient reported no personal history of IV drug abuse. In addition, the Centers for Disease Control and Prevention has reported the largest increases in syphilis in ''men who have sex with men (MSM),''[6] but the patient denied MSM. If this information had been known at presentation, it would have spurred a diagnostic workup much earlier, which might have shortened the time to diagnosis by 4 to 6 weeks in this case. However, because this patient had a good outcome, it is unlikely that an earlier diagnosis would have significantly impacted the anatomic and visual results in this patient.

This case is a good reminder regarding the importance of taking a thorough social and sexual history. Early diagnosis of syphilis is very important to limit potential damage to the central nervous system (neurosyphilis) and with regard to preventing further public spread of the disease since syphilis is highly contagious. Therefore, educating the patient and his/her partners about the communicable nature of the disease and its modes of transmission is a vital public health goal.

In summary, a high index of clinical suspicion and a detailed sexual history are crucial for the accurate and timely diagnosis of ocular syphilis. In addition, our case demonstrates that the evolution of uveitis over time can offer clues to systemic disease contributions to the condition. In this patient, the uveitis evolved from mild unilateral uveitis with fine KPs to moderate unilateral uveitis with mutton-fat KPs and elevated IOP and then to bilateral uveitis with severe inflammatory reaction in one eye, despite concurrent topical steroid treatment. Given that syphilis is a highly contagious, but curable, disease, it should be considered as a possible etiologic cause in all patients presenting with uveitis.

Received July 19, 2015; accepted November 19, 2015.

REFERENCES

1. Ghanem KG, Workowski KA. Management of adult syphilis. Clin Infect Dis 2011;53(Suppl. 3):S110–28.
2. Lukehart SA. Syphilis. In: Kasper DL, Fauci AS, eds. Harrison's Infectious Diseases, 2nd ed. New York: McGraw Hill; 2013;694–704.
3. Garg SJ (Ed). Uveitis: Color Atlas and Synopsis of Clinical Ophthalmology: Wills Eye Institute. Philadelphia: Lippincott Williams & Wilkins; 2012.
4. Moradi A, Salek S, Daniel E, Gangaputra S, Ostheimer TA, Burkholder BM, Leung TG, Butler NJ, Dunn JP, Thorne JE.

Clinical features and incidence rates of ocular complications in patients with ocular syphilis. Am J Ophthalmol 2015;159:334–43.
5. Clinical Advisory: Ocular Syphilis in the United States. Atlanta, GA: Centers for Disease Control and Prevention; 2015. Available at: http://www.cdc.gov/std/syphilis/clinicaladvisoryos2015.htm. Accessed May 21, 2015.
6. Primary and Secondary Syphilis—United States, 2005–2013. Atlanta, GA: Centers for Disease Control and Prevention; 2014. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6318a4.htm. Accessed May 21, 2015.
7. Marra CM. Neurosyphilis. In: Gonzalez-Scarano F, Bartlett JG, eds. UpToDate. Waltham, MA: UpToDate; 2014 Accessed May 21, 2015.
8. Maguire JI, Murchison AP, Jaeger EA. Wills Eye Institute: 5-Minute Ophthalmology Consult. Philadelphia: Lippincott Williams & Wilkins; 2012.
9. Reddy S, Cubillan LD, Hovakimyan A, Cunningham ET, Jr. Inflammatory ocular hypertension syndrome (IOHS) in patients with syphilitic uveitis. Br J Ophthalmol 2007;91:1610–2.
10. Kok H, Barton K. Uveitic glaucoma. Ophthalmol Clin North Am 2002;15:375–87.

Grace L. Tsan
Kaiser Permanente
Rockwood Medical Office
19500 SE Stark Street
Portland, OR 97233
e-mail: gtsan.od@gmail.com