

# Syphilis: Reemergence of an Old Adversary

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**Objective:** To describe the clinical findings in 4 patients with ocular syphilis and to provide a review of the recent rise in syphilis cases in the United States, along with a brief description of current diagnosis and treatment guidelines.

**Design:** Retrospective, observational case series.

**Participants:** Four consecutive patients who presented to our facility during a 6-month interval in 2005 with ocular syphilis.

**Methods:** Review of clinical, laboratory, photographic, and angiographic records of patients with neurosyphilis who underwent intravenous penicillin G treatment.

**Main Outcome Measures:** Resolution of signs and symptoms of ocular syphilis, including changes in visual acuity.

**Results:** Four patients (3 male: mean age, 46 [range, 39–60 years]; 1 female: age 46 years) demonstrated cerebrospinal fluid findings consistent with neurosyphilis, as evidenced by increased leukocyte counts ( $>5$  white blood cells/mm<sup>3</sup>), and positive Venereal Disease Research Laboratory or serum fluorescent treponemal antibody absorbed tests. All 4 patients presented with a variety of clinical findings that led to a delay in diagnosis and treatment. Two patients presented with discrete placoid lesions consistent with acute syphilitic posterior placoid chorioretinitis, a manifestation typically observed among the immunocompromised.

**Conclusions:** Despite a decade of steady decline, syphilis has reemerged in the United States with outbreaks throughout the country in the past few years. Ocular findings, including posterior placoid chorioretinitis, are important diagnostic features in the early treatment of tertiary syphilis and neurosyphilis. Ophthalmologists have the opportunity to play a key role in the early diagnosis and management of this potentially fatal disease. *Ophthalmology* 2006;113:2074–2079 © 2006 by the American Academy of Ophthalmology.

After a decade of steady decline, the annual rate of primary and secondary syphilis in the United States reached its lowest recorded level in 2000.<sup>1</sup> The National Plan to Eliminate Syphilis from the United States announced by the Surgeon General in 1999 aimed to reduce the annual number of syphilis cases to  $<1000$  by 2005. However, the number of syphilis cases steadily increased between 2000 and 2004, from 5979 to 7980, an increase of 33.5%.<sup>1</sup> Syphilis outbreaks were reported in multiple regions of the United States, including Southern California, where 2799 cases of syphilis were reported between 2001 and 2004.<sup>2,3</sup>

Ocular syphilis is an uncommon but diagnostically important manifestation of the disease. The most common ocular finding of syphilis is uveitis, occurring in 2.5% to 5% of patients with tertiary syphilis.<sup>4</sup> However, a multitude of presenting signs have been described among both human immunodeficiency virus (HIV)-positive and HIV-negative patients, including focal retinitis, papillitis, iritis, keratic

precipitates, periphlebitis, vitritis, and serous and exudative retinal detachments.<sup>5–7</sup>

During a 6-month period in 2005, 4 patients with atypical and widely disparate presenting signs and symptoms were examined at our facility and diagnosed with ocular syphilis. We report the clinical findings and management of these cases, demonstrating the importance of a high index of suspicion and early diagnosis and appropriate treatment of ocular syphilis in light of its reemergence in the United States.

## Case Reports

### Case 1

A 46-year-old heterosexual female presented with a 1-week history of decreased vision in her left eye. On examination, her visual acuity was 20/25 in the right eye and 5/200 in the left eye. A 1+ relative afferent pupillary defect of her left eye was observed. Slit-lamp examination was unremarkable with no anterior chamber or vitreous inflammation. On dilated examination, both optic discs were slightly hyperemic with mild pigmentary mottling in the macula of the left eye (Fig 1A, B). Humphrey perimetry (24-2 Swedish Interactive Threshold Algorithm Standard) testing revealed mildly enlarged blind spots and small paracentral scotomas in both eyes. Intravenous fluorescein angiography revealed patchy choroidal filling, focal areas of hypofluorescence in the left macula, and late staining at the level of the retinal pigment epithelium (Fig 1D, E). Late frames demonstrated staining of the optic nerve

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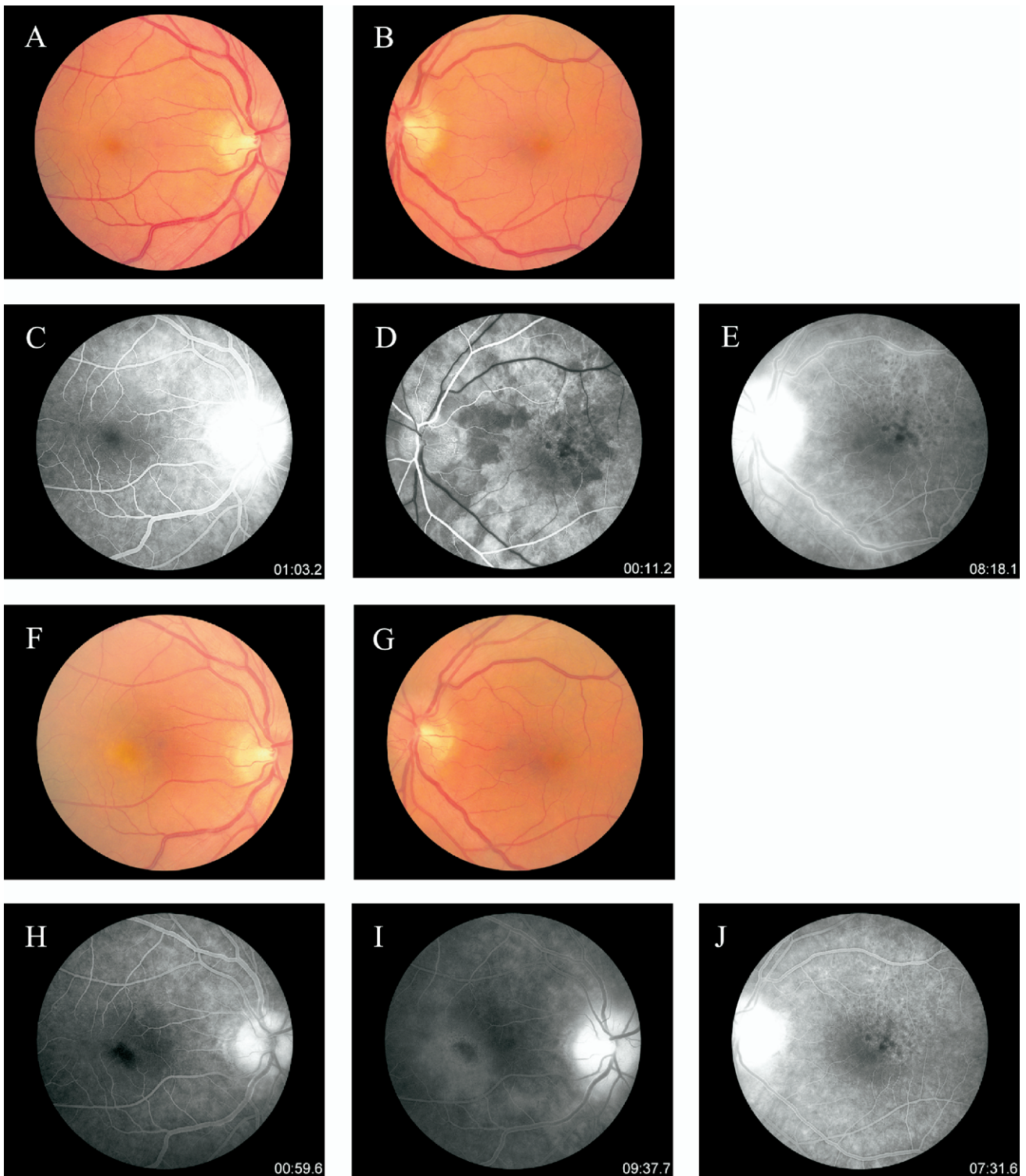
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**Figure 1.** Case 1. Fundus photographs of the right (A) and left (B) eyes reveal mild disc hyperemia in both eyes. Retinal pigment epithelium mottling can be appreciated in the macula of the left eye. C, Disc leakage is seen on fluorescein angiography of the right eye. D, Fluorescein angiography of the left eye reveals patchy choroidal filling and leopard-spot hypofluorescence in the macula. E, Late frames in the left eye show persistence of the focal hypofluorescence as well as leakage at the optic nerve head and staining of the retinal veins. F, Fundus photo shows a new, oval-shaped placoid lesion in the macular region of the right eye. G, Fundus appearance of the left eye remains unchanged. H, Fluorescein angiography of the right eye reveals a focal area of hypofluorescence in the area of the pale, yellow, placoid lesion seen above. In addition, telangiectatic vessels were observed at the optic nerve, which were noted to leak in the later frames. I, The inferotemporal macular lesion is surrounded by hyperfluorescence, increasing in late frames, which is consistent with leakage. Retinal veins in the right eye show staining, previously observed only in the left eye. J, Leopard-spot hypofluorescence remained unchanged in the macula of the left eye.

head in both eyes and staining of the retinal veins in the left eye (Fig 1C, E).

Two days later, the patient reported a new decrease in vision of her right eye (20/400) and improvement in vision of her left eye (20/60). Repeat fundoscopic examination was significant for a new large, pale yellow, subretinal placoid lesion in the macula of the right eye, whereas the examination of the left eye was unchanged (Fig 1F, G). Fluorescein angiography of the right eye revealed early hypofluorescence and leakage in the area of the placoid lesion (Fig 1H, I). Retinal veins in the right eye showed staining, similar to that previously observed in the left eye; the angiogram in the left eye remained unchanged (Fig 1I, J).

The patient returned 2 days later with headache, nausea, vomiting, and unsteady gait. Her visual acuity continued to decrease in the right eye to hand motions and to improve in the left to 20/40. She was admitted for complete evaluation and observation. Laboratory workup was significant only for elevated rapid plasma reagin (RPR) titers of 1:32 and a reactive serum fluorescent treponemal antibody, absorbed test (FTA-ABS). Tests for Lyme, *Bartonella*, herpes simplex virus-1, herpes simplex virus-2, HIV-1, and HIV-2 serum antibodies were negative, as were angiotensin-converting enzyme, lysozyme levels, and a purified protein derivative test. Computed tomography and magnetic resonance imaging of the head were negative; cerebrospinal fluid (CSF) studies revealed 117 white blood cells (WBCs)/mm<sup>3</sup>, a weakly positive Venereal Disease Research Laboratory (VDRL) test, and a reactive FTA-ABS. Gram stain, fungal, and bacterial cultures, Lyme antibody, *Cryptococcus* antigen, and herpes simplex virus polymerase chain reaction of the CSF were negative. The patient was diagnosed with neurosyphilis. Because she was allergic to penicillin, she underwent desensitization, followed by 2 weeks of IV penicillin G treatment (4 million U every 4 hours). Her neurologic symptoms resolved within a few days of beginning treatment, and her visual acuity improved to 20/30 in the both eyes after completion of the antibiotic course. At discharge, she had persistent nyctalopia, decreased color vision in her left eye, and a residual trace relative afferent pupillary defect.

### Case 2

A 39-year-old homosexual man with no significant past medical history presented to an outside ophthalmologist with bilateral vision loss and headaches. His best-corrected visual acuity was 20/200 in his right eye and 20/400 in his left eye. Slit-lamp examination showed 2+ anterior chamber and vitreous cells in both eyes; fundoscopic examination was remarkable for bilateral optic nerve head hyperemia. Fluorescein angiography showed leakage around both optic nerves. The patient was started on topical prednisolone acetate and oral prednisone (60 mg daily). Two weeks later, his visual acuity had improved to 20/30 in the right eye and 20/200 in the left with minimal cell in the anterior chamber and vitreous. However, 1 week later, the patient's visual acuity deteriorated to counting fingers (CF) in both eyes. Prednisone was increased to 80 mg, and he was referred to our facility for further management.

On examination, the patient's visual acuity was CF in both eyes. Relative afferent pupillary responses were intact. There were no cells in the anterior chamber or vitreous. Fundoscopic examination confirmed disc edema in both eyes. The laboratory workup was significant for an elevated WBC count of 10 200/mm<sup>3</sup>, elevated RPR titers of 1:128, a positive serum FTA-ABS test, and a positive HIV test. Cerebrospinal fluid studies showed 64 WBCs/mm<sup>3</sup> and a positive FTA-ABS. The patient was diagnosed with neurosyphilis and admitted for treatment with IV penicillin G (4 million U every 4 hours). After 3 weeks of IV

penicillin treatment, the patient's visual acuity had improved to 20/40 in his right eye and 20/100 in his left eye.

### Case 3

A 60-year-old heterosexual man with a 2-week history of decreased vision in both eyes was transferred to our medical center for further management. Diagnosed by consultants at an outside facility with acute retinal necrosis, he was treated with a 1-week course of IV acyclovir before his transfer. His past medical and ocular history were unremarkable, and he denied any ocular pain. On general examination, he had generalized lymphadenopathy.

Ophthalmic examination showed visual acuities of 20/400 in both eyes. No relative afferent pupillary defect was observed. Anterior segment examination revealed 3+ cell and flare in both eyes, with moderate posterior synechiae in the right eye. There was mild lenticular sclerosis and 3+ anterior vitreous cell bilaterally. Fundus examination showed a central placoid lesion in the right eye, without involvement of the periphery (Fig 2A). The left eye showed similar, semiconfluent placoid lesions along the arcades (Fig 2B). Fluorescein angiography showed early blockage and late staining in these placoid lesions, which seemed larger and more confluent on the angiogram (Fig 2C-E).

A systemic laboratory workup revealed positive serum VDRL and RPR. Serology was negative for HIV antibodies. Cerebral spinal fluid was positive for VDRL (reactive at 1:8) and RPR (1:128). The patient was started on IV penicillin and discharged home with intravenous access for continued infusion; he was unfortunately lost to follow-up.

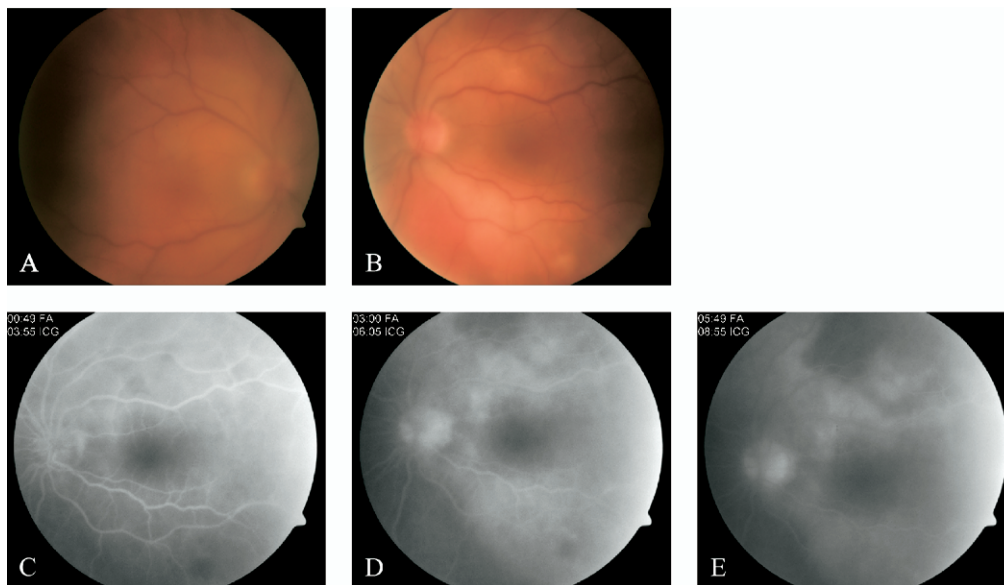
### Case 4

A 40-year-old heterosexual man presented with a complaint of 6 months of left eye pain, photophobia, and left occipital headache and a 2-month history of redness and blurry vision in his right eye. He reported that vision in both eyes had worsened in the past 2 weeks. His past medical history was significant for a sexually transmitted disease of unknown type, which had been diagnosed 5 years ago and for which he had never received treatment. On presentation, his best-corrected visual acuity was 20/70 in his right eye and 20/50 in his left eye. His color vision and relative afferent pupillary responses were intact. Slit-lamp examination was significant for conjunctival injection, keratic precipitates, and 3+ anterior chamber cell and flare. Fundoscopic examination showed 1+ vitreous cell and disc edema in both eyes.

Physical examination revealed multiple hypopigmented macules on his forearms and back (Fig 3). Examination of the palms, soles, oropharynx, and genitalia was unremarkable. Laboratory work-up was positive for serum RPR (1:64), *Treponema pallidum* particle agglutination (TP-PA), and HIV antibodies. Cerebrospinal fluid studies were notable for 6 WBCs/mm<sup>3</sup> and positive VDRL and FTA-ABS tests. The patient completed a 10-day course of IV penicillin (3 million U IV every 4 hours), and his vision improved to 20/30 in both eyes at the time of discharge.

## Discussion

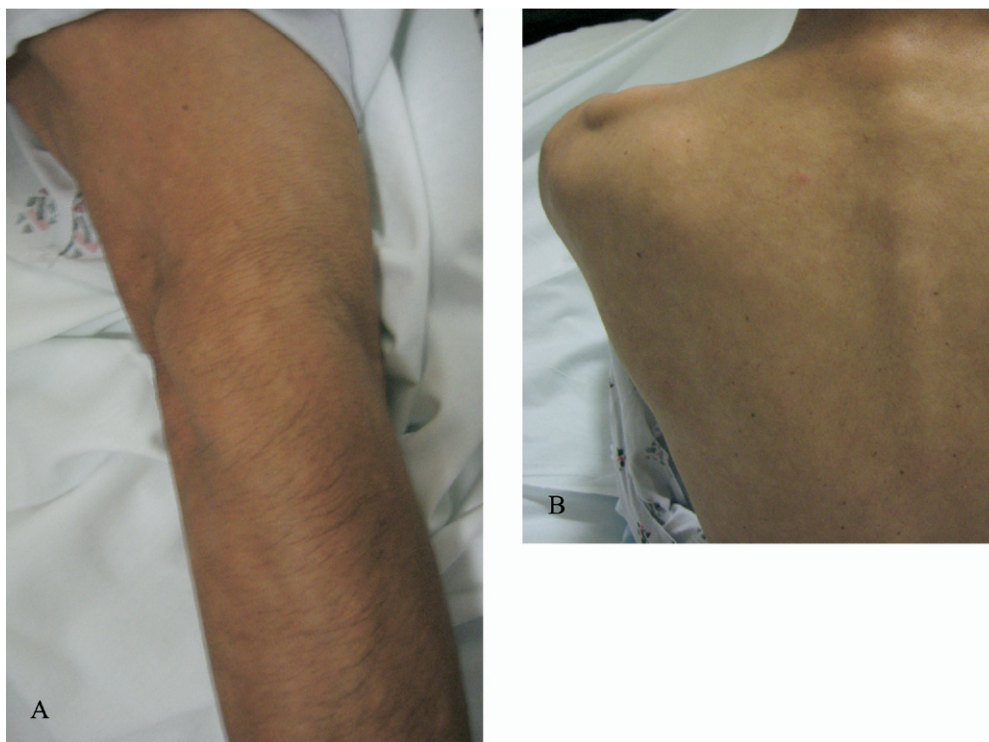
The diagnosis of syphilis based on ocular findings is often elusive because the pathognomonic features of the disease are lacking. Although inflammatory presentations such as chorioretinitis, panuveitis, vitritis, iritis, keratic precipitates, and vascular sheathing are more common, affected eyes may also show disc edema, serous and exudative retinal



**Figure 2.** Case 3. Fundus photographs reveal a central placoid lesion in the right eye, with sparing of the periphery (A) and semiconfluent placoid lesions along the arcade of the left eye (B). C–E, Early blockage and late staining of the placoid lesions were seen in the left and right eyes (latter not shown).

detachments, and necrotizing retinitis.<sup>4,6</sup> We describe 4 cases, 2 of which demonstrated clinical findings of discrete yellowish and grey-white placoid lesions consistent with what has been described as acute syphilitic posterior placoid chorioretinitis (ASPPC).<sup>8</sup> Since the original description by Gass et al<sup>8</sup> in 1990, only 14 cases have appeared in the literature.<sup>8–17</sup> It has been proposed that these placoid lesions are specific to ocular syphilis among HIV-positive or oth-

erwise immunocompromised individuals.<sup>10</sup> Both of our patients (cases 1 and 3) were immunocompetent, however; and the patient described in case 2, who was given large doses of prednisone, did not develop the placoid lesions, contrary to what has been previously suggested.<sup>10</sup> As with all ocular syphilis findings, it is important to distinguish the placoid lesions seen in ASPPC from those of other diseases. The differential diagnosis includes acute posterior multifocal



**Figure 3.** Case 4. Hypopigmented macular skin eruptions are seen on the forearms (A) and back (B) of this affected patient.

placoid pigment epitheliopathy, serpinginous choroiditis, and viral retinitis. Like syphilitic placoid lesions, acute posterior multifocal placoid pigment epitheliopathy lesions can be large, solitary, and ephermal, and can be located in the posterior pole. However, the syphilitic placoids can be distinguished from acute posterior multifocal placoid pigment epitheliopathy and serpinginous choroiditis by the small, leopard-spot changes in the retinal pigment epithelium seen on intravenous fluorescein angiography after ASPPC resolution, as seen in case 1 (Fig 1E, J).<sup>8</sup> Retinitis caused by viruses such as herpes can be distinguished from the chorioretinitis seen in syphilis by the presence of full-thickness opacified retinal lesions found both in the posterior pole and in the periphery. The clinical difference between herpes retinitis and ASPPC can be a subtle distinction,<sup>18</sup> as illustrated by case 3, wherein the patient was initially diagnosed and treated for acute retinal necrosis.

Ophthalmic lesions are signs of tertiary syphilis. Whereas the significance of anterior syphilitic uveitis in the absence of neurologic involvement is more controversial, optic neuritis and retinitis are generally considered neurosyphilis and should be managed accordingly. Although disc edema has been thought to be a relatively infrequent ophthalmic sign of ocular syphilis,<sup>7</sup> this finding was present in all 4 patients reported herein. All of our patients demonstrated CSF findings that were consistent with neurosyphilis, as evidenced by increased leukocyte counts ( $>5$  WBCs/mm<sup>3</sup>) and positive VDRL or FTA-ABS tests. The CSF VDRL test is highly specific but not sensitive, and a negative result should not eliminate the suspicion of neurosyphilis. In addition, the VDRL titer may not be proportional to the level of disease activity, rendering it ineffective for monitoring the effects of treatment.<sup>19</sup> This is underscored in case 1, wherein the CSF VDRL titer was noted by the laboratory as "weakly positive," even though the patient was suffering from physical symptoms of active neurosyphilis, such as vertigo, nausea, and gait disturbances. On the other hand, the FTA-ABS test is highly sensitive but less specific, suggesting that a negative CSF FTA-ABS test may exclude the possibility of neurosyphilis.<sup>19</sup>

The recommended treatment for neurosyphilis is aqueous crystalline penicillin G (18–24 million U IV daily) or procaine penicillin (2.4 million U IM daily) with probenecid (500 mg orally 4 times per day) for 10 to 14 days.<sup>19</sup> Additionally, if CSF pleocytosis is observed at presentation, monitoring is recommended at 6-month intervals until the cell count normalizes.<sup>19</sup> In penicillin-allergic patients, an alternative regimen of ceftriaxone (2 g/day IM or IV for 10–14 days) may be instituted, but this has not been as well tested for the management of neurosyphilis and patients may have a cross-sensitivity to this agent. Therefore, some authors recommend penicillin desensitization for penicillin-allergic patients.<sup>19</sup> The Centers for Disease Control and Prevention (CDC) recommend that all patients with neurosyphilis be tested for HIV and that HIV-positive patients be monitored for treatment failure at 6, 12, 18, and 24 months. Additionally, no alternatives to IV penicillin have been adequately examined for penicillin-allergic HIV-positive patients.<sup>19</sup>

It is important to note that the increase in the total

number of primary and secondary syphilis cases in the United States primarily reflects an increased incidence among men. According to the CDC, the increase in syphilis cases in the United States is thought to reflect recent syphilis outbreaks among men who have sex with men (MSM). These outbreaks have been reported in several metropolitan areas in the United States, including New York City, Miami-Dade County (Florida), King County (Washington), Chicago, Houston, San Francisco, and Southern California.<sup>19–23</sup> A recent CDC analysis estimates that MSM account for 64% of the early-stage syphilis cases in 2004, an increase from just 5% in 1999.<sup>1</sup> In contrast, since 1999, the numbers of syphilis cases have steadily declined among women and African Americans, by 55% and 37%, respectively.<sup>1</sup> These trends differ from those in the United Kingdom, where outbreaks were observed across multiple social demographics, including homosexual men, heterosexual men, and women.<sup>24</sup> Studies have not attributed the increased incidence to better reporting or data ascertainment, implying that the outbreaks are likely to be real, rather than perceived, phenomena.<sup>1,19–23</sup> According to the CDC, their current report continues to underestimate the true burden of disease owing to underreporting of diagnosed cases and lack of data on infected but unscreened persons.<sup>1</sup> Given the reemergence of syphilis among MSM in the United States, it may be appropriate for the clinician to take a sexual history when considering the differential diagnosis of patients presenting with persistent uveitis or other findings consistent with ocular syphilis. In the United Kingdom, where a recent increase in the incidence of syphilis has led to an apparent increase in the number of ocular syphilis cases,<sup>24–26</sup> such in-depth history taking has been suggested to help with early diagnosis and intervention.

The number of syphilis cases diagnosed by ophthalmologists is unknown at this time, but the potential for intervention is considerable. For example, among the 100 cases of confirmed or probable neurosyphilis identified in Los Angeles County between 2001 and 2004, the most common presenting symptoms were visual changes (42%), headache (42%), and altered mental status (23%) (Taylor MM, Aynalem G, Olea L, et al. Consequence of the syphilis epidemic among men who have sex with men (MSM): neurosyphilis in Los Angeles, 2001–2004. Abstract presented at: National Sexually Transmitted Diseases Prevention Conference, May 2006, Jacksonville, Florida). Sixty percent of the symptomatic cases were HIV positive and 52% occurred among MSM. In an earlier study, 29% of all symptomatic early neurosyphilis patients and 9% of all patients with late neurosyphilis syndrome were diagnosed after initially seeking treatment for uveitis.<sup>27</sup> Given the substantial percentage of neurosyphilis patients presenting for symptoms of visual changes, ophthalmologists who maintain a reasonably high suspicion can contribute to the early detection and treatment of a serious illness.

In summary, despite a decade of steady decline, syphilis has reemerged in the United States with outbreaks throughout the country in the past few years. Ocular findings are important diagnostic features in the early treatment of tertiary syphilis and neurosyphilis. Unfortunately, there are no pathognomonic features of ocular syphilis, and uncommon findings may often present alone or, as in the ASPPC cases

we describe here, present similarly to other diseases. However, once it has been correctly diagnosed, syphilis is eminently treatable. Therefore, maintaining an awareness of the protean manifestations of this disease and a reasonably high index of suspicion can allow ophthalmologists to play a key role in the early diagnosis and treatment of ocular syphilis.

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