Diagnosis and management of syphilis after unique ocular presentation

Carla Lutchman MD Daniel J. Weisbrod MD FRCSC Carol E. Schwartz MD FRCSC DABO

Syphilis is a sexually transmitted, systemic infection caused by the spirochete bacterium *Treponema pallidum*. The incidence of syphilis is on the rise, with an estimated 12 million new cases every year worldwide.[1] In Canada, the number of cases of infectious syphilis has increased more than 5-fold from 1998 (177 cases, 0.6 per 100 000) to 2007 (1206 cases, 3.7 per 100 000)[2]; this increased incidence is similar to the number of cases in other developed countries such as the United States (3.8 per 100 000), the United Kingdom (4.4 per 100 000), and Australia (6.7 per 100 000).[2] The increase has occurred in both sexes, although it is considerably greater in men, who accounted for 86.8% of cases in 2007.[2] Syphilis can manifest in almost any organ in the body and presents in a multitude of ways, masquerading as many infectious or immune-mediated diseases. This case describes an unusual presentation of syphilis and discusses the appropriate management to prevent any associated morbidity.

Case description

A 64-year-old healthy man was referred to the retina service at Sunnybrook Health Sciences Centre in Toronto, Ont, for gradual and painless decreasing vision over the past several years. His best corrected visual acuity was 20/60 in the right eye and count fingers in the left eye, in which there was a relative afferent pupillary defect. Slitlamp examination of the anterior segment was unremarkable. Dilated fundus examination revealed diffuse atrophy of the choroid and retina, with areas of retinal hyperpigmentation throughout the macula and posterior pole in both eyes (**Figure 1**). The peripheral retina of each eye was relatively spared. Visual field examination showed central scotomas in both eyes (**Figure 2**). First impressions suggested hereditary macular dystrophy or an acquired retinal disease, such as sarcoidosis, tuberculosis, or syphilis.

The patient underwent a systemic workup, including a complete blood count, angiotensin-converting enzyme (ACE) check, tuberculin skin test, chest x-ray examination, and syphilis serology. Results of all investigations were negative except for those of the syphilis serology. The *T pallidum* chemiluminescent microparticle immunoassay (CMIA) was reactive, indicating recent or previous syphilis. Results of the rapid plasma reagin (RPR) screening test were positive for syphilis, with a low titre of 1:1, as were

This article has been peer reviewed.
Cet article a fait l'objet d'une révision par des pairs.
Can Fam Physician 2011;57:896-9

EDITOR'S KEY POINTS

- It is important to maintain a high index of suspicion in the workup and diagnosis of syphilis, as this increasingly prevalent disease can mimic many other infectious or immune-mediated diseases. If left untreated, the disease can give rise to serious complications, such as damage to the central nervous system, cardiovascular system, eyes, and other internal organs. Although eye involvement in syphilis is rare, it must be suspected in any case of ocular inflammation, particularly uveitis.
- Syphilis is transmissible during the first, second, and early latent stages of onset; during the latent stage, it is easy to miss and can be diagnosed only through serologic testing in conjunction with clinical findings. Most cases of syphilis are curable with systemic antibiotics, but follow-up testing is recommended, particularly lumbar puncture to rule out neurosyphilis in cases with ocular or neurologic complications.
- Transmission occurs in 50% to 75% of sexual contacts with infectious syphilis. Partner notification and testing at the time of diagnosis can help prevent the morbidity and mortality associated with untreated cases.

POINTS DE REPÈRE DU RÉDACTEUR

- Il est important de toujours faire preuve de suspicion dans les investigations et le diagnostic de la syphilis, car cette maladie de plus en plus fréquente peut ressembler à de nombreuses autres maladies infectieuses ou à médiation immunitaire. Sans traitement, la maladie peut entraîner des complications sérieuses, comme des dommages au système nerveux central, au système cardiovasculaire, aux yeux et aux autres organes internes. Quoique les complications aux yeux dues à la syphilis soient rares, il faut la suspecter dans les cas d'inflammations oculaires, en particulier l'uvéite.
- La syphilis est transmissible durant le premier stade, le deuxième stade et les stades latents précoces de son apparition; durant la phase latente, elle est difficile à détecter et ne peut être diagnostiquée que par des analyses sérologiques combinées aux constatations cliniques. La plupart des cas de syphilis peuvent se guérir par des antibiotiques systémiques, mais il est recommandé de faire des tests de suivi, en particulier une ponction lombaire, pour écarter la possibilité d'une neurosyphilis dans les cas de complications oculaires ou neurologiques.
- La transmission se produit dans 50 % à 75 % des cas de contact sexuel avec une personne atteinte de syphilis infectieuse. Il faut avertir les partenaires et leur faire subir des tests au moment du diagnostic pour aider à prévenir la morbidité et la mortalité associées aux cas non traités.

Figure 1. Fundus photograph of both eyes: *Diffuse atrophy of the choroid and retina (white arrows) with areas of retinal hyperpigmentation (black arrows) throughout the macula and posterior pole is evident in both eyes; the peripheral retina is relatively spared. A) Left eye, B) right eye.*

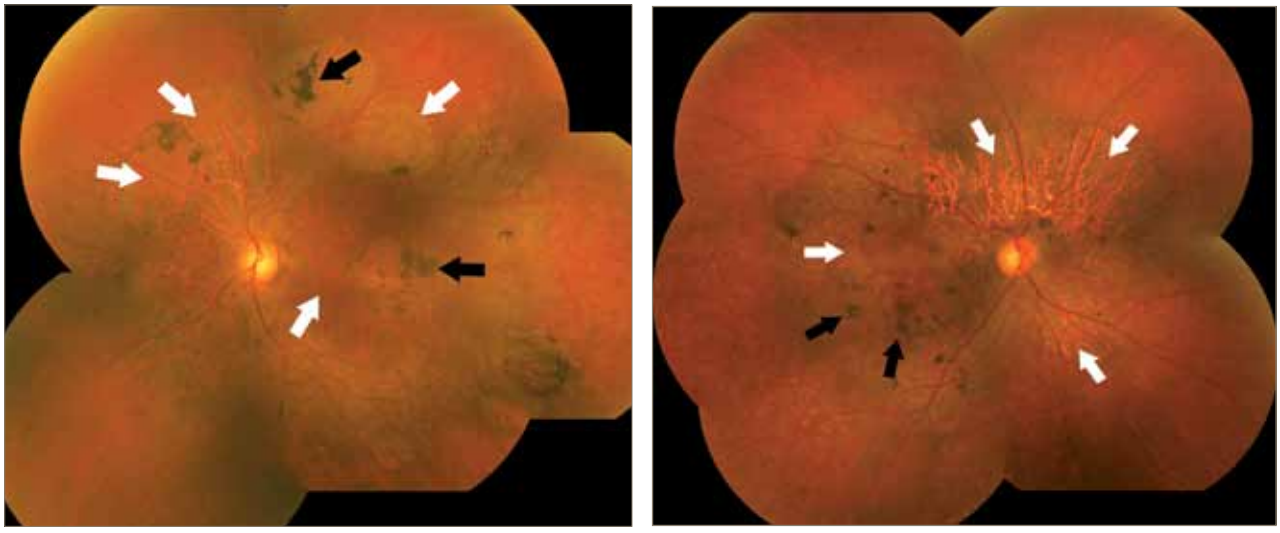
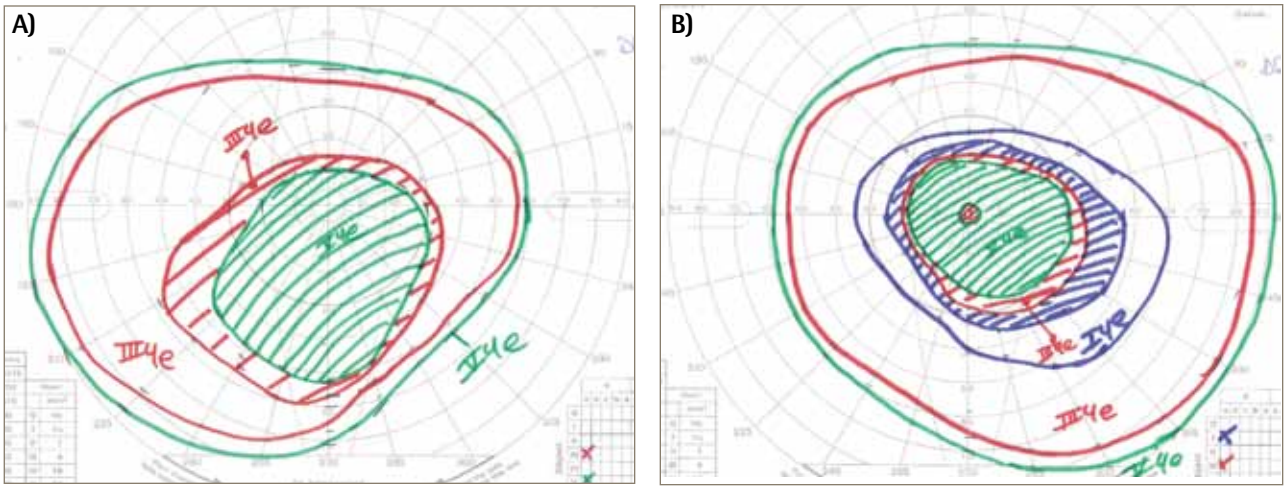


Figure 2. Goldman visual field analysis of both eyes: *The shaded areas in the centres of both eyes highlight areas of vision loss (central visual field scotomas) that correspond to the retinal abnormalities. A) Left eye, B) right eye.*



those of the confirmatory *T pallidum* particle agglutination (TP-PA) test.

The patient's retinal findings were consistent with an inactive retinochoroiditis involving both eyes. The patient then recalled that his wife was positive for syphilis on prenatal testing 35 years previously and was treated with 3 injections of penicillin. Given this history, the clinical findings, and the results of serology, a presumptive diagnosis of syphilis was made. The patient was referred to the infectious disease service, where he was found to have no systemic manifestations of syphilis. A lumbar puncture was recommended to rule out neurosyphilis; however, the patient refused. He was subsequently treated with a 2-week course of intravenous penicillin (4 million units every 4 hours). He tolerated the treatment well.

Discussion

There are 4 stages of syphilis (**Table 1**[3,4]). Syphilis is infectious during the primary, secondary, and early latent stages. Transmission can occur in early latent syphilis owing to a 25% chance of relapse to secondary syphilis.[3-5] During the latent stage, infection can be detected

Table 1. Clinical stages and selected manifestations of syphilis

STAGE	CLINICAL MANIFESTATIONS	INCUBATION PERIOD
Primary	Chancre, regional lymphadenopathy	3 weeks (3 to 90 days)
Secondary	Rash, fever, lymphadenopathy, mucous lesions, condyloma lata, alopecia Hepatic (jaundice, hepatitis) Renal (proteinuria) Neurologic (meningitis, headaches) Ocular (uveitis, retinitis)	2 to 12 weeks (2 weeks to 6 months)
Latent	Asymptomatic	Early (less than 1 year) to late (more than 1 year)
Tertiary		
• Cardiovascular syphilis	Aortic aneurysm Aortic regurgitation Coronary ostial stenosis	10 to 30 years
• Neurosyphilis	Meningoencephalitis, locomotor ataxia, generalized paresis Can range from asymptomatic to headache, cranial nerve palsies, vertigo, personality changes, dementia, intention tremor, ataxia, presence of Argyll Robertson pupil, areflexia, loss of proprioception	2 to 20 years
• Gumma	Tissue destruction of any organ Manifestations depend on site involved	15 years (1 to 36 years)

Data from Wong et al,[3] and Singh and Romanowski.[4]

only by serologic testing. If untreated, tertiary syphilis might develop, giving rise to serious complications, such as damage to the central nervous system, cardiovascular system, eyes, and other internal organs.[3,4]

Ocular involvement in syphilis is rare and typically occurs with secondary or tertiary syphilis.[1,6-10] There are no pathognomonic signs, and the ability of syphilis to mimic other diseases often leads to misdiagnosis and delay in treatment. The differential diagnosis includes infectious diseases, such as tuberculosis, and noninfectious diseases, such as sarcoidosis or hereditary retinal disorders. Although syphilis accounts for only 4.3% of cases of uveitis, it must be suspected in any case of ocular inflammation, particularly in those resistant to conventional therapy.[7,8] The most common ocular manifestation of syphilis is uveitis; however, any part of the eye can be affected.[6,9] Syphilis can manifest as a keratitis, retinochoroiditis, retinal vasculitis, or optic neuropathy. Ocular motor palsies and visual field defects can also develop with central nervous system involvement. Retinochoroiditis typically develops during secondary syphilis. Healed lesions can manifest with nonspecific findings, including atrophy of the choroid and retina, with areas of hyperpigmentation, leading to substantial visual impairment (**Figure 1**).

Treponema pallidum cannot be cultured; therefore, the diagnosis of syphilis depends on the clinical findings as well as serologic analysis, including nontreponemal tests (VDRL and RPR tests), and treponemal tests (CMIA, fluorescent treponemal antibody absorption [FTA-ABS], and TP-PA tests). Screening for syphilis has traditionally entailed a nontreponemal test, and, if reactive, a confirmatory treponemal test. Currently, the CMIA is used as a screening test and detects both immunoglobulin G and immunoglobulin M antibodies to *T pallidum*.[3] This test has a high sensitivity to all stages of disease, but lacks specificity; therefore, confirmation with a second treponemal test (eg, TP-PA test) is required. Only if the RPR and TP-PA test results are nonreactive or indeterminate is a third confirmatory test performed (eg, FTA-ABS test).[3] The treponemal tests usually remain reactive for life in spite of treatment. The RPR test is performed to assess the acuity of disease, to monitor treatment, and to assess for reinfection. It is reported quantitatively as a titre, which decreases with treatment and time (although some patients can remain reactive at a low titre for life).[3] The CMIA, RPR, and TP-PA tests were all reactive in our patient and, together with the clinical findings, indicated a presumptive diagnosis of syphilis. The patient was referred to the infectious disease service to assess for neurosyphilis. Although his ocular disease was inactive, neurosyphilis can be asymptomatic for years; therefore, a lumbar puncture is recommended in all patients with neurologic or ocular complications of syphilis.[3] Cerebrospinal fluid VDRL testing is highly specific, and a positive result confirms neurosyphilis; conversely, cerebrospinal fluid FTA-ABS testing is highly sensitive and a negative test result excludes neurosyphilis.[5]

Most cases of syphilis are curable with benzathine penicillin G (2.4 million units injected intramuscularly in a single dose).[11] In the event of a penicillin allergy, a course of oral doxycycline (100 mg twice daily for 14 days) can be administered. Our patient had late latent syphilis, for which the recommended treatment is benzathine penicillin G, 7.2 million units total administered as 3 doses of 2.4 million units intramuscularly at weekly intervals.[11] Unfortunately, he declined a lumbar puncture and was subsequently treated as though he had neurosyphilis, which required higher doses of intravenous, aqueous, crystalline penicillin G for 10 to 14 days, as neurosyphilis could not be ruled out.[11] Topical, periocular, and systemic steroids can have an adjunct role in the management of the ocular complications of syphilis[9]; however, only systemic antibiotics will provide a cure. In our patient, no local therapy was necessary, as his ocular disease was inactive.

Follow-up after treatment is important in order to ensure a response to treatment and assess sexual contacts. For our patient, although repeat serology was requested after 3 months, given that he had late latent syphilis with a low RPR titre, it is possible that he might remain seropositive for syphilis indefinitely. Transmission occurs in 50% to 75% of sexual contacts with infectious syphilis.[5,12] The patient's wife had been diagnosed and treated for syphilis 35 years before his presentation. Partner notification and testing at the time of his wife's diagnosis could have prevented the ocular damage in this case.

Conclusion

Syphilis is becoming increasingly prevalent, and patients can present at any stage of the disease. A high index of suspicion is necessary, as ocular syphilis can mimic many forms of uveitis. Currently, the CMIA is used as a screening test; if the results are positive, a second confirmatory test is performed. The nontreponemal tests provide a titre to monitor response to treatment and assess for reinfection. Patients presenting with ocular manifestations who are subsequently diagnosed with syphilis should have lumbar puncture to rule out neurosyphilis. These patients should also be tested for HIV.[1,7,9] Syphilis is a curable disease, but can cause substantial morbidity and mortality if left untreated. Prompt diagnosis and treatment is important.

Dr Lutchman is a fifth-year resident in the Department of Ophthalmology at the University of Toronto in Ontario. **Dr Weisbrod** is a lecturer and **Dr Schwartz** is Assistant Professor in the Department of Ophthalmology and Vision Sciences at Sunnybrook Health Sciences Centre in Toronto.

Competing interests
None declared

Correspondence
Dr Carol E. Schwartz, Assistant Professor, Department of Ophthalmology and Vision Sciences, Sunnybrook Health Sciences Centre, 2075 Bayview Ave, Suite M1-201, Toronto, ON M4N 3M5;telephone 416 480-5770;
e-mail **eyecu@rogers.com**

References

1. Gaudio PA. Update on ocular syphilis. *Curr Opin Ophthalmol* 2006;17(6):562-6.
2. Centre for Communicable Diseases and Infection Control. *Brief report on sexually transmitted infections in Canada: 2007.* Ottawa, ON: Public Health Agency of Canada; 2009. Available from: **www.phac-aspc.gc.ca/publicat/2009/sti-its/index-eng.php.** Accessed 2011 Jun 23.
3. Wong T, Kropp R, Mann J, editors. *Canadian guidelines on sexually transmitted infections, 2006 edition.* Ottawa, ON: Public Health Agency of Canada; 2006. Available from: **http://dsp-psd.pwgsc.gc.ca/collection_2007/phac-aspc/HP40-1-2006E.pdf.** Accessed 2011 Jun 23.
4. Singh AE, Romanowski B. Syphilis: review with emphasis on clinical, epidemiologic, and some biologic features. *Clin Microbiol Rev* 1999;12(2):187-209.
5. Golden MR, Marra CM, Holmes KK. Update on syphilis: resurgence of an old problem. *JAMA* 2003;290(11):1510-4.
6. Kiss S, Damico FM, Young LH. Ocular manifestations and treatment of syphilis. *Semin Ophthalmol* 2005;20(3):161-7.
7. Barile GR, Flynn TE. Syphilis exposure in patients with uveitis. *Ophthalmology* 1997;104(10):1605-9.
8. Ross WH, Sutton HF. Acquired syphilitic uveitis. *Arch Ophthalmol* 1980;98(3):496-8.
9. Aldave AJ, King JA, Cunningham ET Jr. Ocular syphilis. *Curr Opin Ophthalmol* 2001;12(6):433-41.
10. Klig JE. Ophthalmologic complications of systemic disease. *Emerg Med Clin North Am* 2008;26(1):217-31.
11. Centers for Disease Control and Prevention, Workowski KA, Berman SM. Sexually transmitted diseases treatment guidelines, 2006. *MMWR Recomm Rep* 2006;55(RR-11):1-94.
12. Garnett GP, Aral SO, Hoyle DV, Cates W Jr, Anderson RM. The natural history of syphilis: implications for the transmission dynamics and control of infection. *Sex Transm Dis* 1997;24(4):185-200.