Syphilitic Uveitis

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4.1 Introduction

Syphilis is caused by infection by the spirochete *Treponema pallidum* and is, in the vast majority of cases, sexually transmitted. Although uncommon, syphilis and syphilitic uveitis continue to be an important cause of patient morbidity. Not only can vision and visual function be severely reduced by ocular involvement in syphilis, but severe and sustained non-ocular complications can also accompany infection. This latter point is particularly important given the high proportion of patients with syphilitic uveitis for whom ocular inflammation is the presenting sign of infection.

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4.2 Epidemiology

Recognized for over 150 years as an important cause of both iritis and chorioretinitis, the prevalence of confirmed cases of syphilitic uveitis has decreased dramatically over this time – first as a result of improved serologic testing and later with the introduction of effective antibiotic therapy [1]. This decline was particularly dramatic in the developed world in the latter half of the twentieth century such that by 2000 the annual rate of primary and secondary syphilis in the United States reached its lowest recorded level of 2.1 cases per 100,000 population [2–4]. Since 2000, however, the rate of primary and secondary syphilis in the United States has more than doubled to 5.3 cases per 100,000 population in 2013 [5]. Estimates in the United Kingdom indicate the incidence of syphilis between 1999 and 2008 have increased 1032 % [4]. This dramatic increase has occurred largely in men, who accounted for 91.1 % of reported early syphilis cases in 2013. The greatest percentage increases were among men having sex with men (MSM), most probably linked to the practice of unprotected sex in the era of effective antiretroviral therapy [4–7].

The British Ocular Syphilis Study utilized a national reporting system (the British Ocular Surveillance Unit) to collect new cases of syphilitic uveitis from 2009 to 2011. They found the annual incidence of ocular syphilis to be 0.3 cases per 1,000,000 persons and that syphilitic uveitis affected 0.6 % of all those affected with

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infectious syphilis every year [4]. This prevalence of ocular syphilis was lower than expected and may have been due to increased awareness of the resurgence of syphilis and, consequently, more prompt treatment. Another study out of Nantes, France, studied 36 patients hospitalized for syphilis from 2000 to 2010. All but one of the patients were MSM and 50 % were HIV positive. Of the 36 patients with severe syphilitic infection requiring hospitalization, 11 (30.6 %) had syphilitic uveitis [8].

4.3 Pathophysiology

Humans are the only known reservoir for syphilis. The spirochete typically enters the body through intact mucosa, whereafter invasion of local and distant tissues ensues. The bacteria do not produce an intrinsic toxin; rather, tissue damage results predominantly from the ensuing adaptive immune response in the host. *T. pallidum* initially elicits a prominent B-cell response, with T-cell-mediated immunity playing a key role in elimination from infected hosts [9]. Dissemination occurs despite the humoral and cellular response of the host, and, without treatment, the bacteria can persist in the body for decades [9, 10].

4.4 Clinical Features

4.4.1 Systemic Manifestations

The systemic manifestations of syphilis have been divided into three clinical stages. Primary syphilis is the first stage of syphilitic infection and occurs about 3 weeks after exposure. It is characterized by an ulcerative chancre at the contact point and is associated with regional lymphadenopathy. Although there is systemic dissemination shortly after inoculation through the lymphatics and blood stream, flu-like systemic symptoms are rarely associated with primary syphilis. The chancre is usually painless and heals spontaneously within a few weeks and, therefore, is often unnoticed.

Untreated, the infection progresses to secondary syphilis 2–12 weeks after initial inoculation. Systemic manifestations such as arthralgias, headache, low-grade fever, and a maculopapular rash can occur and last for a few weeks or linger over many months. After secondary syphilitic infection, the disease moves to a latent stage that can continue for years.

The tertiary phase of syphilis refers to the occurrence of sequelae of infection months or years after the untreated resolution of the signs of secondary syphilis, complications that can affect 15–30 % of those infected [11] and can include focal inflammatory lesions known as gummas, vasa vasorum of the aorta, tabes dorsalis, and general paresis. Although involvement of the central nervous system (CNS) can result in severe manifestations in tertiary syphilis, CNS infection, or neurosyphilis, may be demonstrated at any stage. Ocular involvement, which can also occur either during secondary or latent syphilitic infection, elevates the suspicion of nervous system involvement and is usually treated as such.

Congenital syphilis may manifest at any time throughout life. Symptoms occurring at the age of 2 years or younger are considered early onset of congenital syphilis; symptoms after age 2 are termed late onset of congenital syphilis.

4.4.2 Ocular Manifestations

While direct conjunctival inoculation resulting in primary ocular syphilis is possible [12], ocular syphilis occurs most often during the secondary and latent stages of infection.

4.4.2.1 External Examination

The conjunctiva may be involved in several ways in syphilis. In primary syphilis, an ulcerative conjunctival lesion with a rounded edge and surrounding conjunctival injection may be seen, very similar to chancres seen at a genital inoculation site. There tends to be little or no discharge associated with a primary conjunctival lesion. A nonspecific conjunctivitis usually consisting of a primary papillary reaction can present in secondary syphilis and is usually mild and

often overlooked. In tertiary syphilis, there can be a granulomatous conjunctivitis with secondary necrosis and gumma formation [11].

Scleritis and episcleritis can be seen in conjunction with other ocular findings of syphilitic uveitis however are uncommon in isolation [13, 14]. Anterior nodular scleritis is the most common form of direct scleral involvement and tends not to progress to necrosis. Syphilitic scleritis should show rapid improvement to appropriate antimicrobial treatment [13].

4.4.2.2 Anterior Segment

Corneal manifestations of congenital and acquired syphilis are probably the most recognized ocular findings in syphilis. Nonulcerative stromal keratitis is most commonly a manifestation of late congenital syphilis, appearing between 5 and 15 years of age [15, 16]. However, as the rates of congenital syphilis decrease and the rate of acquired syphilis increases, more cases of adult stromal keratitis are being reported [15–17]. Nonulcerative stromal keratitis presents in adults with syphilis as marginal, central, or multifocal stromal inflammation with neovascularization, usually immediately anterior to Descemet's membrane. The keratitis responds to corticosteroid therapy, but occasionally can recur [16]. With inactive interstitial keratitis, ghost vessels may be seen and can be associated with stromal scarring.

Iritis and iridocyclitis is a nonspecific finding in syphilitic uveitis and may be granulomatous (Fig. 4.1) or nongranulomatous. Hypopyon may be present, but is uncommon. Dilated iris capillaries (iris roseola) are thought to be highly suggestive of syphilitic infection (Fig. 4.2). The classic pupillary finding in syphilis is the Argyll Robertson pupil, usually seen in latent syphilis and diagnostic for neurosyphilis. The pupils are unequal in size, irregular, and miotic, and while the pupil will accommodate, it will not react to light. The pathologic lesion is thought to be in the interneuron connection between the Edinger-Westphal nucleus and the retinal ganglion cells in the midbrain [18].

Cataracts have been described uncommonly in association with both congenital and acquired syphilis.

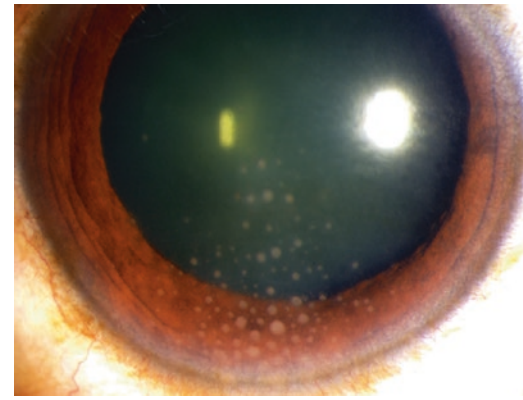

Fig. 4.1 Color slit lamp photograph of large "granulomatous" keratic precipitates in a patient with syphilitic uveitis (Reproduced with permission from Wender J, Eliott D, Jumper JM, Cunningham ET Jr. How to recognize ocular syphilis. Rev Ophthalmol, 2008, November, 124–130)

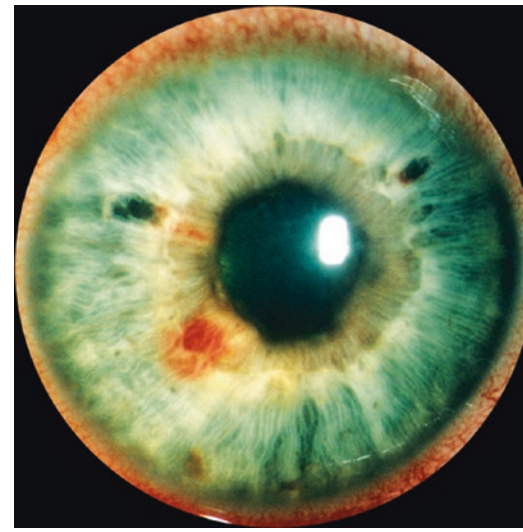

Fig. 4.2 Color slit lamp photograph of iris roseola in a patient with syphilitic uveitis. Two patent iridotomies are visible at 2 and 10 o'clock (Reproduced with permission from Wender J, Eliott D, Jumper JM, Cunningham ET Jr. How to recognize ocular syphilis. Rev Ophthalmol, 2008, November, 124–130)

4.4.2.3 Posterior Segment

Posterior segment complications appear to be particularly common in patients with syphilis [19]. Although the clinical presentation can be varied and a wide assortment of findings has been reported, there are posterior findings that, while not necessarily pathognomonic, are highly suggestive of syphilitic infection.

Isolated vitritis can occur in patients with syphilis; however, vitreous inflammation tends to occur more often in association with other posterior segment findings, most commonly retinitis [19, 20]. One report highlighted three cases of primary vitritis as the initial manifestation of syphilitic uveitis [21]. All the patients in the report were HIV positive.

While isolated optic disc edema has been reported as a presenting sign of syphilis [22, 23], optic disc swelling typically occurs in the setting of active uveitis (Fig. 4.3) [19, 20, 24].

Numerous descriptions and variations of retinitis have been reported in cases of syphilitic uveitis including wedge-shaped retinitis, ground-glass retinitis, and necrotizing retinitis [2, 11, 20, 25, 26]. Active syphilitic retinitis often contains both vasculitis and superficial precipitates or accumulations (Fig. 4.4), which together are quite suggestive of syphilis [26]. Similarly, acute syphilitic posterior placoid chorioretinitis (ASPPC), first described by Gass in 1990 [27], is a classic finding of syphilis (Fig. 4.5). In ASPPC, the lesions are typically yellow-white, placoid, circular, or oval and involve the macular or extramacular area. An active leading edge was often observed. Fluorescein angiography shows a hypofluorescent central lesion in the early-phase frames with progressive hyperfluorescence in the later frames, often observed with leopard spotting [2, 20, 27]. Spectral domain optical coherence tomography imaging shows characteristic outer retinal abnormalities, including disruption of the ellipsoid band, nodular thickening of the retinal pigment epithelium (RPE), loss of the outer segment/RPE junction, and in some cases loss of the external limiting membrane. Subretinal fluid was also observed, although was transient. Usually these findings reversed following appropriate treatment; however in some cases, the damage to the outer retinal anatomy was permanent and poor vision persisted [20, 28].

Localized exudative retinal detachments are relatively common in posterior syphilitic uveitis and have been widely reported [29–31]. Rhegmatogenous retinal detachments, in comparison, are much less common [32, 33]. Rhegmatogenous detachments typically occur early in the course of treatment, as the infection resolves, but prior to the resolution of inflammation,

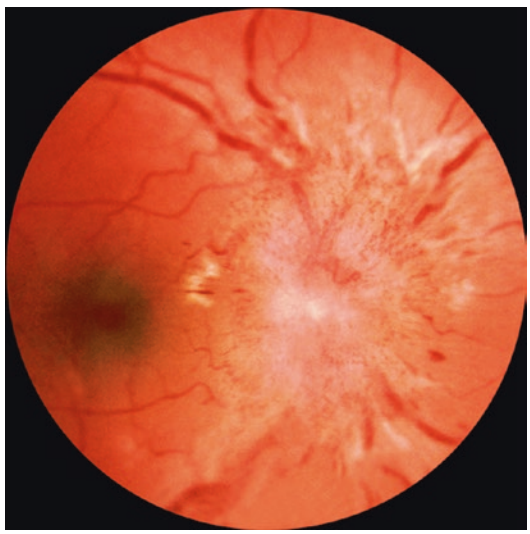

Fig. 4.3 Color fundus photograph of syphilitic papillitis in an HIV-positive patient (Reproduced with permission from Wender J, Eliott D, Jumper JM, Cunningham ET Jr. How to recognize ocular syphilis. Rev Ophthalmol, 2008, November, 124–130)

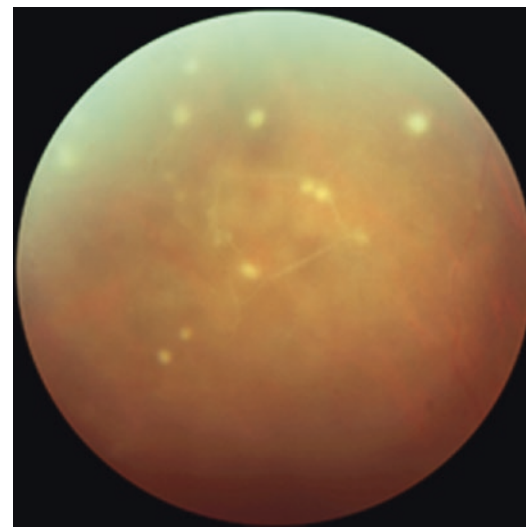

Fig. 4.4 Color fundus photograph of characteristic "ground-glass" retinitis associated with a serous retinal detachment, focal inflammatory accumulations, and retinal vasculitis in an HIV-positive patient with syphilitic uveitis (Reproduced with permission from Wender J, Eliott D, Jumper JM, Cunningham ET Jr. How to recognize ocular syphilis. Rev Ophthalmol, 2008, November, 124–130)

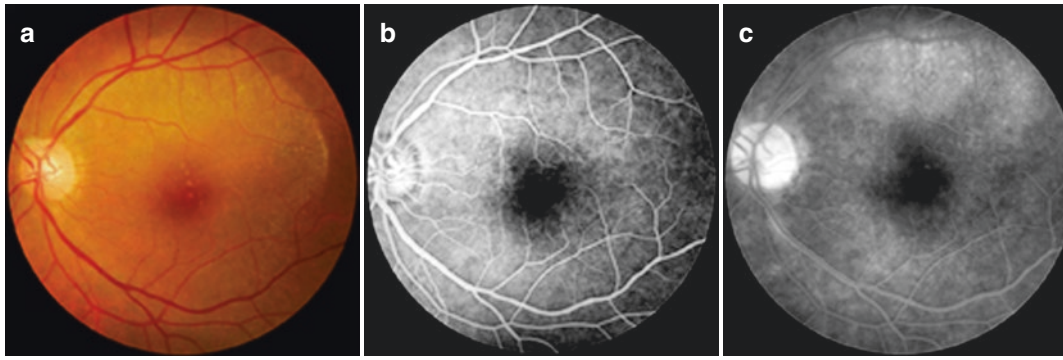

Fig. 4.5 Color fundus photograph (**a**) and serial fluorescein angiographic images (**b**, **c**) of acute syphilitic posterior placoid chorioretinopathy (ASPPC) showing a characteristic macular lesion and progressive hyperfluorescence (Reproduced with permission from Wender J, Eliott D, Jumper JM, Cunningham ET Jr. How to recognize ocular syphilis. Rev Ophthalmol, 2008, November, 124–130)

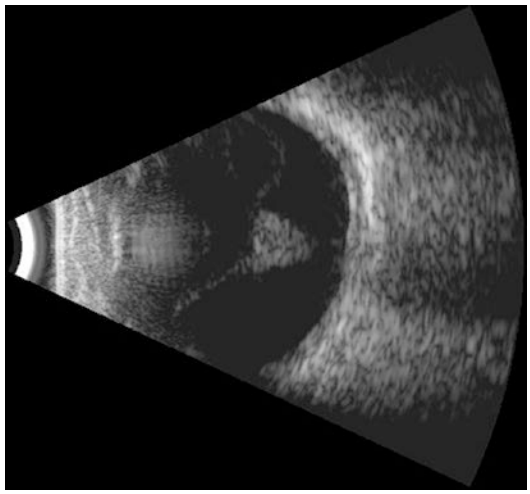

Fig. 4.6 B-scan ultrasonography showing a total rhegmatogenous retinal detachment in a patient with syphilitic panuveitis

and are thought to be due to contraction of the vitreous (Fig. 4.6) [33].

4.5 Diagnosis

Diagnosis of the "great imitator" requires a high level of clinical suspicion. The definitive method for diagnosis is direct visualization of *T. pallidum* using dark-field microscopy; however due to the technological difficulties of this test, it is rarely performed [34]. Serologic testing can be divided into two groups. First, the nontreponemal tests such as the venereal disease research laboratory (VDRL) and the rapid plasma reagin (RPR) tests detect antibodies to cardiolipin (lecithin) cholesterol antigen. The titers of the nontreponemal tests are often used as an indicator of both disease activity and of appropriate and complete treatment. In contrast, direct treponemal tests such as enzyme immunoassays (EIAs) and chemiluminescent immunoassays (CIAs) detect antibodies directed against treponemal antigens and so are used as more sensitive and specific indicators of past or current infection. These direct treponemal assays will remain reactive for years, despite adequate therapy [7].

Most practitioners today use both treponemal and nontreponemal tests to confirm syphilis infection in patients with syphilitic uveitis. The nontreponemal tests are inexpensive and often used for screening; however, they are not specific for syphilis, can produce false-positive results, and can be falsely negative in early stages of infection. If there is discordance between the treponemal and nontreponemal serologies, a confirmatory *Treponemal pallidum* particle agglutination (TP-PA) test can be used for syphilis diagnosis. In patients with confirmed syphilis infection, HIV testing is also warranted.

4.6 Differential Diagnosis

The differential diagnosis is quite broad for syphilitic uveitis, given its varied ocular manifestations. Nonulcerative stromal keratitis is often

associated with congenital or acquired syphilis, but the differential includes tuberculosis, leprosy, sarcoidosis, lymphoma, Lyme disease, herpes simplex virus and herpes zoster virus, Epstein-Barr virus, mumps, human T-lymphotropic virus type 1, leishmaniasis, onchocerciasis, trypanosomiasis, Cogan's syndrome, or trauma such as contact lens overwear. In cases of syphilitic panuveitis, the differential diagnosis includes endogenous endophthalmitis, sarcoidosis, toxoplasmosis, tuberculosis, Lyme disease, Behçet's disease, and viral retinitis such as cytomegalovirus or acute retinal necrosis. The differential diagnosis for posterior placoid chorioretinopathy due to syphilis is similar to the differential for panuveitis, tuberculosis, Lyme disease, toxoplasmosis, and sarcoidosis, but also should include fungal infections, lymphoma, persistent placoid maculopathy, and metastasis.

4.7 Management

Patients with a new diagnosis of syphilis must first be reported in most countries and regions, patients with a new diagnosis of syphilis should be reported to the local health authorities. Penicillin G is the drug of choice for all stages of syphilis, although the specifics of the regimen are debated. In immunocompetent patients with early syphilis, defined as primary, secondary, or latent of less than 1 year's duration, a single intramuscular injection of 2.4 million units of benzathine penicillin G is considered adequate. Recommended treatment for patients with active chorioretinal disease is aqueous crystalline penicillin G (18–24 million units IV daily) or procaine penicillin (2.4 million units IM daily) with oral probenecid (500 mg four times daily) for 10–14 days. Response to treatment is verified by a fourfold decrease in titer by the same nontreponemal test. If there is confirmed neurosyphilis with positive cerebrospinal fluid, patients should be monitored at 6-month intervals with CSF studies until the cell count normalizes. In patients with concurrent HIV infection, the treatment regimen should be for 3 weeks rather than 10–14 days, and serologic testing should be performed at 6-month intervals for 2 years to monitor for treatment failure [11, 25].

The use of corticosteroids to help control the inflammation as a result of the syphilis infection is controversial. Topical corticosteroids should be used liberally; however, intravitreal steroid injections are generally avoided. Oral corticosteroids are also not routinely advised.

4.8 Prognosis

Although neurosyphilis and tertiary syphilis can be devastating, most new cases of syphilis are diagnosed in the primary or secondary stage of syphilis. When diagnosed in these earlier stages, the prognosis is usually quite good. Many of the systemic and ocular symptoms resolve without sequelae.

Conclusions

Syphilis infection is again on the rise globally. Although there are classic findings for syphilitic uveitis, syphilis is the "great imitator" and must be considered in nearly all cases of intraocular inflammation, particularly if a condition is not responding to usual treatment.

Core Messages

- Incidence of syphilis infection has risen following a nadir in 2000, particularly in men who have sex with men. HIV coinfection is common.
- Syphilis is known as the "great imitator," given its wide variety of ocular manifestations. Therefore, a high level of suspicion for *T. pallidum* infection must be maintained in new cases of uveitis, given that a high proportion of undiagnosed patients with syphilis present with uveitic symptoms.
- Diagnosis of syphilitic infection is made with serologic testing. Nontreponemal tests such as rapid plasma reagin (RPR) are used in conjunction with treponemal tests, such as the enzyme immunoassays

(EIAs) or chemiluminescent immunoassays (CIAs). If there is discordance between the treponemal and nontreponemal serologies, the *Treponema pallidum* particle agglutination (TP-PA) test is utilized for diagnosis. Response to treatment is monitored using the nontreponemal tests, which should seroconvert to negative following appropriate treatment.

- Treatment of syphilitic uveitis consists of aqueous crystalline penicillin G (18–24 million units IV daily) or procaine penicillin (2.4 million units IM daily) with oral probenecid (500 mg four times daily) for 10–14 days. If the patients are HIV positive, treatment should continue for 3 weeks. An alternative to this treatment is a single intramuscular injection of 2.4 million units of benzathine penicillin G weekly for three weeks. Within the United States, new cases of syphilis should be reported to the patient's respective State Department of Health.

Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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