Syphilis

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Introduction/Clinical Features

Uveitis is the most common manifestation of ocular syphilis and may present as anterior, intermediate, posterior, or panuveitis. Posterior segment involvement (especially chorioretinitis) and panuveitis are the most common presentations of syphilitic uveitis [1].

Syphilitic anterior uveitis (see Fig. 12.1) is granulomatous in two thirds of patients [2] and bilateral in half. Interstitial keratitis, iris nodules, dilated iris vessels, and iris atrophy may also be seen. The most common form of posterior uveitis is multifocal chorioretinitis, but other manifestations include focal chorioretinitis (see Fig. 12.2), pseudoretinitis pigmentosa, retinal necrosis, neuroretinitis, optic neuritis (see Fig. 12.3), and acute zonal occult outer retinopathy. A pale optic nerve head from prior syphilitic optic neuritis may mimic glaucomatous optic atrophy. Chorioretinitis was the type of uveitis seen in 15 of 20 patients with syphilitic posterior uveitis in one review [1]. A specific type of focal chorioretinitis, acute posterior placoid chorioretinitis, has been described in syphilis and is characterized by large, often solitary yellow lesions that are typically in the macula [3]. Retinal vasculitis may occur in ocular syphilis, and branch retinal vein occlusions have been described [4].

Uveitis may occur in either congenital or acquired syphilis. Typical ocular findings in congenital disease include interstitial keratitis and so-called *salt-and-pepper* fundi. Interstitial keratitis does not usually occur until the patient is a teenager or young adult. It may be accompanied by anterior uveitis. The patient may have no other stigmata of congenital syphilis, but other possible features include prematurity, low birth weight, nonimmune hydrops fetalis, placental and umbilical cord abnormalities, fever, hepatomegaly, failure to thrive, rhinitis, maculopapular rash, vesicular rash (pemphigus syphiliticus), condyloma lata, jaundice, and hematologic, musculoskeletal, neurologic, pulmonary, and/or renal disease.

In acquired syphilis, uveitis may occur in secondary or tertiary syphilis. The chancre of primary syphilis, a painless lesion that develops at the inoculation site (usually genital area) an average of 3 weeks after inoculation, may have been unnoticed by the patient. The chancre lasts 3–6 weeks then spontaneously resolves.

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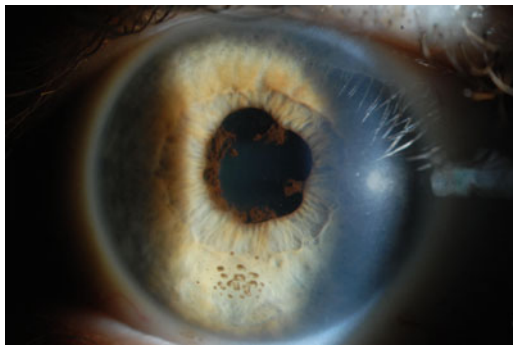

Fig. 12.1 Slit lamp photograph of a patient with syphilitic iritis, pigmented/granulomatous keratic precipitates, and posterior synechiae

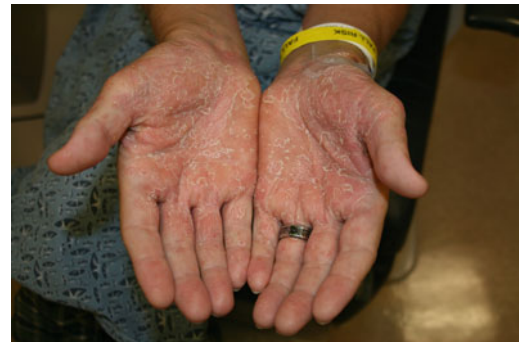

Fig. 12.4 Syphilitic rash involving the palms in a patient with secondary syphilis and uveitis (Photograph courtesy of Dr. George Papaliodis)

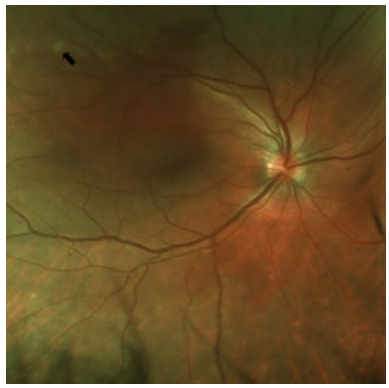

Fig. 12.2 Focal chorioretinitis (*arrow*) in a patient with ocular syphilis

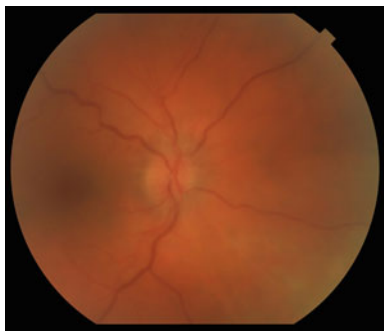

Fig. 12.3 Optic nerve swelling and vitritis in a patient with ocular syphilis

Secondary syphilis typically begins 2–8 weeks after the chancre, but this period is variable. With ocular manifestations that occur during secondary syphilis, eye symptoms are often acute. In older reports, the most common ocular finding in secondary syphilis was iritis, which accounted for more than 70 % of eye findings [4]. More recent reports suggest that posterior segment inflammation predominates; these reports include larger numbers of patients with concomitant HIV infection and low CD4 cell counts, which may predispose to more aggressive and posteriorly-located disease [5, 6]. Other manifestations of secondary syphilis may include fever, rash (classically involving the palms and soles—see Fig. 12.4), swollen lymph glands, sore throat, patchy hair loss, headaches, weight loss, muscle aches, and fatigue.

In contrast, when ocular syphilis develops in tertiary disease, patients often have slowly progressive decrease in vision as their only symptom. The eye findings are protean and include all of the above-listed findings. In contrast to patients with secondary disease, patients with tertiary disease often are middle-aged or older. They often have no knowledge of prior exposure to syphilis, which likely occurred decades earlier. The diagnosis may be missed if only nontreponemal tests are checked, because these tests are often negative in tertiary syphilis. In a series of 50 patients with a reactive treponemal test [absorbed fluorescent treponemal antibody (FTA-ABS)] and eye findings consistent with active or inactive ocular syphilis (e.g., chorioretinitis, optic atrophy, iritis, interstitial keratitis), the average age was 59, and the VDRL was reactive in only 24 % [7].

Epidemiology

The rates of primary and secondary syphilis in the United States dropped by 90 % from 1990 to 2000, then increased from 2001 to 2014; the majority of these diagnoses were in men who have sex with men (MSM) [8]. Although the peak incidence of all cases of primary and secondary syphilis occurs in ages 15–30, this infection is seen in older adults as well—about 5 % of cases occur in adults age 55 and older [9]. Therefore, any patient who presents with eye findings compatible with ocular syphilis should be screened for this treatable condition.

Diagnostic Evaluation

Diagnosis of ocular syphilis typically relies on a compatible history, examination, and positive serologic tests for syphilis. Nontreponemal tests (VDRL, RPR) are not specific for syphilis but yield a titer that can be used to assess for timing of infection and follow response to treatment, particularly in secondary syphilis. As noted above, these tests are less helpful in tertiary disease, as they may revert to negative over time even in patients who have not undergone treatment for syphilis. Treponemal tests (e.g., FTA-ABS) confirm the diagnosis of syphilis but do not revert to negative after treatment. False-positive FTA-ABS may occur in approximately 5 % of cases (e.g., from Lyme disease or rheumatologic conditions), thus all reactive FTA-ABS tests should be confirmed with another specific test such as TPPA (T. pallidum particle agglutination).

All patients with ocular syphilis should be tested for HIV as these infections share common modes of transmission. In a study of 24 patients treated for ocular syphilis between 1998 and 2006, 11 patients were found to be HIV positive, and this was a new diagnosis in seven [10]. HIV-positive patients are more likely than HIV-negative patients to have acute, bilateral uveitis with more extensive eye involvement (vitreous, retina, and optic nerve involvement simultaneously) [4, 11].

All patients with presumed ocular syphilis should undergo lumbar puncture to obtain baseline CSF studies, but antibiotic treatment should not be delayed if a lumbar puncture cannot be performed promptly or if the patient declines the procedure. Concomitant neurosyphilis may be present in up to 40 % of patients with ocular syphilis [7]. Importantly, a normal CSF examination does not exclude ocular syphilis, as ocular syphilis is frequently present without evidence of neurosyphilis. Patients with HIV have a higher rate of concurrent ocular syphilis and neurosyphilis [4, 12].

Treatment and Monitoring

Treatment of ocular syphilis is the same as for neurosyphilis, with penicillin G (3–4 mU IV q 4 h or continuous infusion) for 10–14 days [13]. Because the duration of treatment is shorter for neurosyphilis than for latent syphilis, the CDC notes that IM benzathine penicillin 2.4 mU once weekly for 3 weeks may be given at the end of the IV penicillin course in order to treat any latent treponemes in the periphery (note that benzathine penicillin does not cross the blood brain barrier). Patients with penicillin allergy should be desensitized to penicillin, although the 2015 CDC guidelines note that "Limited data suggest that ceftriaxone 2 g daily either IM or IV for 10–14 days can be used as an alternative treatment for patients with neurosyphilis" and penicillin allergy [13]. Patients starting treatment for syphilis should be advised to anticipate the Jarisch–Herxheimer reaction, an acute febrile syndrome that may be accompanied by headache, myalgias, rigors, sweating, and hypotension. This syndrome occurs in approximately 30 % of patients; patients with early stages of syphilis and a high (≥1:32) RPR titer have an increased risk, while patients previously treated with penicillin for syphilis have a reduced risk [14]. This syndrome typically occurs within the first 24 h after treatment begins. Antipyretics can alleviate the symptoms, which often self-resolve within 12–24 h. The value of corticosteroids in preventing Jarisch-Herxheimer has not been

proven, but patients with worsening vision after penicillin therapy of ocular syphilis have improved with institution of corticosteroids [15], and there may be benefit to treating the inflammatory component of uveitis with prednisone initially.

For patients with a reactive RPR at diagnosis, posttreatment monitoring includes measurement of RPR titers at 3 and 6 months posttreatment, then every 6 months for up to 2 years or until the serology reverts to nonreactive. Titers typically decrease fourfold within a year, and then continue to fall, but serologic responses to treatment are variable, particularly among patients with HIV. If baseline CSF was abnormal, then repeat CSF studies are recommended every 6 months until the cell count has normalized. Changes in CSF VDRL and protein concentrations are slower to resolve. Retreatment should be considered if the CSF cell count has not decreased by 6 months or if the CSF cell count or protein is not normal by 2 years.

Prognosis

Most patients with syphilitic uveitis have a good visual prognosis, and with prompt diagnosis and treatment may return to normal vision. However, irreversible visual loss may occur if diagnosis and antibiotic therapy are delayed, especially in patients with panuveitis or posterior uveitis. For all patients, early diagnosis and treatment as well as careful follow-up after treatment are critical, as even with the standard regimens, the relapse or reinfection rate for ocular syphilis may be as high as 14–25 % [16, 17]. In one case series, 3 of 12 patients with HIV and ocular syphilis required retreatment within 1.5 years [17].

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