Syphilis

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Introduction

Syphilis is an infectious disease caused by the spirochete *Treponema pallidum*, a non-cultivable helical bacterium self-propelled with flagella. It causes disease only in humans. Early origins are unknown, but it was present in Europe around the sixteenth century (Fornaciari et al. 1989). Some historians refer to syphilis as the "Great Pox" as opposed to small pox caused by variola virus and believe that Columbus and his sailors introduced this disease to Europe from the New World (Rothschild et al. 2000). Sir William Osler described syphilis as "the great imitator" because of the varied and complex clinical stages of the disease (Singh and Romanowski 1999; Tramont 1995).

Syphilis can be transmitted by sexual contact, through blood by sharing needles or blood product transfusion, vertically from mother to fetus through the placenta or by direct contact with a cutaneous lesion (Chambers et al. 1969; Rolfs et al. 1990). There was a declining incidence of new infections in the United States until 2000 when there was a reversal of that trend, prompting the Centers for Disease Control and Prevention (CDC) for health care providers to recognize syphilis as an ongoing public health problem.

Epidemiology

Incidence of Syphilis

The World Health Organization estimates that 12 million new cases of syphilis occur each year (Gerbase et al. 1998). The CDC reported an incidence rate of 8.7 cases of primary or secondary syphilis per 100,000 people in 2015–2016, versus 2.1 cases per 100,000 in 2000. In the United States, syphilis is primarily diagnosed in men who have sex with men, but cases in women have increased more rapidly than in men (Centers for Disease Control 2016). The overall rise in incidence was associated with clustering of ocular syphilis cases in Seattle and San Francisco (Matthias et al. 2016) that led the CDC to issue a clinical advisory in 2015 to remind clinicians to screen for visual complaints in patients at risk for syphilis and to report cases to local health authorities within 24 h (Advisory 2016). Congenital syphilis rose each year from 2012 to 2016 with 15.7 cases per 100,000 live births in 2016, reaching the highest rate since 2001 (Bowen et al. 2015).

Incidence of Ocular Syphilis

The CDC investigated the incidence of ocular syphilis in 2014–2015 in eight jurisdictions: California (excluding Los Angeles and San Francisco), Florida, Indiana, Maryland, New York City, North Carolina, Texas, and Washington (Oliver et al. 2016).

Three hundred eighty eight cases were identified as suspected ocular syphilis, accounting for 0.6% of the total reported syphilis cases. Ninety-three percent of cases were in men, of which 68% were men having sex with men and 51% were HIV infected. Of the HIV patients, one third were first diagnosed with HIV at their presentation with ocular syphilis. In addition to shared risk factors, infection with syphilis is felt to facilitate the acquisition of HIV by mucosal injury. Ocular manifestations of syphilis were reported in both eyes in about 53%. The most common reported ocular diagnoses were syphilitic uveitis (45.6%), followed by retinitis (12.7%) and optic neuritis (11.4%). At the same time, an increase in ocular syphilis cases was reported at an Ophthalmologic Reference Center in France (Pratas et al. 2015); Nantes, France (Lefebvre et al. 2013); Manchester, UK (Jones 2015); and Barcelona, Spain (Fonollosa et al. 2009). The CDC subsequently requested pre-antibiotic samples of ocular fluid for molecular typing (Advisory 2016).

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Unlike the United States, United Kingdom has a prospective national registry of ocular syphilis (The British Ocular Surveillance Unit). The British annual incidence of ocular syphilis is 0.3 per 1 million persons, which represent 41 new cases. Of those reported cases, 90% were male patients, 31% were HIV positive, and 56% of the cases had bilateral involvement (Mathew et al. 2014).

Classification of Syphilis

Congenital Syphilis

Syphilis is broadly classified into congenital and acquired types. Congenital syphilis is the oldest recognized congenital infection, first described in the fifteenth century (Shafti et al. 2008). Congenital syphilis is transmitted vertically through the placenta. Syphilis can cause spontaneous abortion, stillbirth, or neonatal death. Among survivors, early congenital syphilis in the first 2 years of life can demonstrate mucocutaneous lesions, periostitis, osteochondritis, and hepatosplenomegaly. Uveitis is the most common ocular complication of early congenital syphilis with associated chorioretinitis and retinal vasculitis producing a salt-and-pepper pattern of retinal pigmentary mottling (Fig. 19.1). Late congenital syphilis presents with bone and dental abnormalities including Hutchinson teeth, mulberry molars, abnormal faces and saber shins, as well as cranial nerve eight deafness, and perforation of the hard palate. The most common ocular manifestation of late congenital syphilis is interstitial keratitis, anterior uveitis, and glaucoma. Interstitial keratitis, neurosensory deafness, and Hutchinson teeth are collectively known as the Hutchinson triad.

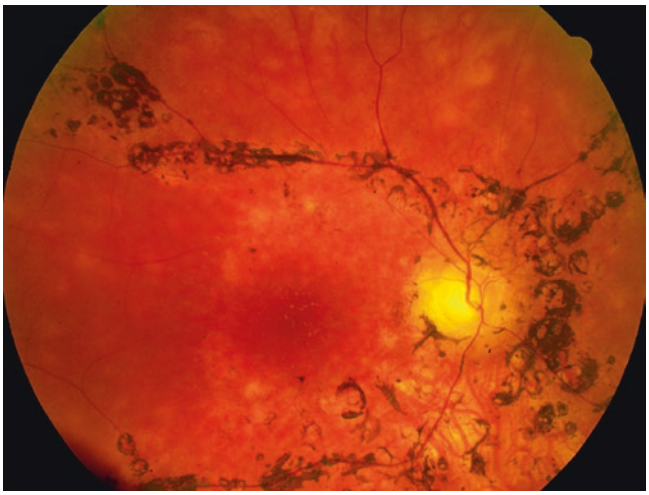

Fig. 19.1 This 59-year-old woman, born in 1923, had lifelong poor vision with chorioretinal scarring and optic atrophy. Serological testing with a treponemal-specific test was positive, and she was felt to have had congenital syphilis infection

Acquired Syphilis

Acquired syphilis is usually transmitted sexually. It is subclassified by its stage in the disease to primary, secondary, latent, and tertiary types. The primary infection appears as a chancre, which may be undetected, with associated painless lymphadenopathy. A delayed hypersensitivity reaction resolves the lesions, but some organisms survive and may cause a persistent infection. Secondary syphilis manifests as a cutaneous eruption with lymphadenopathy, along with fever, malaise, sore throat, and joint pain (Wilhelmus and Lukehart 1996). This stage remits even if not treated, but relapses can occur in up to 25% of people, usually during the first year of infection but up to decades later during the phase of latent syphilis.

Seventy-two percent of patients with latent syphilis will develop no further complications or relapses, but 28% will progress to tertiary syphilis (Kolker et al. 1997). This is an advanced disease state with cardiovascular and neurological conditions involving the meninges, brain vessels, brain parenchyma, optic nerve, and posterior column in the spinal cord. The most common ocular manifestation of secondary and tertiary syphilis is uveitis (Wilhelmus and Lukehart 1996). Ocular syphilis can occur in any stage of disease (Fig. 19.2).

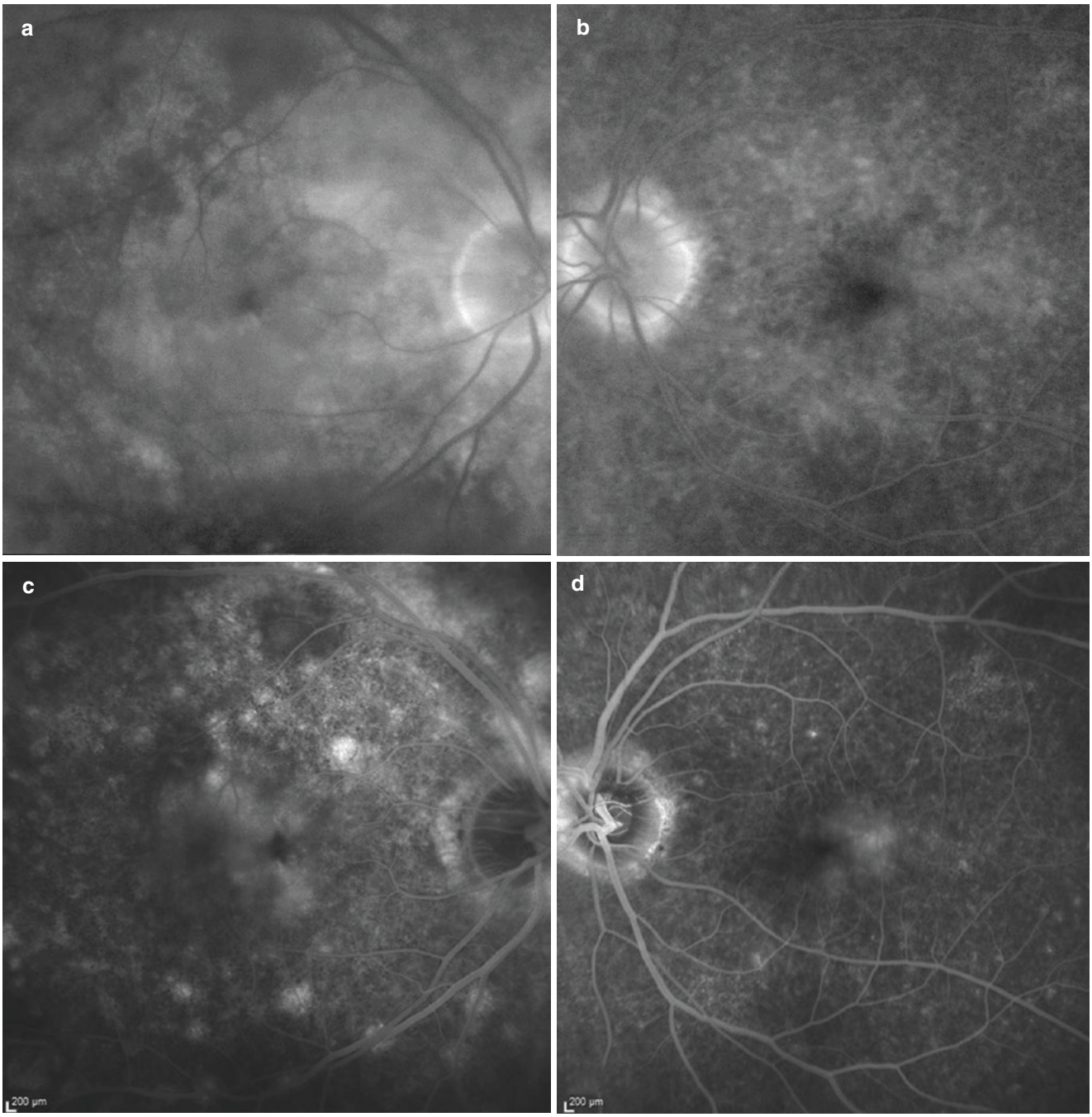

Fig. 19.2 This 56-year-old non-HIV-positive man had been treated for 3 years for a smoldering intermediate uveitis with mild vision loss in the right eye. There was a history of bicillin penicillin treatment for syphilis within the last 5 years. Lumbar puncture revealed a positive VDRL. (**a**) Late stage fluorescein angiogram of the right eye at the time of presentation showing diffuse retinal leakage, optic nerve leakage, and pigmentary changes. The vessels are emptied of dye. Vision was 20/30. (**b**) Late stage fluorescein angiogram of the left eye at presentation showing similar retinal and optic nerve leakage and pigmentary changes. Retinal perfusion was somewhat better in this eye, which was 20/20. (**c**) Late stage fluorescein angiogram of the right eye 2 years after two courses of intravenous penicillin. Optic nerve leakage has resolved, the retina is better perfused. There is persistent leakage in the center of the macula and extensive pigmentary change. (**d**) Late stage fluorescein angiogram of the left eye 2 years after treatment. Retinal perfusion is improved, with resolved optic nerve leakage and residual central leakage. Pigmentary changes are noted

Clinical Presentations

Anterior Segment Findings in Ocular Syphilis

Compared to other infectious and inflammatory etiologies affecting the eye, syphilis is highly variable in presentation with the ability to involve all structures of the eye (Davis 2014) (Table 19.1). Although there are some characteristic features, syphilis can also present as a nonspecific anterior, intermediate, posterior, or panuveitis (Cunningham et al. 2014). Interstitial keratitis typically occurs in children and adolescents with congenital syphilis and is often associated with conjunctival hyperemia and iritis (Aldave et al. 2001; Margo and Hamed 1992). Dilated iris vessels known as roseola are rare but specific (Margo and Hamed 1992). Large granulomatous keratic precipitates, hypopyon, posterior synechiae, and elevated intraocular pressure can accompany iridocyclitis (Reddy et al. 2007). Episcleritis/scleritis has been reported (Fenolland et al. 2016).

Posterior Segment Findings in Ocular Syphilis

Posterior segment findings of acquired syphilis are varied. Rather than necrosis, the infection produces retinal edema, often with subretinal fluid. The inflamed retina usually has an opacified appearance that differs from the classical whitening of herpetic necrotizing retinitis or toxoplasma chorioretinitis. The edema can be focal (Fig. 19.3) or diffuse (Fig. 19.4). If there is substantial subretinal fluid, there can

Table 19.1 Ocular features of syphilis by site and stage of disease

Site/ stage	Congenital	Secondary	Tertiary
Uveal tract	Acute iritis Secondary cataract or glaucoma	Iridocyclitis Iris nodules Isolated vitritis	Iridocyclitis Single or multiple gummas
Retina	Retinal pigmentary mottling in "salt-and-pepper" pattern Retinal vasculitis	Focal or multifocal chorioretinitis Multifocal choroidal infiltrates Necrotizing retinitis Neuroretinitis Retinochoroiditis Retinal vasculitis Serous retinal detachment Cystoid macular edema	Focal or multifocal chorioretinitis Necrotizing retinitis Neuroretinitis Retinochoroiditis Retinal vasculitis Serous retinal detachment Cystoid macular edema
Optic nerve	Optic atrophy	Inflammatory disc edema Papilledema	Inflammatory disc edema Papilledema Optic atrophy Gumma of optic disc

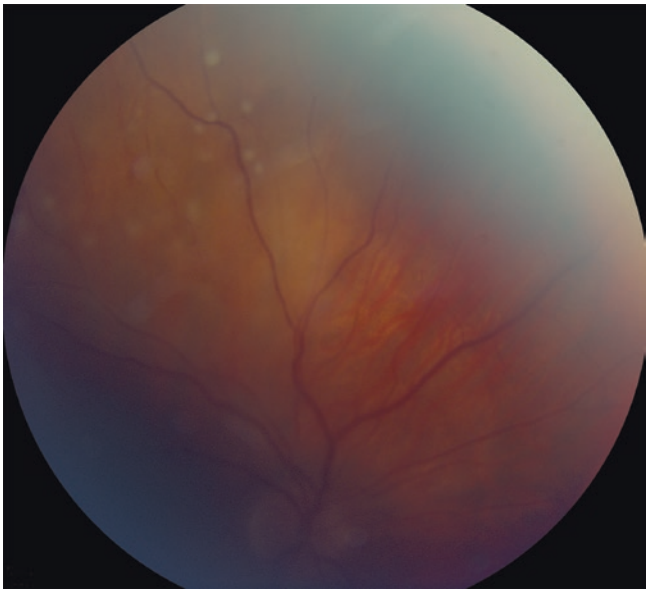

Fig. 19.3 This 43-year-old HIV-positive man complained of cloudy vision in the right eye for a few months. Fundus examination showed a region of retinal swelling above the superotemporal arcade with vitreous inflammation. The photograph depicts white, focal preretinal opacities. There is some irregularity of the vascular caliber in the region of greatest retinal whitening. He was serologically positive by both treponemal and non-treponemal tests, confirming the diagnosis of syphilitic uveitis

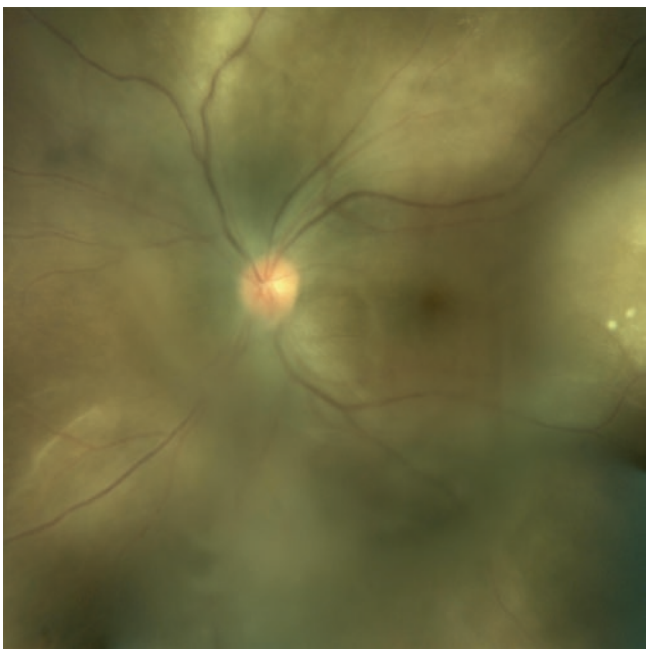

Fig. 19.4 Left fundus photograph of a 36-year-old HIV-positive man who presented with subacute vision loss in both eyes in the setting of secondary syphilis. Diffuse retinal edema with possible shallow subretinal fluid was present in both eyes. Focal preretinal vitreous opacities are visible at the edge of the frame. Sheathing of vessels is seen inferonasally

be actual serous detachment, although this is usually shallow (Fig. 19.5). Fluorescein angiography is important in detecting retinal vasculitis, which is often nonspecific and confused with a noninfectious uveitis (Fig. 19.6). Cystoid macular edema is common in eyes with retinal vascular leakage (Fig. 19.7). Necrotizing retinitis and branch vein occlusion have been described (Jumper et al. 2000; Villanueva et al. 2000; Venkatesh et al. 2002; Yokoi and Kase 2004). Optic nerve manifestations include inflammatory disc edema (Fig. 19.8), neuroretinitis, pallor, and optic nerve gumma, a solid inflammatory lesion (Margo and Hamed 1992).

Some distinctive posterior segment features may help support the diagnosis of syphilis. Superficial retinal precipitates may occur in syphilitic panuveitis, often associated with other inflammatory signs (Fu et al. 2010; Wickremasinghe et al. 2009) (Fig. 19.9). These small,

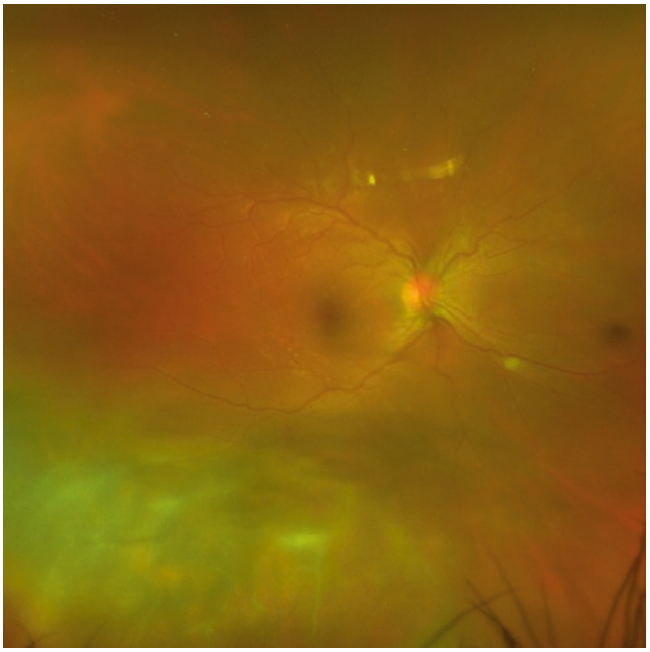

Fig. 19.5 Color photograph of the right fundus of a man presenting with syphilitic uveitis. The inferotemporal quadrant shows retinal whitening and vascular sheathing. There is substantial subretinal fluid and retinal edema around the nerve

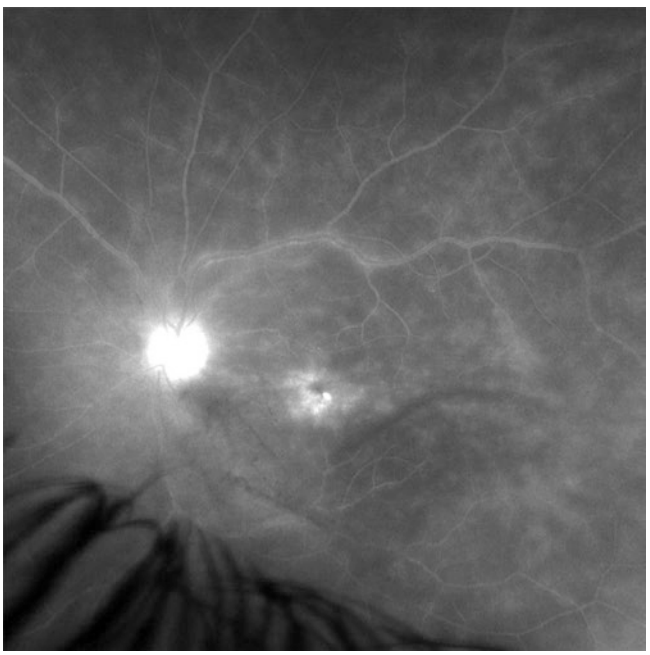

Fig. 19.6 A nonspecific diffuse small and large retinal vasculitis with optic nerve hyperfluorescence and cystoid macular edema is depicted in this late stage fluorescein angiogram of a left eye in a patient with ocular syphilis

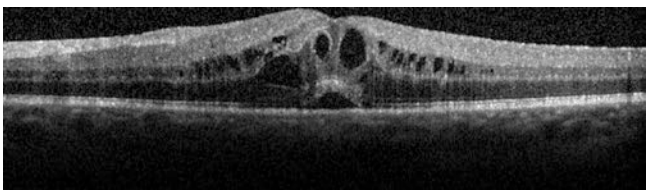

Fig. 19.7 The OCT scan of the macula of the eye depicted in Fig. 19.6. There is typical cystoid macular edema with subfoveal fluid. Although the outer retina can be disrupted in syphilitic uveitis, it appears mostly intact in this patient

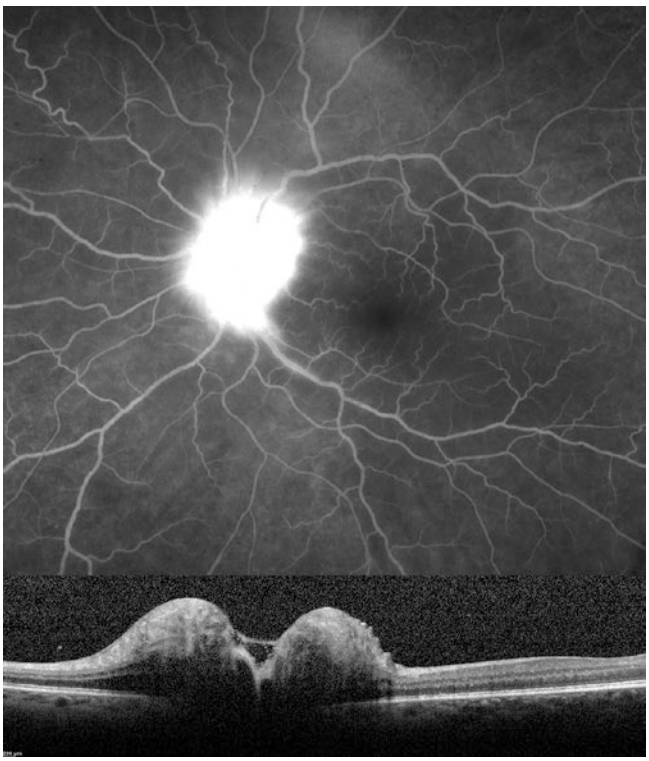

Fig. 19.8 Relatively isolated syphilitic optic nerve edema is depicted in this fluorescein angiogram of a left eye. The OCT scan through the nerve shows diffuse thickening of the perineural tissue. The macular contour is normal. The amount of retinal leakage is small although there is some vascular tortuosity

creamy white focal opacities appear to migrate over the surface of inflamed retina during the course of disease and treatment, but do not float. Other focal opacities line up along the retinal arteries in some cases, similar to the so-called Kyrieleis plaques described in toxoplasma chorioretinitis (Krishnamurthy and Cunningham 2008). The involved retina in cases of syphilitic retinitis usually heals with milder alteration of the retinal pigment epithelium and less retinal scarring than in herpetic retinitis, but chronic cases can experience substantial scarring (Baglivo et al. 2003) (Figs. 19.10 and 19.11).

Another distinctive finding is acute syphilitic posterior placoid chorioretinitis (Gorovoy and Desai 2013; Gass et al. 1990). This finding is attributed to a uniform inflammatory process involving the outer retina and inner choroid in a circular fashion on the posterior pole (Eandi et al. 2012) (Fig. 19.12). On spectral domain optical coherence tomography (OCT), there may be subretinal fluid and disruption of the ellipsoid zones (Pichi et al. 2014) (Fig. 19.13). With treatment, the subretinal fluid resolves with longer persistence of the disruption of the outer retina. Deposits may develop at the level of the RPE, which may resolve in time. Angiography may also help in distinguishing placoid syphilis from other etiologies, such as viral retinitis, lymphoma, and sarcoidosis. On indocyanine green (ICG) angiography, placoid lesions typically show diffuse early and late hypofluorescence, and fluorescein angiography shows a progressive diffuse leakage (Eandi et al. 2012) (Fig. 19.14). This pattern is specific to syphilitic uveitis compared to other types of infectious retinitis. The placoid lesion is hyperautofluorescent, probably due to the loss of the masking effect of the outer retina (Jumper and Randhawa 2012; Knecht et al. 2013).

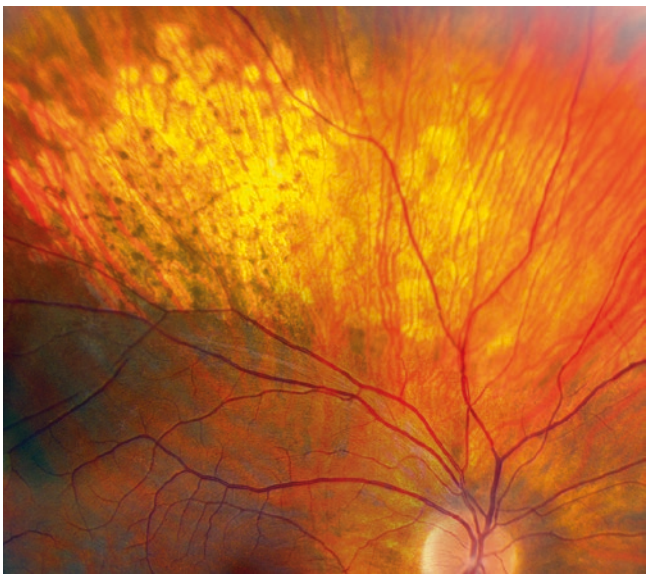

Fig. 19.10 Follow-up photograph of the patient in Fig. 19.3 after treatment of syphilitic uveitis with intravenous penicillin. There is extensive destruction of the retinal pigment epithelium, retinal thinning, and a permanent scotoma

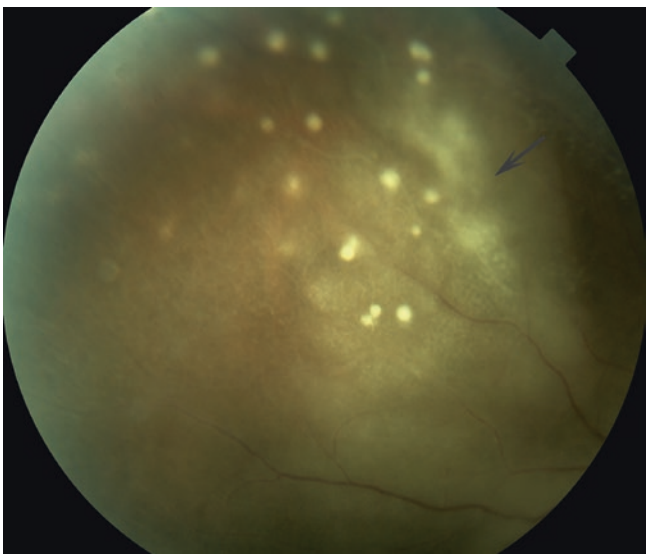

Fig. 19.9 White focal preretinal opacities overlying inflamed retina are virtually pathognomonic for syphilitic uveitis. They are migratory and transient, occurring only in the acute stages of the disease. In this photograph of the superonasal region of a right eye, there are also many sheathed and occluded retinal vessels. In some areas, there appear to be retinal infiltrates (arrowhead)

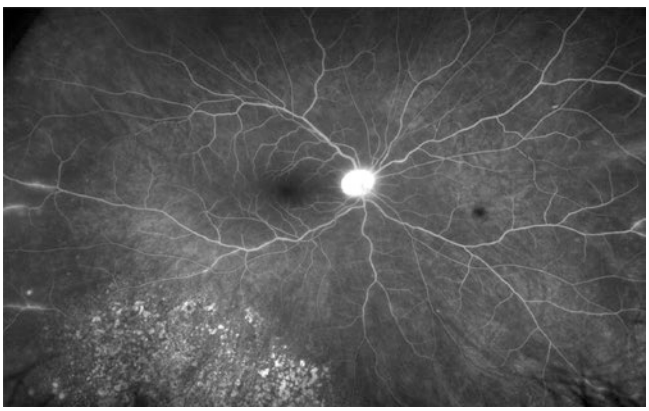

Fig. 19.11 Follow-up photograph of the patient in Fig. 19.5 after treatment of syphilitic uveitis with intravenous penicillin. There is a leopard spot pattern of RPE destruction in the region of subretinal fluid. Retinal vascular closures are present in the areas of pigmentary change. There is residual staining of large retinal veins in the peripheral and hyperfluorescence of the optic nerve

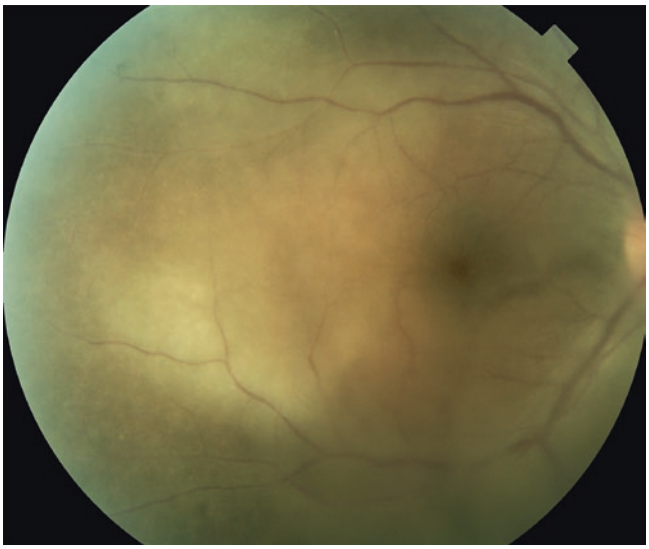

Fig. 19.12 Dense retinal swelling and pigment change affecting the temporal macula. This may be a preferential site of involvement in syphilitic uveitis

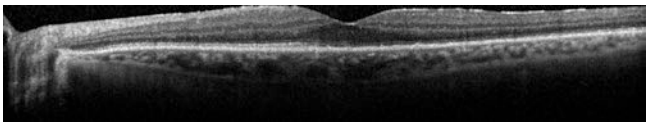

Fig. 19.13 Outer retinal disruption in a man complaining of recent vision loss in the left eye. The outer retina is diffusely abnormal without cystoid macular edema or, in this case, subretinal fluid. Other clinical findings of this case are depicted in Fig. 19.14

Diagnosis

Direct Detection of *Treponema pallidum*

Direct tests for Treponema such as dark field, polymerase chain reaction (PCR), and direct fluorescence test for *T. pallidum* are not commonly done because these methods are not widely available, and their sensitivity is less than optimal for detecting primary syphilis, missing a portion of the cases (Cornut et al. 2011). Multiplex PCR has the capability to test for multiple infectious organisms in a specimen. This technology has an application in ocular specimens where it tests for several causative agents including *Treponema pallidum* (Nakano et al. 2017).

Serologic Testing for Syphilis

Serological testing is the common practice to screen, confirm, and follow up. The CDC recommends a reverse sequence algorithm to test patients for syphilis. This approach has the benefit of detecting early primary as well as treated cases that would have been missed if other testing approaches were applied. The reverse sequence algorithm starts with a treponemal-specific test (fluorescent treponemal antibody, FTA), by either enzyme immunoassay (EIA) or chemiluminescent immunoassay (CIA), since these tests have the highest sensitivity. A negative result has a high negative predicative value. If the treponemal test is positive, a quanti-

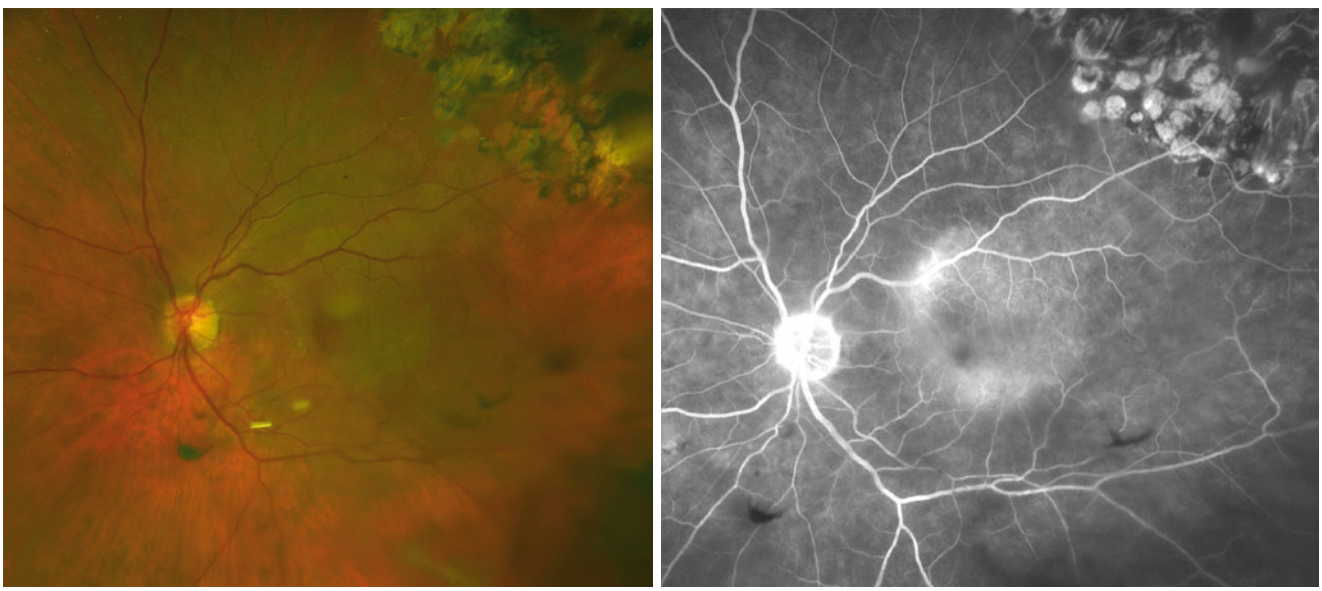

Fig. 19.14 This elderly non-HIV-positive man complained of vision loss. Left: color fundus photograph. The macula appeared to have lost translucency, but there was no thickening on OCT (Fig. 19.13). There was a past history of retinal detachment repair with extensive scarring superotemporally. Right: fluorescein angiography. There was late diffuse leakage in the macula typical for syphilitic posterior placoid retinitis. He was serologically positive for syphilis and responded to treatment with penicillin

tative rapid plasma regain (RPR) test is reflexively performed. If both treponemal and non-treponemal tests are positive, syphilis infection is diagnosed, which is usually considered confirmatory of ocular syphilis. If results are discordant, a treponemal pallidum particle agglutination (TP-PA) is performed, and if negative, it is considered that syphilis is unlikely (CDC 2008, 2011).

Reinfection can occur. If the treponemal test is positive in a previously treated but subsequently re-exposed patient, repeating the non-treponemal test in 2–4 weeks will help confirm a recent infection.

Testing for HIV and CNS Infection

Diagnosing syphilis in a patient with ocular inflammation is a trigger to test the patient for HIV because of the strong association of syphilis with high-risk sexual practices in men (Restivo et al. 2013; Butler and Thorne 2012; Chiquet et al. 2014; Abdul Wahab et al. 2013; Amaratunge et al. 2010). Since ocular syphilis is by definition a neurosyphilis, any patient who presents with ocular symptoms and has a positive serology test for syphilis should undergo a lumbar puncture with the analysis of cerebrospinal fluid. This is important to determine whether a follow-up tap will be needed in 6 months to monitor the effectiveness of treatment. Signs of inflammation such as elevated protein or inflammatory cells may be taken as presumptive evidence of central nervous system infection even in the absence of a positive non-treponemal test.

Treatment

Treatment According to Neurosyphilis Guidelines

Treatment of ocular syphilis should follow the CDC guidelines for neurosyphilis (Centers for Disease Control and Prevention 2010) or those of the local health authority (Nurfahzura et al. 2013). Parenteral penicillin is the drug of choice for ocular syphilis. The recommended adult regimen is aqueous crystalline penicillin G 18–24 million units per day administered as 3–4 million units intravenously every 4 h or by continuous infusion, for 10–14 days. The alternative adult regimen if access to therapy can be insured is procaine penicillin 2.4 million units intramuscularly once daily plus probenecid 500 mg orally four times a day, also for 10–14 days. An extended course of benzathine penicillin 2.4 million units intramuscularly once per week for 3 weeks provides a longer duration of therapy commensurate with that recommended for latent syphilis. In case of penicillin allergy, penicillin is still the drug of choice to treat neurosyphilis, ocular syphilis, HIV patients, and pregnant women. These patients require prior desensitization before starting treatment. Intravitreal administration of ceftazidime to provide rapid control of ocular syphilis during the desensitization process has been described (Sood et al. 2019).

Monitoring Response to Treatment

Aside from diagnosis, non-treponemal tests such as RPR and Venereal Disease Research Laboratory (VDRL) are used to monitor response to treatment. The results are not interchangeable, and only one of the tests should be used for monitoring. A change in titer needs to be at least fourfold to be considered meaningful. Reduction in the RPR titer to 1:1–1:2 and resolution of the cerebrospinal fluid abnormalities is generally accepted as success. Follow-up is necessary as resolution of the indirect measures of infection may be slow. Anatomic recovery on OCT may occur by 1 month, with visual recovery lagging for 6–9 months, and multifocal electroretinogram abnormalities persisting for more than 1 year (Alexander et al. 2012).

Managing Inflammation During Treatment

The Jarisch–Herxheimer reaction is a systemic reaction with fever resembling sepsis due to spirochete death caused by penicillin. It is more common in early syphilis than latent syphilis when the bacterial burden is higher. Neurosyphilis occurring in earlier stages of syphilis, including ocular syphilis by extension, may warrant concomitant treatment with corticosteroid in some cases to limit inflammation (Danesh-Meyer et al. 1999). It has been reported in a case of ocular syphilis (Marty et al. 2015) but not specifically involving the eye. In practical terms, a large increase in ocular inflammation after starting penicillin is uncommon; however, the resolution of inflammatory signs is typically slow. The role of corticosteroid in managing inflammation in cases of ocular syphilis is not clearly established. Topical corticosteroid is almost always used, and intravitreal injections of triamcinolone appear to be harmful (Eandi et al. 2012). Oral corticosteroids increased acute posterior placoid signs in one case (Zamani and Garfinkel 2003). Oral corticosteroid and periocular steroid injections may be useful after antibiotic treatment is completed for non-resolving vitreous opacities or secondary inflammatory complications such as macular edema.

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