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REVIEW

Ocular syphilis

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Abstract

Syphilis is a sexually transmitted systemic disease caused by the spirochete *Treponema pallidum*. If left untreated, syphilis progresses in four stages: Primary, secondary, latent, and tertiary. Since the turn of the 20th century, the global prevalence of syphilis has sharply increased. Syphilis and human immunodeficiency virus (HIV) coinfection are common because they share similar transmission routes. Ocular syphilis (OcS) is a rare syphilis complication, but its prevalence has recently increased as a result of the rise in syphilis cases. OcS may occur at any stage of syphilis. However, it may not always be accompanied by systemic findings. In such cases, ocular involvement may be the disease's first and only manifestation. OcS can affect any structure of the eye, yet the most common manifestations are posterior uveitis and panuveitis. Due to the variety of clinical manifestations, the disease is known as "the great imitator." As a result, syphilis serology is advised for any patient with unknown intraocular inflammation. Although clinical signs can be indicative of OcS, it is diagnosed using laboratory tests. Multimodal ocular imaging is required for differential diagnosis, treatment, and follow-up. It is highly recommended that patients with suspected or confirmed syphilis be tested for HIV infection. OcS is treated just like neurosyphilis with systemic penicillin. If OcS is treated promptly and effectively, a good visual prognosis is possible; otherwise, it may lead to permanent blindness.

Keywords: Diagnosis; manifestations; ocular syphilis; syphilis serology; treatment; uveitis.

Syphilis is a contagious disease caused by the spirochete *Treponema pallidum*. Syphilis is mostly acquired by sexual contact, but it can also be transmitted through direct contact with an infectious oral or anal lesion or a skin scrape. Transplacental transmission during pregnancy results in congenital syphilis. If acquired syphilis is not treated early on, it becomes chronic and may possibly cause serious cardiovascular and neurological morbidity.[1]

Ocular syphilis (OcS) is a rare manifestation of the disease that may occur at any stage. It can affect all eye structures, resulting in uveitis, optic neuropathy, retinal vasculitis, interstitial keratitis, episcleritis or scleritis, and syphilitic conjunctivitis.[1–3] The most common presentation is uveitis. The disease is known as "the great imitator" because of the various clinical manifestations.

Epidemiology and Demographics

Syphilis was first documented in the 15th century in Italy.[2] The discovery of penicillin and the subsequent extensive use of antibiotics marked a turning point in the fight

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against syphilis, helping to reduce the disease's spread in the late 19th century. The Centers for Disease Control and Prevention (CDC) reported a more than 70% rise in syphilis infections in 2019 compared to 2015, with men accounting for the majority of cases (83.1%).[4] The main factors contributing to this rise were an increase in multiple sexual partners, unprotected sex, and human immunodeficiency virus (HIV) coinfection, particularly among men.[1–6]

The incidence of OcS was reported to be 0.3 cases per 1,000,000 in a prospective case series.[7] Many recent reports have shown a rise in OcS, which is consistent with the increase in syphilis cases.[7–12] According to Furtado et al.,[5] the incidence of OcS rose from <1 per year between 2000 and 2012 to 8.33 per year between 2013 and 2015. OcS is more common in males than females with the proportion of male cases recently reaching 90%.[5,7,11] The age range of OcS patients is usually between 20 and 90, with the majority of cases diagnosed in middle age.[5–11]

Natural History of Untreated Syphilis

The symptoms of syphilis differ depending on the stage of the disease. Late-stage findings are becoming less common nowadays. This is mostly due to increased disease awareness and effective antibiotic treatment.

Primary Syphilis

Primary syphilis begins with a painless sore known as a chancre that appears at the inoculation site and contains many infectious spirochetes. This lesion develops 3–6 weeks after infection.[12,13] Lymphadenopathy around the lesion is common. If left untreated, this lesion will heal on its own in 4–6 weeks, but the infection will progress to the secondary stage.[14]

Secondary Syphilis

Secondary syphilis develops 4–10 weeks after the initial infection.[13,14] Red-brown rashes appear most commonly on the palms and/or soles of the feet, but a generalized body rash may occur. Other possible symptoms are fever, swollen lymph nodes, sore throat, weakness, focal alopecia, weight loss, and muscle pain.[12–15] OcS may appear in both the primary and secondary stages.[2,4] In the absence of proper treatment, syphilis progresses, just as it does in the early stage.

Latent Syphilis

In the latent stage, although the disease has no clinical signs, it shows serological positivity.[13–17] This stage is divided into early (≤1 year) and late (>1 year) stages.[16] Syphilis' contagiousness decreases, especially in the late stage.

Tertiary Syphilis

Tertiary syphilis can develop decades after the initial infection. At this stage, the disease is noncontagious. Tertiary syphilis is classified into three categories: Cardiovascular (aortic aneurysm or valvulopathy), neuro (auricular, meningovascular, parenchymatous, or asymptomatic), and gummatous (benign tertiary syphilis with nodules/plaques or ulcers).[12–14] This stage may lead to significant morbidity and mortality.

Clinical Manifestations of OcS

Syphilis can affect all ocular structures (Table 1).[1,2,4] Hence, depending on the affected part of the eye, the symptoms range from mild conjunctival hyperemia to severe vision loss. Patients experiencing ocular symptoms should have a complete ophthalmic examination. Because OcS can be isolated or associated with neurosyphilis, an examination of the cranial nerves that control eye movements is also required.[9,18] Uveitis is the most common ocular manifestation.[5,8,10,11,19,20]

Table 1. Clinical presentations of ocular syphilis

Eyelid	Chancre, gumma, madarosis
Orbit	Periostitis, dacryoadenitis
Conjunctiva	Conjunctivitis, chancre, gumma
Sclera	Episcleritis, Scleritis
Cornea	Interstitial keratitis
Uvea	Granulomatous or non-granulomatous uveitis
	Iridocyclitis, vascularized iris nodules (roseola)
	Intermediate uveitis
	Posterior uveitis (chorioretinitis, placoid chorioretinitis)
	Panuveitis
Vitreous	Vitritis, snowball
Retina	Retinitis, necrotizing retinitis, retinal vasculitis, neuroretinitis, serous retinal detachment
Optic disk	Disk edema, anterior or retrobulbar optic neuritis, papilledema, gumma, optic atrophy
Pupillomotor pathway	Argyll Robertson pupil
Extraocular muscles	Various cranial nerve palsies (3th, 4th, and 6th)
Others	Ocular hypertension, uveitic glaucoma

Syphilitic Uveitis

Syphilitic uveitis accounts for <2% of all uveitis cases.[1,2,11,20,21] Some studies found that syphilitic uveitis develops most frequently in the secondary stage,[2,10,22] whereas others noted that it develops most frequently in the late latent and tertiary stages.[1,9,20] We currently know that syphilitic uveitis can occur at any stage. Syphilitic uveitis can manifest as anterior, intermediate, posterior, or panuveitis.[23] Although it may rarely be isolated, anterior uveitis is usually associated with posterior segment inflammation.[10,20] Syphilis-related anterior uveitis can be granulomatous or non-granulomatous.[1,2,4] There may also be other ocular conditions, such as posterior synechia, iris atrophy, vascularized iris nodules (roseola), and lens dislocation in the anterior segment.[2,24]

The most common subtypes of syphilitic uveitis are posterior uveitis or panuveitis.[19,20,22] Non-specific manifestations of posterior segment involvement include vitreous inflammation, chorioretinitis, retinal vasculitis, serous retinal detachment (RD), necrotizing retinitis, optic neuritis, and disk edema.[24–27] Although syphilis can mimic any posterior segment involvement, it has some distinct clinical manifestations.[24–26]

Syphilitic Superficial and Inner Retinal Precipitates

Superficial and inner retinal precipitations are the first distinguishing manifestation of syphilitic posterior uveitis.[24,25] Superficial or pre-retinal precipitates are multiple small, round, creamy-white inflammatory deposits that can form in areas of active retinitis or retinochoroiditis (Fig. 1a and d). These precipitates may migrate across the retina in the presence of infection and can disappear quickly with treatment.[25–28] Fu et al.[26] described creamy-yellow superficial retinal precipitates and their clinical features in eight OcS patients, emphasizing that precipitates overlying areas of retinitis are highly suggestive of syphilis.[26] These precipitates can be superficial or inner retinal, and this clinical picture is known as syphilitic punctate inner retinitis, a rare OcS manifestation.

Punctate inner retinitis could be associated with retinal vasculitis.[29,30] Pre-retinal and inner retinal precipitates appear as dense hyperreflective dots on optical coherence tomography (OCT). OCT is critical for both differential diagnosis and follow-up of these lesions. According to Schalen et al.,[31] white lesions in the retina show intense inflammatory activity on OCT, and punctate inner retinitis causes retinal thinning and severe damage to the retinal pigment epithelium (RPE).[31]

Syphilitic Retinochoroiditis

Retinochoroiditis lesions, confluent or placoid, are another distinguishing manifestation of syphilitic posterior uveitis.[25,26] Confluent retinochoroiditis may occur in any area of the fundus, but most commonly in the posterior pole and mid-periphery as large creamy, white, triangular areas (Fig. 1a-d).[1,25,32] These lesions are less bright than those in herpetic necrotizing retinitis and toxoplasma retinochoroiditis, so they are described as having a typical "ground-glass" appearance.[1,24–27] Lesions of retinochoroiditis are often associated with the aforementioned superficial and inner retinal precipitates (Fig. 1a-d). These lesions may also include vitritis, retinal vasculitis, serous RD, and optic disk edema.[24,26,32] OCT may show RPE deformations which tend to heal gradually.[25,26]

Placoid Syphilitic Retinochoroiditis

It is another type of manifestation and was first described

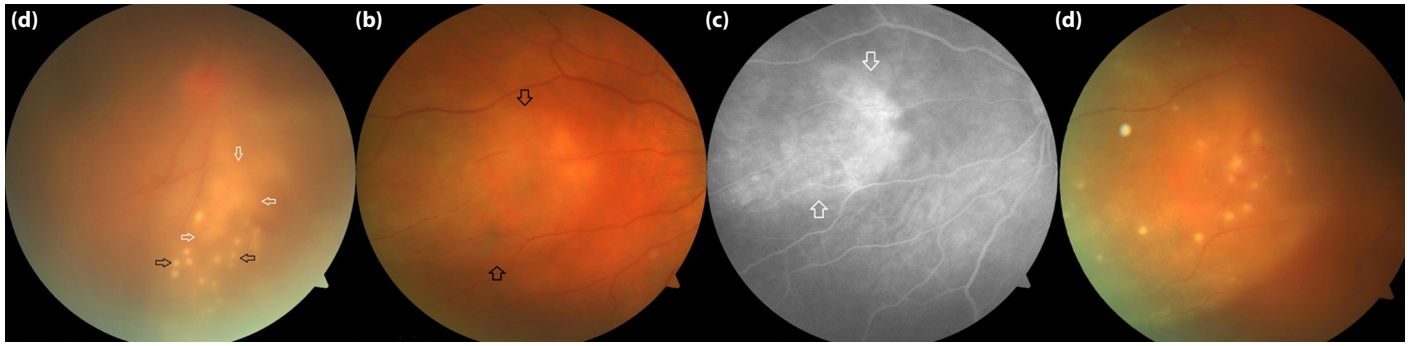

Fig. 1. **(a)** Color fundus photography showing multiple small, round, and creamy-white superficial pre-retinal precipitates (black arrow). These inflammatory deposits are observed together with a ground-glass appearance area of retinochoroiditis (white arrow). Posterior segment involvement is accompanied by intense vitreous inflammation with vitreous haze and vitritis, as well as optic disk hyperemia. **(b)** In a different patient, color fundus photography showing an area of confluent retinochoroiditis in ground-glass apperance (black arrow). **(c)** Fluorescein angiography showing progressive hyperfluorescence in the area corresponding to the lesion in the late period (white arrow). **(d)** A few days later, superficial retinal infiltrates developed on retinochoroiditis area while the patient was in the examination process.

by Souza et al.[32] Gass et al.[33] later observed similar findings in six OcS patients and coined the term "acute syphilitic posterior placoid chorioretinitis" (ASPPC) for this clinical presentation. ASPPC is an intraocular inflammation that affects the outer retina and inner choroid and is characterized by large yellowish oval or circular lesions in the macular and juxtapapillary areas (Fig. 2a).[22,34,35] Fluorescein angiography (FA) and indocyanine green angiography (ICG) findings of ASPPC have been described in the literature.[22,24,34,35] In the early period, FA typically shows central hypofluorescence in the area corresponding to the lesion. Hypofluorescent foci, exhibiting leopard spot patterns with progressive hyperfluorescence in the late period, appear in the lesion (Fig. 2b).[22,35] Other FA findings in the late period are optic disk leakage and hyperfluorescence (Fig. 2b). On ICG, ASPPC lesions exhibit varying degrees of hypofluorescence in both the early and late phases.[22,35]

ICG hypofluorescence may be caused by choroidal fluorescence blockage and disruption of choriocapillary flow.[22,35] Nodular elevations and irregular hyper-reflectivity at the junction of photoreceptors and RPE, as well as segmental distortions in the ellipsoid band and the external limiting membrane, are pathognomonic spectral domain-OCT (SD-OCT features of ASPPC (Fig. 2c).[22,25,27,35–37] Another SD-OCT finding is punctate choroidal hyper-reflectivity.[35] The area corresponding to the lesion is hyperautofluorescent on fundus autofluorescence, often in a punctate pattern (Fig. 2d).[25,34] Systemic antibiotic treatment results in anatomical healing of the outer retinal layers, reorganization of the ellipsoid band, disappearance of hyperreflective spots in the choroid, and eventually, improvement in visual acuity.[35]

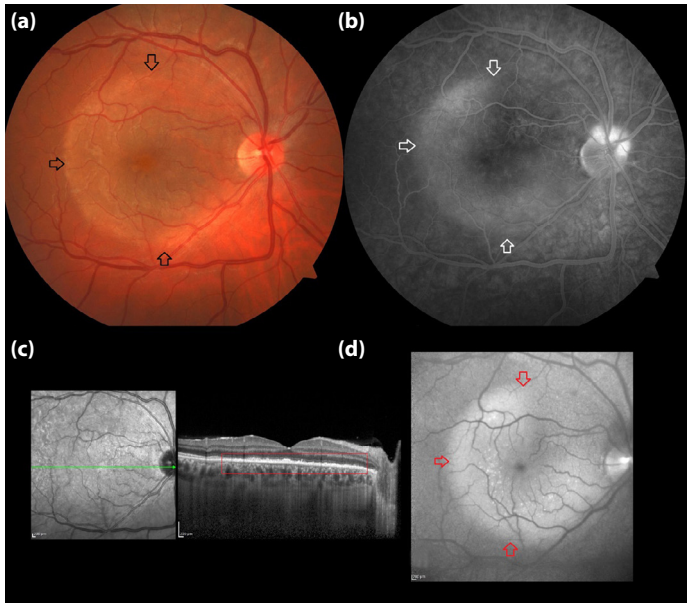

Fig. 2. Multimodal imaging of an OcS patient with syphilitic posterior placoid chorioretinitis (ASPPC). **(a)** Color fundus photography showing a large yellowish circular ASPPC lesion in the macula (black arrow). **(b)** Fluorescein angiography showing hyperfluorescence in the area corresponding to the lesion (white arrow) and optic disk hyperfluorescence in the late period. **(c)** Spectral domain-optical coherence tomography showing irregular hyper-reflectivity at the junction of the photoreceptors and retinal pigment epithelium, as well as segmental distortions in the ellipsoid band and the external limiting membrane (red rectangle). **(d)** Fundus autofluorescence showing hyperautofluorescence with punctate pattern in the area of the APPSCC lesion (red arrow).

Other Presentations of Syphilitic Posterior Uveitis

Syphilitic multifocal retinitis has been described as a condition that occurs in cases of undiagnosed syphilis treated with corticosteroids before anti-treponemal antibiotic therapy (Fig. 3).[25,28] This condition is different than syphilitic punctate inner retinitis and manifests as multiple foci of retinitis without superficial retinal infiltrates or confluent retinochoroiditis.[28]

Syphilis can cause necrotizing retinitis, which can mimic acute retinal necrosis (ARN).[38] Antibiotics are effective in treating *syphilitic necrotizing retinitis*, and it has fewer post-treatment complications than ARN.[38–40]

Syphilitic vasculitis can affect the retinal arteries, arterioles, capillaries, and veins.[41] Occlusive retinal vasculitis, branch retinal vein occlusion, and frosted branch angiitis are some clinical manifestations of retinal vasculitis.[41–43]

Syphilitic retinitis or chorioretinitis may present with *exudative* RD.[34,39,44] OcS patients who have serous RD at the

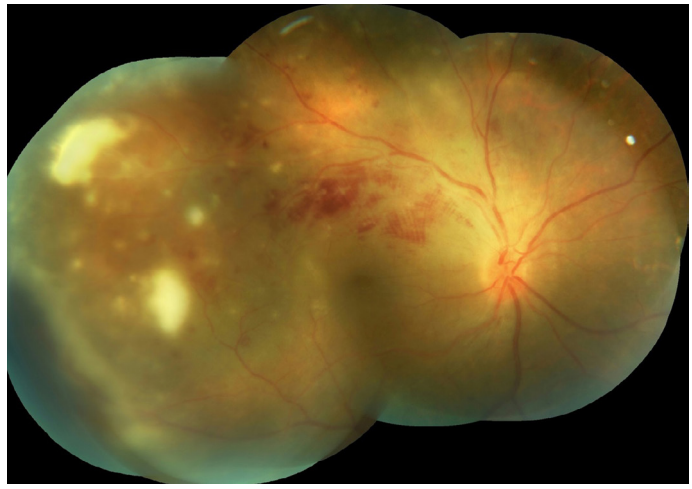

Fig. 3. Color fundus photography of a syphilitic multifocal retinitis case who is treated with corticosteroids monotherapy before anti-treponemal antibiotic therapy. Optic disk edema, retinal hemorrhages, and retinal vasculitis areas accompany multifocal retinitis foci.

time of presentation may be misdiagnosed as Vogt-Koyanagi-Harada disease, posterior scleritis, or central serous chorioretinopathy.[24,45,46] In differential diagnosis, multimodal imaging is extremely effective.[25,27] Syphilis-related serous RD responds favorably to systemic antibiotic therapy.

There have been recent reports of *syphilitic outer retinitis* (SOR) cases with symptoms similar to acute zonal occult outer retinopathy (AZOOR).[47–49] SOR, like AZOOR, is characterized by photoreceptor inner segment/outer segment damage and also disruption of the outer retina.[47–49] SD-OCT findings of SOR may resemble those of clinically more prominent ASPPC. In contrast to ASPPC, FA findings are typically normal and accompanying non-specific findings have been reported.[47–49] Lima et al.[48] discovered macular hypofluorescence in a patient with SOR during the late stages of ICG. SOR is characterized by mottled hyperautofluorescence in the affected retinal region.[47–49] Other inflammatory multifocal chorioretinopathies, such as multiple evanescent white dot syndrome, can be mimicked by SOR (Fig. 4).[50,51] After systemic antibiotic therapy, all reported cases showed reorganization and healing of the outer retina.[47–49]

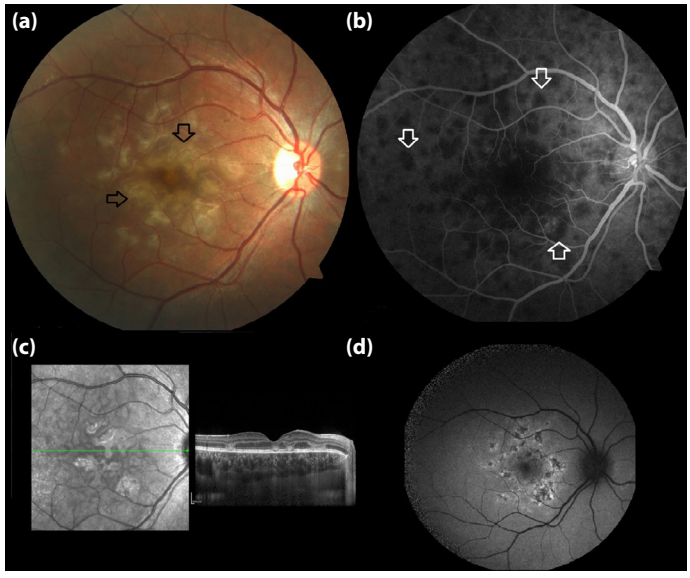

Fig. 4. Multimodal imaging of a case with syphilitic inflammatory multifocal chorioretinopathy presenting with findings similar to bilateral posterior multifocal placoid pigment epitheliopathy (AMPPE) (right eye), **(a)** multifocal white lesions in the macula (black arrow). **(b)** Fluorescein angiography showing numerous hypofluorescent spots in the posterior pole in the early phase (white arrow). **(c)** Spectral domain-optical coherence tomography showing disruption of the outer retinal layers and prominent focal hyperreflective lesions in the outer nuclear layer. **(d)** Fundus autofluorescence showing hypoautofluorescence in the center of the lesions and hyperautofluorescence in around.

Optic Disk Involvement

The optic disk is affected in a significant proportion of OcS patients.[10,20,52,53] Optic disk involvement includes inflammatory disk edema, papillitis, anterior or retrobulbar optic neuritis, neuroretinitis, papilledema, and optic disk gumma in one or both eyes.[1,53] The clinical presentation of syphilitic optic neuritis is similar to that of other types of optic neuritis (Fig. 5). Poor optic nerve function, relative afferent pupillary defects, and impaired vision and/or color vision are all clinical manifestations of optic neuritis.[24,41]

Syphilitic Scleritis and Episcleritis

Scleritis and episcleritis are rare manifestations of OcS, but they should be considered in the differential diagnosis of refractory cases.[54–57] Anterior nodular scleritis is the most common presentation.[54,55] Diffuse scleritis and, in rare cases, necrotizing scleritis can occur.[54,56] Syphilis-associated scleritis and episcleritis respond quickly to antibiotic therapy.[56,57]

Syphilitic Interstitial Keratitis

Syphilis-related corneal involvement presents as interstitial keratitis.[2] Interstitial keratitis is an autoimmune-mediated stromal inflammation of the cornea that can result in permanent scarring. It is believed to be caused by a strong immune response to treponemal antigens in syphilis.[58,59] Syphilitic interstitial keratitis is a late manifestation of con-

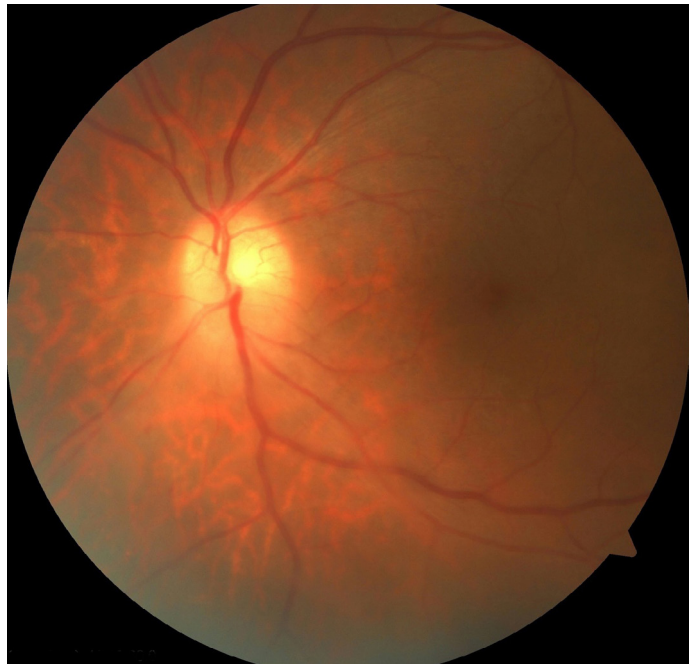

Fig. 5. Color fundus photography of an OcS patient with optic neuritis showing disk hyperemia and disk edema.

genital syphilis that typically occurs during childhood, but rarely in adulthood.[58] In treatment, it has been reported that in addition to use of systemic antibiotics and topical steroids, topical and systemic immunosuppressive drugs can successfully control inflammation and prevent recurrence.[41,58,59]

Syphilitic Conjunctivitis

Syphilitic conjunctivitis can be papillary or granulomatous, and it is frequently associated with conjunctival hyperemia and chemosis. Although uncommon, chancres and gumma lesions can appear in the conjunctiva.

Syphilis may also involve the eyelids (blepharitis, chancre of the eyelid, rash, madarosis) and the orbit (gumma of an extraocular muscle, dacryoadenitis, periostitis) in rare cases.[2,41]

OcS in Patients with HIV Infection

HIV coinfection is common in OcS patients. As a matter of fact, OcS symptoms may be the first signs of HIV infection. Eandi et al.[22] found a 56% HIV coinfection rate in OcS patients. Amaratunge et al.[37] reported that HIV was present in 66% of patients with syphilitic uveitis. As a result, all patients with suspected or confirmed syphilis should be tested for HIV.

Many recent studies have investigated the impact of HIV status on the presentation, treatment response, and prognosis of OcS due to an increase in OcS-HIV coinfection cases.[7,8,19,22,37,60] HIV-positive patients with OcS are typically males and younger than HIV-negative patients.[2,7,35,60] Although some studies have found more severe ocular inflammation and higher panuveitis rates in HIV-positive syphilitic uveitis patients, others reported contradictory results.[7,8,61,19,37,60] OcS can manifest with unusual clinical findings, particularly in patients with low CD4 cell counts (<100 cells/m^3).[61] Despite the differences in presentation patterns, most HIV status studies have reported that both HIV-positive and HIV-negative patients with OcS have similar visual prognoses.[7,19,52,60] However, it is unclear whether a specific subtype of uveitis is more common in HIV-positive patients.[52]

HIV-positive and HIV-negative patients should be treated according to similar recommendations.[37,52,61] However, HIV-positive patients should be closely monitored as they are more likely to relapse than HIV-negative patients.[37,52,61] In addition, while highly active antiretroviral therapy does not prevent OcS, it can improve treatment efficacy by promoting immune recovery.[62]

Laboratory Investigations for OcS

Despite the fact that clinical clues are very helpful, OcS is diagnosed using laboratory tests.[20,24] An international group of uveitis specialists recommends that patients presenting with intraocular inflammation of unknown origin be tested for syphilis[20] because syphilis is known to mimic any presentation of uveitis.

T. pallidum is difficult to cultivate in culture. However, there are numerous direct and indirect methods for detecting the spirochete.[62] Dark field microscopy, direct fluorescent antibody stains, polymerase chain reaction (PCR), and immunohistochemistry are all direct methods that are recommended for use in both primary and secondary syphilis.[62–64] T. pallidum-specific DNA sequences are detected using PCR tests. PCR was used to successfully detect spirochetes in the vitreous fluid of OcS patients.[65] However, PCR is currently used in only a few laboratories.[62] Because of their ease of use, serological tests are commonly used in indirect methods. Serological tests are classified as non-treponemal or treponemal.[2,63]

Non-treponemal Tests

Antibodies against membrane phospholipids such as cardiolipin and lecithin are detected in non-treponemal tests.[66] *T. pallidum* reacts with antigens found in normal mammalian tissues that are not specific to syphilis.[62] The rapid plasma reagin (RPR) and venereal disease research laboratory (VDRL) tests are the most commonly used non-treponemal tests.[63] They are used to detect syphilis activity and assess treatment response.[63,67] Antibody titers correlate with syphilis activity.[63,66] Titers that rise during active disease are expected to fall as the disease is treated.

During early primary and late syphilis, non-treponemal tests have lower sensitivity and their results may be non-reactive at up to 30%.[62,66] Another issue is the possibility of false-negative and false-positive results.[62,63,66] False-positive results can occur as a result of cross-reactions between different infections (viral, bacterial, and parasitic), connective tissue diseases, in pregnancy, intravenous drug addiction, and also in elderly patients. Because of the prozone phenomenon, false-negative results may be obtained due to HIV infection and pregnancy.

Treponemal Tests

Treponemal tests detect serum antibodies against treponemal antigens with high sensitivity and specificity.[62,66] They are, however, more expensive and technically difficult than non-treponemal tests.[66] Moreover, as with

non-treponemal tests, false positivity can occur in infections, connective tissue diseases, and pregnancy.[62,66]

T. pallidum hemagglutination assays (TPHAs), fluorescent treponemal antibody absorption, chemiluminescence immunoassays (CLIAs), enzyme immunoassays (EIAs), and rapid tests are all examples of treponemal tests.[62,63] Regardless of treatment, these tests remain positive throughout the patient's life. As a result, they are used in to confirm reactivity of non-treponemal tests.[63] They are, however, inappropriate for monitoring the treatment because they do not correlate with disease activity.[66]

Serological Diagnosis of OcS

Three serological test algorithms are used for OcS diagnosis.[2,25,63] The first is the traditional test algorithm, which uses a non-treponemal test for screening. A treponemal test is performed if a reactive result is obtained. A false-negative result of the non-treponemal test may cause a delay in diagnosis, especially in the early stages. Hence, if the non-treponemal test yields a negative result, it should be repeated 2–3 weeks later, or alternatively the non-treponemal and treponemal tests can be performed concurrently.[2,63]

The second algorithm is the reverse sequence algorithm recommended by CDC.[67,68] A treponemal test is used for screening (EIA or CLIA).[67] If the test yields a reactive result, a non-treponemal test (usually VDRL or RPR) is performed. If the non-treponemal test is negative, a second treponemal test (typically TPHA) is administered.[68] The patient is diagnosed with syphilis if the second treponemal test is positive. A negative second treponemal test result indicates a false-positive first treponemal test result.[66–68] This algorithm has recently gained popularity because EIA tests are less expensive and easier to administer than other treponemal tests.

The third algorithm is recommended by the European Centre for Disease Prevention and Control.[14] For syphilis screening, a treponemal test is used. If it is reactive, another treponemal test is done to confirm the result. A non-treponemal test is used to evaluate disease activation and treatment response rather than to confirm the result.[69]

Recent research has shown that treponemal and non-treponemal tests performed on OcS patients' aqueous humor and vitreous samples are useful for the diagnosis of syphilis[70,71] and have high sensitivity and specificity in syphilitic uveitis.[72] However, larger sample studies are required to confirm these findings.

Cerebrospinal Fluid (CSF) Evaluation

A CSF examination is required for patients with clinical manifestations of neurosyphilis.[1,68] Patients with isolated ocular involvement and reactive syphilis serology who do not have cranial nerve involvement or other neurological findings do not require a pretreatment CSF examination.[68] Non-treponemal and treponemal tests, cell counts, and protein evaluations are all part of a CSF examination.

Treatment of OcS

Antibiotics

According to CDC recommendations (Sexually Transmitted Infection Treatment Guidelines, 2021), the treatment protocol for OcS is the same as that for neurosyphilis.[68] Treatment with 18–24 million units of aqueous crystalline penicillin G administered intravenously every 4 h or through continuous infusion for 10–14 days is the first choice. An alternative regimen of 2.4 million units of penicillin G procaine administered intramuscularly once daily, plus 500 mg of probenecid orally 4 times daily for 10–14 days may also be used.

Because the treatment period for neurosyphilis is shorter than that for latent syphilis, 2.4 million units of benzathine penicillin administered intramuscularly once a week, for 1–3 weeks, are recommended after 14 days of primary treatment. For patients who are allergic to penicillin, 1–2 g of ceftriaxone (intravenously or intramuscularly) is recommended daily for 10–14 days. Penicillin desensitization is advised for patients who have a proven penicillin allergy or when penicillin is required, for example, during pregnancy.[68]

Doxycycline has been shown to be especially effective in the treatment of early syphilis and is also recommended as a penicillin substitute.[73,74] Doxycycline was used in the previous studies at daily doses of 200 mg, for periods ranging from 14 to 30 days.[73–75]

Corticosteroids

Topical and systemic corticosteroids are used as adjuvant agents in OcS treatment because of their anti-inflammatory properties.[37,41] Scleritis, interstitial keratitis, and anterior uveitis can all be effectively treated with topical steroids.[56–59] Systemic steroids are advised in the case of posterior uveitis and optic nerve involvement.[4,25] In the treatment of OcS, patients with posterior uveitis and cystoid macular edema, periocular or intravitreal steroids can also be used.[76,77] As in other cases of infectious uveitis, the use of systemic or periocular corticosteroids in the absence of antibiotics may result in a more severe course of the infection, which complicates treatment and leads to more serious

complications.[76] As a result, corticosteroids should always be used in conjunction with antibiotics.

Systemic steroids are also used to treat syphilis to avoid a Jarisch-Herxheimer reaction, which may occur within the first 24 h of antibiotic treatment.[1] This is believed to be a systemic hypersensitivity reaction accompanied by increased endotoxin and cytokine secretion.[25,41] Jarisch-Herxheimer reaction appears as a flu-like illness with symptoms such as fever, malaise, myalgia, and headache, and can be accompanied by the progression of ocular manifestations and further vision impairment.[25]

Immunosupressive Drugs

After the infection is effectively treated, some OcS patients (especially with syphilitic uveitis) receive immunosuppressive drugs alongside oral corticosteroids to suppress intraocular inflammation.[19,60,78–80] Methotrexate has been proven to play an adjunctive role in the control of intraocular inflammation and macular edema and in the prevention of recurrence in patients with syphilitic uveitis.[79,80] Moradi et al.[60] found that although OcS patients receiving immunosuppressive therapy had lower CME rates, their complication rates and visual prognoses were similar to those not receiving immunosuppressive therapy. However, further studies are needed to clarify the effectiveness of steroid and/or immunosuppressive drug use for OcS patients.[19,20,60]

Evaluation of the Treatment Response

Non-treponemal tests are repeated in OcS patients 3, 6, and 12 months after treatment to assess treatment response and detect reinfection.[63] CSF should be re-evaluated 6 months after treatment in patients with CSF abnormalities.[68] A 4-fold decrease in non-treponemal test titers is expected after successful treatment.[67] Although the time period varies depending on the stage of the disease (between 2 and 5 years), non-treponemal tests eventually become nonreactive.[66] HIV coinfection, on the other hand, may postpone the decline in test titers.[66] Non-treponemal antibodies may remain reactive at low titers in some patients, particularly in those treated in the late stages for a long time, and sometimes for life (serofast reaction).[63] In addition, non-treponemal tests may be non-reactive in untreated late cases.[66]

Ocular Complications and Prognosis

Several ocular complications including cataract, ocular hypertension, posterior synechia, CME, chorioretinal scars, optic disk atrophy, and RD may occur in the course of OcS.[5,52,60] The prognosis for OcS patients who are treated promptly and effectively is promising, and the majority show visual improvement.[1,7,19] Conversely, delayed treatment and posterior segment involvement, particularly macular involvement, are associated with a poor visual prognosis and may result in permanent blindness.[7,19,28]

Conclusion

OcS is increasing every year due to the rise in syphilis cases. Sometimes, ocular involvement is the first and only symptom of the disease and the lack of systemic findings can be misleading. Syphilis, also known as the great imitator, may have very different clinical manifestations. Therefore, the clinical clues, ocular multimodal imaging, and the clinician's experience are essential for syphilis diagnosis. Serological tests used in diagnosis and monitoring of treatment must be properly interpreted. Early detection and treatment are crucial for the best ocular outcomes.

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