



Ocular Syphilis: Diagnostic Challenges and Current Management Strategies

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Abstract. Ocular syphilis is an important and potentially sight-threatening manifestation of *T. pallidum* infection, capable of occurring at any stage of the disease. Known as “The Great Imitator,” it presents with highly variable and non-specific clinical features that frequently resemble autoimmune or other infectious ocular conditions, leading to delayed diagnosis and potential mismanagement. The pathophysiology involves early hematogenous dissemination, endothelial injury, and immune-mediated inflammation, often overlapping with mechanisms seen in neurosyphilis. Ocular involvement may affect virtually all eye structures, with uveitis being the most common presentation, alongside manifestations such as retinitis, vasculitis, optic neuritis, and interstitial keratitis. Diagnosis is made through an increased index of clinical suspicion, based on the results of treponemal and nontreponemal tests. Imaging studies like optical coherence tomography and fluorescein angiography help assess the condition but are not definitive. Management follows neurosyphilis treatment protocols, with intravenous penicillin as the cornerstone of therapy and adjunctive corticosteroids or immunosuppressive agents in selected cases. Given the global resurgence of syphilis and increasing reports of ocular involvement, early recognition and prompt treatment are essential to prevent irreversible visual impairment.

Keywords: Diagnosis of Ocular Syphilis; HIV Co-Infection; Management of Ocular Syphilis; Neurosyphilis; Ocular Syphilis.

1. INTRODUCTION

Syphilis is a systemic infection resulting from *Treponema pallidum* infection, the transmission mode is mainly through sexual intercourse. Because its clinical features can resemble many other diseases, syphilis has long been known as “The Great Imitator”. The infection may affect almost any organ system, progress through symptomatic and latent phases, relapse over time, and may be passed on to the unborn baby vertically (Workowski et al., 2021). Ocular syphilis is an important and potentially sight-threatening manifestation of *T. pallidum* infection. It can occur at any stage of syphilis, even when systemic symptoms are absent or subtle (Workowski et al., 2021). Although effective antibiotic treatment is available, diagnosis is often delayed because ocular syphilis may present with diverse and non-specific signs that overlap with other inflammatory or infectious eye diseases (Furtado et al., 2022; Mathew et al., 2022). Recent surveillance data show a re-emergence of syphilis in many regions worldwide, with incidence increasing to levels not seen for decades. In parallel, more cases of ocular involvement have been reported, including regional clusters of ocular syphilis (Oliver et al., 2016). This trend emphasizes the need for clinicians to remain alert to ocular syphilis as a possible diagnosis, especially in patients presenting with unexplained ocular inflammation. The clinical presentation of ocular syphilis is highly variable and may mimic autoimmune uveitis, other inflammatory eye disorders, or infectious conditions. As a result, some patients

may initially be misdiagnosed and treated with corticosteroids or other immunosuppressive agents, which can worsen the underlying infection and increase the risk of visual impairment (Mathew et al., 2022; Tuddenham & Zenilman, 2022). Therefore, an accurate diagnosis needs an index of suspicion, proper clinical evaluation, and appropriate interpretation of serologic testing (Workowski et al., 2021; Park et al., 2020). Given its broad clinical spectrum and the continuing development of diagnostic and imaging techniques, ocular syphilis remains highly relevant in routine ophthalmologic and dermatovenerologic practice. This review summarizes the current understanding of ocular syphilis, including its pathophysiology, clinical manifestations, diagnostic challenges, imaging characteristics, and treatment strategies, with emphasis on aspects that are most useful for everyday clinical decision-making.

2. RESEARCH METHOD

This article was conducted as a narrative literature review to provide an overview of ocular syphilis, with particular emphasis on its pathophysiology, clinical manifestations, diagnostic challenges, imaging findings, and current management strategies. Relevant scientific literature concerning ocular syphilis and its association with neurosyphilis and HIV co-infection was identified and reviewed. The literature included peer-reviewed research articles, review articles, clinical guidelines, and other relevant scientific publications addressing the clinical features, pathophysiology, diagnostic evaluation, serologic testing, cerebrospinal fluid examination, ocular imaging, and treatment of ocular syphilis. Publications were selected based on their relevance to the objectives and scope of this review. Relevant information from the selected literature was reviewed and synthesized narratively. The findings were organized into five main topics: pathophysiology and spectrum of ocular involvement, clinical presentation, diagnostic approach and common pitfalls, imaging and ancillary investigations, and management of ocular syphilis. Particular attention was given to evidence relevant to early diagnosis, appropriate interpretation of diagnostic tests, and current treatment strategies aimed at preventing permanent visual impairment.

3. RESULTS AND DISCUSSION

Pathophysiology and Spectrum of Ocular Involvement

Mechanisms of Ocular Invasion

The development of ocular syphilis is strongly linked to the systemic spread of *Treponema pallidum* after the initial infection. Once the organism enters the body, it can disseminate rapidly through the bloodstream and may invade the central nervous system early

in the disease course, even before neurological or systemic symptoms appear. This early neuroinvasion may allow the spirochete to remain within neural and ocular tissues, creating the basis for ocular involvement at different stages of syphilis (Hook & Marra, 2020; Gonzalez et al., 2019). One important feature of *T. pallidum* is its tendency to interact with vascular endothelial cells. This interaction may damage the endothelium, stimulate inflammation around blood vessels, and disturb microvascular flow in ocular tissues, particularly the retina and choroid. Such vascular injury is thought to contribute to posterior segment involvement, including retinal vasculitis, chorioretinitis, and other inflammatory changes commonly described in ocular syphilis (Hook & Marra, 2020; Gonzalez et al., 2019; Marra, 2022). Histopathological and clinical evidence suggests that endothelial injury with perivascular inflammatory cell infiltration is a central process in ocular syphilis (Hook & Marra, 2020). When the vascular endothelium is damaged, the blood–ocular barrier may become disrupted, allowing inflammatory cells and mediators to enter intraocular structures. This mechanism can lead to a broad range of manifestations, such as anterior chamber inflammation, vitritis, chorioretinitis, and optic nerve involvement (Gonzalez et al., 2019; Marra, 2022). The diverse clinical appearance of ocular syphilis likely results from both direct treponemal invasion and the host inflammatory response. The presence of the organism within ocular tissues may cause local tissue damage, while the immune reaction against the infection can further intensify inflammation and structural injury. The combination of these processes helps explain why ocular syphilis may present in many different and sometimes unpredictable ways (Hook & Marra, 2020; Gonzalez et al., 2019; Marra, 2022).

Immunologic and Inflammatory Response

In addition to direct infection, immune-mediated mechanisms play an important role in determining the severity of ocular damage. Both humoral and cell-mediated immune responses may contribute to intraocular inflammation. Delayed-type hypersensitivity reactions against treponemal antigens may also maintain inflammation, even when active bacterial replication has decreased (Gonzalez et al., 2019; Marra, 2022). HIV co-infection can further influence the clinical course of ocular syphilis. Impaired cellular immunity may allow greater spirochetal proliferation and may be associated with atypical or more severe ocular presentations. In some patients, immune recovery after antiretroviral therapy may also intensify inflammatory responses. These interactions show that ocular damage in syphilis is not caused by the organism alone, but also by the patient's immune status and inflammatory response (Gonzalez et al., 2019; Marra, 2022; Queiroz et al., 2020).

Relationship to Neurosyphilis

Ocular syphilis is often considered closely related to neurosyphilis because the eye and central nervous system share important anatomical and pathological connections. Inflammation involving the optic nerve, retina, or uveal tract may occur with neurological symptoms, but it may also appear without obvious nervous system involvement (Hook & Marra, 2020; Marra, 2022; Queiroz et al., 2020). This overlap supports the need for systemic evaluation and treatment approaches that follow neurosyphilis management principles (Hook & Marra, 2020; Marra, 2022). Overall, ocular syphilis develops through a complex interaction between vascular injury, immune-mediated inflammation, direct microbial invasion, and possible neurologic involvement. These mechanisms provide a biological explanation for the wide clinical spectrum of the disease and highlight why early recognition and appropriate management are essential (Hook & Marra, 2020; Gonzalez et al., 2019; Marra, 2022; Queiroz et al., 2020).

Clinical Presentation: Ocular Syphilis as a Masquerader

Stages of Syphilis

Acquired Syphilis, The spirochete bacterium can directly invade CNS via blood vessels and the meninges. This invasion is responsible for various neurological and neuro-ophthalmic manifestations. Syphilis is divided into primary, secondary, latent, and tertiary forms. Notably, neurosyphilis and ocular syphilis can develop at all stages of the disease; however, they occur more often in the secondary stage (Park et al., 2020). Primary Syphilis. Primary Syphilis arises following a latency period of 10 to 90 days (average being 21 days) at the inoculation site as a painless papule that rapidly enlarges and ulcerates, known as a chancre. The ulcer is characterised by induration (firm or hard to touch), a clean surface, no undermining, painless (unless secondarily infected by other bacteria), and solitary. Chancres are generally found this usually involves infection of the genital region, but can also involve infection of the anal region and oral regions and spread to regional lymph nodes. The ulcer may heal within 3-6 weeks without treatment or within 1-2 weeks with treatment, and rarely results in scarring (Park et al., 2020; Gonzalez et al., 2019). Secondary Syphilis. This secondary stage begins when the spirochetes spread into the bloodstream, characterised by fever, lymphadenopathy, and headache. Lesions usually reappear 3-12 weeks after the chancre onset in the form of erythematous macules (*roseola syphilitica*) or symmetrical maculopapular rashes on the trunk and extremities (Gonzalez et al., 2019). Latent Syphilis. The condition of Latent Syphilis is characterized by an asymptomatic phase with a positive (seroreactive) test result for serology.

Early latency occurs during the first year since infection, while late latency occurs beyond the first year since infection (Gonzalez et al., 2019).

Congenital Syphilis

The transmission of syphilis from the mother to the fetus may happen at any trimester through the placenta or directly due to the contact with the syphilis-infected lesions during childbirth. The risk of vertical transmission of syphilis varies depending on the stage of syphilis in the mother. An untreated pregnant woman with primary syphilis transmits syphilis vertically to her baby with 70-100% efficiency (Gonzalez et al., 2019). The most common outcomes of congenital syphilis are intrauterine fetal death and preterm labour in the second or third trimester. Thus, syphilis serology testing must be done for all pregnant women. Babies born from the mothers having positive serology tests need to be tested for clinical manifestations of early congenital syphilis (Mathew et al., 2022). The most common manifestations include fever, rash (syphilitic pemphigus), hepatosplenomegaly, and haemorrhagic rhinitis (bloody snuffles), hydrops fetalis, generalised lymphadenopathy, blood disorders (leucocytosis and thrombocytopenia), bone abnormalities (periostitis and osteochondritis), condyloma lata, perioral fissures, glomerulonephritis, and chorioretinitis. Meanwhile, late congenital syphilis (age > 2 years) manifests as interstitial keratitis, Clutton's joints, Hutchinson teeth and mulberry molars, rhagades (scars from perioral fissures), high palatal arch, sensorineural deafness, mandibular protrusion, sternoclavicular thickening, saddle nose deformity, and neurological involvement, most of which result from injuries during the early stages and often persist despite treatment (Mathew et al., 2022; Gonzalez et al., 2019).

Clinical Manifestations of Ocular Syphilis

Ocular syphilis is considered one of the uncommon conditions caused by syphilis. Ocular syphilis can develop at any phase but most commonly happens during the secondary stage. It can cause inflammation in almost all ocular structures. Symptoms can range from mild conjunctival injection to complete loss of vision (Park et al., 2020; Gonzalez et al., 2019; Chen et al., 2023). Conjunctivitis. Conjunctival inflammation in syphilis can present as papillary conjunctivitis or granulomas, usually characterized by conjunctival injection and chemosis (swelling). While rare, chancres and gummas can occur in the conjunctival area. Syphilis can also cause eyelids inflammation (blepharitis, eyelid chancre, rash, madarosis) and the orbit (gumma of the extraocular muscles, dacryoadenitis, periostitis) (Park et al., 2020; Chen et al., 2023). Scleritis and Episcleritis. Scleritis and episcleritis are rare cases. However, anterior nodular scleritis and diffuse scleritis can also occur and show a well response when treated with antibiotics (Chen et al., 2023). Uveitis. Uveitis is the most common condition

associated with ocular syphilis and most common at secondary stages of syphilis. It can affect anterior, intermediate, or posterior uvea or may even lead to panuveitis. Anterior uveitis commonly affects one eye and can be both granulomatous or non-granulomatous in nature. One rare and distinctive feature of ocular syphilis includes iris roseola. It refers to dilated vascular bundle, commonly observed on the midportion of the iris, which can be diagnosed under slit lamp illumination (Park et al., 2020; Marra, 2022; Chen et al., 2023). Vitritis, necrotizing retinitis, chorioretinitis, retinal vasculitis, and optic neuritis are few other conditions that have been observed during secondary syphilis. A rare ocular condition associated with syphilis includes acute syphilitic posterior placoid chorioretinopathy. This condition is marked by the occurrence of one or more yellowish placoid lesions commonly affecting macula (Queiroz et al., 2020). Interstitial Keratitis. Syphilis involvement in corneal inflammation is marked by interstitial keratitis. Interstitial keratitis due to syphilis is caused by an autoimmune-mediated inflammation of the corneal stroma that can result in permanent scarring. It is caused by treponemal antigens and is usually a clinical manifestation of congenital syphilis, being rare in acquired syphilis (Park et al., 2020; Chen et al., 2023).

Diagnostic Approach and Common Pitfalls

Serologic Testing Strategies

Accurate diagnosis of ocular syphilis requires integration of clinical suspicion with targeted laboratory evaluation, as no ocular finding is pathognomonic (Workowski et al., 2021; Tuddenham & Zenilman, 2022). Because its manifestations frequently resemble autoimmune or other infectious inflammatory disorders, serologic testing should be incorporated into the routine evaluation of unexplained uveitis (Mathew et al., 2022; Tuddenham & Zenilman, 2022). Current diagnostic strategies rely on the combined use of treponemal and non-treponemal assays (Workowski et al., 2021). Tests like the RPR test and VDRL are ideal for evaluating the disease activity and therapeutic response, while treponemal serological tests help detect *T. pallidum*-specific antibodies that are usually persistently positive (Park et al., 2020). Both traditional and reverse screening tests are employed in medical practice; they have unique strengths and weaknesses in discriminating between current and previously-treated disease (Park et al., 2020).

Common Diagnostic Pitfalls

A recognized diagnostic pitfall is the prozone phenomenon, where an excessively high titer of antibodies prevents the lattice formation between antigens and antibodies and gives a false-negative test result (Workowski et al., 2021). In addition, atypical serologic responses may occur in early infection, late-stage disease, or partially treated patients, underscoring the

need for careful interpretation in cases with strong clinical suspicion (Workowski et al., 2021). In individuals living with HIV, serologic interpretation may be further complicated by altered immune responses (Queiroz et al., 2020). Although most patients mount appropriate antibody responses, unusually high titers or discordant results have been reported, necessitating close clinical correlation (Queiroz et al., 2020). These considerations emphasize that laboratory findings should always be interpreted within the broader clinical context (Tuddenham & Zenilman, 2022).

Cerebrospinal Fluid Evaluation

The role of cerebrospinal fluid (CSF) examination in ocular syphilis remains debated (Workowski et al., 2021). Because ocular involvement is regarded as a form of neurosyphilis, current guidelines recommend treatment according to neurosyphilis protocols regardless of CSF findings (Workowski et al., 2021). However, CSF analysis may provide supportive evidence of central nervous system involvement, particularly in patients with neurological symptoms (Gonzalez et al., 2019; Marra, 2022). A reactive CSF-VDRL test is highly specific but lacks sensitivity, and a negative result does not exclude neurosyphilis (Gonzalez et al., 2019). Routine lumbar puncture in patients presenting solely with ocular manifestations remains controversial, and selective CSF evaluation is often considered in cases of neurological signs, treatment failure, or significant immunosuppression (Workowski et al., 2021; Tuddenham & Zenilman, 2022).

Implications for Clinical Practice

Delayed consideration of syphilis in the differential diagnosis may result in inappropriate initiation of corticosteroids or immunosuppressive therapy before antimicrobial coverage is established (Mathew et al., 2022). Early serologic screening in inflammatory eye disease is therefore strongly recommended to minimize diagnostic delay and prevent irreversible visual sequelae (Workowski et al., 2021; Tuddenham & Zenilman, 2022).

Imaging and Ancillary Investigations

Optical Coherence Tomography

Advances in ocular imaging have significantly improved the characterization of inflammatory patterns in ocular syphilis (Furtado et al., 2022; Pichi et al., 2021). Although imaging findings are not diagnostic in isolation, they provide important structural information that supports clinical suspicion and assists in monitoring therapeutic response (Pichi et al., 2021). When a patient has posterior uveitis or ASPPC, an optical coherence tomography scan can reveal disruptions of the ellipsoid zone, abnormalities of the retinal pigment epithelium, presence of subretinal fluid, and hyper-reflective lesions of the outer retina (Pichi et al., 2021).

These structural changes correlate with placoid lesions observed clinically and may improve following appropriate antimicrobial therapy (Pichi et al., 2021).

Fluorescein Angiography and Multimodal Imaging

Fundus fluorescein angiography (FFA) further delineates vascular and inflammatory abnormalities. Findings may include vascular leakage, vessel wall staining, capillary non-perfusion, or areas of ischemia in cases of retinal vasculitis (Furtado et al., 2022; Eandi et al., 2022). While these angiographic features are not specific to syphilis, they contribute to differentiation between infectious and non-infectious posterior uveitis when interpreted alongside serologic findings (Eandi et al., 2022). Multimodal imaging, integrating OCT and angiographic techniques, enhances recognition of active inflammatory lesions and assists in distinguishing ongoing inflammation from residual structural damage (Pichi et al., 2021; Eandi et al., 2022). This distinction is clinically important when assessing treatment response and determining the need for adjunctive therapy (Eandi et al., 2022).

Neuroimaging in Optic Nerve Involvement

Neuroimaging may be considered in patients with optic nerve involvement to exclude alternative causes of optic neuropathy (Gonzalez et al., 2019; Marra, 2022). Although magnetic resonance imaging findings are not pathognomonic, optic nerve enhancement may support the diagnosis when interpreted in conjunction with clinical and laboratory data (Marra, 2022). Emerging evidence suggests that optical coherence tomography angiography (OCT-A) may demonstrate microvascular alterations and areas of capillary dropout corresponding to inflammatory activity, although findings are not specific to syphilis (Eandi et al., 2022). Fundus autofluorescence can reveal retinal pigment epithelium dysfunction in placoid lesions, potentially aiding in the assessment of lesion activity and recovery (Pichi et al., 2021; Eandi et al., 2022).

Management of Ocular Syphilis

Antibiotics. First choice in the treatment of ocular syphilis is according to the recommended treatment of neurosyphilis. In this treatment regimen, aqueous crystalline penicillin G at 3 to 4 million units IV every four hours, amounting to 18 to 24 million units each day via continuous infusion, for 10 to 14 days will be administered (Mathew et al., 2022; Park et al., 2020). The other method is to inject procaine penicillin G 2.4 M units IV daily together with probenecid 500 mg four times daily, for 10 to 14 days (Mathew et al., 2022; Park et al., 2020). Because the period of treatment required for neurosyphilis is shorter compared to latent syphilis, another mode of treatment of benzathine penicillin G 2.4 million units IM once a week for three weeks might be used after treatment for 10-14 days initially (Mathew et al.,

2022; Park et al., 2020). If there is penicillin sensitivity or the administration of penicillin through injection IV cannot be performed, an alternative study has tested ceftriaxone 2 g/day for 10-14 days (Eandi et al., 2022; Bettuzzi et al., 2021). Daily dosage of 200 mg of doxycycline for 14-30 days could also be used in some cases, especially in cases of primary syphilis where standard treatment cannot be administered (Eandi et al., 2022; Bettuzzi et al., 2021). Corticosteroids. The topical and systemic corticosteroids containing anti-inflammatory agents can be useful as adjuvant therapy in ocular syphilis. Topical corticosteroids in particular are reported to be effective as therapy for scleritis, interstitial keratitis, and anterior uveitis. Meanwhile, systemic corticosteroids are recommended for cases of posterior uveitis and optic neuritis (Mathew et al., 2022; Chen et al., 2023). Immunosuppressive Agents. The administration of immunosuppressive agents after completion of the primary infection treatment serves as an intraocular inflammation suppressant in selected cases. Methotrexate has demonstrated efficacy as adjunct therapy in controlling intraocular inflammation and macular edema, as well as preventing recurrence in syphilitic uveitis patients (Pichi et al., 2021). Jacob et al. (2021) reported that tacrolimus is effective therapy for syphilitic interstitial keratitis in children.

4. CONCLUSION

Ocular syphilis remains a diagnostically challenging yet treatable cause of vision loss in the era of syphilis resurgence. Its protean clinical manifestations and frequent overlap with autoimmune or other infectious inflammatory conditions necessitate a high index of suspicion and routine incorporation of syphilis serology in the evaluation of unexplained intraocular inflammation. Timely diagnosis and prompt initiation of neurosyphilis-directed therapy are critical determinants of visual outcome. While antimicrobial treatment is highly effective, delayed recognition may result in irreversible structural damage and permanent visual impairment. In the context of increasing global incidence and evolving diagnostic algorithms, a systematic and multidisciplinary approach integrating ophthalmology, infectious disease, and neurology expertise is essential to optimize patient outcomes and reduce preventable visual morbidity.

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