Double trouble: Challenges in the diagnosis and management of ocular syphilis in HIV-infected individuals

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Abstract:

Syphilis and HIV infection may coexist in the same individual. Ocular syphilis and/or neurosyphilis may develop at any stage of coinfection, with a stronger association between ocular and neurosyphilis in individuals living with HIV, than in HIV-uninfected individuals. The diagnosis of ocular syphilis in HIV-infected and –uninfected patients remains with some controversy due to unspecific clinical manifestations and limited diagnostic tests. Penicillin is the mainstay of treatment of ocular syphilis, but alternative options are warranted.

This review describes the epidemiology, pathophysiology and clinical manifestations, as well as the diagnostic and therapeutic challenges posed by ocular syphilis against the background of HIV coinfection.

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Introduction

It is well described that syphilis and HIV infection may coexist in the same individual and it is therefore recommended that all patients with syphilis should be tested for HIV infection.[1] Ocular syphilis (OS) occurs in patients with and without HIV infection; some reports suggest that its clinical picture may differ depending on the HIV status of the patient.[2–4] HIV-infection may be associated with a stronger link between ocular syphilis and neurosyphilis (NS) in HIV-infected than in HIV-uninfected patients.[5] At present there is still a fair amount of controversy regarding how OS and NS should be diagnosed in HIV-infected and HIV-uninfected patients. However, ocular syphilis is still treated as presumed neurosyphilis regardless of the patient's HIV status.

In this review we shall first describe the epidemiology and pathophysiology of OS in the context of HIV-infection and then consider its clinical manifestations before discussing the diagnostic and therapeutic challenges faced by clinicians confronted with this disease.

Epidemiology

Syphilis, also called "the great imitator", is an ancient infectious disease that occurs across the globe. Over the past century, the burden of syphilis has reduced dramatically following the introduction of penicillin treatment in the 1940s, the advance and implementation of diagnostic tests, and, in lower- and middle-income countries, the use of syndromic management of genital ulcers.[6] In recent years, however, there has been a strong rise in syphilis cases reported from across the world; case numbers have almost doubled over a period of ten years according to surveillance reports from the Centers for Disease Control (CDC) and the European Centre for Disease Prevention and Control.[7,8]

This recent rise in the prevalence of syphilis in Europe and the USA is largely attributed to a sharp increase in incidence among men and particularly among men who have sex with men (MSM). In contrast, the syphilis epidemic in low- and middle-income countries extends

across the general population. For example, Brazil has seen a dramatic increase in syphilis cases across the population over the past years including maternal and congenital syphilis, but also in MSM.

The World Health Organization estimates a global prevalence of 0.5%, with incidence of 6.3 million new syphilis cases every year.[9] The global prevalence of maternal syphilis was estimated at 0.69% resulting in a congenital syphilis rate of almost 500 per 100,000 live births.[10] Syphilis prevalence is inversely related to socio-economic status and the highest seroprevalence rates (1.6%) are observed for the African region.[9]

There is only a limited number of studies that addressed the prevalence of OS (Table 1); these are mostly retrospective studies and record reviews.[11–23] These studies were conducted in three different types of study population: individuals with syphilis, individuals presenting with uveitis, and HIV-infected individuals. The prevalence of OS observed was 0.5% to 1.5% among HIV-infected patients and ranged from 1.2% to 26% in patients presenting with uveitis.

Although the numbers of OS cases are relatively small in these syphilis and uveitis cohorts, the reported OS prevalence is usually higher among HIV-infected individuals compared to those living without HIV. In line with this observation, Hamze and colleagues reported higher frequency of HIV coinfection in patients with OS compared to syphilis without OS in a case-control study.[18] Similarly, the study by Cope and colleagues of syphilis patients reported a prevalence of OS of 1.5%; 2.1% among individuals with HIV coinfection and 1.1% among those without HIV.[13]

There no surveillance data of syphilis OS incidence and prevalence over time. A study from the USA reported a decline in the prevalence of OS in patients with chronic anterior uveitis over time: 5.3% in period 1975-1984, 2.9% in 1985-1994 and 1.2% in 1995-2004.[11] As with other types of NS, HIV is associated with an increased risk of OS: HIV-infected patients have a two

Table 1. Occurrence of ocular syphilis by HIV status (excluding cases series of OS)

Country	Study design (year)	Sample size	Study population	Overall prevalence or incidence of OS	Prevalence of OS in HIV-infected individuals	Prevalence of OS in HIV-uninfected individuals	Reference
USA	Record review (1995-2004)	686	Patients with chronic AU	1.2% (n=8)	-	-	Birnbaum AD[11]
USA	Record review (2001-2002)	221	HIV-infected patients	1.4% (n=3)	1.4%** (n=3)		Balba GP[12]
Japan	Retrospective study (2004-2013)	1515	HIV-infected patients	0.3% (n=4)	0.3% (n=4)	-	Nishijima T[16]
USA	Retrospective cohort (2005-2008)	509	HIV-infected patients	0.8% (n=4)	0.8%* (n=4)	-	Biotti D[17]
Canada	Case-control study (2010-2018)	6716	Patients with syphilis	0.98% (n=66)	-	-	Hamze[18]
Taiwan	Retrospective cohort (2006-2016)	1242	HIV-infected patients	0.8% (n=10)	0.8% (n=10)	-	Tsen CL[19]
Netherlands	Retrospective study (2012-2016)	1354	Patients with uveitis	0.9% (n=12)	-	-	Rothova A[20]
South Africa	Cross-sectional study (2013-2015)	103	Patients with uveitis	4.9% (n=5)	6.1% (4/66)	2.7% (1/37)	Schaftenaar E[21]
South Africa	Cross-sectional study (2014-2015)	198	Patients with uveitis	16% (n=32)	29% (21/72)	10% (11/108)	Rautenbach W[22]
USA	Record review (2014-2015)	4232	Patients with syphilis	1.5% (n=63)	2.0% (35/1744)	1.1% (28/2488)	Oliver SE[23]
USA	Record review (2014-2016)	7123	Patients with syphilis	1.5% (n=109)	2.1% (59/2846)	1.1% 38/3197	Cope AB[13]
France	Record review (2015-2019)	1493	Patients with uveitis	1.4% (21/1493)	n=6	n=15	Pratas AC[14]
France	Retrospective cohort (2016-2017)	2890	HIV-infected patients	0.2 per 100 person-years	-	-	Menard A[15]

times higher risk of presenting with OS than HIV-negative individuals; especially those with CD4 cell count below 200 cells/mm3 and with unsuppressed viral load are at risk.[13,15,18]

Pathophysiology

Syphilis is a bacterial infection caused by the spirochete *Treponema pallidum* subspecies pallidum.[24,25] Transmission is predominantly through sexual contact and from mother to child as the spirochete crosses the placenta easily; transmission through blood transfusion is rare. The mode of transmission does not affect the risk of development of OS or NS. The spirochetes are present in open skin lesions, such as in primary chancres, mucous patches and condylomata lata, and are transmitted upon sexual contact. Transmission rate is around 30% in case of open skin lesions, but much lower when the skin is intact and the number of spirochetes is low, e.g. during secondary syphilis. Individuals with early latent syphilis can still be infectious due to healing or unnoticed skin lesions. Inoculation of *T. pallidum* from secretions can lead to infection at any site of contact and result in primary chancres of lips, oral cavity, breasts and genitals through kissing, touching and sexual contact.

The natural history of syphilis has three stages: a primary chancre develops an average of three weeks (10-90 days) after infection. Following dissemination of the spirochetes through the body, the secondary stage may develop, with a typical muco-cutaneous rash and condylomata lata as the most common clinical presentations. At this time, spirochetes can be detected from the blood, lymph nodes and various tissues that they may invade. From this secondary stage, syphilis moves to a latent, asymptomatic stage. This stage can be divided in early latent, i.e. within a year from infection, and late latent infection. Secondary manifestations may present or recur during early latent infection.[25] Most individuals with late latent syphilis remain asymptomatic as a result of coincidental antibiotic therapy or clearance of the infection, but long-term tertiary disease may develop in up to one-third of latently infected individuals.[24–26] Manifestations of tertiary syphilis include NS, paresis, personality changes, tabes dorsalis, gumma, aneurysms and aortitis.

Interestingly, there is a bidirectional synergistic effect facilitating acquisition and transmission as result of biological parameters, overlapping risk factors and concurrent exposure, and also altering disease progression in both syphilis and HIV infections.[27] Recent syphilitic seroconversion can increase likelihood of HIV seroconversion by 2.5 times, possibly not only because of formation of genital ulcers, but also associated with a proinflammatory local immune response increasing HIV infection of CD4+ lymphocytes mediated by dendritic cells. In addition, peripheral cytokine profiles in these patients further facilitate subsequent HIV infection.[27] HIV coinfection also leads to reduced opsonic activity of macrophages, decreasing clearance of *T. pallidum*.[27,28] Conversely, in patients living with HIV, recently acquired syphilis may increase HIV load, leading to elevation of infectiousness and favouring HIV transmission, and intermittently cause a small drop in the CD4 cell count.[29],

From the clinical perspective, HIV coinfection alters presentation of syphilis, occasionally with multiples chancres primarily, but also leading to overlapping of clinical stages (simultaneous primary and secondary lesions, for instance) and to earlier progression to neurosyphilis.[27]

Classically, ophthalmic complications of syphilis have been associated with tertiary disease, however, OS may occur at any stage of infection (Figure 1); there is no data to suggest that this is different between HIV-infected and HIV-uninfected individuals. Cases of concurrent primary chancre as well as generalised muco-cutaneous rash with OS have been reported.[30–32] It is estimated that 80% of cases of OS develops within two years of systemic infection.[33] Currently, there is no evidence that specific strains of *Treponema pallidum* are more or less likely to affect the eye (oculotropism) during systemic infection.[34] Any of the ocular structures can be affected by *T. pallidum*. In general, a presentation of acute anterior uveitis may be more often seen in the early stages of syphilis whereas chronic posterior uveitides and optic neuritis are more commonly seen in later stages of syphilis; the latter is often associated

with subclinical signs of NS.[32,33,35] Other than increased prevalence, there is little data that suggests that presentation or severity of OS is different between HIV-infected and HIV-uninfected individuals, although optic neuritis may be more common among those with concurrent HIV infection.[35–37] The prognosis of OS is generally good if targeted treatment is provided soon after onset of ocular symptoms.[35]

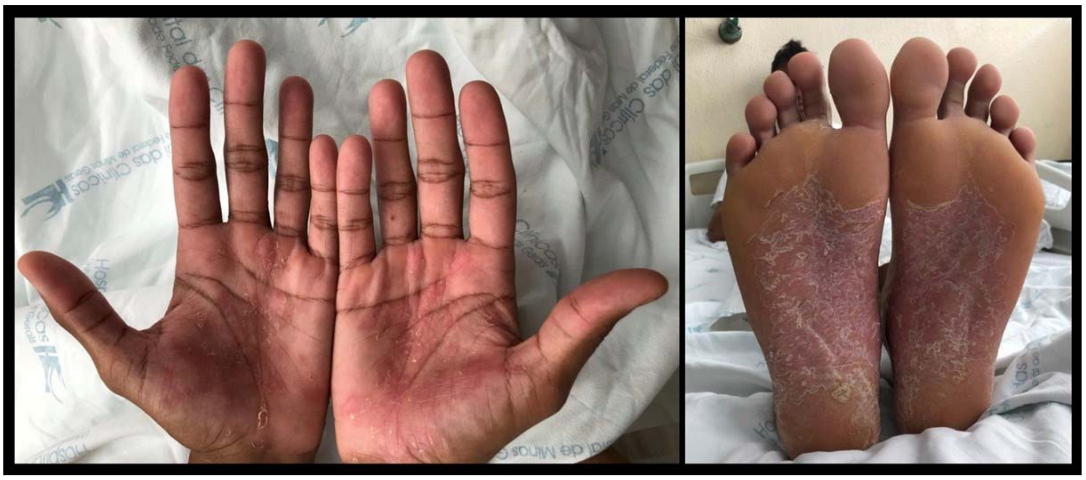

Figure 1. Palmar and plantar rash in an HIV-positive individual with syphilitic uveitis

Clinical manifestations of ocular syphilis

Ocular syphilis can present in at any stage of the systemic infection, although it most often occurs during the secondary and tertiary stage. Syphilitic uveitis is, by far, the most common form of eye involvement and can occur as soon as 6 weeks after primary infection.[38]

In fact, the spirochetes probably invade the central nervous system (CNS) early during the course of primary infection, but it is thought that the bacteria may be cleared from the cerebrospinal fluid (CSF) without therapy.[39] However, reports of neurological relapse after treatment with intramuscular (IM) benzylpenicillin appropriate to their disease stage without

probenecid in HIV-infected patients with presumably no OS may suggest that the clearance of the spirochete from CNS might be impaired in these immunosuppressed individuals.[40,41]

In addition, it has been proposed that a serum rapid plasma regain (RPR) titer $\geq$ 1:32 may be predictive of neurosyphilis, regardless of HIV status, and that a peripheral blood CD4+ T cell count $\leq$ 350 cells/mL may be an additional risk factor in HIV-positive individuals.[39]

Data on lumbar puncture (LP) performed in relatively large cohorts of patients with active syphilitic uveitis showed prevalence of CSF abnormalities varying from 25-69.7%, with higher rates in HIV-infected individuals.[37,42–44] Still, routine laboratory serological CSF tests will fail to identify some patients with CNS invasion.[39]

Posterior uveitis is the most common manifestation of ocular syphilis overall (Figures 2 and 3). In addition, posterior and panuveitis may be more frequently found in HIV-positive than in HIV-negative patients.[3,37,45] Increased severity of uveitis at presentation (assessed by anterior chamber cells, vitreous haze, flare and posterior synechiae) was also reported more frequently in HIV-infected individuals.[46]

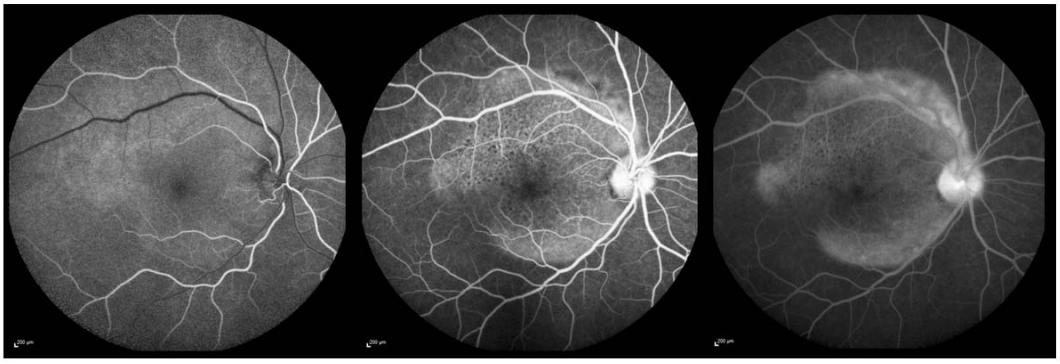

Figure 2. Fluorescein angiography syphilitic posterior placoid chorioretinitis, revealing progressive placoid hyperfluorescence at the macula. Hyperfluorescence of the optic disc can also be seen.

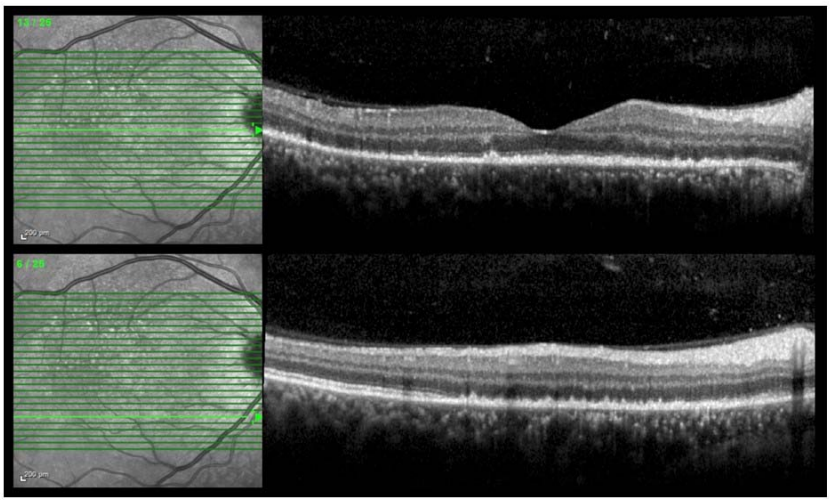

Figure 3. Retinal pigment epithelium (RPE) changes in syphilitic posterior uveitis, revealed by spectral-domain optical coherence tomography. Irregular thickening of the RPE band is seen, in addition to vitreous hyper-reflective dots, corresponding to inflammatory cells.

On the other hand, according to the largest cohort of syphilitic uveitis reported to date, there was no significant difference in frequency of each clinical finding of involvement of anterior and of posterior segment of the eye between the two groups. Reduced best-corrected visual acuity (BCVA) on first examination was also not significantly different.[37]

Anterior uveitis, vitritis, neuritis, neuroretinitis, retinitis, choroiditis, chorioretinitis and vasculitis may all be present in the setting of syphilis, and thus syphilis should be kept in mind in the evaluation of any uveitis patient (Table 2 – Ocular manifestations of syphilis).

The ability of syphilitic uveitis to lead to distinct patterns of inflammation and mimic any ocular disorder can lead to misdiagnosis and consequent delay in adequate treatment and therefore laboratory tests for syphilis must be carried out in any patient presenting with uveitis.

Table 2 – Ocular manifestations of syphilis

Extraocular inflammation		
Conjunctival chancre		
Interstitial keratitis		
Scleritis	Anterior scleritis Posterior scleritis	(nodular / diffuse)
Intraocular inflammation		
Anterior uveitis	Granulomatous iridocyclitis Nongranulomatous iridocyclitis	(including iris roseola)
Intermediate uveitis	Granulomatous intermediate uveitis Nongranulomatous intermediate uveitis	
Posterior uveitis	Optic neuritis† Posterior placoid chorioretinitis† Inner punctate retinitis† Necrotizing retinitis† Outer retinopathy / AZOOR-like changes† Retinal vasculitis† Chorioretinitis NOE† Pigmentary retinopathy	 (occlusive/nonocclusive arteritis and/or phlebitis) (pseudoretinitis pigmentosa after chronic/longstanding inflammation)
Panuveitis	Granulomatous Nongranulomatous	

† Combination of these forms of presentation may be present in posterior or in panuveitis; NOE: not otherwise specified

Diagnostic dilemmas and challenges

Serology

At present, OS is diagnosed if a patient has ocular inflammation compatible with syphilis upon physical examination as well as positive syphilis serological results (serum), provided that other possible causes of intraocular inflammation have been excluded. Serological tests for syphilis include both treponemal and non-treponemal tests. The Centers for Disease Control (CDC) recommend using a treponemal test such as an enzyme immunoassay (EIA) as an initial screening test for syphilis. These tests detect antibodies to specific treponemal antigens. If the treponemal test is positive, it should be followed by a non-treponemal test, which detects antibodies against membrane phospholipids such as cardiolipin. Examples of non-treponemal tests include the Venereal Disease Research Laboratory (VDRL) and the rapid plasma reagin (RPR) tests. These tests screen for active disease and are able to quantify

antibodies but may give false positive results in conditions other than syphilis.[47] If specimens return discordant results (for example EIA positive but VDRL negative) a confirmatory test such as *Treponema pallidum* particle agglutination (TP-PA) should be performed since a positive result would confirm the diagnosis of syphilis. It should also be noted that, contrary to conventional wisdom, treponemal test results may revert to negative in 5 – 17% of patients treated for early syphilis.[48]

At this point it should be noted that OS is currently diagnosed based on the results of blood tests alone whereas NS is diagnosed based on results obtained from testing CSF which circulates within the central nervous system. This discrepancy raises the question as to whether OS could not be diagnosed more accurately if testing was to focus on ocular fluid, whether it be aqueous humor (AH) or vitreous humor (VH), instead of blood.

Polymerase chain reaction (PCR)

PCR is a nucleic acid amplification technique that brings interesting new diagnostic possibilities in OS. In 2006, Rajan et al described a case of unilateral panuveitis in a homosexual male with positive EIA on serology and RPR titre of 1:512. Subsequent real-time PCR detected *T. pallidum* DNA in the VH and a diagnosis of syphilitic panuveitis was confirmed.[49] Müller et al described another 2 patients with acute chorioretinitis where the diagnosis was changed from presumed viral infection to confirmed syphilis based on positive PCR results on vitrectomy specimens.[50] Cornut et al demonstrated that real-time PCR could also deliver positive results when testing AH since 3 patients with panuveitis had positive PCR results.[51] According to Troutbeck et al, PCR testing of VH samples also assisted in making a definitive diagnosis in 2 cases with atypical clinical presentations.[52] It is interesting to note that, according to these authors, the second case underwent PCR testing for syphilis twice on AH, with negative results in both instances. Only when the VH was sampled did syphilis PCR return a positive result. This may partly explain why PCR testing for syphilis on

AH samples from a prospective study conducted in South Africa returned negative results in all 10 samples tested.[53]

Immunoblot (IB)

Immunoblot, or Western blot, is a molecular technique that detects antibodies to specific antigens and may also be used to confirm the diagnosis of syphilis. A study that compared an immunoblot and FTA-ABS as confirmatory test for syphilis found that both tests had sensitivities of 100% whereas specificities were 100% and 94.5% respectively.[54] In patients with NS, IB has been used to detect antibodies against T. pallidum antigens in the CSF[55] but to date there are no reports of IB having been used to detect treponemal antibodies in AH or VH. However, in a prospective study from South Africa, the authors were able to demonstrate antibodies to treponemal antigens in AH samples of 3 of 13 patients, 2 of whom were HIV+.[53] Going forward, it is therefore possible that IB could play a role in confirming a diagnosis of OS on AH. Larger prospective studies are currently being conducted to determine the true diagnostic value of IB in this setting.

Biomarkers/cytokines

In recent years there has been increasing interest in the field of 'omics' which refers to high-throughput analyses of genes, proteins or metabolites in biological systems. These are increasingly being used for research in different fields in Ophthalmology.[56] 'Omics' makes use of systems-based approaches to unravel disease-related mechanisms and is often valuable in finding biomarkers for certain processes. 'Omics' techniques have been applied in several eye diseases including age-related macular degeneration, diabetic retinopathy, cataract, keratoconus and dry eye but not much is known about its potential applications in ocular inflammation.

In a prospective study from South Africa, blood samples were collected from 92 uveitits patients of whom 38% were HIV+.[53] Concentrations of 47 cytokines/chemokines were

measured in unstimulated QuantiFERON supernatants using the Luminex® platform. Of the 92 participants, 11 had syphilis while the rest had herpetic uveitis, other infectious causes (mostly TB), established non-infectious causes such as sarcoidosis and HLA-B27 associated uveitis or no cause was found. Biomarker analysis revealed 3 proteins (Apo-A1, Apo-CIII and CRP) that differed between syphilis and all other causes.[57] Furthermore, a 3-marker bio-signature (CCL4/MIP-1β, ApoCIII and CRP) distinguished syphilis from other groups with an area-under-curve=0.83 [95% CI 0.68 – 0.98]. A bio-signature that could distinguish herpetic uveitis from other causes of uveitis was also identified in the same study. These preliminary findings appear to suggest that 'omics' could play a role in future uveitis diagnostics although a considerable amount of research is still required in this field – especially in order to determine whether any notable differences exist in biomarker profiles between HIV+ and HIV- patients.

The benefit of using diagnostic markers and/or bio-signatures in the diagnosis of OS and other uveitic entities lies in the possibility that they could potentially be incorporated into a point-of-care diagnostic test which could serve as a screening tool to distinguish between different infectious causes of uveitis.

Clinical management

Lumbar puncture

Whether or not LP is indicated in patients with ocular syphilis is still a matter of debate. Considering that ocular involvement may suggest CNS infection, routine CSF analysis could be important in establishing the diagnosis of NS and evaluating the extent of CSF abnormalities.

The frequency with which LP is performed in the setting of OS in clinical practice may differ from one centre to another. A recent study from South Africa showed that LP was performed in 77.4% of 146 patients with ocular syphilis, 52.1% of whom had HIV co-infection. In total,

37.1% of patients who underwent LP had evidence of neurosyphilis with no differences in numbers between HIV-positive and HIV-negative patients.[58]

However, one could argue that this practice should be questioned if the patient is treated with the regimen recommended for neurosyphilis, with intravenous penicilin,[59] yet the diagnosis of neurosyphilis is important and could alter the follow-up of these patients, demanding repeated lumbar puncture to assess for normalization of an initially altered CSF.[43]

Therefore, the current recommendation is for LP to be performed in all patients with ocular involvement, regardless of HIV status.[60,61]

Multimodal imaging

Multimodal imaging may help in improved delineation of intraocular inflammation associated with syphilis, in its differential diagnosis, and in assessment / follow-up of vitreoretinal complications. This may allow better correlation of clinical features with underlying uveoretinal pathology.

Fluorescein angiography may aid in demonstrating the extent of inflammation and findings differ according to the anatomic structures involved. Distinct angiographic patterns have been described, such as staining of focal punctate retinal lesions, capillary leakage, staining of retinal blood vessels, disc hyperfluorescence, macular and/or optic disc edema, retinal ischemia and “leopard spots”. The classic picture of syphilitic posterior placoid chorioretinitis has been characterized by Gass mainly on angiographic grounds.[62] (Figure 2)

Indocyanine green also can also aid in choroidal assessment. Patterns already reported are persistent dark spots, vanishing dark spots, fuzzy choroidal vessels, and hot spots.[63,64] Apparently silent choroidal pathology can be demonstrated in cases with overt clinical changes in optic disc and/or retina.

Optical coherence tomography (OCT) is also useful to assess the macula, optic disc, vitreoretinal interface or other chorioretinal lesions at presentation and after treatment. It may also help in documentation and follow-up of complications. OCT findings also vary depending on the type and location of inflammation. Findings include thickening of the neurosensory retina, subretinal fluid, macular edema, disruption of external retinal layers (external limiting membrane, ellipsoid zone, myoid zone) and irregular/-nodular hyperreflectivity of the retinal pigment epithelium (RPE).[65–67] These RPE changes can also be documented by fundus autofluorescence (FAF) - Figure 3. In the setting of syphilitic outer retinopathy / AZOOR-like changes, combination of FAF and spectral-domain OCT has been shown to be particularly useful for the diagnosis.[68]

B-scan ultrasound can be helpful in those cases where posterior segment evaluation is not possible. It may be useful to rule out retinal detachment in the setting of opaque media, or other vitreoretinal complications arising from the infection.

Medical treatment

Penicillin is the drug of choice and has been the mainstay of treatment for syphilis since its discovery, with no resistant cases reported to date.[69]

Following current CDC recommendations, all cases of ocular syphilis should be treated according to neurosyphilis treatment protocol (aqueous crystalline penicillin G 18–24 million units per day, administered as 3–4 million units IV every 4 hours or continuous infusion, for 10–14 days). Alternative regimen consists of 10-14 days of procaine penicillin G 2.4 million units daily plus probenecid 500mg orally four times a day.

Between 2014 and 2016, around 39 countries reported penicillin shortage, supposedly due to the fact that few companies produce the active ingredient, with production levels kept low possibly due to low profit. Furthermore, it is an off-patent drug that is sold for a very low price, but needs to be manufactured under controlled conditions, demanding considerable

financial investment.[70] In the context of the global re-emergence of syphilis, the demand has grown much larger than the supply of the antibiotic, prompting countries to look for alternative treatment regimens.

Alternative therapeutic regimens, namely ceftriaxone and doxycycline/tetracycline, are well-established for treatment of early syphilis. However, even though serological response rates did not differ significantly between these agents and penicillin, treatment with doxycycline/tetracycline led to a significantly higher serological failure rate at 12-month follow-up than treatment with penicillin at this stage of the disease.[71]

Regarding OS, no comparative controlled studies have been conducted to date. However, while intravenous ceftriaxone was used with success in retrospective studies, use of oral doxycycline is restricted to case reports.[64,72–74]

At present, there are no reliable studies to support or discourage the use of systemic or local steroids as adjunctive therapy in OS, and consequently there are no current guidelines for it. However, there is rationale for its use, since ocular inflammation may cause irreversible complications, and in fact they are frequently employed in conjunction with antibiotic treatment in subjects with sight-threatening syphilitic uveitis.[36,37,42,44,75–77]

Impact of HIV on management choice

There are not many studies comparing syphilis treatment outcomes between HIV-infected and uninfected patients,[78] and the risk of failure of serological response following antibiotic therapy in patients with HIV infection is controversial.[79,80] In accordance with this evidence, the so-called "serofast state" may not be more frequent in seropositive individuals.[81,82]. Therefore, treatment should not differ depending on the patient's HIV status. Careful follow-up, however, is very important, including monitoring for possible reinfection.

Prognosis

Visual prognosis in syphilitic uveitis is classically considered as favourable, with good response to adequate antibiotic therapy,[46,74,83,84] even though complications are not uncommon and poor outcome may be seen in a significant number of cases.[37,44,85]

HIV coinfection is not associated with a worse visual outcome.[42,75,76,84,86] However, posterior segment complications and incidence rates of visual acuity loss, but not rates of vision loss and changes in visual acuity, are slightly more common among those with HIV infection.[37]

Use of systemic and local corticosteroids prior to definite diagnosis and initiation of antibiotic therapy may negatively affect the outcome.[46] Others findings also appear to be associated with poor visual prognosis, including delayed diagnosis, higher VDRL titers, and worse initial BCVA.[42,44,75,76,82]

Perspectives

Syphilis, including OS, is on the rise globally for various reasons. Awareness by clinicians of syphilis in the differential diagnosis of ocular symptoms without clear aetiology is essential in both HIV-infected and HIV-uninfected individuals.

However, this current epidemic may possibly pose a dilemma for future diagnosis of uveitis, since a good number of patients will test positive for treponemal tests in the years to come. With the ongoing lack of conclusive diagnostic tests for OS and the reliance on clinical presentation in the ophthalmological exam for the recognition of the disease, making it a presumptive diagnosis, this might add still another confounding factor for the clinician to deal with. Therefore, more accurate diagnostic tests are warranted.

Novel diagnostic options are still limited, but molecular and immune biomarkers may provide a good alternative to improve accuracy of diagnosis and to initiate early targeted treatment.

Visual outcome is usually good providing early diagnosis is made and inadvertent/unopposed use of corticosteroid is avoided. Penicillin continues to be the mainstay of OS treatment, but, in light of the threat of global penicillin shortage, research studies of alternative drugs and treatment regimens are urgently needed.

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