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CLINICAL INVESTIGATION

Posterior syphilitic uveitis: clinical characteristics, co-infection with HIV, response to treatment

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Abstract
Purpose To describe the characteristics and clinical course of patients with active posterior syphilitic uveitis evaluated between 1991 and 2009.
Methods Retrospective chart review.
Results Thirteen patients with active posterior syphilitic uveitis were identified at a single institution. All were men, and all with available data were men having sex with men (MSM). Ten of 12 (83%) with available data were HIV positive. Four (31%) had a history of syphilis. Clinical findings included infiltrative retinitis, necrotizing retinitis and optic neuritis. Two of 8 patients tested (25%) had a positive Venereal Disease Research Laboratory test in the cerebrospinal fluid. Treatments included intravenous penicillin, intramuscular penicillin and intramuscular ceftriaxone. All treated cases improved and, in some cases, inflammatory lesions completely resolved without scarring.
Conclusions In this series, syphilitic posterior uveitis presented only in men, and all with available data were MSM. The majority were concomitantly infected with HIV. Clinical presentations varied and all patients demonstrated either significant improvement or complete resolution of inflammation.

Keywords Syphilis · Uveitis · Retinitis · AIDS · HIV · Optic neuritis

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Introduction

Syphilis is a potentially devastating multi-system bloodborne disease caused by the spirochete *Treponema pallidum*. The acquired form is transmitted primarily by sexual contact. Its broad clinical spectrum is organized into overlapping stages [1]. The primary stage is characterized by a painless chancre at the site of penetration. The secondary stage, characterized by systemic symptoms and skin lesions, marks the hematogenous dissemination of the organism. This typically occurs 2–12 weeks after initial contact [1]. The tertiary stage includes cardiovascular complications as well as severe neurologic sequelae. Between the secondary and tertiary stages there is a latent stage in which the patient is asymptomatic. This stage can last for months or a lifetime, with most relapses occurring within the first year [1].

Ocular manifestations of syphilis can occur at any stage of the disease. Known as the "great masquerader," syphilis is notorious for its broad clinical spectrum and ability to mimic many other diseases. Syphilis can affect almost any tissue of the eye (e.g., conjunctivitis, scleritis, interstitial keratitis, uveitis) [2]. It is an uncommon cause of uveitis (estimated, from 1970 to 1980, to comprise 1.1% of cases [3]). Syphilitic uveitis can include anterior segment findings such as iridocyclitis, as well as posterior segment findings including vitritis, chorioretinitis and optic neuritis [3–5].

The diagnosis of syphilis should be considered in any patient with ocular inflammation. Diagnostic testing should include serologic testing with specific treponemal tests such as the fluorescent treponemal antibody-absorption test (FTA-ABS) or *T. pallidum* agglutination tests (e.g., TPPA), as well as non-specific tests such as the Venereal Disease Research Laboratory (VDRL) test and rapid plasma reagin (RPR). The latter tests may become negative with prolonged infection [1] and so cannot be relied upon as the

sole testing method. The recommended treatment for ocular syphilis is 10–14 days of intravenous penicillin (3–4 million U every 4 h) [1].

A strong association between HIV and ocular syphilis has been reported [5–8]. The highly active antiretroviral therapy (HAART) era has seen an increase in the number of cases of ocular syphilis [9, 10], which may be due to a decrease in AIDS-associated mortality [6].

In this study, we describe the clinical spectrum of patients with active posterior syphilitic uveitis seen at a tertiary referral center in the United States, the incidence of co-infection with HIV, the utility of laboratory and CSF analysis, and the response to treatment.

Methods

We obtained approval from the Institutional Review Board at the University of Illinois at Chicago to review the medical records of patients seen by the uveitis service of the University of Illinois at Chicago and diagnosed with syphilitic uveitis between 1991 and 2009 with a waiver of informed consent. Inclusion criteria included a clinical diagnosis of ocular syphilis, active intraocular inflammation (e.g., iritis, iridocyclitis, vitritis, optic neuritis), posterior segment findings attributable to syphilis (e.g., retinitis, choroiditis), and positive serologic testing with both non-treponemal (RPR) and treponemal (FTA-ABS) tests.

Exclusion criteria included inactive ocular disease, isolated anterior uveitis, and negative RPR or FTA-ABS. Because of its ability to masquerade as other diseases, strong serologic data were considered essential in confirming the diagnosis of syphilitic uveitis. In addition, because isolated anterior uveitis can often be idiopathic, making a diagnosis of syphilis questionable even in the face of positive syphilis serology, such patients were excluded from this study.

Medical records of patients included in the study were reviewed to determine the clinical presentation, results of diagnostic testing for syphilis and HIV, and response to treatment.

Results

Incidence

Thirteen patients were diagnosed with active syphilitic posterior uveitis between 1991 and 2009 (Table 1), which represents 0.32% of the 4049 new uveitis patients seen during this time period. In the first half of this time period (May 1991 to mid-August 2000), 5 patients were found to have syphilitic posterior uveitis, which represents 0.27% of the 1827 new uveitis patients seen in this period. In the latter half of this time period (mid-August 2000 through November 2009), 8 patients were diagnosed. This represents 0.36% of the 2222 new uveitis patients seen during

Table 1 Demographics, history of syphilis, and HIV status of patients presenting with syphilitic posterior uveitis

Patient	Age	Race	Gender	MSM	History of syphilis	HIV status	HIV viral load (RNA PCR) copies/mL	CD4 count (cells/μL)
1	42	W	M	UR	None	UR	NA	NA
2	32	B	M	Yes	None	+	66977	150
3	67	B	M	Yes	None	+	81900	526
4	30	B	M	Yes	Treated with IM PCN and oral doxycycline	+[a]	843	469
5	32	W	M	Yes	None	+	UR	UR
6	32	B	M	Yes	None	+[a]	31000	206
7	35	B	M	Yes	Undergoing treatment with IM PCN weekly	+[a]	UD	390
8	36	UR	M	Yes	Treated with IM PCN	+[a]	2203	426
9	43	B	M	Yes	Treated with IM PCN	–	NA	NA
10	31	UR	M	Yes	None	+[a]	50	151
11	39	UR	M	UR	None	+	UR	UR
12	42	B	M	UR	None	+	96481	46
13	59	W	M	Yes	None	–	NA	NA

W white, *B* black, *UR* unrecorded, *UD* undetectable, *M* male, *MSM* men having sex with men, *IM PCN* intramuscular penicillin, *NA* not applicable

[a] Patient on HAART therapy at time of presentation with syphilis

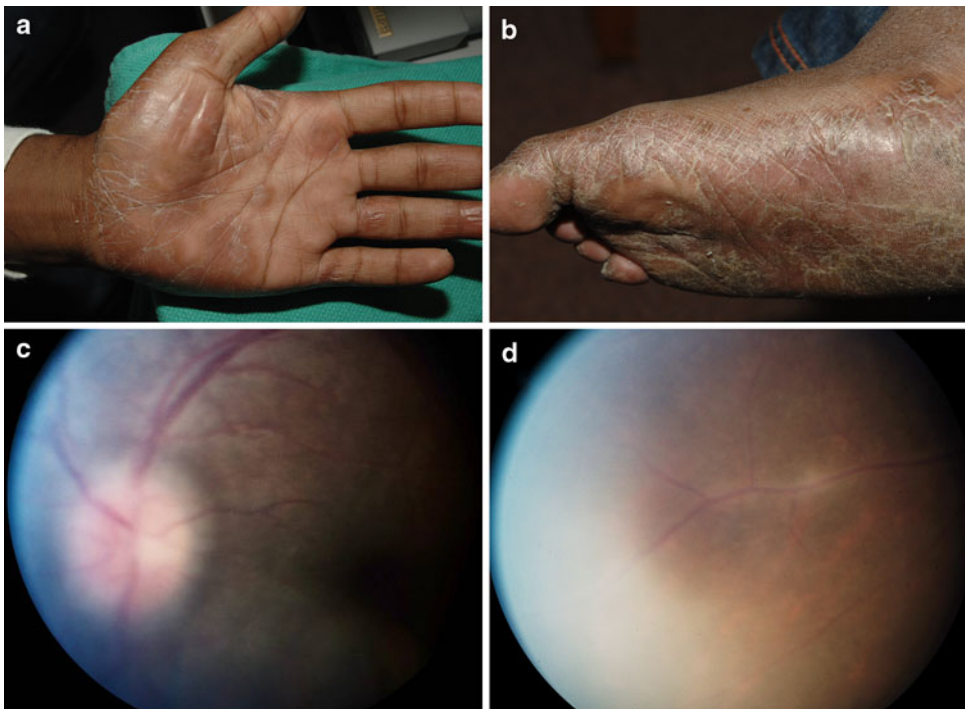

Fig. 1 Patient 2 with desquamating rash of palms and soles (**a**, **b**), disc edema OU with overlying vitritis (**c**), and retinal vasculitis (**d**)

this time. This increase did not represent a statistically significant difference ($p = 0.41$).

Patient population

Average age at presentation to the uveitis service of the patients diagnosed with syphilitic posterior uveitis was 40 years (range 30–67 years). All patients were men, and all with available data ($n = 10$) were men having sex with men (MSM). Ten of 12 (83%) patients tested were HIV positive. Of these, seven patients had a known history of HIV, of which five were on HAART. Three were newly diagnosed with HIV after their presentation with ocular syphilis. Two patients were HIV negative, and one was not tested. Three of 13 patients (21%) had CD4 counts <200 cells/μL at the time of presentation. One patient had recent pneumocystis pneumonia (patient 10), another had recent shingles (patient 12), and a third had been treated for pulmonary tuberculosis (patient 8).

Three patients reported a prior history of syphilis, and all recalled being treated with intramuscular (IM) penicillin (PCN) up to 2 years prior to presentation. One of the three patients (patient 4) also received oral doxycycline for treatment of syphilis 4 months prior to presentation. A fourth patient was receiving IM PCN from the infectious disease service for secondary syphilis at the time of his presentation to the uveitis service.

Clinical presentation

Presenting symptoms included decreased vision (54%), floaters (31%), photopsias (15%), redness (15%), pain (8%) and photophobia (8%). Two patients (15%) were asymptomatic. Symptoms were present for 5 days to 9 months. Eight (62%) patients had been previously seen by an eye care specialist, and half of these were on a topical steroid regimen for uveitis at the time of diagnosis.

Five patients had systemic symptoms (38%). These included weight loss, fever, fatigue and a desquamating rash of the palms and soles (patient 2, Fig. 1a, b). Neurologic symptoms included headache (patient 2, 12), ataxia (patient 12), hearing loss (patient 2) and tremor of the hand (patient 2). Patient 13 had a recent diagnosis of polyneuropathy (characterized by pain radiating down one arm with numbness in the ulnar distribution), and had multiple inflammatory foci adjacent to dilated perivascular spaces on brain MRI. He reported improvement in neuropathy symptoms with IV PCN.

Uveitis was bilateral in 11 of 13 (85%) patients overall and 8 of 10 (80%) HIV-positive patients. Clinical findings are presented in Table 2 and summarized in Table 3. Prominent findings included optic disc edema or disc pallor (42% of eyes), vasculitis (38% of eyes), and retinitis (29% of eyes; Figs. 2a, 3). One patient had retinal necrosis (patient 9). Other findings included vitreous hemorrhage (patient 1), presumably from underlying retinal involvement and

Table 2 Clinical findings of syphilitic posterior uveitis, laboratory findings, and response to treatment

Patient	Presenting Va (OD; OS)	Anterior segment	Posterior segment	FTA-ABS	RPR (dilutions)	CSF profile	Treatment	Response (as of last follow-up)	Follow-up time (from start of tx)	Final Va (OD; OS)
1	20/20; 20/20	Iridocyclitis OU	Vitritis OU Vitreous hemorrhage OD Disseminated choroiditis OU Disc edema OD	+	+	NA	IV PCN 10 days	Residual chronic intermediate uveitis; atrophic scars	7 months	20/20; 20/20
2	20/50; 20/60	Iridocyclitis OU	Vitritis OU Retinal edema and flame-shaped retinal hemorrhage OD Phlebitis OU Disc edema OU	+	512	**CSF VDRL weakly reactive**; **WBC 147 (0–5)**; **L 84% (40–80)**; glucose nl; **protein 128 (15–45)**	IV PCN 14 days	Improvement of disc edema and vasculitis	14 days	20/50; 20/50
3	20/25; 20/100	Granulomatous iridocyclitis OS	Vitritis OS Infiltrative retinitis in macula OS	+	128	NA	IV PCN 14 days	Complete resolution of infiltrative lesion without scarring	4 months	20/25; 20/30
4	20/25; 20/20	None	Vitritis OD Retinochoroiditis OS Phlebitis OD	+	+	NA	IV PCN 10 days	Resolution of inflammation; small residual depigmented lesions	3 years	20/20; 20/20
5	20/100; 20/200	Iridocyclitis OU; keratic precipitates OU; posterior synechiae OU	Vitritis OU Retinochoroiditis OU Chorioretinal atrophic scars OU	+	128	NA	IV PCN[a]	Resolution of inflammation; atrophic chorioretinal scars	1 year	20/20, 20/25
6	20/20, 20/30	Keratic precipitates OU	Vitritis OU Infiltrative retinitis along arcades OS Phlebitis OS RPE changes in macula OS	+	256	CSF VDRL negative; **WBC 6 (0–5)**; **L 99% (40–80)**; glucose and protein nl	IV PCN 10 days[b]	Resolution of inflammation; RPE pigmentary changes throughout and ERM OS	26 months	20/25; 20/25
7	20/25, 20/20	None	Disc edema OD	+	128	CSF VDRL negative; WBC nl; glucose nl; **protein 54 (15–45)**	IM PCN (weekly for 3 weeks)	No follow-up exam	NA	NA
8	20/30, 20/40	None	Vitritis OS Choroiditis OS Dot blot retinal hemorrhage OS Vascilitis OU Optic nerve pallor OU	+	1	CSF VDRL negative; WBC nl; **L 95% (40–80)**; glucose and protein nl	IV PCN loading dose, then IM ceftriaxone for 10 days	Resolution of inflammation; peripheral non-perfusion OU; old sheathing OU, RPE changes OU	7 years	20/30; 20/70

Table 2 continued

Patient	Presenting Va (OD; OS)	Anterior segment	Posterior segment	FTA-ABS	RPR (dilutions)	CSF profile	Treatment	Response (as of last follow-up)	Follow-up time (from start of tx)	Final Va (OD; OS)
9	20/50; 20/20	Iridocyclitis OU Keratic precipitates OU Koeppe nodules OU	Vitritis OU Extensive peripheral chorioretinitis OD Extensive areas of retinal necrosis OS with adjacent vascular occlusion Vasculitis OU	+	2	CSF VDRL negative; other details UR	IV PCN 10 days[c]	Residual chronic iritis OU with resolution after 6 years; atrophic chorioretinal scars OU	16 years	20/200 (dense cataract); 20/30
10	20/400; 20/200	Iridocyclitis OU Keratic precipitates OU	Vitritis OU Retinitis OU Disc edema OU	+	256	CSF VDRL negative; other details UR	IV PCN 10 days	Resolution of inflammation; retinal detachment OD with PPV/scleral buckle	14 months	20/50: 20/20
11	20/30; HM	Iridocyclitis OS Keratic precipitates OS	Vitritis OS Extensive "thumb-print" chorioretinal scars OD Dot blot retinal hemorrhage OD Extensive active peripheral retinitis (yellow–white) OS Vasculitis OS Optic nerve hyperemia OS	+	>1024	NA	Tetracycline 500 PO QID for 30 days[d]	Stable exam with limited follow-up	4 days	UR; CF
12	20/100; 20/50	Iridocyclitis OU	Vitritis OU Infiltrative retinitis OU Optic nerve pallor OD Scleritis OD	+	>1024	CSF VDRL negative; WBC, L, glucose, and protein nl	IV PCN 10 days[a,c]	Improvement of inflammation with fading of retinitis OU	5 days	20/60; 20/60
13	20/20; 20/20	None	Anterior vitritis OU Intraretinal hemorrhages OD Multifocal choroiditis OU	+	1024	**CSF VDRL positive**; other details UR	IV PCN 10 days	Minimal residual inflammation OU	15 days	20/20; 20/20

Abnormalities in CSF profile are in bold with normal range in parentheses

Va visual acuity, *NA* not available, *UR* unrecorded, *tx* treatment, *nl* normal, *L* lymphocytes

[a] Initially treated for toxoplasmosis

[b] Initially treated with IV and intravitreal foscarnet and ganciclovir for progressive outer retinal necrosis (PORN)

[c] Initially treated with IV antiviral (acyclovir or ganciclovir) for bilateral acute retinal necrosis (BARN)

[d] Allergic to PCN, refused desensitization, also treated with IV acyclovir and intravitreal ganciclovir and foscarnet for BARN

scleritis (patient 12). Eight patients had significant anterior chamber inflammation in addition to their posterior segment findings.

Laboratory evaluation

All patients had positive RPR and FTA-ABS (by inclusion criteria). Eight patients underwent lumbar puncture (Table 2), with only two positive for cerebrospinal fluid CSF-VDRL (25%). One positive result was weakly positive. Three other patients had other CSF abnormalities (pleocytosis, lymphocytosis, or elevated protein), and a total of five patients (63%) had CSF abnormalities.

Treatment and outcome

Ten patients were treated with IV PCN for at least 10 days. One patient (patient 7) was treated with IM penicillin, another (patient 8) was treated with IM ceftriaxone following an IV PCN bolus, and a third (patient 11) who was allergic to PCN refused desensitization and was treated with oral tetracycline. Follow-up was available in 12 of 13 patients, with an average follow-up of 31 months (4 days–16 years).

All cases treated with IV PCN for 10–14 days showed improvement in the degree of intraocular inflammation. The patient treated with IM ceftriaxone (patient 8) also demonstrated resolution of uveitis and had improved visual acuity at the 1 month follow-up. Patient 11, who was treated with oral tetracycline, was lost to follow-up, so the response to treatment could not be accurately determined. It is worth noting that we did not see any worsening of inflammation associated with immune reconstitution inflammatory syndrome (IRIS), even in a patient who began HAART around the time of his presentation.

One patient (patient 10) developed a retinal detachment that was repaired with pars plana vitrectomy and a sclera buckle; he had good final visual outcome (20/20 at 14-month follow-up). No interventions other than IV PCN were necessary for the patient with limited vitreous hemorrhage (patient 1) or the patient with scleritis (patient 12).

In the cases of retinal and choroidal involvement for which long-term data are available, the inflammation

Table 3 Clinical findings summarized for 24 affected eyes of 13 patients with posterior syphilitic uveitis

Clinical finding	Number of eyes affected/% eyes/% pts
Vitritis	20/83/92
Iridocyclitis or iritis	14/58/62
Disc edema or pallor	10/42/54
Vasculitis	9/38/46
Retinitis	7/29/38
Choroiditis	5/21/23
Retinal hemorrhage	4/17/31
Chorioretinitis or chorioretinal scars	4/17/23
Retinochoroiditis	3/13/15
Retinal necrosis	1/4/8
Vitreous hemorrhage	1/4/8
Scleritis	1/4/8

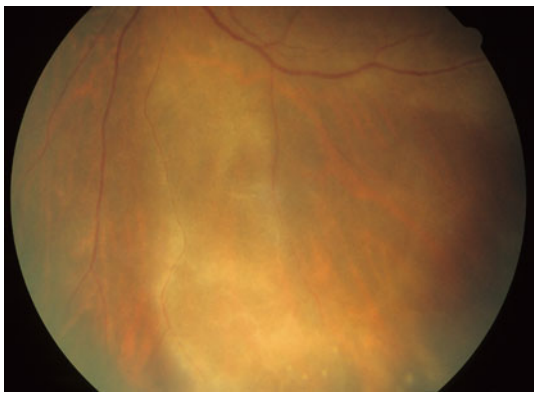

Fig. 3 Patient 12 with infiltrative retinitis. The patient improved after only 5 days of IV PCN

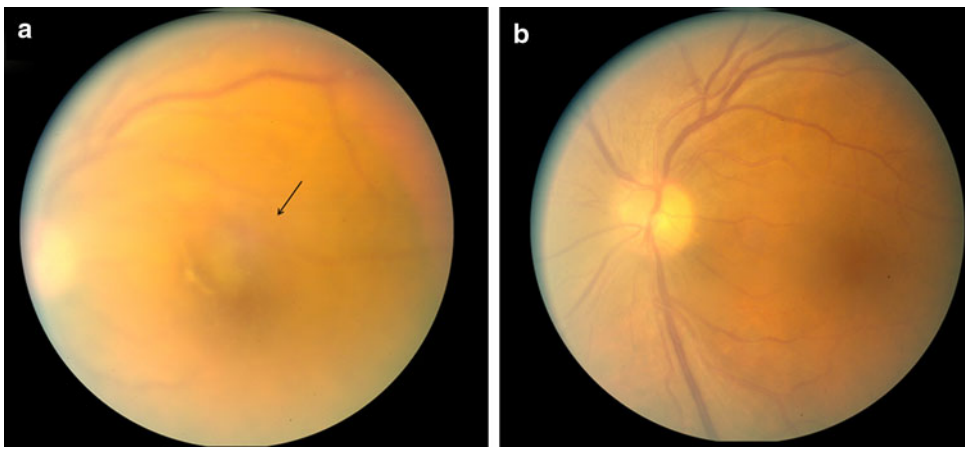

Fig. 2 Patient 3 with an infiltrative macular lesion and overlying vitritis before (**a**) and 5 days after (**b**) the completion of a 14-day course of IV PCN

resolved, leaving atrophic scars and pigmentary change ($n = 6$). In one instance, the retinitis completely resolved without associated scarring (patient 3; Fig. 2a, b), with a final visual acuity of 20/30, though an epiretinal membrane was visible at the 1 year follow-up.

One patient (patient 9) developed chronic iritis, and another (patient 1) developed chronic intermediate uveitis. The patient with chronic iritis had resolution after 6 years, and the patient with intermediate uveitis remained on treatment with topical corticosteroids at the last follow-up (7 months) but had only mild inflammation OU and visual acuity of 20/20 OU.

In 22 eyes with follow-up data, final visual acuity was ≥20/70 in 20 eyes (91%) and ≥20/30 in 14 eyes (64%). One patient (patient 9) had 20/200 vision due to a dense cataract. In all the patients treated with IV PCN, visual acuity improved or remained unchanged.

Discussion

Several authors have published series on ocular syphilis [3–19]. Most studies include patients with anterior and posterior uveitis, and few look at posterior uveitis specifically [4, 5, 14]. To our knowledge, ours is one of the larger series of syphilitic posterior uveitis, and of such patients co-infected with HIV.

While most series on syphilitic posterior uveitis [4, 5, 14] demonstrate co-infection rates of between 27 and 36%, ours demonstrates a much higher rate of HIV co-infection (83%). This is likely due to a progressive decline in AIDS-related mortality, as other series [4, 5, 14] studied patients seen earlier (1986–1996) than the current series. In contrast, Fonollosa et al. [6] observed a 75% co-infection rate among 12 patients seen between 2005 and 2007, all of whom had iritis and vitritis. The high rate of HIV co-infection observed in our series underscores the importance of HIV testing in patients presenting with ocular syphilis.

All patients in this series were men, which is in agreement with other series on ocular syphilis demonstrating a predominance of men [4, 6, 11, 15–17]. Although an early report [20] suggests an increase in the number of cases of syphilis among women, most series on ocular syphilis, including ours, have not reflected this change. The predominance of men with ocular syphilis is likely related to increased high risk sexual behavior among MSM, as all our patients for whom data was available were self-reported as MSM, and CDC data reflect an increase in syphilis among MSM [21].

We compared the clinical characteristics of our patients with those of other large series on posterior syphilitic uveitis [4, 6, 14]. It is often difficult to compare the prevalence of clinical findings among series because of the different ways in which results are presented. Nevertheless, some conclusions about the clinical presentation of posterior syphilitic uveitis and the differences in presentation between HIV-negative and -positive populations can be drawn.

We found bilateral involvement in 85% of cases overall and in 80% of HIV-positive cases, though the presentation was often asymmetric. Other series report bilateral disease in 44% [6] and 81% [15] of HIV-positive patients with ocular syphilis, all of whom had posterior involvement. A third series with a minority of HIV-positive patients (36%) report bilateral involvement in 71% of cases of posterior syphilitic uveitis [4]. We conclude, therefore, that bilateral involvement is common in posterior syphilitic uveitis among both HIV-positive and HIV-negative populations.

Another common feature of posterior syphilitic uveitis found in our series is optic neuritis (42% of eyes; 50% of eyes in HIV-positive patients). In comparing rates across other series, we found that 44% (15) and 46% [6] of eyes had optic nerve findings in HIV-positive patients with posterior involvement. DJ Browning [4], however, found only 13% of eyes with disc edema in his series of posterior syphilitic uveitis, which may be a result of the smaller HIV positive population (36%) studied. Optic nerve involvement, therefore, appears to be a more common feature of ocular syphilis in the HIV-positive population, suggesting a higher rate of neurosyphilis [11], and possibly reflecting the more severe presentation of ocular syphilis in this population.

We found several cases of syphilitic retinitis (29% of eyes), and one case of retinal necrosis. Though previously thought to be uncommon, recent studies [15, 18] demonstrate increasing rates of syphilitic retinitis. Tran et al. [15] found 7 of 19 eyes (39%) in HIV-positive patients with posterior uveitis to have necrotizing retinitis. Some studies report a lower rate [6], whereas a recent series [18] reports 6 of 6 HIV positive patients with retinitis. It is striking that the majority of cases of syphilitic retinitis, and necrotizing retinitis in particular, are reported in HIV-positive patients [6, 15, 26, 28, 30] suggesting a more severe presentation of syphilitic uveitis in the HIV population [31]. Though the increase in syphilitic retinitis may partially be due to increased recognition, it may also reflect an increase in HIV co-infection among cases of ocular syphilis.

In our experience, syphilitic retinitis is more common than the previously described placoid chorioretinitis [22] that has been considered pathognomonic for syphilis. In our series, syphilitic retinitis did, in some instances, lead to erroneous diagnoses, including toxoplasmosis and herpetic retinitis. In a study of 16 patients clinically diagnosed with acute retinal necrosis, 12.5% were found to be secondary to syphilis [23]. Other case reports [24–30] describe cases of

necrotizing or hemorrhagic syphilitic retinitis, often located in the peripheral retina, that were initially treated as viral retinitis.

All patients in the present study demonstrated either improvement or resolution of their uveitis with standard therapy (IV PCN 10–14 days). One patient received nonstandard therapy (IV PCN followed by IM ceftriaxone) for which we conducted a significant follow-up; his condition also resulted in complete resolution of the uveitis. The response to treatment did not appear to be influenced by the HIV status or the CD4 count of the patient. Although co-infection with HIV has been associated with a more severe presentation [31], our series demonstrates that an excellent prognosis is still possible with aggressive treatment (Fig. 2a, b), with the majority of patients maintaining good visual acuity. This finding is in agreement with other series [4, 5, 11, 13, 15]. Recurrence rates are reported to be higher in HIV co-infected patients [5, 11, 32], although this was not observed in our series.

One patient, who was HIV positive, had residual chronic iritis, and another had residual intermediate uveitis. In both cases, the disease of the retina or choroid resolved with therapy, so neither was considered a treatment failure. The residual inflammation was well controlled with topical corticosteroids in both cases. To our knowledge, chronic residual inflammation after treatment for ocular syphilis has not been reported.

CSF-VDRL was found to be an inadequate marker for ocular syphilis in this series, given that it was only found to be positive in a minority of cases (25%). Some other series report anywhere from 11% [15] to 75% [6] of patients with a positive CSF-VDRL. Though other authors [13] report a high incidence of CSF-VDRL (63%) among HIV-positive patients, we did not find this to be true in our series. Note that the incidence of CSF-VDRL in this series (25%) may be an underestimate, as CSF data for five patients were not available. However, even if all of these five patients had tested positive for CSF-VDRL, 46% of the total would still have negative CSF serology. Negative CSF serology, therefore, does not rule out syphilis as a cause of posterior uveitis.

Other abnormalities of the CSF profile (e.g., pleocytosis, lymphocytosis, elevated protein) were more common in this series, although only detectable in 63% of patients tested. Although these nonspecific CSF abnormalities may be due to neurosyphilis, they may also be secondary to HIV in co-infected individuals [32].

Given the potential for negative CSF markers in patients with syphilitic uveitis, the decision to treat for ocular syphilis should not be based on lumbar puncture results, but rather on clinical impression in conjunction with serologic studies.

In conclusion, our series demonstrates that syphilis can present as various forms of posterior uveitis. Therefore, a low threshold of suspicion for this possibility is crucial. Testing for HIV is important, as the majority of patients in this series were co-infected. HIV-positive status may confer an increased risk of neurosyphilis and a more severe presentation. Appropriate treatment is important in ensuring a good prognosis, even in patients who present with severe disease.

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