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Syphilitic uveitis in patients infected with human immunodeficiency virus

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Abstract *Background:* This work investigates the incidence and clinical features of syphilitic uveitis in patients infected with human immunodeficiency virus (HIV). *Material and methods:* We retrospectively reviewed syphilitic uveitis in patients coinfected with HIV that presented at a referral center between July 2001 and November 2003. *Results:* Twelve patients (20 eyes) were included. The ocular manifestations of syphilis led to the discovery of HIV-1 seropositivity in three patients. All patients were male and homosexual. One patient has been previously treated for syphilis with benzathine penicillin G. One patient presented with anterior uveitis and 11 patients had panuveitis or posterior uveitis. Necrotizing retinitis was noted in seven eyes (35%), posterior placoid chorioretinitis in six eyes (30%) and optic nerve involvement in five eyes (25%). Of nine patients with available cerebrospinal fluid (CSF) studies, seven (77.8%) had CSF abnormalities. Eleven patients were treated with intravenous penicillin G and one with intravenous ceftriaxone sodium. One patient required a second course of antibiotics to control uveitis. Ocular inflammation decreased and visual acuity improved in all nine patients for whom follow-up was available after treatment. *Conclusion:* Manifestations of syphilitic uveitis in HIV-infected patients are multiple, with high frequencies of posterior uveitis, posterior placoid chorioretinitis, necrotizing retinitis and optic nerve involvement. Syphilitic uveitis in HIV-infected patients seems to have a more severe course and may relapse despite high-dose intravenous penicillin therapy.

Keywords Antibiotics · Homosexual · Human immunodeficiency virus infection · Syphilis · Retinitis · *Treponema pallidum* · Uveitis

Introduction

Syphilis was the most common cause of intraocular inflammation during the 1920s. Its prevalence dramatically decreased during the 1950s through the use of specific antibiotics [33]. However, over the last decade, the incidence of syphilis has been rising due to increased high-risk sexual behaviour which is also a risk factor for HIV infection [30].

Manifestations of ocular syphilis in HIV-infected hosts are manifold: iridocyclitis, papillitis, optic neuritis, branch retinal vein occlusion, chorioretinitis, intermediate uveitis, panuveitis, necrotizing retinitis, periphlebitis, serous retinal detachment and vitritis [4, 20, 21, 29, 32]. Syphilitic uveitis is more rapidly progressive [25], and relapses are more frequent in this population than in immunocompetent hosts [4].

The goal of this study was to determine the incidence of syphilitic uveitis in a tertiary eye care referral center and to analyze the clinical features and the response to therapy in HIV-infected patients.

Table 1 Demographic and clinical features

Number	Sex	Age (years)	Risk factors for HIV infection	CD4 counts (/ml)	Initial VA		Final VA		Ocular findings	
					OD	OS	OD	OG	OD	OS
1	M	39	Homosexual	50	20/20	CF	NA		Normal	Vitritis, necrotizing retinitis
2	M	47	Homosexual	424	HM	20/20	20/100	20/20	Posterior placoid chorioretinitis	Normal
3	M	56	Homosexual	400	20/40	20/25	20/20	20/20	Vitritis, disc edema	Vitritis, Disc edema
4	M	42	Homosexual	77	20/40	20/50	20/20	20/20	Disc edema, chorioretinitis	Disc edema
5	M	40	Homosexual	40	20/70	20/70	20/50	20/50	Vitritis, necrotizing retinitis, papillitis	Vitritis, necrotizing retinitis, papillitis
6	M	44	Homosexual, Injected drug users	265	HM	CF	20/20	20/20	Vitritis, posterior placoid chorioretinitis	Vitritis, posterior placoid chorioretinitis
7	M	40	Homosexual	252	20/400	20/30	20/50	20/20	Vitritis, disc edema, placoid posterior chorioretinitis	Vitritis, disc edema
8	M	40	Homosexual	240	20/50	20/200	NA		Vitritis, necrotizing retinitis	Vitritis, Necrotizing retinitis
9	M	39	Homosexual Injected drug users		20/30	20/25	NA		Posterior placoid chorioretinitis	Normal
10	M	35	Homosexual Injected drug users	421	CF	20/50	20/50	20/25	Vitritis, necrotizing retinitis	Vitritis, necrotizing retinitis
11	M	28	Homosexual	300	20/40	20/40	20/25	20/25	Anterior uveitis	Anterior uveitis
12	M	46	Homosexual	907	20/20	20/100	20/20	20/25	Normal	Vitritis, posterior placoid chorioretinitis

CF Counting fingers, *HM* hand motion, *NA* not available, *OD* right eye, *OS* left eye, *VA* visual acuity

Materials and methods

This study is a retrospective chart review from one center between July 2001 and November 2003. Inclusion criteria were active uveitis and a positive treponemal serologic test (MHA-TP or FTA-ABS) in HIV-infected patients. HIV infection may have been known before uveitis or have been discovered after uveitis work-up. HIV-1 exposure was confirmed by the presence of both a positive serum HIV-1 enzyme-linked immunosorbent assay (ELISA) and a Western blot assay. Patients with old scarring of prior disease were excluded. Patient charts were reviewed for the following data: age, gender, sexual practice, known previous syphilis, duration of symptoms, initial and final visual acuity, ocular and systemic findings, CD4 counts, dosage and duration of intravenous penicillin therapy, disease recurrence, CSF analysis, and follow-up duration.

Results

Twelve HIV-infected patients with syphilitic uveitis were included (Table 1). In the same period, five HIV-negative patients presented with ocular syphilis. Routine syphilitic

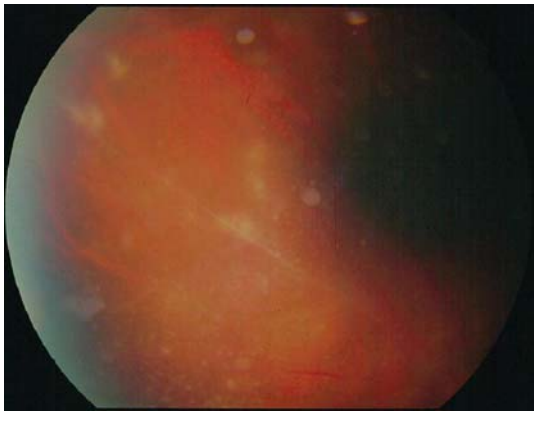

Fig. 1 Necrotizing retinitis and vasculitis in patient 10

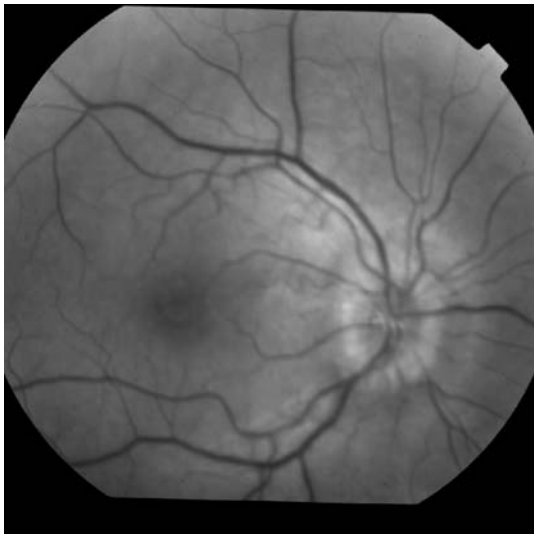

Fig. 2 Optic disc photograph of case 5 that demonstrates the swelling of the disc that occurs in syphilitic optic perineuritis

testing (MHA-TP and VDRL) is performed in all patients presenting with uveitis at our center. These 17 patients represented 0.85% of the 2,000 patients with uveitis that were treated for the first time in our department during this period of time.

All of the HIV-infected patients with syphilic uveitis were male. Risk factors for HIV infection were: homosexuality in all patients (100%) and intravenous drug abuse in three patients (25%). Uveitis was bilateral in eight patients (67%) and unilateral in four patients (33%). The duration of symptoms ranged from two days to three weeks (median 14 days). Syphilitic uveitis led to the diagnosis of HIV infection in three patients (25%). CD4 counts at the time of diagnosis were available in 11 patients and ranged from 50 to 907 cells/mm^3 (median 307 cells/mm^3). All patients had ocular complaints as initial manifestations of syphilis, although two patients (16.7%) had headaches and three patients (25%) presented with concomitant maculopapular rash.

Pretreatment visual acuity ranged from 20/25 to hand motion. Anterior uveitis was found in one case (8.3%). Eleven patients (91.7%) presented with posterior uveitis or panuveitis associated with necrotizing retinitis (seven eyes,

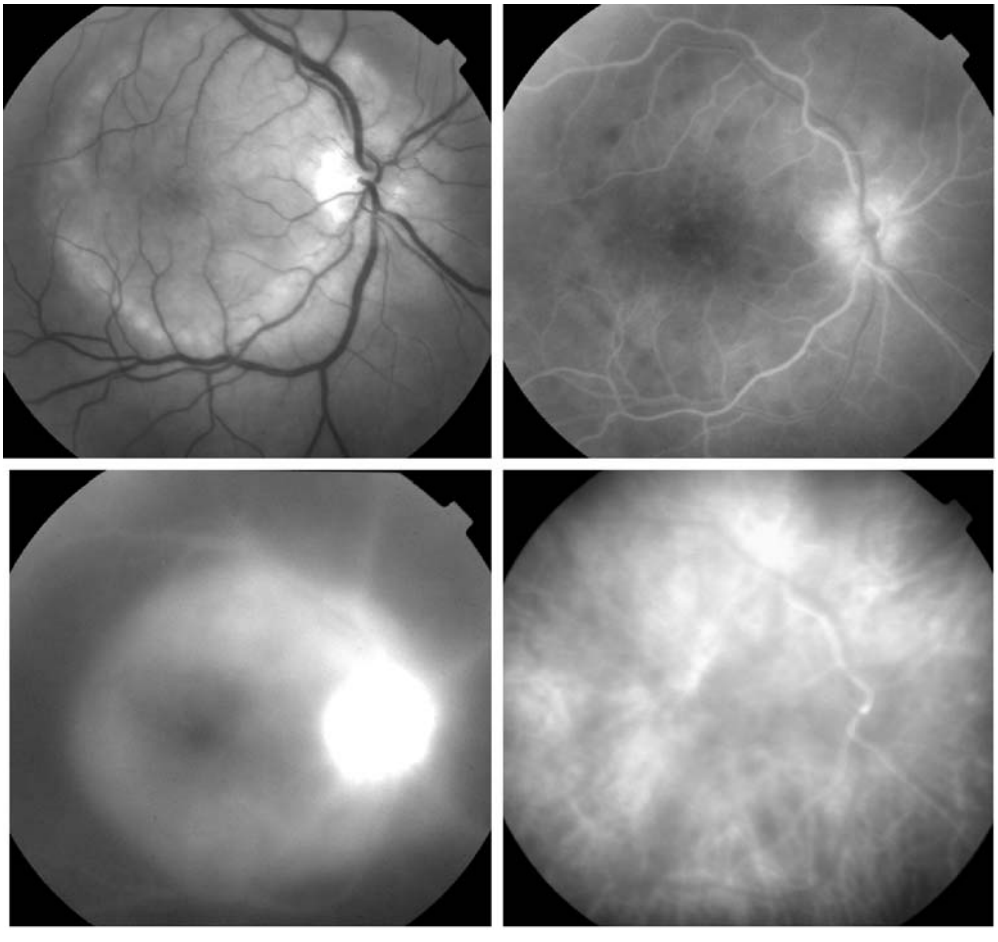

Fig. 3 Case 6. *Top left*: right eye. Note the crescent at the posterior pole that extends superior to the major vascular arcade and the optic disc. *Top right*: leopard spot hypofluorescence at an early phase of the fluorescein angiogram. *Bottom left*: late diffuse staining. *Bottom right*: Hypofluorescence at an early phase of the indocyanine green angiogram

35%) (Fig. 1), optic disc edema (five eyes, 25%) (Fig. 2), posterior placoid chorioretinitis (six eyes, 30%) (Fig. 3). Panuveitis associated with necrotizing retinitis was found in four patients (1, 5, 8, 10) leading to a diagnosis of acute retinal necrosis in three patients (3, 8, 10). These patients were initially treated with intravenous acyclovir or foscarnet. Routine syphilitic testing confirmed ocular syphilis three days later.

All patients had positive MHA-TP or FTA-ABS (Table 2). Of nine patients with available CSF studies, seven (77.8%) were abnormal with pleocytosis, three (33%) were MHA-TP-positive and reactive, and two had normal CSF. Post-treatment CSF analysis was not performed.

Eleven patients (66.7%) received intravenous penicillin (24 millions units per day for at least 14 days). One patient was treated with intravenous ceftriaxone sodium (2 g/day for 21 days). One patient (patient 9) had a previous history of syphilis, that was treated with intramuscular benzathine penicillin G. His syphilic uveitis did not resolve and he was referred for high-dose intravenous penicillin G therapy. Neither relapse nor reinfection has been observed.

All patients were re-examined shortly after initiation of treatment (1–21 days). Follow-up was available in nine patients. Mean follow-up was 29 weeks (ranging from 2 to 135 weeks). Nine patients treated with antibiotics (15 eyes) improved with follow-up or resolved their intraocular inflammation. Improvement of visual acuity was achieved in all patients.

Patient 6 presented with bilateral posterior uveitis, vitritis and posterior placoid chorioretinitis. He was first treated with intravenous penicillin (24 million units per day for 21 days). Vitritis was cleared after treatment and visual acuity improved from hand motion to 20/100 in the right eye and from counting fingers to 20/70 in the left eye two months

Table 2 Tests results and treatment

Number	Sera	Cerebrospinal fluid	Treatment	Follow-up
1	MHA-TP=1/20480; VDRL=1/256	Pleocytosis, elevated protein level, nonreactive	I.v., ceftriaxone 2 g/day×21 days	Not available
2	FTA-ABS=1/1600; VDRL=1/64	No cells, nonreactive	I.v., penicillin 24 mU/day×14 days	6 weeks
3	FTA-ABS=1/20480, MHA-TP=1/10240, VDRL=1/12	Pleocytosis, elevated protein level, nonreactive	I.v. penicillin 24 mU/day×10 days then i.m. ceftriaxone 2 g/day×21 days	24 weeks
4	MHA-TP=1/1280, VDRL=1/8	Pleocytosis, elevated protein level, nonreactive	I.v., penicillin 24 mU/day×14 days	12 weeks
5	MHA-TP=1/320, VDRL=1/128	Pleocytosis, elevated protein level, nonreactive	I.v., penicillin 24 mU/day×21 days	12 weeks
6	MHA-TP=1/20180, VDRL=1/64	Not available	I.v., penicillin 24 mU/day×21 days. Then second treatment 2 months later with penicillin 24 mU/day×10 days then ceftriaxone 2 g/day×10 days	54 weeks
7	FTA-ABS=1/1250, MHA-TP=1/20 480 VDRL=1/512	Pleocytosis, elevated protein level, MHA-TP=1/80	I.v., penicillin 24 mU/day×14 days	12 weeks
8	MHA-TP=1/10000 VDRL=1/16	Pleocytosis, elevated protein level, MHA-TP=1/1280	I.v., penicillin 24 mU/day×14 days	2 weeks
9	MHA-TP=1/225360, VDRL=1/128	Not available	I.m. extencillin 2.4 mU×3 before admission then i.v. penicillin 24 mU/day×14 days	Not available
10	MHA-TP=1/10240, VDRL=1/128	Pleocytosis, elevated protein level, MHA-TP=1/160, VDRL=1/2	I.v., penicillin 24 mU/day×21 days	135 weeks
11	FTA-ABS=1/800, MHA-TP=1/5120 VDRL=1/32	Not available	I.v., penicillin 24 mU/day×14 days	Not available
12	MHA-TP=1/4120 VDRL=1/32	No cells, nonreactive	I.v., penicillin 24 mU/day×14 days	12 weeks

MHA-TP Microhemagglutination assay with *Treponema pallidum* antigen, *FTA-ABS* fluorescent treponemal antibody absorption test, *i.v.* intravenous, *i.m.* intramuscular, *VDRL* Venereal Disease Research Laboratory.

later. The chorioretinitis remained active and a second cure of antibiotics was administered three months later (penicillin G 24 million units per day for 21 days followed with intramuscular ceftriaxone sodium 2 g/day for ten days). With this antibiotic combination, the best visual acuity was achieved (20/20 ODS) six months later. The MHA-TP dropped from 1/20180 to 1/1750 and the VDRL from 1/64 to 1/1.

In the same period, five HIV-negative patients presented with ocular syphilis: bilateral posterior uveitis with vitritis and vasculitis in three cases, bilateral anterior uveitis in one case, and unilateral episcleritis in one case. Necrotizing retinitis and posterior placoid chorioretinitis were not observed in this group. Visual acuity was preserved in all cases after intravenous penicillin treatment, except in the case of one patient who presented visual loss in one eye due to neovascular glaucoma.

Discussion

Previous reports suggest that syphilis accounts for 0.8–4.3% of cases of uveitis [3, 32, 33]. The incidence of syphilitic uveitis is 0.85% in our center and is increasing, predominantly in HIV-infected patients. The reported frequency of syphilitic uveitis in the HIV-infected population is 0.6% [32]. The incidence of ocular syphilis in HIV-infected patients is comparable to the incidence of ocular toxoplasmosis and progressive outer retinal necrosis [32].

In France, surveillance has indicated that the rate of new cases of AIDS has remained stable since 1999, with about 850 cases every six months. Since 2001, syphilis has increased among homosexual men living in the Paris area. Syphilis was mainly associated with homosexual or bisexual men. Half of them were coinfected with HIV [9]. The reported risk factors for syphilis and HIV infection in this population were multiple sex partners and unprotected sexual practices. Rises in the incidence of ocular syphilis have also been reported (especially among homosexual men) in other European cities [28].

Syphilis is the most common bacterial eye infection in HIV-positive patients and should be tested for in all HIV-infected patients with uveitis [11]. Specific treponemal serum antibody tests, such as FTA-ABS or MHA-TP, are sensitive and specific but provide no indication of disease activity. Non-specific treponemal serum antibody tests, such as the rapid plasma reagin (RPR) test or the Venereal Diseases Research Laboratory (VDRL) test, do provide information on disease activity, but false negatives have been reported in 11–30% of cases [11, 32]. The sensitivity of treponemal tests for previous syphilitic episodes is estimated to be 93% in asymptomatic HIV-positive patients, but this drops to 62% in symptomatic patients. This poor sensitivity is most likely due to progressive immune dysfunction [14].

The fact that ocular symptoms led to the discovery of HIV seropositivity in three of our patients (25%) and in half of the patients in another study [24] highlights the need for HIV infection screening in patients with syphilitic uveitis. Patients diagnosed with ocular syphilis should be tested for HIV, because the presence of a primary genital chancre increases the risk of acquiring or transmitting HIV, and because the risk factors for the two diseases are similar [1]. Males are predominantly afflicted with this coinfection in our study, and in most other reports [4, 24, 32].

Ocular syphilis is not correlated with HIV-infection staging. CD4+ lymphocyte counts varied considerably in our series and in previous reports [4, 7, 21, 24]. Ocular syphilis in patients with HIV-1 infection does not seem to be correlated with low CD4 counts.

Uveitis can occur at all stages of syphilis and clinical manifestations of ocular syphilis may be manifold: anterior uveitis, intermediate uveitis, posterior uveitis, posterior placoid chorioretinitis, necrotizing retinitis [7, 12, 33]. Results of this study and previous reports might suggest that syphilis is more aggressive in the HIV-infected population [17, 19]. Most patients present with bilateral disease (67 to 89%) [4, 24, 32]. The posterior segment is more frequently involved with optic neuropathy, necrotizing retinitis and posterior placoid chorioretinitis [4, 12, 21, 24, 32]. Necrotizing retinitis can be indistinguishable from acute retinal necrosis, and three patients received antiviral (acyclovir or foscarnet) due to high suspicion of acute retinal necrosis syndrome in our series. Ocular syphilis was diagnosed after a negative result from a herpesvirus polymerase chain reaction-based assay from aqueous humor and positive specific treponemal serum antibody tests. Cubillan et al [10] has previously reported a case of syphilitic uveitis which was initially misdiagnosed as an acute retinal necrosis. The term “syphilitic posterior placoid chorioretinitis” was first described by Gass in 1990 [12] in six patients who presented with secondary syphilis. These are large, placoid, yellowish lesions with faded centers at the level of the pigment epithelium in the macular and the juxtapapillary areas. All of these lesions showed similar angiographic patterns of early hypofluorescence and late staining. Three of the four patients were seropositive for HIV. According to the authors, the ophthalmoscopic and angiographic appearance of these lesions was sufficiently characteristic to suggest a diagnosis of syphilis [12]. This chorioretinitis was later described in an HIV-negative patient [5].

In our series, seven of nine patients with available CSF studies (88.9%) presented with cerebrospinal pleocytosis and elevated protein levels. Involvement of the central nervous system may occur in all stages of syphilis [23]. In the pre-antibiotic era, 30% of patients with syphilis went on to develop neurosyphilis. The use of antibiotics reduced this prevalence to 3%, but HIV coinfection may alter the natural history of neurosyphilis [17]. HIV-infected people may be at a higher risk of developing neurosyphilis, even after penicillin therapy for the initial disease [25].

Performing a lumbar puncture is a source of debate in the medical literature. CSF abnormalities were noted in 23–40% of untreated immunocompetent patients with primary

and secondary syphilis [31]. Even in the absence of syphilis or other infective pathogens, CSF abnormalities were common in HIV-infected patients [16]. CSF abnormalities are more frequent, with higher mean white blood cell counts and higher mean protein levels, in the HIV-positive group than in the HIV-negative group [4, 19]. It is difficult to attribute these alterations to HIV infection alone [22] or/and neurosyphilis [8, 18, 19]. Although these patients require high-dose intravenous penicillin whatever the cerebrospinal fluid discloses, it is important to quantify the activity of the disease of the central nervous system and to establish baseline CSF titers to monitor the efficacy of therapy [13]. CSF evaluation is recommended if one of the following is noted: treatment failure, evidence of central nervous system involvement, or ocular involvement [2].

In a randomised trial of enhanced therapy for early syphilis, the authors found that HIV-infected patients responded less well serologically than HIV-negative patients, but clinically-defined failure was uncommon in both groups. Detection of *Treponema pallidum* did not predict treatment failure [31, 34].

However, failure of benzathine penicillin G treatment for early stages of syphilis has been reported in HIV-infected patients [33] and relapse with ocular syphilis or neurosyphilis is not rare after adequate therapy for early syphilis with benzathine penicillin G [4, 13, 24, 32]. The failure rate after recommended penicillin regimens for early syphilis is estimated to 0.8% in HIV-negative patients and is probably higher in HIV-positive patients [13]. In patient 9 of this series, uveitis remained active with intramuscular benzathine penicillin G and was controlled only with intravenous high-dose penicillin. It has been suggested that HIV-positive patients may be more prone to progressive syphilitic infection [17]. Given these findings and the difficulty of diagnosing associated neurosyphilis, most authors advocate the neurosyphilis regimen of intravenous penicillin for ocular syphilis, regardless of the immune status, but recommendations vary on dose and duration [4, 7, 24, 32, 35].

Most patients treated with high-dose intravenous penicillin G therapy improved or resolved ocular inflammation and improved their visual acuity. One patient was treated successfully with intravenous ceftriaxone sodium because of an allergy to penicillin. This treatment was also effective in an HIV-positive patient [32] and in an HIV-negative patient [6] in other studies, and may be proposed in some patients allergic to penicillin. Patient 6 responded slowly to intravenous penicillin G therapy, and since the uveitis remained active, an intramuscular ceftriaxone sodium treatment was administered. Visual improvement was obtained with this treatment and no reactivation was observed at the end of follow-up.

The limit of this study is the relatively short follow-up. Although relapse has not been observed and visual improvement has been achieved in all patients, one must be cautious regarding long-term prognosis. Some authors have reported relapses of ocular syphilis despite intravenous penicillin therapy in HIV-positive and HIV-negative patients [4, 7, 13, 15, 24, 26, 27, 33, 36]. It is possible that prolonged treatment is necessary in this group of patients [26].

In conclusion, ocular syphilis may be atypical in HIV-infected patients and may be the initial manifestation of HIV infection. The neurosyphilis regimen of intravenous penicillin is necessary for ocular syphilis, and it improves the visual prognosis. Long-term ophthalmologic and systemic follow-up is required because relapses may occur in HIV-infected patients despite penicillin therapy.

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