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Ocular Syphilis among HIV-Infected Individuals

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Abstract

We describe a human immunodeficiency virus (HIV)-infected individual with ocular manifestations of secondary syphilis. Twelve other cases of HIV-associated ocular syphilis are also presented. Six of 12 individuals had normal cerebrospinal fluid study results, and 3 patients required retreatment within 1.5 years. In patients with HIV infection, clinicians should be vigilant for ocular syphilis despite normal cerebrospinal fluid measures and for syphilis reinfection.

During the past decade, syphilis has reemerged as a growing public health problem in the United States and Europe [1–4]. This resurgence has been especially notable among individuals coinfecting with human immunodeficiency virus (HIV) [3,5], in whom central nervous system and ocular involvement may be particularly common [1,6–10]. Although there have been several small studies specifically focused on ocular syphilis [11–14], the clinical manifestations, laboratory findings, and appropriate treatment of ocular syphilis in HIV-infected individuals remain uncertain. We describe an HIV-infected patient with ocular syphilis that recurred despite appropriate therapy and summarize the clinical course for an additional 12 previously unreported cases.

Case report

A 41-year-old HIV-infected man presented with a 1-month history of decreasing vision in the left eye. He also reported 2 weeks of fevers, fatigue, nasal congestion, and sore throat; 2 days of frontal headache; and patchy loss of his scalp and beard hair. Approximately 6 months earlier, his CD4⁺ T cell count was 331 cells/ μ L and a serum rapid plasma reagin (RPR) test was nonreactive. He had not received antiretroviral therapy (ART) for 2 months and had recently ended a relationship with a male partner.

Important examination findings included patchy alopecia of the scalp, faint erythematous macular rash on the hands and extremities, and shotty cervical and axillary lymphadenopathy. Visual acuity was 20/30 in the right eye and 20/400 in the left eye. Slit

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lamp and funduscopy examination showed bilateral panuveitis and optic disk edema. His CD4⁺ cell count was 228 cells/ μ L, HIV type 1 RNA count was 188,000 copies/mL, and serum RPR was reactive at a titer of 1:2048. Cerebrospinal fluid (CSF) findings included a white blood cell count of 20 cells/ μ L (90% lymphocytes), a protein level of 60 mg/dL, and CSF-VDRL test reactive at a titer of 1:2.

The patient received a diagnosis of secondary syphilis with ocular and neurosyphilis and was administered a 2-week course of intravenous penicillin G (24 MU/day). On hospital day 3, the patient complained of worsening vision and was administered intravenous methylprednisolone (80 mg every 8 hours) followed by oral prednisone that was tapered for 2 months. A follow-up ophthalmologic examination 1 month later showed 20/20 visual acuity bilaterally and complete resolution of inflammation. The patient restarted his ART, and during the ensuing months, RPR decreased to a titer of 1:64. He did not undergo a reexamination of the CSF.

Fifteen months later, the patient returned with recurrent panuveitis in the right eye. He had engaged in 1 episode of unprotected oral sex ~9 months before. His CD4⁺ cell count was 405 cells/ μ L, plasma HIV RNA was undetectable, and serum RPR titer was 1:128. CSF examination revealed a white blood cell count of 28 cells/ μ L (72% lymphocytes), a protein level of 84 mg/dL, and VDRL test titer reactive at 1:2. He was treated with 2 weeks of intravenous penicillin G (24 MU/day) and 1 intramuscular dose of penicillin G benzathine (2.4 MU) at the completion of intravenous therapy. A follow-up ophthalmologic examination 1 month later showed complete resolution of ocular inflammation, and a CSF examination 7 months later showed resolution of the lymphocytosis and a nonreactive CSF VDRL test.

Methods

The Partners Healthcare Research Patient Data Registry (RPDR) is a centralized clinical and laboratory database containing data for >4 million patients and 8000 HIV-infected patients seen at Brigham and Women's Hospital or Massachusetts General Hospital. The RPDR was searched for cases using a combination of *International Classification of Diseases, Ninth Revision, Clinical Modification*, codes for HIV infection and syphilis with ocular or neurologic involvement. Two additional patients were identified from a neurosyphilis cohort observed at the University of Washington Harborview Medical Center by one of the authors (C.M.M.). Patients were defined as individuals with HIV, a reactive serum RPR or treponemal antibody test result, and a diagnosis of uveitis or optic neuritis. An ophthalmologist (A.M.L.) reviewed all available ophthalmologic examination reports. The Spearman rank correlation test, Fisher exact test, and Wilcoxon rank sum test were performed with SPSS, version 11.5 (SPSS). The Mantel-Haenszel χ^2 test was performed with SAS, version 9.2 (SAS Institute). This study was approved by the institutional review boards of Partners Healthcare, Massachusetts Eye and Ear Infirmary, and the University of Washington.

Results

We describe 13 HIV-infected patients with ocular syphilis (Table 1). Whereas the RPDR database contains records from the past 2 decades, 12 cases (92%) occurred after 2000. All subjects were male, and 11 (85%) were men who have sex with men. Nine patients (69%) had manifestations of secondary syphilis, including rash, mucous patches, alopecia, fever, and night sweats. Nine patients had bilateral ocular syphilis, and 5 had optic neuritis.

Four patients (31%) received a diagnosis of concomitant HIV infection at the time of ocular syphilis diagnosis. There was no significant correlation between CD4⁺ cell count and any syphilis-related ocular manifestations or laboratory findings. Twelve patients underwent lumbar puncture. One patient with anterior uveitis and signs of neurosyphilis declined a lumbar puncture. All CSF measures (white blood cell count, protein level, and CSF-VDRL test) were normal or nonreactive in 6 of 12 individuals. Patients receiving ART had lower CSF protein levels (median, 38 vs 63 mg/dL; $P = .04$) and lower CSF white blood cell counts (median, 3.5 vs 16.0 cells/mL; $P = .09$) than patients who were not receiving ART. None of the 6 individuals receiving ART had a reactive CSF VDRL test, but 5 of 6 patients who were not receiving ART had reactive CSF VDRL test titers (Fisher exact test; $P = .02$). Patients with higher serum RPR titers were more likely to have a reactive CSF VDRL test: none of the 4 subjects with RPR titers less than or equal to 1:128 had a reactive CSF VDRL titer, whereas 2 of 5 subjects with RPR titers of 1:256 and all 3 subjects with RPR titers of 1:512 or greater had reactive CSF VDRL titers (Mantel-Haenszel χ^2 ; $P = .01$).

Ten patients were initially treated with 2 weeks of intravenous penicillin (24 MU/day) (Table 1). Six (46%) of 13 patients received weekly intramuscular penicillin G benzathine (2.4 MU) for 1–3 weeks afterward. There were no significant differences in initial ocular manifestations or laboratory values between the groups who did and did not receive additional intramuscular penicillin. For 1 patient, the intravenous penicillin regimen was extended by 1 week because of signs of persistent ocular inflammation. Another patient was treated with 28 days of oral doxycycline (200 mg twice per day) when he developed rash and angioedema while receiving penicillin despite desensitization. Six patients received a tapered regimen of systemic steroids lasting up to 2 months. There were substantial improvements in visual acuity among all patients within 3 months (Table 1).

In addition to the patient noted above, 2 other patients required syphilis re-treatment within 18 months after their original episode. Both patients had unprotected sexual encounters in the interim that were thought to have resulted in reinfection. Patient 7 complained of visual changes 18 months after his initial presentation. His serum RPR titer increased from 1:8 to 1:128. His fundoscopic examination revealed no signs of inflammation, and a second lumbar puncture was not performed. Patient 9's RPR titer increased from 1:2 to 1:64 on follow-up screening 8 months later. He was asymptomatic, and on repeated testing, CSF measures were normal. Both patients were treated with 3 weekly doses of intramuscular penicillin G benzathine (2.4 MU).

Discussion

A review of the literature showed that ocular syphilis may be a manifestation of either early or late syphilis in both HIV-positive patients [12,13,15] and HIV-negative patients [15–17]. All of the HIV-infected individuals described in this case series likely had early syphilis on the basis of their symptoms or elevated serum RPR titers. Whereas uveitis and optic neuritis are common to all patients with ocular syphilis, some studies suggest that HIV-infected patients have a tendency toward acute posterior uveitis [11,15,18] and, in particular, posterior placoid chorioretinitis [19]. However, we did not observe a disproportionately high rate of posterior segment involvement in our population, and there were no cases of posterior placoid chorioretinitis.

Although our patients frequently showed evidence of neurosyphilis on the basis of a reactive CSF VDRL test result, individuals receiving ART were less likely to have evidence of neurosyphilis. Whether this relationship reflects a higher organism burden, an increased risk of central nervous system penetration by *Treponema pallidum*, or another etiology in patients with uncontrolled HIV replication is unclear. Studies of HIV-negative patients with

ocular manifestations of early syphilis have also revealed frequent CSF abnormalities consistent with neurosyphilis [15,16,20]. No consistent differences in CSF characteristics have been demonstrated between HIV-infected and -uninfected individuals in these small studies [15,20].

Past studies have revealed a higher risk of neurosyphilis with lower CD4⁺ cell counts [8,10], but we did not find any significant correlation between CD4⁺ cell count and any clinical manifestation or laboratory findings. However, this may be explained by the limitations of this study, which include a relatively small sample size and only 1 subject with advanced HIV disease.

Previous studies reporting high rates of treatment failure have raised the question of whether a longer course of antibiotic treatment may be needed in HIV-infected patients with neurosyphilis than in HIV-negative patients with neurosyphilis [8,21]. Most patients in our series received the standard 2-week course of intravenous penicillin, and a subset received intramuscular penicillin G benzathine and/or systemic steroids. There was substantial initial clinical improvement in all patients, but within 1.5 years, 3 patients in our case series required retreatment for syphilis, including 1 with recurrent ocular syphilis. Although treatment failure cannot be discounted, these patients were at risk of reinfection as a result of persistent high-risk sexual behavior.

Ocular syphilis can cause blindness if untreated, and clinicians must be vigilant in making this diagnosis. Although abnormal CSF study results are not necessary to make a diagnosis of ocular syphilis, lumbar punctures are warranted in HIV-infected patients with ocular disease, because a substantial proportion will have evidence of neurosyphilis. Behavioral counseling and close follow-up, including repetition of CSF studies in patients with neurosyphilis, are required because of the risk of relapse and reinfection. Larger studies are needed to further define the manifestations and optimal treatment strategy for ocular syphilis and neurosyphilis in the HIV-infected population.

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Table 1
Clinical Characteristics, Laboratory Results, and Treatment of Ocular Syphilis among Human Immunodeficiency Virus–Infected Patients

Patient	Age, years	CD4 ⁺ cell count, cells/ μ L	HIV RNA copies/mL ^a	Serum RPR level	CSF VDRL test result	CSF WBC count, cells/ μ L	Ocular examination result	Visual acuity		Antibiotic regimen ^d	Syphilis recurrence
								Before treatment ^b	After treatment ^c		
1	31	217	25,740	1:256	1:2	141	Panuveitis	20/800	20/63	Intravenous penicillin for 2 weeks, intramuscular penicillin for 3 weeks	No
2	38	532	<400	1:128	NR	12	Anterior uveitis	Intravenous penicillin for 2 weeks, intramuscular penicillin for 1 week	No
3	54	539	<50	1:256	NR	2	Posterior uveitis, optic neuritis	20/80	20/25	Intravenous penicillin for 2 weeks	No
4 ^e	41	228	188,000	1:2048	1:2	20	Panuveitis, optic neuritis	20/400	20/20	Intravenous penicillin for 2 weeks	Yes
5	52	237	174,000	1:128	NR	1	Anterior uveitis, optic neuritis	20/25	20/20	Intravenous penicillin for 3 weeks	No
6	36	745	54,500	1:1024	1:1	12	Panuveitis, optic neuritis	CF	20/20	Intravenous penicillin for 2 weeks, intramuscular penicillin for 1 week	No
7	36	472	<50	1:256	NR	4	Posterior uveitis	20/320	20/25	Intravenous penicillin for 2 weeks, intramuscular penicillin for 3 weeks	Yes
8	36	780	3380	1:256	1:4	11	Posterior uveitis			Intravenous penicillin for 2 weeks, intramuscular penicillin for 3 weeks	No
9 ^f	26	348	1850	1:128	Anterior uveitis	20/20		Intramuscular/intravenous penicillin for 10 days	Yes
10	46	599	<50	1:256	NR	5	Anterior uveitis	20/60	20/25	Intramuscular penicillin for 10 days	No
11	23	747	240,222	1:512	1:16	187	Anterior uveitis	CF	20/40	Intravenous penicillin for 2 weeks	No
12	45	305	<48	1:64	NR	3	Optic neuritis	20/20	16/15	Intravenous penicillin for 1 week, oral doxycycline for 28 days	No
13	55	142	<48	1:128	NR	1	Panuveitis, optic neuritis	20/200	20/32	Intravenous penicillin for 2 weeks, intramuscular penicillin for 1 week	No

NOTE. CSF, cerebrospinal fluid; NR, nonreactive; RPR, rapid plasma reagin; WBC, white blood cell.

^aAll 5 patients receiving antiretroviral therapy had viral loads less than the limit of detection.

^bVisual acuity scores of the more severely affected eye; CF, able to count fingers only from \leq 3 feet; original reports detailing visual acuity examination unavailable for 2 patients.

^cAll posttreatment visual acuities tested within 3 months.

^dIntravenous penicillin dosage was 24 MU daily; intramuscular penicillin, 2.4 MU weekly; oral doxycycline, 200 mg twice daily; patients 9 and 10 were treated with 2.4 MU intramuscular procaine penicillin daily with probenecid 500 mg 4 times per day; patient 9 was switched to intravenous penicillin after the fourth day.

^ePatient described in the case report.

^fDeclined lumbar puncture.

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