Original Article

Syphilitic Uveitis in HIV-Positive and -Negative Patients: A Multicenter Cohort Study

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Abstract

Objectives: To evaluate the clinical manifestations and visual outcomes of patients with syphilitic uveitis, and to compare these features based on human immunodeficiency virus (HIV) infection status.

Materials and Methods: The records of patients diagnosed with syphilitic uveitis between 2014 and 2024 were analyzed retrospectively. Demographics, history, ocular examination findings, syphilis and HIV serology, lumbar puncture test, treatment approaches, and best-corrected visual acuity (BCVA) results of all patients were documented.

Results: A total of 51 eyes of 33 patients were included in the study. Twenty-seven patients (82%) were male, with a mean age of 44 years (range, 21-69). HIV co-infection was present in 39% of the patients (all male). Prior to presentation, 9 patients (27%) had received an incorrect diagnosis or inappropriate treatment. The most common form of syphilitic uveitis was panuveitis (63%), followed by posterior uveitis (31%). Anterior segment inflammation and optic nerve involvement were observed at higher rates in patients with HIV co-infection ($p<0.05$). All patients received systemic penicillin therapy, and 51% received systemic corticosteroids. Visual acuity improved significantly after treatment in all patients ($p<0.01$). HIV co-infection status was not associated with age, laterality, lumbar puncture findings, the development of ocular complications, or baseline and final BCVA outcomes ($p>0.05$).

Conclusion: Syphilitic uveitis is an important clinical entity due to its broad spectrum of ocular manifestations. In this study, severe intraocular inflammatory findings, including panuveitis and optic nerve involvement, were more frequently observed in patients with HIV co-infection. However, HIV co-infection did not influence final visual acuity or the rate of ocular complication development.

Keywords: Syphilis, ocular syphilis, syphilitic uveitis, treatment, HIV

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Introduction

Syphilis is a sexually transmitted infection caused by the bacterium *Treponema pallidum* that can cause systemic and ocular involvement.[1] Since the beginning of the twentieth century, syphilis has undergone a resurgence and remains a significant public health concern worldwide.[1,2,3,4] Co-infection with human immunodeficiency virus (HIV) is common among patients with syphilis due to their common routes of transmission. If left untreated, syphilis progresses through various stages: primary, secondary, latent, and tertiary.[1] Ocular involvement of syphilis is uncommon and usually presents as syphilitic uveitis.[1,3] Syphilitic uveitis can occur at any stage of syphilis. Epidemiological studies have demonstrated that syphilitic uveitis accounts for a small proportion (<3%) of all uveitis cases.[5] This rate varies

regionally, reported in the literature as 1.4% in Japan,[6] 2.5% in France,[4] and 6.08% in Brazil.[7] According to a national registry report, syphilitic uveitis accounts for 0.1% of all uveitis in our country.[8] However, the rising incidence of syphilis in recent years has been accompanied by a parallel increase in syphilitic uveitis cases, both in Türkiye and globally.

Ocular involvement in syphilitic uveitis can present with a variety of anterior and posterior segment manifestations, including scleritis, anterior uveitis, retinitis, choroiditis, retinal vasculitis, optic neuritis, and panuveitis.[1,3,9] Although advances in ocular imaging have enabled the identification of the distinctive features of syphilitic uveitis, including acute syphilitic posterior placoid chorioretinitis (ASPPC), confluent retinochoroiditis, and superficial retinal precipitations, the condition can still mimic a wide spectrum of ocular inflammatory and infectious diseases.[9,10,11] This is why syphilis is called the "Great Imitator." This frequently results in misdiagnosis and delayed initiation of appropriate treatment.[9,12]

Given the increasing frequency of ocular syphilis and HIV co-infection, studies in recent years have aimed to investigate how HIV status affects the presentation, treatment response, and prognosis of syphilitic uveitis.[13,14,15,16,17,18,19] Although some studies suggest that HIV-positive patients present with more severe disease than those who are HIV-negative, the findings in the literature remain conflicting.[13,14,15,16,17] Despite these discrepancies, most studies show that both groups generally have comparable visual prognoses.[14,15,16,17] This multicenter study aimed to comparatively assess the demographic characteristics, clinical findings, disease course, and visual outcomes of patients with syphilitic uveitis according to HIV co-infection status.

Materials and Methods

This was a retrospective, multicenter medical record review of patients diagnosed with syphilitic uveitis between January 2014 and March 2024. Four ophthalmology departments from different tertiary referral centers across Türkiye participated in the study. The study was conducted in accordance with the principles of the Declaration of Helsinki. Ankara Training and Research Hospital Ethics Committee approval was obtained prior to study initiation (decision no: 95/2024, approval date: 17.04.2024, protocol number: E-24-95). Given the retrospective nature of the study, individual informed consent was not obtained.

Study Population and Data Collection

The diagnosis of ocular syphilis was established by uveitis specialists at each center based on clinical history, ocular examination and multimodal imaging findings, and positive syphilis serology. Treponemal tests used in the serological diagnosis of syphilis included fluorescent treponemal antibody absorption test, *Treponema pallidum* hemagglutination test, and enzyme immunoassay test. Non-treponemal tests included the Venereal Disease Research Laboratory (VDRL) and rapid plasma reagin tests. The serological testing algorithms used for the diagnosis of syphilis varied between centers and within centers over time.[1,11]

In addition to syphilis serology, complete blood count, biochemical parameters, acute-phase reactants (erythrocyte sedimentation rate and C-reactive protein), and enzyme-linked immunosorbent assay results for hepatitis viruses and HIV were reviewed for all patients. If performed on clinical grounds, additional laboratory investigations to exclude alternative causes of uveitis were also noted. In patients who underwent lumbar puncture (LP), the results of cerebrospinal fluid (CSF) analysis (non-treponemal testing [VDRL], cell count, and total protein) were recorded. CSF examination via LP is recommended for ocular syphilis patients presenting with neurological symptoms or signs.[2] Conversely, CSF examination is not imperative in patients without neurological findings who have ocular symptoms consistent with ocular syphilis (e.g., uveitis, optic neuritis, neuroretinitis) and confirmatory syphilis serological results.[2] Nevertheless, there are some advocates for routine LP in all patients with ocular syphilis. In the present study, LP was performed by the departments of neurology or infectious diseases. Syphilis staging was determined on the basis of clinical symptoms, serological findings, and examination results.

Demographic data, presenting complaints, history of syphilis and HIV infection, HIV status, and sexual history were retrieved from medical records. Best-corrected visual acuity (BCVA, assessed by Snellen chart), intraocular pressure (measured by non-contact tonometry), slit-lamp biomicroscopy findings, and fundus examination results at the time of admission were documented. When available, optical coherence tomography (OCT), fundus autofluorescence imaging, and fundus fluorescein angiography (FFA) results were also reviewed. All visual acuity data were converted to logarithm of the minimum angle of resolution (logMAR) for analysis. Assessment of ocular inflammation was performed according to the Standardization of Uveitis Nomenclature Working Group criteria.[20] Additionally, posterior segment involvement patterns described in the literature as distinctive of syphilitic uveitis (ASPPC, superficial retinal precipitations, confluent retinochoroiditis, and punctate inner retinitis) were specifically evaluated.[10,11] Treatment data, including the route of administration, dose, and

duration of systemic antibiotics and corticosteroids, were recorded and analyzed. Data regarding periocular and intravitreal injections administered as local therapy were also noted.

Patients with a prior history of misdiagnosis before referral were identified, and details of any systemic or periocular corticosteroid therapy administered were recorded. The clinical characteristics of the patients were evaluated according to HIV co-infection status. Sex, age, clinical features, and laboratory findings were compared between the HIV-negative and HIV-positive patient groups. The BCVA measured at the final post-treatment visit was defined as final BCVA for each patient.

Statistical Analysis

The data were analyzed using IBM SPSS Statistics version 22.0 (IBM, Armonk, NY, USA). Descriptive statistics were presented as mean, standard deviation, median, frequency, and percentage. Categorical variables were compared using chi-square test and Fisher's exact test. Continuous variables were compared using the Mann-Whitney U test or Student's t-test for independent samples and the Wilcoxon signed-rank test for paired samples. A p value <0.05 was considered statistically significant.

Results

Demographic and Clinical Characteristics

We initially identified 38 patients diagnosed with ocular syphilis. Of these, 5 patients (13.2%) with indeterminate HIV status were excluded from the analysis. A total of 51 eyes of 33 patients were included in the study. Thirteen patients (39.4%) were HIV-positive and 20 patients (60.6%) were HIV-negative. Twenty-seven patients (81.8%) were male. The mean age at admission was 43.8±11.9 years (range: 21-69 years). The mean follow-up duration was 9.2±5.9 months (range: 3-26 months). Sexual history data were available for only 13 patients (39.4%). Of these, 8 (24.2%) were heterosexual men with a history of multiple sexual partners, and 5 (15.2%) reported a history of male-to-male sexual contact. The most frequent presenting complaints were reduced visual acuity (22 patients, 66.6%), blurred vision (7 patients, 21.2%), and ocular redness (4 patients, 12.1%). None of the patients had a prior history of syphilis diagnosis or treatment. HIV co-infection was identified in 13 of 33 patients (39.4%), of whom 8 (24.2%) had a pre-existing diagnosis of HIV infection. The remaining 20 patients (60.6%) tested negative for HIV. CD4+ T-cell count data were unavailable for HIV-positive patients. No additional co-infections were identified other than HIV.

Syphilis stage was determinable in 16 patients (48.4%). Secondary syphilis was most common (9 patients, 27.2%), followed by latent (5 patients, 15.2%) and tertiary (2 patients, 6.1%) disease. At presentation, dermatological manifestations (maculopapular rash or genital ulcer) were evident in 11 patients (33.3%) (Figure 1). Four patients (12.1%) reported neurological symptoms at presentation: headache in 2 patients (6.1%), balance disorder in 1 patient (3.0%), and speech disorder in 1 patient (3.0%). However, neurological examination findings were normal in all patients. LP was performed in 12 patients (36.3%). CSF analysis revealed a positive VDRL in 4 patients (12.1%), pleocytosis in 5 patients (15.1%), and elevated protein in 5 patients (15.1%). The demographic and laboratory characteristics of the study population are summarized in Table 1.

Ocular Findings and Treatment

Bilateral ocular involvement was present in 18 patients (54.5%). At presentation, the median logMAR BCVA was 0.70 (range: 0-2.5) and the mean intraocular pressure was 13.1±0.8 mmHg (range: 10-21 mmHg). Panuveitis was the most common clinical presentation of syphilitic uveitis (32 eyes, 62.7%). This was followed by posterior uveitis (16 eyes, 31.4%), intermediate uveitis (2 eyes, 3.9%), and isolated anterior uveitis (1 eye, 1.9%). The most common anterior segment inflammatory findings at admission included anterior chamber cells (28 eyes, 54.9%) and keratic precipitates (19 eyes, 37.3%). The most frequent posterior segment inflammatory findings were vitreous cells (36 eyes, 70.6%) and retinochoroiditis (33 eyes, 64.7%) (Table 2). Regarding the distinctive posterior segment features of syphilitic uveitis, the most common patterns were ASPPC (14 eyes, 27.5%) (Figure 2), confluent retinochoroiditis (8 eyes, 15.7%), superficial retinal precipitations (8 eyes, 15.7%) (Figure 3), and punctate inner retinitis (3 eyes, 5.9%). Syphilitic multifocal chorioretinitis (2 eyes, 3.9%) presented as bilateral acute posterior multifocal placoid pigment epitheliopathy in one patient (Figure 4). Concomitant macular edema was present in 7 eyes (13.7%).

On FFA, the most prevalent findings were optic disc hyperfluorescence secondary to disc leakage (27 eyes, 52.9%), late-phase hyperfluorescence corresponding to areas of retinochoroiditis (21 eyes, 41.2%), and hyperfluorescence attributable to vascular leakage (12 eyes, 23.5%). On OCT, the most common finding was disruption of the outer retinal layers and disorganization of the retinal pigment epithelium (15 eyes, 29.4%), followed by macular edema (7 eyes, 13.7%), punctate hyperreflective lesions in the inner retinal layers (3 eyes, 5.9%), subretinal fluid (2 eyes, 3.9%), and placoid hyperreflective lesions in the outer nuclear layer (2 eyes, 3.9%). The imaging findings are

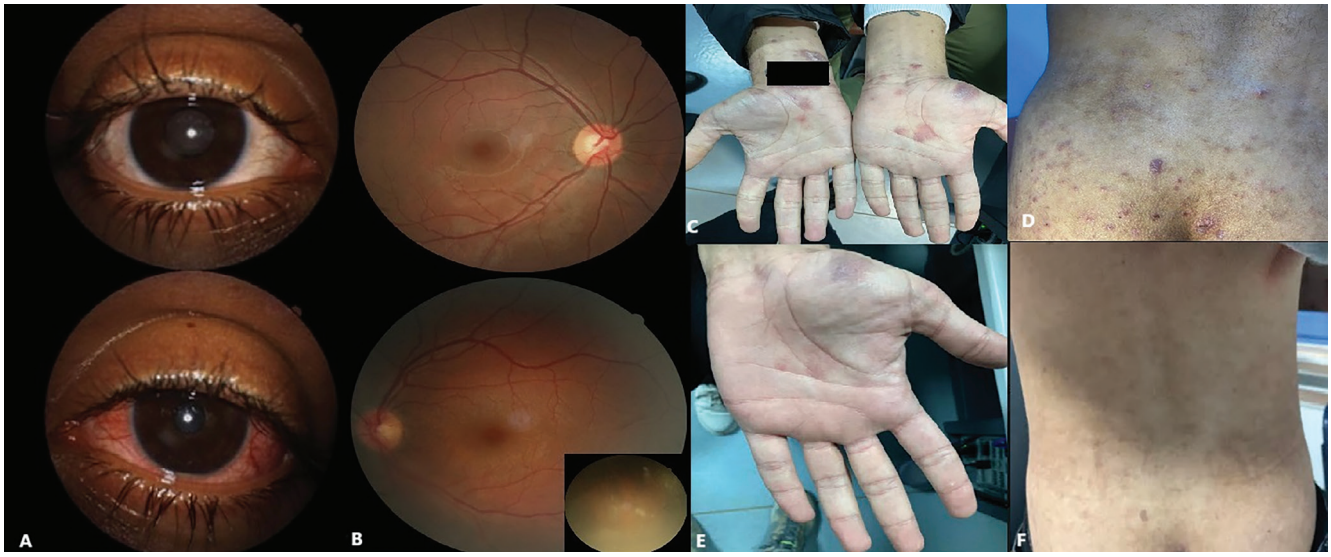

Figure 1. A 25-year-old man had been misdiagnosed with psoriasis for one month on the basis of dermatological findings. He was referred to the ophthalmology department for panuveitis in the left eye. A) The anterior segment of the right eye was quiet (upper), while the left eye showed ciliary injection, anterior chamber cells, and non-granulomatous keratic precipitates (lower). B) Color fundus photography shows a normal right fundus (upper) and vitreous haze with inferotemporal retinitis foci in the left eye (lower). C, D) Clinical photographs show a diffuse maculopapular rash involving the palms and entire body surface. Syphilis serology and human immunodeficiency virus testing were both positive. Following systemic antibiotic and topical corticosteroid therapy, both the cutaneous (E, F) and ocular findings regressed

Table 1. Demographic and clinical characteristics of patients with syphilitic uveitis (n=33 patients)	
Age (years)	
Mean ± SD Median	43.8±11.9 44.0
Sex, n (%)	
Female Male	6 (18.2) 27 (81.8)
Laterality, n (%)	
Unilateral Bilateral	15 (45.5) 18 (44.5)
Syphilis serology tests, n (%)	
Positive TPHA and VDRL Positive FTA-ABS and VDRL Positive TPHA and RPR Positive EIA and TPHA, negative VDRL	10 (30.3) 15 (45.5) 5 (15.2) 3 (9.0)
HIV co-infection, n (%)	
Positive HIV test Negative HIV test	13 (39.4) 20 (60.6)
Lumbar puncture, n (%)	12 (36.4)
Positive VDRL Pleocytosis Elevated protein	4 (12.1) 5 (15.2) 5 (15.2)

SD: Standard deviation, TPHA: *Treponema pallidum* hemagglutination assay, VDRL: Venereal Disease Research Laboratory test, FTA-ABS: Fluorescent treponemal antibody absorption, RPR: Rapid plasma reagin test, EIA: Enzyme immunoassay, HIV: Human immunodeficiency virus

reported in grouped categories due to the heterogeneous clinical presentations.

All patients received intravenous (18-24 MU crystallized penicillin G; Kristapen, Deva İlaç, İstanbul, Türkiye) or intravenous and intramuscular (2.4 MU benzathine penicillin G; Deposilin, Ulagay İlaç, İstanbul, Türkiye) antibiotic therapy. None of the patients required alternative antibiotic therapy. Seventeen patients (51.5%) with severe posterior uveitis or optic nerve involvement received adjunctive oral corticosteroids (0.5 mg/kg/day; Prednol, Mustafa Nevzat İlaç, İstanbul, Türkiye), initiated 24 to 48 hours after the commencement of systemic antibiotic therapy. Four eyes (7.8%) received posterior sub-Tenon triamcinolone acetonide injections (Kenacort-A, Deva İlaç, Istanbul, Türkiye) for macular edema. One of these eyes (1.9%) subsequently required an intravitreal dexamethasone implant (Ozurdex, AbbVie, Chicago, IL, USA) for refractory macular edema. Treatment details and durations are summarized in Table 2. The most frequent post-treatment ocular complications were optic atrophy (6 eyes, 11.7%), cataract (3 eyes, 5.9%), retinal detachment (3 eyes, 5.9%), and atrophic maculopathy (3 eyes, 5.9%). Recurrence was not observed in any of the patients. The median final BCVA was 0.10 (range: 0-2.5) logMAR, representing a significant improvement from the presenting BCVA (Table 2). No statistically significant difference in median final BCVA was observed between

Table 2. Ocular involvement findings and treatment approaches (n=51 eyes)	
Anterior segment inflammatory findings, n eyes (%)	
Anterior chamber cell (≥1+)	28 (54.9)
Keratic precipitates	19 (37.3)
Granulomatous	3 (5.9)
Non-granulomatous	16 (31.4)
Hypopyon	3 (5.9)
Iris nodules	0 (0)
Posterior synechiae	9 (17.6)
Posterior segment inflammatory findings, n eyes (%)	
Vitreous cells (≥1+)	36 (70.6)
Optic nerve involvement	30 (58.8)
Retinochoroiditis	33 (64.7)
Retinal vasculitis	13 (25.5)
Macular edema	7 (13.7)
Exudative RD	5 (9.8)
Systemic treatment, n patients, (%)	
IV and IV + IM penicillin G	33 (100)
Duration of antibiotic treatment (days), median (range)	21 (14-21)
Oral corticosteroid	17 (51.5)
Oral corticosteroid duration (days), median (range)	14.0 (7-60)
Local treatment, n eyes (%)	
Posterior sub-Tenon triamcinolone acetonide	4 (7.8)
Intravitreal dexamethasone implant	1 (1.9)
logMAR BCVA, median (range)	
Presenting	0.70 (0-2.5)
Final	0.10 (0-2.5)
p value	<0.001*

Statistically significant at p<0.05, *Wilcoxon signed ranks test, n: number, RD: Retinal detachment, IV: Intravenous, IM: Intramuscular, logMAR: Logarithm of the minimum angle of resolution, BCVA: Best-corrected visual acuity

patients who received systemic corticosteroids (0.10; range: 0-1.5) and those who did not (0.10; range: 0-2.5) (p=0.681).

Prior to the diagnosis of ocular syphilis, 9 patients (27.2%) had been misdiagnosed at other centers as having optic neuritis (4 patients, 12.1%), non-infectious posterior uveitis (1 patient, 3.0%), psoriasis (3 patients, 9.1%), or vitreous hemorrhage (1 patient, 3.0%). Seven of these patients (77.7%) had received corticosteroids, without systemic antibiotic therapy. Four patients (44.4%) had received intravenous pulse corticosteroid, 1 patient (11.1%) received oral corticosteroid, and 1 patient (11.1%) received subconjunctival corticosteroid injections in both eyes. All of these patients had been referred to a tertiary center owing to progressive worsening of ocular symptoms and visual acuity. Notably, syphilis serology had not been conducted for any of the misdiagnosed patients. Among the misdiagnosed patients, 4 (44.4%) were HIV-positive and 5 (55.6%) were HIV-negative. Following confirmation of ocular syphilis, all prior corticosteroid therapies were discontinued and systemic antibiotic treatment was promptly initiated. The median logMAR BCVA at presentation was significantly worse in patients who had been initially misdiagnosed (1.60; range: 0.1-2.5) compared to patients without a prior misdiagnosis (0.40; range: 0-2.5) (p=0.002). Despite appropriate treatment, the final median logMAR BCVA was significantly worse in the initially misdiagnosed group (0.40; range: 0-2.5) than in patients diagnosed correctly at first presentation (0.07; range: 0-1.51) (p=0.048).

Clinical Characteristics According to HIV Co-infection Status

Of the 33 ocular syphilis patients with known HIV status, 13 (39.4%) were HIV-positive and 20 (60.6%) were HIV-negative. There was no statistically significant difference in median age between HIV-positive and HIV-negative patients (p=0.06). Regarding sex distribution, all of the HIV-positive patients were male (p=0.032). The laterality of ocular involvement did not differ according to HIV status (p=0.515). Demographic characteristics, laterality of ocular involvement, IOP values, and syphilis staging stratified by HIV co-infection status are summarized in Table 3.

In both groups, panuveitis and posterior uveitis were the most common anatomical patterns; however, the rate of panuveitis was significantly higher among HIV-positive patients (p=0.002). Anterior segment inflammatory findings (anterior chamber cells, keratic precipitates, and posterior synechiae) were more frequent in HIV-positive patients (all p<0.01). The prevalence of optic nerve involvement was significantly higher among HIV-positive patients than HIV-negative patients (p=0.035). The rates of the distinctive posterior segment findings of syphilitic uveitis according to HIV co-infection status are presented in Table 4. ASPPC, confluent retinochoroiditis, and superficial retinal precipitations were more common among HIV-negative patients, but these differences did not reach statistical significance (all p>0.05). There were no significant differences in LP findings between HIV-positive and HIV-negative patients (p=0.208). Median logMAR BCVA values at presentation and at the final visit did not differ statistically between HIV-positive and HIV-negative patients (p>0.05 for all). Patients with and without HIV co-infection developed at least one ocular complication at comparable rates (p=0.673). No clinical findings suggestive of immune reconstitution inflammatory syndrome-associated uveitis were identified in the HIV-positive patients. Clinical characteristics, ocular findings, and presenting and final BCVA values stratified by HIV co-infection status are presented and compared between the groups in Table 4.

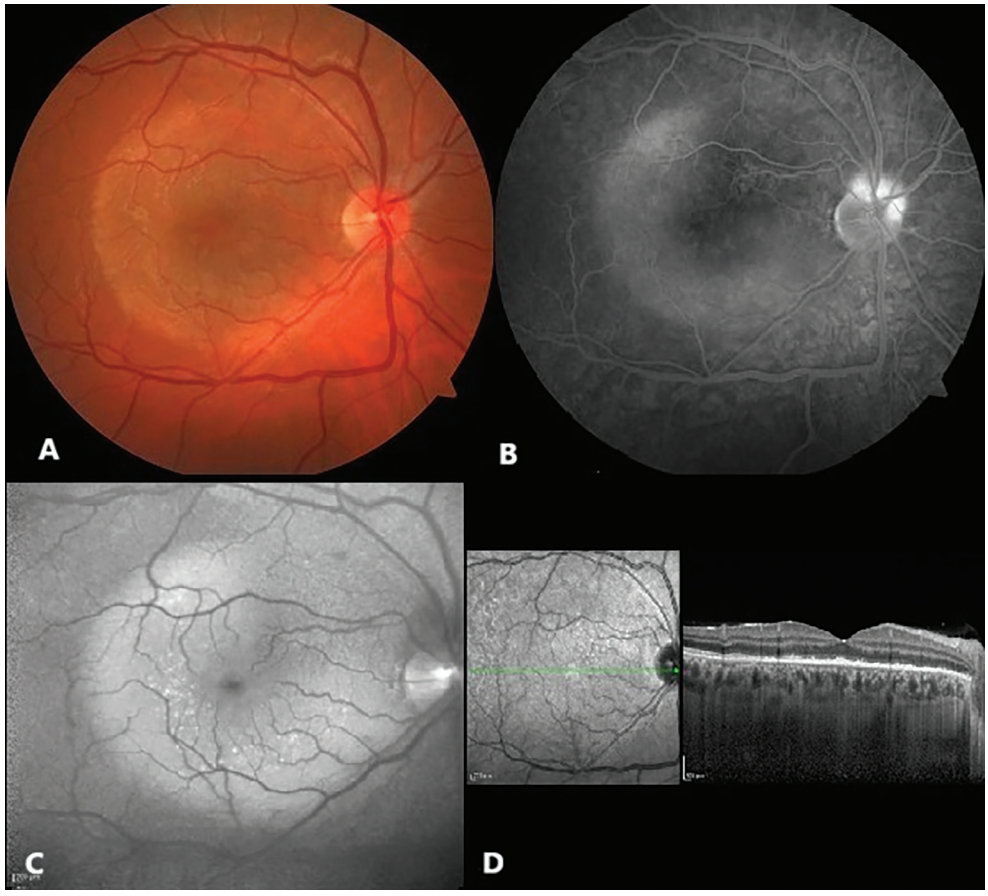

Figure 2. Color fundus photograph (A) demonstrates a large, yellowish, circular syphilitic posterior placoid chorioretinitis (ASPPC) lesion in the macula. Fundus fluorescein angiography (B) shows hyperfluorescence in the lesion area and late-phase optic disc hyperfluorescence. Fundus autofluorescence imaging (C) reveals punctate hyperautofluorescence within the ASPPC lesion. Optical coherence tomography (D) demonstrates irregular hyperreflectivity at the photoreceptor-retinal pigment epithelium junction, with segmental disruption of the ellipsoid zone and outer limiting membrane

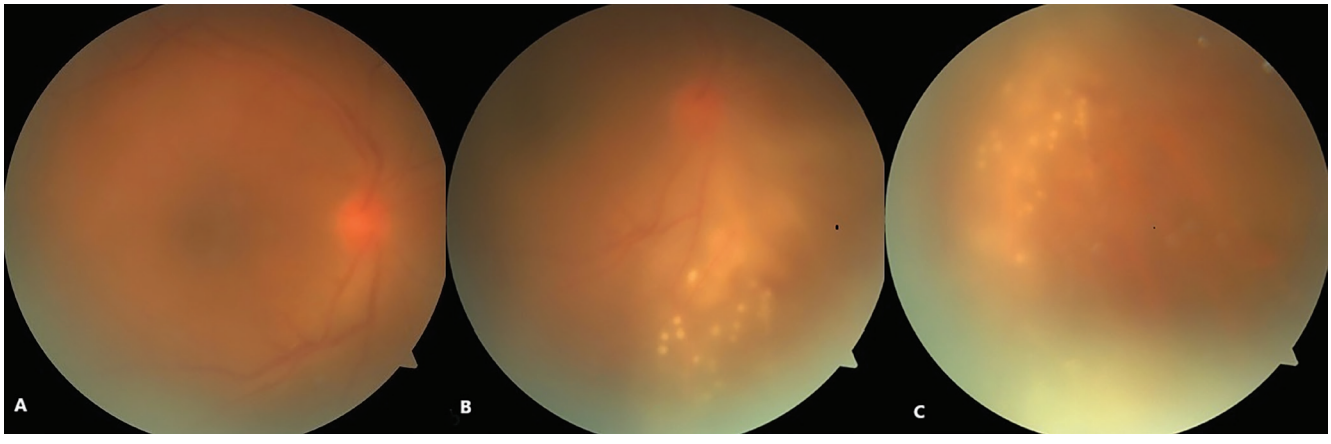

Figure 3. Color fundus photographs of a patient with syphilitic posterior uveitis. A) There is marked vitreous inflammation with vitreous haze and cells, as well as optic disc hyperemia. B) A ground-glass appearing confluent retinochoroiditis lesion is evident inferior to the optic disc. C) In addition to the area of retinochoroiditis, numerous small, round, cream-white superficial preretinal precipitations are observed

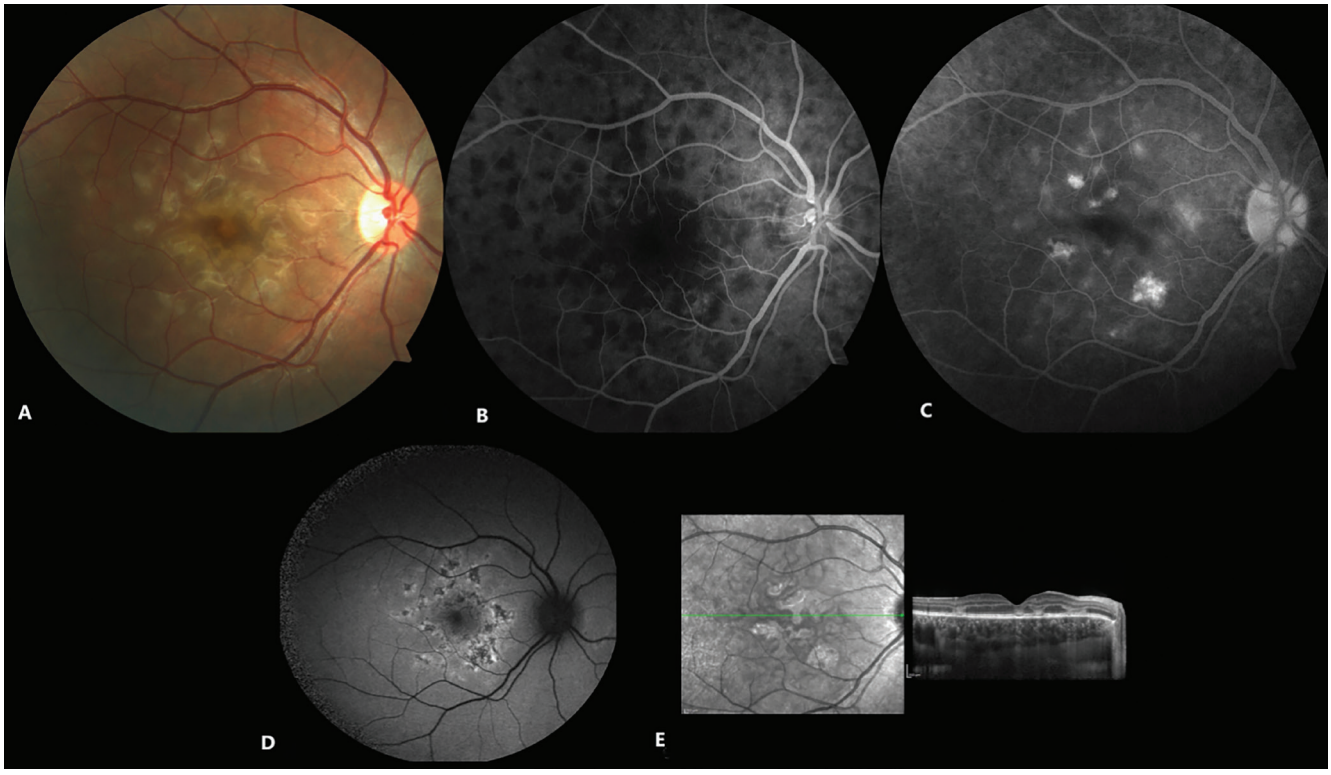

Figure 4. Features mimicking acute posterior multifocal placoid pigment epitheliopathy. Color fundus photograph (A) shows multifocal white lesions in the macula. Fundus fluorescein angiography reveals multiple hypofluorescent spots at the posterior pole in the early phase (B) and hyperfluorescence and optic disc hyperfluorescence in placoid lesions in the late phase (C). On fundus autofluorescence imaging (D), the lesions show central hypoautofluorescence surrounded by hyperautofluorescence. Optical coherence tomography (E) demonstrates disruption of the outer retinal layers with prominent focal hyperreflective lesions in the outer nuclear layer

Table 3. Demographic and clinical characteristics by HIV co-infection status

	HIV-positive (13 patients, 21 eyes)	HIV-negative (20 patients, 30 eyes)	p value
Age (years), median (range)	37 (23-59)	43 (21-64)	0.125¶
Sex, n (%) Female Male	 0 (0) 13 (100)	 6 (30) 14 (70)	0.032*
Laterality, n (%) Unilateral Bilateral	 5 (38.5) 8 (62.2)	 10 (50) 10 (50)	0.515*
IOP (mmHg), median (range)	15 (10-20)	15 (10-21)	0.513¶
Syphilis stage, n (%) Secondary Tertiary Latent	 6 (46.1) 0 (0) 0 (0)	 3 (15) 2 (10) 5 (5)	0.061*

Statistical significance at p<0.05, *chi-square test or Fisher's exact test, ¶Mann-Whitney U or Student's t-test, HIV: Human immunodeficiency virus, IOP: Intraocular pressure

Table 4. Ocular involvement characteristics according to HIV co-infection status			
	HIV-positive (13 patients, 21 eyes)	**HIV-negative (20 patients, 30 eyes)**	**p value**
Uveitis by anatomical classification, n (%)			
Isolated anterior uveitis	0 (0)	1 (3.3)	
Intermediate uveitis	0 (0)	2 (6.7)	
Posterior uveitis	2 (9.5)	14 (46.7)	0.002*
Panuveitis	19 (90.5)	13 (43.3)	
Anterior segment inflammatory findings, n (%)			
Anterior chamber cells (≥1+)	18 (85.7)	10 (33.3)	<0.001*
Keratic precipitates	14 (66.7)	5 (16.7)	<0.001*
Hypopyon	2 (9.5)	1 (3.3)	0.561*
Posterior synechiae	8 (38.1)	1 (3.3)	0.002*
Posterior segment inflammatory findings, n (%)			
Vitreous cells (≥1+)	18 (85.7)	18 (60)	0.064*
Optic nerve involvement	16 (76.2)	14 (46.7)	0.035*
Retinochoroiditis	15 (71.4)	18 (60)	0.401*
Retinal vasculitis	6 (28.6)	7 (23.3)	0.750*
Macular edema	2 (9.5)	5 (16.7)	0.685*
Exudative RD	1 (4.8)	4 (13.3)	0.391*
Distinguishing posterior segment findings, n (%)			
ASPPC	5 (23.8)	9 (30.0)	0.610*
Confluent retinochoroiditis	3 (14.3)	5 (16.7)	1.000*
Syphilitic multifocal chorioretinitis	0 (0)	2 (6.7)	0.506*
Superficial retinal precipitations	3 (14.3)	5 (16.7)	1.000*
Punctate inner retinitis	2 (9.5)	1 (3.3)	0.561*
Lumbar puncture, n (%)			
Yes	4 (30.8)	8 (40)	0.719*
No	9 (69.2)	12 (60)	
At least 1 positive LP finding	4 (30.8)	4 (20)	0.208*
logMAR BCVA, median (range)			
Presenting	1.00 (0-2.5)	0.40 (0-2.5)	0.332¶
Final	0.10 (0-1.5)	0.10 (0-2.5)	0.960¶
p value	<0.001ϕ	<0.001ϕ	
Any ocular complication, n (%)	6 (28.6)	7 (23.3)	0.673*

Statistical significance at p<0.05, *chi-square test or Fisher's exact test, ¶Mann-Whitney U or Student's t-test, ϕWilcoxon signed-rank test, HIV: Human immunodeficiency virus, RD: Retinal detachment, ASPPC: Acute syphilitic posterior placoid chorioretinitis, LP: Lumbar puncture, LogMAR: Logarithm of the minimum angle of resolution, BCVA: Best-corrected visual acuity

Discussion

This is the first multicenter study in Türkiye to evaluate the clinical features of syphilitic uveitis. Furthermore, the study provides a comparative analysis of the demographic and clinical profiles of syphilitic uveitis in HIV-positive and HIV-negative patients. Although syphilis can affect any ocular structure, uveitis is the most common ophthalmic manifestation.[11] Over the past decade, numerous published studies have substantially advanced our understanding of the clinical and multimodal imaging characteristics of syphilitic uveitis.[13,14,15,16,21,22,23]

Ocular syphilis predominantly affects men, with male patients comprising up to 90% of cases in recent series.[13,14,21] Key contributing risk factors include multiple sexual partners, unprotected sex, HIV co-infection, and the increasing prevalence of male-to-male sexual contact.[1,3,15,21] In a large ocular syphilis series by Vadboncoeur et al.,[13] HIV co-infection was detected in 32% of patients, all of whom were male, and 63% of those patients had a history of male-to-male sexual contact. Consistent with the literature,[13,14,15,21] the majority of patients in our study (82%) were male and HIV co-infection was detected in 39% of the patients, all of whom were men. Additionally, over one-third of the

patients reported a history of multiple sexual partners or male-to-male sexual contact. Ocular syphilis typically presents in the fourth and fifth decades of life; the mean age at presentation was 44 years in our cohort, consistent with previously published data.[3,10,13,16,24] Although previous studies have reported a younger mean age among HIV-positive patients with ocular syphilis compared to their HIV-negative counterparts,[13,23] no significant age difference was found between the two groups in the present study. Ocular involvement in syphilis is often bilateral, although unilateral presentation may also occur, as observed in our cohort. HIV co-infection in syphilis patients does not appear to influence the laterality of ocular involvement, and our results support this observation.[3,13,15,17,25]

Ocular syphilis most commonly manifests during the secondary and tertiary stages of the disease. However, ocular manifestations may arise at any stage and can occasionally represent the initial or sole presenting feature of syphilis in the absence of systemic findings.[1,9] In our study, syphilitic uveitis was most commonly identified in the secondary stage, with no significant difference in disease staging according to HIV co-infection status. In ocular syphilis patients presenting with uveitis, optic neuritis, or neuroretinitis in the absence of neurological signs and with confirmatory serology, routine pre-treatment CSF examination is not currently recommended.[2] However, approaches may vary according to the individual patient in clinical practice. Vadboncoeur et al.[13] identified at least one abnormality in 71% of patients who underwent CSF analysis, including positive VDRL (22%), pleocytosis (44%), and elevated protein (60%). In the present study, CSF analysis was performed in 36% of patients, and at least one abnormal finding was detected in 66% of those examined.

Syphilitic uveitis most commonly presents as posterior uveitis and panuveitis.[14,15,16,17] Ly et al.[14] reported posterior uveitis as the most prevalent form of syphilitic uveitis, and intermediate uveitis as the rarest presentation. In a more recently published series, panuveitis was the predominant presentation, whereas isolated anterior uveitis was the least common form.[26] Consistent with the literature, panuveitis was the most frequent presentation in our series, while intermediate uveitis and isolated anterior uveitis were rare. Common posterior segment manifestations of syphilitic uveitis include chorioretinitis, optic disc inflammation, necrotizing retinitis, and retinal vasculitis.[25,26] ASPPC has been described as a rare but distinctive posterior segment finding of syphilis.[10,18] In the present study, ASPPC was identified in 27% of the patients but was not significantly associated with HIV co-infection status. Hoogewoud et al.[25] reported a higher frequency of panuveitis among HIV-positive patients, along with more pronounced inflammatory signs such as vitreous haze, anterior chamber cells, flare, and posterior synechiae. Similarly, in addition to a higher rate of panuveitis, anterior segment inflammatory signs were significantly more prevalent among HIV-positive patients in the present study. Optic nerve involvement is a serious sign of posterior segment inflammation that has been reported with greater frequently in ocular syphilis patients with HIV co-infection.[15,19,26] Ahmed et al.[26] reported higher rates of diffuse necrotizing retinitis and optic nerve involvement in syphilitic uveitis patients with HIV co-infection. Additionally, marked ocular inflammation has been documented in syphilitic uveitis patients with HIV-coinfection, despite low CD4+ T-cell counts.[26,27] In our series, HIV-positive patients exhibited a higher burden of inflammatory findings, including optic nerve involvement and more pronounced anterior segment and vitreous inflammation. Although the retrospective study design precluded a formal analysis of the relationship between CD4+ T-cell counts and inflammatory burden, the current findings suggest that HIV co-infection may be associated with a more pronounced inflammatory phenotype in ocular syphilis.

According to the 2021 Sexually Transmitted Infections Treatment Guidelines published by the United States Centers for Disease Control and Prevention, the treatment protocol for syphilitic uveitis is equivalent to that of neurosyphilis. The recommended regimen is intravenous aqueous crystallized penicillin G at 18-24 MU for 10-14 days. Alternatively, 2.4 MU penicillin G procaine can be administered intramuscularly with concomitant oral probenecid for 10-14 days.[28] All patients in our cohort received penicillin G therapy, with treatment durations ranging from 14 to 21 days. As the recommended duration for neurosyphilis treatment is shorter than that for latent syphilis, some clinicians opted to extend therapy by an additional week. Systemic corticosteroids may be administered adjunctively, particularly in cases of ocular syphilis with severe posterior uveitis or optic nerve involvement.[11,14,16] Corticosteroids are also employed to mitigate the Jarisch-Herxheimer reaction, an acute febrile hypersensitivity response that can develop within the first 24-48 hours of initiating antibiotic therapy for syphilis.[11,16]

Bollemeijer et al.[16] reported a statistically significant improvement in visual acuity in patients with syphilitic uveitis who received periorbital or systemic corticosteroids in combination with antibiotic therapy. In contrast, Moradi et al.[15] found no significant difference in ocular complications or visual impairment among ocular syphilis patients treated with immunosuppressive therapy, including oral corticosteroids and immunomodulators. In our study, systemic corticosteroids were administered to approximately half of the patients (51%), and visual

outcomes were comparable between those who did and did not receive corticosteroid therapy. Furthermore, posterior sub-Tenon and intravitreal corticosteroid injections proved effective in the treatment of patients with macular edema (7.8%).

The majority of published studies report significant visual improvement following treatment in patients with ocular syphilis.[13,14,17,23] Our findings are consistent with the literature, demonstrating significant improvement in final BCVA compared to baseline across the entire cohort and within both the HIV-positive and HIV-negative subgroups. Mathew and Smit[23] reported that HIV status did not influence final visual acuity in patients with ocular syphilis, 92% of whom exhibited visual improvement. Furtado et al.[3] similarly reported no difference in rates of visual loss according to HIV status. Ly et al.[14] and Vadboncoeur et al.[13] also reported no significant difference in presenting or final visual outcomes in patients with HIV co-infection. In the present study, post-treatment final BCVA was similar in HIV-positive and HIV-negative patients.

Syphilis responds favorably to appropriate antibiotic therapy, with inflammatory signs typically resolving promptly after treatment.[1,15,16] Serious ocular complications of syphilitic uveitis are generally uncommon. The most frequently reported complications in the literature include macular edema, epiretinal membrane, macular scarring, glaucoma, and optic atrophy.[14,15,25,26] Hoogewoud et al.[25] reported that complication rates did not differ significantly between HIV-positive and HIV-negative patients with ocular syphilis. In our study, optic atrophy and cataract were the most frequently observed complications, and no significant association was identified between HIV co-infection status and the development of complications.

A report by the International Ocular Syphilis Working Group assessing current ophthalmological practices in syphilitic uveitis identified failure to request serological testing (30%) and initial misdiagnosis (21%) as the leading contributors to diagnostic delay.[12] Furthermore, various studies have demonstrated that patients with syphilitic uveitis who experience diagnostic or therapeutic delays present with worse visual acuity and have a poorer visual prognosis.[16,25] As the "Great Imitator," syphilis can manifest with a broad spectrum of clinical findings, rendering its recognition challenging and frequently resulting in misdiagnosis.[1,12] In our cohort, 27% of patients were misdiagnosed at initial presentation, primarily because syphilis serological tests had not been conducted. Both presenting and post-treatment BCVA were significantly worse in patients with prior misdiagnosis compared with those without. Moreover, the majority of misdiagnosed patients had been treated with systemic corticosteroids without concurrent antibiotic therapy. These findings once again underscore the importance of maintaining clinical suspicion and routine syphilis serological testing in all patients presenting with intraocular inflammation of undetermined etiology.[9,12,29] As with other forms of infectious uveitis, clinicians should bear in mind that corticosteroid use in the absence of antibiotic coverage may exacerbate syphilitic uveitis.[16,30]

Study Limitations

The main limitation of this study is the relatively small sample size, which limits the statistical analysis. Other limitations include the retrospective study design and variability in data collection protocols across participating centers. Due to the retrospective nature of the study, CD4+ T-cell count data were not available for HIV-positive patients, which precluded an assessment of the relationship between immune status and ocular findings. Future prospective, larger-scale studies employing standardized data collection protocols would be valuable in further characterizing this disease entity.

Conclusion

Panuveitis and posterior uveitis represent the most common anatomical patterns of syphilitic uveitis. Panuveitis was more prevalent in HIV-positive patients, who also demonstrated a higher burden of intraocular inflammatory signs, including anterior segment inflammation and optic nerve involvement. However, the presence of HIV co-infection did not impact final BCVA or the rate of ocular complication development. Misdiagnosis of syphilitic uveitis remains an important problem because of its wide range of clinical manifestations. Therefore, clinical suspicion and syphilis serology testing are essential for timely diagnosis of the disease. Systemic antibiotic therapy is effective for the treatment of ocular syphilis. However, the use of systemic corticosteroids had no benefit in terms of visual prognosis in our cohort. With proper diagnosis and treatment, syphilitic uveitis is a readily treatable condition with potential for visual recovery, irrespective of HIV serostatus.

Ethics

Ethics Committee Approval: Ankara Training and Research Hospital Ethics Committee approval was obtained prior to study initiation (decision no: 95/2024, approval date: 17.04.2024, protocol number: E-24-95).

Informed Consent: Given the retrospective nature of the study, individual informed consent was not obtained.

Declarations

Authorship Contributions

Surgical and Medical Practices: K.Ö.Y., M.O., M.İ.T., H.E-Ö., S.Ö., N.Z.K., B.T., P.Ç.Ö., Concept: K.Ö.Y., M.O., M.İ.T., Design: K.Ö.Y., M.O., M.İ.T., Data Collection or Processing: K.Ö.Y., M.O., M.İ.T., H.E-Ö., S.Ö., N.Z.K., B.T., P.Ç.Ö., Analysis or Interpretation: K.Ö.Y., M.O., M.İ.T., H.E-Ö., S.Ö., N.Z.K., B.T., P.Ç.Ö., Literature Search: K.Ö.Y., M.O., Writing: K.Ö.Y.

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