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ASSOCIATION BETWEEN CD4 CELL COUNT AND OCULAR SYPHILIS IN HIV-INFECTED POPULATION: A CROSS-SECTIONAL ANALYSIS

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ABSTRACT

Background: Ocular syphilis (OS) often presents with symptoms similar to other eye diseases and can be an initial indicator of HIV infection. CD4 cell count serves as an important marker of immune status in HIV-positive individuals. This study aimed to investigate the relationship between CD4 cell counts and ocular syphilis manifestations in people living with HIV.

Methods: A cross-sectional retrospective review was conducted on medical records of 21 HIV-positive patients diagnosed with OS at the Voluntary Counseling and Testing Clinic of Prof. dr. I.G.N.G. Ngoerah General Hospital between 2018 and 2023. Data collected included demographics, CD4 counts, ocular symptoms, and visual acuity.

Results: Among 21 patients, 18 were male (85.7%) and 3 female (14.3%), with a mean age of 35.8 ± 10.7 years. The most common ocular manifestation was bilateral panuveitis. Statistical analysis revealed no significant association between CD4 cell count and ocular manifestations or visual acuity in this population.

Conclusion: Although no significant link was found between CD4 counts and ocular syphilis features, the frequent coexistence of HIV and syphilis supports routine HIV testing for all syphilis patients. Early detection and management of co-infection remain critical for improving clinical outcomes.

Keywords: Ocular syphilis., CD4 cell count., uveitis

INTRODUCTION

Ocular syphilis (OS), arising from *Treponema pallidum* infection, poses challenges in diagnosis and management, especially when coupled with human immunodeficiency virus (HIV). OS, known as the great masquerader, can mimic various ophthalmic conditions, adding complexity to the clinical diagnosis.[1]

The worldwide resurgence of syphilis necessitates its inclusion in the list of potential diagnoses for uveitis in every individual.[2] British Ocular Syphilis Study (BOSS) established that OS manifests at a frequency of 0.3 instances per one million individuals annually.[3] In total, suspected OS cases made up 0.60% of all reported syphilis cases. This percentage was 0.53% in 2014 and increased to 0.65% in 2015. This resurgence is particularly prevalent in individuals co-infected with the HIV.[4] The Integrated Behavioral and Biological Survey (IBBS) in Indonesia for the year 2011 reported that the prevalence of syphilis in the population of commercial sex worker infected with HIV was 16.7%. The prevalence of syphilis in the population of men who have sex with men (MSM) who were HIV positive was 23.8%.[5]

Ocular syphilis typically appears during the active secondary syphilis stage but can also emerge during the tertiary or latent phase.[6] It's a rare condition effectively treated with appropriate antimicrobials, even in HIV coinfections.[2] The introduction of highly active antiretroviral therapy (HAART) has transformed the landscape of HIV-related ocular manifestations, potentially influencing the natural history of OS. The role of immunosuppression, indicated by cluster of differentiation 4 (CD4) cell count, in OS development and progression among HIV-positive individuals remains a topic of significant interest and clinical relevance.[4]

A reliable indicator of immune system status, the CD4 cell count guides preventive measures against opportunistic infections. Low CD4 counts are significantly linked to increased ocular lesions and discomfort. Developing standardized eye care guidelines, including screening and follow-up for individuals with

HIV, is essential and should ideally be linked to CD4 cell count monitoring.[7,8]

About half of patients diagnosed with both OS and HIV underwent HIV testing when seeking medical attention for OS-related symptoms.[2] The presentation of OS in individuals with HIV/AIDS, its association with systemic immune status (CD4 cell count), and its response to HAART and anti-syphilitic therapy remain insufficiently documented, particularly in regions with a high HIV prevalence, such as Bali.This study aims to improve clinical decision-making by examining the interaction between OS and HIV. It explores the epidemiology, clinical features, and the relationship between CD4 cell count and OS, using patient history and clinical data to enhance understanding of OS in HIV patients.

METHODS

Study Design and Participants

This research was a cross-sectional investigation within the Departement of Ophthalmology of a tertiary care teaching hospital located in Bali, Indonesia. All patients enrolled at Prof. dr. I.G.N.G. Ngoerah Hospital Voluntary Counseling and Testing (VCT) Clinic with a diagnosis of HIV and OS seen in the previous 5 years (2018-2023) were included.

Data Collections

Patient data were retrospectively collected through a medical record and patients register of individuals diagnosed with OS at Prof. dr. I.G.N.G. Ngoerah Hospital VCT Clinic between 2018 to 2023. Records were screened for inclusion based on documentation of an OS diagnosis confirmed by clinical and laboratory findings. Each case underwent a detailed chart review by two independent researchers to ensure diagnostic consistency. The following clinical evaluations were confirmed to be available for each patient: ocular symptoms (e.g., visual disturbances, pain, redness), visual acuity assessed using a Snellen chart, slit-lamp examination of the anterior segment, and posterior segment evaluation using indirect ophthalmoscopy or fundus photography

Additional data were extracted on: demographic characteristics (age, sex), HIV serostatus, serological test results for syphilis, including Treponema pallidum hemagglutination assay (TPHA) and Venereal Disease Research Laboratory (VDRL) test, and treatment modalities and timing of syphilis therapy. Records with incomplete diagnostic, serological, or treatment data were excluded from analysis. Discrepancies in chart interpretation were resolved by consensus or adjudicated by a third reviewer.

Statistical Analysis

The gathered data underwent analysis using IBM SPSS statistics software, version 26.0. Descriptive statistics and frequency analysis were applied to describe the data, utilizing percentage analysis for categorical variables, and mean with standard deviation (SD) for continuous variables. Statistical correlation for categorical data was tested by Fisher's exact test with $p < 0.05$ was considered statistically significant

Ethical Approval

Ethical approval for this study was obtained from the Research Ethics Committee Facullty of Medicine Udayana University, with approval number 0408/UN 14.2.2.VII.14/LT/2025.

RESULTS

The study involved 21 subjects, consisting of 18 males (85.71%) and 3 females (14.29%), with an average age of 35.76 ± 10.70 years. The majority of participants were inhabitants of Denpasar (Table 1).

Table 1. Demographic Data of Subjects

Parameter	Total n (%) / mean ± SD
Gender	
Male	18 (85.71)
Female	3 (14.29)
Age (years)	35.76 ± 10.70
≤40	16 (76.2%)
41-50	2 (9.5%)
51-60	2 (9.5%)
>60	1 (4.8%)
Domicile	
Denpasar	11 (52.38)
Badung	4 (19.05)
Gianyar	3 (14.29)
Buleleng	3 (14.29)

In this study, all subjects displayed blurry vision symptoms related to OS, with one noting redness and another reporting a visual field disturbance. Predominant clinical manifestations included panuveitis in 42.86% of cases. High prevalence of OS manifestations in both eyes was observed in 80.95% of cases. All subjects tested positive for TPHA, with 16 also showing positive VDRL results. CD4 cell counts below 200 cells/mm³ were seen in

47.62%. The average CD4 count was 225.71 ± 161.97 cells/mm³. Notably, 61.90% of patients were on HAART at their OS diagnosis (Table 2).

Table 2. Data of Ocular Syphillis and HIV Status

Parameter	Total n (%) / mean ± SD
Ocular symptoms	
Blurry vision	21 (100)
Eye redness	1 (4.76)
Visual field defect	1 (4.76)
Clinical manifestations	
Anterior uveitis	2 (9.52)
Intermediate uveitis	2 (9.52)
Posterior uveitis	5 (23.81)
Panuveitis	9 (42.86)
Isolated optic neuritis	5 (23.81)
Eye laterality	
Bilateral	17 (80.95)
Unilateral	4 (19.05)
VDRL	
Positive	16 (76.19)
Negative	3 (14.29)
No data	2 (9.52)
TPHA	
Positive	21 (100)
Negative	0 (0)
CD4 cell count (cells/mm^3)	225,71 ± 161.97
<200	10 (47.62)
200-499	9 (42.86)
≥500	2 (9.52)
Use of HAART	
Yes	13 (61.90)
No	8 (38.10)

Table 3 displays OS clinical manifestation prevalence by gender and age. Male patients exhibited higher rates, with a significant association found between panuveitis and gender ($p<0.05$). While OS manifestations were more prevalent in patients under 40, the distribution across age groups did not show statistical significance ($p>0.05$).

Among 21 OS-diagnosed patients, panuveitis (42.9%) was the most common, followed by posterior uveitis and isolated optic neuritis (both 23.8%). OS manifestations were more frequent in patients with CD4 counts below 200 cells/mm³. While Table 4 indicates a higher prevalence of OS in those with lower CD4 counts, the association lacked statistical significance ($p>0.05$) for each ocular manifestation.

All patients received weekly intramuscular injections of Penicillin G Benzathine as syphilis therapy. Three patients were lost to follow-up. The median initial visual acuity (VA) on the best eye was 0.70 (0.10 – 3.00) LogMar, improving significantly to a median VA of 0.40 (0.00 – 3.00) LogMar on the last visit after syphilis therapy ($p<0.05$). No correlation was found between the best eye initial VA and CD4 cell count, as well as the best eye last presenting VA in HIV-positive patients with OS (Table 5 & 6).

Table 3. Distribution and Analysis of Ocular Syphilis Manifestation Based on Gender and Age

Parameter	Ocular syphilis clinical manifestations n (%)				
	Anterior uveitis	Intermediate uveitis	Posterior uveitis	Panuveitis	Isolated optic neuritis
Gender					
Male	2 (9.5%)	2 (9.5%)	5 (23.8%)	6 (28.6%)	5 (23.8%)
Female	0 (0%)	0 (0%)	0 (0%)	3 (14.3%)	0 (0%)
p-value	0.544	0.544	0.296	0.031	0.296
Age					
≤40	2 (9.5%)	1 (4.8%)	4 (19.0%)	7 (33.3%)	4 (19.0%)
41-50	0 (0%)	0 (0%)	0 (0%)	1 (4.8%)	1 (4.8%)
51-60	0 (0%)	1 (4.8%)	1 (4.8%)	0 (0%)	0 (0%)
>60	0 (0%)	0 (0%)	0 (0%)	1 (4.8%)	0 (0%)
p-value	0.875	0.299	0.296	0.410	0.636

Table 4. Distribution and Analysis of Ocular Syphilis Manifestation and CD4 Cell Count

OS clinical manifestations n (%)	CD4 cell count (cells/mm^3)			Total	*p*-value
	<200	200-499	≥500		
Anterior uveitis	2 (9,5%)	0 (0%)	0 (0%)	2 (9,5%)	0.296
Intermediate uveitis	1 (4,8%)	1 (4,8%)	0 (0%)	2 (9,5%)	0.887
Posterior uveitis	3 (14,3%)	1 (4,8%)	1 (4,8%)	5 (23,8%)	0.413
Panuveitis	5 (23,8%)	4 (19,0%)	0 (0%)	9 (42,9%)	0.424
Isolated optic neuritis	1 (4,8%)	3 (14,3%)	1 (4,8%)	5 (23,8%)	0.323

Table 5. Distribution and Analysis of Ocular Syphilis Best Eye Initial VA and CD4 Cell Count

OS Best eye initial VA n (%)	CD4 cell count (cells/mm^3)			Total	*p*-value
	<200	200-499	≥500		
≥0.30	1 (4,8%)	2 (9,5%)	0 (0%)	3 (14,3%)	0.879
<0.30 - ≥1.30	5 (23,8%)	3 (14,3%)	1 (4,8%)	9 (42,9%)	
<1.30	4 (19,0%)	4 (19,0%)	1 (4,8%)	9 (42,9%)	

Table 6. Distribution and Analysis of Ocular Syphilis Best Eye Last Presenting VA and CD4 Cell Count

OS Best eye initial VA n (%)	CD4 cell count (cells/mm^3)			Total	*p*-value
	<200	200-499	≥500		
≥0.30	5 (23,8%)	4 (19,0%)	1 (4,8%)	10 (47.62%)	0.850
<0.30 - ≥1.30	2 (9,5%)	3 (14,3%)	0 (0%)	5 (23,8%)	
<1.30	3 (14,3%)	2 (9,5%)	1 (4,8%)	6 (28.57%)	

DISCUSSION

This study highlights the clinical characteristics and demographics of OS patients, with 85.71% being male, aligning with previous findings that report a higher prevalence in males. This gender disparity may be influenced by risk behaviors, particularly among MSM, as well as differences in healthcare-seeking patterns.[4,9,10]

OS is more prevalent in older HIV-infected individuals.[11] In 2017, the majority of reported syphilis cases occurred in age groups over 24 years, with rates highest among those aged 25-34 (30%) and 45 years and older (31%).[12] A 2011-2012 study at the same center reported a mean age of 35.93 ± 6.391 years for male patients with positive syphilis[13], aligning with the mean age of 35.76 years in this study, reflecting the consistent demographic pattern in OS cases from earlier research.

Most severe cases of OS occurred in HIV-positive individuals, even in the early stages of syphilis. However, disease stage did not reveal specific symptoms, diagnostic markers, or degree of eye involvement.[3,4,9,14] Initial symptoms commonly included blurred vision and sudden onset of new floaters, aligning with the study's findings where all OS patients reported blurred vision.[9,15] It is advisable to routinely assess ocular symptoms in individuals with syphilis, particularly those presenting with recent vision loss or new visual disturbances.

Syphilitic uveitis is a preventable cause of ocular and neurological complications, with its incidence rising

since 2014. Panuveitis remains the most common clinical presentation, consistent with existing literature on OS.[4,16] Typically, panuveitis affects both eyes simultaneously, leading to various visual disturbances. The majority of patients in this study showed bilateral involvement. While optic neuritis occurrence matched a previous study[3], posterior placoid chorioretinitis, deemed a unique OS characteristic in some research[17], was rare in our study. A fundamental eye evaluation should include visual acuity assessment and examination of external OS indicators. Patients presenting with characteristic ocular findings should be promptly referred to an ophthalmologist for a definitive diagnosis.[9]

Nontreponemal antibodies correlate positively with disease activity, rising in primary or secondary syphilis and decreasing with spirochete dormancy or effective antibiotic treatment. They serve as reliable metrics for monitoring therapeutic progress in both systemic and ocular manifestations. Treponemal tests turn positive during secondary syphilis, remaining positive throughout the patient's lifetime.[2] The study by Tyagi *et al*. found 45% (9/20) of patients reactive in VDRL tests, with all patients showing positive TPHA test results.[18] The consistently positive TPHA and VDRL results in our study underscore the reliability of these tests in diagnosing syphilis and reinforce the importance of early detection and treatment in preventing severe complications like OS.

Higher OS prevalence in younger males aligns with broader syphilis patterns, although the lack of statistical significance in age distribution may be due to the small sample size.[11,18] Larger studies are needed for deeper insights into age and gender-related trends in OS manifestations.

The absence of a statistically significant correlation between CD4 cell count and specific OS manifestations in this study is noteworthy. Although previous research associates lower CD4 levels with a higher risk of ocular complications in HIV patients, these findings indicate a more complex relationship between immunosuppression and OS.[7,8] Other factors, like host immune responses or *Treponema pallidum* strain variations, may contribute. OS in HIV/AIDS individuals appears unrelated to CD4 count; instead, HIV positivity increases the likelihood of posterior segment infection.[20] Interaction between syphilis and HIV at tissue and cellular levels may facilitate transmission and coinfection. Studies highlight the importance of suspecting syphilis in AIDS patients with optic neuroretinopathy, emphasizing timely examinations and treatment upon positive test results.[21,22]

CDC recommends intravenous benzyl penicillin for ocular syphilis, neurosyphilis, and auricular syphilis, with a dosage of 18–24 million units per day, administered every four hours for 10 to 14 days. Primary, secondary, and early latent syphilis are treated with a single dose of 2.4 million units of benzathine penicillin G. For latent syphilis of unknown duration, late latent syphilis, and tertiary syphilis without neurosyphilis evidence, 7.2 million units of benzathine penicillin G are suggested in three 2,4-million-unit injection at weekly intervals. Long-term complications persisted despite symptom improvement in all cases.[23] For penicillin-allergic individuals without neurosyphilis and negative HIV tests, doxycycline or tetracycline are alternatives. In penicillin-contraindicated ocular syphilis cases, ceftriaxone and chloramphenicol are effective substitutes.[2] All patients in this study received intramuscular Penicillin G Benzathine.

Penicillin G Benzathine therapy is well-established for syphilis. Improved visual acuity post-treatment (from a median of 0.70 to 0.40 LogMar) highlights timely management's crucial role in mitigating visual sequelae in OS. In HIV-positive individuals with OS, no relationship was observed between initial VA of the better eye and CD4 count, suggesting visual impairment severity may not be primarily influenced by current immune status. Other factors, like ocular involvement extent and location, may play a more significant role.[24]

CONCLUSION

This study provides comprehensive insights into OS, emphasizing male preponderance and frequent panuveitis. Bilateral OS underscores the need for thorough eye care. OS prevalence doesn't correlate with CD4 cell count in HIV patients, but HIV testing is advisable for all syphilis diagnoses. Timely diagnosis and treatment are crucial for preventing irreversible ocular damage. Further research on the CD4 count-OS relationship is needed, and larger cohorts will advance understanding of OS presentation in HIV patients.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest to disclose concerning the research, authorship, and publication of this manuscript.

AUTHOR CONTRIBUTION

Saphira Evani conceptualized and designed the study, collected and analyzed the data, and drafted the manuscript. Ida Ayu Ary Pramita contributed to the data collection, provided critical revisions to the manuscript, and supervised the study process. I Gusti Ayu Made Juliari provided critical revisions to the manuscript and supervised in the manuscript editing. All authors reviewed and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

LIST OF ABBREVIATIONS

OS: ocular syphilis; HIV: human immunodeficiency virus; BOSS: British Ocular Syphilis Study; IBBS: The Integrated Behavioral and Biological Survey; MSM: men sex with men; HAART: highly active antiretroviral therapy; CD4: cluster of differentiation 4

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