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RESEARCH ARTICLE

The Clinical Spectrum and Outcomes of Ocular Syphilis in Saudi Arabia: The Emergence of a Uveitic Masquerader

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Abstract

This retrospective multicenter cohort study aimed to describe the clinical features and report the outcomes of the management of ocular syphilis in Saudi Arabia. Thirty-three eyes of 19 patients with ocular syphilis were reviewed, including data on visual acuity, signs of anterior and posterior uveitis, systemic work-up, and treatment outcomes. A total of 38 eyes from 19 patients were examined, with 33 eyes showing manifestations of ocular syphilis. The majority of patients (89.5%; $n=17$) were males, with an average age of 40.6 ± 12 years. About one half of the patients (52.6%; $n=10$) reported previous unprotected sexual encounters, and 26.3% had positive human immunodeficiency virus (HIV) testing. Systemic manifestations of syphilis were observed in 68.4% of the patients. Fourteen patients (73.7%) had bilateral disease. At presentation, the average Log MAR visual acuity was 0.81 ± 0.80 (Snellen equivalent = 20/120). Anterior chamber inflammation was seen in 72.7% of eyes ($n=28$ eyes), while posterior segment examination revealed vitritis in 48.5% ($n=18$ eyes), hyperemic optic discs in 62.5% ($n=24$ eyes), and vascular sheathing in 46.9% ($n=17$ eyes). Placoid lesions were observed in 51.5% of eyes ($n=20$ eyes). The most common ocular syphilitic phenotypes were acute syphilitic posterior placoid chorioretinitis (ASPPC) in 54.5% of eyes ($n=21$ eyes) and necrotizing retinochoroiditis in 15.2% ($n=6$ eyes). Treatment included intravenous penicillin G for 14 days in 12 patients, intramuscular penicillin G in 2 patients, and systemic ceftriaxone in 2 patients. All treated patients showed clinical improvement, with a mean follow-up duration of 6.5 ± 4.5 weeks and a significant improvement in mean Log MAR visual acuity to 0.23 ± 0.46 (Snellen equivalent = 20/30; $P<0.001$). These findings highlight the emergence of ocular syphilis in Saudi Arabia and the need for ophthalmologists to recognize its diverse clinical and multimodal retinal imaging features to ensure timely diagnosis and treatment.

Keywords Sexually transmitted infections · Saudi Arabia · Syphilis · Uveitis · Eye disease

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1 Introduction

Syphilis, a systemic infection caused by *Treponema pallidum* progresses through four clinical stages primary, secondary, latent, and tertiary stages. Ocular involvement can occur at any stage except the primary stage, with the highest likelihood during the secondary or latent stages [1].

Ocular syphilis can present with a wide range of clinical manifestations, often mimicking other inflammatory diseases. This resemblance has led ophthalmologists to routinely include syphilis as a differential diagnosis (masquerade disease) during the workup of uveitis cases [1]. A common presentation of ocular syphilis is posterior uveitis, typically in the form of posterior placoid chorioretinopathy [1, 2]. Other ocular manifestations include anterior uveitis, intermediate uveitis, panuveitis, interstitial keratitis, scleritis, and optic nerve involvement, such as optic neuritis or optic nerve atrophy [2, 3].

The outcomes of syphilis have improved significantly after the discovery of penicillin [4, 5]. In 2000–2001, the syphilis rate in the United States reached its lowest level since 1941, with 2.1 cases per 100.1000 population (6103 cases [6]. However, syphilis is considered a re-emerging disease due to recent global increases in prevalence [6–8].

In Saudi Arabia (SA), studies on syphilis remains limited. Between 1995 and 1999, syphilis was reported in 3385 (8.7%) out of 39049 sexually transmitted infections (STIs) that were reported to the Ministry of Health. Similarly, from 2005 to 2012, 1,769 cases (2.6%) were recorded out of 68,886 STIs [9, 10]. Historically, experience with syphilitic uveitis in SA was primarily associated with Bejel disease (endemic syphilis), a non-vernal treponemal infection [11–13]. Venereal Uveitis related to syphilis in SA was infrequently described in the literature. Between 1995 and 2013, the most prevalent infectious causes of uveitis presenting to referral eye centers in SA were herpes, tuberculosis (TB), and toxoplasmosis [14–16].Syphilis was notably rare, with only two cases reported s out of 200 uveitis cases evaluated in an eye center in SA in the period from 1995 to 2000 [13]. More recently, in 2020, Shajry I et al. reported a case of acute syphilitic posterior placoid chorioretinopathy (ASPPC) in a young healthy, Saudi male [17]. The recent emergence of syphilis in SA appears to allign with its re-emergence in other parts of the world. This study aims to outline the clinical spectrum of ocular syphilis in SA.

2 Methods

The study was approved by the local Institutional Review Board (IRB) committee at King Khaled Eye Specialist Hospital (KKESH) in Riyadh, Saudi Arabia, which adheres to the principles of the Declaration of Helsinki. IRB was also obtained from each contributing institution. This retrospective multicenter study analyzed data from patients diagnosed with syphilitic uveitis between January 2021 and December 2023 at various hospitals across the Kingdom of Saudi Arabia including King Khaled Eye Specialist Hospital (KKESH) in Riyadh, King Abdulaziz University Hospital in Riyadh, Imam Abdulrahman University Hospital in Khobar, Dhahran Eye Specialist Hospital in Dhahran, and Jeddah eye hospital in Jeddah. The diagnosis of syphilis was made using the reverse sequence algorithm, which involves an initial positive treponemal test, such as an immunoassay for total treponema palladium antibodies (TP Abs), Treponema pallidum hemagglutination assay (TPHA), or fluorescent treponemal antibody absorption (FTA-ABS) followed by confirmation with a positive non-treponemal test, such as a venereal disease research laboratory (VDRL) or rapid plasma reagin (RPR). All patients were referred to general hospitals for further assessments and screening for other sexually transmitted infections and for further management of systemic manifestations by infectious disease and neurology specialists. Medical records were reviewed, and the following data were collected: age, gender, race, clinical history, pre-and post-treatment ocular examination, pre-and post-treatment multimodal imaging findings including fundus autofluorescence (FAF) (Optos® PLC, Dunfermline, UK), fundus fluorescein angiography (FFA) and spectral-domain optical coherence tomography (SD-OCT) (Spectralis®, Heidelberg Engineering, Heidelberg, Germany). Treatment details, including the type, route and duration of the medications used, as well as the follow up duration, were also recorded and analyzed.

3 Results

Thirty-eight eyes of 19 patients (18 Saudis and one non-Saudi) were examined, and 33 eyes were found to have manifestations of ocular syphilis, with a trend of increasing cases observed over the study period: four cases in 2021, six cases in 2022, and nine cases in 2023. (Fig. 1). Fourteen patients (73.7%) had bilateral involvement, while 5 patients (26.3%) had unilateral disease. Seventeen patients (89.5%) were males, and 2 patients were females (10.5%). The average age was 40.6 ± 12 years. Ten patients (52.6%) reported previous unprotected sexual encounters. Human immunodeficiency virus (HIV) coinfection was confirmed in five patients (26.3%). The most common presenting symptoms was visual impairment-related complaints, reported by 18 patients (94.7%), followed by eye pain and photophobia in four patients (21%). Table 1 and supplemental Table 1 summarize the demographic characteristics, initial ocular examination and multimodal imaging of

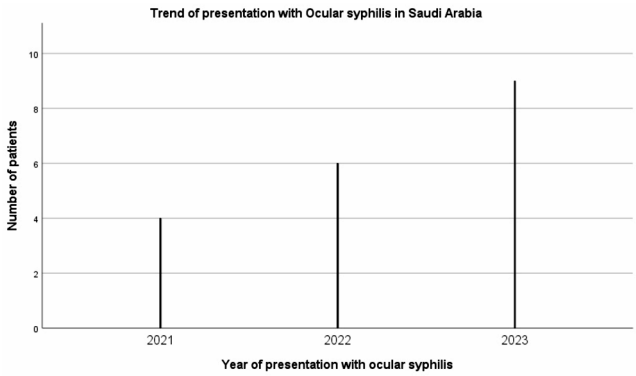

Fig. 1 Occurrence trend of ocular syphilis over 3 years period

Table 1 Demographic data and baseline characteristics of 19 patients with ocular syphilis disease

Variable		*N* = 19 (%)
Laterality	Unilateral	5 (26.3)
	Bilateral	14 (73.7)
Gender	Male	17 (89.5)
	Female	2 (10.5)
Age in years (mean ± SD)		40.6 ± 12
Unprotected Sexual Encounters	Yes	10 (52.6)
	No	9 (47.4)
HIV testing	Positive	5 (26.3)
	Negative	13 (68.4)
	No available	1(5.3)
Symptoms	Sudden vision decrease	5 (26.3)
	Gradual vision decrease	6 (31.6)
	Blurred vision	7 (36.8)
	Pain and photophobia	4 (21)
	Floaters	2 (10.5)
	Flashes	4 (21)
Duration of complaints in days (mean ± SD)		30.1 ± 27.8

the 19 patients. Thirteen patients (68.4%) exhibited systemic manifestations of syphilis. Among these: 11 patients (84.6%) had skin rashes and ulcerations on different body parts including the trunk, axilla, genitals, palms and soles. Three patients presented with neurological symptoms of neurosyphilis such as seizures, tremors and dysphagia and were referred for further neurological evaluations. Three patients had oral or genital ulcers. Two patients showed skin pigmentations changes, and 2 patients had alopecia. Other systemic comorbidities included diabetes mellitus in 4 patients, hypertension in 3 patients, dyslipidemia and ischemic heart disease in one patient and bronchial asthma in one patient. The nail findings of paronychia and onychoptosis were found in 2 patients.

Three patients were misdiagnosed upon referral. One case was misdiagnosed as acute retinal necrosis (ARN) and treated with systemic antivirals, while 2 were misdiagnosed with Behçet's disease and initially treated with systemic steroids, azathioprine, and adalimumab. These treatments were stopped after the patients' conditions worsened.

At presentation, the average Log MAR visual acuity was 0.81 ± 0.80 (Snellen = 20/120). Anterior chamber inflammation was observed in 24 eyes (72.7%). Posterior segment examination revealed vitritis in 16 eyes (48.5%), hyperemic optic discs in 20 eyes (62.5%) and vascular sheathing in 15 eyes (46.9%). Seventeen eyes (51.5%) had placoid lesions. Fundus autofluorescence imaging revealed placoid lesions that were not detected clinically in one eye and a more extensive distribution of the placoid lesions than the clinical picture in one eye. The most common SD-OCT findings included ellipsoid zone (EZ) loss or disruptions in 23 eyes (79.3%) and hyper-reflective nodular retinal pigment epithelium (RPE) elevations in 23 eyes (79.3%). Among 29 eyes that had fundus fluorescein angiography (FFA), 27 eyes (93.1%) had optic disc hyperfluorescence, 24 eyes (82.8%) had vascular leakage, and 18 eyes (62.1%) had staining at the sites of placoid lesions.

The diagnosis of acute syphilitic posterior placoid chorioretinitis (ASPPC) (Fig. 2A-F) was made in 18 eyes (54.5%), necrotizing retinochoroiditis (Fig. 3A-F) in 5 eyes (15.2%), panuveitis with pigmentary retinopathy in 4 eyes (12.1%), punctate inner retinitis (PIR) in 2 eyes (6.1%), non-granulomatous anterior uveitis in 2 eyes (6.1%), intermediate uveitis in 1 eye (3%) and frosted branch angiitis (Fig. 4A-C) in 1 eye (3%).

Among the 19 patients, 16 patients (84.2%) had undergone systemic treatments, while 3 did not show up for treatments. Twelve patients received intravenous (IV) penicillin G for 14 days, 2 patients received intramuscular (IM) penicillin G for 14 days and 2 patients received systemic ceftriaxone (IV in a patient who was allergic to penicillin and IM in one patient, both for 14 days). Two patients had had short courses of oral doxycycline after completing systemic penicillin treatments. Systemic and topical steroids were initiated according to the severity of the clinical picture and the response to the systemic antibiotics. Following treatment, 4 patients did not show up for follow-ups (2 were treated with IV penicillin and 2 were treated with IM penicillin).

All treated patients who came for follow-up after treatment (12 patients) had improved clinically. Among the treated eyes evaluated after treatments, 11 eyes that had placoid lesions showed complete clinical resolution of the placoid lesion in 10 eyes and partial resolution in one eye. Clinically resolved placoid lesions could be appreciated on multimodal imaging in 7 eyes. The ellipsoid zone (EZ) was completely restored in 10 eyes and partially restored EZ in 3 eyes. All eyes with necrotizing retinochoroiditis showed atrophic retinal changes at the sites of the lesions on OCT after resolution. Vasculitis and PIR were completely resolved in all eyes after treatment. The mean follow-up duration after treatment was 6.5 ± 4.5 weeks and the mean log MAR final visual acuity after treatment was 0.23 ± 0.46 (Snellen = 20/30). The improvement in visual acuity was statistically significant ($P < 0.001$).

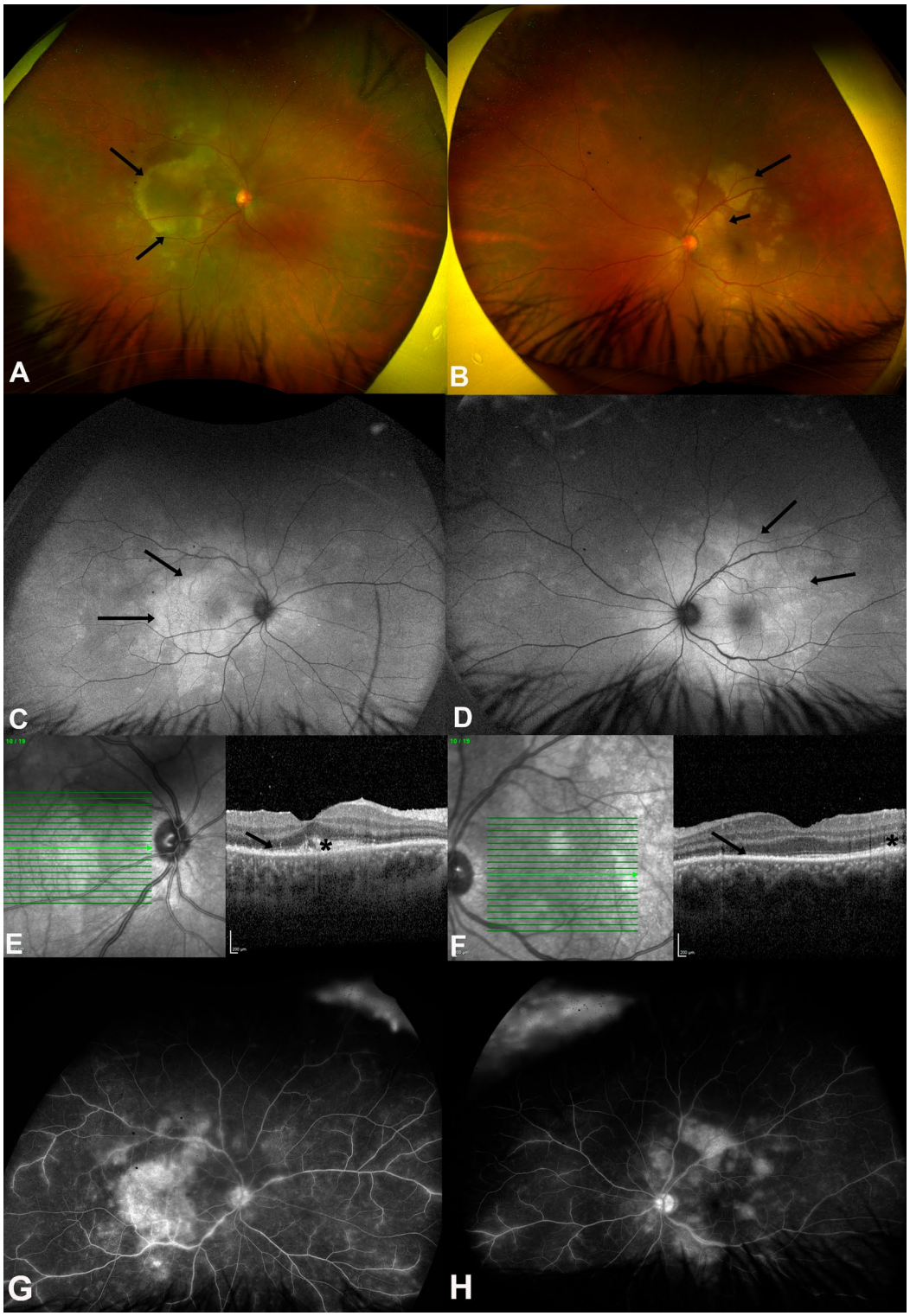

Fig. 2 (**A**) and (**B**) are color fundus photos of both eyes of a 25-year-old male (case 4) showing multiple posterior placoid lesions at the macula (black arrows) and posterior pole indicating acute syphilitic posterior placoid chorioretinopathy (ASPPC). (**C**) and (**D**) are fundus autofluorescence (FAF) photos showing hyperautofluorescent areas more extensive than the lesions that were found clinically (black arrows). (**E**) and (**F**) are spectral domain optical coherence tomography (SD-OCT) of both eyes showing disrupted ellipsoid zones (black arrows), nodular elevations (asterisks) of retinal pigment epithelium (RPE) and intraretinal hyperreflective lesions. (**G**) and (**H**) are fundus fluorescein angiography (FFA) photos showing hyperfluorescent discs, late staining of the placoid lesions, and vascular leakage at the posterior pole in both eyes

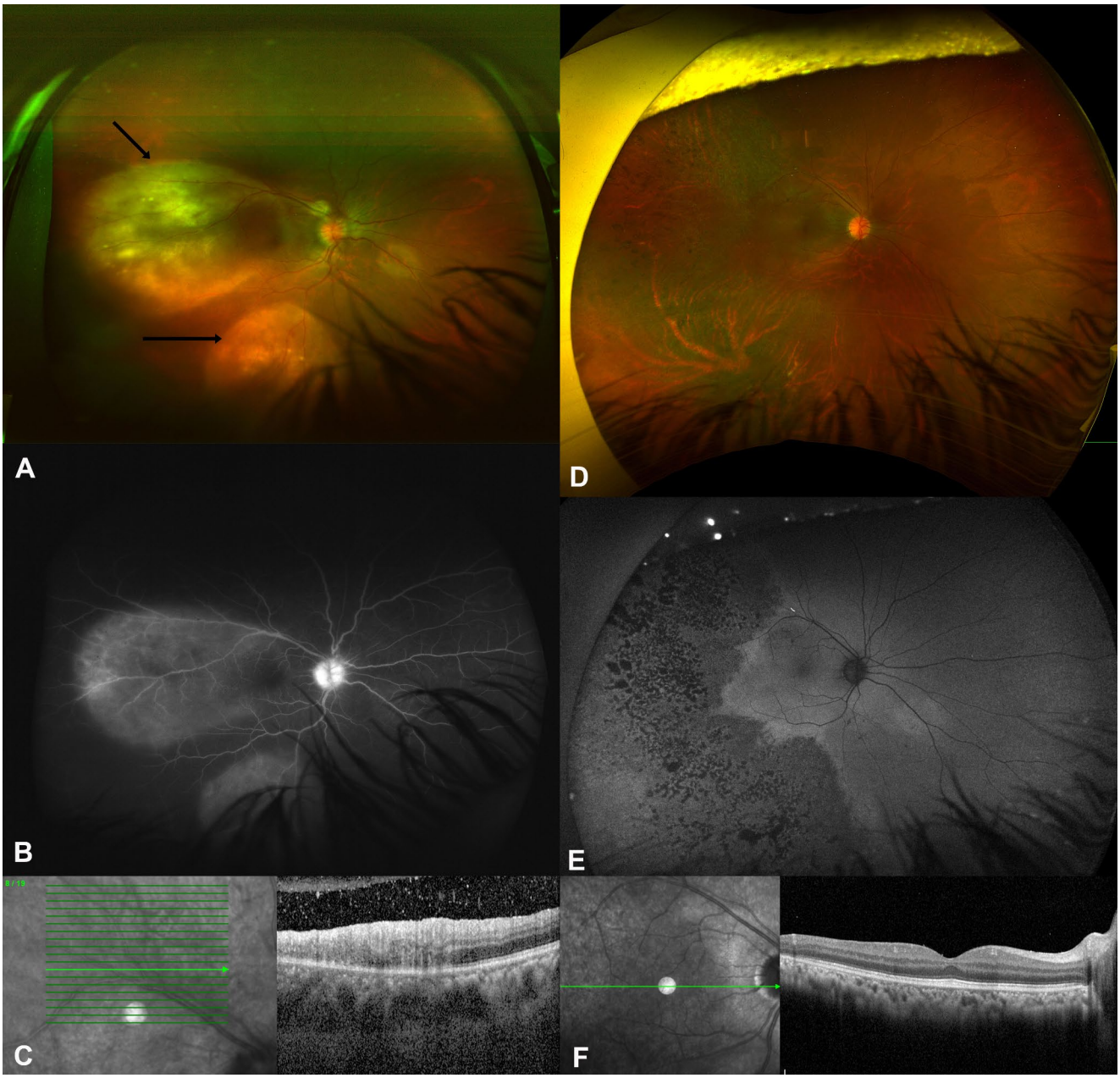

Fig. 3 (**A**) is a color fundus photo of the right eye of a 35-year-old male (case 5) on presentation showing two large temporal and inferotemporal lobulated subretinal lesions (black arrows) with elevated overlying retina along with multiple focal and punctate retinitis over the temporal lesion and an inferonasal flat lesion. (**B**) is a fluorescein angiography of the right eye on presentation showing fluorescein leakage at the sites of the retinochoroiditis lesions. (**C**) is an SD-OCT at the level of the retinochoroiditis lesion showing vitreous cells and swollen and disrupted retinal structures. (**D**) is a color fundus photo of the right eye showing the resolution of the retinal lesions with retinal thinning and pigmentary changes. (**E**) is an FAF showing stippled hypoautofluorescence at the sites of the resolved retinal lesions. (**F**) is an SD-OCT of the macula showing a normal ellipsoid zone and disappearance of RPE elevations and outer retinal changes

4 Discussion

This study summarizes the experience with ocular syphilis in SA. Historically, only a few reports of "Bejel disease" or "endemic syphilis" a non-venereal treponema pallidum infection, are found in the literature [11, 12]. In the past two to three decades, the prevalence of syphilis among uveitis patients was very low, with only two cases among the total visitors of referral eye centers in SA [13–16]. However, several studies have documented a rise in syphilis cases globally between 1984 and 2013 [18–27].

The predominance of bilateral manifestations is in line with previous studies which have found bilateral dominance of ocular syphilis disease in various populations [22, 26, 28,

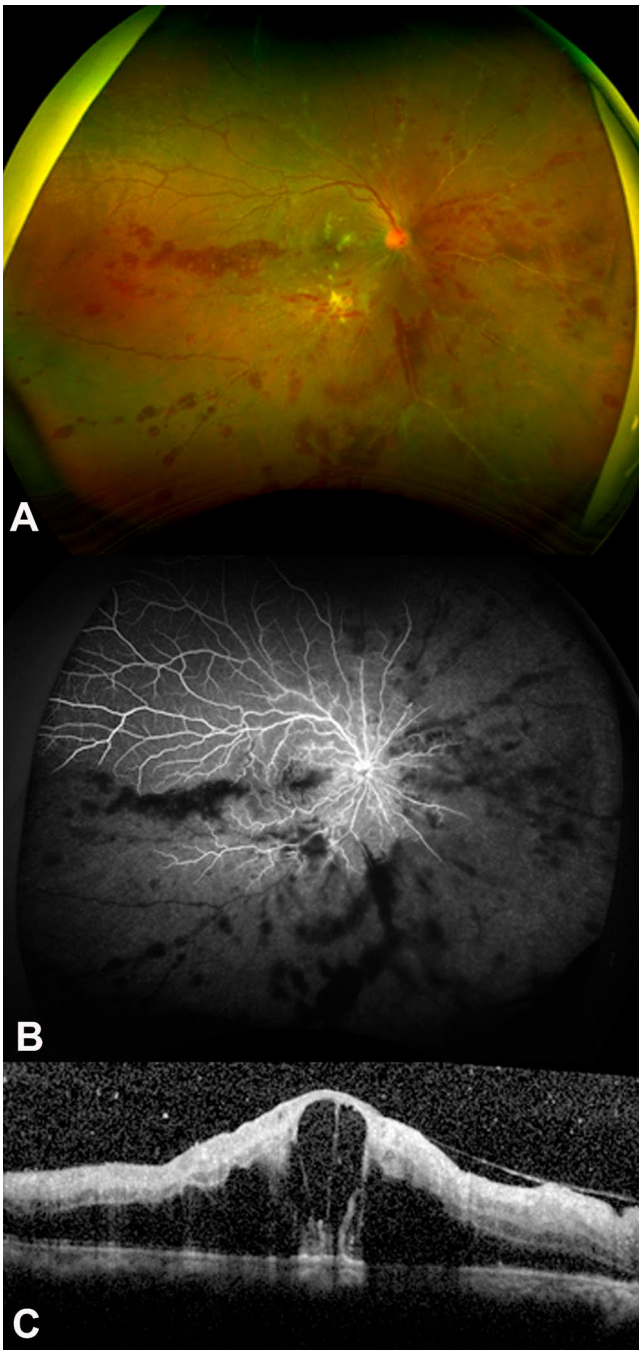

Fig. 4 (**A**) is a color fundus photo of the right eye of a 34-year-old male (case 12) showing diffuse vascular sheathing, hyperemic disc, diffuse retinal hemorrhages and cotton wool spots in a frosted branch angiitis picture. (**B**) is a fluorescein angiography showing choroidal nonperfusion, defective retinal vascular filling in the inferotemporal and inferonasal retinal quadrants and to a lesser extent the superonasal quadrant. (**C**) is an SD-OCT showing cystoid macular edema

29]. The majority of ocular syphilis patients were males (89.5%). This is in agreement with the majority of the previous reports in the literature [21, 26, 29, 30]. The reasons behind male predominance among ocular syphilis patients are not completely understood but might be related to higher likelihood of engagement in unprotected sexual encounters which is a known risk factor for syphilis among the male gender.

Co-infection with HIV was seen in 26.3% of our cohort. This rate is within the same range that was found in previous studies between 27% and 36% [27, 29–32]. However, some studies have reported higher rates [21, 26]. The reason for the low rates might be related to the low prevalence of HIV infections in Saudi Arabia [33]. All HIV patients had bilateral disease. However, bilateral involvement was also common in HIV-negative patients. This is in agreement with the previous conclusions from the literature [21]. There were no relationships between visual acuity on presentation or visual outcomes with HIV co-infection. There was also no difference in the severity of the clinical picture between HIV-positive and HIV-negative patients. These findings are consistent with previous findings of large cohorts with ocular syphilis which found similar clinical pictures in both cohorts of patients [24, 26]. This might be related to the availability of highly active antiretroviral therapy (HAART) and the prompt initiation of treatment which might have prevented the worsening of the clinical picture and other complications [26]. On the other hand, previous studies have suggested more posterior segment involvement and more severe retinitis in HIV-positive patients [20, 22, 34–36].

There was a high frequency of optic nerve involvement, vitritis and vasculitis in our cohort. Other findings of posterior placoid chorioretinitis, necrotizing retinochoroiditis, macular edema and punctate inner retinitis (PIR) are known as well [20, 26]. Although the ASPPC which was first described by Gass [37] is known to be suggestive of ocular syphilis, it was found in only 21 eyes (54.5%), including lesions that were not clinically visible but found on FAF. The use of FAF can be beneficial during the follow-ups, especially for the assessment of response to treatment by comparing the size of the hyper auto fluorescent areas to the baseline imaging on presentation.

The high rates of involvement of optic disc inflammation and vitreous reaction along with the necrotizing retinitis or retinochoroiditis provide a clinical challenge for ophthalmologists, as these findings provide a similar clinical picture to viral retinitis as well as Behcet's disease. Not only the ophthalmic features but also the systemic findings (Syphilis and Behcet's disease share similar systemic manifestations such as oral ulcers, genital ulcers, and skin rash). Furthermore, the diagnosis of syphilis is more challenging due to the fewer number of cases in our region where previous studies documented that Behcet's disease and ARN are more prevalent in Saudi Arabia [13–16]. Three patients in this cohort were initially misdiagnosed with viral retinitis or Behcet's disease. Such misdiagnosis is well documented in

the literature [21]. Nevertheless, all of these diseases require prompt management and initiation of treatment. However, it is critical to rule out viral retinitis and ocular syphilis before establishing the diagnosis of Behcet's disease and starting the immunosuppressive treatment. In our uveitis workup, and despite the fact that syphilis is rarely encountered in our community, all patients must be investigated for syphilis. Two out of the three misdiagnosed patients were given systemic immunosuppressive medications and systemic steroids, after which their clinical conditions worsened. Fortunately, timely initiation of syphilis treatment resulted in significant visual improvements and prevented irreversible clinical and visual deteriorations.

According to Centers for Disease Control and Prevention (CDC) Atlanta guidelines, using the reverse algorithm sequence in which the diagnosis of syphilis starts with treponemal tests like TPHA or enzyme immunoassay (EIA) as screening tests for syphilis, with positive tests, subsequently confirmed with nontreponemal tests [38].we routinely performed both treponemal and nontreponemal tests simultaneously. All patients who were admitted for treatment in the present study showed either improvement or resolution of their ophthalmic disease with the timely initiation of the appropriate systemic treatment (IV or IM penicillin for 10–14 days). Two patients were also improved on systemic ceftriaxone treatment for 14 days. The response to treatment was obvious not only on the clinical examination but on FAF and SD-OCT as well. Reported OCT features in ocular syphilis include vitreous cells, disruption of the ellipsoid zone (EZ), and multinodular hyperreflective elevations of the RPE [39, 40]. After treatment, all patients showed improvement of the multinodular elevations and most of them had restoration of the EZ, while atrophic changes were seen at the sites of the necrotizing retinitis lesions after resolution. Intravitreal ceftazidime has been used as an adjunct therapy in 3 patients who had suboptimal or slow response to systemic penicillin therapy [41]. Unlike the cohort described in this study, these patients developed significant vitritis which was improved with intravitreal ceftazidime injections. Moreover, all patients in our cohort had good response to systemic penicillin treatment.

Limitations of the study include its retrospective design, including nonstandardized collection of data, variable duration of follow-up, and assessments performed at different intervals. In addition, given syphilitic uveitis comprises a small percentage of all uveitis presentations, the sample size of this series remains small.

In conclusion: The present study demonstrated that ocular syphilis is emerging in Saudi Arabia, therefore, ophthalmologists should be aware of the diverse clinical pictures and findings of multimodal imaging of ocular syphilis to prevent misdiagnosis or any delay in the treatment.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s44197-025-00374-1.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Ethics Approval and Consent to Participate The study received approval from the Institutional Ethical Review Committee of King Khled Eye Specialist Hospital (No. 23143-R). All participants gave consents to participate in the study.

Consent for Publication All participants were consented for publication of this paper.

Competing Interests The authors declare no competing interests.

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