Original Article

Clinical manifestations and outcomes of ocular syphilis in Asian Indian population: Analysis of cases presenting to a tertiary referral center

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Purpose: To describe disease manifestations and outcomes of ocular syphilis in Asian Indian population. **Methods:** Retrospective analysis of patients diagnosed with ocular syphilis at a tertiary referral center in India. Demographics, history, extraocular and ocular manifestations, ocular and systemic investigations, treatment and visual acuity outcomes were noted. All patients were diagnosed after necessary laboratory investigations including HIV ELISA (Human immunodeficiency virus, enzyme-linked immunosorbent assay), VDRL (venereal disease research laboratory), and TPHA (treponema pallidum hemagglutination). **Results:** Totally, 20 patients with mean age at presentation 38.25 ± 9.76 were analyzed. 9/20 patients had bilateral involvement. 8/20 had concurrent HIV at presentation with an average CD4 counts of 592.25 ± 411.34 cells/microliter. The mean duration of symptoms at time of presentation was 15.45 ± 35.15 weeks. VDRL test was reactive in 45% (9/20) patients whereas, all patients had a reactive TPHA test. Clinical manifestations included outer retinal placoid chorioretinitis lesions (8/20, 40%), followed by retinitis mimicking acute retinal necrosis as the second most common phenotype (4/20, 20%). Other presenting manifestations noted were panuveitis, miliary retinitis lesions, retinal vasculitis, intermediate uveitis, and anterior uveitis. The clinical phenotypes in immunocompromised included panuveitis, acute retinal necrosis and isolated anterior uveitis. Mean follow up duration was 6.32 ± 6.15 months. An improvement in mean best corrected visual acuity (BCVA) of (0.63 LogMAR, approximately 6 Snellen lines, $P < 0.02$) was noted at last follow-up. **Conclusion:** Phenotypic manifestations of ocular syphilis are varied. Non-treponemal tests like VDRL may be unreliable when compared with treponemal tests in diagnosing ocular syphilis. Syphilitic uveitis is considered equivalent to neurosyphilis and is treated similar to neurosyphilis.

Key words: HIV, luetic, ocular syphilis, panuveitis and granulomatous, syphilis

Syphilis is a sexually transmitted disease (STD) caused by the spirochete *Treponema pallidum*. Syphilis has been on the rise globally over the past decade. The 2015 statistics from the Center for disease control and prevention (CDC) reported a 7.5 per 100,000 population of primary and secondary syphilis.[1] There has been a recent resurgence in cases of syphilis in the last few years. In 2018, the total case count of reported syphilis was the highest recorded since 1991. The total number of reported cases of syphilis (all stages) increased 13.3% during 2017–2018 (from 101,584 cases to 115,045 cases).[2] The incidence of syphilis among STD clinic attendees in north India in 2004 was estimated to be 24.2%.[3] Another study on syphilis from India estimated the seroprevalence to be around 1.79% in 2011.[4] People at highest risk of developing syphilis are men who have sex with men, who are also at an increased risk of developing human immunodeficiency virus (HIV) infection.[5] There is an increasing incidence of ocular syphilis in HIV positive patients in the post HAART era, probably indicating poor protection offered by immune reconstitution in preventing syphilis.[6]

Ocular manifestations occur in about 0.6–2% of all patients with syphilis at any stage of disease.[7] Clinical manifestations of ocular syphilis pose a diagnostic challenge to all clinicians. Some ocular findings described in syphilis include scleritis, interstitial keratitis, granulomatous or non-granulomatous anterior uveitis, intermediate uveitis, retinitis, chorioretinitis, choroiditis, papillitis, neuroretinitis, retinal vasculitis and placoid chorioretinitis[8,9] Hence, syphilitic uveitis may be considered a great masquerader.

Various findings have been described in literature to help differentiate ocular syphilis from the other posterior segment involving infectious and non-infectious entities including posterior placoid lesions and superficial creamy yellow precipitates.[10] We had earlier described findings consisting of multiple fine well demarcated discrete miliary lesions,

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which involved full thickness of retina as a possible clue to diagnosing syphilitic uveitis.[11] In this study, we describe the characteristic clinical manifestations and presentations of ocular syphilis in both HIV positive and negative individuals and their serological correlation.

Methods

We retrieved clinical records of all patients presenting with anterior, intermediate, posterior and panuveitis at our institutions between January 2013 to January 2019. All patient information was obtained through detailed review of medical records. The study was approved by the Institutional Review Board and adhered to the guidelines of the declaration of Helsinki. The inclusion criteria were (1) diagnosed cases of ocular syphilis with or without HIV infection, (2) complete clinical examination including visual acuity, intra ocular pressure, slit lamp biomicroscopy and posterior segment examination using indirect ophthalmoscopy, (3) fundus photography (seven-field montage or wide field) and autofluorescence at baseline view permitting, optical coherence tomography (OCT), (4) relevant laboratory investigations for confirmation of system infection with *T. pallidum* including a reactive treponemal test—treponema pallidum hemagglutination (TPHA) test and/or a reactive non treponemal test—venereal disease research laboratory (VDRL) or rapid plasma regain (RPR) test, and (5) complete resolution of inflammation with treatment based on etiological diagnosis. Criteria for exclusion were: (1) incomplete medical records and (2) absence of laboratory investigations despite clinical suspicion. The stage of syphilis at presentation for each patient was however not known.

The following signs of intraocular inflammation were specifically noted in all eyes with ocular syphilis—scleritis, anterior chamber reaction ≥2+, keratic precipitates, posterior synechiae, peripheral anterior synechiae, vitritis grade ≥2+, cotton ball exudates, pre retinal exudates and snowbanking, disc edema, active retinal vasculitis, retinitis—including full thickness retinitis, placoid outer retinitis, acute retinal necrosis, choroiditis, and choroidal granuloma. Anatomical classification of uveitis was done as per Standardization of Uveitis Nomenclature (SUN) classification.[12]

Serology including non-treponemal and treponemal tests were performed at diagnosis for each patient. Laboratory investigations in addition to treponemal and non-treponemal tests were sought to exclude other uveitic entities, including complete blood counts, peripheral blood smear, tuberculin skin test (TST), QuantiFERON TB gold test (QFT), serum angiotensin converting enzyme (ACE), liver function test, HIV and chest radiography. Patients, once diagnosed as ocular syphilis, received intravenous injection crystalline penicillin or intravenous ceftriaxone as per the guidelines given by Centers for Disease Control and Prevention (CDC).[2] Statistical analysis was done using the InStat statistical software version Win 3.0× (GraphPad Software Inc., CA, USA). Descriptive statistics were used for demographic data. Snellen visual acuity was converted to LogMAR for data analysis.

Results

Medical records of 26 patients diagnosed as ocular syphilis were analyzed, retrospectively. Few were excluded due to inadequate records and loss to follow up. We included 29 eyes of 20 patients in this study, 16 of which were male [Table 1]. The mean age at presentation was 38.25 (±9.76, range 23–59 years). Nine of 20 patients had bilateral involvement. Eight patients had concurrent HIV infection, with four of them on anti-retroviral therapy at presentation. The other 12 patients were immunocompetent. The average CD4 counts in these eight cases was noted to be 592.25 cells/microliter (±411.34, range 58–1116 cells). The mean duration of disease in weeks was 15.45 (±35.15, range 1–152) and mean follow up duration in months was 6.32 months (±6.15, range 0.5–24). Systemic history of exposure to unprotected sexual intercourse, recent sudden weight loss, skin manifestations on genitals was noted in four patients (20%). One of the 20 patients gave a history of the partner having been a diagnosed case of systemic syphilis with a positive TPHA test.

Phenotypically, outer retinal placoid chorioretinitis lesion (8/20, 40%) [Figs. 1 and 2] were the most common finding, followed by retinitis mimicking acute retinal necrosis as the second most common diagnosis (4/20, 20%) [Fig. 3]. Apart from cases diagnosed as panuveitis, significant anterior chamber with posterior segment inflammation was encountered in 6 eyes of 4 patients presenting with the morphological pattern of acute retinal necrosis. One patient

Table 1: Demographic characteristics and clinical features of patients

Parameter 29 eyes of 20 patients	Mean/*n*	% or +/- SD
Age	38.25	±9.76
Gender	16 male/4 female	-
Bilateral disease	9/20	45%
HIV Co-infection	8/20	40%
On ART at presentation (of patients with HIV)	4/8	50%
Duration of disease (w)	15.45	±35.15
Follow up duration (m)	6.32	±6.15
Systemic History (H/o unprotected sexual intercourse/ exposure, Weight loss, Ulcerative lesions on Penis)	4/20	20%
VDRL test Reactive	9/20	45%
TPHA Reactive/Positive	20/20	100%

n - Number, SD - Standard deviation, HIV - Human immunodeficiency virus, ART - Anti retroviral therapy, w - Weeks, m - Months, VDRL - Venereal disease research laboratory, TPHA - Treponema pallidum hemagglutination
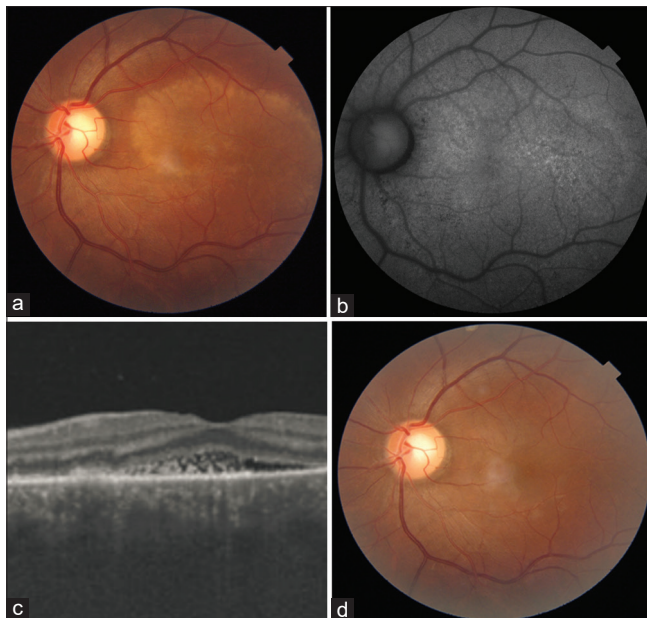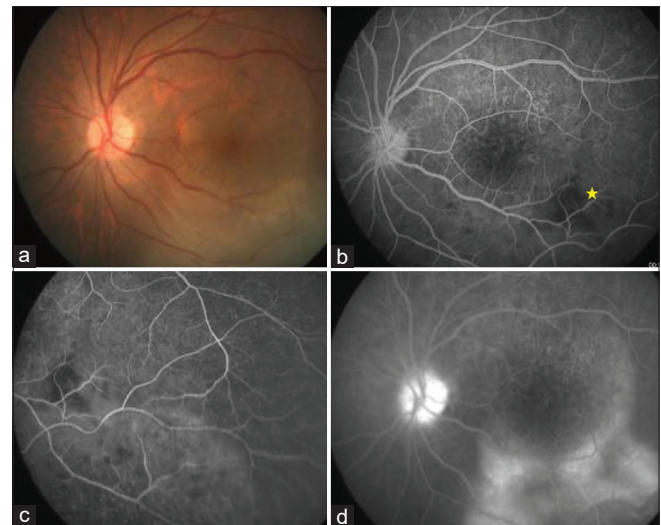
Figure 1: Fundus photograph of the left eye showing outer retinal placoid lesion (a), with the autofluorescence showing speckled hyperautofluorescent dots corresponding to the lesion and within, interspersed with pin point hypoautofluorescent dots (b). Optical coherence tomography (OCT) line scan through the lesion shows areas of irregularity or loss of ellipsoid zone, neurosensory detachment with hyperreflective dots, areas of thinned and thickened retinal pigment epithelium (RPE), inflammatory subretinal and subRPE deposits/lesions (c). (d) Left eye after treatment showing resolution
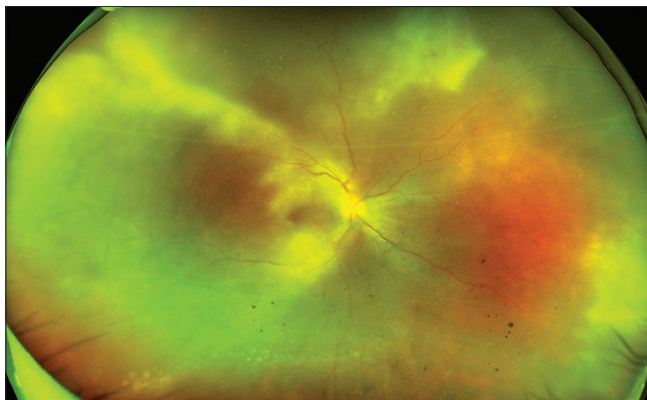

Figure 3: An Optos widefield image of the right eye showing multiple full thickness retinitis lesions extending along the vessels. Multiple areas of perivascular sheathing may also be noted. Inferior part of the picture shows multiple small full thickness retinitis lesions or scars

with phenotypic manifestation of acute retinal necrosis initially presented with anterior nodular scleritis. The other phenotypes encountered have been detailed in Table 2. Anterior segment manifestations included keratic precipitates (fine (10.3% eyes) and granulomatous (10.3% eyes)) anterior chamber cells and flare and posterior synechiae. Iris nodules were noted in one eye with panuveitis. Significant vitritis (grade ≥2+) was noted in 15 eyes of 11 patients (15/29, 51.7%) whereas, cotton ball exudates were noted in 3 eyes of 3 patients (3/29, 10.3%) and pre retinal exudates in one eye [Table 3]. None of the cases in our cohort presented with optic disc involvement alone. We

Figure 2: (a) Fundus photograph of the left eye showing a posterior outer retinal placoid retinitis lesion with perivascular sheathing in the inferotemporal quadrant, (b). Mid phase FA showing hyper fluorescence with interspersed small areas of hypo fluorescence (leopard spotting) and an area of marked hypo fluorescence along the active retinitis edge (yellow star), (c). Inferotemporal periphery showing the area of retinitis with hypo fluorescence and mild staining of vessel walls and (d). Late phase showing disc hyperfluorescence and increased hyper fluorescence corresponding to active retinitis edge
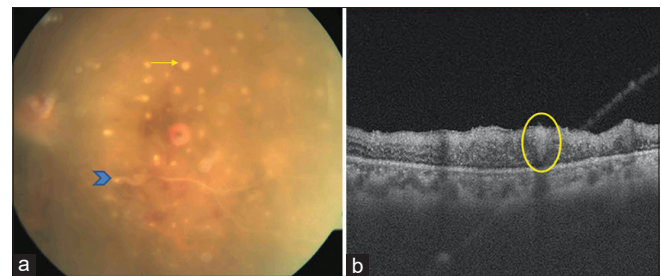
Figure 4: A fundus photograph of the left eye showing miliary retinal lesions (yellow arrow), with presence of retinal perivascular sheathing (a, chevron), OCT vertical line scan through the miliary lesions reveals hyperreflectivity through the full thickness of the retina (b, yellow oval)

could not find any correlation between outer retinal placoid chorioretinitis lesions and low CD4 counts in cases with HIV in our cohort. Full thickness retinitis lesions were wedge shaped with the apex pointing towards the posterior pole when present. Miliary retinal lesions were noted in six eyes of 4 patients (20%) [Fig. 4]. They were associated with ground glass retinitis lesions and retinal vasculitis in these patients. Optic disc involvement in the form of disc hyperemia or disc edema was noted in 3 patients (15%). One patient with HIV had abduction limitation due to bilateral sixth nerve palsy.

The imaging characteristics of each of the lesions have been described in the Table 4. Autofluorescence characteristics of outer retinal placoid lesions include hypoautofluorescent to isoautofluorescent center at the macula surrounded by a ring of pinpoint hyperautofluorescent dots. On OCT, loss of ellipsoid zone (EZ) at the fovea, perifoveal thickening of photoreceptors, hyperreflectivity of the choroid at the fovea,

with or without cystoid degeneration or CME were all noted. The outer ring of the active placoid lesion corresponded to the hypoautofluorescent ring in this study. The resolution of these lesions occurred with minimal RPE alterations and pigment mottling, resolution of photoreceptor thickening and schitic cavities/cystoid spaces involving inner and outer retina noted on OCT. Four cases (20%) presented with multiple pinpoint hypopigmented lesions, associated with retinal vasculitis or outer retinal placoid lesions. These lesions involved full

thickness of the retina and healed with pigmentation, which has recently been described.[11]

Non treponemal test—VDRL was reactive in 9/20 (45%) patients. All patients had a positive TPHA test. Therefore, we found VDRL to be false negative in 55% of cases. Three patients had a positive tuberculin skin test. One of our patients who had features of scleritis was also investigated for cANCA or pANCA which were both negative. Nineteen patients were treated with intravenous (IV) injection crystalline penicillin 4 million units every 4 h for 14 days. One patient was treated with IV ceftriaxone 2 g daily for 21 days due to unavailability of penicillin. Two patients (2/20, 10%) needed additional therapy with oral doxycycline 100 mg twice daily for a period of two more weeks after completion of intravenous therapy to aid resolution of disease. In majority of the patients, lesions responded well to 14 days course of IV penicillin. The mean visual acuity improved from LogMAR 1.037 ± 1.14 to LogMAR 0.41 ± 0.94 (P = 0.02, Wilcoxon Signed Rank Test) at the last clinical follow up visit [Table 5]. The VDRL titres after 1 month showed a four-fold reduction and this along with the resolution of lesions, were taken as a markers for complete clinical cure.

Table 2: Phenotypic manifestations of ocular syphilis

Clinical feature	Number n/20 (%)
Anterior Uveitis	2 (10%)
Intermediate Uveitis	2 (10%)
Panuveitis	2 (10%)
Acute Retinal Necrosis	4 (20%)
Isolated Retinal Vasculitis	1 (5%)
Placoid outer Retinitis	8 (40%)
Choroidal Granuloma/Multifocal Choroiditis	1 (5%)

Table 3: Other associated clinical features noted in this cohort

Clinical feature	Patients N/20	Eyes N/29
Granulomatous keratic precipitates	2 (10%)	3 (10.3%)
Posterior Synechiae	7 (35%)	8 (27.5%)
Vitritis ≥2+	11 (55%)	15 (51.7%)
Cotton ball exudates	3 (15%)	3 (10.3%)
Miliary retinal lesions	4 (20%)	6 (20.7%)
Optic Disc involvement (Disc hyperemia or edema)	3 (15%)	6 (20/7%)
Abduction Limitation due to Bilateral Sixth Nerve Palsy	1 (5%)	1 (3.4%)

Table 4: Imaging characteristics of retinitis lesions in ocular syphilis in our cohort

Clinical feature	Fundus Photo	Autofluorescence	OCT	Pattern of Healing
Retinitis	Full thickness, Wedge-shaped, ground glass appearance, vitritis	Hypoautofluorescent	Hyperreflective dots in vitreous, inner and outer retinal cysts, loss of differentiation of inner retina and ELM, irregular elevations of RPE	Pigmented scarring
Placoid outer Retinitis	Granular outer retinal placoid lesion	Diffuse hyper autofluorescence involving the posterior pole and the arcades along the margins of the lesion with scattered stippled hypo autofluorescence	Edematous inner retinal layers, ILM folds, loss of EZ, inflammatory subretinal deposits/lesions, Intra retinal hyper reflective dots and dipping down of inner retinal layers specifically IPL and GCL into INL, thinned RPE	Resolved without pigmentation
Miliary retinal lesions	Full thickness lesions associated with ground glass retinitis and retinal vasculitis	Hypoautofluorescent lesion with minimal perilesional hyper autofluorescence	Involving entire thickness of retina as a hyperreflective small focus	Resolved with pigmentation and scarring
Choroidal Granuloma/ Multifocal Choroiditis	Elevated choroidal granuloma with full thickness retinitis, overlying tortuous vessels, multiple subvascular chorioretinal scars, disc edema, peripheral small active choroiditis lesions at the margins	Uniform hyper autofluorescence corresponding to the choroidal elevation, hypoautofluorescent scars	Elevated choroidal lesion with full thickness retinal involvement, focal vitreous attachment, surrounding NSD, CME with intra retinal hyper-reflective dots at the macula	Resolution of granuloma with pigmented scarring, straightening of overlying vessels

OCT - Optical coherence tomography, ELM - External limiting membrane, RPE - Retinal pigment epithelium, ILM - Internal limiting membrane, EZ - Ellipsoid zone, IPL - Inner plexiform layer, GCL - Ganglion cell layer, INL - Inner nuclear layer

Table 5: Mean pre-treatment and post-treatment best corrected visual acuity (BCVA) in affected eyes

Visual Acuity	Value
Mean BCVA at presentation	1.04±1.14
Mean post-treatment BCVA	0.41±0.94
Mean difference LogMAR	0.63
P of mean difference	0.02

BCVA - Best corrected visual acuity

Discussion

This is a retrospective descriptive study of all patients presenting with various phenotypic manifestations of ocular syphilis with a confirmed serological diagnosis. Numerous prior studies have described the ability of syphilis to mimic various uveitic entities. The most common syphilitic manifestation in the eye is uveitis and the most common phenotypic manifestation in posterior uveitis is chorioretinitis.[13,14] In a case series consisting of syphilitic posterior uveitis, three fourths of them presented with chorioretinitis.[15] In a larger series by Vadboncoeur *et al.*, posterior uveitis (29%) was the most common presentation of ocular syphilis followed by anterior uveitis and panuveitis.[16] In our series, posterior uveitis accounted for (14/20) 70% of all presentations followed by panuveitis (2/20, 10%), intermediate (2/20, 10%) and anterior uveitis respectively (2/20, 10%). The phenotypes in posterior uveitis included retinal vasculitis, acute retinal necrosis, placoid outer retinitis, retinitis, retinochoroiditis, multifocal choroiditis, and choroidal granuloma.

HIV test was performed for all patients in our series where 8/20 (40%) were HIV positive. Various studies have looked at the relationship of HIV and syphilis and concluded that these patients stand a higher chance of developing neurosyphilis, though the relation between the two is not entirely clear.[17] Though the CDC guidelines recommend performing a lumbar puncture (LP) for patients with ocular syphilis, we could not do this in our patients with HIV and ocular syphilis in our cohort.[18] The disease manifestation in these patients with HIV and ocular syphilis consisted of panuveitis (2/8, 25%), acute retinal necrosis (2/8, 25%), placoid outer retinitis (3/8, 25%), and isolated anterior uveitis (1/8, 12.5%). Various studies in literature have reported varied manifestation of ocular syphilis in HIV positive individuals. A larger series of HIV and ocular syphilis revealed panuveitis and optic nerve involvement as the most common diagnosis followed by posterior uveitis in their cohort (16). Posterior segment involvement in ocular syphilis is common in patients with HIV. Superficial retinal precipitates have also been described in patients with HIV and syphilis. It has also been suggested that placoid outer retinitis is more common in those with HIV.[10] Atypical clinical manifestations, serological responses and poor response to therapy have all been described in literature in patients with HIV and syphilis coinfection.[19]

It is interesting to note that only 9/20 patients (45%) had a positive VDRL test. 5/8 (62.5%) of patients with ocular syphilis and HIV co infection had a positive VDRL test. On the contrary, all patients had a reactive TPHA test in this cohort. Non-treponemal tests are used to monitor the disease and detect reinfection.[20] Seroconversion with non-treponemal tests may take 3–6 weeks.[21] Poor sensitivity (70%) in primary and late syphilis, false positive tests due to cross reactivity with other antigens and false negativity due to prozone phenomenon, previous treatment, HIV coinfection and long latency especially late neurosyphilis are the main limitations of non-treponemal tests like VDRL.[22] More than 50% of patients were non-reactive for VDRL in our cohort. Hence, non-treponemal tests cannot be solely relied upon and must be combined with a treponemal test like TPHA. The high false negativity of VDRL highlights the importance of using treponemal tests like TPHA to diagnose ocular syphilis. Other studies have also shown that treponemal tests like TPHA have a sensitivity and specificity of more than 90 percent for tertiary syphilis.[9] Although VDRL titres were repeated at 1 month in this series, as per CDC recommendation, treatment response should also be monitored with serological evaluation at 6 and 12 months after treatment.[18]

According to the CDC guidelines, a single intramuscular (IM) administration of 2.4 million units (MU) of benzathine penicillin G has been recommended for the treatment of primary, secondary, and early latent syphilis and a total of 7.2 MU of benzathine penicillin G, administered as three IM doses of 2.4 MU each at one-week intervals is recommended for the treatment of latent syphilis of unknown duration, late latent syphilis, and tertiary syphilis without evidence of neurosyphilis. Syphilitic uveitis, however, is considered equivalent to neurosyphilis and therefore its treatment has been defined according to the treatment and other recommendations for neurosyphilis. Currently aqueous crystalline penicillin G 18–24 million units per day, administered as 3-4 million units IV every 4 hours or continuous infusion, for 10-14 days is the treatment of choice.[18] 19 out of 20 patients in our series were treated with intravenous (IV) injection crystalline penicillin 4 million units every 4 hours for 14 days. One patient was treated with IV ceftriaxone 2 gm daily for 21 days due to unavailability of penicillin. Amode *et al*. have also demonstrated the use of oral doxycycline at 200 mg/day, divided into two equal doses, for 28 days in a patient with syphilitic uveitis.[23] Two patients (2/20, 10%) needed additional therapy with oral doxycycline 100 mg twice daily for a period of 2 more weeks after completion of intravenous therapy to aid resolution of disease. The strength of this study is it describes the clinical and imaging findings of patients presenting to a tertiary center with ocular syphilis which has shown a recent resurgence. Furthermore, various investigations and treatment regimens have been highlighted. However, this study suffers from a drawback due to the inherent weakness of a retrospective study design.

Conclusion

Re-emergence of syphilis and varied manifestations make it necessary to keep it as a differential diagnosis for most uveitic entities. Posterior uveitis was the most common phenotypic manifestation of ocular syphilis in our cohort. Testing with treponemal and non-treponemal tests at the first visit itself is of utmost importance, as non-treponemal tests like VDRL may be frequently non-reactive and treponemal tests are more reliable in diagnosing ocular syphilis. Syphilitic uveitis is considered equivalent to neurosyphilis and therefore its treatment has been defined according to the treatment and other recommendations for neurosyphilis.

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