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Clinical manifestations and treatment outcomes of syphilitic uveitis in HIV-negative patients in China

A retrospective case study

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Abstract

Syphilitic chorioretinitis should be included in differential diagnosis of any form of ocular inflammation. A significantly higher proportion of human immunodeficiency virus (HIV)-positive patients with ocular syphilis as compared to HIV-negative cases have been reported in published studies. However, the clinical signs and symptoms are more insidious in HIV-negative patients who are easily misdiagnosed. We report a series of cases of ocular syphilis and describe the clinical manifestations and treatment outcomes of syphilitic chorioretinitis in HIV-negative patients in China.

This was a retrospective case series study. The clinical records of patients with syphilis chorioretinitis were reviewed. Demographic information and findings of fundus fluorescein angiography (FFA), indocyanine green angiography (ICGA), and spectral domain optical coherence tomography (SD-OCT) were analyzed. All patients received the standard treatment. Ophthalmology examination and laboratory evaluation were repeated every 3 months. All changes were recorded. The treatment was considered successful if the patients had no inflammation in both eyes and rapid plasma reagin titer was negative after therapy.

The study examined 41 eyes of 28 HIV-negative patients. The main complaints were blurry vision, floaters, and visual field defect. Twenty-seven eyes presented with panuveitis, and all had posterior involvement, including uveitis, vasculitis, chorioretinitis, and optic neuritis. The most common manifestations were uveitis and retinal vasculitis. Disc hyperfluorescence and persistent dark spots were the most common findings on FFA and ICGA. The ill-defined inner segment/outer segment junction was the most frequent manifestation on SD-OCT. Patients were diagnosed with syphilitic uveitis based on positive serological tests. Best-corrected visual acuity (BCVA) was improved in 34 eyes after treatment. Eleven patients were misdiagnosed before serological tests were performed. The delay in treatment led to long-standing cystoid macular edema and optic neuropathy, which were associated with poor BCVA ($P = .037$).

The common manifestations of syphilitic chorioretinitis were uveitis, retinal vasculitis, and optic neuritis. Further diagnosis should be prompted by FFA, ICGA, and SD-OCT when ocular manifestation is suspected. The standard treatment for neurosyphilis was effective. If patients are presumed to be in low-risk groups such as HIV-negative, delays in diagnosis, and therapy may be likely. It is necessary to reiterate the importance of including syphilis uveitis as a differential diagnosis for any form of ocular inflammations, especially posterior uveitis and optic neuropathy.

Abbreviations: AC = anterior chamber, BCVA = best-corrected visual acuity, FFA = fundus fluorescein angiography, HIV = human immunodeficiency virus, ICGA = indocyanine green angiography, IS/OS = inner segment/outer segment, RPR = rapid plasma reagin titer, SD-OCT = spectral domain optical coherence tomography, SRF = subretinal fluid, TPPA = *Treponema pallidum* particle agglutination assay.

Keywords: FFA, ICGA, SD-OCT, syphilis uveitis

1. Introduction

Acquired syphilis is a sexually transmitted disease caused by *Treponema pallidum*. It can cause morbidity in almost any part of the body.[1] It can involve all parts of the eye and may be the only manifestation of syphilis. In recent years, ocular syphilis has been reported in numerous countries, and uveitis is the most common manifestation of syphilitic chorioretinitis.[2,3] Syphilitic uveitis can develop at any stage of the disease.[4] The ocular manifestations of acquired syphilis are protean, and syphilitic chorioretinitis may be included in the differential diagnosis of any form of ocular inflammation.[5] Thus, it is termed the great masquerader. A classic treatment regimen for neurosyphilis with intravenous penicillin G is considered successful in the treatment of syphilitic chorioretinitis and results in good prognosis.[6]

After near eradication with the use of antibiotics, the incidence of syphilis has increased worldwide since 2000. Resurgent syphilis epidemics have been reported in numerous developed

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countries, including the United States.[7] However, 90% of new syphilis cases are in developing countries.[8] In Asia, Singapore and Japan have recently reported several cases of ocular syphilis.[9,10] The prevalence of syphilis in China has also rapidly increased in recent years.[11,12] Hence, vigilance is required in the diagnosis of ocular syphilis.[13] A significantly higher proportion of human immunodeficiency virus (HIV)-positive patients with ocular syphilis as compared to HIV-negative cases have been reported.[14,15] However, the clinical signs and symptoms are more insidious and protean in HIV-negative patients who are easily misdiagnosed, which leads to delayed treatment. In China, especially in the Northwestern region, ocular syphilis has rarely been reported in HIV-negative individuals. Herein, we report a series of cases of ocular syphilis and describe the clinical manifestations and treatment outcomes of syphilitic chorioretinitis in HIV-negative patients in Northwest China.

2. Methods

This is a retrospective case series of 28 consecutive patients with syphilitic uveitis presenting at the Xi'an No. 4 Hospital, China, between January 2014 and July 2016. All processes were approved by the Ethics Committees of Xi'an No. 4 Hospital. Written informed consent was obtained from the patients before collection of blood samples. Patient information was anonymized and de-identified prior to analysis.

Patients who visited the hospital with eye-related symptoms suspected of syphilis were suggested to undergo a blood test for syphilis. The diagnosis of syphilitic uveitis was confirmed by positive serological tests, including rapid plasma reagin (RPR) titer and *T pallidum* particle agglutination assay (TPPA).[10] Each patient underwent complete ophthalmology examination including best-corrected visual acuity (BCVA), slit-lamp biomicroscopy, applanation tonometry, and ophthalmoscopy. Color photograph, fundus fluorescein angiography (FFA), indocyanine green angiography (ICGA), and spectral domain optical coherence tomography (SD-OCT) were obtained in each case. The International Uveitis Study Group criteria were used for the classification of uveitis.[16] Anterior chamber (AC) cells and flare were graded on the ordinal scales, and vitreous cells and haze were graded based on standard photographs developed by Nussenblatt et al.[16,17] The gradings of vitreous cells, vitreous haze, and location of inflammation were made with dilated pupils.[18]

All patients received the standard treatment for neurosyphilis, intravenous penicillin G at 18 to 24 million units/d for 2 weeks,[19] or an alternative regimen of intravenous ceftriaxone at 2 g/d for 2 weeks for those who were dermatologically allergic to penicillin. Topical corticosteroid and cycloplegic drops were used in patients with AC inflammation. All patients were followed-up by the same uveitis specialist for 6 to 24 months. Every patient had a return visit every 3 months. Ophthalmology examination and laboratory evaluation for syphilis were repeated every 3 months. Any changes of ocular inflammation and visual acuity were recorded. The treatment was considered successful if the patients had no ocular inflammation in both eyes and serological test of RPR was negative after completion of therapy.

3. Results

During the 31-month period, 28 patients with syphilis were identified who initially presented with ocular symptoms. The average age at presentation was 50.5 years (range 35–72). All patients were of Han ethnicity. Eighteen (64.3%) patients were males, and 10 (35.7%) were females. Of the 28 patients, 4 (14.3%) had a history of macular rash on the trunk and palms or soles of the feet, 4 (14.3%) had mucocutaneous manifestation of secondary syphilis, 3 (10.7%) reported previous genital ulcers, 1 (6.7%) suffered from headache, and 19 (67.9%) had no systemic signs. Patients with comorbidities included hypertension (21.4%, 6 cases), diabetes mellitus (28.6%, 8 cases), and hypercholesterolemia (7.1%, 2 cases). No patient had autoimmune disease. All patients had positive serum TPPA and RPR results. The range of serum RPR titer ranged from 1:16 to 1:512. None of the patients tested positive for HIV infection. The main complaints were blurry vision in 28 patients (100%), floaters in 6 patients (21.4%), visual field defect in 5 patients (17.9%), and ocular pain in 5 patients (17.9%). Ocular involvement was bilateral in 13 patients (46.4%) and unilateral in 15 patients (53.6%). The initial BCVA in the 41 affected eyes ranged from 0.6 to hand movement (Table 1).

Twenty-seven (65.9%) eyes presented with panuveitis, and all patients (100%) had posterior involvement, including uveitis, vasculitis, and optic neuritis. Anterior involvements included chamber inflammation, mutton-fat keratic precipitates, and posterior synechiae. Mild-to-severe vitreous opacities were observed in 37 eyes (90.2%). Ten eyes (24.4%) developed secondary cataract and 7 eyes (17.1%) had increased intraocular pressure.

The most common manifestations were uveitis and retinal vasculitis (Table 1). The ocular preliminary diagnosis included: uveitis (53.6%, 15 cases), retinal vasculitis (28.6%, 8 cases), optic neuritis (17.9%, 5 cases), ischemic optic neuropathy (14.3%, 4 cases), branch retinal vein occlusion (3.6%, 1 case), and age-related macular degeneration (3.6%, 1 case) (Table 1).

FFA was performed in all patients, while ICGA was performed in 20 patients (Table 2). The features most frequently found on FFA were disc hyperfluorescence (70.7%), retinal vascular leakage (65.9%), optic disc leakage (39.0%), vascular wall staining (31.7%), "Leopard spots" (24.4%), retinal staining (22.0%), retinal nonperfusion area (19.5%), hemorrhage beside disc (7.3%), and hemorrhage beside retinal vasculature (2.4%). Late disc staining and macular edema were both found in 12 eyes (29.3%). A normal retinal area was observed in 4 eyes (9.8%). The patterns most frequently found on ICGA were persistent dark spots (68.6%), fuzzy choroidal vessels (57.1%), and normal (25.7%) (Table 2).

Macular and Optic SD-OCT (Table 2) was performed in all patients. The most common findings were ill-defined inner segment/outer segment (IS/OS) junction in 36 eyes (87.8%), increased thickening of neurosensory retina in 26 eyes (63.4%), irregular retinal pigment epithelium (RPE) in 21 eyes (51.2%), optic disc edema in 20 eyes (48.8%), subretinal fluid (SRF) in 7 eyes (17.1%), epiretinal membrane in 4 eyes (9.8%), and elevated hyper-reflective sub-RPE in 1 eye. The SD-OCT was normal in 6 eyes (Table 2).

Signs and symptoms of all patients improved with systemic standard therapy for syphilis. After treatment, inflammatory cells in the AC and vitreous body decreased, and BCVA was improved in 34 of 41 eyes (82.9%). BCVA at final visit ranged from 1.2 to 0.05. The follow-up duration was 6 to 24 months, with a mean of 11.9 months. Eleven patients denied a previous history of syphilis and were unsuccessfully treated with nonspecific therapy for ocular symptoms before the correct diagnosis was made. These patients were misdiagnosed before serological tests and the delay in treatment with penicillin was associated with poor final visual acuity, especially the 3 patients preliminarily diagnosed as

Table 1

Demographic, clinical, and laboratory data and treatment results of patients with ocular syphilis.

Case	Age/ gender	RPR/TPPA	Presenting complaint	Systemic disease	Ocular preliminary diagnosis	Initial BCVA	Final BCVA	Follow-up time, m
1	46/F	1:32/+	OU Blurry vision, ocular pain	—	OU uveitis, retinal vasculitis	0.4/0.6	0.8/1.0	24
2*	58/F	1:64/+	OS Blurry vision, ocular pain	Hypertension	OS ischemic optic neuropathy	0.8/0.1	0.8/0.1	9
3	46/M	1:64/+	OU Blurry vision	—	OU uveitis, retinal vasculitis	0.4/0.2	0.8/0.8	18
4*	39/F	1:32/+	OD Blurry vision	—	OD optic neuritis	0.2/1.2	0.5/1.2	18
5*	47/F	1:64/+	OS Blurry vision, visual field defect	Diabetes	OS optic neuritis	0.6/0.1	0.6/0.4	12
6	60/M	1:512/+	OU Blurry vision	Diabetes	OU uveitis	0.1/0.2	0.5/0.5	9
7*	59/M	1:64/+	OD Blurry vision	Diabetes, hypercholesterolemia	OD BRVO	0.05/0.5	0.2/0.5	9
8*	36/M	1:32/+	OD Blurry vision	—	OD retinal vasculitis	0.3/1.2	0.8/1.2	18
9	59/M	1:64/+	OD Blurry vision	Hypertension	OD uveitis, retinal vasculitis	0.3/0.5	0.5/0.5	9
10	45/M	1:32/+	OS Blurry vision, shadow float	—	OS uveitis, retinal vasculitis	0.25/0.05	0.25/0.15	6
11	39/M	1:128/+	OD Blurry vision, shadow float	—	OD retinal vasculitis	0.3/0.6	0.6/0.6	9
12	41/F	1:64/+	OU Blurry vision, ocular pain	—	OU uveitis	0.2/0.6	0.5/0.6	12
13	57/M	1:16/+	OU Blurry vision	—	OU uveitis	0.15/0.3	0.4/0.3	9
14*	53/F	1:128/+	OD Blurry vision, visual field defect	Hypertension	OD ischemic optic neuropathy	0.05/0.1	0.1/0.1	6
15*	42/F	1:32/+	OS Blurry vision	—	OS optic neuritis	1.0/0.3	1.0/0.6	15
16	35/M	1:128/+	OU Blurry vision, shadow float	—	OU retinal vasculitis	0.3/0.5	1.0/1.0	18
17	64/F	1:256/+	OD Blurry vision, ocular pain	Hypertension	OD uveitis	0.4/0.6	0.4/0.6	12
18	41/M	1:64/+	OU Blurry vision, shadow float	—	OU uveitis	HM/0.3	0.1/0.3	6
19	50/M	1:64/+	OU Blurry vision	Diabetes	OU uveitis	0.25/0/15	0.8/0.8	15
20*	68/M	1:128/+	OS Blurry vision, visual field defect	Diabetes	OS AMD	0.6/0.05	0.5/0.05	6
21	49/M	1:32/+	OU Blurry vision	—	OU uveitis	0.4/0.2	0.6/0.6	9
22	46/F	1:64/+	OU Blurry vision, shadow float	—	OU uveitis	0.6/0.6	1.2/1.0	18
23*	60/M	1:256/+	OS Blurry vision, visual field defect	Hypertension, diabetes, hypercholesterolemia	OS ischemic optic neuropathy	0.6/0.4	0.6/0.6	12
24	59/M	1:64/+	OU Blurry vision, ocular pain	Diabetes	OU optic neuritis	0.3/0.1	0.5/0.4	12
25*	72/M	1:32/+	OS Blurry vision	Hypertension	OS ischemic optic neuropathy	0.2/0.05	0.3/0.05	6
26	42/F	1:16/+	OU Blurry vision	—	OU uveitis	0.4/0.5	1.2/1.0	12
27	47/M	1:64/+	OU Blurry vision, shadow float	—	OU uveitis, retinal vasculitis	0.5/0.5	1.0/0.8	15
28*	55/M	1:32/+	OD Blurry vision, visual field defect	Diabetes	OD uveitis, optic neuritis	0.25/1.0	0.5/1.0	9

AMD = age-related macular degeneration, BCVA = best-corrected visual acuity, BRVO = branch retinal vein occlusion, F = female, M = male, RPR = rapid plasma reagin, TPPA = *Treponema pallidum* particle agglutination assay.

* The patients were initially misdiagnosed, which led to delayed treatment.

Table 2

FFA, ICGA, and SD-OCT results.

	N (%)
Findings in FFA (41 eyes in 28 patients)	
Disc hyperfluorescence	29 (70.7)
Late disc staining	12 (29.3)
Optic disc leakage	16 (39.0)
Hemorrhage beside disc	3 (7.3)
Retinal vascular leakage	27 (65.9)
Vascular wall staining	13 (31.7)
Retinal staining	9 (22.0)
Hemorrhage beside retinal vascular	1 (2.4)
Macular edema	12 (29.3)
Leopard spots	10 (24.4)
Retinal nonperfusion area	8 (19.5)
Normal	4 (9.8)
Findings in ICGA (35 eyes in 20 patients)	
Persistent dark dots	24 (68.6)
Fuzzy choroidal vessels	20 (57.1)
Normal	9 (25.7)
Findings in SD-OCT (41 eyes in 28 patients)	
Ill-defined IS/OS junction	36 (87.8)
Increased thickening of neurosensory retina	26 (63.4)
Subretinal fluid	7 (17.1)
Irregular RPE	21 (51.2)
Epiretinal membrane	4 (9.8)
Optic disc edema	20 (48.8)
Elevated hyper-reflective sub-RPE	1 (2.4)
Normal	6 (14.6)

FFA = fundus fluorescein angiography, ICGA = indocyanine green angiography, IS/OS = inner segment/outer segment, SD-OCT = spectral domain optical coherence tomography.

ischemic optic neuropathy (Table 1). Independent-samples *t*-test revealed that the patients with delayed treatment had a lower ascension of BCVA than the others ($P = .037$). Syphilis was cured in all patients after completion of therapy. Systemic manifestations had simultaneously improved.

4. Discussion

A global resurgence of syphilis has been recently reported.[20]This is in accordance with the syphilis epidemic in China in these years.[6] In Western countries, numerous ocular syphilitic cases have been studied over the past decade, while only a few studies have been reported in Chinese patients. In previous reports, most of the increase in the incidence of syphilis occurred among men, especially young men who were homosexual, and was associated with the HIV epidemic.[21–23] Our case series included 64.3% males and 35.7% females. All patients were HIV-negative and identified themselves as heterosexuals. The bias might be partially explained by different races, ethnicities, and levels of economic development. The result is in agreement with other reports from China, which indicated that despite a high syphilis rate in some high-risk populations, the HIV infection rate was relatively low.[24,25] If patients are presumed to be in low-risk groups, delays in diagnosis, and therapy may be likely.

The most common presenting ocular symptom in our study was blurred vision, consistent with an earlier report.[10] Uveitis and retinal vasculitis were the most common presentations. Involvements of retina and/or choroid were found in all eyes

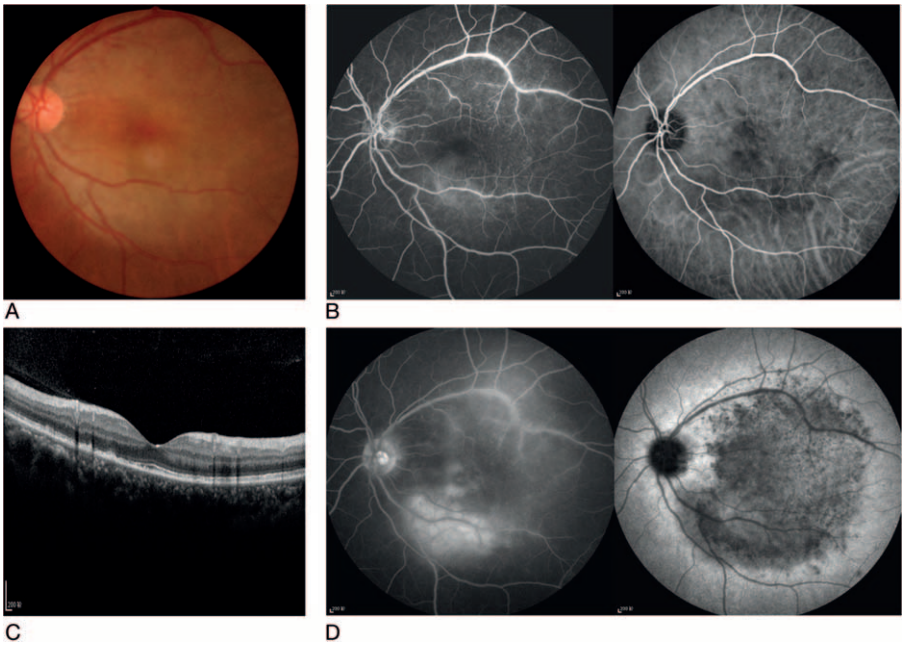

Figure 1. Patient 16 with chorioretinitis. (A) Fundus photograph of the left eye showing yellowish, outer retinal lesion. (B and D) Fundus fluorescein angiography showing hyperfluorescence with leakage of dye from retinal vessels. "Persistent dark dots" were present on indocyanine green angiography. (C) Ill-defined inner segment/outer segment junction and irregular RPE were seen on spectral domain optical coherence tomography.

(Fig. 1). Isolated anterior involvement was not found in our cohort, which was in contrast to Yap et al study.[9] The difference could be partially due to frequent use of FFA, ICGA, and SD-OCT in our series, which can help to identify tiny lesions in retina and choroid that may not be visualized by fundus exam.

The characteristics of ocular syphilis determined by FFA and ICGA are well documented.[1,26] The presentations seen on FFA included retinal/capillary leakage, vascular staining, disc hyperfluorescence, and macular edema (Fig. 2). Gass et al[1] found that "Leopard spots" on FFA are a characteristic of acute syphilitic posterior placoid chorioretinitis. Balaskas et al[26] reported that dark dots on ICGA might indicate active inflammation and hotspots might suggest a longer disease duration, while vascular staining on FFA seemed to be associated

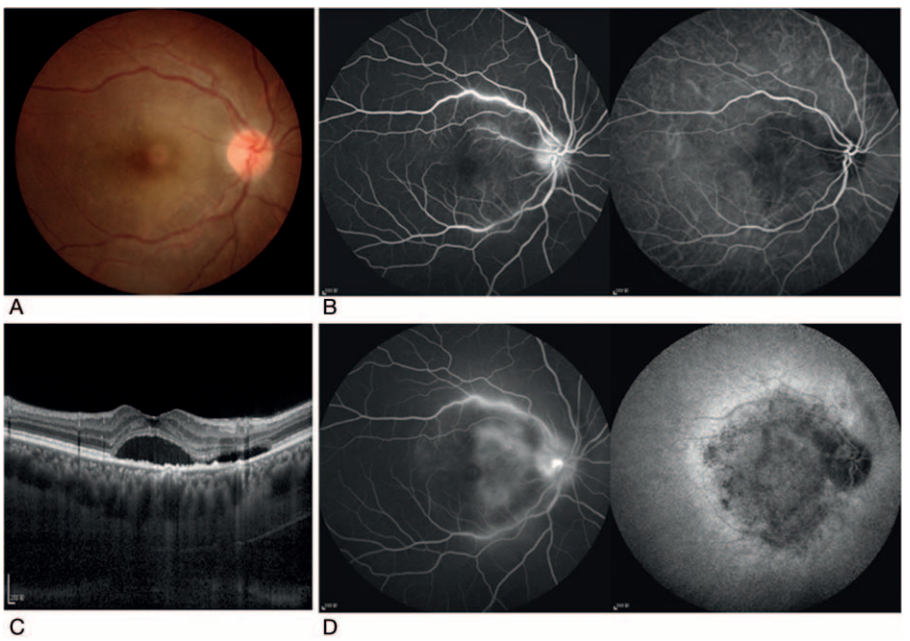

Figure 2. Patient 4 with optic neuritis. (A) Fundus photograph of the right eye showing edema and disc congestion. (B and D) Fundus fluorescein angiography showing hyperfluorescence with leakage of dye from retinal vessels as well as optic nerve head. "Persistent dark dots" were present on indocyanine green angiography. (C) Subretinal fluid was seen on spectral domain optical coherence tomography.

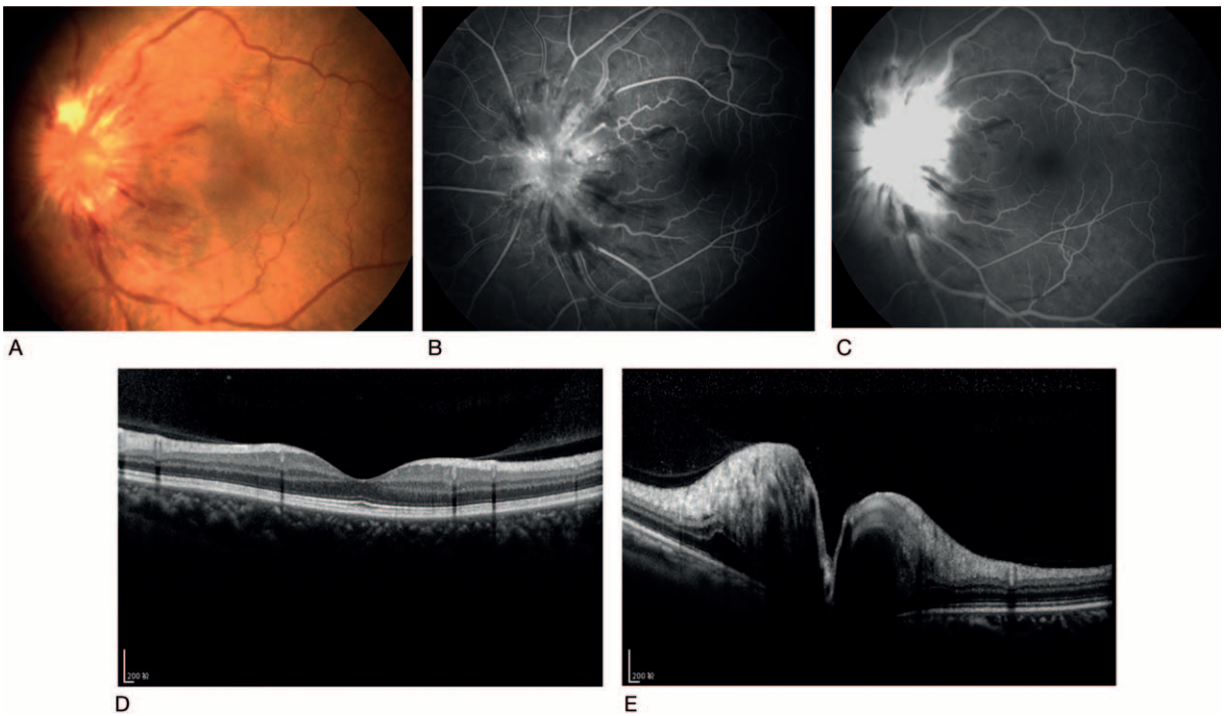

Figure 3. Patient 2 with optic disc edema and hemorrhage. (A) Fundus photograph of the left eye showing yellowish, outer retinal lesion. (B and D) Early phase FFA showing disc hyperfluorescence, hemorrhage beside disc, and late phase FFA showing optic disc leakage. (D and E) Normal macular and increased thickening of optic disc edema were seen on spectral domain optical coherence tomography. FFA = fundus fluorescein angiography.

with severe ocular inflammation. Mora et al[27] reported 2 typical anomalies: late-phase scattered hyperfluorescent spots and persistent staining of retinal vessels. In our study, the most common findings on FFA were disc hyperfluorescence (29 eyes, 70.7%) and retinal vascular leakage (27 eyes, 65.9%), which was similar to Shen et al study[28] but differed from a report in which the most common finding was retinal staining.[16] "Vascular wall staining," which was observed in 13 eyes, was a typical manifestation on FFA. Disc lesions (disc hyperfluorescence, optic disc leakage, late disc staining, and hemorrhage beside disc) were more common in FFA. Therefore, disc lesion was an important sign in Chinese patients suffering from syphilitic uveitis. Patients with manifestations of disc were more easily misdiagnosed (Fig. 3). Persistent dark dots on ICGA in our case series was the most common presentation, which was similar to a previous report.[26]

There are few descriptions of the SD-OCT characteristics of ocular syphilis. Recently, Pichi et al[29] described the SD-OCT appearance in patients with acute syphilitic posterior placoid chorioretinitis; 43.3% of the eyes presented with SRF, IS/OS disruption, and hyper-reflective thickening of the RPE within 1 to 2 days of the initial presentation. Burkholder et al[30] described 3 cases of acute syphilitic posterior placoid chorioretinitis that demonstrated hyper-reflective nodularity, thickening of the RPE, and disruption of the IS/OS. Lima et al[31] reported 2 types of syphilitic outer retinopathy, a loss of the IS/OS, and an irregular RPE. In our case series, the most common presentation was ill-defined IS/OS junction, followed by increased thickening of neurosensory retina and irregular RPE, which was consistent with the above-mentioned results. These characteristic presentations on macular SD-OCT might help to evaluate the BCVA after the treatment. In addition, the optic SD-OCT also showed that 48.8% eyes had optic disc edema, which was rarely mentioned in the past and in accordance with the FFA result.

Syphilitic uveitis is one of the few ocular entities that can be cured with appropriate antimicrobial therapy. As the eye is an extension of the CNS, the International Union against Sexually Transmitted Infections recommended that ocular syphilis should be treated with a neurosyphilis regimen.[19]

Most patients with syphilitic uveitis were cured after treatment with an appropriate penicillin regimen. In our case series, RPR titer was negative in all patients at the end of follow-up, and most of the patients had an improved BCVA after the treatment. Eleven patients in our cohort were initially misdiagnosed. The delay in treatment with penicillin led to long-standing cystoid macular edema and optic neuropathy, which was associated with poor BCVA. The patients with delayed treatment had a lower ascension of BCVA than the others ($P = .037$). Therefore, early diagnosis and prompt treatment of syphilis are important, and any delay may increase the risk of severe ocular complications and irreversible visual loss. It is necessary to reiterate the importance of including syphilis uveitis as differential diagnosis for any form of ocular inflammation, especially posterior uveitis and optic neuropathy.

This study had a few limitations. First, this was a retrospective case series. Second, the sample size was relatively small; thus, selection bias may have been present. However, the results were correct and objective. In the future, large, multicenter, prospective studies need to be conducted in China.

Our study reported the objective characteristics of ocular syphilis in Northwest China that has a relatively underdeveloped economy than other parts of China. The manifestations of ocular syphilis can mimic any eye disease. Uveitis and retinal vasculitis

were the most common findings in our study. Disc hyperfluorescence was the characteristic manifestation on FFA. Persistent dark spots was the most common finding on ICGA. The ill-defined IS/OS junction was the most common finding in patients with posterior uveitis on SD-OCT. The treatment for ocular syphilis was effective. The patients with delayed treatment had a lower ascension of BCVA than the others ($P = .037$). If patients are presumed to be in low-risk groups such as HIV-negative, delays in diagnosis, and therapy may be likely. It is necessary to reiterate the importance of including syphilis uveitis as differential diagnosis for any form of ocular inflammation, especially posterior uveitis and optic neuropathy.

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