



## The multifaceted presentation of syphilitic chorioretinitis examined by multimodal imaging: A case series

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### ABSTRACT

Ocular syphilis is also known as the 'great masquerader' for the wide variety of clinical features associated with this infection. Although chorioretinitis represents the most frequent manifestation in the posterior pole, other clinical entities can be described, including retinal vasculitis, optic disc disorders, necrotizing vasculitis and acute syphilitic posterior placoid chorioretinopathy (ASPPC).

This latter is an infrequent ocular manifestation of syphilis, whose pathophysiology remains still unknown; however, multimodal imaging, including optical coherence tomography angiography (OCTA), has enabled us to better describe its pathophysiology and clinical course.

In this study we report a case series of 3 different patients with syphilis-related chorioretinopathies; in this regard, the role of multimodal imaging has emerged as an extremely useful approach in order to better understand the pathophysiology of syphilitic chorioretinopathies. This could help clinicians (both ophthalmologist and infectious disease specialists) to early treat and prevent the severe ocular complications related to this fearsome disease.

### 1. Introduction

Syphilis is a sexually transmitted, infectious disease with systemic involvement caused by the Gram-negative spirochete *Treponema pallidum*.<sup>1</sup> This infectious disease is also called the great masquerader, in virtue of the multiplicity of the syphilitic ophthalmological manifestations, including interstitial keratitis, anterior and intermediate uveitis, retinal vasculitis, chorioretinitis, retrobulbar neuritis and optic atrophy.<sup>2</sup> In particular, the involvement of the posterior pole in ocular syphilis is characterized by a large spectrum of clinical manifestations.<sup>3</sup> The most common manifestation in HIV-negative patients is posterior uveitis, in particular chorioretinitis with vitreitis, accounting for almost 75% of the cases. Differently, panuveitis is the most frequent diagnosis performed in HIV-positive patients.<sup>4</sup> A cute syphilitic posterior placoid chorioretinitis (ASPPC) represents an infrequent ocular manifestation occurring in secondary or tertiary stages of the disease and it is characterized by the presence of yellowish, round-shaped placoid lesions in the posterior pole.<sup>5</sup> In this regard, although the pathogenesis of ASPPC

has not been fully understood yet, several studies have highlighted the possible role of an inflammatory reaction with immune complex deposition occurring in the outer retinal layers (photoreceptors and retinal pigmented epithelium (RPE) and choroid).<sup>6</sup> Furthermore, necrotizing retinitis a rare but fearsome complications of ocular syphilis, which is often similar to acute retinal necrosis; however, necrotizing retinitis in syphilitic patients tends to resolve the retinal lesions with minimal disruption of the RPE and outer retinal layers.<sup>7</sup> In addition to this, ocular syphilis may also be associated with retinal vasculitis and optic disc involvement, including pallor, neuroretinitis and solid inflammatory lesions.<sup>8,9</sup> Considering the increasing incidence of syphilis worldwide, clinicians should always consider this infectious disease in the differential diagnosis, when evaluating a patient with ocular inflammation even also the presence of systemic syphilitic signs. In this study, we discuss the role of multimodal imaging in 3 cases of ocular syphilis with posterior pole involvement, allowing to better characterize the pathophysiology of the disease and to describe the structural and vascular alterations occurring in the chorioretina by adopting novel imaging

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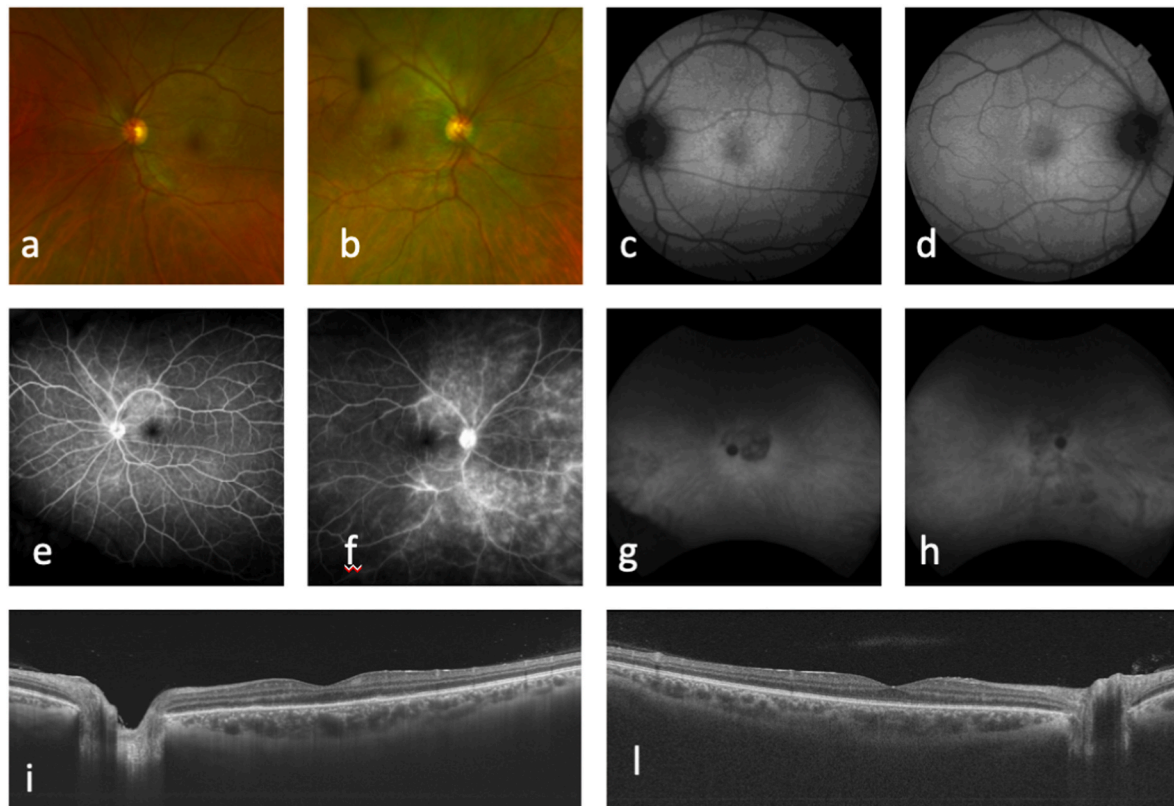
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techniques, including also optical coherence tomography angiography (OCTA).

## 2. Case report 1

A 29-year-old man presented to University Eye Clinic- IRCCS Polyclinic San Martino, Genoa (Italy) complaining of pain and acute vision loss with a central scotoma in the left eye worsened in the last few days after almost a month with a blurred vision. He had a medical history positive for Hashimoto thyroiditis and mononucleosis one year earlier. The patient denied viral prodrome or recent illness. Blood analysis showed reactivity to the venereal disease research laboratory (VDRL) (1:64) and positivity of IgG and IgM against the membrane protein A of *Treponema pallidum* by ELISA, suggesting acute syphilitic infection. Serum anti-HIV antibodies were negative. No ulcers or mucocutaneous lesions or other systemic symptoms were reported. Brain MRI imaging was unremarkable at baseline. Cerebrospinal fluid was weakly positive for VDRL and reactive for TPHA after lumbar puncture. The patient was also referred to the infectious disease academic unit and treatment with high-dose intravenous ceftriaxone was started. From an ophthalmological perspective, baseline best corrected visual acuity (BCVA) was 20/20 in his right eye and 20/40 in the left eye. Intraocular pressure was 15 mmHg in both eyes. Slit-lamp examination showed the presence of diffuse keratic precipitates (more evident in the right eye), mild flare (1+) in the anterior chamber and mild vitritis (2+) in both the eyes. Dilated fundus examination revealed a normal right eye and a yellowish placoid lesion in the macular area of the left eye. Fundus autofluorescence examination (FAF) showed the presence of some foci of punctate hyperfluorescence in the left eye, corresponding to the placoid

area revealed by fundus examination. At presentation, fluorescein angiography (FA) examination revealed the presence of late peripapillary focal leakage and leakage along the superior retinal vascular arcade in the left eye, whereas the leakage was extended to the optic disk, both the vascular arcades and to the temporal periphery in the asymptomatic right eye. Furthermore, at indocyanine green angiography (ICGA) a well-demarcated hypofluorescent area corresponding to the placoid macular lesion was visible in the late phases in the left eye and, to a lesser extent, also in the right one. Swept source OCT (SS-OCT, DRI OCT Triton; Topcon Corporation) imaging revealed a preserved macular profile in the right eye, whereas in the left eye hyperreflective granular changes of the retinal pigment epithelium (RPE), disruption of the ellipsoid zone and of the external limiting membrane and some hyperreflective foci in the underlying choroid were evident. SS-OCT angiography (SS-OCTA) imaging revealed the presence of nodular areas of flow void in the choriocapillaris in association with the placoid lesion in the left eye. Moreover, also in the right eye some areas of reduced vascular density were found in the choriocapillaris (Fig. 1). After having completed the antibiotic therapy from 1 month, BCVA improved to 20/20 in the left eye and the outer retinal lesions were completely restored by SS-OCT imaging; however, SS-OCTA showed that the choriocapillaris reperfusion was still incomplete after the 3 month-follow-up visit. In fact, after 3 months from the baseline visit, fundus examination showed the complete regression of the placoid lesion in the left eye. Also, SS-OCT images revealed the disappearance of the granular hyperreflective changes at the RPE and the absence of the hyperreflective foci in the choroid; however, at FAF, patchy areas of increased fluorescence were present in the perifoveal region of the left eye. By contrast, no alterations were visible at FAF of the right eye. Furthermore, SS-OCTA images



**Fig. 1.** Case 1- Fundus examination reveals the presence of moderate vitritis and a yellowish round lesion in the temporal region outside the vascular arcades in the left eye (a), whereas in the right eye only mild vitritis was detectable (b). Fundus autofluorescence shows a hyperfluorescent round area in correspondence of the lesion in the left eye (c), while the right one was normal (d). At wide-field fluorescein angiography examination, the presence of mild vascular leakage in the mid-periphery was observed in both eyes as sign of retinal vasculitis (e, f) with a hypofluorescent ischemic area in the temporal region in correspondence of the lesion in the left eye (e). Swept source optical coherence tomography imaging shows the presence of vitritis with a normal foveal profile (i,l) however, in the temporal region of the left eye a hyperreflective intraretinal lesion suggesting active retinitis (l).

documented the partial regression of the nodular areas of fluid void in the choriocapillaris of the left eye, which were nevertheless still detectable as areas of slightly decreased vascular density (Figs. 2 and 3). After 9 months from the baseline visit, BCVA was stable (20/20 in both eyes) and a preserved macular profile was visible both at fundus examination and also at structural OCT images. FAF images were normal in the right eye and showed that the patchy hyperfluorescent areas in the perifoveal region remained unchanged in the left eye. Likewise, in the choriocapillaris of the left eye the areas of decreased vascular density were still detectable by SS-OCTA.

### 3. Case report 2

Another 29-year-old man presented to University Eye Clinic- IRCCS Polyclinic San Martino, Genoa (Italy) complaining of acute vision loss in the left eye, while no visual disturbances were referred in right eye. In the medical history, previous inguinal hernia operation and varicella-zoster chickenpox were documented. The patient referred to have had a history of substance abuse. Also, he had no pain or fever, no viral prodrome or recent illness were referred. Moreover, he denied history of any sexual exposure in the past. At baseline visit, the reported BCVA was 20/40 in both eyes and anterior slit-lamp examination documented the presence of keratic precipitates, anterior chamber cells (2+) and, while the right eye was normal. IOP was 9 mmHg in both eyes. Fundus examination of the left eye showed moderate vitreitis (2+) and a yellowish round lesion in the temporal region outside the vascular arcades, while

in the right eye only mild vitreitis (1+) was detectable. FAF revealed a hyperfluorescent round area in correspondence of the lesion in the left eye, while the right one was normal. At wide-field FA examination, the presence of mild vascular leakage in the mid-periphery was observed in both eyes as sign of retinal vasculitis; in addition to this, in the left eye FA showed the presence of a hypofluorescent ischemic area in the temporal region in correspondence of the above-mentioned lesion. SS-OCT imaging revealed the presence of vitreitis (more severe in the left eye), but the normal foveal profile was preserved in all its retinal layers in both eyes; however, in the temporal region of the left eye a hyper-reflective intraretinal lesion suggesting active retinitis was evident (Fig. 4). Blood analysis revealed reactivity to VDRL and positivity of IgG and IgM against the membrane protein A of *Treponema pallidum* by ELISA. Serum anti-HIV antibodies were negative. Also, cerebrospinal fluid was positive for VDRL (1:32). The ocular diagnosis was confirmed by vitreous biopsy, which detected the presence of the spirochete by PCR examination. Thus, penicillin intravenous therapy was started. Brain RM examination was performed and no pathological findings were found. After 15 days from having started the antibiotic therapy, BCVA remained stable (20/40) in both eyes and anterior slit-lamp examination of both eyes was unremarkable in both eyes, with the disappearance of anterior chamber inflammation signs in the left eye. Fundus examination of the left eye revealed still the presence of mild vitreitis (1+), while the yellowish temporal lesion was less evident. The right eye was completely unremarkable at fundus examination. Likewise, FAF revealed a barely discernible hyperfluorescent area in correspondence of

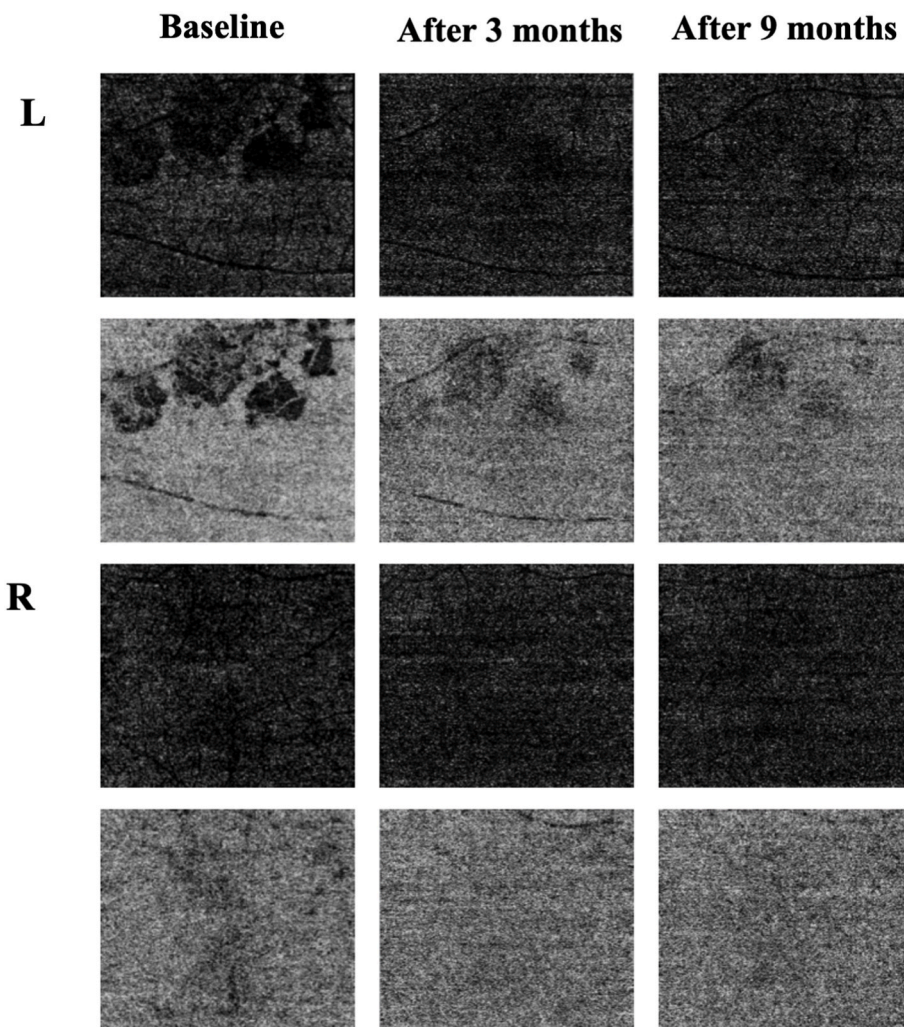
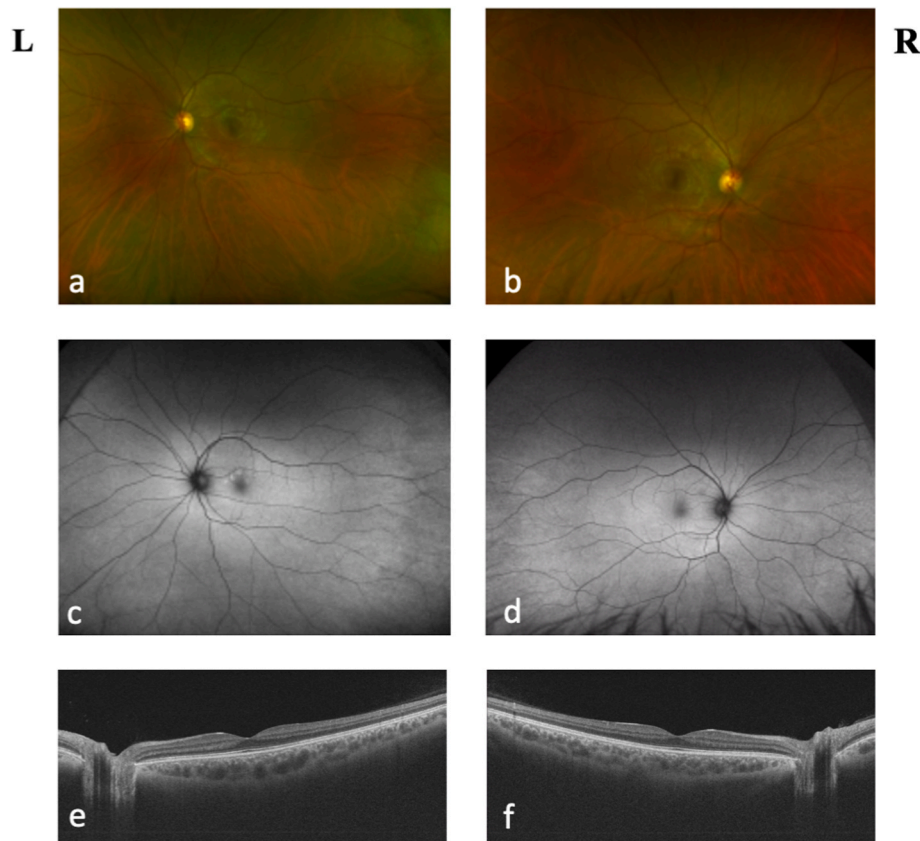


Fig. 2. Case 1- Follow-up images after 3 and 9 months by swept-source optical coherence tomography angiography. At baseline it is evident the presence of nodular areas of flow void in the choriocapillaris in association with the placoid lesion in the left eye and also in the right eye some areas of reduced vascular density were found in the choriocapillaris. After 9 months, regression of the nodular areas of fluid void was only partial in the choriocapillaris of the left eye, while they were there was just a slightly decreased vascular density in the right one.





**Fig. 3.** Case 1- After 9 months, the macular profile is preserved at fundus examination (a, b) in both eyes. Fundus autofluorescence images shows patchy hyperfluorescent areas in the perifoveal region in the left eye (c) and a normal profile in the right eye (d). Structural optical coherence tomography is preserved (e, f).

the recovered temporal, round lesion. SS-OCT images confirmed the disappearance of the temporal hyperreflective lesion in the left eye, with the development of an atrophic area (involving all retinal layers) in the temporal region previously affected by active retinitis and only mild vitreitis.

After 1 month follow-up period, wide-field fundus examination, FAF and SS-OCT images showed the complete recovery of the acute event; however, in the left eye, although no signs of vitreitis were evident anymore, the atrophic area persisted in the temporal region.

#### 4. Case report 3

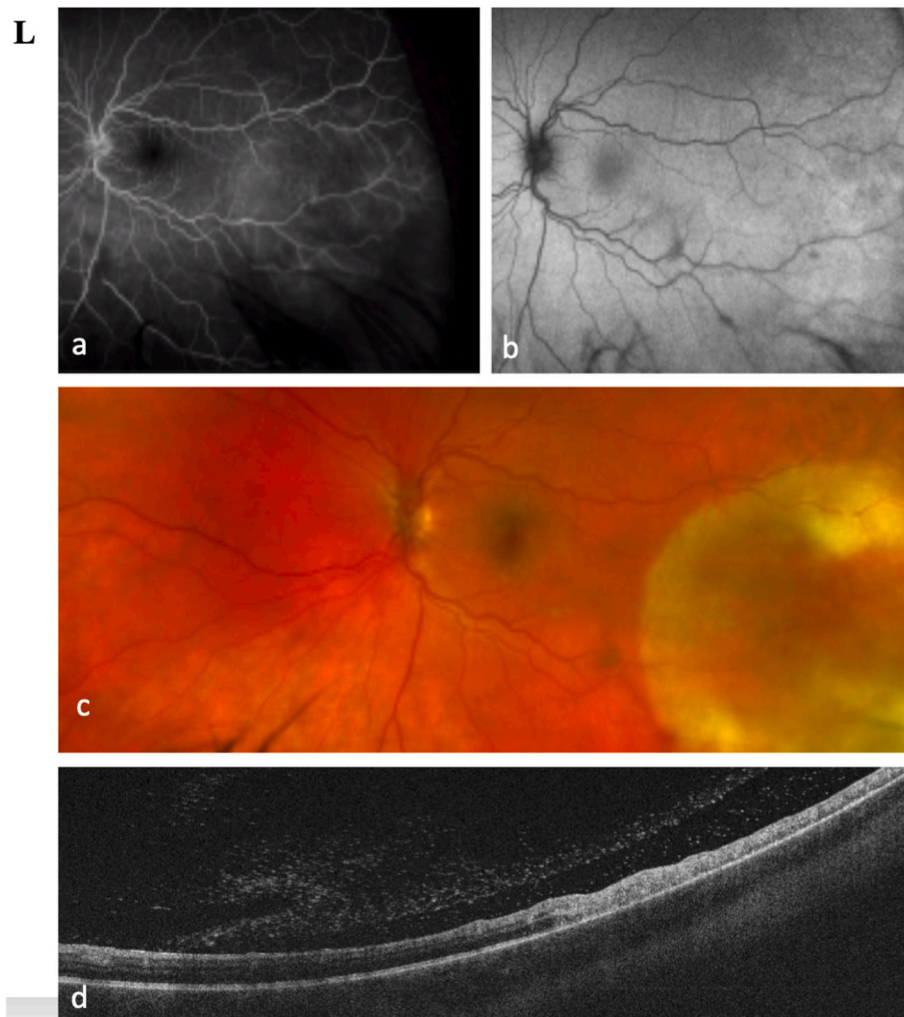
A 44-year-old man presented to University Eye Clinic- IRCCS Policlinic San Martino, Genoa (Italy) referring vision loss in the right eye in the last few days, while no visual disturbances were referred in left one. His past medical history was unremarkable. The patient denied a history of substance abuse and/or sexual promiscuity. Also, he had no pain or fever, no viral prodrome or recent illness were documented. At baseline visit, BCVA was 20/50 in the right eye and 20/32 in the left one. Anterior slit-lamp examination documented the presence of moderate flare in the anterior chamber (2+) of the right eye, while the left eye was unremarkable. IOP was 14 mmHg in both eyes. Fundus examination showed the presence of mild vitreitis (1+) in the right eye, while the macular region had no significant alterations in both eyes; however, FA examination revealed the presence of moderate vasculitis in the mid-periphery (with leakage of dye due to breakdown of the inner blood-retinal barrier) and presence of mild papillitis in the right eye, whereas the left eye was normal. OCT images reported the presence of vitreitis and some scattered hyperreflective granular spots and the disruption of the ellipsoid zone were detectable in the right eye, while the left one showed a preserved macular profile. Patient underwent blood analysis, which documented VDRL and TPHA positivity,

suggesting acute syphilitic infection. Serum anti-HIV antibodies were negative. No ulcers or mucocutaneous lesions or other systemic symptoms were found. Furthermore, brain MRI imaging was unremarkable at baseline and cerebrospinal fluid was positive for VDRL and reactive for TPHA. Thus, he was treated with penicillin and follow-up. After 4 months, blood analyses were negative and patient referred visual improvement in right eye (20/40 in the right eye and 20/32 in the left eye). Both anterior segment and fundus examinations were unremarkable. Moreover, OCT images revealed the regression of vitreitis and the changes observed in the previous visit in the outer retina.

Afterwards, after other 5 months patient referred a visual loss in the right, whose BCVA was 20/63, whereas BCVA was stable in the left eye (20/32). Slit-lamp examination of the right eye revealed mild flare (+1) in the anterior chamber and IOP was 14 mmHg. In the relapsing right eye, fundus examination showed the presence of vitreitis and moderate macular edema. In this regard, the OCT acquisition of the right eye documented the presence of a small foveolar RPE detachment and an isolated intraretinal cyst. FA showed the relapse of retinal vasculitis in the mid-periphery and moderate papillitis in the right eye. Blood analyses confirmed the relapse of syphilitic infection and patient underwent another course of high-dose penicillin and dexamethasone (Fig. 5).

#### 5. Discussion

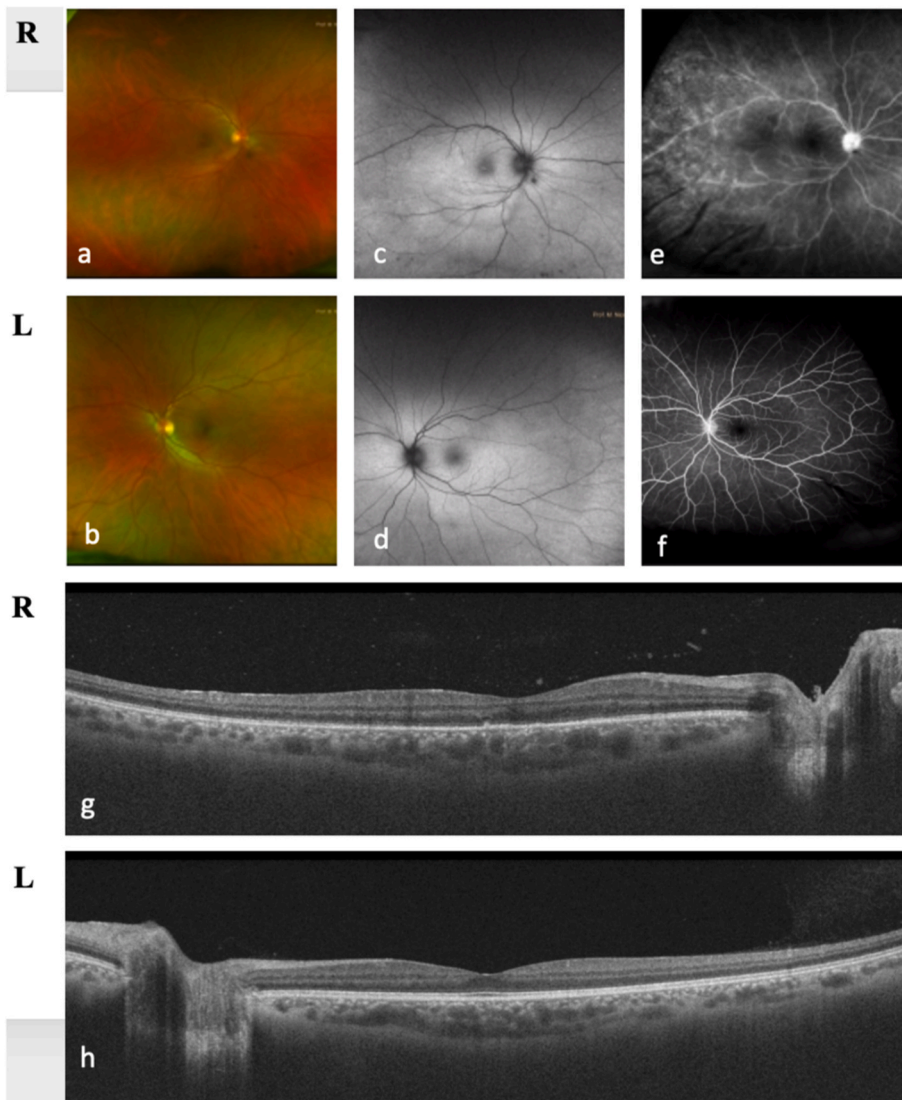
Syphilitic uveitis can occur at any stage of acquired syphilis, leading to visual loss if unrecognized or handled as a non-infectious ocular inflammation. Considering the multifaceted clinical features of syphilitic uveitis, manifesting in anterior uveitis, posterior uveitis, chorioretinitis or papillitis, this disease is also known as the “great masquerader”.<sup>103</sup> For this reason, it appears crucial to know all the possible clinical expressions of syphilitic uveitis, in order to allow an early diagnosis and to start prompt, appropriate antibiotic therapy. The



**Fig. 4.** Case 2- Baseline images of the left eye. At wide-field fluorescein angiography the presence of mild vascular leakage in the mid-periphery is present combined with a hypofluorescent ischemic area in the temporal region in correspondence of the lesion (a). Fundus autofluorescence reveals a hyperfluorescent round area in correspondence of the lesion (b). Fundus examination shows moderate vitreitis and a yellowish round lesion in the temporal region outside the vascular arcades (c). At swept-source optical coherence tomography, vitreitis is evident and the foveal profile is preserved; however, in the temporal region, a hyperreflective intraretinal lesion suggesting active retinitis is present (d).

most frequent ocular manifestation in syphilitic patients is chorioretinitis; however, ASPCC represents a less common variant occurring in a minority of patients.<sup>211</sup> In this regard, although initially most of the cases of ASPCC were diagnosed in patients coinfecting with HIV, some studies have reported the incidence of this subtype of chorioretinitis also in immunocompetent patients.<sup>12</sup> Our findings are similar to those of Pichi et al., which documented at FAF localized hyperautofluorescence in correspondence of the placoid lesion, suggesting the presence of subretinal deposition of hyperfluorescent material beneath the RPE-photoreceptor complex.<sup>13</sup> Moreover, we found at OCT imaging the reversible presence of hyperreflective granular changes of RPE, disruption of the ellipsoid zone and hyperreflective foci in the choroid; these findings are in line with previous studies on patients with ASPCC. In this regard, Brito et al. revealed acute but reversible disruption of the ellipsoid layer and external limiting membrane in the outer retina. Furthermore, other studies have reported hyperreflective granularity of the RPE by OCT, corresponding to the pointed hyperfluorescent area of the placoid lesion at FAF imaging.<sup>14 15 16</sup> In addition, also the pointed hyperreflective foci in the choroid have already been described in literature; these foci are thought to represent the inflammatory process occurring at the level of the choriocapillaris.<sup>13 17</sup> To the best of our knowledge, only 2 studies have previously investigated the role of OCT for studying ASPCC pathophysiology. In a recent study by Barikian et al. on a patient with ASPCC, a flow deficit in the choriocapillaris was detected by SS-OCTA together with presence of reversible disruption of the outer retina layers; however, both the structural and vascular alterations were restored after penicillin treatment.<sup>18</sup> In another study on

a patient with ASPCC, bilateral choriocapillaris was documented as a non-perfused area by OCTA; in this case, although after penicillin therapy the recovery of the outer retinal layers was found by structural OCT, only a mild perfusion improvement in the choriocapillaris was documented by OCTA in the follow-up visits.<sup>19</sup> Our findings are in line with this latter study, because we found a partial improvement in the choriocapillaris flow area, which was not completely restored after successful antibiotic therapy and a 9-month follow-up period. In this regard, the presence of an inflammatory reaction or an immune complex dysfunction occurring at the level of the choriocapillaris was already postulated by Gass et al.<sup>19</sup> Although in other patients with ASPCC the choriocapillaris flow void was found reversible after few months of follow-up, in our patient a more severe ischemic event is likely to have been occurred, leading to a larger non-perfusion area and longer time needed to completely restore the physiological choroidal perfusion.<sup>20</sup> Thus, OCTA may represent a useful diagnostic tool in the early diagnosis of a flow void in the choriocapillaris due to choriocapillaris, which is a typical presentation of ASPCC. Further studies by adopting multimodal imaging are needed in order to better understand the pathophysiology of ASPCC and to follow-up its clinical course. In the second patient, ocular syphilis presented as a severe retinitis, characterized by vitreitis, a retinitis mimicking an acute retinal necrosis (ARN) with the formation of a yellowish round lesion in the temporal region and a mild peripheral vasculitis. In this regard, other authors have previously documented the onset of a necrotizing retinitis in patients with ocular syphilis.<sup>2122</sup> The first case of syphilitic necrotizing retinitis was reported in 1984 by Mendelson et al. in a young homosexual patient who was seronegative



**Fig. 5.** Case 3- Baseline images. At fundus examination mild vitreitis is present in the right eye, while the macular region had no significant alterations are detectable in both eyes (a, b). Fundus autofluorescence is unremarkable (c, d). At fluorescein angiography, moderate vasculitis in the mid-periphery and mild papillitis are present in the right eye, whereas the left eye was normal (e, f). At optical coherence tomography, there is vitreitis and some scattered hyperreflective granular spots and the disruption of the ellipsoid zone in the right eye, with a preserved macular profile in the left one (g, h).

for HIV.<sup>23</sup> Rahman et al. referred a case of a patient with ocular syphilis (coinfected with HIV) presenting a diffuse infiltrative retinitis and vitreitis, which dramatically improved after 3 weeks from having started penicillin antibiotic therapy.<sup>24</sup> Importantly, ocular syphilis-induced ARN are more often associated with retinal lesions, which tend to rapidly heal with minimal disruption of the RPE after antibiotic therapy.<sup>21</sup> This was also the case of our patient, which showed a rapid regression of the acute retinal inflammatory lesions, which were followed by an atrophic area involving all retinal layers. In this regard, further, larger-scale clinical studies should provide more evidence about the pathophysiology and course of necrotizing retinitis in patients with ocular syphilis. In the third patient, ocular syphilis was characterized by relapsing, important retinal vasculitis and mild optic disc inflammation, which were clearly visible by FA. Vascular involvement in ocular syphilis has been previously documented, including alterations in retinal arteries, arterioles, capillaries and veins. In particular, FA displays an important role in detecting subtle vascular involvement, but also overt cases of increased vascular tortuosity, perivascular fibrosis and occlusive vasculitis.<sup>25,28</sup> In some cases, syphilitic retinal vasculitis can imitate the FA appearance of branch vein occlusion, due to the presence of an inflammatory phlebitis occurring in retinal veins.<sup>26</sup> Moreover, the most common optic disc involvement include perineuritis, anterior or retrobulbar optic neuritis and papilledema.<sup>9</sup> While often syphilitic optic perineuritis occurs with no symptoms, optic neuritis in these patients

leads often to rapid vision loss.<sup>27</sup> With regard to our patient, the relatively moderate severity of visual loss and the FA findings suggested the presence of a mild and transient anterior optic neuritis.

## 6. Conclusions

Ocular syphilis represents a significant diagnostic challenge because it can simulate most other causes of uveitis; for this reason, along with a detailed medical history of the patient, multimodal imaging with novel diagnostic techniques (including OCTA) could provide the appropriate tools to handle with the multifaceted clinical features of this disease. Moreover, other conventional diagnostic techniques, including FA and ICGA, remain crucial, as they are capable of visualizing the early vascular alterations occurring in the choroid of patients with syphilitic uveitis. Nonetheless, a prompt diagnosis of syphilitic uveitis may enable both ophthalmologist and infectious diseases physicians to establish a prompt and often decisive antibiotic therapy.

## Patient consent

Oral informed consent was obtained from the patient for publication of this case report. This report does not contain any personal identifying information.



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## Authorship

All authors attest that they meet the current ICMJE criteria for authorship.

## Declaration of competing interest

None of the authors had conflicts of interest.

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