Exposing the Great Masquerader: Five Consecutive Cases of Ocular Syphilis with Heterogeneous Clinical Presentations

Expondo a Grande Imitadora: Cinco Casos Consecutivos de Sífilis Ocular com Apresentações Clínicas Heterogéneas

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ABSTRACT

Ocular syphilis has a highly heterogeneous clinical presentation, which can overlap with many other etiologies. Its diagnosis requires a high index of suspicion. Ophthalmological manifestations may appear in virtually all anatomical regions of the eye, in both the anterior and posterior segments. Uveitis is the most common ophthalmologic presentation of syphilis, and the timing of onset is variable and unpredictable. The purpose of this work is to describe 5 consecutive cases of ocular inflammation, with heterogeneous manifestations, eventually diagnosed as ocular syphilis.

A case-series report of consecutive eyes, including 5 cases of patients diagnosed and treated for ocular syphilis in Hospital Pedro Hispano – Unidade Local de Saúde de Matosinhos, in the year of 2022. Patients were managed in collaboration between the ophthalmologic and infectious diseases departments and were hospitalized for systemic treatment.

Case 1 reports a 29-year-old man with bilateral non-granulomatous iridocyclitis. Case 2 refers to bilateral asymmetrical papillitis. Case 3 consists of a unilateral panuveitis with dense vitritis, in a patient with HIV co-infection. Case 4 depicts bilateral asymmetrical neuroretinitis. Case 5 reports granulomatous iridocyclitis in a patient with a hypermature cataract, initially regarded as lens-induced uveitis.

Syphilitic uveitis may occur at any stage of the systemic disease. A high clinical suspicion is necessary, and it must be considered in all cases of unexplained ocular inflammation. HIV-coinfection is common, and results in more severe disease, with worse prognosis. Poor initial visual acuities appear to be related to bad visual outcomes. Systemic treatment should be started promptly when there is suspicion of the infection. Detailed medical history and systemic physical examination are essential tools to help the diagnosis.

KEYWORDS: Eye Infections, Bacterial/diagnosis; Syphilis/diagnosis; Uveitis/diagnosis.

RESUMO

A sífilis ocular tem uma apresentação clínica altamente heterogénea, que se pode sobrepor à de muitas outras etiologias. O seu diagnóstico requer um alto índice de suspeição. As manifestações oftalmológicas podem afetar praticamente todas as regiões anatómicas do olho, tanto no segmento anterior como no posterior. A uveíte é a apresentação oftalmológica mais frequente, e o *timing* do aparecimento é variável e imprevisível. O objectivo deste trabalho foi descrever 5 casos consecutivos de inflamação ocular, com manifestações heterogéneas, eventualmente diagnosticados como sífilis ocular.

Série de casos consecutivos, incluindo 5 doentes diagnosticados com sífilis ocular e tratados no Hospital Pedro Hispano – Unidade Local de Saúde de Matosinhos, no ano de 2022. A abordagem dos doentes envolveu os Serviços de Oftalmologia e Infecciologia. Todos os doentes foram internados para cumprir o tratamento sistémico.

O caso 1 relata um homem de 29 anos com iridociclite bilateral não granulomatosa. O caso 2 corresponde a uma papilite bilateral assimétrica. O caso 3 consiste numa panuveíte unilateral com vitrite densa, num doente com co-infeção por VIH. O caso 4 descreve uma neurorretinite bilateral assimétrica. O caso 5 representa uma iridociclite granulomatosa numa doente com uma catarata brunescente, inicialmente diagnosticado como uma lens-induced uveitis.

A uveíte sifilítica pode surgir em qualquer fase da doença sistémica. É necessária uma elevada suspeita clínica, que deve levar a que este diagnóstico seja considerado em casos de inflamação ocular inexplicada. A co-infeção por VIH é comum, e resulta numa doença mais grave e com pior prognóstico. Acuidades visuais inicialmente baixas estão relacionadas com resultados visuais a longo prazo desfavoráveis. O tratamento sistémico deve ser iniciado prontamente quando há suspeita da infecção. Uma anamnese detalhada e um exame físico sistémico são ferramentas essenciais para guiar o diagnóstico.

PALAVRAS-CHAVE: Infecções Oculares Bacterianas/diagnóstico; Sífilis/diagnóstico; Uveíte/diagnóstico.

INTRODUCTION

Syphilis is an infectious disease caused by *Treponema pallidum*, a spirochaete bacterium that has various subspecies, namely *T pallidum pallidum*, *T pallidum endemicum*, and *T. pallidum pertenue*.[1] It has a helically coiled shape, a length of about 6-15 µm, and minimal metabolic activity due to the lack of tricarboxylic acid cycle and oxidative phosphorylation.[2] Its particular shape allows it to move in a corkscrew motion through the tiny breaches in squamous or columnar epithelium present on the human skin and mucous membranes. Through this mechanism, it infects the patient, usually during sexual activity, or by congenital transmission *in utero*, either by transplacental passage during later stages of pregnancy or by contact with an active genital lesion during delivery.[1] Animal studies showed that the microorganism is present on lymph nodes within just a few minutes of inoculation, and widely dispersed throughout the body in the first hours.[3]

The pathophysiology of syphilis is complex and is usually divided into several stages. The primary stage begins 10-90 days after the initial contact, with the appearance of chancres, which are painless skin lesions, usually in the genital region, that are often not noticed, due to their painless nature.[1] They usually resolve spontaneously after 4 weeks, but during this phase, the patient is contagious since they contain spirochetes. After 4-10 weeks of the initial appearance of the chancre, untreated patients will develop secondary syphilis. This phase is the result of the haematogenic dissemination of the organism and may lead to skin, neurologic, ophthalmologic, and gastrointestinal disease. The eye is affected in about 10% of the cases. The characteristic skin lesions, present in more than 70% of the patients, include a diffuse maculopapular rash, which affects the palms of the hands and soles of the feet. Other systemic symptoms may include fever, lymphadenopathies, headache, malaise, anorexia, nausea, joint pain, mouth ulcers, and hair loss in a specific pattern, called moth-eaten alopecia.[4] After the resolution of the secondary manifestations, the infection becomes latent, if not treated. About a third of the untreated patients in the latent phase will eventually develop tertiary syphilis.[1] The tertiary phase is characterized by severe cardiovascular and neurologic involvement. Cardiovascular involvement consists of aortitis, aortic aneurysms, and aortic valve insufficiency. Neurologic involvement includes meningeal, meningovascular, and parenchymatous lesions in a pattern known as tabes dorsalis, or manifesting as general paresis.

Syphilis is often called the great imitator, due to the fact that it has a highly heterogeneous clinical presentation, which can overlap with many other etiologies. The diagnosis of syphilitic infection in the eye requires a high index of suspicion. Ocular manifestations may appear in virtually all anatomical regions of the eyeball, in both the anterior and posterior segments. Uveitis is the most common ophthalmologic presentation of syphilis, and syphilitic uveitis may be the only systemic sign of the disease. The timing of the onset of symptoms can be very variable and unpredictable, as they can occur as soon as 6 weeks after the primary infection, or just years after the initial infection, even during the latent stage.[4-8] The manifestations are very variable, as it may present with non-granulomatous or granulomatous inflammation, which can involve the anterior segment, the posterior segment, or both. It may be unilateral or bilateral. Barile and Flynn reported that the most common entities were granulomatous iridocyclitis (46%), non-granulomatous iridocyclitis (25%), panuveitis (13%), posterior uveitis (8%), and keratouveitis (8%).[9] Additional findings may include iris nodules, dilated iris vessels, iris atrophy, and posterior synechiae.[4] Given the heterogeneous presentation, it is difficult to diagnose syphilitic uveitis based on the clinical presentation, so this entity should be considered in cases of unexplained ocular inflammation.[4] Syphilis can also affect the optic nerve unilaterally or bilaterally. The most common manifestations are perineuritis, anterior or retrobulbar optic neuritis and papilledema. Although there are no specific characteristics of syphilitic neuritis from other causes, the course of the disease is severe, with the potential for rapid vision loss. Finally, the Argyll-Robertson pupil is a rare, but classic finding in neurosyphilis, where the pupils are miotic and manifest a light-near dissociation, constricting in response to near vision, but not to light, due to presumed damage in the neurological pathways between the Edinger-Westphal and pretectal nuclei.[4-7]

The purpose of this work is to describe 5 consecutive cases of ocular inflammation, each one with its heterogeneous manifestations, that despite having a very distinct clinical picture, were eventually diagnosed as ocular syphilis.

CASE REPORTS

A case-series report of consecutive eyes, including 5 cases of patients diagnosed and treated for syphilis with ophthalmological involvement, in Hospital Pedro Hispano – Unidade Local de Saúde de Matosinhos.

All consecutive cases were diagnosed during the year of 2022. Information regarding best-corrected visual acuity, intraocular pressure, slit-lamp examination, fundus examination, laboratory studies, multi-modal imaging, and concomitant ophthalmological and systemic pathology was gathered. All patients were managed with collaboration between the ophthalmology and infectious diseases departments and were subsequently hospitalized for systemic treatment.

Whenever the standard treatment protocol for uveitis[4,7] is mentioned, it refers to the therapeutic scheme adopted in our center, which includes topical prednisolone (10 mg/mL) 1/1 hour for 1 day, then 2/2 hours for 3 days, followed by 5x/day for 1 week, which is then slowly tapered at a rate of 1 daily drop per week, or according to the evolution of inflammation and patient's response. It also includes the application of topical prednisolone ointment at night, and at least 1 week of cyclopentolate, given 2x/day.

The systemic study for uveitis comprised a complete blood count, renal function, ionogram, aldosterone-converting enzyme, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), HLA-B24, anti-nuclear, anti-cytoplasmic MPO, anti-cytoplasmic PR-3, anti-dsDNA, rheumatoid factor, serological tests for toxoplasmosis, syphilis (IgG *T. pallidum* + VDRL, if IgG positive) and IGRA.

The systemic treatment for neurosyphilis,[7,8] initiated in all of the presented patients, consisted of benzylpenicillin, 4 million international units, 4/4 hours, for 14 days.

CASE 1

A 29-year-old man with no relevant systemic or ophthalmologic history presented to the emergency department with complaints of red eye and unilateral ocular pain in his right eye (OD), with 1 week of evolution. He had BCVA of 0.22 logMAR and an IOP of 16 mmHg. Objective examination revealed ciliary injection, mild corneal edema, moderate anterior chamber inflammatory reaction, and posterior synechia at 2 and 4 hours. The posterior segment was innocent, with no vitritis or chorioretinal lesions. Standard uveitis treatment was started.

At the first re-evaluation, 3 days after the initial presentation, he reported improvement of the symptoms on his OD, but now he had the same complaints in his left eye (OS). The OD had an improved visual acuity of 0 logMAR (with the pinhole), no corneal edema and the synechiae had resolved. On the other hand, his OS had a BCVA of 0.4 logMAR, ciliary injection, and moderate anterior chamber reaction. The exam of the posterior segment of the OS was also normal. Treatment was also started in the OS.

Since the presentation was bilateral, with almost simultaneous onset, a systemic study was carried out, which came positive for syphilis (VDRL 1/64). Following the diagnosis, the patient was observed in the infectious diseases department, which found that he had a history of recent unprotected receptive sexual intercourse. The systemic study showed a slight elevation of inflammatory parameters, with a ESR of 24 mm/h and a CRP of 23 mg/L, with the remaining serologies negative. The objective examination showed a macular exanthema, spread over the dorsum and the limbs (Fig. 1), and multiple plaques of moth-eaten alopecia in a pattern consistent with the disease. A lumbar puncture was performed, which showed 26 predominantly mononuclear cells, and normal levels of proteins, without glucose consumption. TPHA was positive in the cerebrospinal fluid (CSF). He was subsequently admitted for systemic treatment with benzylpenicillin for 14 days. A systolic heart murmur (III/VI) was also objectified, and he

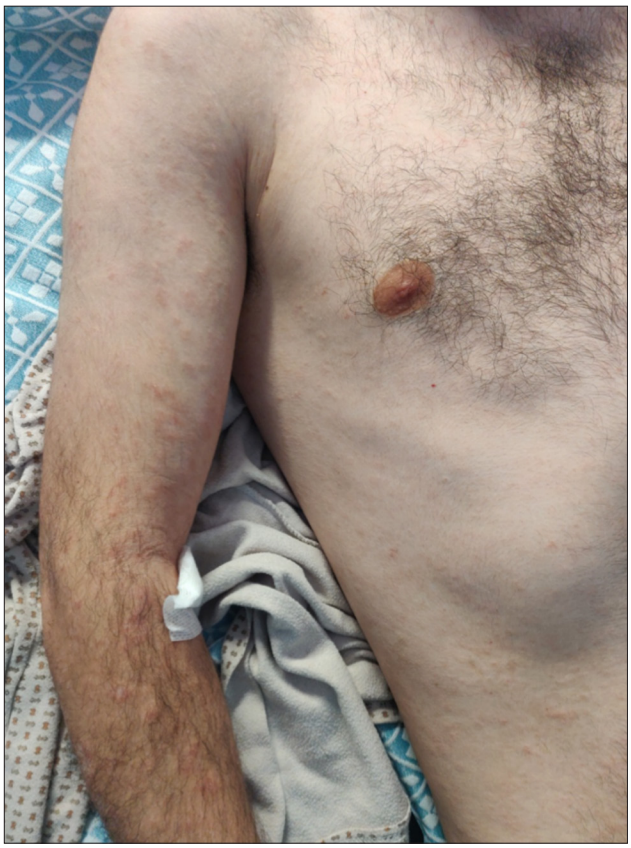

Figure 1. Macular exanthema spread over the dorsum and the limbs (Case 1).

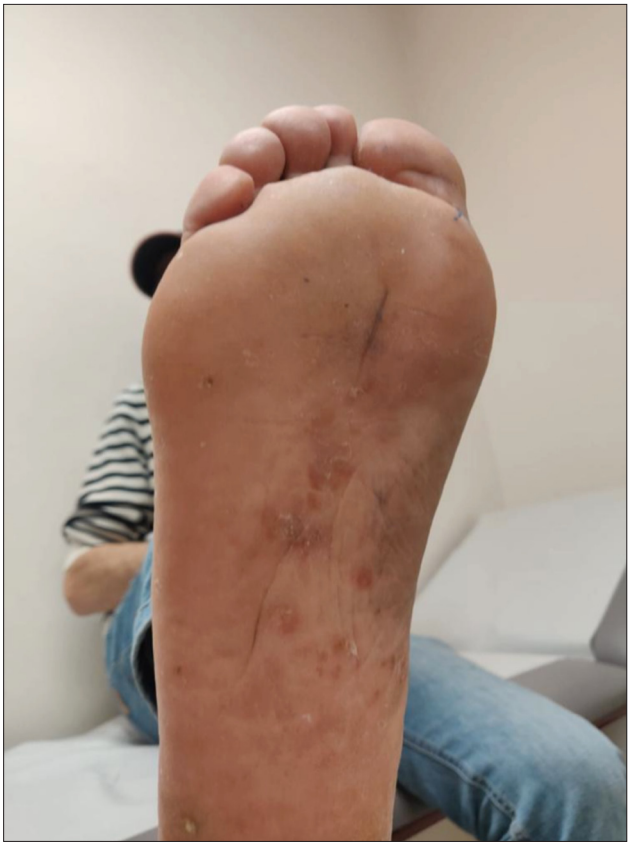

Figure 2. Plantar macular lesions (Case 2).

underwent a transthoracic echocardiogram, which showed no valvular dysfunction or aneurysmal dilations. The rest of the hospitalization was uneventful. In a follow-up appointment, after 3 months, he no longer presented any signs or symptoms of ocular inflammation, and his BCVA was 0 logMAR in both eyes.

CASE 2

A 46-year-old male with no relevant past medical history, presented in the emergency department with complaints of floaters and decreased vision of the OS, with 4 days of evolution. He had a BCVA of 0.7 logMAR and the examination of the anterior segment was normal. Fundoscopy revealed mild edema of the OD optic disc with normal peripapillary vasculature, and severe edema of the OS optic disc with elevated borders, peripapillary hemorrhages, and vascular tortuosity. Spectral-domain-optical coherence tomography (SD-OCT) of the disc confirmed the presence of bilateral edema. He was observed in the neurology department, which objectified a normal neurological exam, and underwent a head computed tomography (CT) scan, that did not evidence space-occupying endocranial lesions or other relevant changes. Posteriorly, he was examined in the infectious diseases department. After a detailed anamnesis, the patient described a penile lesion in the previous 6

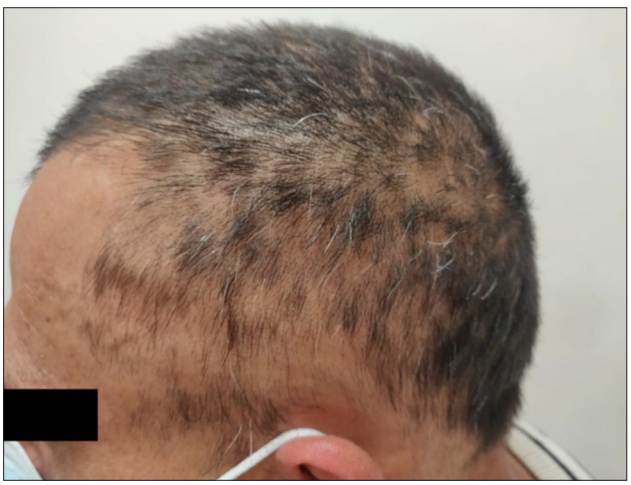

Figure 3. Moth-eaten alopecia (Case 2).

months, which he did not value. The objective examination revealed plantar macular lesions (Fig. 2) and several infracentimetric plaques of alopecia, compatible with moth-eaten alopecia (Fig. 3), very characteristic of syphilis. He had no exanthema in other locations. The remaining systemic examination was innocent. Considering the clinical picture, a systemic study was done, which was positive for syphilis (VDRL 1/16). The remaining analytical study showed no el-

evation of inflammatory parameters, with ESR of 19 mm/h and CRP of 6 mg/L. Other serological tests were negative. The lumbar puncture showed 77 cells, with mononuclear predominance, and a slight increase of proteins (52.2 mg/dL), without glucose consumption. Although the TPHA and VDRL in the CSF were negative, the PCR testing for *T. pallidum* was positive. His partner was subsequently tested and was also positive. He was subsequently admitted, and started benzylpenicillin treatment for 14 days, and standard topical medication without intercurrences. In a follow-up visit 2 months after treatment the visual complaints did not relapse. The signs of papillitis had subsided, and he had BCVA of 0 logMAR bilaterally.

CASE 3

A 46-year-old man was referred to the emergency department with complaints of a sudden decrease in his visual acuity during the last 3 days, pain, and photophobia in his OS. He had a known history of HIV-1 infection, diagnosed in 2016, treated with antiretroviral therapy, currently in stage A2, with an undetectable viral load and a CD4+ lymphocyte count of 422 cells/µL. His BCVA was "hand motion" and the anterior segment examination showed mild hyperemia, abundant endothelial keratic precipitates (PKs), and severe anterior chamber reaction. Fundoscopy showed dense, diffuse vitritis with inferior vitreous densification. Fluorescein angiography (FA) was performed which showed bilateral papillitis (Fig. 4) and a peripheric temporal chorioretinal lesion on his OS. The patient was subsequently examined by the infectious diseases department, which identified multiple infra-centimetric plaques of alopecia, compatible with moth-eaten alopecia (Fig. 5). He had no cutaneous rash. He underwent a systemic study, which was positive for syphilis (VDRL 1/32). Systemic inflammatory markers were normal. A lumbar puncture was done, which revealed 14 cells, slightly increased protein levels (47.4 mg/dL), and no glucose consumption. TPHA was positive in the cerebrospinal fluid. After a more detailed anamnesis, it was found that the patient had a penile skin lesion 2 years before, at the time treated with a topical antibiotic. He was subsequently admitted for treatment with benzylpenicillin for 14 days. Standard topical medication was also started. The hospitalization did not have intercurrences, and, in the last appointment, he had an OS BCVA of 0.7 logMAR, without papillitis. The vitritis in the OS was significantly better and the chorioretinal lesion did not show signs of activity.

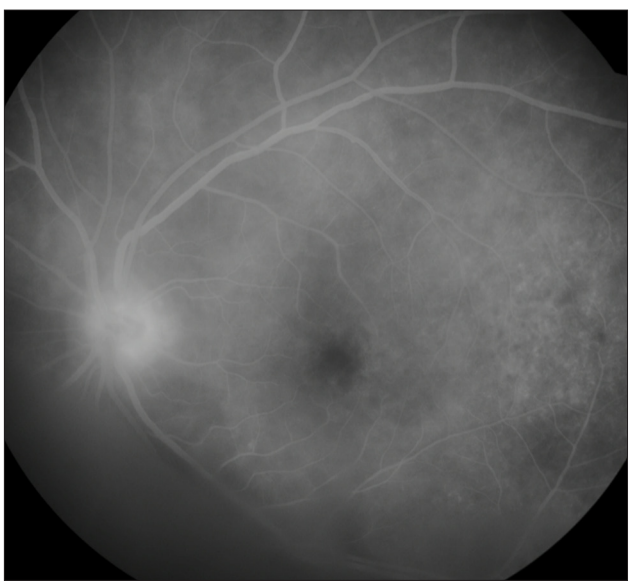

Figure 4. Vitritis and papillitis in the OS (Case 3).

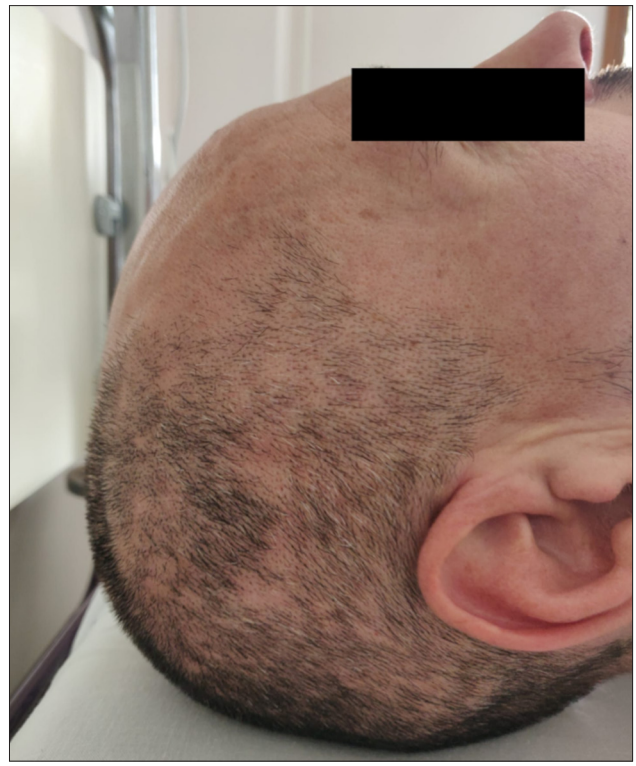

Figure 5. Moth-eaten alopecia (Case 3).

CASE 4

A 42-year-old male presented in the emergency department with complaints of floaters and a decrease in vision of the OS with 2 weeks of evolution. He had no relevant history of systemic or ophthalmological diseases. His BCVA was 0.4 logMAR in both eyes. Anterior segment examination showed the absence of conjunctival hyperemia and corneal endothelium did not have PKs, but there was a mild anterior chamber reaction in his OS. Fundoscopy showed bilateral diffuse pigmentary abnormalities, altered foveal reflexes, and mild optic disc edema, especially on the nasal side. He underwent FA and SD-OCT, which confirmed bilateral papillary edema, vasculitis with a predominance of phlebitis, and bilateral cystoid macular edema (Fig. 6). The examination by the infectious diseases' specialist detected mild psychomotor depression, but no other signs of neuro-

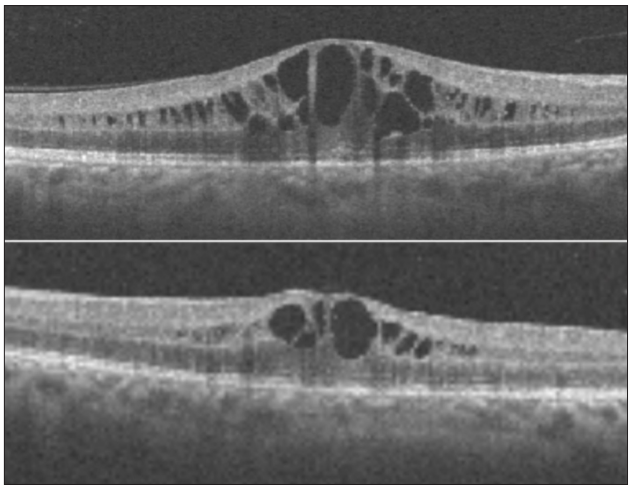

Figure 6. SD-OCT showing bilateral macular edema at presentation (Case 4).

logical or systemic disease. The patient eventually recalled that he had a cutaneous lesion on his penis and macular lesions on the palms of his hands, a few months prior. His partner also had the same lesions. A systemic study was requested, which was positive for syphilis (VDRL 1/128). Inflammatory markers were negative, and the results of the lumbar puncture showed normal levels of proteins, without glucose consumption. VDRL, TPHA and PCR of *T. pallidum* were negative in the CSF. He is currently waiting for the result of FTA-ABS. The patient was immediately admitted for systemic treatment with benzylpenicillin for 14 days. During the hospitalization period, there was an improvement in visual acuity, with a BCVA of 0.2 logMAR. In the last observation before discharge, moderate cystoid macular edema was still present in his OD, but there was an almost complete improvement in the OS. Optic discs maintained slight bilateral edema. Since the patient's discharge was given only 1 week before this report, he has not yet been seen in a follow-up consultation, which will occur in the short term.

CASE 5

A 59-year-old female patient was seen in the emergency department with complaints of red OD and decreased visual acuity for 15 days. She also reported ocular pain starting 2 days ago. Her medical background consisted of obesity, musculoskeletal pathology, and anxiety disorder. She presented a BCVA of "hand motion" and the anterior segment examination revealed ciliary injection, dense, thin PKs, and severe anterior chamber reaction, including a thin lamina of inflammatory hypopyon, along with a hypermature cataract. Gonioscopy was done, which showed an open iridocorneal angle, with few peripheral synechiae. Fundus visualization was impossible due to media opacity, so an ocular B-scan ultrasound was carried out, which revealed no signs of vitritis or significant posterior segment changes. Considering the severity of the inflammation, a subconjunctival injection of triamcinolone was given, and the standard uveitis protocol was started. At the first re-evaluation, 1 week after the initial observation, there was an important improvement in the hyperemia and the anterior chamber reaction, and hypopyon was no longer present. One month after the initial presentation, as the inflammation subsided, she was referred for OD cataract surgery. After 6 weeks, on the setting of the pre-operative consultation, inflammation of the OS was objectified, with the presence of PKs and mild anterior chamber reaction. This led to the surgery being canceled, and a systemic study was requested, which was positive for syphilis, with a very high VDRL titer value of 1/712. The patient was then examined by the infectious diseases department, to whom she reported a skin rash about 1 month before the inaugural episode, which was diagnosed as shingles by her primary care physician. She had no other signs of systemic or neurological involvement. No lumbar puncture was performed. Subsequently, she was referred for admission to her hospital of residence, where she was treated with benzylpenicillin for 14 days. The hospitalization was uneventful, and there was no symptomatic relapse. She is currently awaiting cataract surgery in her OD.

DISCUSSION

Syphilis is one of medicine's great masqueraders, given the lack of specificity of its systemic, often multi-organic symptoms. These characteristics also apply to the ocular inflammation it causes. Syphilitic uveitis may occur at any stage of the evolution of the disease.[8] Its inflammation can affect virtually any structure of the eye, and the involvement may be unilateral or bilateral, either simultaneously or asynchronously.

During the last decades, the incidence of syphilis, and consequently ocular syphilis, has increased. The Manchester Uveitis Clinic's study, which included 3000 consecutive cases of uveitis diagnosed between 1991 and 2013, noted a significant increase in the syphilitic etiology.[10] Epidemiological studies suggest that, although the disease can occur in any age, gender, race, or sexual preference, it is most common in men aged 37-58, especially in men who have sex with men (MSM).[11] The demographic characteristics of the patients in our series are concordant with these data. Of the 5 cases described, 4 were men, and 3 of them were MSM. The age range was also similar, with ages ranging from 29 to 59 years old. Reports show that HIV coinfection is common, which supports the screening for HIV in all patients diagnosed with syphilis. One of the patients of our series had a known HIV co-infection, which was under chronic treatment with antiretroviral treatment, with an undetectable viral load. All the remaining patients were screened for the infection and had a negative result. The epidemiological and pathophysiological interaction between HIV and syphilis is important. HIV and syphilis patients tend to cluster in the same groups, and, in many cases, HIV-positive patients usually present ocular syphilis before the HIV infection is known.[12] It is also known that the risk of neuro-

logical and ocular involvement is higher when co-infection with HIV is present, which is related to the altered immune response to *T. pallidum*, increasing the likelihood and the severity of neurological involvement. Furthermore, ocular syphilis in untreated HIV patients is more commonly bilateral, and the involvement of the posterior segment of the eye is more frequent.[13]

Case 1 depicted an unspecific case of a seemingly standard non-granulomatous iridocyclitis, first thought to be unilateral, but then regarded as bilateral, due to the asynchronous onset of the symptoms. Bilateral involvement raised suspicions about the etiology. The history of recent unprotected sexual intercourse was a major factor leading to the final diagnosis. Systemic examination, which should not be disregarded, played an important role. Moth-eaten alopecia and the characteristic skin rash are easily identifiable signs that are often overlooked. Barile and Flynn reported non-granulomatous iridocyclitis as the identifiable presentation of syphilis in 25% of cases.[9] The fact that the patient had no co-infections, or concomitant systemic pathology may have contributed to the exclusive involvement of the anterior segment, the fast response to treatment, and full visual recovery with final visual acuity of 0 logMAR.

Case 2 had a more atypical presentation, with the exclusive and asymmetric involvement of the posterior segment, in the absence of inflammatory reaction of the anterior chamber. Papillitis was present and vascular involvement was shown by perivascular hemorrhages and vascular tortuosity. This patient also had several infra-centimetric plaques of alopecia, compatible with syphilitic lesions. A detailed anamnesis was invaluable since he reported a penile skin lesion, 6 months before. Despite the severity of the papillitis, with exuberant optic disc edema, the patient also fully recovered his visual function with timely treatment.

In case 3, we could see an example of syphilitic panuveitis, in the setting of an HIV co-infection. As previously mentioned, the presence of HIV infection drastically increases the likelihood of posterior segment involvement and the severity of the disease. Nevertheless, in this case, HIV was actively treated with antiretroviral therapy, with suppressed viral load, corresponding to a stage A2 infection. At presentation, he had very low visual acuities of "hand motion", mainly due to the dense vitritis that he presented. Papillitis was also present. This case was the most severe presentation in our series. Visual recovery was far from total, with visual acuities of 0.7 logMAR in the last observation, despite having completed the treatment under hospitalization. Unlike the previously mentioned cases, this one shows that severe disease, with simultaneous involvement of the anterior and posterior segments and the optic nerve may be associated with a poorer visual prognosis, even after finding the right diagnosis and establishing the correct treatment.

Case 4 depicts a bilateral neuroretinitis with mild unilateral anterior chamber reaction, in a patient with no relevant history of systemic or ophthalmological diseases. Once again, the importance of the systemic anamnesis and objective exam is highlighted. The ocular involvement showed neuroretinitis without features characteristic of any specific diagnosis. The fact that the patient reported the presence of a cutaneous lesion on the penis, which was undervalued and treated with a topical antibiotic, was a valuable clue for the final diagnosis. His partner had a similar penile lesion at the same time, showing the importance of screening sexual partners when the disease is first diagnosed, as they may be in the latent phase of the disease, and timely diagnosis and treatment may be able to prevent serious long-term complications.

Finally, case 5 showed severe granulomatous iridocyclitis in a patient with a hypermature cataract, which raised suspicion for lens-induced uveitis. Initially, the condition fully resolved with the standard topical treatment, including a subconjunctival injection of corticosteroids. The only reason why a secondary cause was suspected was because the other eye started a mild anterior chamber reaction before the initially affected eye went through cataract surgery. Syphilitic uveitis was subsequently diagnosed, with extremely high VDRL titers. This case is an example where the diagnostic suspicion firmly points to a specific disease, which is subsequently disproved, showing that the syphilitic etiology should always be considered, even if the patient reports no other systemic signs of the infection.

It is important to emphasize that a negative VDRL and TPHA in the CSF does not exclude infection if clinical suspicion is high, especially if the CSF has features of inflammation such as pleocytosis or high levels of proteins. The final visual prognosis, even after the correct treatment, was variable, with cases where visual recovery was absolute, and others where the final visions were unsatisfactory. Widespread and severe damage to the ocular structures is naturally linked to incomplete visual recoveries.

The role of systemic corticosteroids in the treatment of ocular syphilis is not entirely clear, with conflicting evidence. A recent meta-analysis concluded that the coadministration of systemic corticosteroids or immunosuppressants did not elicit further improvements in the clinical outcomes of antibacterial agents.[11] Despite this, the use of systemic corticosteroids in clinical practice is not uncommon, especially when optic neuritis is present. Solebo[14] considered that a definite role exists for adjunctive oral or intravenous corticosteroids in syphilitic optic neuritis, posterior uveitis, and scleritis. In the described cases, the therapeutic approach was decided in conjunction between the ophthalmology and infectious diseases teams, and none of the patients was given systemic corticosteroids.

Studies addressing the prognostic results of ocular syphilis are scarce. Factors associated with a worse visual outcome include the time between the onset of the uveitis and treatment, being exponentially worse for periods over 12 weeks, the duration of ocular symptoms, or the presence of long-standing macular edema or neuropathy. HIV co-infection is a well-known factor that translates into a poor prognosis. Poor initial visual acuities also appeared to be related to worse visual outcomes.[1,2,15]

CONCLUSION

Ocular syphilis is a complex disease due to the diversity of manifestations, in practically all anatomical regions of the eye, without specific signs or symptoms directly leading to this entity. A high clinical suspicion is necessary in atypical, bilateral, or persistent cases of ocular inflammation. Immunological testing for *T. pallidum* should generally be included in the differential diagnosis of ocular inflammation with undetermined cause. A detailed history, including behavioral factors, and the past or present existence of other systemic symptoms of the disease is important to help the diagnosis. A systemic physical examination is also an essential tool. Since ocular involvement may occur at any stage of the disease's development, the various multi-organic manifestations must be ruled out.

The main limitation of this analysis relates to the fact that it is a series of consecutive cases, which implies a small sample of patients. Nevertheless, the objective of the study was to show the variety of manifestations between random consecutive cases of the same disease. Future contributions to this work may include a prospective, long-term study, with a larger sample of patients.

CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO:

RCB and SO: Writing.

All other authors collaborated equally in data collection, analysis and in the discussion of the results.

RESPONSABILIDADES ÉTICAS

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

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Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.

Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pela Comissão de Ética responsável e de acordo com a Declaração de Helsínquia revista em 2013 e da Associação Médica Mundial.

Consentimento: Consentimento dos doentes para publicação obtido.

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REFERENCES

1. Singh AE, Romanowski B. Syphilis: review with emphasis on clinical, epidemiologic, and some biologic features. Clin Microbiol Rev. 1999;12:187-209. doi: 10.1128/CMR.12.2.187.
2. Norris SJ, Cox DL, Weinstock GM. Biology of Treponema pallidum: correlation of functional activities with genome sequence data. J Mol Microbiol Biotechnol. 2001;3:37-62.
3. Raiziss GW, Severac M. Rapidity with which Spirochaeta pallida invades the bloodstream. Arch Dermatol Syphilol. 1937;35:1101-9.
4. Kiss S, Damico FM, Young LH. Ocular manifestations and treatment of syphilis. Semin Ophthalmol. 2005;20:161-7. doi: 10.1080/08820530500232092.
5. Margo CE, Hamed LM. Ocular syphilis. Surv Ophthalmol. 1992;37:203-20. doi: 10.1016/0039-6257(92)90138-j.
6. Mendelsohn AD, Jampol LM. Syphilitic retinitis. A cause of necrotizing retinitis. Retina. 1984;4:221-4.
7. Dutta Majumder P, Chen EJ, Shah J, Ching Wen Ho D, Biswas J, See Yin L, Gupta V, Pavesio C, Agrawal R. Ocular Syphilis: An Update. Ocul Immunol Inflamm. 2019;27:117-25. doi: 10.1080/09273948.2017.1371765.
8. Smit DP, Cunningham ET Jr, Thorne JE, Tugal-Tutkun I. Ocular Syphilis. Ocul Immunol Inflamm. 2023;31:1313-4. doi: 10.1080/09273948.2023.2221622.
9. Barile GR, Flynn TE. Syphilis exposure in patients with uveitis. Ophthalmology. 1997;104:1605-9. doi: 10.1016/s0161-6420(97)30089-x.
10. Jones NP. The Manchester Uveitis Clinic: the first 3000 patients--epidemiology and casemix. Ocul Immunol Inflamm. 2015;23:118-26. doi: 10.3109/09273948.2013.855799.
11. Zhang T, Zhu Y, Xu G. Clinical Features and Treatments of Syphilitic Uveitis: A Systematic Review and Meta-Analysis. J Ophthalmol. 2017;2017:6594849. doi: 10.1155/2017/6594849.
12. Lee SY, Cheng V, Rodger D, Rao N. Clinical and laboratory characteristics of ocular syphilis: a new face in the era of HIV co-infection. J Ophthalmic Inflamm Infect. 2015;5:56. doi: 10.1186/s12348-015-0056-x.
13. Amaratunge BC, Camuglia JE, Hall AJ. Syphilitic uveitis: a

review of clinical manifestations and treatment outcomes of syphilitic uveitis in human immunodeficiency virus-positive and negative patients. Clin Exp Ophthalmol. 2010;38:68-74. doi: 10.1111/j.1442-9071.2010.02203.x.
14. Solebo AL, Westcott M. Corticosteroids in ocular syphilis. Ophthalmology. 2007;114:1593. doi: 10.1016/j.ophtha.2007.04.017.
15. Davis JL. Ocular syphilis. Curr Opin Ophthalmol. 2014;25:513-8. doi: 10.1097/ICU.0000000000000099.

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