Visual loss resulting from immunosuppressive therapy in patients with syphilitic uveitis

VIVIAN CRISTINA COSTA AFONSO1, HELOISA NASCIMENTO1, RUBENS M. BELFORT1, EMILIA INOUE SATO2, CRISTINA MUCCHIOLI1, RUBENS BELFORT JR.1

ABSTRACT
Permanent visual loss can be caused by improper use of immunosuppressive therapy in cases of uveitis without differential diagnosis of syphilitic uveitis. We present four cases of syphilitic uveitis that were incorrectly diagnosed as being secondary to rheumatic diseases and were subsequently treated with immunosuppressive therapy, leading to permanent visual loss. These cases highlight the importance of ruling out syphilis in the differential diagnosis of inflammatory ocular diseases before starting use of immunosuppressive therapy.

Keywords: Syphilis; Uveitis/drug therapy; Immunosuppressive agents/therapeutic use; Immunosuppressive agents/adverse effects; Vision disorders/etiology; Case reports

INTRODUCTION
Syphilis can affect the eyes in the secondary and tertiary stages of the disease, and ocular syphilis can be difficult to diagnose due to variation in presentation. The most common presentation is uveitis, which can be in the posterior or diffuse form, as well as unilateral or bilateral.

Biologic immunosuppressant agents have been used to treat non-uveitis, but the evidence supporting this approach is not strong. In addition, the use of immunosuppressant agents has been related to exacerbation of infectious uveitis. Non-treponemal serologic tests, such as the venereal disease research laboratory (VDRL) test, followed by tests to identify Treponema, such as enzyme-linked immunosorbert assay, fluorescent Treponema antibody (FTA-ABS), and the microhemagglutination assay for Treponema pallidum antibodies, are the gold standard for diagnosing syphilis. The non-treponemal tests are important for monitoring disease progression, because they are quantitative and can identify titer level, determining the response to antibiotic treatment. Given the differences in uveitis etiology, it is important that treatment decisions are based on the results of both treponemal and non-treponemal tests (Table 1).

The purpose of this report is to raise awareness in the medical community of the possibility of permanent ocular damage caused by the inappropriate use of immunosuppressive therapy in cases of uveitis associated with undiagnosed syphilis.

CASE REPORTS
A 61-year-old woman presented with a bilateral decrease in visual acuity, with best-corrected visual acuity (BCVA) levels of 20/400 and 20/800 in the right and left eyes, respectively. Examination showed 2+-inflammatory anterior chamber (AC) cells bilaterally, granulomatous keratic precipitates, vasculitis, and intense vitritis bilaterally.

The patient had skin lesions on the palms of her hands and soles of her feet, as well as hypacusia. She was being treated with 60 mg of prednisone daily and had undergone pulse therapy with methylprednisolone, due to ophthalmic and suspected inflammatory disease (anticardiolipin antibody-positive), without clinical improvement. Her VDRL titer was 1/128 and her FTA-ABS test was positive. She was negative for human immunodeficiency virus (HIV), and her cerebrospinal fluid (CSF) was negative for syphilis. She was started on 16 million units of intravenous penicillin daily for 14 days. The vitreitis and vasculitis in her right eye improved; however, optic atrophy was observed and a rheumatogenous retinal detachment developed in the left eye, causing permanent blindness bilaterally. Her dermatologic signs improved substantially (Figure 1).

A 49-year-old woman presented with progressive visual loss bilaterally for 6 months, with a corrected VA of 20/400 and 20/800 in the right and left eyes, respectively. She also had 2+ AC cells, granulomatous keratic precipitates, intense bilateral vitreitis, oral and genital ulcers, hypacusia, and mental confusion. After diagnosing her with neuro-Bechet’s disease, a rheumatologist prescribed prednisone, mofetil, and infliximab. Two ophthalmologists and internists also evaluated the patient. Her VDRL titer was 1/128 and she was negative for HIV. CSF tests revealed that her FTA-ABS test was positive. Sixteen million international units (IU) of IV penicillin were prescribed for 14 days. After treatment, VA improved to 20/20 in both eyes.

A 51-year-old man presented with clinical signs of uveitis for 3 months, with VA of 20/120 and 20/80 in the right and left eyes; res-
Table 1. Interpretation of diagnostic tests for syphilis in cases of uveitis(6)

<table>
<thead>
<tr>
<th>Treponemal test</th>
<th>Non-treponemal test</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>Negative</td>
<td>Immunologic window or is not syphilis</td>
</tr>
<tr>
<td>Positive</td>
<td>Negative</td>
<td>Already treated syphilis or tertiary syphilis; inquire about previous treatment of syphilis. In previously untreated cases or inadequately treated cases, consider retreatment. Evaluate the prozone effect. Dilute sample of non-treponemal test and reassess positivity</td>
</tr>
<tr>
<td>Positive</td>
<td>Positive</td>
<td>Evaluate titers of non-treponemal tests. In previously treated cases, the titers probably have declined. In previously untreated or inadequately treated cases, consider retreatment</td>
</tr>
<tr>
<td>Negative</td>
<td>Positive</td>
<td>Immunologic window or false positive (consider rheumatic diseases)</td>
</tr>
</tbody>
</table>

![Figure 1. Case 1: funduscopy of right eye after treatment.](image)

respectively. He also had 2+ AC cells, keratic precipitates, and non-granulomatous keratic precipitates. He had undergone pulse therapy with methylprednisolone, but the clinical signs worsened. At the time of his visit, he was taking 200 mg/day of azathioprine and 60 mg/day of prednisone, which was prescribed by a rheumatologist after a previous ophthalmic evaluation. His VDRL titer was 1/128, and his FTA-ABS test was positive. He was also HIV negative, and his CSF test was negative for syphilis. The patient was treated with intramuscular penicillin G benzathine 2,400,000 IU/week for 3 weeks. His VA improved to 20/40 and 20/25 in the right and left eyes, respectively. After 4 months, his VA decreased and the uveitis recurred. Treatment with IV crystalline penicillin was performed for 14 days. This resolved the uveitis and the patient’s VA improved to 20/25 in both eyes.

A 51-year-old woman presented with a bilateral BCVA of 20/400, 2+ AC cells in the aqueous humor, granulomatous keratic precipitates, intense vitreitis, and dermatologic symptoms (rashes on the palms and soles). She was treated with 60 mg prednisone, methotrexate, and adalimumab, which was prescribed by a rheumatologist who suspected possible Behcet’s disease. The patient’s VDRL titer was 1/128, her FTA-ABS test was positive, and she was negative for HIV. CSF tests also showed positive FTA-ABS results. She was treated with 16 million units of IV penicillin daily for 14 days. Following treatment, her VA improved to 20/40 in both eyes, but paralytic mydriasis and photophobia persisted.

**DISCUSSION**

In case 1, we observed systemic involvement associated with the clinical signs of uveitis. However, because the patient was anti-cardiolipin-positive, the disease was considered rheumatic in nature. A positive test for anticardiolipin antibody can occur in cases with a high Treponema load(6), even when VDRL may be negative. Serology for Treponema, which would have facilitated a correct diagnosis, had not been performed initially. In addition in cases of antiphospholipid syndrome, steroid pulse therapy is generally not prescribed, although this patient had previously received it.

In case 2, the patient had systemic involvement with neurologic changes and oral and genital ulcers. The systemic clinical signs could have been compatible with neuro-Behçet’s disease. However, the differential diagnosis did not include syphilis. In case 3, the patient had clinical signs of uveitis only, with no improvement during the 3 months of immunosuppressant therapy.

Cases 1, 2, and 4 had systemic involvement with dermatologic symptoms. After immunosuppressant therapy, the symptoms worsened.

The clinical signs of uveitis in these cases were treated with immunosuppressive therapy using corticosteroids and other immunosuppressants, without syphilis being excluded. This led to worsening of the ocular symptoms, because corticosteroids and immunosuppressants can increase Treponema load, resulting in increased syphilis-related ocular and non-ocular complications(3,4). The potential complications following the use of immunosuppressive therapy in syphilitic uveitis, which may lead to blindness, include retinal vasculitis, exudative retinal detachment, retinal chorioretinitis, and optic atrophy.

When the disease is treated early and aggressively, even severe uveitis tends to resolves without major permanent visual loss(7).

In the cases described here, ocular disease became more evident after the use of immunosuppressive drugs. Other studies have reported the development of ocular syphilis after the use of anti-TNF α(3,4). Moreover, syphilitic uveitis is often associated with neurosyphilis, and patients with symptoms consistent with this diagnosis should be treated according to the recommendations for neurosyphilis(8,9).

The cases described here demonstrate that syphilis should always be included in the differential diagnosis of inflammatory ocular diseases before a patient receives any immunosuppressive treatment.

**REFERENCES**


