ABSTRACT

Syphilis is a sexually transmitted infection commonly associated with painless skin lesions of the genitalia. It is also known as the “great imitator” since it can manifest in a variety of other presentations, including in the eye.

A 44-year-old immunocompetent male presented with acute vision loss in one eye. Fundus examination revealed a unilateral central serous detachment with whitening of the retina near the fovea. Fundus fluorescein angiogram showed leakage from vessels surrounding the affected macula. Optical coherence tomography demonstrated significant unilateral abnormality: macular thickening, subretinal fluid accumulation, and inner segment-outer segment junction disruption. Despite negative nontreponemal serological screening, clinical findings were most consistent with acute syphilitic posterior placoid chorioretinitis. The patient was treated with intravenous penicillin for 14 days. Following treatment, the lesion resolved and a chorioretinal scar remained.

INTRODUCTION

Although syphilis had been nearly eradicated from the United States in 2000, the Centers for Disease Control and Prevention (CDC) reports an accelerated increase in the rates of syphilis infection from 2005 to 2013. 1 Syphilis is a sexually transmitted infection caused by the spirochete bacterium Treponema pallidum. After initial infection of a host, T. pallidum is able to invade the bloodstream and disseminate from its primary site of infection. 2,3 This unique biological property accounts for the myriad of systemic manifestations associated with syphilis, which could easily be misdiagnosed as another condition. With the increased incidence of syphilis in the United States, it is essential to raise physician awareness of syphilis’ unusual presentations. This case report describes an ocular manifestation of syphilis and discusses the limitations of serological diagnostic tools.
CASE PRESENTATION

A 44-year-old male presented to the retina clinic after awaking with a gray spot in his left eye that increased in size as the day progressed. Four days prior, he was treated for left deep thigh infection with overlying cellulitis; he received a single dose of intravenous (IV) vancomycin 1000 mg and piperacillin/tazobactam 3.375 mg, and subsequently began a 9-day oral regimen of amoxicillin 875mg/clavulante 125mg. Also of note, he had previously been treated for secondary syphilis with intramuscular (IM) penicillin 18 years prior.

On examination, visual acuity was 20/20 in his right eye (OD) and 20/300 (pinhole 20/100+1) in his left eye (OS), qualifying the patient as legally blind in his left eye. Dilated fundus examination revealed a central serous detachment inferior to the left fovea, with whitening of the retina and multiple intra-retinal hemorrhages surrounding the elevation (Figure 1a). Fundus fluorescein angiogram (FFA) showed progressive leakage from vessels surrounding the left macula, most pronounced superior temporally and inferior temporally (Figure 1b, 1c). Optical coherence tomography (OCT) scans of this region demonstrated significant macular thickening, with accumulation of subretinal fluid and disruption of the inner segment-outer segment (IS-OS) junction (Figure 2a).

Rapid plasma reagin (RPR) and cerebral spinal fluid Venereal Disease Research Laboratory (CSF VDRL) were both negative, with no growth in the CSF sample. Tuberculosis (TB) gold and HIV tests were also negative.

After 2 weeks, his vision had improved to 20/20 OD and 20/50+1 OS. Clinically, his serous detachment had resolved, though areas of retinal whitening persisted. OCT scans at this time revealed that the macula had flattened with resolution of subretinal fluid; however, disruption of the IS-OS junction remained evident (Figure 2b). Despite negative syphilis serology, OCT findings were consistent with the diagnosis of acute syphilitic posterior placoid chorioretinitis (ASPPC) and the patient was treated with IV penicillin G 4 million units every 4 hours for 14 days.

One month from initial presentation, the patient’s vision had improved markedly though he was still bothered by a blind spot. Visual acuity was 20/20 OD and 20/30 OS. OCT scans demonstrated persistent disruption of the IS-OS junction. One month later, the patient’s visual acuity continued to improve to 20/20 OD and 20/20 OS. Fundus exam revealed no edema and resolved whitening of the retina (Figure 1d). FFA did not show any leakage (Figure 1e-1f). OCT confirmed the absence of edema, but also revealed a small area of choroidal thickening underlying the original retinal lesion suggestive of scarring (Figure 2c). No further treatment was warranted and the patient was advised to continue monitoring his vision for any new changes.

At 5 months following the initial presentation, the patient’s vision remained 20/20 bilaterally and clinical exam was stable.

DISCUSSION

If untreated, syphilis progresses through a series of four stages, with each demonstrating generalizable characteristics (Table 1). After approximately 3 to 6 weeks of incubation, primary syphilis manifests as a painless chancre at the original site of inoculation.2,4 Local immune responses are typically able to clear T. pallidum, healing the chancre within 3 to 8 weeks.3 As a result, primary syphilis may often go undetected. But within hours of infection, T. pallidum has already invaded the bloodstream and spread systematically.2,3 Despite this early dissemination,
**Figure 1.** Clinical picture at presentation versus at 2 month follow-up visit. (a) Color fundus photograph of the left eye at presentation showed a round creamy white lesion with multiple hemorrhages inferotemporal to the fovea and associated subretinal fluid which extended to the fovea. Fundus fluorescein angiogram (FFA) showed (b) early blockage in the area of the retinal whitening and (c) late leakage finding consistent with an actively inflamed lesion. (d) In the color fundus photograph of the left eye at 2 month follow-up, there was complete resolution of the retinal whitening, hemorrhages, and subretinal fluid. A circular atrophic chorioretinal scar was present in the area of the resolved retinal lesion. FFA showed (e) early hyperfluorescence with well-defined borders in area of the resolved retinal lesion which (f) progresses to staining hyperfluorescence of the entire lesion, while maintaining the border of the lesion in the late phases; angiographic findings consistent with chorioretinal scar.

**Figure 2.** Spectral domain ocular coherence tomography images. (a) At presentation, there was subretinal fluid, hyperreflectivity, thickening of the inner and outer retinal layers, and disruption of the inner segment-outer segment (IS-OS) junction. (b) At 2 week follow-up, there was resolution of the subretinal fluid, persistent disruption of the IS-OS junction, and irregularity of the outer retinal layers, consistent with scar formation. (c) At 2 month follow-up, there was atrophy of the outer retinal layers and an area of choroidal hyperreflectivity in the region of the resolved retinal lesion.
Table 1. Stages and Manifestations of Syphilis

<table>
<thead>
<tr>
<th>Stage</th>
<th>Clinical Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>Painless chancre at site of initial inoculation</td>
</tr>
<tr>
<td></td>
<td>Maculopapular rash, fever, malaise, weight loss, muscle aches, alopecia, lymphadenopathy, mucosal lesions</td>
</tr>
<tr>
<td></td>
<td>Hepatic (jaundice, hepatitis)</td>
</tr>
<tr>
<td></td>
<td>Renal (nephrotic syndrome, proteinuria)</td>
</tr>
<tr>
<td></td>
<td>Gastric (dysmotility)</td>
</tr>
<tr>
<td></td>
<td>Neurologic (meningitis, headaches)</td>
</tr>
<tr>
<td></td>
<td>Ocular (uveitis, retinitis)</td>
</tr>
<tr>
<td>Secondary</td>
<td>Tissue destruction of any organ, depending on site involvement</td>
</tr>
<tr>
<td>Gummata</td>
<td>Aortic regurgitation</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Coronary ostial stenosis</td>
</tr>
<tr>
<td>Syphilis</td>
<td>Saccular aneurysm</td>
</tr>
<tr>
<td></td>
<td>Vertigo, insomnia, personality changes, seizures</td>
</tr>
<tr>
<td></td>
<td>Meningencephalitis</td>
</tr>
<tr>
<td></td>
<td>Ocular (uveitis, retinitis, optic neuropathy)</td>
</tr>
<tr>
<td>Neurosyphilis</td>
<td>Paresis: emotional instability, memory impairment,</td>
</tr>
<tr>
<td></td>
<td>hallucinations, hyperactive reflexes</td>
</tr>
<tr>
<td></td>
<td>Tabes dorsalis: sensory ataxia, paresthesia, sudden-onset vomiting</td>
</tr>
</tbody>
</table>

Based on information from LaFond and Lukehart, “Ho and Lukehart,” and Lutchman et al.4

The symptoms of secondary syphilis do not appear until 3 to 6 months after initial inoculation.2,4 When secondary syphilis does manifest itself, it may present with involvement of various organ systems depending on the seeding of T. pallidum.2,3 Again, the immune system is able to mount an inflammatory response against T. pallidum, resolving symptoms within 3 months of onset.2 However, a subpopulation of T. pallidum develops resistance to phagocytosis and is able to persist in an asymptomatic latent stage.2,3,5 This latent stage can be divided into early (less than 1 year after infection) and late (more than 1 year after infection), with 25% of early latent patients relapsing to secondary syphilis.2,3 Approximately one-third of patients with latent syphilis progress to tertiary syphilis.2

Though a rare occurrence typically seen with secondary or tertiary syphilis,2,4 ocular involvement has been reported in all structures of the eye.6 Specifically, posterior uveitis has been reported to be the most common complication of ocular syphilis.6,8 This posterior segment involvement is most often manifested as ASPPC.8 Early cases reported by de Sousa et al.9 and Gass et al.10 described a large, yellowish placoid lesion in or near the macula at the level of the retinal pigment epithelium (RPE), with diffuse leakage apparent on FFA. A recent study by Pichi et al.8 described the OCT findings characteristic of ASPPC: IS-OS junction disruption, nodular RPE thickening, and, in some cases, subretinal fluid accumulation, external limiting membrane loss, and choroidal punctate hyperreflectivity. Additionally, although early work10 suggested that immunocompromised status was responsible for ASPPC, more recent findings8,11 have demonstrated the prevalence of ASPPC in immunocompetent patients as well.
Because *T. pallidum* has limited metabolic capacity² and cannot be cultured, diagnosis of syphilis relies upon clinical presentation and serological analysis. Typically, highly sensitive nontreponemal tests (RPR and VDRL) are used as frontline screening measures, followed by highly specific treponemal tests (fluorescent treponemal antibody absorption [FTA-ABS]) only in cases of reactive nontreponemal tests.⁴,¹²,¹³ However, studies have noted rather high false-negative rates (roughly 30%) in nontreponemal tests.⁸,¹⁴ Tamesis and Foster¹⁴ even went on to recommend that routine FTA-ABS tests be conducted in conjunction with nontreponemal screenings.

The standard treatment for syphilis is parenteral penicillin, with dosage and method of administration depending upon the stage of syphilis. Adequate alternative treatments in cases of penicillin allergy have been reported to include macrolides, cephalosporins, and tetracyclines.³,¹⁵ Amoxicillin has also been reported to possess antitreponemal activity equivalent to that of penicillin, though at noticeably higher concentrations (0.018mg/L penicillin vs. 0.42mg/L amoxicillin).¹⁵ Additionally, vancomycin has been observed to demonstrate some, though not therapeutically effective, activity against *T. pallidum*.¹⁵

Although the presented patient had negative RPR and CSF VDRL tests, his clinical findings were most consistent with ASPPC and his symptoms resolved with antibiotic treatment. While it remains unclear if the patient experienced relapse of or reinfection with syphilis, his ocular manifestations of syphilis may have been precipitated by his immune system’s inflammatory response to his groin infection. The subsequent rounds of antibiotics he received for his groin infection are likely to have incidentally treated his ASPPC. Although no known studies have explored the use of amoxicillin in the context of ASPPC, Morrison et al.¹⁶ and O’Mahoney et al.¹⁷ have demonstrated amoxicillin’s antitreponemal activity in the settings of neurosyphilis and late stage syphilis, respectively. This hypothesis is supported by the patient’s early resolution of central serous detachment and subretinal fluid accumulation prior to initiation of IV penicillin G. Also of note, the presentation of ASPPC in his left eye is in accordance with the unexplained preponderance of left-sided unioocular ASPPC recently reported by Matthew et al.¹⁸

Incidental treatment of syphilis by antibiotics prescribed for other infections has been hypothesized to explain the low incidences of tertiary syphilis observed.² This hypothesis may certainly explain the events described in this case report.

As the incidence of syphilis infection is on the rise, the usual manifestations of syphilis will become more pervasive in all fields of medicine. It is imperative to recognize these early symptoms of syphilis before infection progresses to its more debilitating forms. Therefore, the authors emphasize the importance of considering the possible diagnosis of syphilis in patients presenting with acute ocular inflammation. Additionally, the authors recommend that gold standard FTA-ABS tests be conducted in these patients, regardless of nontreponemal test reactivity.

---

**LEARNING POINTS**

1. Syphilis can manifest in a variety of presentations, including as acute ocular inflammation.

2. Both nontreponemal and treponemal tests should be conducted to accurately screen for syphilis.
ACKNOWLEDGEMENTS

The authors would like to extend a special thanks to Mr. Donald Spellman from the Baltimore VA Medical Center for his imaging expertise.

REFERENCES


17. O’Mahony C, Bradley MG, McKeown J, Arya OP. Treponemocidal levels of amoxicillin can be achieved in cerebrospinal fluid following oral treatment with only 4 g amoxicillin and 2 g probenicid daily in late stage syphilis. Int J STD AIDS. 2012;23(10):758.