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Isolated Optic Neuropathy as the Presenting Sign of Neurosyphilis

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Isolated Optic Neuropathy as the Presenting Sign of Neurosyphilis

Abstract

Background: Detection and treatment of syphilitic ocular disease without a known history of syphilis is often difficult due to its varied presentations. Early diagnosis and treatment are the key to reducing risk of permanent vision loss, particularly with optic nerve and retinal manifestations.

Case Report: This case report describes a 44 year-old male who was diagnosed with neurosyphilis through his work-up for unilateral optic neuropathy.

Conclusion: This report illustrates the importance of including syphilis lab testing in the setting of optic nerve edema. Syphilis should be considered in any inflammatory ocular disease, especially in patients with atypical presentations and high-risk populations. As the incidence of syphilis continues to rise, it is important that eye care providers play a vital role in prompt diagnosis to decrease the risk of vision loss and limit further spread of the disease.

Keywords

Syphilis, Optic Neuropathy, Neurosyphilis

INTRODUCTION

The origin of syphilis has been greatly debated due to the stigma associated with it. Evidence of syphilis has been found in literature, art, and skeletal remains for hundreds of years, but the causative agent, a spirochete bacterium Treponema pallidum, was not discovered until 1905.[1] Incidence declined when effective treatment in the form of penicillin became available in the 1940s.[2] Unfortunately, the prevalence of syphilis is on the rise[3] and it is important that eye care providers identify the ocular manifestations early for prompt management to reduce potential ocular disease burden. As syphilis can mimic or masquerade many ocular conditions, it is important to recognize it as a differential, especially in cases that present with features atypical for more common etiologies.

CASE REPORT

A 44 year-old Hispanic male presented to clinic with complaints of sudden onset, painless decrease in the peripheral and central vision of his left eye. He reported that the defect was initially small, but it had slowly gotten much larger over the subsequent two weeks. He denied any headaches or associated symptoms. He denied any pain with eye movement but did describe a pulling sensation behind his eye.

His ocular history was unremarkable for trauma or surgery. He denied any family history of ocular conditions or blindness. His medical history was significant for sleep apnea, migraines, and erectile dysfunction (ED). His migraines were well controlled with sumatriptan. He reported compliance with his continuous positive airway pressure (CPAP) therapy for sleep apnea. He had been taking sildenafil for years but was unsure if he used it in the time preceding his vision loss. He was in a monogamous relationship with a female and denied any new partners within the past 6 months.

His uncorrected entering visual acuities were 20/40 in his right eye (OD) and 20/30 in his left eye (OS). With refraction his best corrected visual acuities measured 20/20 OD and 20/25 OS. His ocular motilities were normal without pain, restrictions, or diplopia. His pupils were round and reactive with a 2+ afferent pupillary defect (APD) in his left eye. His confrontation visual fields were full in each eye, although he reported fingers appeared dimmer with the left eye. His color vision was normal with Ishihara testing (14/14 OD and OS).

The anterior segment examination and his intraocular pressures were normal (14 mm Hg OD and 12 mm Hg OS) by Goldman applanation tonometry. The anterior chambers were deep and quiet. The dilated examination of his right eye was normal with 0.25 round optic nerve cupping without hemorrhages, pallor, or edema. The

dilated examination of his left eye revealed 2+ optic nerve edema without a discernable cup and a few adjacent small retinal nerve fiber layer hemorrhages. The vitreous, macula, vessels and peripheral exam were normal (Figure 1).

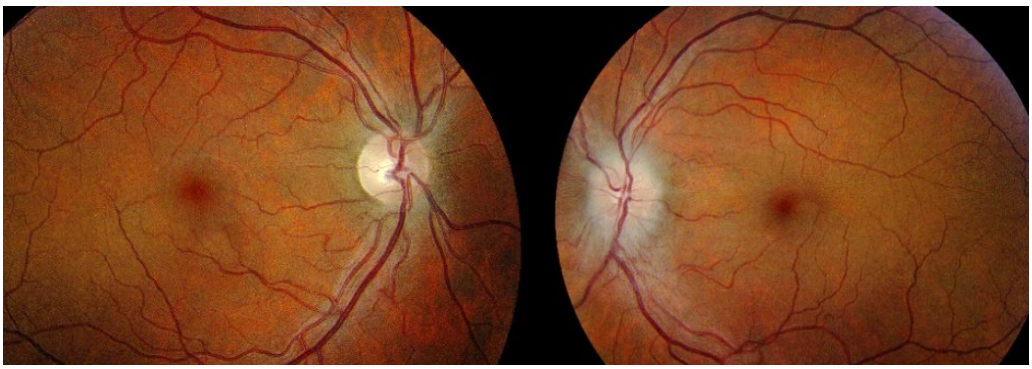

Figure 1: Fundus photographs taken at initial presentation

Humphrey visual field (HVF) 30-2 SITA Standard tests were performed on the day of presentation with a size III stimulus. The right eye test was reliable without significant defects. The left eye was also reliable and demonstrated superior greater than inferior arcuate defects with a relative inferior nasal central scotoma (Figure 2). Optical Coherence Tomography (OCT) was also performed on the same day with normal optic disc cube scan of the right eye and diffuse retinal nerve fiber layer thickening in the left eye (Figure 3).

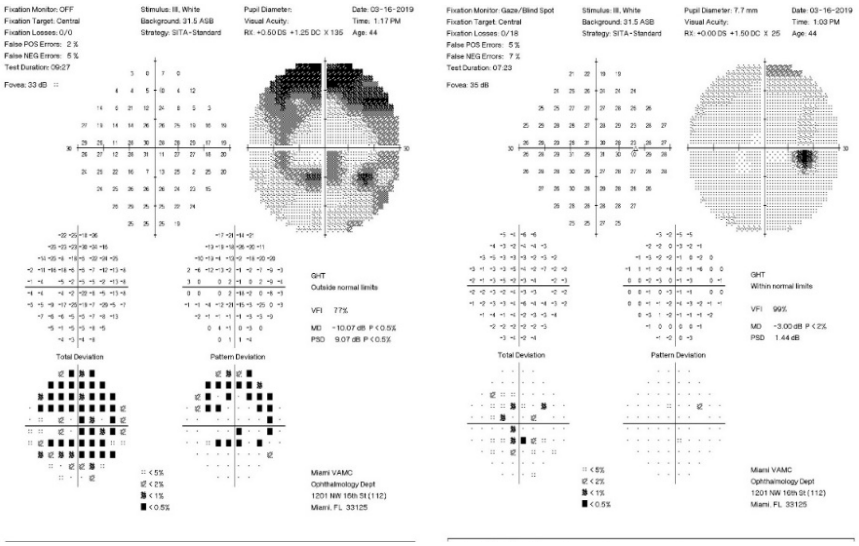

Figure 2: Humphrey visual field 30-2 testing on day of presentation

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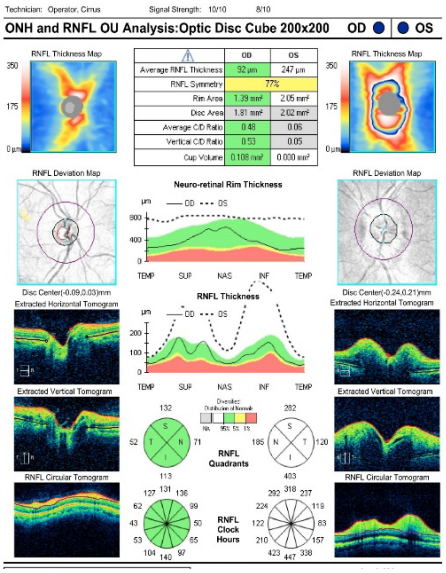


Figure 3: Optic Disc Cube OCT performed on day of presentation

Due to the patient's history of obstructive sleep apnea (OSA), sildenafil use, and lack of additional symptoms, non-arteritic anterior ischemic optic neuropathy (NAION) was the leading differential diagnosis. Additionally, atypical neuritis and Leber hereditary optic neuropathy (LHON) were considered due to his age.

Given that his presentation was not classic for NAION or optic neuritis, magnetic resonance imaging (MRI) of the brain with and without contrast along with thin cuts through the orbit and fat saturation was ordered and performed within 48 hours through facilitation of our emergency department. The patient also completed laboratory testing including complete blood count (CBC), rapid plasma reagin (RPR), fluorescent treponemal antibody absorption (FTA-ABS), quantiferon-plus, homocysteine and glucose. CRP and ESR was not run due to the patient's young age and lack of giant cell arteritis symptoms.

The MRI report indicated a normal brain MRI. Neuro-ophthalmology was available to review the imaging the same day it was done and agreed with the radiology report of unremarkable orbits and brain. The patient was started on a course of oral prednisone 40 mg for one week, with a taper of 10 mg per week.

The CBC showed elevated white blood cells and neutrophils but was otherwise normal. Lab results were positive for syphilis including FTA-ABS of 4+ and a reactive RPR with a titer of 1:32. HIV testing was ordered in response to the positive syphilis tests and came back negative. The remainder of his testing was normal.

He was referred to the infectious disease department immediately following the positive syphilis labs results. He underwent lumbar puncture with cerebrospinal fluid (CSF) analysis. His opening pressure was not measured given the unilaterality of findings. The fluid was nonreactive for venereal disease research laboratory test (VDRL). As the CSF-VDRL is highly specific but not sensitive, CSF analysis of cell count and protein was evaluated at the same time. His white blood cells were elevated (10/µL) and his total protein was 58mg/dL. This along with his ocular findings and serologic testing, was considered diagnostic for neurosyphilis and he was admitted for treatment with IV penicillin G of 3 million units every four hours for 14 days. Counseling was provided regarding notification of at-risk partners.

He was followed in the eye clinic three days after systemic treatment completion with improvement in subjective symptoms and clinical appearance. His optic nerve edema had markedly improved. He had started to develop optic atrophy with nerve pallor evident on dilated exam and RNFL thinning on OCT (Figures 4 and 5). The RNFL hemorrhages had resolved. Despite reporting that his subjective vision had improved, he had stable BCVA of 20/25 OS. A taper of his prednisone was initiated.

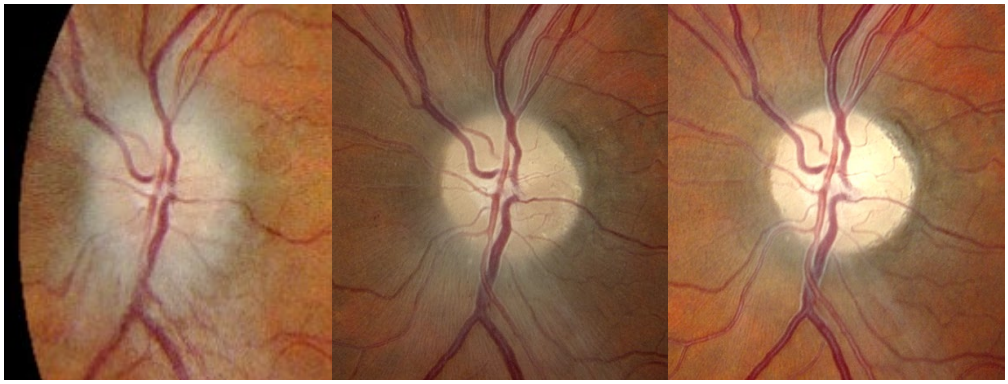


Figure 4: Fundus photos the day of presentation, 3 days post treatment, and 6 months post treatment.

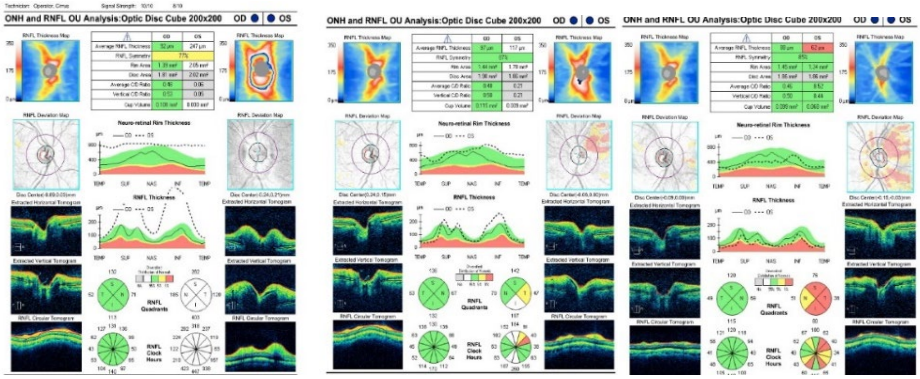
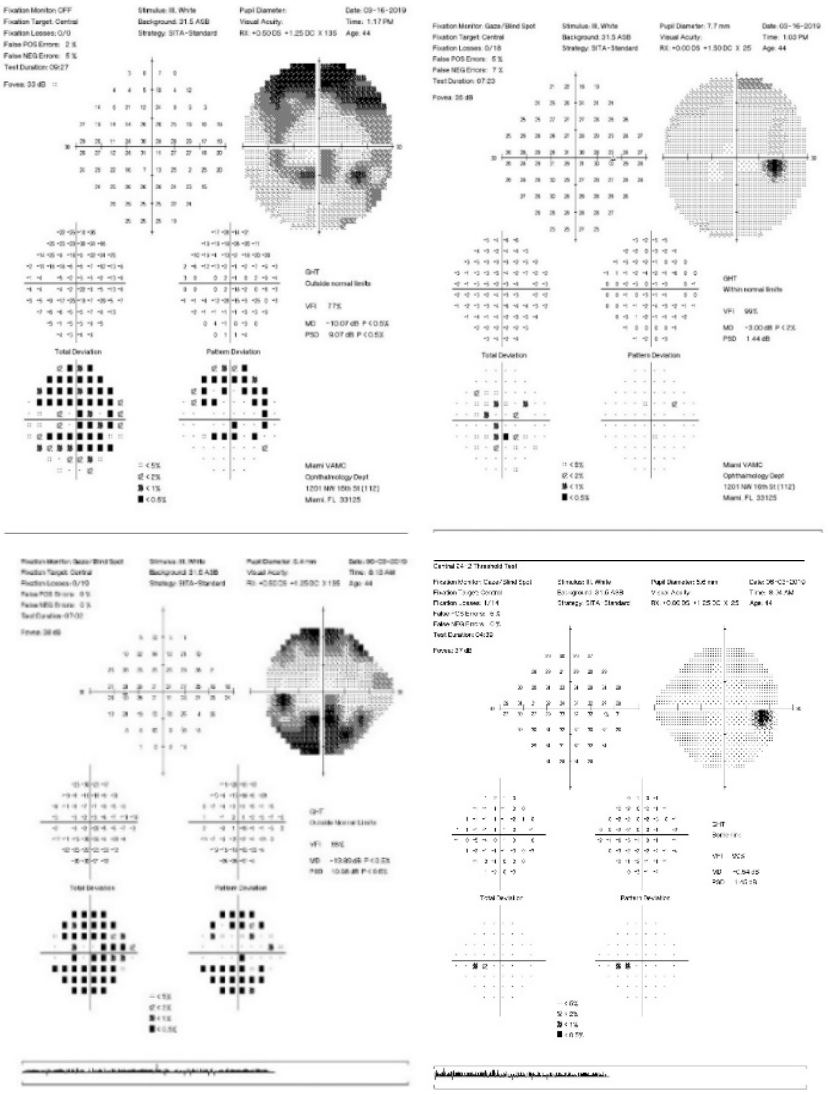


Figure 5: OCT Optic Disc Cube at day of presentation, 3 days post treatment and 6 months post treatment.

He was followed at 1, 3, 6, and 9 months post treatment. His optic nerve edema was clinically resolved at one-month post treatment. His best corrected acuity remained stable at 20/25 in the left eye at all follow-up exams. He had progressive optic atrophy and a correlating diffuse RNFL thinning on OCT disc cube (see Figures 4 and 5). His HVF testing showed persistent defects with possible inferior arcuate progression at his 3-month testing which was stable at 9 months. The inferior nasal central scotoma decreased from 11dB at presentation to 8dB at 9 months (see Figure 6).



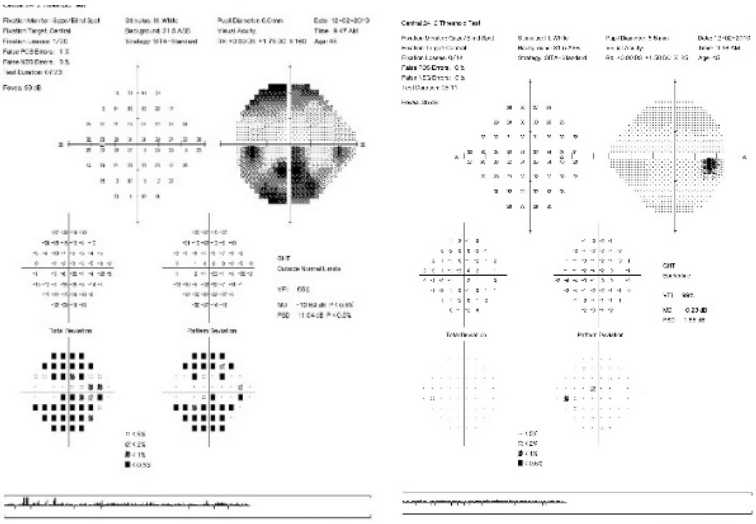


Figure 6: HVF testing performed at day of presentation, 3 months post treatment and 9 months post treatment.

RPR lab titers decreased from 1:32 down to 1:2 at 6 months and remained stable at his 9-month testing. The infectious disease department recommended repeating the titers every 3 months for one year, and then every 6 months until the titer results are negative.

DISCUSSION

The primary differential diagnoses were NAION and optic neuritis. Optic neuritis was ruled out as he did not have pain with eye movement, his MRI was normal, and his visual field defect did not improve with time.

NAION was strongly considered given his possible sildenafil use preceding symptoms, nerve anatomy, and sleep apnea. Although possible, this patient's presentation would have been atypical. He was younger than the usual age for NAION as patients under 45 account for only 11% of cases.[4] His visual field defect was more insidious in nature with a sudden onset of a small defect and slow progression over two weeks per his history.

The classic presentation of NAION has traditionally been a sudden onset of an inferior altitudinal defect upon waking. Recent studies have concluded that a combination of relative inferior altitudinal with an absolute inferior nasal defect is most common.[5] These defects usually remain stable or improve but may continue to deteriorate within 6 months of onset in 15-19% of cases.[6] As posterior ciliary artery anatomy varies tremendously,[7] the presence of other field defects does not

rule out NAION, but other etiologies should be considered when the presentation is not classic.

Sleep apnea has been found to be a significant risk factor for NAION. The patient in this case had sleep apnea but reported that he was compliant with CPAP treatment. Stein et al. found that adjusted hazard of NAION was not significantly different in those on treatment compared to those without sleep apnea.[8] This does not rule out an NAION, but compliance with treatment may negate the apnea risk factor.

Given the potential mechanism of enhancing the vasodilation effect of nitric oxide and subsequent hypotension, sildenafil was also considered as a potential risk factor for NAION. The research regarding association between phosphodiesterase type 5 inhibitor (PDE5-Is) use and NAION has not provided conclusive evidence, with some studies reporting no association and others reporting a significant increased risk after use. [9-12] A recent systematic review with meta-analysis by Bing in 2018 concluded that there was no association between NAION and PDE5-Is with use within a one-month or one-year period.[9]

The patient reviewed in this case report had a sudden but more insidious course with both superior and inferior field defects. He was younger than the typical age for NAION. He did not have hypertension or diabetes. He did have sleep apnea but was compliant with CPAP therapy. He had a history of sildenafil use, but to date conclusive evidence of associated risk is lacking. Given all these factors, his presentation was atypical for NAION, and other etiologies were appropriately considered and tested. As he had positive serologic and CSF testing as well as dramatic improvement in his optic nerve edema immediately post treatment with IV penicillin, his ocular findings were most likely secondary to neurosyphilis. The referral to the infectious disease department for his confirmatory CSF testing was an important step in expediting his treatment with penicillin.

Penicillin was introduced as an effective curative treatment for syphilis in the 1940s, however the rates of syphilis infections began to increase again in developed countries around the year 2000.[2-3] As the primary mode of transmission is sexual contact, the rise has been attributed to an increase in unsafe sex practices associated with improved HIV treatment and prophylaxis. In the United States, the CDC reports that rates have increased from 19.9 to 35.3 per 100,000 people from the year 2014 to 2018.[13] As the prevalence of syphilis continues to rise, and its ocular disease burden along with it, eye care providers have a key role in early identification for prompt management.

Ocular involvement with syphilis has been reported in 0.6-25% of systemic syphilis infections.[14-15] The most common presenting symptom was blurred vision

in either one (38-47%) or both eyes (53-62%)[15-16] with floaters and visual field defects also reported.[17] Ocular manifestations vary but the most common are uveitis, optic neuropathy, and retinitis. [14-16, 18]

Uveitis most often presents as posterior but may be anterior, intermediate or panuveitis.[19] The inflammation is more often non-granulomatous and it can occur in isolation or involve other structures.[20] As syphilitic uveitis can vary so greatly in presentation, syphilis labs are recommended in all uveitis workups as they have been found to be the etiology for up to 2% of cases.[21]

Like uveitis, the retinal presentations of syphilis also vary tremendously. It can affect any area of the retina and can be either necrotizing or non-necrotizing. Placoid lesions have been reported that tend to be found in the posterior pole. Although syphilis may mimic many retinal conditions, it tends to progress more slowly than many differentials and responds well to IV penicillin.[22-24]

Optic nerve involvement can occur as optic nerve edema, papilledema, peri-neuritis, retrobulbar optic neuritis or optic atrophy. There are no specific diagnostic features related to optic nerve involvement, therefore syphilis should be considered in all neuropathies, particularly atypical presentations. Recent studies by Klein et al. indicate optic nerve involvement may be more common in recently diagnosed syphilis patients than originally thought, occurring in 78% of patients with ocular syphilis. Isolated optic disc edema was present in 44% of ocular syphilis and occurred bilaterally in nearly 30% of these cases.[14]

Diagnosis is made with serologic testing. Typically, non-treponemal (VDRL or RPR) are used first with treponemal tests (FTA-ABS or TP-PA) used to confirm a positive result. The diagnosis of neurosyphilis can be more difficult. While CSF-VDRL is considered diagnostic due to its high specificity, 50% of cases of neurosyphilis have a negative CSF-VDRL when clinical suspicion is high.[25] When VDRL is negative, other testing including CSF cell count and/or protein should be considered in persons with neurologic signs or symptoms.[26] In patients who do not have HIV and have negative CSF-VDRL, a CSF lymphocyte count above 5 cells/μL or protein concentration above 45 mg/dL is considered consistent with neurosyphilis. In some cases, FTA-ABS testing of CSF may be helpful as it is highly sensitive but less specific.[27] As HIV can cause elevated CSF labs with both protein and pleocytosis it is important to be aware of HIV status when interpreting results and other CSF tests may be helpful for diagnosis.[28] Ocular syphilis is treated as neurosyphilis even if CSF testing is normal.

Penicillin G remains the preferred treatment in all stages of syphilis, with the form used, dose, and length of treatment depending on the manifestation of the disease. Aqueous crystalline penicillin G may be administered by IV as 3-4 million units

every four hours or 24 million units daily as continuous infusion for 10-14 days. This is preferred for neurosyphilis due to better penetration into the CSF than intramuscular treatments.[29] Patients should be monitored closely to ensure they respond to treatment. A reaction can occur within the first 24 hours of initial treatment that has been labeled the Jarisch-Herxheimer reaction in which fever, headache, myalgias, hypotension and rashes may develop. This reaction is not fully understood but thought to be a result of an immune response precipitated by killed organisms and is not an indication to stop treatment.[30] Use of systemic steroids or TNF-α antibodies in a patient with neuro-ophthalmic manifestations when starting penicillin treatment may by protective.[30]

As this patient's presentation did not fit classic disease patterns, same days labs were ordered, including an infectious panel and urgent MRI. The prompt referral to the infectious disease department was critical in getting the lumbar puncture with CSF testing as well as his treatment expedited. Our patient had no adverse reactions to treatment with IV penicillin G. Although he reported considerable subjective improvement with treatment his visual field defect persisted. This was most likely due to lag in seeking care for symptoms. Fortunately, prompt testing and work-up allowed for no further delay in treatment.

The role of steroid use has not been well defined for either NAION or neurosyphilis, but there has been evidence to support its use in both conditions. Hayreh and Zimmerman published a large study that included 613 NAION patients that concluded significant improvement in acuity and visual field with the use of systemic corticosteroids.[31] Meta-analysis of subsequent smaller trials did not show significant improvement leading to questioning of use given risk profile.[32] As this is the case, each patient's risks of treatment should be considered independently. The patient described in this case was young and did not have any vascular conditions. It was determined that the potential benefits of steroid use outweighed the risk. Once the syphilis labs were received, he was kept on the steroids as they may provide protection against Jarisch-Herxheimer reactions as addressed above.

It is important to remember that there can be considerable social implications with the diagnosis of syphilis that may make patients hesitant to disclose a complete history. Ocular manifestations can occur at any stage of syphilis which can also make the infectious timeline unclear. This patient may have had a sub-clinical infection from a non-disclosed exposure or a remote nondisclosed inadequately treated infection. Involvement of practitioners who are experienced in the treatment of sexually transmitted disease was beneficial in obtaining testing of the cerebrospinal fluid, facilitating treatment, navigating the mandatory reporting, and handling the nuances of counseling to ensure that at-risk partners were also evaluated and treated.

CONCLUSION

Recognizing syphilis as a differential and ordering appropriate labs as part of the initial work-up were key to early detection and initiation of proper treatment. Syphilis should be considered in any inflammatory ocular disease, especially in patients with atypical presentations and high-risk populations such as HIV positive individuals. Infectious disease and primary care should be involved in the treatment and management of these patients. As the incidence of syphilis continues to rise, it is important that eye care providers play a vital role in prompt diagnosis to decrease the risk of vision loss and limit further spread of the disease.

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