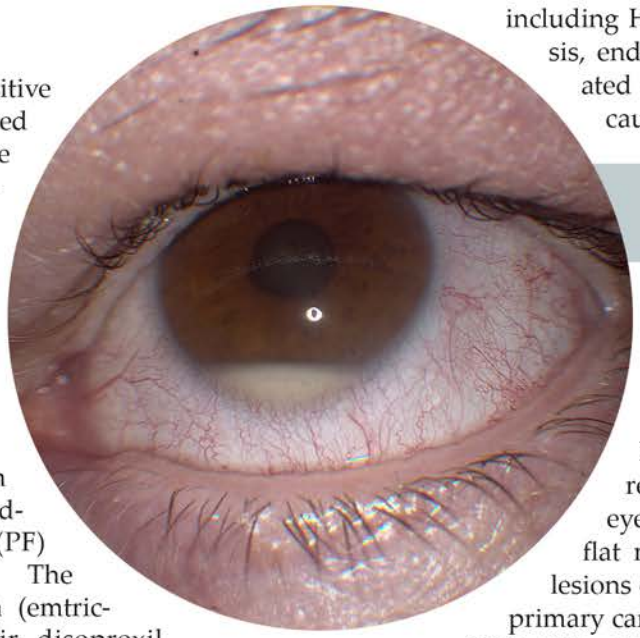
A 51-Year-Old Male Referred for Possible Endogenous Endophthalmitis

Vincent Y. Ho MD; Bradley T. Smith, MD

Introduction:

A 51 year-old HIV positive white male was referred to The Retina Institute for evaluation of possible endogenous endophthalmitis in his left eye. The patient reported pain, photophobia, redness, and tearing for several days. An outside ophthalmologist started him on ciprofloxacin and prednisolone acetate (PF) drops every hour. The patient took Truvada (emtricitabine and tenofovir disoproxil fumarate) for HIV as well as medications for hypertension and depression. He has a single partner and reports a 32 pack year history of smoking. Review of systems was negative for recent illness, fever,chills, night sweats, joint pain, chronic cough, skin lesions, recent travel/cat/tick/tuberculosis exposure.



Visual acuity measured 20/20 in right eye and 20/50 in the left eye. There was no relative afferent pupillary defect and the intraocular pressure was normal. Anterior segment exam of the right eye was unremarkable but the left eye exhibited 4+ white blood cells, 1.6 mm hypopyon, and posterior synechiae, Figure 1.

Dilated fundus exam was normal in the right eye. Anterior segment inflammation precluded a view of the left fundus but an ultrasound exhibited clear vitreous and attached retina. The patient was instructed to continue the PF hourly, start cyclopentolate 1% BID, and discontinue ciprofloxacin drops.

Differential Diagnosis:

The differential diagnosis for hypopyon uveitis is broad and includes inflammatory/infectious etiologies including HLA-B27, rheumatoid arthritis, sarcoidosis, endophthalmitis, and toxoplasmosis associated uveitis as well as medication-induced causes (cidofovir and rifabutin).

Figure 1: Anterior segment photograph OS exhibiting hypopyon and posterior synechiae

Clinical Course:

At 2 weeks follow-up, the vision was subjectively better at 20/50+, the hypopyon resolved, and 2-3+ AC cell remained. Dilated fundus exam of the left eye exhibited 1-2+ vitreous cell, sharp nerve, flat macula and attached periphery without lesions or vasculitis. A systemic work-up by his primary care physician (CBC, CMP, ESR, ACE, CXR, RPR, FTA-ABS, Toxoplasmosis IgM/IgG, HLA B27, ANCA, RF, PPD) was negative except for positive rheumatoid factor (RF) and mildly elevated liver enzymes. He was continued on PF every 2 hours and cyclopentolate 1% BID. Four weeks after presentation, the exam was stable and visual acuity improved to 20/25. Despite a positive RF, rheumatology evaluated the patient and did not find any evidence of autoimmune disease (cyclic citrullinated peptide was negative).

Five weeks after presentation, the patient reported increased floaters with 1+ AC cell/flare, 2+ vitreous cells/haze, and the OCT exhibited superficial hyperreflective retinal deposits, Figure 2. The patient was not compliant with his PF regimen so a sub-tenon Kenalog injection was given. Nine weeks after presentation, his vision was 20/40 and his vitreous cell/haze was slightly worse. Although there were no signs of retinal necrosis, a viral etiology was considered and the patient opted for empiric treatment with Valtrex 1 gram PO TID rather than vitreous tap/injection of antiviral medication. At 2.5 months after presentation, there was no interval improvement in the vitritis so an Ozurdex implant was injected, Figure 3.

Around 4 months after presentation, the patient presented to a local emergency department with flu-like symptoms. His liver enzymes (ALT, AST, ALP) were more elevated and interestingly his repeat syphilis testing turned out to be positive (RPR 1:64 titer and treponema pallidum antibody). He was admitted to the infectious disease service and started on intravenous penicillin (PCN) therapy. His visual acuity improved to 20/25+ with stable vitreous cell/haze and the OCT superficial retinal deposits resolved, Figure 4.

At the completion of 2 weeks of IV PCN therapy and 1 out of 2 weekly PCN intramuscular injections, the patient developed an abrupt uveitis flare. His vision fell to 20/150 vision and he had 3+ AC WBCs, small hypopyon, 3+ vitreous haze, and inferior snowballs, Figure 5. The patient self-medicated with hourly PF which improved his symptoms so he was told to continue this until his 2 week follow up visit.

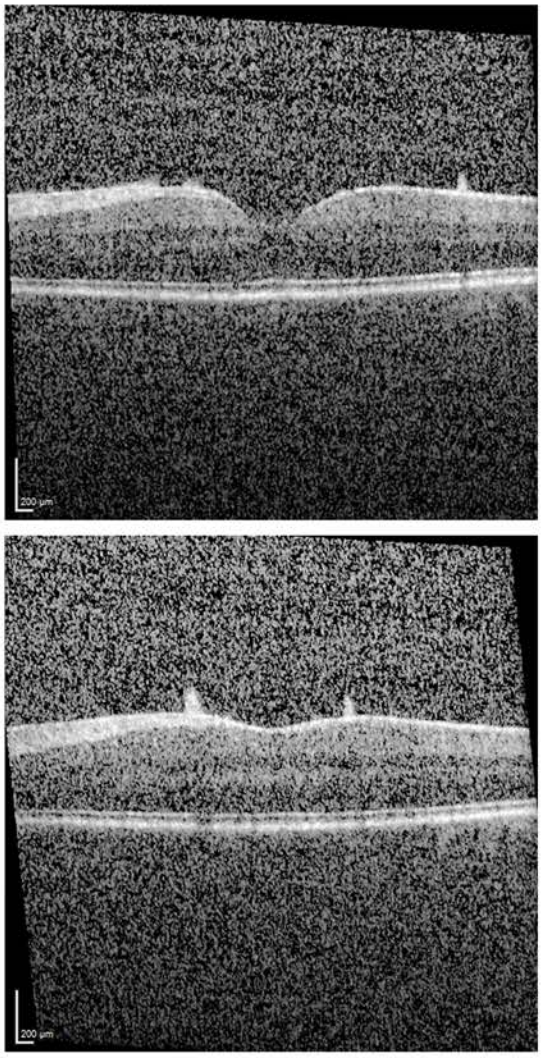


Figure 2: OCT imaging demonstrating vitritis and superficial hyperreflective deposits

Discussion:

This was an interesting case of ocular syphilis with anterior/intermediate uveitis with hypopyon formation. Infection with the spirochete Treponema pallidum most commonly occurs with sexual transmission but direct contact with an active lesion or spread via transfusion can occur. In recent years, changing socioeconomic factors and increases in high-risk sexual behavior, infection with HIV, and antibiotic resistance have all contributed to resurgence of the disease. Worldwide, there are an estimated 12 million new cases annually, with 90% found in developing nations.

Ocular and Systemic Findings:

While uncommon, ocular manifestations occur in 2.5-5% of patients during or shortly after the secondary stage (roughly 2–6 months after initial infection). The most common ocular finding is uveitis manifesting as granulomatous or nongranulomatous iritis/iridocyclitis, episcleral/scleral inflammation, interstitial keratitis, vitritis, vasculitis, papillitis, periphlebitis, exudative RD, necrotizing retinitis, and even subretinal neovascularization. Acute syphilitic posterior placoid chorioretinitis can also occur exhibiting yellow or gray placoid lesions with atrophic centers. These lesions show early hypofluorescence and late staining with a distinctive "leopard spot" hypofluorescence on FA. An Argyll Robertson pupil can be seen in late syphilis or neurosyphilis (anisocoria and light-near dissociation)[1].

The primary stage of syphilis includes chancre formation at the location where syphilis enters the body. This last 3-6 weeks and heals regardless of treatment. The secondary stage can exhibit as skin rashes and/or sores on the body, commonly on the palms of hands and plantar aspects of the feet. Other symptoms include fever, lymphadenopathy, sore throat, patchy hair loss, headaches, weight loss, myalgias, and fatigue. The latent stage of syphilis begins when all early symptoms disappear. Most people with untreated syphilis do not develop tertiary (late) stage syphilis. However, late stages can occur as late as 30 years after initial infection. Symptoms of the late stage of syphilis include gummata inside the body or on the skin as well as stroke-like symptoms such as paresis, tabes dorsalis, cranial nerve palsies, dementia, numbness, Horner syndrome, internuclear ophthalmoplegia, and visual field defects. Internal organ damage including the liver and cardiovascular system can occur which can lead to death.

Testing/Diagnosis:

Diagnosing clinicians are responsible for reporting cases to their state Department of Health. Sexual partners of the infected individual also need to be evaluated. Visualization of the organism in tissue or lesion exudates via dark-field microscopy with immunofluorescent staining is considered the gold standard and is the quickest and most direct approach for establishing a diagnosis. However, this patient's test was sent to Utah for testing and the availability of such facilities can limit its utility in clinical practice. These tests are highly

specific but not very sensitive for widespread detection of infection like serologic tests with nontreponemal and treponemal tests.

Nontreponemal tests detect the antibody to cardiolipin cholesterol antigen such as VDRL and RPR are best suited for general screening in a population with a low prevalence of syphilis, as well as for monitoring treatment efficacy as the titers decrease with appropriate therapy. Treponemal tests, such as FTA-ABS and MHA-TP, generally remain positive for life and are just as sensitive and more specific than nontreponemal tests. However, they are more expensive and a proportionate increase in false positives can occur if they are applied to a low-risk population. Thus, they may be used initially in patients who have a high probability of infection.

The use of a singular type of serologic test can sometimes be insufficient for diagnosis, as each has its limitations, specifically the false positive test results in patients without syphilis. False-positive test results may be associated with certain infections (e.g., Lyme disease, leptospirosis, malaria) and medical conditions (e.g., autoimmune disorders, intravenous drug use, pregnancy). Many laboratories will obtain a treponemal test only if a nontreponemal test is positive but obtaining both types of tests may be helpful. For those individuals with a positive treponemal screening test, a standard nontreponemal test with titer should be ordered to guide therapeutic decisions. If the nontreponemal test is negative, a different treponemal study should be ordered to confirm the results of the initial test. If the second treponemal test is positive, treatment should be initiated.

Newer testing is sparsely available and includes polymerase chain reaction (PCR) assays and rapid specific treponemal tests. PCR assays should be conducted on frozen specimens (shipped according to the laboratory specifications). The rapid tests, which require as little as 10–50 microliter samples, are considered to be equivalent to the older specific treponemal antibody tests. Availability of such tests is limited.

Consideration of cerebral spinal fluid analysis is warranted in patients with syphilitic uveitis, tertiary syphilis, or neurosyphilis. CSF of infected individuals may exhibit leukocytosis, high protein concentration, and CSF VDRL.

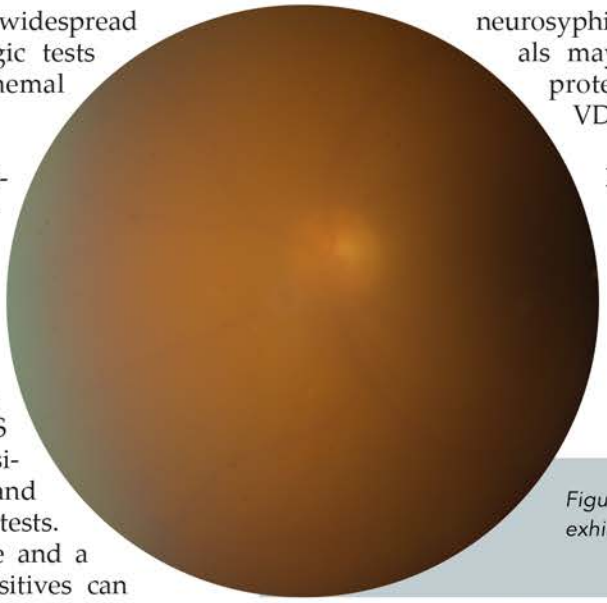


Figure 3: Color fundus photograph exhibiting 2-3+ vitritis, sharp nerve and normal vasculature.

False Negative Tests:

False negative syphilis testing has been reported in literature. For HIV-infected individuals, serologic tests are often accurate and reliable for diagnosis as well as following the response to therapy. However, insufficient antibody production to bacterial proteins and overall lack of immunoreactivity can lead to false negatives. In addition, the prozone phenomenon, especially with the RPR test, may hinder the prompt diagnosis and management of syphilis. The prozone phenomenon generally refers to cases where high antibody titers interfere with the antigen-antibody lattice network formation that is necessary for visualizing a positive flocculation test in undiluted samples. Therefore, in highly suspicious patients, the laboratories should be instructed to test diluted samples. Reports have shown that the prozone phenomenon can occur during any clinical phase (mostly during primary and secondary syphilis) and has a low prevalence (0.83%). Pregnancy and neurosyphilis were associated with the prozone phenomenon while sex, age, and prior treatment were not[2].

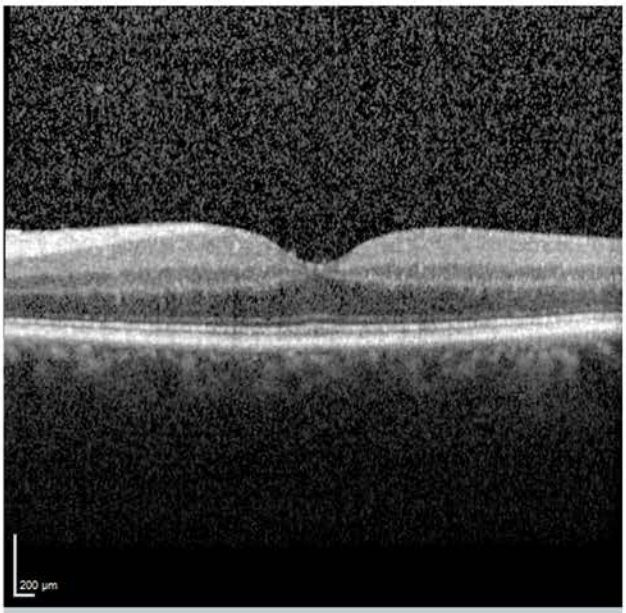
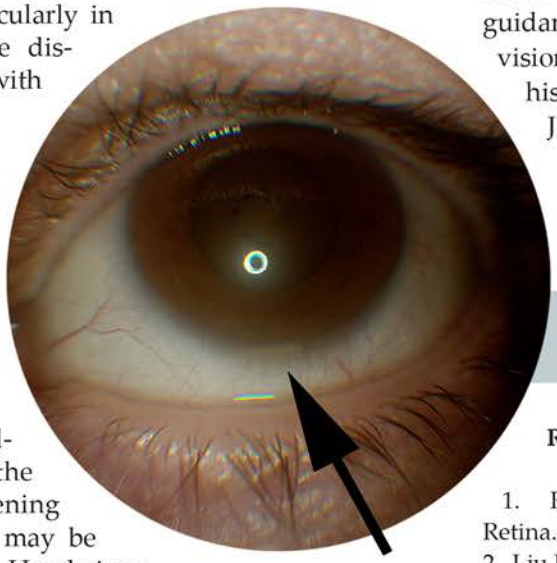


Figure 4: OCT exhibiting decreased vitritis and resolution of superficial retinal deposits

Treatment:

It is recommended that ophthalmologists treat patients in consultation with an infectious disease specialist. PCN G is the preferred treatment for all stages of syphilis. The dose, route of administration (IM or IV), and duration of therapy are determined by the

stage and clinical findings. For patients with a penicillin allergy, alternative antibiotics may be used. However, these other medications are not as effective so skin testing and desensitization is recommended, particularly in patients with severe disease or co-infected with HIV.



Jarisch-Herxheimer Reaction (JHR)

Our patient experienced an acute uveitis flare after initiation of PCN therapy. While this could represent inadequate treatment, the peridoxical worsening seen in our patient may be the result of a Jarisch-Herxheimer reaction which has also been described after treatment of tuberculosis, Whipple's disease, leptospirosis, and Lyme disease[3-7]. Proposed mechanisms of JHR include endotoxin release following death of inciting organisms, delayed hypersensitivity, or decreased suppressor mechanisms. Systemic manifestations can also occur which include fever, chills, headache, confusion, pruritus, and rigors. Steroids are the mainstay for treatment of JHR.

Conclusion:

Syphilis untreated can lead to severe ocular and systemic disease. This patient exhibited tertiary syphilis with syphilitic uveitis and liver damage. Repeat syphilis testing confirmed the diagnosis but highly suspicious individuals should have diluted samples tested by the laboratory to decrease the chance of false negatives. Prompt treatment (IV and IM PCN) under the guidance of an infectious disease initially improved his vision but a possible rare case of JHR may have caused his uveitis to flare-up.This would be the first case of JHR treated with an intravitreal Ozurdex implant. Future follow-up visits will elucidate adequacy of local/systemic therapy and overall visual recovery.

Figure 5: Anterior segment photograph exhibiting recurrence of hypopyon

References:

1. Ryan, SJ. Spirochetal Infections: Syphilitic Uveitis. Retina. 5th Edition. 1486-9.
2. Liu LL, Lin LR, Tong ML. Incidence and risk factors for the prozone phenomenon in serologic testing for syphilis in a large cohort. Clin Infect Dis. 2014 Aug 1;59(3):384-9
3. Fathilah J1, Choo MM. The Jarisch-Herxheimer reaction in ocular syphilis. Med J Malaysia. 2003 Aug;58(3): 437-9.
4. Neunhoffer H, Gold A, Hoerauf H, et al. Isolated ocular Jarisch-Herxheimer reaction after initiating tuberculostatic therapy in a child. Int Ophthalmol. 2014 Jun;34(3):675-77.
5. Cheung CM, Chee SP. Jarisch-Herxheimer reaction: paradoxical worsening of tuberculosis chorioretinitis following initiation of antituberculous therapy. Eye (Lond). 2009 Jun;23(6): 1472.
6. Playford RJ, Schulenburg E, Herrington CS, et al. Whipple's disease complicated by a retinal Jarisch-Herxheimer reaction: a case report. Gut. 1992 Jan;33(1):132-4
7. Karma A, Mikkila H. Ocular manifestations and treatment of Lyme disease. Curr Opin Ophthalmol 1996; 7: 7–12.

Spring Retina Update

Mark Your Calendar:

SPRING RETINA UPDATE
May 14, 2016
Drury Inn; 8700 Eager Road
St. Louis, MO 63144

Contact Kelly McKittrick for more info or to register:
kelly.mckittrick@rc-stl.com
314-367-1181 x-2157