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Acute Syphilitic Posterior Placoid Chorioretinitis

The prevalence of sexually transmitted infections (STIs) has been steadily increasing in the United States over the past two decades. Not only is the cost of healthcare high, the consequences of untreated STIs can be devastating. It is estimated that in 2018 alone, 20% of the US population had an STI at any given day during that year, giving prevalence of about 68 million cases. The direct yearly cost to the economy was estimated at 16 billion. While it is uncommon for STIs to affect the eyes, when they do, it might be an indication of a potentially sight- or life-threatening condition.

Acquired syphilis is an STI caused by the spirochete bacterium Treponema pallidum. Although the disease is known to be sexually transmitted since the Middle Ages, it wasn't until 1905 that Schaudinn and Hoffman discovered the etiologic agent of syphilis. They isolated the spirochetal bacterium from various syphilis lesions. Shortly after, several tests to identify T. *pallidum* became available, making the detection of syphilis somehow more precise. Among these tests, the most used were the direct visualization of the bacteria with dark-field microscopy and the *Treponema pallidum* immobilization test, a serologic test to detect the spirochete in blood. These tests confirmed the diagnosis and allowed monitoring for response to different available treatments. Until the early 1900s, the treatment for syphilis consisted in medicinal herbs with purgative effects and mercury and other bismuth salts that usually resulted in no significant improvement or cure. In 1908, Paul Ehrlich discovered *arsphenamine*, a compound with antibiotic properties that became the gold standard therapy for syphilis until 1943, when penicillin became the mainstay therapy. Penicillin, the antibiotic discovered by Alexander Fleming in 1928, has been the treatment of choice since then.

The natural history of acquired syphilis has four defined stages of infection. The primary stage where a single or multiple skin sores, denominated chancres, occurs in the site of inoculation (e.g., genitals, mouth). During the secondary stage, a maculopapular rash or mucocutaneous lesions develop. Untreated, the bacteria then enter a latent stage for years, to later develop tertiary stage. During this last stage multiple organs and systems may get affected and serious life-threatening conditions can develop. Syphilis can affect the central nervous system, including the eyes, at any stage of the disease, but it usually does so during the secondary stage. It is important to recognize that ocular involvement in syphilis is considered and treated as neurosyphilis. This means that patients will need a referral to infectious disease specialist for consideration of a lumbar puncture and cerebrospinal fluid analysis once the syphilitic eye disease has been suspected.

Syphilis can affect any part of the visual system and it can imitate other ocular inflammatory disorders making the diagnosis difficult and sometimes frustrating. The ability to mimic other ocular disorders earned it the nickname the "Great Imitator". Over the past 2 decades, there has been a resurgence of syphilis with rising numbers in North America. It has been estimated that the prevalence of syphilis in patients referred for uveitis evaluation to tertiary centers ranges between 1 - 8%. Therefore, syphilis must be ruled out in all cases of unexplained anterior or posterior ocular inflammation. However, the posterior segment is the most commonly affected site.

In the posterior segment, ocular syphilis can manifest as vitritis, multifocal chorioretinitis, necrotizing retinitis, vasculitis, optic neuritis, and as serous retinal detachments. One of the distinct manifestations of ocular syphilis is acute posterior placoid chorioretinitis (ASPPC). In this condition, patients develop one or more placoid, yellowish lesions in the deep retina and choroid that can severely affect visual acuity (Figure 1). Patients may complain of blurred vision, flashes, floaters and pain, but symptoms may vary between patients. The overlap of the symptoms of patients with ASPPC with other more common pathologies such as posterior vitreous detachment, vitreous syneresis, and ocular migraines can make the diagnosis challenging. The physiopathology of ASPCC remains unknown, but the site of primary inflammation is believed to be at the level

of the choriocapillaris-retinal pigment epithelium complex. The placoid lesions might be difficult to catch on fundus examination. Especially early in the disease course, fundus autofluorescence can be extremely useful in identifying subclinical areas of choroidal-retinal pigment epithelium inflammation. Typically, there is an increase in autofluorescence in the area corresponding to the inflammatory placoid lesions, and with
ASPPC, in particular, there are focal intensely hyperautofluorescent spots within the placoid area (Figure 2).

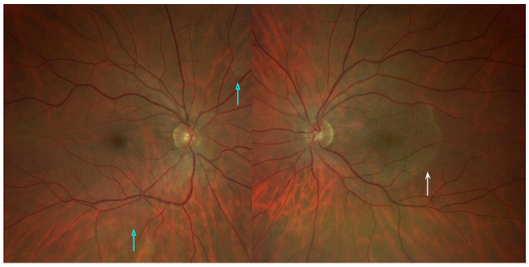

Figure 1:
Wide-field fundus photograph of a 36 year old male with recent onset of intermittent flashes and floaters in the right eye. (A) Right eye: visual acuity 20/20. Note the subtle deep yellow small plaques marked by the blue arrows. (B) Left eye: visual acuity count fingers. Note the large yellow placoid infiltrate affecting the whole macular area, edge marked by the white arrow.

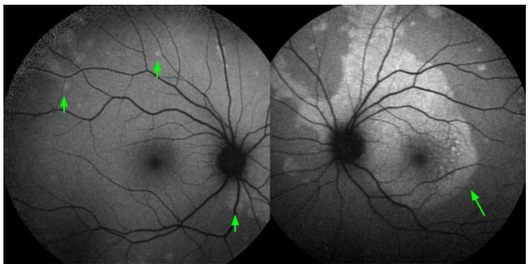

Figure 2:
Fundus autofluorescence photographs of the same patient. The areas of hyperautofluorescence correspond to areas of choroidal-retinal pigment epithelium inflammation. Note the area is more extensive than noted on fundus examination. Note the multiple foci of intensely hyperautofluorescent spots within the placoid area in the left eye.

The OCT findings also suggest a disruption of the ellipsoid zone (inner/outer segment junction), thickening of the RPE with formation of nodules and hyperreflectivity of the choroid (Figure 3). Subretinal fluid has been described in some cases. Angiographically, there is early hypo or hyperfluorescence with scattered hypofluorescent spots referred to as leopard spotting. Mid and late phases show progressive hyperfluorescence. (Figure 4) ICG angiography usually shows early and late hypofluorescent spots.

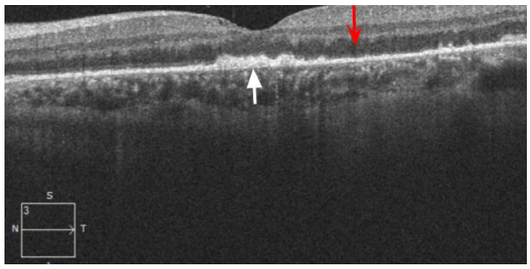

Figure 3:
OCT of the left eye showing a disruption of the ellipsoid zone (inner/outer segment junction) and nodular thickening of the RPE typically seen in patients with ASPCC.

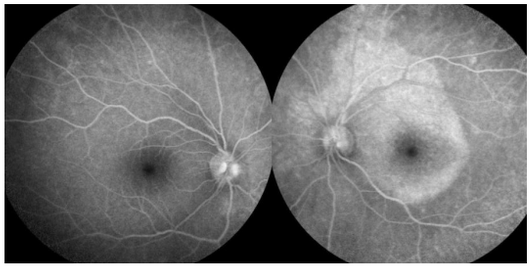

Figure 4:
Fluorescein angiography in the mid to late phases showing an extensive area of hyperfluorescence corresponding to the area of inflammation seen as placoid lesions.

One of the main diagnostic challenges of ASPPC is that it resembles the clinical features also seen in some of the white dot syndromes, especially the placoid type. For instance, acute posterior multifocal placoid pigment epitheliopathy (APMPPE), persistent placoid retinopathy and relentless placoid chorioretinitis are idiopathic ocular inflammatory disorders that also present with similar clinical and imaging findings. It is therefore important to always rule out infectious etiologies in ocular inflammatory disorders. HIV, treponemal (FTA-ABS) and nontreponemal (RPR or VDRL) tests, PPD or Quantiferon Gold are critical tests in the work up of patients with uveitis.

In ASPPC, it is unclear if the inflammatory process is a direct invasion of the tissues by the T. pallidum or an immune-mediated hypersensitivity reaction. Co-infection with HIV is high, and although the treatment does not change whether a patient is HIV positive or negative, all patients with ASPPC must be tested for HIV.

The natural history of ASPPC is that of worsening without treatment, and although there has been one case of spontaneous resolution reported in the literature, most authors agree on treatment with penicillin early on to prevent permanent vision loss. More importantly, ocular syphilis might be indicative of neurosyphilis, a life-threatening infection that requires immediate treatment.

As per the CDC guidelines, ocular syphilis must be treated with intravenous penicillin G for 10 -14 days. This usually results in significant improvement of both the lesions and symptoms. (Figure 5 - 7).

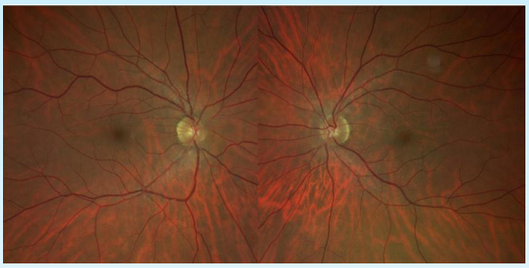

Figure 5:
Wide-field fundus photograph of the same patient showing total resolution of placoid lesions in both eyes post treatment with intravenous penicillin G. Visual acuity 20/25 both eyes.

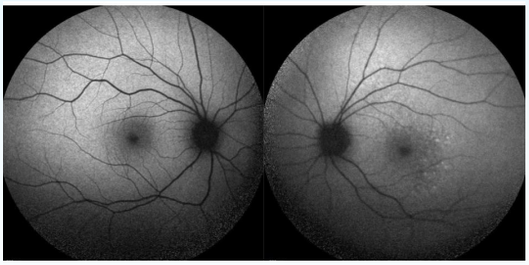

Figure 6:
Fundus autofluorescence photos showing total resolution of lesions post treatment with IV penicillin G. Note some residual hyperautofluorescent spots in the left eye.

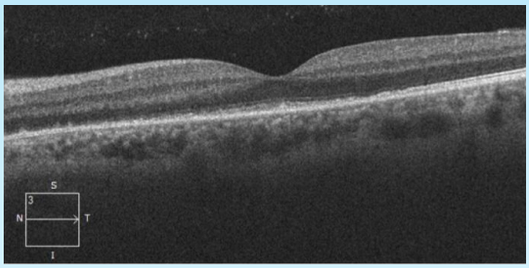

Figure 7:
OCT of the left eye showing significant improvement in the nodular thickening of the RPE and restitution of inner/outer segment junctions post treatment with IV penicillin G.

The prevalence of STIs is steadily increasing in the United States. Syphilis has been consistently rising in incidence over the past 2 decades, and with it, its ocular manifestations. Of the infectious disorders that affect the eye, syphilis is particularly interesting as it can mimic multiple autoimmune disorders and can be easily missed. For this reason, it is important for many patient's presenting with ocular inflammatory disorders to be evaluated by an eye provider trained in the work up and management of complex ocular inflammatory disorders. In some instances, patients presenting with anterior or posterior uveitis will require testing for infectious etiologies. ASPPC is a unique manifestation of ocular syphilis. The clinical and imaging features are quite distinctive. However, these features can easily mimic those seen in placoid white dot syndromes, tuberculosis or sarcoidosis. Patients presenting with ASPPC must be tested for HIV and neurosyphilis (ID referral and LP/CSF analysis). Patients with ASPPC have a favorable prognosis, often with an excellent response to antibiotic treatment resulting in improvement in visual acuity and resolution of findings.

References:

1. *CDC. Sexually Transmitted Infections Prevalence, Incidence, and Cost Estimates in the United States. Available at: https://www.cdc.gov/std/statistics/prevalence-2020-at-a-glance.htm Last accessed 03/5/2021*
2. *Tampa M, Sarbu I, Matei C, Benea V, Georgescu SR. Brief History of Syphilis. J Med Life. 2014 Mar 15; 7(1): 4–10.*
3. *CDC Syphilis Fact Sheet. Available at: https://www.cdc.gov/std/syphilis/stdfact-syphilis.htm Last accessed 3/5/2021*
4. *Ghanem KG, Ram S, Rice PA. The modern epidemic of syphilis. N Engl J Med, 382 (2020), pp. 845-854*
5. *Choudhri Y, Miller J, Sandhu J, Leon A, Aho J. Infectious and congenital syphilis in Canada, 2010-2015. Canada Commun Dis Rep, 44 (2018), pp. 43-48*
6. *Eandi CE, Neri P, Adelman RA, Yannuzzi LA, Cunningham Jr ET, International Syphilis Study Group. Acute syphilitic posterior placoid chorioretinitis: report of a case series and comprehensive review of the literature. Retina. 2012 Oct;32(9):1915-41.*
7. *Schulz DC, Orr SMA, Johnstone R, Devlin MK, Sheidow TG, Bursztyn LLCD. The many faces of ocular syphilis: case-based update on recognition, diagnosis, and treatment. Can J Ophthalmol. 2021 Feb 4;S0008-4182(21)00016-8.*
8. *Franco M, Nogueira V. Severe acute syphilitic posterior placoid chorioretinitis with complete spontaneous resolution: The natural course. GMS Ophthalmol Cases. 2016; 6: Doc02.*

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At the forefront of clinical research

NJRetina continuously conducts clinical trials at key locations. Our clinical research coordinators will be happy to discuss the inclusion/ exclusion criteria or any other aspect of these studies with you or your patients. If you have any questions, please feel free to contact:

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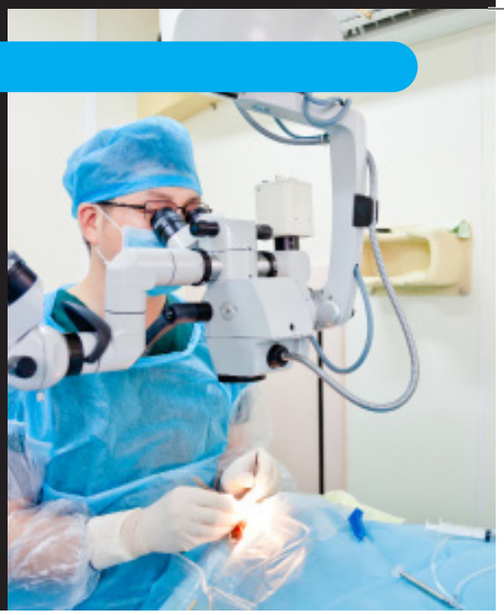

Enrolling Studies:

Dry AMD

Vauxhall

GTSCOPE: A Study of Disease Progression in Genetically Defined Subjects With Geographic Atrophy Secondary to Age-Related Macular Degeneration

Teaneck

Catalina: A Phase 2 Multicenter, Randomized, Double-Masked, Sham-Controlled Study of the Safety and Efficacy of Intravitreal Injections of NGM621 in Subjects with Geographic Atrophy (GA) Secondary to Age-Related Macular Degeneration (AMD)

Teaneck and Toms River

Gallego: A phase II, multicenter, randomized, single-masked, sham-controlled study to assess safety, tolerability, and efficacy of intravitreal injections of FHTR2163 in patients with geographic atrophy secondary to age-related macular degeneration (Gallego)

Wet AMD

Edison

Pulsar: Randomized, Double-Masked, Active-Controlled Phase 3 Study of the Efficacy and Safety of High Dose Aflibercept in Patients with Neovascular Age-Related Macular Degeneration

Diabetic Macular Edema (DME)

Teaneck

Gleam: A prospective, randomized, double-masked, active comparator-controlled, multi-center, two- arm, phase 3 study to evaluate the efficacy and safety of intravitreal KSI-301 compared with intravitreal aflibercept in participants with visual impairment secondary to treatment- naive diabetic macular edema.

Teaneck

Pagoda: A Phase III, multicenter, randomized, visual assessor-masked, active-comparator study of the efficacy, safety, and pharmacokinetics of the Port Delivery system with Ranibzumab in patients with diabetic macular edema

Edison and Teaneck

Photon: A Randomized, Double-Masked, Active-Controlled Phase 2/3 Study of the Efficacy and Safety of High-Dose Aflibercept in Patients with Diabetic Macular Edema

Diabetic Retinopathy

Teaneck

Pavilion: A Phase III, Multicenter, Randomized Study of the Efficacy, Safety, and Pharmacokinetics of the Port Delivery System with Ranibizumab in Patients with Diabetic Retinopathy

Soon to Enroll Studies:

Diabetic Retinopathy:

- Altitude: A Phase 2, Randomized, Dose-escalation, Observation-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of RGX-314 Gene Therapy Delivered via One or Two Suprachoroidal Space (SCS) Injections in Participants with Diabetic Retinopathy (DR) Without Center Involved-Diabetic Macular Edema (CI-DME) (ALTITUDE) – Teaneck

Retinal Vein Occlusion

- Balaton: A Phase III, Multicenter, Randomized, Double-Masked, Active Comparator-controlled Study To Evaluate The Efficacy And Safety Of Faricimab In Patients With Macular Edema Secondary To Branch Retinal Vein Occlusion – Toms River