The Return of Syphilis: Throwing Light to Save Sight

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Abstract
Syphilis is an emergent public health problem with systemic manifestations. We present a case of secondary ocular compromise that was promptly recognized and successfully treated. The purpose of the reported clinical case is to emphasize how neurological involvement of syphilis can occur at any stage of the disease and should be ruled out considering existing remedial therapeutic strategies.

Keywords: Syphilis; Neurological; Therapeutic Strategies; Treponema Pallidum

Introduction
Syphilis is a sexually or congenital acquired bacterial infection, caused by Treponema pallidum subspecies representing a re-emerging public health problem. Among its systemic manifestations, it can prompt to irreversible vision loss, thus, awareness of infection is essential for primary care practitioners. [1] We here report a case of severe ocular involvement secondary to neurosyphilis promptly recognized and treated with sight regaining.

Case Presentation
A forty-year-old Caucasian woman was admitted in our Emergency Department with persistent headache and progressive bilateral visual impairment, worsened in the previous week. She was not under any medication and her clinical history encountered cigarette smoking, recurrent genital papillomatosis (HPV), and anorexia in her teens.

Blood tests resulted normal and brain CT scan with CT angiography excluded any possible hemorrhagic/ischemic lesion, or vascular malformations/ aneurysm of the carotid, vertebrobasilar, and epiaortic system bilaterally. A complete neurological examination
detected mydriatic pupils, with a sluggish photomotor response, and a binasal hemianopsia on a manual campymetric evaluation. A following brain magnetic resonance imaging (MRI) promptly performed in the Emergency setting, excluded parenchymal and arteriovenous abnormalities. She was thus admitted in the Emergency Medical Unit to assess whether the suspected optic neuritis was of infectious or inflammatory/autoimmune nature.

A thoroughly neuro-ophthalmologic evaluation excluded signs of additional ophthalmologic pathology, other than the binasal hemianopsia and initial disc swelling. Flash pattern visual evoked potentials (VEPs) showed normal amplitude of P100 responses, but bilateral and asymmetrical increased latencies confirmed involvement of the optic nerve. Since no signs of the anterior segment of the eye were detected, an optic neuritis was assumed. The detailed metabolic analysis identified a normochromic normocytic anemia due to a combined iron (serum iron 36mcg/dl) and cyanocobalamin deficiency (B12 174ng/ml), treated successfully. Furthermore, in consideration of the previous infection of HPV, at the general examination the patient revealed a painless papule of the vulvo-vaginal region, reason why she underwent dermatologic examination. The result of the genital inspection was the absence of papillomavirus genital warts, but the appearance of painless rounded erosions covered with gray macerated secretion suggestive of secondary papuloerosive syphiloderma (mucous patches). (Figure 1)

![Figure 1: Secondary papuloerosive syphiloderma.](image)

Therefore, suspecting an infectious cause of this disorder, a concurrent comprehensive serologic screening test for syphilis was performed resulting completely positive both on treponemal and nontreponemal testing (i.e., *Treponema pallidum* hemagglutination (TPHA)) with a titer of 1/1280, venereal disease research laboratory (VDRL) and Rapid plasma regain (RPR)tests) with a cerebrospinal fluid (CSF) examination that demonstrated presence of *Treponema Pallidum* IgG by Western blot. Other infectious causes were ruled out, with serology resulting negative for hepatitis B, C (HBV, HCV), and human immunodeficiency virus (HIV). Based on these clinical and laboratory findings, the diagnosis of secondary ocular syphilis was made.

Therapy with ceftriaxone at a dosage of 2g daily for two weeks was then rapidly initiated, given the hospital shortage of penicillin G, with progressive visual recovery and regression of mucocutaneous genital lesions in 4 weeks. The patient was then discharged, with subsequent referral to the Neurology outpatient clinic for follow up (up to 18 months), with no medium- to long-term reporting of any infectious recurrence or visual relapses.

**Discussion**

Syphilis is a sexually or congenital multiorgan infection caused by *Treponema pallidum*, characterized by three principal phases (primary, secondary, early latent, late latent, and tertiary), where humans represent the only natural host. With its different and various manifestations, syphilis can imitate disparate disorders, shaping up like a mimicker.

Its prevalence has risen 300% ever since 2000 in many high-income countries. [2] Incidence increases especially if accompanied by other sexually transmitted infections (i.e. herpesvirus, HIV). Considering similar transmission routes and epidemiology, HIV coinfection is common, thus must always be sought. When remaining untreated or unrecognized, the condition may progress throughout the stages with devastating neurological and cardiological sequelae. [3] Ocular syphilis can involve any part of the eye, in any stage, but most commonly presents as uveitis. [4] The manifestations of syphilis are primarily consequence of the inflammatory ineffective responses, with an adaptive immune system only partially effective explaining why syphilis may remain dormant in the body for years. [5]

Primary syphilis manifests clinically as a solitary chancre, in the site of inoculation, (appearing between 10 to 90 days after exposure – mean 21 days) indurated, ulcerative, painless with a localized adenopathy resolving in 3 to 6 weeks without scarring, when untreated. [6] Regional lymphadenopathy and diffusion to other organs, (e.g. the central nervous system (CNS)), occur in the early stages of infection and manifest belatedly with interindividual variability.

Clinical manifestations of secondary syphilis (determined by bacterial dissemination) occur concurrently with or up to eight weeks after chancres, disappearing spontaneously after 4 to 12 weeks. [7] A mild, diffuse, symmetrical, nonpruritic rash of any morphology (except vesicular) represents the typical cutaneous manifestation. More often maculopapular or macular (roseola syphilitica) rashes are detected. The rash typically involves palms and soles. [8] Cutaneous manifestations often associate to diffuse lymphadenopathy, hepatosplenomegaly, hepatitis, alopecia, and kidney involvement. [9]
they may appear exuberant with a verrucous surface defined as condyloma lata or, as in our case, circular erosive buttons covered by gray exudate (i.e. mucous patches) may develop. [10]

Early latent syphilis represents an asymptomatic phase following the resolution of the secondary period or occurring in between. It can be furtherly interrupted by recurrency of infection, mostly occurring within one year, cut-off that distinguishes the early versus late latent syphilis (>1 year). [11]

Tertiary syphilis represents the final and irreversible stage of the untreated disease. It occurs within 1 to 46 years with damage being primarily neurologic (e.g., meningovascular or parenchymatous), cardiovascular, and gummatous (i.e., painless noduloulcerative necrotic granulomatous destructive lesions called gummas). [6] Early neurosyphilis can develop in this phase in 25-60% of affected patients characterized by cranial nerve palsies, eye redness, meningitis, and mental status alteration. [12] Meningovascular syphilis occurs 5 to 12 years after initial infection with manifestations including hemiplegia, aphasia, and seizures. The parenchymatous forms occur after 15 years from inoculation and include paresis, tabes dorsalis, cognitive and memory impairment. [13] Neurologic involvements per se, asymptomatic or symptomatic, may occur during any stage of syphilis, throughout hematogenous dissemination. CNS invasion by treponemases associates to abnormal CSF findings in up to 50% of patients after early infection, even in absence of clinical manifestations, resolving after recommended therapy. [14]

Ocular syphilis may occur at any stage and affect any part of the eye (uveitis most commonly) with no pathognomonic characteristics. [15] Patients may complain eye redness, pain, vision loss, floaters, photopsia, and photophobia, depending on which part of the eye is involved. Long term complications may bring to irreversible severe vision impairment. Ocular syphilis has variable clinical presentations: the most common one is uveitis, nongranulomatous or granulomatous, with or without intraocular inflammation. It could appear as well as, episcleritis, scleritis, conjunctivitis and, optic neuritis. Rarely, gumma of optic disc could be the only manifestation, with or without involvement of posterior segments. [3] For a correct diagnosis of ocular syphilis, other granulomatous and inflammatory ocular diseases must be excluded in the differential diagnosis: ocular tuberculosis, cytomegalovirus (CMV) retinitis, Herpetic retinitis, Vogt-Koyanagi-Harada syndrome, sarcoidosis and, Behçet disease.

Considering the severe complications and the long natural course of the disease, prompt diagnosis is mandatory. The gold standard in detecting the spirochaetes is its direct identification by using dark field microscopy, direct fluorescent antibody testing (e.g., Western Blot format), or nucleic acid amplification tests (by PCR). [16] On a practical basis, diagnosis is indirect relying on a serologic two-stage testing. Beginning with a nontreponemal test (e.g., RPR or a VDRL that measure tissue damage determined by syphilis detecting antibodies to cardiolipin, cholesterol and lecithin) followed by a confirmatory highly sensitive and specific treponemal test (e.g., the Treponema pallidum particle agglutination test [TPPA] or the TPHA). Both categories of testing are necessary as treponemal tests cannot distinguish active from treated infections and generally remain positive throughout life. [17] Since serologic results are non-reactive in 30% of subjects with primary disease, testing should be repeated at two weeks when the initial exam results nonspecific. [18]

For neurosyphilis the situation is more complex considering that there are no standard tests for diagnosis, requiring a combination of clinical signs and laboratory tests. Indeed, a reactive CSF non-treponemal test is highly predictive of neurological involvement although lacking in sensitivity (<80%) and a CSF treponemal test lacks in specificity owing to passive transfer of serum treponemal IgG antibodies across the blood CSF barrier. [19] Nevertheless, all patients with neurologic signs require CSF examination. Ocular syphilis diagnosis requires confirmation integrating specific ocular analysis (e.g., Optical Coherence Tomography (OCT)) to the systemic in-depth testing (non-treponemal and treponemical).

The goal of treatment is clinical and serological cure. The latter refers to a drop of 4 times or more in nontreponemal titers at 6 and 12 months in early syphilis and at 12 and 24 months in late syphilis. [20] The serologic nonresponsiveness requires clinical reassessment (e.g., throughout CSF examination) in order to decide whether additional antibiotic therapy is warranted. [11]

In any case, clinical and serologic follow up should track a determined interval at 1, 3, and 6 months after therapy. [21] First line treatment relies on penicillin, for all stages of syphilis representing the drug of choice. [22] A single dose of long acting benzathine penicillin G (BPG) 2.4 x 106 units given intramuscularly is effective in the treatment of uncomplicated early syphilis. [11]

For neurosyphilis intravenous aqueous penicillin G is preferred, since the inability to achieve sufficient levels of BPG in the CSF. [23]

Ceftriaxone has been shown to penetrate the CNS well representing an optimal option of treatment in neurosyphilis when penicillin in unavailable, though data is restricted to observational studies. [24] For ocular involvement, the combination of topical and systemic corticosteroids has an additional role in reducing inflammation. [3]

**Conclusions**

Our clinical case aims to draw attention to the possible neurological (i.e., ocular) involvement of syphilis, regardless of the stage of the disease, keeping in mind, on the one hand, the neurologic tropism of the spirochaetes and, on the other hand, how this etiology should always be considered as a causative agent in the diagnostic
algorithm of visual loss. Finally, our case report is intended to emphasize how ceftriaxone can also be an excellent alternative to penicillin (gold standard), calling, nevertheless, for additional randomized clinical trials to confirm its routine use in daily clinical practice.

Disclosure

Conflict of Interest: The authors declare no conflict of interest.

Patient Consent: Obtained.

References