CLINICAL VIGNETTE

Syphilis, the Great Imitator Presenting as Vague Symptoms in a 66-Year-Old Female

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Introduction

Syphilis is caused by the spirochete *Treponema pallidum* as a sexually and vertically transmitted infection (STI).[1,2] Known for its immune evasion, T. pallidum is an obligate human pathogen that initially causes a local inflammatory response secondary to replication within tissues prior to hematogenous spread.[1,3,4] Aside from congenital syphilis, syphilis is mainly spread through direct contact with lesions and less commonly through blood products.[1,2] We present a 66-year old female diagnosed with late latent syphilis and neurosyphilis (ocular syphilis) after months of vague symptoms including eye pain, blurred vision, rash, joint pain, and fatigue.

Case Presentation

A 66-year-old female was admitted to the VA Medical Center with worsening vision and morbilliform rash. Past medical history includes asthma, migraines, insomnia, hyperlipidemia, hypothyroidism, chronic joint pain, and chronic fatigue. She reported several months of floaters and blurred vision. Two weeks prior to admission, she developed a non-pruritic rash initially on the back of her neck, which gradually spread to the trunk and extremities sparing the face. She also described paresthesia-like sensations in the distribution of the rash. Other symptoms included worsening chronic joint pain, with recent negative rheumatologic evaluation. Prior to admission, she received two 5-day oral prednisone tapers as well as topical steroids without relief. She denied vaginal ulcers, fevers, chills, and weight loss.

Physical exam revealed a diffuse, morbilliform rash composed of erythematous, edematous pink papules of varying sizes on the back, chest, abdomen, and upper and lower extremities without scaling (Figure 1). There was no involvement of the palms and soles, nails and no oral ulcers, or facial rash or edema. Initial differential diagnosis included pityriasis rubra pilaris, drug eruption, as well as other infectious and rheumatologic etiologies. Punch biopsy of a mid-abdomen lesion revealed focal vacuolar dermatitis, spongiosis, and a superficial and mid dermal lymphocyte predominant inflammatory dermatitis with scattered plasma cells and rare eosinophils. The non-specific findings were suggestive of a viral etiology or drug reaction.

Serologic testing for Hepatitis, HSV, VZV, Bartonella Henselae, West Nile Virus, HIV, tuberculosis, CMV, Coccidiomycosis, Rickettsia Typhi were negative. Thorough autoimmune antibody testing was also negative. Other emergency department testing included CRP 0.960 and ESR of 19. Rapid Plasma Reagin (RPR) test was 1:128 and Treponema pallidum Particle Agglutination (TP-PA) was 2+. The patient was diagnosed with latent syphilis and neurosyphilis and began treatment with IV penicillin G of 4 million units every 4 hours for 14 days hospitalization.

During the hospitalization, she was evaluated by ophthalmology for her blurry vision and found to have bilateral panuveitis, and acute syphilitic posterior placoid chorioretinitis. ASPPC is characterized by large, round, yellow, placoid lesions at the level of the retinal pigment epithelium (RPE) in the macular/paramacular area (Figure 2A).[5]

The patient reported only one lifetime sexual partner, her husband, with whom she had unprotected intercourse. Her male husband died two years prior and she was not sexually active since his death. During a prior temporary separation, her husband remarried and had children in the Philippines. However, the patient denied personal history of STDs or history of STDs in her partner.

The patient was discharged with visual improvement and resolution of her rash. She will continue to receive intramuscular penicillin two times weekly for late latent syphilis. She will have titers checked at 6, 12, and 24 months to evaluate serologic response.

Discussion

A diagnosis of syphilis can be established with direct detection techniques and serologic testing. Lesions of primary, secondary and congenital syphilis can be directly swabbed or biopsied for direct microbiological diagnosis using of darkfield microscopy, fluorescent antibody staining and immunohistochemistry and PCR. Aside from PCR, these techniques are largely obsolete due to lack of sensitivity and requirement of active lesions to sample for diagnosis. Serology testing can be used to screen

asymptomatic individuals and in symptomatic patients for definitive diagnosis.

Non-treponemal serologic tests measure immunoglobulins produced in response to released materials from spirochetes and infected host cells. Examples include the Rapid Plasma Reagin (RPR) test and the Venereal Disease Research Laboratory (VDRL) test. Limitations include detection only after 10 to 15 days from initial lesion onset, missing 25 to 30% of primary cases.[1,6] Treponemal tests detect antibodies against T. pallidum antigens and are widely used as a reflexive, confirmatory test after non-treponemal serologic testing. Treponemal test include the fluorescent treponemal antibody absorbed (FTA-ABS) test, the microhemagglutination assay for antibodies to T. palladium, the T. pallidum passive particle agglutination (TPPA) test and T. pallidum hemagglutination (TPHA) assays.[1]

Syphilis is a chronic infection well characterized by distinct disease stages. The organism has slow growth after an initial inoculation period of around three weeks after incubation. The appearance of a primary syphilitic lesion known as a chancre presents as painless, solitary lesions that can be indurated with ulceration. Tender or nontender associated lymphadenopathy may be present with the initial lesion. Without treatment, chancres tend to clear in three to six weeks without scarring. With treatment, the chancres clear within days.[2,7]

Following the initial inoculation and primary stage of syphilis of 6 to 8 weeks, the organism spreads during the secondary stage of disease. The rash of secondary syphilis is a painless, macular rash consisting of 1-2 cm red or copper colored lesions on the palms and soles of the hands and feet. Although this is the traditional description, secondary syphilis can manifest in countless ways, even involving the mucous membranes. Involvement of mucous membranes leads to a verrucous-like lesion known as condyloma lata. Other presentations include local or generalized macular, pustular or papular rashes that can imitate psoriasis, pityriasis rosea, or a drug eruption. Systemic signs may be present, such as fever, myalgias, malaise, sore throat, lymphadenopathy, hepatosplenomegaly, hepatitis and nephrotic syndromes. As with primary syphilis, secondary lesions resolve spontaneously without scarring.[2]

If untreated, syphilis will enter a latent stage categorized into early and late phases. Years to decades later, syphilis can reactivate as tertiary syphilis characterized by neurosyphilis, cardiovascular syphilis, and gummatous syphilis.[2,8] Gummas represent granulomatous, reactive lesions that can occur anywhere on the body.[2] Additionally, neurosyphilis can occur anytime over the course of infection with a variety of presentations including ocular syphilis (uveitis, cranial nerve palsies), syphilitic meningitis, general paresis, and tabes dorsalis.[2,9] Our patient presented with a widespread erythematous morbilliform rash suggestive of the broad, varying rash of secondary syphilis. However, the patient also presents with features of tertiary syphilis, which correlate with the timeline of infectivity and ocular symptoms.

Placoid lesions pertaining to ocular syphilis were seen in our patient. These are clinically distinct manifestations frequently seen with secondary and late latent syphilis.[10] They are hypothesized to develop due to spread of T. pallidum infection to the RPE layer and/or as a consequence of indirect immune-mediated hypersensitivity. Differential diagnosis for ASPPC includes: acute posterior multifocal placoid pigment epitheliopathy (APMPPE); serpiginous choroiditis; and viral retinitis. The progression timeline on spectral-domain optical coherence tomography (SD-OCT) was consistent with previously reported case series of ASPPC (Figure 2B-C).[10,11] Pichi et al. reported transient subretinal fluid (SRF) within days of disease onset associated with thickened and granular hyperreflective RPE (Figure 2B) followed by segmental loss of the ellipsoid zone within one week after presentation (Figure 2C).[12] Fundus autofluorescence (FAF) showed hyper-autofluorescence (Figure 2D), while fluorescein angiography (FA) showed a classic pattern of early hypofluorescence followed by late staining of the lesions (Figure 2E). With treatment, there was gradual restoration of the ellipsoid zone (Figure 2F) and improvement in bilateral vision at three-week follow-up.

The mainstay of treatment for syphilis is penicillin, specifically long-acting intramuscular benzathine penicillin G. In patients with penicillin allergy, alternatives include ceftriaxone, and doxycycline. Early syphilis requires only one dose of IV penicillin G whereas late syphilis requires weekly doses for three weeks based on WHO treatment guidelines.[13]

Our patient demonstrates the vast spectrum of rashes representing syphilitic infection. This highlights the importance of including syphilis, the great imitator, on the initial differential for patients with a spectrum of symptoms across organ systems and importantly over time.

Figures

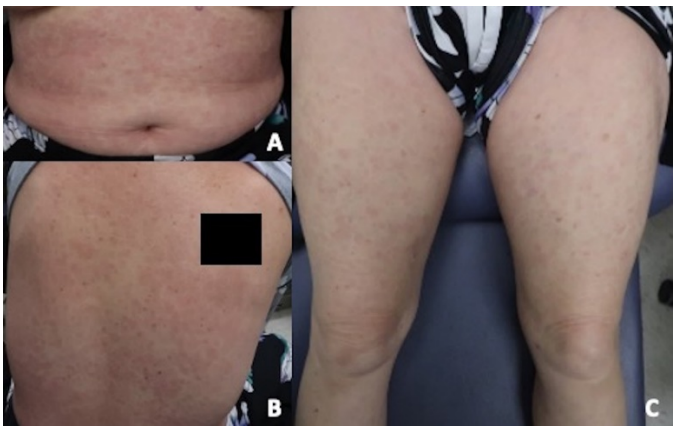

Figure 1. Diffuse morbilliform rash presenting on the abdomen (A), back (B), and lower extremities (C).

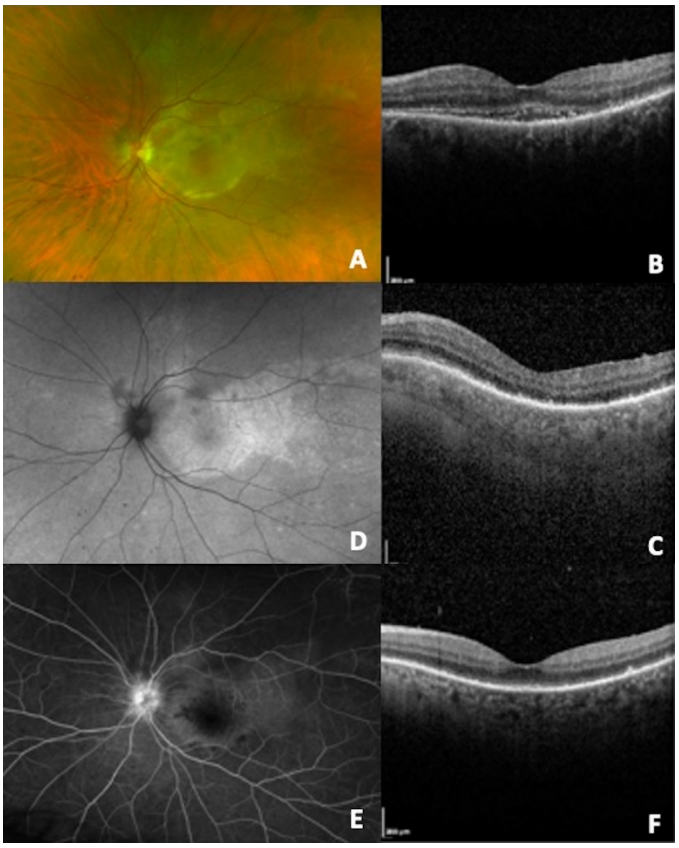

Figure 2. Fundus photograph of yellow placoid lesion involving the macula (A). Optical coherence tomography at initial visit (B) and three days later (C) illustrating loss of ellipsoid zone corresponding to placoid lesion. Fundus auto-fluorescence shows hyper-fluorescence of the placoid lesion (D) while fluorescein angiography shows late staining (F). OCT at three weeks follow up shows gradual restoration of ellipsoid zone (F).

REFERENCES

1. **Peeling RW, Mabey D, Kamb ML, Chen XS, Radolf JD, Benzaken AS**. Syphilis. *Nat Rev Dis Primers*. 2017 Oct 12;3:17073. doi: 10.1038/nrdp.2017.73. PMID: 29022569; PMCID: PMC5809176.
2. **Hook EW 3rd**. Syphilis. *Lancet*. 2017 Apr 15;389(10078): 1550-1557. doi: 10.1016/S0140-6736(16)32411-4. Epub 2016 Dec 18. Erratum in: *Lancet*. 2019 Mar 9;393(10175):986. doi: 10.1016/S0140-6736(19)30483-0. PMID: 27993382.
3. **Penn CW**. Avoidance of host defences by Treponema pallidum in situ and on extraction from infected rabbit testes. *J Gen Microbiol*. 1981 Sep;126(1):69-75. doi: 10.1099/00221287-126-1-69. PMID: 7038039.
4. **Cruz AR, Ramirez LG, Zuluaga AV, Pillay A, Abreu C, Valencia CA, La Vake C, Cervantes JL, Dunham-Ems S, Cartun R, Mavilio D, Radolf JD, Salazar JC**. Immune evasion and recognition of the syphilis spirochete in blood and skin of secondary syphilis patients: two immunologically distinct compartments. *PLoS Negl Trop Dis*. 2012;6(7):e1717. doi: 10.1371/journal.pntd.0001717. Epub 2012 Jul 17. PMID: 22816000; PMCID: PMC3398964.
5. **Neri P, Pichi F**. Acute syphilitic posterior placoid chorioretinitis: when the great mimicker cannot pretend any more; new insight of an old acquaintance. *J Ophthalmic Inflamm Infect*. 2022 Feb 22;12(1):9. doi: 10.1186/s12348-022-00286-2. PMID: 35192047; PMCID: PMC8864036.
6. **Creegan L, Bauer HM, Samuel MC, Klausner J, Liska S, Bolan G**. An evaluation of the relative sensitivities of the venereal disease research laboratory test and the Treponema pallidum particle agglutination test among patients diagnosed with primary syphilis. *Sex Transm Dis*. 2007 Dec;34(12):1016-1018. PMID: 18080352.
7. **Mertz KJ, Trees D, Levine WC, Lewis JS, Litchfield B, Pettus KS, Morse SA, St Louis ME, Weiss JB, Schwebke J, Dickes J, Kee R, Reynolds J, Hutcheson D, Green D, Dyer I, Richwald GA, Novotny J, Weisfuse I, Goldberg M, O'Donnell JA, Knaup R**. Etiology of genital ulcers and prevalence of human immunodeficiency virus coinfection in 10 US cities. The Genital Ulcer Disease Surveillance Group. *J Infect Dis*. 1998 Dec; 178(6):1795-8. doi: 10.1086/314502. PMID: 9815237.
8. **Gjestland T**. The Oslo study of untreated syphilis; an epidemiologic investigation of the natural course of the syphilitic infection based upon a re-study of the Boeck-Bruusgaard material. *Acta Derm Venereol Suppl (Stockh)*. 1955;35(Suppl 34):3-368; Annex I-LVI. doi: 10.2340/00015555343368. PMID: 13301322.
9. **Merritt HH, Adams RD, Solomon HC**. Neurosyphilis. New York: Oxford University Press, 1946.
10. **Mathew RG, Goh BT, Westcott MC**. British Ocular Syphilis Study (BOSS): 2-year national surveillance study of intraocular inflammation secondary to ocular syphilis. *Invest Ophthalmol Vis Sci*. 2014 Jun 12;55(8):5394-400. doi: 10.1167/iovs.14-14559. PMID: 24925878.
11. **Pichi F, Ciardella AP, Cunningham ET Jr, Morara M, Veronese C, Jumper JM, Albini TA, Sarraf D, McCannel C, Voleti V, Choudhry N, Bertelli E, Giuliari GP, Souied E, Amer R, Regine F, Ricci F, Neri P, Nucci P**. Spectral domain optical coherence tomography findings in patients with acute syphilitic posterior placoid chorioretinopathy. *Retina*. 2014 Feb;34(2):373-84. doi: 10.1097/IAE.0b013e3182993f11. PMID: 23860561.
12. **Eandi CM, Neri P, Adelman RA, Yannuzzi LA, Cunningham ET Jr; 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. doi: 10.1097/IAE.0b013e31825f3851. PMID: 22863970.
13. **World Health Organization**. WHO guidelines for the treatment of Treponema pallidum (syphilis) [online]. 2016. Available at: https://iris.who.int/bitstream/handle/10665/249572/9789241549806-eng.pdf.