

Prozone Phenomenon and Penicillin Allergy in Hiv-Infected Male with Ocular Syphilis

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Abstract

The incidence of syphilis is increasing especially among men who have sex with men (MSM) infected with Human Immunodeficiency Virus (HIV). However because of its multitudinous unusual manifestations, it remains a diagnostic and therapeutic challenge to the modern era. Throughout the years, penicillin is the treatment of choice for all stages of syphilis. However, hypersensitivity reaction, like in this case, is the major problem in the use of penicillins.

The case presents a 25-year-old homosexual male, recently-diagnosed with HIV who presented with progressive blurring of vision following a history of pruritic rashes on both lower extremities. Important examination findings include madarosis with patchy loss of scalp hair; hyperemic conjunctivae with multiple erythematous macules and papulovesicular lesions with some collarette scaling over both lower extremities. During initial consultation, the RPR was negative and CD4+ T cell count was 34 cells/ μ L. The persistence of symptoms prompted consult to an Infectious Disease specialist and subsequent referral to an Ophthalmologist. Slitlamp and funduscopy showed hyperemic disc with indistinct borders. Fluorescein Angiography showed leakage of the optic nerve head with diffuse areas of retinal vasculitis in the retinal midperiphery. Repeat RPR remained positive at the dilution of 1:256 and a positive Fluorescent Treponemal Antibody Absorption Test yield the diagnosis of Secondary Syphilis with Ocular Syphilis. Due to known history of Penicillin allergy, oral desensitization with Penicillin V was initiated first then subsequently administered a two-week course of intravenous penicillin G. The patient tolerated the antibiotic course and was discharged stable and improved.

Having both diagnostic and therapeutic dilemma, this case report prompts the clinicians to have a high index of suspicion and continued familiarity with protean manifestations of syphilis, and acquainted with prozone effect when necessary. Since syphilis is a great masquerader, it requires high index of suspicion and should be included in the differential diagnoses of visual complaints.

Summary of Case

The case presents a 25-year-old homosexual male, recently-diagnosed with HIV who presented with progressive blurring of vision following a history of pruritic rashes on both lower extremities. Important examination findings include patchy alopecia of the scalp, madarosis with patchy loss of scalp, hyperemic conjunctivae with multiple erythematous macules and papulovesicular lesions with some collarette scaling over both lower extremities. During initial consultation, the Rapid Plasma Reagin (RPR) was negative and a CD4+ T cell count was 34 cells/ μ L. The persistence of symptoms prompted consult to an Infectious Disease specialist and subsequent referral to an Ophthalmologist. Slitlamp and funduscopy showed a clear media, hyperemic disc with indistinct disc borders and multiple whitish dots in the retinal mid-periphery. Fluorescein Angiography showed leakage of the optic nerve head with diffuse areas of retinal vasculitis in the retinal mid-periphery.

A repeat RPR was requested, which remained positive at the dilution of 1:256. The false negative result during the initial non-treponemal test therefore demonstrated the Prozone Phenomenon which occurs in <1% of cases when high titers of antibodies interferes with the proper formation of the antigen-antibody lattice network.

The history, self-report of unprotected sexual intercourse and the correlation between rashes, several diagnostic findings, and a positive Fluorescent Treponemal Antibody Absorption Test yield the diagnosis of Secondary Syphilis with ocular Syphilis. Due to known history of Penicillin allergy, oral desensitization with Penicillin V was initiated first then subsequently administered a 2-week course of intravenous penicillin G (24 MU/day). The patient tolerated the antibiotic course and was discharged stable and improved. Follow-up ophthalmologic examination one month later showed 20/20 visual acuity bilaterally and complete resolution of inflammation. The patient was started on antiretroviral therapy thereafter.

Introduction

The incidence of syphilis is increasing especially among men who have sex with men (MSM) infected with Human Immunodeficiency Virus (HIV). However because of its multitudinous unusual manifestations, it remains a diagnostic and therapeutic challenge to the modern era. Syphilis is one of the oldest recognized sexually transmitted infections, and despite the availability of inexpensive and effective therapy, the incidence is increasing in many parts of the world. The diagnosis of syphilis, caused by the spirochete *Treponema pallidum*, is usually straightforward and Penicillin is the treatment of choice for all stages of syphilis. However, hypersensitivity reaction, like in this case, is the major problem in the use of penicillins.

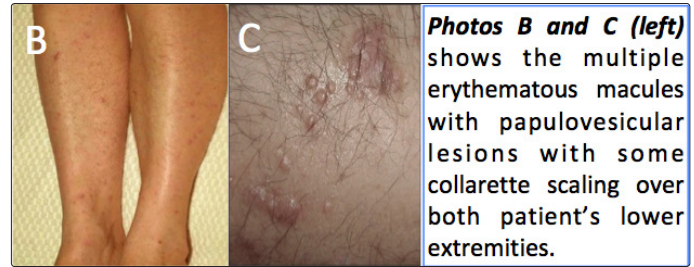
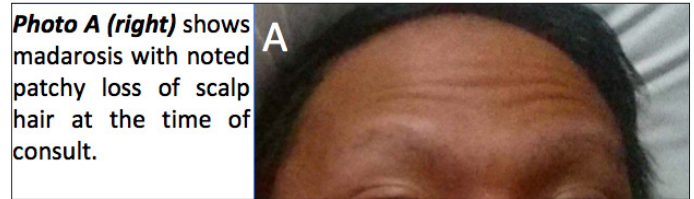
The study also provides emphasis on the prozone phenomenon in the setting of syphilis, which may become more prevalent due to increasing HIV incidence. This is a case of secondary syphilis presenting with HIV co-infection. It demonstrated a false negative reaction to the serum rapid plasma reagin (RPR) test, and discuss the expected increased incidence of the prozone effect of syphilis testing in HIV-infected patients.

Having both diagnostic and therapeutic dilemma, this case report prompts the clinicians to have a high index of suspicion and continued familiarity with protean manifestations of syphilis, and acquainted with prozone effect when necessary.

Case Presentation

Mr. C.C. is a 25 years old male, Single, Filipino, Roman Catholic, Bank employee who came in the clinic due to blurring of vision. History started two months prior to admission when the patient noted weight loss (14kg in 4 weeks), drying of skin, and undocumented fever episodes. There was no cough, rhinorrhea, pains, dyspnea, dysuria, changes in bowel movement, hematochezia, melena, nor other symptoms at that time. He consulted a general physician and due to his risk sexual behavior, HIV screening was advised and turned out to be positive. (Note: CD4 count at the time is 34.) The initial Rapid Plasma Reagin test was “non-reactive”. MTB-PCR, Sputum AFB and HbsAg, anti-HBs were also non-reactive at that time. The patient did not follow up.

After a month however, the patient had macular and some papulovesicular rashes on both of his lower extremities. The rashes eventually progressed to erythematous eruptions and scales with pruritus; and accompanied by bilateral ankle joint and knee joint pains. There was no other lesion on his other body parts. There were no discharges, fever, bruising, nor bleeding. He consulted a dermatologist was started on oral antihistamine and topical steroids and was applied over affected lesions. Two weeks prior to admission, the patient noted redness of both eyes that eventually persisted. There was no trauma, pain nor itchiness. There was no loss of vision, color blindness, diplopia, trauma, discharge, nor lacrimation. There was also no fever, headache, difficulty of breathing, rhinorrhea, sneezing, coughing. Ophthalmologic consult was done at a private institution and the patient was diagnosed with Allergic Conjunctivitis. He was given antihistamine drops and NSAIDs but symptoms persisted despite treatment. He was also advised to seek opinion from an Infectious Disease specialist. The patient eventually noted eye floaters then eventually blurring of vision accompanied by malaise few days prior to consult. There was no eye pain, headache, lacrimation, smell disturbances, paresthesias, facial weakness, focal weakness, seizures, nor dizziness.



The persistence of symptoms prompted consult to an Infectious Disease specialist and subsequent referral to Ophthalmology service.

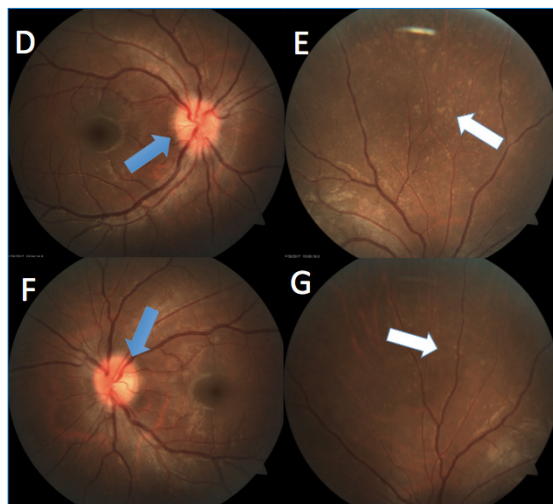
Review of systems was unremarkable. The past medical history showed no previous STI or genital ulcer, hypertension, pulmonary tuberculosis, and heart diseases. The patient has history of penicillin allergy. There was no recent vaccination for pneumonia or influenza. The patient denies smoking, exposure to second-hand smoke nor use of illicit drugs. He drinks alcohol occasionally. As a Graduate of BS Management, he works as a bank employee at least 8 hours a day at the office with good baseline functional capacity and independent on all ADLs. He has no recent travel. He is engaged in sexual practice with inconsistent condom use to both males and females (around 2 different persons in a month for ~8 years). Family Medical History was unremarkable.

Table 1: Ophthalmologic examination done at the time of ophthalmologic evaluation

Right Eye		Examination	Left Eye	
SC	PH		SC	PH
20/20	NI	VA	20/20	NI
No swelling		Lids	No swelling	
(+) Madarosis		Lashes	(+) Madarosis	
None		Discharge	None	
Hyperemic		Conjunctiva	Hyperemic	
Clear		Cornea	Clear	
12,12		IOP	12,12	
(+) cells, (-) flares		Anterior chamber	(+) cells, (-) flares	
		EOMs		
2-3 mm BRTL		Pupils	2-3 mm BRTL	
(-)		RAPD	(-)	
(+) Vitreous Cells		Media	(+) Vitreous Cells	
0.3, Hyperemic disc; (-) pallor		Disc	0.3, Hyperemic disc; (-) pallor	

(+) Multiple whitish dots throughout the retinal midperiphery	Periphery	(+) Multiple whitish dots throughout the retinal midperiphery
Dull foveal reflex	Macula	Dull foveal reflex

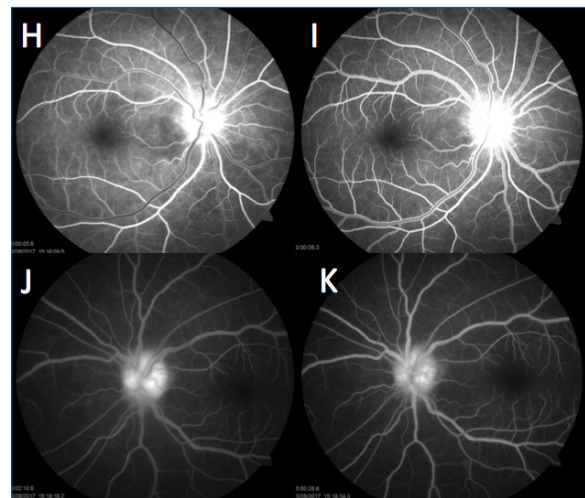
Physical examination at the time of consult shows that he is alert and coherent. Vita signs: BP: 110/80 mmHg HR: 80 bpm RR: 18cpm Temperature: 36.8 C O2 Sat 98% at room air. Funduscopic findings noted a clear media and hyperemic disc with indistinct borders. Cup disc ratio of 0.3 AV ratio of 2:3. No hemorrhages or exudates. Both eyes noted visual acuity of 20/20 with normal visual field and pupils. Multiple erythematous macules with papulovesicular lesions with some collarette scaling over both lower extremities were seen. The lungs, hear and gastrointestinal exam is normal. There were no genital lesions nor discharge. Neurologic examination is unremarkable.



Right fundus photo:
(D) Hyperemic disc with indistinct disc borders
(E) Multiple whitish dots in the retinal mid-periphery
Left fundus photo:
(F) Hyperemic disc with indistinct disc borders
(G) Multiple whitish dots in the retinal mid-periphery

A repeat Rapid Plasma Reagin (RPR) was suggested and revealed reactive at 1:256. Fluorescin Angiography, on the other hand, showed leakage of the optic nerve head. There are diffuse areas of retinal vasculitis in the retinal midperiphery. Fluorescent Treponemal Antibody Absorption Test (FTA-Abs) was positive which supported the diagnosis of Ocular Syphilis. However due to known history of Penicillin allergy, oral re-challenge desensitization with Penicillin V was done prior to giving the recommended treatment of Penicillin G 24 M units IV daily for 14 days.

Due to known history of Penicillin allergy, oral desensitization with Penicillin V was initiated first then subsequently administered a 2-week course of intravenous penicillin G (24 MU/day). The patient tolerated the antibiotic course and was discharged stable and improved. Follow-up ophthalmologic examination one month later showed 20/20 visual acuity bilaterally and complete resolution of inflammation. The patient was started on antiretroviral therapy thereafter.



Fluorescein Angiography Exam (above)
Right Eye: (H) Arteriovenous phase **(I)** Venous phase
Left Eye: (J) Arteriovenous phase **(K)** Venous phase
 The study shows leakage of the optic nerve head and diffuse areas of retinal vasculitis in the retinal mid-periphery

Discussion

As of March 2017, there are 968 new HIV antibody seropositive individuals reported to the HIV/ AIDS & ART Registry of the Philippines (HARP). This was 32% higher compared to the same period last year (735 individuals) and the highest number of cases ever reported in the Philippines since 1984.

Since the beginning of HIV/AIDS epidemic, there has been a high rate of HIV-1 (HIV) coinfection among syphilis patients. In 2002, the CDC reported that 25% of primary and secondary syphilis cases occurred in persons coinfecting with HIV, and the incidence rate of syphilis in HIV-infected persons was 77 times greater than in the general population [1].

Syphilis is an infection of the spirochete *Treponema pallidum*. It is spread through direct contact with a chancre; transmission occurs during sexual contact. It is dubbed “the great masquerader” due to wide variety of clinical presentations, which are highly variable, and with multiple clinical stages. To make the diagnosis even more challenging the stages can be overlapping. From its site of primary infection, bacteria disseminate systemically through the blood to potentially any organ.

Initially the lower extremity lesions in in this patient may appear like seborrheic dermatitis, but the picture of papulovesicular with collarette pattern, self-report of unprotected sexual intercourse and several diagnostic findings point to a single disease entity – secondary syphilis with ocular manifestations.

The patient exhibited a negative result on initial screening by the RPR test, although the clinical suspicion for secondary syphilis remained high. Between 0.2-2% with secondary syphilis will have a result that is nonreactive, a finding known as the prozone phenomenon. This is believed to be higher in the secondary Syphilis and Human Immunodeficiency Virus (HIV) co-infection [2]. It refers to a false negative response resulting from overwhelming antibody titers [3]. In our case, a high clinical suspicion for secondary syphilis led to a quantitative RPR being requested, which returned positive when

diluted and remained positive past a dilution of 1: 256.

The prozone phenomenon in the setting of syphilis may become prevalent because of the current acquired immunodeficiency syndrome (AIDS) epidemic [4]. As syphilis and HIV mutually increase the chance of contracting other diseases, anomalous B-cell behavior can lead to hyper-responsiveness to antigenic stimulation, leading to excess antibody production [5]. Many hospital laboratories do not routinely test for the prozone phenomenon which is performed by diluting the patient's serum to bring the antibody concentration into the zone of equivalence. Therefore, it is important to notify the laboratory in this regard, when the clinical findings strongly suggest syphilis and when the nontreponemal serological test results are negative.

Ocular syphilis can cause blindness if untreated, and clinicians must be vigilant in making this diagnosis. Lumbar puncture was offered to this patient but he refused. Although abnormal CSF study results are not necessary to make a diagnosis of ocular syphilis, lumbar punctures are warranted in HIV-infected patients with ocular disease, because a substantial proportion will have evidence of neurosyphilis. Syphilis with ocular involvement should be treated as neurosyphilis with intravenous penicillin G 24 million units daily for days [6]. Therefore even without the benefit of the lumbar puncture, treatment would be the same.

On the other hand, the therapeutic dilemma in this case is the history of penicillin allergy. Hypersensitivity reactions are the major problem in the use of penicillins. An individual who has exhibited immediate type of hypersensitivity with one penicillin should not be given any other type of penicillin. We take into consideration that *T. pallidum* replicates once every 30 hours, so sustained elevated intraocular levels of penicillin are required to achieve a bactericidal effect. Treatment failure may occur in patients treated solely with intramuscular penicillin, which does not achieve adequate, sustained intraocular concentrations [7]. This is therefore an absolute indication for penicillin desensitization where in such lifethreatening or serious infections no other alternative antibiotic is available for treating such cases [8].

The term desensitization traditionally applies to IgE-mediated drug reactions and relates to the induction of a temporary state of unresponsiveness to the drug, which caused the original hypersensitivity reaction. Desensitization comprises incremental administration of doses of the drug to which the patient is sensitized, with the aim of reducing immune responsiveness [9]. Drug desensitization requires considerable experience and specialist knowledge and should only be undertaken in specialist centers.

The patient underwent desensitization with Penicillin V first then subsequently administered a 2- week course of intravenous penicillin G (24 MU/day). The patient tolerated the antibiotic course and was discharged stable and improved. Follow-up ophthalmologic examination one month later showed 20/20 visual acuity bilaterally and noted to have complete resolution of inflammation. The patient was started on antiretroviral therapy thereafter.

Conclusion

Treponema pallidum is a challenging infectious agent to study because of its inability to be cultured or genetically manipulated, its physical fragility, and its outbred animal model. Hence, in the era of increasing HIV cases, the incidence of syphilis is increasing as well.

The case exhibited many of the prominent clinical findings associated with secondary syphilis. Although no large studies have been undertaken to determine the incidence of this prozone phenomenon in HIV-infected patients, particular care in this regard should be exercised in those patients in whom the clinical suspicion for syphilis is high when the RPR test returns negative. The RPR test in these situations should always be performed in a quantitative manner with serial dilutions to exclude the prozone phenomenon.

Acquired syphilis with ocular involvement should be treated as neurosyphilis with intravenous penicillin G 24 million units daily for two weeks. Sustained elevated intraocular levels of penicillin are required to achieve a bactericidal effect against *Treponema pallidum*. Hence, in patients with penicillin allergy, penicillin desensitization should be done since no other alternative antibiotic is available for treating such cases.

In conclusion, clinicians need to remain familiar with the protean manifestations of syphilis and familiar with prozone phenomenon when necessary. Since syphilis is a great masquerader, it requires a high index of suspicion and should be included in the differential diagnosis of visual complaints.

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