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Relapsing Syphilis with an Abnormal Timeline and Presentation in an HIV- Negative Patient

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Abstract

Despite the advent of effective and curable penicillin, the incidence of syphilis in the United States has returned to alarming levels. Consequently, the Centers for Disease Control and Prevention (CDC) 2022 Sexually Transmitted Infection (STI) surveillance report underscored that syphilis must be a public health priority. We report a case of a 52-year-old male, HIV-negative, who presented with laboratory-confirmed neurosyphilis, ocular syphilis and typical secondary-stage cutaneous syphilis. The patient was previously diagnosed with primary syphilis almost 20 years ago and was treated with the proper regimen of benzathine penicillin G. About 25% of patients with secondary syphilis will experience a relapse, usually within the first year of infection. There have been cases of relapsed syphilis in the past, however, these relapses tend to be because of either lack of treatment or treatment failure which is associated with being HIV positive or immunocompromised in some form. Typically, patients would have experienced a dormant period and then progression to tertiary syphilis. However, it is unreported to present with a secondary syphilitic rash at a timeframe of 20 years from the onset of infection, without evidence of reinfection.

Keywords: Secondary syphilis; Relapsed syphilis; Syphilis reinfection; Immune competent syphilis; Treatment resistant syphilis; Penicillin G

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Introduction

Treatment with penicillin G is the standard of care for patients at any early stage (primary, secondary and early latent) of syphilis. Penicillin G must be dosed appropriately based on the stage of the disease and circumstances of the patient, such as pregnancy status, time from initial infection, and if signs of neurosyphilis, ocular syphilis otosyphilis are present. This novel case outlines a patient that had contracted primary syphilis two decades ago, was treated per standard of care, and subsequently developed secondary syphilis while never evolving to the tertiary stage after 20 years. Normally an asymptomatic duration of this length would progress to the final stage with symptoms such as gummas, cardiovascular abnormalities, and tertiary syphilis neurologic signs or treatment would have eradicated the pathogen. Syphilis relapse presents more challenges to treat than re-infection due to the pathogens penetrance and is usually due to treatment failure. When a patient experiences treatment failure for syphilis, there is a strong association with an underlying HIV-positive status. Our patient, based on clinical diagnosis and patient history, experienced a relapse despite not being HIV-positive or immunocompromised.

Case Presentation

We describe a 52-year-old male that presented to the hospital with an acute onset diffuse maculopapular rash, affecting hands and soles and genitalia, night sweats, axillary and inguinal lymphadenopathy, headache and right-sided blurry vision. He denied ulcerative genital lesions, neurologic deficits, sensory changes, hearing loss, tinnitus, personality changes, psychiatric manifestations, ataxia, or spinal pain. He denied sexual contact for many years due to being the primary caregiver for his elderly parents. Physical exam showed the presence of diffuse red pruritic maculopapular rash with evidence of pan-uveitis and optic neuritis. Comprehensive workup showed non-reactive HIV 1/O/2 antibodies and p24 antigen, hepatitis B surface antigen and hepatitis C antibodies. Rapid Plasma Reagin (RPR) titer was 1:128. Brain computed tomography and magnetic resonance imaging showed no acute or chronic parenchymal or vascular disease. Spinal fluid analysis

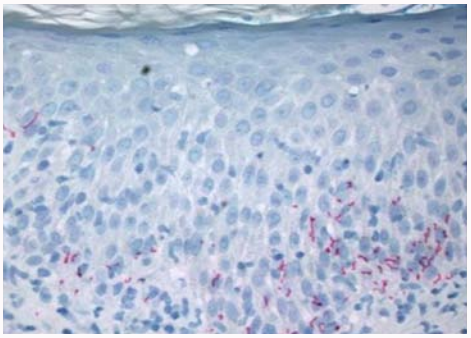

Figure 1: 40x with a Treponema pallidum stain showing numerous spirochetes in the bottom portion of the epidermis.

revealed pleocytosis with lymphocytic predominance (cell count=278/mm^3 with 91% lymphocytes) with mild proteinorachia of 62 mg/dL. CSF gram stain and India Ink did not identify any pathogens and culture yielded no growth. Meningoencephalitis panel was negative however, FTA-ABS of cerebrospinal fluid was reactive. Punch biopsy from the abdominal cutaneous lesions was performed and confirmed the diagnosis of syphilis (Figure 1). Transthoracic echocardiogram and computed tomography of the chest with IV contrast showed no evidence of aortic valve disease or thoracic aortitis. He received 14 days of IV aqueous crystalline penicillin G 24 million IU daily x10 days resulting in resolution of optic symptoms and cutaneous lesions. Repeat RPR titers showed >4 -fold drop in 6 months (1:16) ensuring response to therapy.

Discussion

Overall, in 2022, more than 2.5 million cases of syphilis, gonorrhea, and chlamydia were reported in the United States, which has been consistent between 2018 and 2022 [1]. However, syphilis cases (all stages and congenital syphilis) have increased by 80% in 2022, signaling an urgent need for immediate innovation to stop the tide of this raging treponema. During 2018 to 2022, 41.1% of men with incident primary and secondary syphilis reported having sex with men (MSM; 94,342). The number of cases among MSM increased 6.6% (18,760 in 2018 to 20,004 in 2022), while the number of cases increased 193.3% among women (4,995 in 2018 to 14,652 in 2022), increased 146.7% among men who have sex with women only (MSW; 5,416 in 2018 to 13,359 in 2022), and increased 86.9% among men who have sex with unknown sex of sex partners (MSU; 5,858 in 2018 to 10,946 in 2022). About half (47%) of MSM diagnosed with syphilis in the United States also live with HIV [2]. In addition, one in 20 MSM are diagnosed with HIV within a year of being diagnosed with syphilis, a finding that highlights the strong association between incident syphilis and an increased risk of HIV infection. Alarmingly, the rising substance use disorder appears to be an unfolding driver for syphilis especially in women. In 2022, 11.8% (women; 17.4%) of the incident syphilis cases reported methamphetamine use, 7.0% (women; 11.8%) reported injection drug use, 3.8% (women; 4.8%) reported cocaine use, 2.2% (women; 4.5%) reported heroin use, and 1.5% (women; 3%) reported crack use [1]. The alarming increase in the number of cases of syphilis among women of childbearing age is mirrored by increasing numbers of Congenital Syphilis (CS) cases [1]. In 2022, more than 3,755 newborns were diagnosed with congenital syphilis, which is more than 10 times the number diagnosed in 2012 and a 30% increase from 2021. All stages of syphilis in pregnant women pose a risk of transmission to the fetus, but the risk is substantially higher with early syphilis (~80%) than with later stages of disease. These data suggest a link between substance use disorder, primarily intravenous drug use and methamphetamine, and the rise of CS in the United States [3]. The primary solitary indurated and ulcerative lesion (chancre) in patients with syphilis develops two to six weeks after infection occurs, presenting with a clean base, heaped-up borders, and is usually painless [4]. It typically appears at the site of inoculation and is often unnoticed [4]. The chancre may occur at extragenital sites such as the perirectal area, the rectum, and the oral cavity. Multiple painful anogenital ulcers may also occur [3,5]. The primary chancre resolves spontaneously, and, without treatment, the infection progresses to a more advanced stage. However, Treponema pallidum disseminates within days of infection, resulting in early invasion of the distant tissues, including the Central Nervous System (CNS), eyes, and placenta in pregnant women [6]. Clinical manifestations of secondary syphilis include evanescent, nonpruritic, non-vesicular, maculopapular rash, particularly on the palms and soles; fever; lymphadenopathy; mucosal lesions (e.g., mucous patches or condyloma latum-wart-like lesions); alopecia; periostitis; and occasionally hepatitis (often with high alkaline phosphatase values but minimally elevated aminotransferase levels) or nephritis [3]. Primary syphilis and secondary syphilis are highly contagious and are considered the sexually transmissible stages of infection [3]. Concurrent chancre and rash may occur up to 9% of syphilis cases [3]. The secondary syphilis rash can frequently go unrecognized or misidentified. Early asymptomatic latent syphilis (<1 year from the time of infection) can occur between the primary and secondary stages and can also occur after the resolution of the secondary stage lesions [3]. In up to a quarter of patients, early latent syphilis is interrupted by relapse with recurrent, infectious secondary lesions [3]. However, secondary stage cutaneous lesions are unusual later in the disease during the late asymptomatic latent syphilis (>1 year from the infection) and tertiary syphilis, and our finding is unprecedented.

Following exposure, at least 30% of infected individuals experience CNS involvement during any stage of syphilis [3,7,8]. Early asymptomatic neurosyphilis has been documented in 25% to 35% of persons with early syphilis [8]. Treponemal invasion of the CNS (neurosyphilis) is accompanied by abnormal Cerebrospinal Fluid (CSF) findings in up to 50% of persons after early infection, regardless of the presence of absence of symptoms [3]. These cerebrospinal fluid abnormalities will resolve in most persons without treatment. Early symptomatic neurosyphilis occurs in 6% to 10% of all cases of neurosyphilis and manifests primarily as acute basilar meningitis (some of acute syphilitic meningitis may never have had early asymptomatic neurosyphilis) [3,7,8]. Among those with late syphilis (excluding symptomatic neurosyphilis), 13.5% have asymptomatic neurosyphilis [8]. It is not known whether all persons with late asymptomatic neurosyphilis had early asymptomatic neurosyphilis or if only a subset. The late tertiary neurologic manifestations of syphilis, whether meningovascular (stroke, meningomyelitis, and spinal vascular syphilis; 11% of all cases of neurosyphilis), parenchymatous (general paresis and tabes dorsalis; 58%) and CNS gummas (1%), likely progress from late asymptomatic neurosyphilis; however, some cases may not have experienced antecedent asymptomatic neurosyphilis. They can occur 2 to 50 years after the initial infection (meningovascular and parenchymatous forms tend to occur 2-15 years and >15 year after infection, respectively) [7]. Ocular syphilis (any part of the eye but primarily uveitis) and otosyphilis (hearing loss and tinnitus) are, theoretically,

distinct entities from neurosyphilis but may occur concomitantly [9,10]. Like neurosyphilis, they can occur during any stage of infection [8]. Clusters of cases of ocular syphilis have been recently reported throughout the United States [11,12]. In addition to the neurologic manifestations, cardiovascular disorders and gummas are the other tertiary manifestations of syphilis [3]. Cardiovascular syphilis occurs 15 to 30 years after infection and may lead to the development of aortic aneurysms (often involving the ascending aorta), aortic insufficiency, coronary-artery stenosis, and myocarditis. Gummatous syphilis (also called late benign syphilis) represents a proliferative granulomatous process that can occur in any tissue, including the brain [3,8]. Direct detection of T. pallidum with darkfield microscopy and nucleic acid amplification when lesions are present can be used to diagnose primary syphilis [13]. However, a negative nucleic acid amplification test does not exclude syphilis. When tissue sections are available, immunohistopathological identification of organisms is the preferred method for detecting T. pallidum (Figure 1). Most syphilis cases are diagnosed by means of serologic testing with either a nontreponemal lipoidal antigen test (e.g., a Rapid Plasma Reagin [RPR] or Venereal Disease Research Laboratory [VDRL]) or treponemal serologic test (e.g., Enzyme Immunoassay [EIA] or Chemiluminescence Assay [CIA]. Serologic results are nonreactive in up to 30% of persons with primary syphilis, and testing should therefore be repeated in 2 weeks if the initial test result is nonreactive [3]. Nontreponemal test titers often decline rapidly after treatment but may also decline, although more slowly, in the absence of treatment. Treponemal tests remain reactive irrespective of the treatment history, but up to 24% of patients treated in the early stage of syphilis have seroreversion years after therapy [14].

Neurosyphilis is diagnosed based on a combination of CSF tests, reactive serologic test results, and neurologic signs and symptoms. Pleocytosis (>5 cells/mm^3; >20 cells/ mm^3 in HIV-infected patients who are not receiving antiretroviral therapy) is a sensitive but not a specific marker for neurosyphilis. CSF protein levels may be elevated in patients with neurosyphilis, but this finding has limited sensitivity and specificity. A reactive CSF nontreponemal test (e.g., VDRL) is highly predictive of neurosyphilis, although it is less than 80% sensitive. A CSF treponemal test (e.g., Fluorescent Treponemal Antibody Absorption Test [FTA-ABS]) can be sensitive, but it lacks specificity owing to passive transfer of serum treponemal IgG antibodies across the blood–CSF barrier or to traces of blood in the CSF. Although not usually recommended, a CSF treponemal test may be useful to rule out neurosyphilis when the pretest probability is moderate to low [15]. A polymerase-chain reaction assay of CSF for T. pallidum, although specific, is insensitive [13]. Routine CSF examination in early syphilis is not indicated, irrespective of HIV status, unless neurologic signs and/or tertiary syphilis are present [16]. Furthermore, a CSF examination may be considered in neurologically asymptomatic patients with inadequate serologic responses on nontreponemal testing after therapy [16]. Risk factors for neurosyphilis in HIV-infected patients include a serum RPR titer of ≥1:32, a peripheral blood CD4 count of ≤350 cells/mm3, and an absence of antiretroviral therapy [17,18]. Asymptomatic neurosyphilis does not predict treatment failure, even in patients with HIV infection [19]. A CSF examination is not necessary to diagnose ocular or otic syphilis in patients with reactive serologic tests because up to 30% of patients with ocular syphilis and up to 90% of patients with otosyphilis have a normal CSF examination [20-22]. All women should be screened for syphilis early in pregnancy to prevent congenital syphilis. Women at high risk for infection should be screened again at 28 weeks of gestation and at delivery [16]. Penicillin is highly effective for all stages of syphilis and is the drug of choice [23]. A single dose of 2.4 million units of long-acting intramuscular penicillin G benzathine sustains treponemicidal drug levels in blood for 7 to 10 days and is effective in the treatment of uncomplicated early syphilis [16]. An additional dose of penicillin G benzathine 1 week after the first dose for the treatment of early syphilis in pregnancy can be considered because of an increase in the volume of distribution. Late latent syphilis is treated with a total of three doses of penicillin G benzathine, given at weekly intervals (7-10 days may be acceptable in non-pregnant adults) [16]. For persons with a documented penicillin allergy, desensitization and treatment with penicillin are recommended, primarily during pregnancy. Alternative antibiotic agents (e.g., doxycycline and ceftriaxone) should be considered only when treatment with penicillin is not possible or is absolutely contraindicated [24-28]. Persons with neurosyphilis or ocular or otosyphilis are treated with intravenous aqueous penicillin G because of the inability to achieve measurable levels of penicillin G benzathine in the CSF [29]. Ceftriaxone penetrates the CNS well and is an option for treating neurosyphilis in nonpregnant adults with penicillin allergy in whom desensitization is not possible. Despite the lack of consistent treponemicidal concentrations in the CSF, three weekly doses of penicillin G benzathine was an approved alternative regimen for the treatment of neurosyphilis until the early 1980s and was reasonably effective [30,31].

The major goal of treatment for syphilis is a clinical and serologic cure. A decline in nontreponemal titers by 4 -fold (2 dilutions), 6 to 12 months after therapy for early syphilis and 12 to 24 months after therapy for late syphilis, is considered the best judgement of serologic cure [16]. Clinical data show that 10% to 20% of patients with early syphilis do not achieve serologic cure (serofast), indicating treatment failure [32,33]. Seroconversion of the nontreponemal test titer measured 1 year after receiving antibiotics occurs in only 22% of patients who are treated for early syphilis [14]. Clinically, it is unclear whether patients with a serologic nonresponse are at increased risk for disease progression albeit the current recommendation is to consider a CSF examination [16,34,35]. Currently, the rates of serologic screening are lagging even among the highest risk groups [36]. Furthermore, preexposure HIV prophylaxis (PrEP) might have contributed to the increase rates of syphilis and reinfection [37]. Hence, the effectiveness of syphilis treatment is closely related to the effectiveness of antibiotics. Intramuscular benzathine penicillin G, very effective for early uncomplicated syphilis, does not result in appropriate penicillin therapeutic levels in the CSF for those suffering from T. pallidum neuroinvasion. Such patients are likely to encounter subtherapeutic levels of antibiotics, which serve as a selection pressure for mutants with low-level penicillin resistance [38]. This resistance would not be immediately detectable and would be easy to overcome if the patients are retreated with higher doses of intravenous penicillin for clinical relapse [38]. In fact, additional intramuscular benzathine penicillin therapy in patients with syphilis and a serologic non-response did not reveal improved serologic outcomes [39]. Prior to treatment of relapsing infection, the continued transmission of treponemes with low-level penicillin resistance to new hosts and the recurrent exposure to increasing levels of penicillin of these treponemes may eventually select mutants with a clinically relevant degree of penicillin resistance [38]. The mechanisms of penicillin resistance include producing β-lactamases to degrade the

penicillin, acquiring additional or expressing endogenous low-affinity Penicillin Binding Proteins (PBPs), altering PBPs via point mutations or homologous recombination, decreasing outer-membrane permeability, exporting the penicillin, or multifactorial [40]. There is little evidence supporting the emergence of penicillin-resistant T. pallidum, possibly because it takes a multistep mutational process to develop penicillin resistance [41]. Nonetheless, recent studies have reported various Single-Nucleotide Polymorphisms (SNPs) of T. pallidum that appear to be related to penicillin resistance [41-44]. Recently, an abundant membrane protein of T. pallidum, Tp47, was found to have a unique β-lactamase activity, capable of producing a novel, true penicillin resistance [45,46]. A better understanding of the real causes of treatment failure contributes to devising proper treatment regimens for patients with early syphilis in clinical practice and to the prevention and control of syphilis.

Conclusion

This patient presents with a potential clinical relapse of an original T. Pallium infection diagnosed 20 years prior having clinical features of secondary syphilis with ocular syphilis, late neurosyphilis, and absent gummas, tabes dorsalis, and aortitis. He failed weekly intramuscular benzathine penicillin G x3 which is most likely secondary to neuroinvasion. Intramuscular benzathine penicillin G, very effective for early uncomplicated syphilis, does not result in appropriate penicillin therapeutic levels in the CSF for those suffering from T. pallidum CNS involvement. Regardless of whether this was a relapse from the original infection 20 years ago or a reinfection with late latent stage of syphilis (>1 year without sexual contact), secondary cutaneous manifestation is an unusual presentation that should be considered in tertiary syphilis. With syphilis currently on the rise, it is imperative that strides are made to ensure that treatment success is achieved by reaching a deeper level of penetrance with penicillin to eradicate traces of treponema that lie in the deeper structures of the central nervous system, otherwise, patients could end up with recurrent symptoms of secondary syphilis and spreading treponema to other patients. Primary care physicians should continue to observe for signs of reinfection or relapse of primary infection post initial treatment with targeted physical exams and labs to ensure patient health outcomes and adherence to safe sex practice. It cannot be overstated that physicians should continue to educate their patients on their treatment and safe sexual practices to prevent disease before obtaining it.

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