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Case Report
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Secondary Syphilis and Human Immunodeficiency Virus (HIV) Co-infection in Men Who Have Sex with Men (MSM) with Triple Doses Benzathine Penicillin G Treatment: A Case Report

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ABSTRACT

Background: World Health Organization (WHO) reported that there are 6 million new cases of syphilis worldwide per year. The incidence of syphilis in Indonesia has increased over the past few years, particularly among men who have sex with men (MSM). **Purpose:** To report a case of secondary syphilis with Human Immunodeficiency Virus (HIV) coinfection in MSM, thereby increasing understanding of high-risk sexual behavior among MSM. **Case:** A 26-year-old man with a chief complaint of rashes on both palms, soles of the feet, and face. The rashes spread with no itching, heat, or pain, which occurred two weeks ago. The patient was diagnosed with HIV in 2019. Physical examination found multiple violaceus macules with clear boundaries, 0.5–1 cm in size, covered with scales. Venereal Disease Research Laboratory (VDRL) serology titer was 1:16 and Treponema Pallidum Haemagglutination Assay (TPHA) was 1:20.480. The recent CD4 count was 440 with an undetectable HIV RNA viral load. Benzathine penicillin G 2.4 million units was given intramuscularly 3 times at 1-week intervals. The patient experienced clinical improvement and decreased VDRL and TPHA titers. **Discussion:** Syphilis patients with or without HIV would have similar clinical symptoms. However, syphilis patients with HIV tend to have more extensive lesions. The treatment option with three doses of benzathine penicillin G is still very effective in cases of syphilis with HIV. **Conclusion:** Syphilis has a higher incidence in MSM patients with extensive clinical manifestations of skin lesions. It can be observed in syphilis patients with HIV; therefore, close monitoring is needed.

Keywords: Sexually Transmitted Disease, secondary syphilis, human immunodeficiency virus (HIV), Men Who Have Sex with Men (MSM), benzathine penicillin G.

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BACKGROUND

Syphilis is an infection caused by *Treponema pallidum* sub-species *Pallidum*. It is mostly transmitted through sexual contact, but vertical transmission from mother to fetus could also occur. Syphilis is a chronic disease that can infect almost all body organs and has a varied clinical presentation It can resemble many other skin diseases, so it is known as "the great imitator".[1] Syphilis has primary, secondary, latent, and tertiary stages. Each stage has different clinical symptoms.[2]

Most people with Human Immunodeficiency Virus (HIV) continue to have active sexual intercourse, thus increasing the risk of sexually transmitted infections (STIs). Syphilis is associated with high-risk sexual behavior and increased transmission and acquisition of HIV infection.[3]

According to World Health Organization (WHO) and European Center for Disease Prevention and Control, there are 6 million new syphilis cases worldwide per year.[4]

The incidence of syphilis in men who have sex with men (MSM) has increased globally over the past few years, especially in western countries.[5,6] In Europe, the incidence of syphilis is 5.1 cases per 100,000 population. Since 2009, the incidence of syphilis in men has increased in Europe, especially in Western European countries, while the incidence in women has

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concomitantly decreased.[7] From 2001 to 2004, the number of reported syphilis cases in Germany doubled to more than 3,000 cases per year and remained stable until 2009. While in 2010 to 2014, the number increased by approximately 11% and 22% per year.[8]

In 2016, a study in Germany reported 54,747 new syphilis cases between January 1st, and December 31st, 2015. Also, the number of cases has increased since 2010. In 2015 alone, there were 6,834 cases, which corresponds to an increase of 19.4%. The incidence was 8.5 cases per 100,000 population as a whole, with the highest incidence above 20.0, especially in big cities such as Berlin (39.0), Cologne (35.6), Munich (30.0), Frankfurt am Main (29.5), Dusseldorf (26.6), Leipzig (23.7), Hamburg (21.4), and Stuttgart (20.4). The incidence of syphilis is higher in the Berlin city center area, with an incidence rate of 62.8-117.8 cases per 100,000 population. An increase in the cases was reported in 14 of Germany's 16 states in 2015.[9]

In 2015, the case incidence in men was 93.8%, with 84.7% in the MSM group, 15.0% in the heterosexual group, and 0.3% in other groups. In a sub-sample analysis of men who identify as gay, aged 30-44 years, and living in a city with more than 500,000 inhabitants, the HIV prevalence was 15.9% in 2003, 14.9% in 2007, 16, 9% in 2010, and 22.3% in 2013.[9]

In 2003 and 2013, the proportion of MSM infected with HIV and newly diagnosed syphilis increased from 9.3% to 19.0%. The proportion of MSM not infected with HIV and newly diagnosed syphilis ranges between 1.7% and 2.7%.[8,9]Approximately one-third of cases in the MSM group have tertiary stage syphilis, and such infection may return to remission. This emphasizes the importance of sex education and STI screening in the MSM group.[10]

In Indonesia from nine provinces in 2005 involving 2,500 female sex workers, seroprevalence of syphilis was 8.7%. A recent review studies conducted worldwide reported a 9.5% prevalence of syphilis among adults with HIV infection.[11]

In Indonesia, HIV prevention efforts have been carried out for over a decade, but a decrease in HIV prevalence among MSM has yet to be seen. Analysis of the 2011 Integrated Biological and Behavioral Survey reported that HIV prevalence among MSM increased from 5% in 2007 to 12% in 2011. In the same year, the prevalence of HIV and syphilis among MSM in Surabaya was 5.6% and 4%, respectively.[12]

We report a case of secondary syphilis with HIV coinfection in MSM. This case is reported due to give an alternative treatment for secondary syphilis with HIV patient using triple doses of benzathine penicillin 2.4 million units with 1 week interval.

CASE REPORT

A 26-year old male patient came to the Hospital, with a chief complaint of red rash on the palms of the hands, the soles of the feet, and the face. This complaint was first noticed about two weeks prior to examination. Initially, it appeared on the palms, soles, the face and kept spreading. Futhermore, the patient also complaint of reddish round with scales on his palms and soles. Itchy, burn and pain on his red rash were denied by the patient. The patient reported that he had been using steroid ointment, for 2 weeks before hospital visit but showed no improvement. No abnormal hair loss or history of sores in the genital area was observed.

The patient was first diagnosed with HIV at the beginning of 2019 and has received antiretroviral (ARV) therapy and routinely monitored for the past two years. During the initial diagnosis of HIV, the patient's CD4 cell was 72 cells/μL. The patient was also diagnosed with pulmonary tuberculosis (TB) and cerebral abscess in early 2019, which caused decreased of consciousness and weakness in the right leg and hand. After the patient received ARV, treatment for TB and cerebral abscess, CD4 cell increased to 163 cells/μL. In the last 9 years, the patient has been sexually active with multiple same-sex partners. One of them was infected with HIV, history of using drugs, blood transfusions, or sharing needles were absent and had no history of drug allergies. During the visit, his other complaints were fever, headache, weakness, diarrhea, and cough. Also, weight loss was denied.

The physical examination showed blood pressure of 110/70 mmHg, pulse 90x/minute, respiratory rate 19x/minute, and body temperature of 36.4 °C. The head and neck examination showed no anemia, icterus, cyanosis, or dyspnea. Cardiac and pulmonary examinations were within normal limits. Abdominal examination was within normal limits. Bowel sounds were audible and normal, and the liver and spleen were not palpable. There was no edema in the upper and lower extremities, and the extremities felt warm, dry, and red. No enlarged lymph nodes.

Dermatological examination of the face (Fig. 1–2), palms, and soles showed multiple violaceous macules with clear boundaries, varying sizes on average about 0.5 cm x 1 cm. Also, a few scales were observed (Fig. 3–4), and no abnormalities were found in the genitalia and oral mucosa.

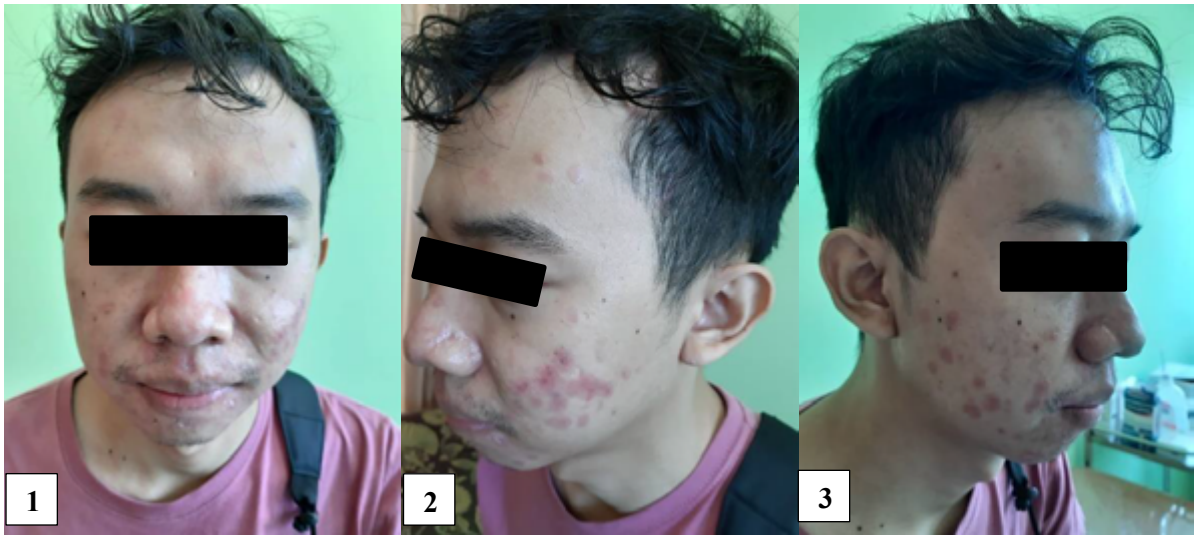

Figure 1–3. Physical examination of the facial region before being given treatment. Multiple violaceous macules with clear boundaries in the facial area, varying sizes and little scaling on top.

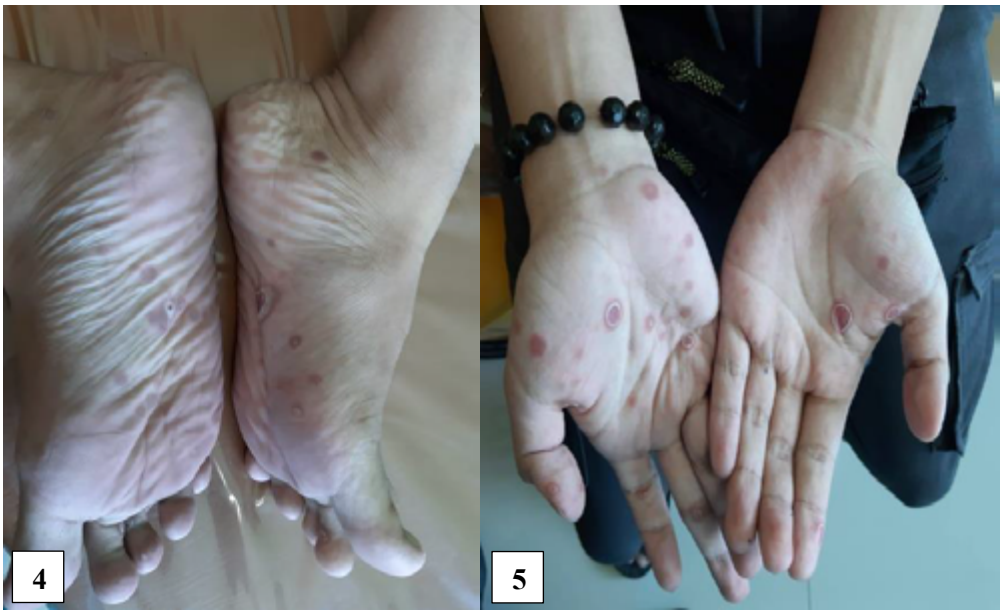

Figure 4–5. Physical examination of right/left plantar pedis region and right/left plantar manus before treatment was given, multiple macula violaceus with clear boundaries with scales on the palms and soles of the feet, varying sizes and scales on top.

The result of Venereal Disease Research Laboratory (VDRL) examination, the titer was 1:16, and Treponema Pallidum Haemagglutination Assay (TPHA) result was 1:20,480.

The patient's working diagnosis was secondary syphilis and HIV. The treatment given was the injection of benzathine penicillin G 2.4 million units intramuscularly 3 times at 1 week intervals. One week after treatment completion, the multiple macula violaceus began to shrink and fade, but some became hyperpigmented with overlying scales. No enlarged lymph nodes were found. After one month of therapy, the VDRL and TPHA examination showed reactive VDRL/Rapid Plasma Reagin (RPR) with a titer of 1:2 and reactive TPHA with a titer of 1:1,280. The result of the patient's CD4 examination was 440, and the HIV Ribo Nucleic Acid (RNA) viral load examination result was not detectable.

Serological examination as an evaluation one month after treatment was done. A decrease in the value of VDRL and TPHA titers and clinical improvement was found, indicating a good response to the therapy.

Figure 6–8. Physical examination of the facial region after one month of treatment. It showed violaceus macula with clear boundaries. Some had begun to fade, others disappeared, and some became hyperpigmented.

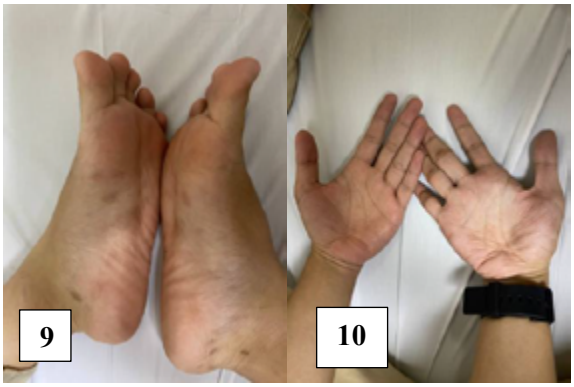

Figure 4–5. Physical examination of right/left plantar pedis and right/left plantar manus after one month of treatment. It showed violaceus macula with clear boundaries. Some had begun to fade, others disappeared, and some became hyperpigmented.

DISCUSSION

Syphilis is a sexually transmitted disease with a high incidence.[2] According to WHO, the highest prevalence of syphilis and HIV is found in Africa and Asia. However, epidemiological data are still lacking, especially in sub-Saharan Africa. A source reports that the average prevalence of syphilis in HIV-infected persons is 9.5%.[13] Globally, MSM groups are at high risk for syphilis infection.[14]

The United States Centers for Disease Control and Prevention (CDC) states that more than half of homosexual men with primary and secondary syphilis have been infected with HIV. [15]

Men who have sex with men (MSM), commonly referred to as homosexual men, describe varied behaviors, identities, and health. High-risk MSMs are those who have HIV infection or other sexually transmitted infections, such as viruses or bacteria. This further increases the risk of transmission because MSM usually engages in anal sex. Anal mucosa is more susceptible to certain sexually transmitted infection pathogens. In addition, most of them do not use practice safe sex and have multiple partners. In this case we reported, a 26-year-old patient with secondary syphilis and HIV has several risk factors, such as having multiple partners with new individuals, having anal sex, not using a condom, and being infected with HIV.[16,17,18]

Syphilis has four stages: primary, secondary, latent, and tertiary. Each stage of syphilis has specific clinical characteristics. In the early stages, there is a painless ulcerative phase. In the second stage, there are systemic manifestations such as rash, symptoms such as viral infection, lymphadenopathy, and hepatosplenomegaly. In the latent stage, usually, there are no symptoms (asymptomatic). The tertiary stage is usually characterized by chronic infection. In addition, neurosyphilis can develop at any stage of infection.[2]

Syphilis patients with and without HIV infection have similar clinical symptoms. In the early stages of syphilis, it is characterized by well-defined, relatively painless ulcers that evolve from papules on the genitals. These papules usually appear 10–90 days (mean 3 weeks) after sexual contact. The sizes vary from 0.5 cm to 1.5 cm in diameter, and after one week, these papules turn into ulcers with the characteristics of primary

syphilis, round or slightly elongated ulcers. These ulcers have a clean base without exudate and are painless. Usually, these ulcers appear on the external genitalia but can also appear in other places, such as the cervix, mouth, and area around it, perianal and anal canal. These ulcers can heal spontaneously without treatment and scarring. The healing process of this ulcer usually takes about 10–14 days. However, it can develop into a secondary infection without adequate treatment.[19,20] Unilateral or bilateral lymphadenopathy may also occur in primary syphilis. Patients infected with syphilis and HIV have ulcers characteristic of primary syphilis. These ulcers are usually larger, deeper, and multiple.[19] In 2–12 weeks or even a year after primary infection, signs and symptoms will disappear with the formation of an effective immune response.

Secondary syphilis usually accounts for about a quarter of all untreated syphilis cases. It results from *Treponema pallidum* multiplication and lesion formation from multiple sites on the skin and internal organs, despite a significant antibody response. Secondary syphilis occurs after the hematogenous spread of the ulcer, usually 4–10 weeks after the appearance of primary syphilis in an immunocompetent patient. In 75% of HIV patients, secondary syphilis may be present, even though ulcers from primary syphilis are still present.[21] Secondary syphilis has several symptoms: fever, headache, anorexia, weight loss, sore throat, and myalgia. The most characteristic symptom of secondary syphilis is a diffuse papular rash, usually on the trunk, extremities, palms, and soles. The lesions are generally 0.5 to 2 cm in diameter with a moderate degree of peripheral (collarette) scale that is typically seen on the palms of the hands and soles of the feet.[19] Other dermatological signs include mucosal lesions, condyloma lata, alopecia, and lymphadenopathy. In patients with advanced HIV, secondary syphilis may present as malignant syphilis. It is characterized by severe ulceration and infiltration of the gums, mouth, eyes, subcutaneous tissue, bones, joints, and the cerebrospinal system [19]. Closer observation is needed in HIV patients with secondary syphilis because aggressive secondary syphilis symptoms may develop. In syphilis patients with HIV, the clinical stages can progress rapidly, often having atypical clinical symptoms. In addition, HIV-co-infected patients often have neurological disease progression and usually respond poorly to conventional syphilis treatment.[22] In this case, the patient we observed showed no signs of aggressive secondary syphilis. Our patient came with chief complaints of the appearance of multiple violaceus macula on the palms, the soles, and the face.

Latent syphilis is a stage that has few symptoms and a reduced rate of transmission. However, the untreated latent stage will develop tertiary syphilis.[19]

Cardiovascular symptoms in tertiary syphilis, such as coronary aortitis, aortic regurgitation, and aortic aneurysm, are the three most common manifestations and develop 10 to 30 years after initial infection.[19] Gumma can appear one year after infection but is most likely to occur 15 years after the initial infection. Gumma lesions can form in any organ and can cause ulcers. Neurosyphilis, which occurs in the tertiary stage, is known as late-phase neurosyphilis, while neurosyphilis, which occurs in the early stages, is known as early-phase neurosyphilis. In the early stages of syphilis, *Spirochetes* enter the central nervous system and cause early-phase neurosyphilis with symptoms, such as meningitis, stroke, seizures, myelopathy, brainstem disorders, cranial nerve disorders, vestibular disease, and eye disease. Late-phase neurosyphilis usually involves the brain and spinal cord parenchyma, causing symptoms of dementia, tabes dorsalis, generalized paresis, sensory ataxia, and bowel or bladder dysfunction.[19]

The diagnosis of syphilis is made based on clinical symptoms, physical examination, and laboratory results. Laboratory tests for the diagnosis of syphilis include direct detection methods (dark field microscopy examination, direct fluorescence antibody test), serology (treponemal and non-treponemal tests), and cerebrospinal fluid examination. The direct detection method requires exudate from lesions in primary or secondary syphilis. Darkfield microscopy examination showed the morphological character and motility of *treponema* in the exudate taken from the lesion. Direct fluorescence antibody test uses a fluorescent microscope to detect *Spirochetes* stained with the fluorescent anti-globulin *Treponema Pallidum*. In the serological examination, the specimen used is blood serum. The most commonly used non-treponemal serological tests are VDRL (Veneral Disease Research Laboratory) or RPR (Rapid Plasma Reagin). Non-treponemal tests can be negative up to 4 weeks after the first lesion appears in primary or secondary syphilis and can be negative in latent late-phase syphilis. Treponemal tests include TPHA (Treponema Pallidum Haemagglutination Assay), TPPA (Treponema Pallidum Particle Agglutination Assay), and FTA-BS (Fluorescent Treponemal Antibody Absorbed). This test is highly specific because it detects antibodies against specific treponemal antigens.[23]

Patients with primary syphilis and secondary syphilis can receive an injection of benzathine penicillin G 2.4 million units intramuscularly single

dose. This antibiotic is bactericidal by inhibiting the synthesis of bacterial cell walls during the active multiplication phase. Alternative therapy when penicillin can not be used is doxycycline 2x100 mg orally for 14 days and tetracycline 4x500 mg orally for 14 days or ceftriaxone injection 1x1g intramuscularly for 10 days or azithromycin 2g single dose orally. In latent syphilis cases, injection of benzathine penicillin G 2.4 million units is given 3 times with an interval of 1 week. If penicillin can not be given, doxycycline 100 mg twice daily or tetracycline 500 mg 4 times daily for 28 days can be used.[24] Some authorities, in contrast, believe that minimum therapy for primary or secondary infection without neurologic involvement in HIV-infected patients should be three doses each of 2.4 million units of benzathine penicillin at weekly intervals. According to the American Centers for Disease Control and Prevention, the treatment option for primary or secondary syphilis with HIV coinfection is the injection of benzathine penicillin G 2.4 million units intramuscularly once a week for 3 weeks.[25] This is in accordance with this case, where the patient was given injection therapy of benzathine penicillin G 2.4 million units intramuscularly 3 times with an interval of 1 week. The patient experienced improvement with a reduced red rash on the face, palms, and feet soles. There was also a decrease in the VDRL and TPHA titers, indicating a good response to the therapy.

A patient diagnosed with secondary syphilis and HIV had a significantly improvement with triple doses benzathine penicillin G injection therapy.

The high incidence of syphilis in the MSM group, screening for STIs is important. In syphilis patients with HIV, close monitoring is required because, in progressing HIV cases, secondary syphilis can also appear as malignant syphilis and manifest in more extensive skin lesions. Aggressive treatment is also needed for HIV patients with syphilis.

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