Sifilis Sekunder pada Pasien HIV: Laporan Kasus

(Secondary Syphilis and Human immunodeficiency virus (HIV) Coinfection: A Case Report)

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ABSTRAK

Latar Belakang: Sifilis merupakan penyakit menular seksual yang disebabkan oleh mikroorganisme *Treponema pallidum.* Infeksi *Human Immunodeficiency Virus* (HIV) dapat terjadi bersamaan dan saling mempengaruhi. **Kasus:** Pria, 33 tahun dengan keluhan bercak-bercak merah di badan, kedua tangan dan kaki sejak 1 bulan, tidak nyeri ataupun gatal. Awalnya bercak merah timbul di tangan kemudian menyebar ke bagian tubuh lainnya. Pasien memiliki riwayat luka di kelamin yang sembuh sendiri 3 bulan sebelumnya. Pemeriksaan fisik ditemukan makula eritematosa multipel batas jelas, diameter 0,5-1 cm, beberapa tertutup skuama tipis. Pasien telah didiagnosis HIV sejak 1 tahun yang lalu dan mendapatkan antiretroviral (ARV) secara rutin. Titer serologi *Venereal Disease Research Laboratory* (VDRL) 1:128 dan *Treponema pallidum* Hemagglutination Assay (TPHA) 1:1280. Pasien diberikan terapi penisilin G 2,4 juta intramuskular dosis tunggal. Kasus ini menunjukkan adanya fluktuasi nilai tes serologis pada bulan keenam dan ke sembilan. **Penatalaksanaan:** Diagnosis sifilis ditegakkan berdasarkan anamnesis, pemeriksaan fisik, dan pemeriksaan laboratoris. Terapi sifilis sekunder adalah benzathine penisilin G 2,4 juta unit intramuskular dosis tunggal. Diperlukan waktu lebih lama pada terapi pasien sifilis dengan HIV dan *follow up* tes serologis lebih lanjut masih dibutuhkan hingga 24 bulan. **Simpulan:** Hasil tes serologis nontreponemal (dapat tinggi, rendah, atau berfluktuasi) dapat ditemui pada pasien sifilis dengan HIV. Kesesuaian antara gambaran klinis, diagnosis, dan strategi manajemen pada pasien sifilis dengan HIV harus dikenali oleh seorang klinisi.

Kata kunci: sifilis sekunder, koinfeksi HIV, tes serologis, penisilin.

ABSTRACT

Background: Syphilis is a sexually transmitted disease caused by spirochete microorganism *Treponema pallidum*. Significant risk factors include HIV infection, thus coinfection is common, and the two diseases affect each other in several ways. **Case:** Thirty-three years old man came with chief complaint multiple rash on his trunk and extremities since 1 month before, painless and not itchy. At first the lesion was found in his arms and spreads to other site of body. He had history of getting wound on his genital, which spontaneously heal. From dermatological examination, on regio trunk and extremities superior dextra et sinistra there were multiple eritematous macule sharply marginated, 0,5-1 cm in diameter, some covered with thin scale. The patient was diagnosed with HIV about 1 year ago and taking anti retroviral (ARV) routinely. In this case, the serology of Venereal Disease Research Laboratory (VDRL) test was 1: 128 and *Treponema Pallidum* Hemagglutination Assay (TPHA) was 1:1280. The patient was treated with benzathine penicillin G 2.4 million unit intramuscular single dose. In this case, shows fluctuating serological testing in month sixth and nineth **Case management:** Syphilis diagnosis is based on the patient's history, physical examination, and laboratory testing. The drug of choice for this case is benzathine penicillin G 2.4 million units intramuscular in a single dose. Because of the condition we have to wait and be patient to treat syphilis in HIV patients. Further serological testing follow up will still need to be done at month 24. **Conclusions:** Atypical nontreponemal serologic test results (i.e., unusually high, unusually low, or fluctuating titers) might occur regardless of HIV-infection status. Clinically relevant differences in presentation, diagnosis, and management strategies must be recognized by clinicians**.**

Key words: *secondary syphilis, HIV coinfection, serology test, penicillin.*

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INTRODUCTION

Syphilis is a sexually transmitted disease caused by *Spirochaete* microorganism, *Treponema pallidum* and remains as public health problem worldwide. Syphilis has been termed the "great mimic" due to its versatile and varied disease presentations. The World Health Organization (WHO) estimated that in 2008, there were 36 million prevalence cases of syphilis and

11 million incident cases in adults between the age of 15 and 49. A recent review of studies conducted worldwide reported a 9.5 % prevalence of syphilis among adults living with HIV infection. In 2013, the incidence of primary and secondary syphilis increased is 5.3 cases per 100,000 people in the US, more than doubling the lowest rate of 2.1 per 100,000 in 2000. From cross sectional study in 2005 involving 2,500 female sex workers in nine provinces in Indonesia, the seroprevalence of syphilis was 8.7%. A recent review studies conducted worldwide reported a 9.5 % prevalence of syphilis among adults with HIV infection.[1] Atypical and aggressive presentations of syphilis occur more frequently among HIV-infected patients.[2]

Syphilis is transmitted in several ways: direct contact (generally intimate sexual contact) with the active cutaneous lesions of an infected person, a kiss or other contact with an active lesion, across the placenta (congenital syphilis) or during blood transfusions.[2,3] Clinical manifestations of syphilis are divided into primary, secondary, latent, and tertiary stages. The diagnosis of syphilis is established either through dark field microscopy examination or by serologic test, depending on the stage of the disease. Dark field microscopy is used to evaluate of the bacteria in the ulcer by analyzing a sample of the exudate of the chancre. Samples from oral lesions are not useful because the bacterium cannot be distinguished from nonpathogenic treponemas, and therefore only samples from genital lesions are used.[4]

Serologic test is used in the diagnosis of the other disease stages. Two types of serological tests exist: nontreponemal (i.e., nonspecific) and treponemal (i.e., specific). The major nontreponemal tests are the Rapid Plasma Reagin (RPR) and the Venereal Disease Research Laboratory (VDRL) test, and the treponemal tests are the *Treponema pallidum* Hemagglutination Assay (TPHA), the *Treponema pallidum* Particle Agglutination (TPPA) test, the Fluorescent Treponemal Antibody absorption (FTA-abs) test and an Enzyme Immunoassay (EIA). To confirm the response to treatment, it is necessary to see a change in titer on the nontreponemal tests. This change should be a 4-fold decrease from the initial levels, and the tests should be conducted in the same laboratory.[4,5]

In most coinfected patients, syphilis can be accurately diagnosed with serologic tests, however, it has been reported that the results of VDRL showed differences in people infected with HIV. This usually results in extremely high titers and a failure to decrease in response to adequate treatment, however persons with no serologic response have also been seen.[6] It has been reported in the studies that VDRL titer higher than expected and the false positive results can be seen and also negative VDRL result may not exclude syphilis in HIV-infected patients.[7] When clinical findings are suggestive of syphilis but serologic tests are nonreactive, or the interpretation is unclear, there is a need for alternative tests, such as biopsy of the lesion, darkfield examination and PCR.[6]

Penicillin is still the gold standard for syphilis treatment, with or without HIV coinfection.[8] Serologic tests for HIV-positive patients, should be repeated at 1, 2, 3, 6, 9, and 12 months.[9] This case report syphilis in HIV coinfection patient. This case is interesting because of the specific dermatological lesion that shows secondary syphilis, and confirmatory serological testing. The patient was also HIV patient. However, follow up serologic testing showed higher antibody titer after therapy.

CASE REPORT

R, 33 years old man came to UPIPI (*Unit Perawatan Intermediet dan penyakit infeksi*) outpatient clinic Dr. Soetomo General Hospital, Surabaya, on April 6th 2016 with chief complaint multiple rash on his trunk and extremities since 1 month before, painless and not itchy. At first, the lesion in his arms, which was small in numbers, spread to other site of body. Patient had a history of sore throat, malaise, headache, weight loss, fever, visual disturbances, vomiting, hair loss, and node enlargement in the neck, groin, and underarms was denied. He also complaint about diarrhea for 1 month. Patient denied of applying any topical medicine at the lesion. Patient had a history of ulcer at his penis 3 months ago that healed spontaneously in a few days. Patient had multiple sexual partners (bisexual), but he denied that his partners have the same symptoms. He was diagnosed as HIV-positive about 1 year ago and taking fixed drug combination (FDC) medicine routinely.

General physical examination showed the blood pressure was 120/80 mmHg, pulse rate was 80 times per minute, and body temperature was 37^0 C. From head and neck examination, chest, abdomen, upper and lower extremities within normal limit. There were no enlargement of the cervical, axillar, and inguinal lymph nodes. From dermatological examination, multiple eritematous macule sharply marginated, 0,5-1 cm in diameter, some covered with thin scale can be found on the trunk, palms and upper extremities (**Figure 1**).

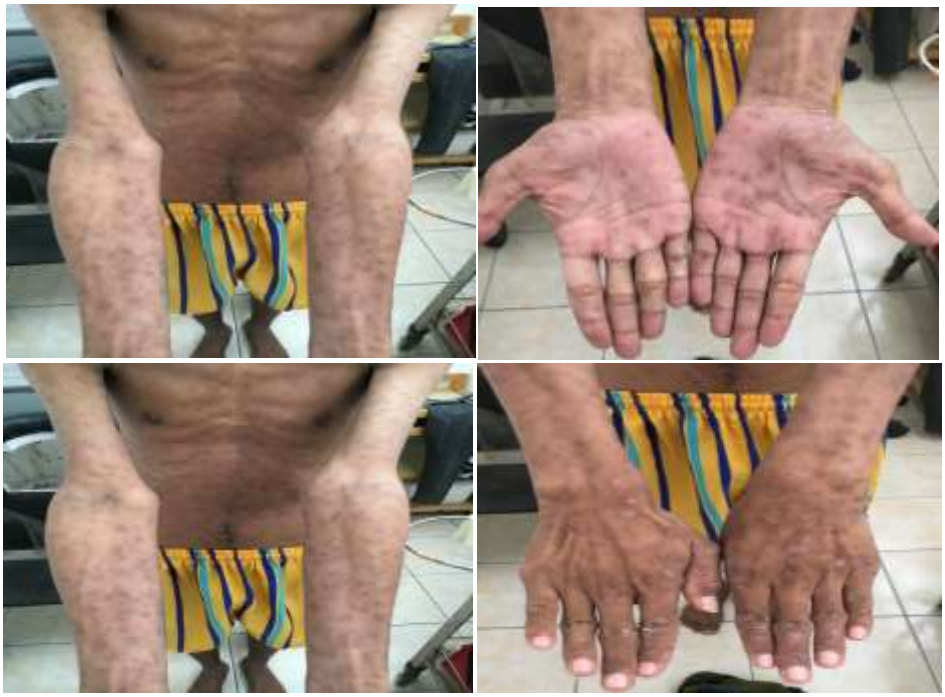

Figure 1. The dermatological examination on regio arms and palms of patient, on April 6th2016, there were multiple rash, 0,5-1 cm in diameter, covered with thin scales.

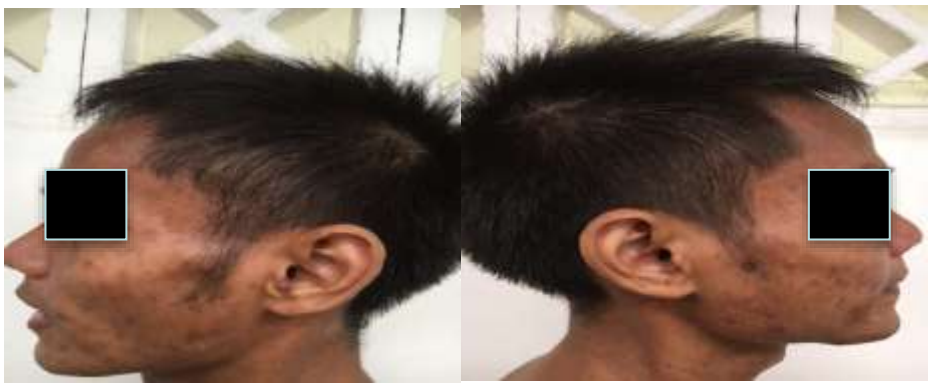

Figure 2. On Regio scalp, on April 6th2016, there were no alopecia.

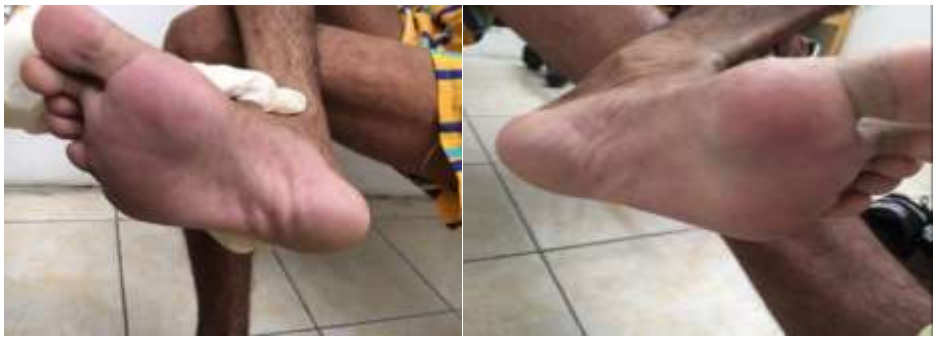

Figure 3. On regio soles of patient on April 6th 2016, no lesions on his soles

The laboratory examination on April, 6th 2016 showed that haemoglobin was 14.0 g/dL, white blood count 8000/mm^3, thrombocyte 214.000/L, Hct 38.2% and CD4: 28. The urinalysis results were within normal limit. The serology titer of VDRL was 1:128 and TPHA 1:1280. The patient was treated with Penicillin G 2.4 million unit intramuscular single dose and consulted to neurology department to evaluate the posibility of neurosyphilis. After 1 month of treatment, red rash became hiperpigmented plaques, with no scales. Serology tests were repeated for syphilis 3 months after completed therapy, the result for VDRL is persist 1:128 and TPHA 1:1280.

In six months after therapy, VDRL result declined to 1:64 and TPHA 1:1280. Nine months after therapy, the VDRL titer increased to 1:128 and TPHA titer was 1:1280. There were no new lesion, the serological test were perfomed to re-evaluate the titer and the results are the VDRL titer was 1:64 and TPHA titer was 1:1280 (Figure 4). Twelve months after theapy, the VDRL titer persist was 1:64 and TPHA titer was 1:1280.

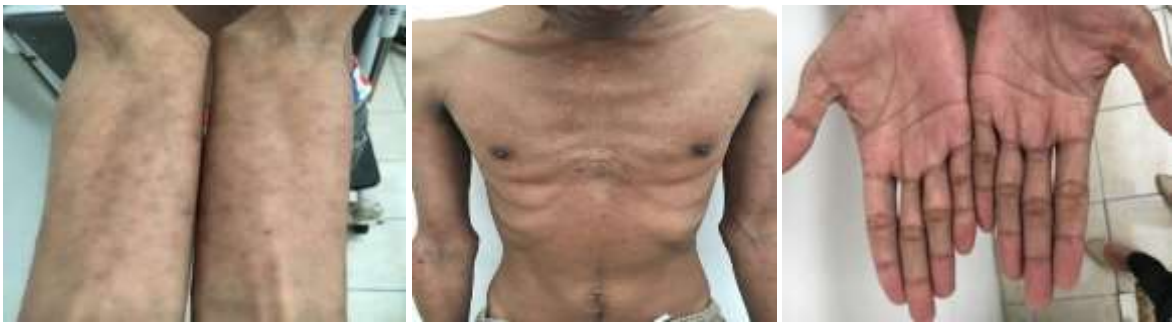

Figure 4. Dermatological state of patient at 9 month after treatment, erytematous macules dissepeared leaving hypopigmented macules on regio ekstremities superior.

Table 1. Progress of the disease

	6th April 2016 (First come)	1 month	3 months	6 months	9 months	12 months
Subjective						
Rash	+	+	-	-	-	-
Objective						
• Multiple erythematous macules	+	+	-	-	-	-
• Scales	+	+	-	-	-	-
• Lymph node enlargement	-	-	-	-	-	-
Laboratory examination:						
Serology examination (TPHA and VDRL)	VDRL 1/128 TPHA 1/1280	VDRL 1/128 TPHA 1/1280 -	VDRL 1/128 TPHA 1/1280	VDRL 1/64 TPHA 1/1280	VDRL 1/128 TPHA 1/1280 Re-checked : VDRL 1/64 TPHA 1/1280	VDRL 1/64 TPHA 1/1280
CD4 count	28	-	4	-	-	-
Treatment:						
Benzathine penicillin G 2,4 million units IM in a single dose	+	-	-	-	-	-

DISCUSSION

Syphilis is a sexually transmitted disease caused by the *Spirochaeta* microorganism *Treponema pallidum*. *T. pallidum* may penetrate through normal mucosal membranes and minor abrasions on epithelial surfaces.[9] Concomitant syphilis and HIV infection are particularly common among men who have sex with men, intravenous drug abusers, and prostitutes.

Although syphilis presentation in patients with HIV is largely similar to that in patients without HIV, differences in disease manifestation may be present.[8]

The first stage of syphilis, known as primary syphilis, is marked by the presence of a chancre, a well-demarcated, relatively painless, ulcerated lesion evolving from a papule that appears at the site of venereal contact, 10–90 days (average 3 weeks) after exposure.The papule grows to a size of 0.5–1.5 cm in diameter and after about a week ulcerates, producing the typical chancre of primary syphilis, a round or slightly elongated ulcer, 1–2 cm across, with an indurated margin. The ulcer has a clear base, without an exudate, 1–2 cm in diameter, and painless. External genitalia is the most common affected, but lesions can also appear in other sites, such as the cervix, mouth, perianal region and anal canal. The chancre heals spontaneously without treatment and without scarring after 10 to 14 days, but if adequate treatment is not administered, the infection progresses to the secondary phase and become generalized.[2,3,4] Unilateral or bilateral inguinal limphadenopathy may also be present in primary syphilis. Patients infected with both HIV and syphilis show chancres characteristic of primary syphilis, although these chancres may be more numerous, larger, and deeper.[2] After 2 to 12 weeks or even a year after primary infection, the signs and symptoms disappear with the establishment of an effective immune response and the beginning of the latent stage, even if the patient receives no treatment.[5] In this case, patient had a history of painless single genital ulcer three months before he came to our outpatient clinic, which healed without taking any medication.

Between 4 and 8 weeks after the appearance of the primary chancre, signs and symptoms of secondary syphilis typically develop.[3,4,10] Symptoms may include malaise, fever, headache, sore throat, and other systemic complaints. Most patients have generalized lymphadenopathy, including involvement of the epitrochlear nodes. Approximately 30% of patients have evidence of a healing chancre, although many patients give no history of a primary lesion. Patients with secondary syphilis have cutaneous or mucocutaneous lesions at some point in their illness. The rashes are quite varied in appearance but have certain characteristic features. The lesions are usually widespread, involving the entire trunk and the extremities, including palms of the hands and soles of the feet, symmetrical in distribution, frequently pink, coppery, or dusky red (particularly the earliest macular lesions) usually 0.5–2 cm in diameter. They are generally nonpruritic, although occasional exceptions have been reported.[3,4,9] In this case, the clinical manifestation was multiple eritematous macule on his arms and trunk since 1 months before, painless and not itchy. At first the lesion was small in number, then spread all over the body, including palms. These symptoms combined with history of selflimiting genital ulcer and coitus suspectus suggested secondary syphilis as a possible diagnosis.

Syphilis diagnosis is based on the patient's history, physical examination, laboratory testing and sometimes radiology found. The causative organism, the spirochete *Treponema pallidum*, cannot be easily cultured or identified under a standard microscope therefore the diagnosis depends very much on special techniques and serology. The exudates from primary chancres or from the mucous membrane lesions of secondary syphilis may be examined using dark field microscopy for characteristic movement and morphology.[11] In this case, diagnosis of syphilis was concluded when the patient gave positive results on clinical and serologic test. The serology titer of VDRL was 1:128 and TPHA 1:1280. Patient already HIV positive since 1 year ago and consumed FDC for HIV routinely.

Serologic testing is a useful tool for diagnosing syphilis in both HIV-infected and HIV-uninfected patients.[9,12] When serologic tests do not correspond with clinical findings of suggestive early syphilis, presumptive treatment is recommended for persons with risk factors for syphilis, and use of other tests (e.g., biopsy and PCR) should be considered. However, there are no pathognomonic features and skin biopsies of secondary syphilitic lesions have a wide variety of histological appearances that usually correlate with the clinical picture.

The standard nontreponemal tests are the VDRL and rapid plasma reagin (RPR) tests. Nontreponemal test antibody titers might correlate with disease activity and are used to follow treatment response. False-positive nontreponemal test results can be associated with various medical conditions and factors unrelated to syphilis, including other infections (e.g., HIV), autoimmune conditions, immunizations, pregnancy, injection-drug use, and older age. Therefore, persons with a reactive nontreponemal test should always receive a treponemal test to confirm the diagnosis of syphilis. Atypical nontreponemal serologic test results (i.e., unusually high, unusually low, or fluctuating titers) might occur regardless of HIV-infection status. Persisting nontreponemal antibodies after effective therapy may represent failure of immune tolerance rather than lack of pathogen clearance. Recent work on HIV has shown that many antibodies against the virus are autoreactive and under tolerance controls.

Sequential serologic tests should be performed using the same testing method (VDRL or RPR), preferably by the same laboratory. Serological cure was defined as a ≥ four-fold decline (at least two titers, such as 1:64 to 1:16) in nontreponemal titers or seroreversion to nonreactive results after therapy. Patients with HIV infection might take longer to experience serological improvement after recommended therapy.[1,14]

Penicillin G, administered parenterally, is the preferred drug for treating persons in all stages of syphilis. Persons with HIV infection who have primary or secondary syphilis should be treated as those without HIV infection. The chosen drug for all secondary syphilis stages is benzathine penicillin G, 2.4 million units IM in a single dose.[13,15,16] 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 benzathine penicillin at weekly intervals.[3] Regimens of doxycycline 100 mg orally twice daily for 14 days and tetracycline (500 mg four times daily for 14 days) have been used for many years to treat syphilis patients who allergic to penicillin. All persons with HIV infection and syphilis should have a careful neurologic exam.[13-16] In this case, the patient was given benzathine penicillin G, 2.4 million units IM in a single dose. Patient was also consulted to neurology departement to know about posibility to be affected neurology syphilis, and there is no neurological abnormality.

For the follow up, persons with HIV infection and primary or secondary syphilis should be evaluated clinically and serologically for treatment failure at 3, 6, 9, 12, and 24 months after therapy.[13] In addition, CSF examination and retreatment can be considered for persons whose nontreponemal test titers do not decrease fourfold within 12–24 months of therapy.[14] In this case, month-3, the non-treponemal titer was 1:128 and TPHA was 1:1280. We also checked his CD4 count which was 4 cells/μL. At month-6 non-treponemal (VDRL) titer decrease from 1:128 become 1:64 and TPHA was 1:1280. At month-9 there were 2-fold increase for VDRL become 1:128 and TPHA 1:1280. There is no new lession, then we suggest to re-evaluate serological status. After reevaluation, non treponemal titer is 1:64 and TPHA 1:1280. At month-12 the titer do not decrease to 4-fold.Because of the condition we have to wait and be patient to treat syphilis in HIV patients. Further STS follow up will still need to be done at month 24.

Patient had been educated about his condition and recommended the sexual partner to have a syphilis and HIV testing. Patient had also been educated about safe sexual behavior to prevent transmission of diseaseand control further follow up.

CONCLUSION

Atypical nontreponemal serologic test results (i.e., unusually high, unusually low, or fluctuating titers) might occur regardless of HIV-infection status. Despite several advances in the understanding of the interaction between HIV infection and syphilis achieved during the past few years, the clinical treatment of coinfected patients remains challenging. Clinically relevant differences in presentation, diagnosis, and management strategies must be recognized by clinicians**.**

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