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(CASE REPORT)

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Secondary syphilis with tuberculosis co-infection: A rare case

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Abstract

Syphilis is an infection that could be transmitted sexually and caused by certain bacteria called Treponema pallidum with almost 21.000 new cases in Indonesia. Regularly positive blood serologic tests and similar abnormalities in cerebrospinal fluid (CSF) examination, including a positive Venereal Disease Research Laboratory (VDRL) test, are typically observed in cases of syphilis, except in instances of burned-out or previously treated cases. Tuberculosis (TB) is also a common infectious disease in Indonesia with a prevalence of 759 per 100.000 persons, but co-infection of syphilis and TB is a rare finding. A 29-year-old female was diagnosed with syphilis and TB referred from a public health center with red rashes found on the palm and soles bilaterally a month before the visit. Dermatological examination of the palms and soles showed multiple violaceous macules with clear boundaries, with varying sizes between 0.5 cm x 1 cm. No abnormalities were found in the genitalia and oral mucosa. The result of the VDRL examination, the titer was 1:128 and the Treponema Pallidum Haemagglutination Assay (TPHA) result was 7,59. The patient was prescribed by single dose of Benzathine Penicillin injection 2.4 million IU IM. The patient experienced clinical improvement and decreased VDRL and TPHA titers after a month of evaluation. Co-infection of syphilis and tuberculosis is a rare finding. TB infection is found to have decreased interferon production and CD25 expression which causes immunosuppression as a risk for syphilis. Otherwise, treponemes may potentially contribute to reactivation in immunosuppression individuals.

Keywords: Sexually Transmitted Disease; Infectious Diseases; Tuberculosis; Sexually Transmitted Infection; Sexual Risk Behavior

1. Introduction

Syphilis is a sexually transmitted infection caused by a specific bacterium known as Treponema pallidum. It's a significant global illness, capable of leading to lifelong health issues, often presenting with various skin and internal organ manifestations.[24] Due to its complex clinical presentation, syphilis is often challenging to diagnose, earning it the nicknames "great imitator" and "mimicker." While the exact origin of syphilis remains uncertain, DNA evidence suggests its presence as far back as 1490. Some theories suggested that syphilis came from Europe in 1490s with Columbus's Arrival in America.[1] *Treponema pallidum* itself was only discovered in 1905 by German scientists. This bacterium was first sequenced in 1998. *Treponema* is a genus of spiral-shaped bacteria with outer membrane that contains a phospholipid membrane.[2] Even after the discovery of antibiotics incidence of syphilis is still concerning. In 2016, Center for Disease Control and Prevention reported more than 80 thousand new cases of syphilis in 2016. Almost a quarter of those cases were primary and secondary syphilis. Men aged between 20-29 are the highest demographical group for syphilis. Syphilis is also very common among sex. Workers with the incidence of active syphilis among was 10.8% in 2018. Syphilis in the developed world is quite rare although, in the developing world, syphilis is still endemic, especially in people who are poor and bad access to health care. Syphilis is also very common among people with multiple sexual partners. Syphilis is also linked with other sexually transmitted disease such as *Human Immunodeficiency Virus* (HIV).[3]

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Tuberculosis is a disease caused by infection of *Mycobacterium tuberculosis.* This bacterium is an acid-fast bacillus with alcoholic properties, capable of inducing various clinical manifestations in the human body. The active form of tuberculosis is a multiorgan disease that could be caused by primary infection or latent tuberculosis that got reactivated. Primary TB happens when the immune system cannot fight off TB and succumb to infection. Reactivation of TB is when a patient who has been exposed to TB then suffers from a TB infection. Reactivation TB is the most common TB infection with 90% of the cases happening in that way.[4] Tuberculosis is a very common infection among developing countries. The World Health Organization estimated that about 8 million people globally will develop active TB. About two million people will die from TB annually. About one in ten people will be infected with active tuberculosis once in their life. In developing countries such as India, Pakistan, China, and Indonesia, TB can cause high morbidity and mortality rates. WHO estimated that 64% of all TB deaths in 2016 happened in India, Pakistan, the Philippines, China, South Africa, Indonesia, and Nigeria.[5,6] Some studies suggested that TB infection can cause immunosuppression. This process is thought to be caused by decreased interferon production and CD25 expression.[7] Immunosuppression is a risk factor for syphilis infection.[8] We report a case of secondary syphilis with TB coinfection. This case is reported due to the rare nature of TB and syphilis co-infection.

2. Case Study

A 29-year-old woman was referred from a public health center to a dermatologist due to red rashes discovered on her palms and soles. The patient reported that the rashes were non-itchy and remained relatively stable. These rashes persisted for about a month before the examination. The patient has never complained of similar symptoms before and never had a genital ulcer before. The patient never had sex with another man except her husband.

Patient visits to the public health center stemmed from the patient's husband being diagnosed with tuberculosis during a medical evaluation prompted by a persistent cough lasting over a month. Concerned about potential exposure, the patient tested for tuberculosis at the public health center. Additionally, due to the presence of rashes on her palms and soles, syphilis testing was also conducted, revealing positive results for both tuberculosis and syphilis. The patient's husband, a 31-year-old male. Three to four months before the visit he complained of a painless lesion in the genital area. But the lesion was gone quickly without treatment. The patient had a history of sexual contact with escorts. Both the patient and her husband received tuberculosis treatment regimens from the public health center.

The vital signs of the patient were normal. There are no signs of anemia, icterus, cyanosis, and dyspnea. Chest physical examinations were clear. A dermatological examination showed no painless ulcer (*chancre*) found in the genitalia and oral mucosa. No alopecia, papular macular rash, condyloma lata, lymphadenopathy, nickles and dimes, rupioid, corona veneris, and hyperkeratotic lesion were found in the rest of the examination. Dermatological examination of the palms and soles showed multiple macular exanthems with clear boundaries, with varying sizes between 0.5 cm x 1 cm. The result of the VDRL examination is 1:128 and TPHA 7,59. Rapid HIV tests showed negative results.

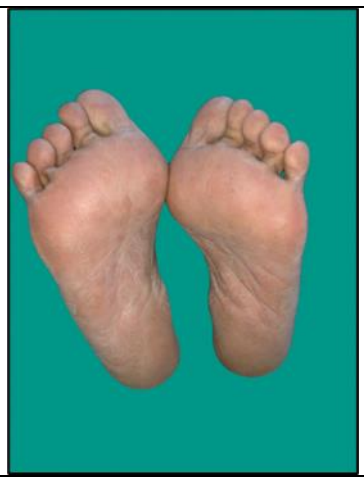
The patient was diagnosed with secondary syphilis co-infection with tuberculosis infection. For the secondary syphilis patient was prescribed by single dose of Benzathine Penicillin injection 2.4 million IU IM from the dermatologist. After getting therapy from the dermatologist, the patient was planned for serial VDRL and TPHA tests for 1, 3, 6, 12, and 24 months after treatment. A first month after treatment patient stated that rashes on the soles and palms had vanished. VDRL titer after treatment is 1:16 and TPHA 9.41. Improvement in clinical examination and serologic examination showed a good response to therapy.

During the visit, the lab result of the patient's husband is VDRL 1:512 and TPHA 8.81. The HIV test was negative. The husband was diagnosed with secondary syphilis. The husband was also prescribed by single dose of Benzathine Penicillin G 2.4 million IU IM. A month after the treatment, the lab result of the patient's husband is VDRL 1:16 and TPHA 10,96. And also planned for serial VDRL and TPHA tests for 1, 3, 6, 12, and 24 months after treatment.

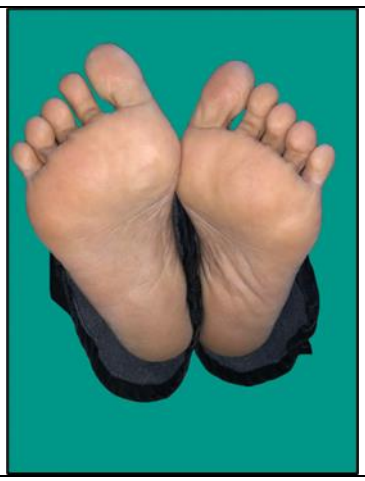
A

B

Figure 1 Physical examination of plantar manus; a. Multiple macular exanthems with clear boundaries were found in varying sizes; b. Showed a vanished rash after a month of treatment with a single dose of Benzathine Penicillin G 2,4 million IU IM.



A



B

Figure 2 Physical examination of plantar pedis; a. Multiple macular exanthems with unclear boundaries were found in varying sizes; b. Showed a vanished rash after a month of treatment with a single dose of Benzathine Penicillin G 2,4 million IU IM.

3. Results and Discussion

Syphilis is a global disease. In 2000, the incidence of syphilis in the USA reached 11.2 per 100.000 people.[9] According to Kementerian Kesehatan Republik Indonesia, the incidence of syphilis in Indonesia also kept increasing. In 2016 the incidence of syphilis was about 12.000 cases. In 2022, the incidence of syphilis is 21.000 cases. Another problem of syphilis in Indonesia is the low treatment rate in syphilis patients which only reached 40% of the cases.[10]

Treponeme pallidum also infiltrates lymphocytes, macrophages, and plasma cells. CD4+ T cells are dominant in chancres and CD8+ cells are dominant in secondary syphilis lesions. The humoral response initiates the production of IgM antibodies approximately two weeks after exposure, followed by IgG two weeks later [23]

There are several risk factors for syphilis infection. One of the common risk factors for syphilis is doing anal sex without protection. Other risk factors such as drug consumption, blood donors, and group sex have also been linked with several infections. Coinfection with HIV is also highly reported in several studies with more severe clinical manifestations being

reported in HIV-positive patients. [11] In this case found that the husband's patient had sex with several escorts during 2022-2023 mostly without protection.

Syphilis infection could be classified as primary, secondary, and tertiary syphilis. Primary syphilis usually appears early about 10-90 days after the patient gets exposed to infection. The clinical manifestation of primary syphilis is painless indurated ulcer that is usually found at the side of infection. In immunocompromised patients such as HIV-positive patients, the lesions are usually much more prominent and severe, and multiple lesions are usually also found. Lymphadenopathy is also a common finding in primary syphilis.[1]

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This case is secondary syphilis with Tuberculosis co-infection caused by sexual partner transmission. On physical examination, found mucous patches on palms and soles with clear boundaries and varying sizes between 0.5 cm x 1 cm. Mucous patches appear 3 months after the painless ulcer on the husband's genital disappears. Meanwhile, the husband didn't have any symptoms of secondary syphilis. Secondary syphilis occurs in 2-8 weeks after the lesions from primary syphilis disappear. The manifestations of secondary syphilis could also vary in clinical manifestation with findings such as mucous patches, palmar or truncal rash, papulosquamous rash, condyloma lata, or alopecia.[1] The diverse dermatological symptoms of secondary syphilis make it known as "The Great Imitator".[25] Tertiary syphilis is a chronic form of syphilis that could manifest months or even years after the first primary infection. The manifestation of tertiary syphilis could be cardiovascular syphilis, neurosyphilis, or gummatous syphilis.[1] We did not find these findings in our patient.

Detecting and treating secondary syphilis is the combination of clinical findings with pathology and using serologic tests. An exact diagnosis can ensure appropriate treatment and avert complications. [25] Clinicians usually refer to laboratory testing. The most common test for syphilis is VDRL. VDRL has 78% sensitivity for primary syphilis and 100% sensitivity for secondary syphilis with 98% specificity. Another useful test for syphilis is TPHA. TPHA has 85% sensitivity for primary syphilis and 100% sensitivity for secondary syphilis with 96% specificity. Combining TPHA and VDRL yields better sensitivity and specificity, especially in difficult cases. [12] The patient's initial TPHA and VDRL tests revealed results of TPHA 7.59 and VDRL 1:128 before treatment. A month later, subsequent TPHA and VDRL tests conducted at the same laboratory showed TPHA 9.41 and VDRL 1:16.

Table 1 The diagnostic test for syphilis.[22]

	Primary syphilis	**Secondary syphilis**	**Latent syphilis**
VDRL	Reactive or non-reactive	Reactive, titer increased	Reactive
TPHA	Reactive	Reactive	Reactive

Tuberculosis is still a global disease. In 2019 TB is the highest cause of death globally caused by infectious disease. About 7.1 million people globally are treated for TB every year. About 10 million incidence cases are found annually.[13] Indonesia is one of the developing countries of the world and holds a great deal of TB burden. In Indonesia, the prevalence of TB is estimated at around 759 per 100.000 people.[14] Mantoux test is one of the most common tests for tuberculosis. It is done by administering 0.1 ml of tuberculin intradermally and normally the test is given to the left forearm. The result could be read 2-3 days later.[15] Patients tested positive for Mantoux even though the patient didn't show any symptoms of tuberculosis. The patient got tuberculosis from the husband who also tested positive for Mantoux because he had a cough that didn't heal for a month.

Coinfection of tuberculosis and syphilis is a very rare finding, especially in HIV-negative patients. Coinfection of tuberculosis and syphilis has been reported before. However, the reports do not specifically discuss this particular co-infection.[16–18]

According to a study by Roberts *et al.,* TB infection could interfere with the immune system. Patient with active TB infection is found to have decreased interferon production and CD25 expression. Both are important factors in the natural immune system regulated by T cells. The TB case-patients exhibited reduced levels of CD4+CD25hiCTLA-4+ T cells, along with increased overall expression of FOXP3, TGF-b, and IL-4, indicating immune dysregulation. However, couldn't directly correlate the immunosuppressive cytokines with a specific cell type. [7] This finding could theoretically be the ground for syphilis coinfection in TB patients. In this case, a positive Mantoux test could be interpreted as latent TB.

Treatment for syphilis depends on the phase of syphilis. In primary, secondary, or early latent syphilis, the patient is treated with a single dose of intramuscular benzathine penicillin G with doses of 2.4 million IU IM. As an alternative, the patient could be prescribed Ceftriaxone 1-2 grams for 10 days IM/IV. A patient who refuses injection can be prescribed doxycycline 100 mg orally twice a day for 14 days or Erythromycin 500 mg four times a day for 14 days.[1,22,23] This patient was injected with a single dose of Benzathine penicillin 2,4 million IU. Penicillin G is a penicillin beta-lactam antibiotic used in the treatment of bacterial infections caused by susceptible, usually gram-positive, organisms. These enzymes play a vital role in the final stages of peptidoglycan cross-linking in both gram-negative and gram-positive bacteria by stopping bacterial growth by inhibiting cell wall formation.[20] After a month, the patient exhibited significant improvement, with reduced complaints of redness on the palms and soles, alongside a VDRL decrease of over fourfold. The patient will have follow-up appointments scheduled at 1, 3, 6, 12, 18, and 24 months after receiving treatment, but until this case report was published we only followed the patient in the first month after treatment.

4. Conclusion

Coinfection with both syphilis and TB is an uncommon occurrence. A positive Mantoux test indicates latent tuberculosis infection. The simultaneous presence of syphilis and tuberculosis may result from the immune system being compromised by the tuberculosis infection, possibly due to reduced interferon production and CD25 expression. The patient received treatment for TB from public health care and a single dose of Benzathine Penicillin G, 2.4 million IU IM from the dermatologist. The syphilis treatment has been shown to effectively reduce VDRL levels in secondary syphilis cases occurring alongside tuberculosis. Syphilis patients co-infected with tuberculosis require comprehensive and regular evaluations. Even with successful treatment, treponemes can endure and potentially contribute to reactivation in immunosuppression individuals. Partner notification, health education, and screening in high-risk populations and pregnant women are crucial elements in controlling the infection and preventing congenital syphilis. [21]

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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