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Case Report
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Secondary Syphilis with Multiple Co-Infections of Human Immunodeficiency Virus (HIV), Tuberculosis (TB), and Oral Candidiasis in a 19-Year-Old Men Who Have Sex with Men (MSM): A Case Report

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ABSTRACT
Background: Syphilis is an infection of the Treponema pallidum bacteria that often occurs along with conditions such as Human Immunodeficiency Virus (HIV) infection, tuberculosis (TB), and oral candidiasis. A weakened immune system affects the complex interactions between these conditions and the clinical presentation as well as the therapeutic management provided to patients. **Case:** A 19-year-old male with a history of HIV complained of lesions on the skin and mouth. Anamnesis, physical examination, and serological test results establish the diagnosis of secondary syphilis and pulmonary tuberculosis, characterized by a one-month history of phlegm coughing and weight loss, was confirmed via sputum testing. Additionally, oral candidiasis was identified based on clinical examination. **Discussion:** The patient exhibited complex complications from secondary syphilis, HIV infection, TB, and oral candidiasis. In cases of syphilis with HIV, the appropriate treatment is three doses of Benzathine Penicillin G. Anti-Tuberculosis Drugs administration for TB was adjusted based on HIV status and therapy response, and antifungal fluconazole for oral candidiasis. Conclusions: This case highlights the importance of proper management and close monitoring of patients with multiple infectious conditions, including treatment of syphilis patients that has a higher incidence in men who have MSM, HIV, TB, and oral candidiasis. Timely and appropriate therapy strategies are essential to minimize complications and improve clinical outcomes.

Keywords: Sexually Transmitted Diseases, Secondary Syphilis, *Human Immunodeficiency Virus* (HIV), *Men who sex with men* (MSM), *Tuberculosis* (TB), benzathine penicillin *G.*

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BACKGROUND

Syphilis is a sexually transmitted disease caused by the microorganism *Treponema pallidum*. Syphilis can appear with various HIV coinfections, tuberculosis (TB), and some comorbid diseases such as oral candidiasis.[1] In 2018, the Ministry of Health of the Republic of Indonesia reported 7,055 new cases of syphilis in Indonesia, primarily among transvestites, male sex men (MSM), sex peddlers (WPS), and drug users.[2] According to US Department of Health and Human Services data in 2018, there were 45.5% of HIV-positive cases in the MSM population diagnosed with syphilis.[3] Several studies highlight that there is a complex relationship between syphilis and HIV. The synergistic interaction between syphilis and HIV increases the risk of transmission and disease progression, as well as the importance of comprehensive evaluation in diagnosis.

Syphilis can also cause lesions of the oral mucosa in the form of canker sores (oral candidiasis), especially in HIV-infected patients who have weakened immune systems. This comprehensive approach is crucial in managing complex cases involving syphilis with TB infection, HIV, and oral candidiasis. Secondary syphilis develops from primary syphilis about 6-8 weeks after primary infection in untreated patients. The clinical presentation of secondary syphilis is very diverse and may not be preceded by a detected primary lesion, often delaying diagnosis until this stage.[4] The *Mycobacterium* group of bacteria, specifically *Mycobacterium tuberculosis*, causes the infectious disease TB. This bacteria is known as acid-resistant bacteria (BTA).[5] Sputum

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splashes from sneezing or coughing can spread the BTA-positive tuberculosis disease. Infection will occur if other people inhale sputum splashes containing TB bacteria. In 2021, there were 1.6 million people who died from TB (including 187,000 people with HIV).[6]

People with HIV positive have a 30 times greater risk of developing TB compared to people with HIV negative.[7] Co-infection with TB and HIV can occur in a person with active TB or latent TB. Both TB and HIV infections will accelerate the process of worsening other diseases. HIV infection will accelerate the process from latent TB to active TB, while TB bacterial infection will worsen the condition of people with HIV.[8] According to WHO, an estimated 1.2 million people were infected with HIV positive TB in 2015. About 57% was undiagnosed and untreated, leading to 390,000 deaths from TB/HIV co-infection.[9]

CASE REPORT

On June 13, 2024, a 19-year-old male was admitted to the hospital with primary complaints of productive cough lasting one month, generalized weakness, odynophagia, upper left abdominal pain, an 8 kg weight loss over the past two months, and oral ulcers. The patient has complained of red patches on both palms since the last month. The results of the Venereal Disease Research Laboratory (VDRL) laboratory examination showed a titer of 1:32 and Treponema Pallidum Haemagglutination Assay (TPHA) 1:640. From the history of the disease, it is known that patient was diagnosed with reactive HIV on June 12, 2024, at previous hospital and was currently undergoing secondary syphilis treatment.

The physical examination showed blood pressure 114/68 mmHg, pulses 112x/minute, body temperature 36.5°C, respiratory rate 20x/minute, and saturation of 98%. The radiological thorax photo examination revealed the presence of pneumonia. Initial diagnoses include general weakness, low intake, HIV (code B20), secondary syphilis, suspected pulmonary tuberculosis, and oral candidiasis. A dermatological examination was conducted on the right and left plantar area and palmar region, revealing multiple macula violaceus with clear boundaries and scales on the palms and soles of the feet in various sizes.

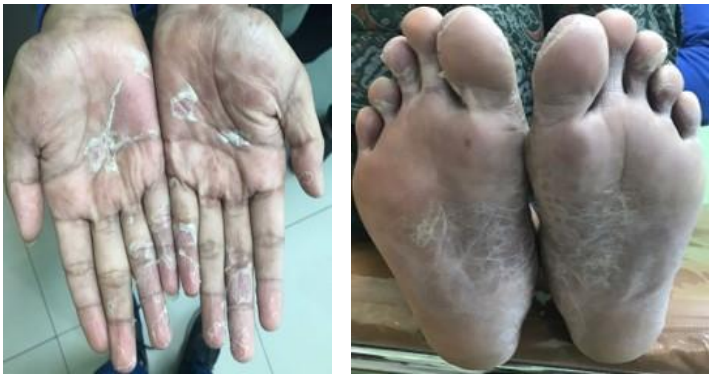

Figure 1. The right and left plantar pedis and palmar areas shows several violaceus macules on the palms and soles of the feet, each one a different size and with clear edges and scales.

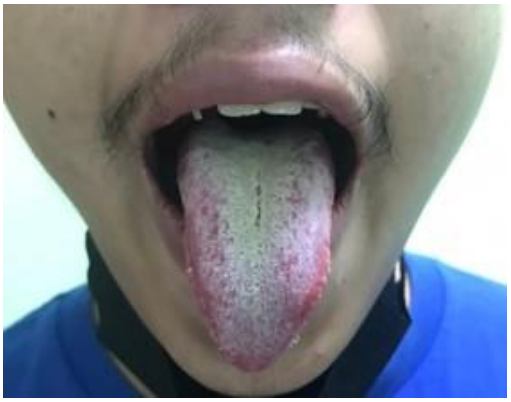

Figure 2. Intra-oral examination showed pseudomembranous plaques found on the tongue and palate and white area at the corner of the bilateral lip.

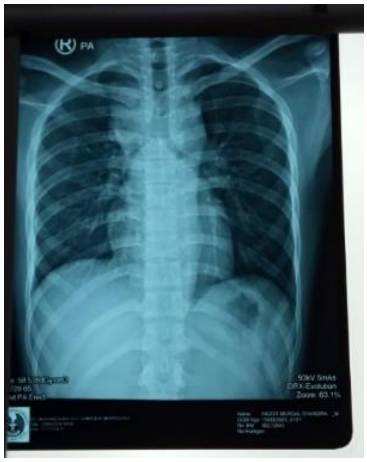

Figure 3. Radiology examination results showed reticulogranuler with patchy infiltrates in the right and left. parahilar and paracardial regions.

The initial management includes the infusion of PZ at a rate of 14 drops per minute, Ceftriaxone injection 2 times a day, Ranitidin injection 2 times a day, Antrain injection 3 times a day, and antiretroviral therapy (ARV). Recommended supporting examinations include RMT (Rapid Molecular Test), VDRL, TPHA, and sputum checks. The patient had a lab test on June 20, 2024, and the results were as follows: hemoglobin 12.0 g/dL, hematocrit 36.0%, erythrocytes 4.68 million/µL, MCV 81.2 fL, MCH 25.6 pg, MCHC 31.6 g/dL, RDW 15.0%, platelets 400,000/µL, leukocytes 8,000/µL, basophils 0.4%, eosinophils 0.8%, neutrophils 65.0%, lymphocytes 24.3%, monocytes 9.5%, NLR value of 2.7, L/T ratio 1, lymphocyte count 2.05 x10^3/µL, neutrophil count 5.47 x10^3/µL, and blood sedimentation rate (LED) mm/hour The blood chemistry test recorded an SGPT of 45 U/L and an SGPT of 17 U/L. The blood creatinine level was 0.87 mg/dL, the eGFR was 125 mL/min/1.73m random blood glucose at 73 mg/dL, the sodium level at 139 mmol/L, the potassium level at 3.8 mmol/L, and the chloride level yet 103 mmol/L. The RMT examination confirmed the patient's *Mycobacterium tuberculosis* infection, revealing a low detection rate and no resistance to Rifampicin. Thus, patients can receive standard therapy for TB without the need for specific modifications to Rifampicin.

Management for this patient included a 2.4 million IU intramuscular injection of benzathine penicillin G three times a week and advanced phase of anti-tuberculosis drugs therapy, which includes rifampicin 400 mg/day and isoniazid 200 mg/day. Other therapies were ambroxol 30 mg/day, a single dose of fluconazole 150 mg orally, nystatin drops three times daily, and Tupepe® cream 30 gr as a moisturizer for the palms and feet. Other therapies are continued as needed.

One month after the treatment was completed, the skin lesions of multiple macula violaceus began to shrink and disappear. The patient's physical condition has improved, the canker sores have disappeared, and he no longer feels weak or has a desire to eat. The patient still takes an ARV (dolutegravir, lamivudine, tenofovir disoproxil fumarate) once a day. However, the serological examination for VDRL/TPHA, intended as an evaluation one month after treatment, was not conducted because the patient returned to his parents' house outside of the city after the last follow-up.

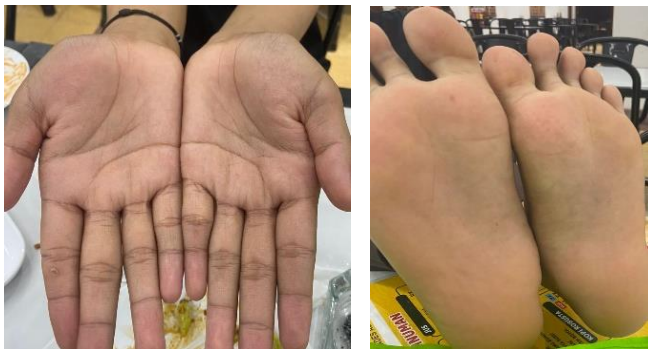

Figure 4. After one month of treatment on the right and left pedis plantar and palmar regions. The skin lesions of multiple violaceous macules began to shrink and disappear.

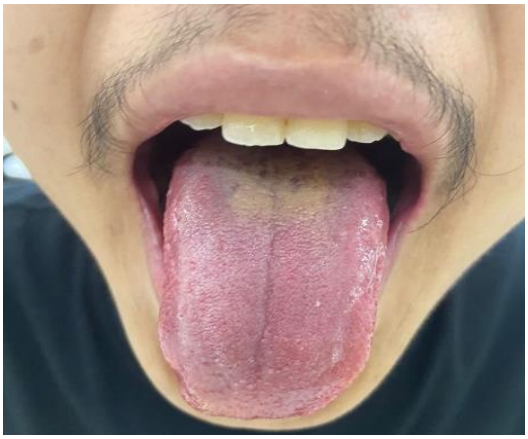

Figure 5. Canker sores have disappeared after being given of antifungal medication.

DISCUSSION

In this case, a very young male patient aged 19 years old with a history of sexual intercourse with MSM and often change partners; both of these are risk factors for the transmission of syphilis and HIV. Treponema pallidum has spread to various organs in syphilis, a systemic disease that can accompany *Treponema pallidum* has spread to various organs in syphilis, a systemic disease that can accompany constitutional clinical manifestations such as fever, malaise, myalgia, arthralgia, and headache. People refer to Syphilis as "the great imitator" due to its diverse and rapidly changing manifestations. Painless general enlargement of the lymph nodus occurs in 70% to 85% of patients.[10] In syphilis, the clinical picture are various, depending on the stage. The stages of syphilis consist of primary, secondary, latent, and tertiary. Primary syphilis has a clinical picture of a painless ulcer (chancre), induration, and will usually heal on its own. Secondary syphilis lesions are diverse and frequently mimic those of other diseases. Roseola Syphilitica is a non-itchy copper-red rash or patch, spreading almost all over the body, most often on the palms and feet. Laryngitis, hepatitis, and meningitis can also manifest at this stage. 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. [11,12]

The U.S. Centers for Disease Control (CDC) classifies infections acquired for less than one year without symptoms as early latent syphilis and those that do not fall within it as late latent syphilis.[11,12] Secondary syphilis emerges as a disseminated and systemic form of infection. Within a few hours of inoculation, the spirochete spreads through the lymphatic and hematogenous systems to most organs of the body. Because Treponema pallidum reproduces best at lower temperatures, most clinical signs and symptoms appear on the skin and mucous membranes. Secondary dermatological manifestations include a variety of rashes that usually involve the palms and soles of the feet, warts, mucous patches, and alopecia. Skin findings are often accompanied by general, painless lymphadenopathy and nonspecific systemic symptoms such as fever, headache, muscle aches, and fatigue, as well as a variety of other less common manifestations.[10]

In some patients who come with symptoms of secondary syphilis, primary lesions may still be present. Both the patient and the doctor may be unaware of ulcerations that occur in the primary stage but do not cause pain, particularly in the rectum or vagina. Thus, early evidence of infection in MSM and women may actually be a secondary sign or symptom, not primary syphilis. No clinical manifestations of primary or secondary syphilis are visible during the latent period, and typically only serological screening detects the infection. To determine the appropriate treatment, the rate of transmission, and the expected serological response to therapy, latent syphilis is divided into three stages: early latent (duration of infection less than or equal to 1 year), late latent (duration of infection more than 1 year), or unknown latent syphilis (there is not enough information to determine the duration of the infection). [10]

Benzathine penicillin G (BPG) is a first-line drug for all stages of syphilis. According to the recommendations of the Centers for Disease Control and Prevention (CDC), the treatment option for primary syphilis or secondary syphilis with HIV infection is 2.4 million IU of BGP administered by intramscular (IM) three times at intervals of one week.[10] Research suggests that administering penicillin

benzathine in a 3-dose regimen at 1-week intervals can enhance the success rate of syphilis treatment, especially in HIV-infected individuals with early syphilis. Although experts recommend a single dose of penicillin benzathine for early syphilis, observational studies reveal a higher failure rate among syphilis patients with other diseases who receive the BPG 1 dose. Andrade et al. looked at how well a single dose of intramuscular BPG worked versus a 3-dose regimen for treating early syphilis in people who had HIV. In this analysis, the treatment success rate was 80% for the single-dose group and 93% for the 3-dose group. [13] Cassir's 2023 study supports the idea that a 3-dose regimen could be more effective in reaching and sustaining therapeutic penicillin concentrations for syphilis treatment.[13]

In patients who have an allergy to penicillin, alternative regimens may be given, such as oral 500 mg tetracycline four times daily for 14 days, oral 100 mg doxycycline twice daily for 14 days, 1 gram ceftriaxone injection once daily for 10 days, or oral 1g azitromicin as a single dose. 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.[15] In the context of HIV co-infection and syphilis, the synergistic effects of benzyl penicillin and doxycycline with antiretroviral drugs are attributed to their potential as antiviral drugs. Various studies have described HIV as one of the risk factors for syphilis infection. HIV is a sexually transmitted infection that affects the immune system by gradually destroying CD4 cells. HIV-positive patients are more vulnerable to a variety of infections, including some types of tuberculosis, and candidiasis. Syphilis and HIV co-infection are conditions that must be taken into account because they interact synergistically, increasing the risk of transmission, and accelerating the progression of the disease. Some studies show that HIV affects syphilis and vice versa.[16]

The complex interactions between HIV infection and syphilis are very important for optimizing clinical treatment in patients. HIV-positive patients are more likely to develop neurosyphilis during the early stages of syphilis infection. The United Kingdom's Health Protection Agency recommends annual serological testing for syphilis in all seropositive patients.[18] The stage of the disease determines the clinical manifestations of syphilis, which include skin lesions, musculoskeletal manifestations, eye involvement, and neurological implications in advanced stages. Several studies have proposed a higher sensitivity to neuro-ophthalmological complications in HIV-positive patients affected by syphilis infection.[17] According to research about the oral syphilis symptoms in HIV patients, many of the patients in the study had other skin infections as well. These included maculopapular rashes on the torso, palmar and plantar lesions, baldness on the eyebrows and eyelashes, and oral lesions that looked like candidiasis infections.[18]

Candidiasis is a fungal infection caused by the organism *Candida albicans*. *Candida* exists in two forms, namely pseudo-hyphae and yeast. These organisms are generally found in the oral cavity, digestive tract, and vagina in normal people. However, when conditions are right, the non-pathogenic form of yeast changes to a pathogenic form of hyphae. When the body's immunity is weak, *Candida* can easily attack the body. Infections can be classified into two main categories: primary oral candidiasis – in oral tissue and secondary oral candidiasis – a manifestation of systemic mucocutaneous candidiasis. This can manifest in both acute and chronic forms, exhibiting clinical patterns such as pseudomembranous, erythematous, hyperplastic, angular cheilitis. The first two variants of the infection are closely linked to immunosuppressive conditions like HIV.[23] As many as 52% of HIV-infected individuals have *Candida* lesions in the early stages of infection.

This is in accordance with the condition in cases where the patient have oral lesions due to oral candidiasis and are given oral antifungal diflucan 150mg single dose and nystatin drop.[19] In this case, the patient has received an HIV diagnosis and is currently undergoing anti-retroviral treatment. Researchers have also confirmed that TB is an opportunistic infection that can easily infect individuals with HIV. People with weak immune systems can inhale the TB infection through coughing or sneezing, which is known as a droplet infection. When the bacteria *Mycobacterium tuberculosis* has successfully entered the lungs, they will soon develop into globular colonies. If the patient's immune status is good, lung cells can inhibit the immunological reaction to the growth of *Mycobacterium tuberculosis* bacteria by forming a wall around the bacteria.

The process of wall formation transforms the surrounding tissue into scar tissue, causing the *Mycobacterium tuberculosis* bacteria to become inactive and dormant (resting). Latent TB refers to TB infections that only reach the dormant stage, asymptomatic and incapable of transmission. However, if the infected person lacks a healthy immune

system, which can be caused by various factors such as immunosuppressive drugs, HIV infection, malnutrition, aging, or other conditions, the number of TB bacteria can grow uncontrollably. At this point, the surviving TB bacteria can spread throughout the lung field (active pulmonary TB) and even to other tissues through the lymphatic and blood systems (military or extrapulmonary TB). The patient becomes infected and experiences clinical manifestations of TB, including respiratory and systemic symptoms. Respiratory symptoms include coughing, shortness of breath, and chest pain. Systemic symptoms include fever, rapid weight loss in a short period of time, night sweats, anorexia, and malaise.[20]

The symptoms above are in accordance with the symptoms experienced by the patient at the beginning of hospital admission; in this case, the patient came with initial complaints of coughing up phlegm for 1 month, accompanied by weakness and weight loss. Positive results from the RMT examination confirm that these symptoms are a manifestation of opportunistic infection due to HIV, specifically pulmonary tuberculosis. Treatment for HIV-positive patients with TB begins with anti-tuberculosis drugs therapy and followed by ARV therapy after 2 to 8 weeks.

Syphilis co-infection in HIV is a systemic disease that can occur simultaneously because it has the same risk factors, predisposition factors, and modes of transmission. Individuals who suffer from weakened immune systems due to syphilis and HIV are at a higher risk of developing several severe diseases, including pulmonary tuberculosis and candidiasis. Patients with primary syphilis and secondary syphilis with HIV benefit more from the drug of choice, BPG, which is administered at 1-week intervals and can increase treatment success. The treatment of this patient requires adequate therapy, concrete measures, and periodic monitoring.[19]

Sexually Transmitted Infection (STI) such as syphilis and HIV-AIDS patients in Indonesia continue to pose a significant challenge in addressing global and national health issues. The importance of introducing sex education to children from an early age is a must to achieve Three Zeroes ending aids i.e no new HIV infections, no deaths due to AIDS, no stigma and no discrimination to achieve HIV elimination by 2030.

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