



Clinical and laboratory evaluation 9 months after the benzathine penicillin treatment in secondary syphilis patients

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Abstract

Syphilis is one of the sexually transmitted infections caused by *Treponema pallidum*, having clinical features that vary depending on its stage. Early stage consists of primary, secondary, and early late syphilis, whereas advanced stage consists of late latent and tertiary syphilis. The serological examination of syphilis is used for presumptive diagnosis. Venereal disease research and laboratory (VDRL) test and treponema pallidum hemagglutination assay (TPHA) are among the serological tests that are easy to conduct and inexpensive. Proper diagnosis and treatment are necessary not only to reduce transmission rates but also to avoid complications that occur in the advanced stage of this disease because no single typical dermatological clinical features are present at this stage. Follow-up and response to treatment should be considered. By comparing the post-treatment VDRL titer with the titer at the start of treatment, a serologic response after treatment may be evaluated, whether the patient is cured or not. Here, a case of a 55 year-old man who suffered from secondary syphilis is reported based on anamnesis, physical examination, and investigation of VDRL and TPHA. The patient was treated with benzathine penicillin with a single dose of 2.4 million UI intramuscularly and provided a good clinical response. On VDRL clinical and laboratory evaluations after 9 months of treatment, there was significant progress, meaning the treatment was success.

Keywords: benzathine penicillin, secondary syphilis, VDRL

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INTRODUCTION

Syphilis, also known as lues, is a sexually transmitted infection caused by *Treponema pallidum*. These bacteria are spiral and are motile in nature, and humans are the only natural hosts. Bacteria are surrounded by a cytoplasmic membrane, which is surrounded by a loose outer membrane. A thin layer of peptidoglycan, which provides structural stability, and endoflagella, the organelle responsible for the motility of *T. pallidum*, can be found between these membranes. This bacterium has a length of about 6–15 µm and a width of 0.15 µm, and the curved body reaches 8–24 curves. The cause of this disease remains unknown in Europe until 1492. Some assumed that this disease originated from Indian residents brought by Columbus's men upon returning to Spain. (Gudjonsson, et al. 2008, French, Rogstad, & Wiley, 2011).

The World Health Organization estimated that there are around 12 million new cases of syphilis worldwide each year, mainly in the North and Southeast Asia, sub-Saharan Africa, Latin America, and the Caribbean.

Comparing the incidence from one country to another is difficult because the reports are different. (French, Rogstad, & Wiley, 2011). The number of syphilis events ever reported in western countries reached its peak during the World War II, but thereafter, it declined dramatically when penicillin became available. (Golden, et al. 2019, Peterman, 2005). La Fond, Lukehart, 2006). Since 2001, the incidence of primary and secondary syphilis has increased again every year. (Peterman, 2005). The incidence of syphilis in men is six times higher than in women. (Celum, 2010). According to the Indonesian Ministry of Health in 2012 through Integrated Biological and Behavioral Surveillance, in 2011, in Indonesia, among those who suffered syphilis, 25% were transgenders, 10% were direct sex workers, 10% were men who had sex with men (MSM), 3% were indirect sex workers, and 3% were prisoners.

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Syphilis, when untreated, will go through two main stages: early and advanced. Early stage consists of primary, secondary, and early latent syphilis, whereas advanced stage consists of late and tertiary syphilis. (Horvath, 2011). Clinical features of syphilis vary widely and can mimic a variety of other skin diseases. (Gudjonsson, et al. 2008). The clinical diagnosis of syphilis must be confirmed by laboratory diagnosis. One of the diagnoses is a syphilis serological test that can be divided into two types: nontreponemal tests (for example, venereal disease research laboratory [VDRL] and rapid plasma regain [RPR]) and treponemal tests (for example, treponema pallidum hemagglutination assay [TPHA], fluorescent treponemal antibody absorption [FTA-ABS], and MHA-TP). Proper diagnosis and treatment are very important not only to reduce transmission rates but also to avoid complications that occur at the advanced stage of this disease. (Nayak,, Achariya, 2012, Gemala, 2018).

Follow-up and response to treatment should be considered, in which quantitative nontreponemal serological tests must be repeated at 1, 3, 6, 12, and 24 months after treatment. Serological titers must be compared with the titers at the start of the treatment to evaluate serological responses after treatment. The therapeutic criteria are considered successful if the nontreponemal serological titers decrease fourfold within 6–12 months after treatment for primary and secondary syphilis; otherwise, the treatment is considered a failure. The response to treatment seems to be related to syphilis stage (early stages tend to fall four times easily and become negative), and early titers are nontreponemal (low titers tend to be more difficult to fall four times than high titers). (Gemala, 2018).

A case of a 55 year-old man who suffered from secondary syphilis is reported based on anamnesis, physical examination, and investigation of VDRL and TPHA. This patient was treated benzathine penicillin with a single dose of 2.4 million UI intramuscularly. There was a significant progress in clinical and laboratory evaluation of VDRL after 9 months of treatment.

CASE REPORT

A 55 year-old man came to the Dermatology and Venereology Polyclinic Hospital Central Gatot Soebroto Jakarta Hospital with red rashes on the palms, soles, arms, legs, body, and face complaints.

The red rashes initially appeared thin on the arm since about 3 weeks ago then spread throughout the body, back, legs, palms, and soles of the feet up to the face, and the rash became even redder. As the rash spreads, some become red bumps or what is medically known as roseola sifilitica. The patient did not experience itching or pain from the rashes. There is a fine-line surrounding the rash on the palm. During this

condition, the patient felt weak, experienced aches such as headache, and sometimes felt feverish. The patient claimed to have suffered an injury in the penis, 1 month before the symptoms healed by itself in 1 week without special treatment.

The patient is married and works as a teacher in one of the state junior high schools in Bandar Lampung, Indonesia. He had an unprotected sexual intercourse with a woman other than his wife approximately 3 months before. The disease was unknown to the patient until physical examination. The patient has no history of food allergies and drug allergies. There is no family history of similar diseases.

On physical examination, good general condition, awareness of *compos mentis*, vital signs within normal limits, and adequate nutrition were found. Dermatological examination of the anterior and posterior trunk regions, superior extremities, and facial features showed multiple lesions that spread; some were partially irregular in shape, well-defined, and varying in size. Some lesions arise, were dry, in the form of erythema macules, erythema papules, crusting, and thin squama. In the palmar region of the right and left limbs, macular erythema features accompanied by squama surround the lesion edge. Hyperpigmentation macules were found in the plantar pedis region. On venereological examination, enlargement of the inguinal lymph node accompanied by tenderness was found. No ulcer was found in genitalia, no lesions were found in the mucosa, and there was no hair loss.

The patient was advised to conduct routine blood tests, VDRL test, TPHA, and anti-HIV. Based on the results of the examination found routine blood within normal limits, VDRL titers showed reactive 1/512 results and qualitative reactive TPHA. Rapid test results for HIV showed negative results.

Based on history, physical examination, and investigations, the patient was diagnosed with secondary syphilis. The patient received benzathine penicillin treatment with a single dose of 2.4 million UI intramuscularly. After treatment, the patient was educated for possible reactions due to benzathine penicillin injection. The patient was also educated not to have sexual relations to anyone other than his wife.

On the 8th-day control, clinical improvement of syphilis showed that erythema lesions in the trunk and facial regions had turned into hyperpigmented macules. In the palmar manus region, erythema macules are still seen accompanied by a thin squama. The patient was advised to conduct regular control at 1, 3, 6, 12, and 24 months post-treatment for a repeat VDRL examination. However, the patient returned to his hometown in Bandar Lampung and did not come in controls 1, 3, and 6 months because he felt the symptoms disappeared.



Fig. 1. Photo of the patient when it comes to polyclinic. Dermatological status: multiple lesions that spread in the form of erythema macules, erythema papules, crusting, and thin squama were found in the regio facialis and anterior and posterior trunks (A, B, C). Palmar erythema and macular lesions accompanied by squama are shown in the palmar manus region (D). Macules hyperpigmentation is shown in the plantar pedis region (E)

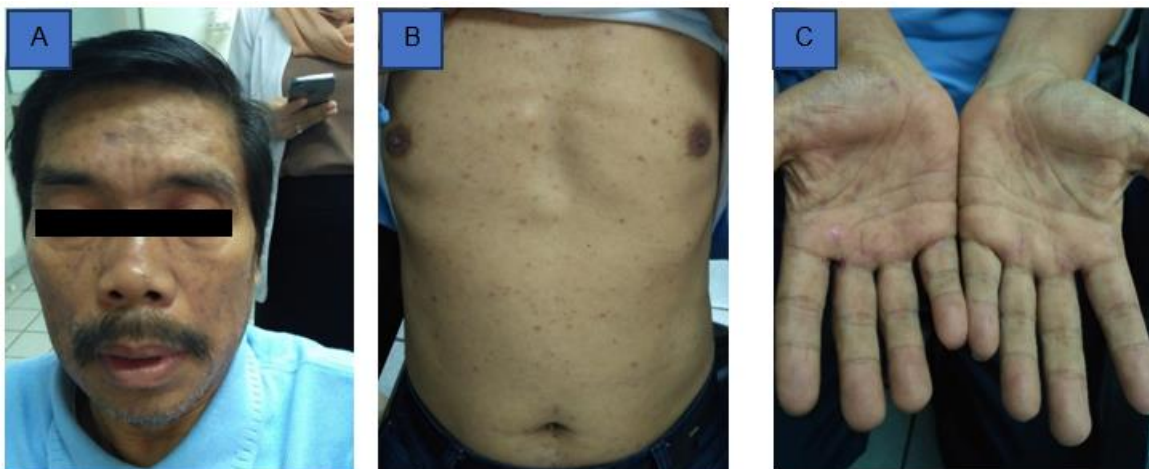


Fig. 2. Control photos of the 8th-day post-treatment. Dermatological status: lesions in the facial and trunk regions were found to turn into hyperpigmented macules and thin squares (A, B). The palmar manus region still showed erythema, macular lesions accompanied by squama (C)

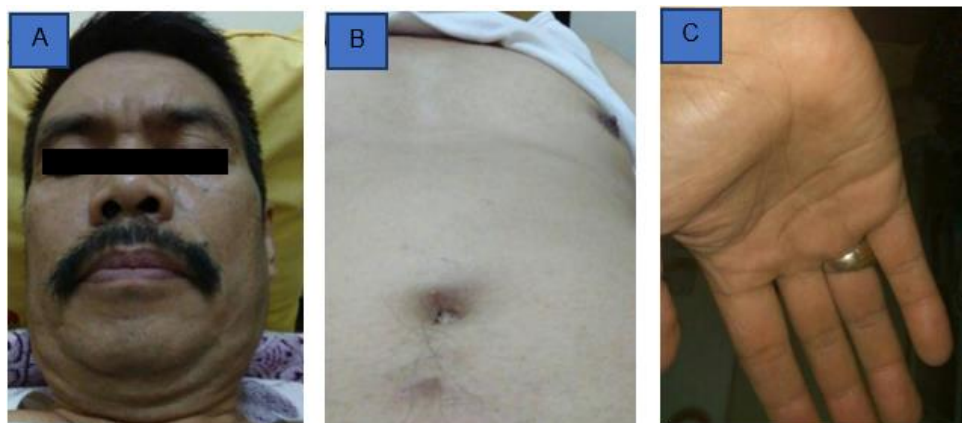


Fig. 3. Photograph of the 9th-month post-treatment control. Dermatological status in the regio facialis, trunk, and palmaris manus showed there were no recurring lesions or new lesions (A, B, C)

In the 9th-month post-treatment, the patient was successfully contacted again and was requested to show the clinical feature of his current condition, which was seen that the facial region, anterior trunk, and palmar manus was clean, and no new lesions appeared. The patient was also convinced to re-check VDRL, and the results obtained were 1/64 VDRL titer. Then, the patient was re-educated on the importance of re-examining VDRL in the 12th month. The patient also said that he never had unprotected free sex again.

DISCUSSION

Syphilis has a variety of clinical manifestations, depending on the stage of the disease: primary, secondary, latent, and tertiary. The diagnosis of syphilis can be made based on the typical clinical symptoms at each stage and based on investigations, such as serological examination. (Gemala, 2018, Sary, 2008).

Syphilis begins with the entry of *T. pallidum* through the surface of the mucosa or the intact skin at the site of trauma, usually during sexual intercourse. (Gudjonsson, et al. 2008, Kinghorn, 2010). Some organisms will multiply at the site of entry, and some will enter the lymphatic system into the nodules regional lymphatics and through blood vessels, and then, spread throughout the body. (Kinghorn, 2010). After an incubation period of 10–90 days (average 3 weeks), a primary lesion will arise at the site of inoculation in the form of a chancre ulcer. (Gudjonsson, et al. 2008, Golden, et al. 2019). The lesions begin as reddish macules that develop into papules and undergo ulceration in the middle. The ulcers are usually have the form of single, round, and oval, with a diameter of 1–2 cm, well-defined, solid, and painless. (Golden, et al. 2019, Kinghorn, 2010, Kent, Romanelli, 2008). In the patient's case, he claimed to have suffered an injury to the penis shaft approximately 1 month after unprotected sexual intercourse with a woman other than his wife, but the wound heals by itself within 1 week without special treatment. According to the literature, untreated ulcers can persist for 1–6 weeks

and may eventually disappear, while treated lesions will heal within 1–2 weeks without leaving scars. In men, ulcers are often found in the penis, whereas in women, they are found in the cervix, labia, and fourchette. (Gudjonsson, et al. 2008, Golden, et al. 2019).

When the primary lesion improves, *T. pallidum* will spread hematogenous and lymphogenic throughout the body, causing secondary syphilis, characterized by systemic symptoms such as low fever, malaise, sore throat, headache, and skin rashes. (Golden, et al. 2019, Sary, 2008, Baughn, Musherr, 2005). Secondary syphilis usually lasts 4–12 weeks and progresses to the latent stage. The clinical symptoms of secondary syphilis vary greatly because of the disseminated distribution of *T. pallidum*. (Gudjonsson, et al. 2008, Kinghorn, 2010). In 80%–95% of cases of secondary syphilis, a rash on the skin occurs, which can affect almost the entire body, including the palms and feet. These skin disorders can mimic a variety of other skin diseases with clinical manifestations of macular lesions, maculopapular, papules, and papulosquamous, as well as pustules. The form of the lesion can be in the form of annular, serpiginous, concentric, or arsenic. (Gudjonsson, et al. 2008, La Fond, Lukehart, 2006, Kent, Romanelli, 2008). Skin disorders can heal eventually in a few weeks without treatment and leave scars in the form of hyperpigmentation or hypopigmentation macules and sometimes in the form of a scar. (La Fond, Lukehart, 2006, Kinghorn, 2010). Skin disorders in this case in the form of red rashes that appear 3 weeks after the wound in the genitals healed, spread throughout the body to the palms and soles were also found to have several papules, crusts, and squama. The patient felt no itching or pain in the lesions. During the complaint, the patient felt weak, experienced aches such as and headache, and sometimes felt feverish.

Clinical symptoms of secondary syphilis can also occur in the mucous membranes and are generally very infectious. Abnormalities arising from mucous membranes can include condyloma lata, mucosal

patches, and pharyngitis. (Gudjonsson, et al. 2008, Talhari, Talhari, 2006). The constitutional symptoms that occur in secondary syphilis are flu-like symptoms such as fever, malaise, nausea, vomitus, arthralgia, myalgia, decreased appetite, and headaches that can occur with skin rashes (Gudjonsson, et al. 2008, La Fond, Lukehart, 2006, Horvath, 2011). Generalized lymphadenopathy without pain can be found in 50%–80% of cases, with a springy, discrete, bilateral consistency and can be moved from the surrounding tissue. Other abnormalities can also be found in the eyes, hearing system, musculoskeletal, blood, kidney, liver, gastric, cardiopulmonary, central nervous system, and hair loss that give a picture of moth-eaten appearance. (Kent, Romanelli, 2008, Talhari, Talhari, 2006). Enlargement of the inguinal lymph node and accompanied by tenderness, but no lesions, was found in the mucosa, and there was no hair loss. In the latent stage, clinical symptoms are not found, although serologically showing active syphilis. In the tertiary stage, clinical syndromes consist of three main groups, namely, neurosyphilis, cardiovascular syphilis, and advanced benign syphilis. (Gemala, 2018).

Investigations to establish a diagnosis of syphilis are direct detection of *T. pallidum* and syphilis serological tests. (Golden, et al. 2019, Goh, 2005). The method of direct detection of *T. pallidum* is to establish a definitive diagnosis of syphilis, which can be done through dark-field microscope examination, direct fluorescent antibody (DFA) test, and nucleic acid amplification test or polymerase chain reaction (PCR). (Gudjonsson, et al. 2008, 9) Darkfield examination has a sensitivity of 75%–95% depending on the expertise of the examination. (Zetola, Klausner, 2007). Tests DFA is higher in sensitivity and specificity compared with darkfield microscopy, whereas the sensitivity of PCR reaches 95% for primary syphilis and 80% in secondary syphilis. (Gemala, 2018). This direct detection method can help diagnose syphilis. (Ballard, Hook, 2013).

Syphilis serological examination is used for presumptive diagnosis. There is no single serological test capable of distinguishing syphilis from other treponematoses. (Gemala, 2018). Serological examination in syphilis consists of two types of tests, namely, nontreponemal tests (e.g., Wasserman reaction, RPR, VDRL, and toluidine red unheated serum test) and treponemal test (e.g., FTA-Abs, TPHA, *T. pallidum* passive particle agglutination assay, enzyme immunoassay, chemiluminescence, and rapid tests). (Gemala, 2018, Ballard, Hook, 2013). Nontreponemal tests are generally used for screening tests and looking at therapeutic responses, whereas treponemal tests are conducted to confirm the diagnosis. (Gudjonsson, et al. 2008, Zetola, Klausner, 2007, Emerson, 2009).

The current nontreponemal test can detect regains (a mixture of IgM and IgG antibodies in the serum of syphilis patients) that can react with complex antigens

(mix of cardiolipin, lecithin, and cholesterol) in the test (La Fond, Lukehart, 2006, Zetola, Klausner, 2007). This test is very sensitive and can be measured; however, it is less specific for syphilis, false-positive reactions are estimated to occur in 0.2%–0.8% of the tests, which are associated with non-syphilis health conditions. Acute false-positive reactions (lasting less than 6 months) are commonly found in other infectious diseases, malaria, hepatitis, chickenpox or measles, or by vaccinations that have not been done for a long time. By contrast, chronic false-positive reactions (lasting more than 6 months) are associated with connective tissue disease, malignancy, chronic leprosy infection, aging, and intravenous drug abuse. Serum with a false-positive reaction shows antibody titer $<1/4$. False-negative test results are often found in early or late phase infections with low antibody titers. Sometimes, false-negative test results can be found in secondary syphilis with a very high titer, a condition called a prozone phenomenon. The phenomenon of prozone can occur in 2% of patients and is often found in pregnancy and HIV infection. To prevent this event, the patient's serum must be diluted up to 1/16, if strongly suspected as syphilis. (Gemala, 2018). A nontreponemal test that is often used is VDRL, generally reactive 4–5 weeks after infection. (Lautenschlager, 2006). VDRL in syphilis has sensitivity 100% and specificity 98%. A high titer, $>1/32$, indicates active disease, whereas a titer $<1/8$ can be found in advanced syphilis that has been treated and can persist for years. (Lautenschlager, 2006). The results of this examination must be reported quantitatively to be used to monitor and evaluate disease activity. This type of nontreponemal test is easy to conduct and inexpensive. (Gemala, 2018).

The treponemal test is specific and is used as confirmation of diagnosis. (Gudjonsson, et al. 2008, Lautenschlager, 2006). This test can detect specific antibodies against *T. pallidum* but cannot distinguish syphilis from another treponematoses, because the antigenic structure of all these pathogens is almost the same. Very rare false-positive results occur. (Gemala, 2018). This examination has a sensitivity in primary syphilis of 70% to 100%, secondary syphilis by 100%, and advance-stage syphilis by 95%. (Stary, 2008). Most patients with reactive treponemal test results will remain reactive throughout his life, even though they had received adequate treatment; therefore, this test could not be used for therapeutic evaluation. Among all the treponemal tests available, TPHA is the most commonly used because, technically, it is inexpensive and the easiest to conduct. (Baughn, usherr, 2005, Lautenschlager, 2006).

FTA-Abs is a treponemal test that is considered the gold standard, with the greatest sensitivity, especially in early syphilis. The specificity of FTA-Abs is also high; hence, it is rarely negative when the nontreponemal test results are reactive. Generally, FTA-Abs is very

sensitive for all stages of syphilis. Conversely, the fluorescent evaluation is subjective, sometimes complicated; hence, it is suitable to be used as a confirmation test but not for screening. The results of reactive VDRL with titer 1/512 and qualitative reactive TPHA were obtained, which support the diagnosis of secondary syphilis in patients.

Syphilis can increase the risk of contracting HIV 2 - 4 times higher and transmit the HIV 2 - 9 times higher. Conversely, HIV-infected individuals also have a high risk of developing syphilis. (Hall, Klausner, Bolan, 2004). Syphilis coinfection with HIV generally occurs in groups of sex workers, MSM, and those who use drug via injection. (Dhaliwal, Patel, Menter, 2012). In this cases, the results of rapid test patient are negative, it means the patient did not have HIV. Anti-HIV testing can be negative even though studies are stating that the incidence of syphilis is high in patients with HIV/AIDS. (González-Domenech, et al. 2015). According to a research study conducted in Brazil that examined the prevalence of coinfection syphilis and HIV/AIDS, it was found that, in the prevalence of syphilis coinfection and HIV/AIDS, there were several positive cases, but the statistical tests did not increase significantly. Therefore, in the case of syphilis, HIV/AIDS can be found positive and can also be negative. (Da Silva, et al. 2017). Diagnosis of HIV infection is based on the detection of antibodies to HIV through screening for confirmation and confirmation examinations. Currently, rapid tests are routinely used in most developing countries. Rapid tests have a sensitivity of 99.9% and specificity of 99.6% and have the ability to detect IgG and IgM antibodies. This makes rapid tests useful in the early detection of HIV infection. (Alemnji, 2011, Coombs, 2008).

The first drug of choice for syphilis is benzathine penicillin with a single dose of 2.4 million UI intramuscularly. This antibiotic is bactericidal by inhibiting the synthesis of the walls of bacterial cells during the active multiplication phase. (Gudjonsson, et al. 2008, Golden, et al. 2019) The patient was treated with benzathine penicillin with a single dose of 2.4 million UI intramuscularly, and clinical improvement is seen in control day 8.

To follow up and monitor the response of treatment that has been given, a quantitative VDRL examination must be repeated at 1, 3, 6, 12, and 24 months after treatment. Serological titers should be compared with the titers at the start of the treatment. However, serological responses after treatment can be difficult to evaluate; hence, it is difficult to determine the criteria for recovery or definitive failure. Moreover, nontreponemal test titers can decrease very slowly in people who have been treated for syphilis. (Gemala, 2018). Adequate treatment will be characterized by a decrease in titer four times in 6–12 months in primary and secondary syphilis. In secondary syphilis, nontreponemal test results

generally become nonreactive within 12–24 months after treatment. Other studies report that VDRL titers become nonreactive 6 months after adequate treatment in 72% of patients with secondary syphilis and become nonreactive 30 months after treatment in 92% of patients with secondary syphilis. (Gudjonsson, et al. 2008, La Fond, Lukehart, 2006). VDRL titers may not decrease in latent syphilis patients early and remained reactive with low levels (<1/8) for many years. (Nayak, Achariya, 2012). In this case, a VDRL was re-inspected after 9 months, and a 1/64 result was obtained. TPHA examination was not conducted again during the 9th month. According to the literature, it is said that TPHA cannot be used for therapeutic evaluation because it can last a lifetime even though the treatment is successful. (Gemala, 2018). Anti-HIV testing was not conducted again during the 9th month, and this is a limitation in this case report because the inspection is not repeated.

Criteria for treatment failure can be evaluated from the following findings: finding symptoms and clinical features of syphilis that are persistent, recurrent, or progressive; in the repetition of the nontreponemal test, it was found that the titer value increased four times (with two dilutions) and remained for more than 2 weeks. Nontreponemal test results do not show a fourfold decrease in 6–12 months for primary, secondary, and early latent syphilis or 12–24 months for late latent syphilis, and their duration is unknown. (Nayak, Achariya, 2012). In this case, the clinical feature showed good results and decreased VDRL titers by more than fourfold after 9 months of treatment, that is, 1/64 and planned to be continually observed for 24 months.

CONCLUSION

Syphilis is a sexually transmitted infection caused by *Treponema pallidum*, which has clinical features that vary according to the stage, in which serological laboratory tests can help establish the diagnosis and evaluate the success or failure of the treatment. It is hoped that this case report can be a valuable reference for doctors to routinely evaluate patients who have been diagnosed and given treatment and always screen other sexually transmitted infections such as HIV/AIDS. Detection and other examinations are expected to continue to be studied and further investigated to improve the quality of health services in the community. Moreover, case studies on the factors that can influence the success of treatment are important.

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