eISSN (Online): 2598-0580

Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: www.bioscmed.com

Latent Syphilis Unresponsive to Doxycycline and Azithromycin

Cayadi Sidarta Antonius[1*], Mutia Devi[1], M. Izazi Hari Purwoko[1], Suroso Adi Nugroho[1], Fitriani[1], Susanti Budiamal[1]

[1] Department of Dermatology and Venereology, Faculty of Medicine, Universitas Sriwijaya, Palembang, Indonesia

ARTICLE INFO

Keywords:
Syphilis
Antibiotic
Benzathine penicillin
Hypersensitivity reaction
Azythromycin

***Corresponding author:**
Cayadi Sidarta Antonius

E-mail address:
cayadi_a@yahoo.com

All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/bsm.v6i5.503

ABSTRACT

Background. Syphilis management is based on the syphilis stage classification. The main treatment for syphilis is currently benzathine penicillin. However, patients allergic to penicillin antibiotics or who are not willing to be injected can be given doxycycline or erythromycin antibiotics. **Case presentation.** We present a case of a female with latent syphilis. The patient was previously treated with oral antibiotics, such as doxycycline for 30 days and followed by azithromycin for 30 consecutive days. Clinical laboratory examinations show an increase in TPHA and VDRL, and the case was considered an unresponsive case. Later, the patients received benzathine penicillin G for three weeks and showed clinical improvement. **Conclusion**. For a patient who refuses to be treated with penicillin injection, the alternative treatments are oral antibiotics. However, there is a reduced number of successful treatments for patients treated with oral antibiotics.

1. Introduction

Syphilis is a sexually transmitted disease caused by Treponema pallidum subspecies pallidum.[1] Syphilis can be transmitted through sexual and non-sexual contact or transplacental in case of congenital syphilis. Transmission through sexual contact, resulting from exposure to mucosal or moist skin lesions in primary or secondary syphilis. Syphilis management is based on the syphilis stage. Primary, secondary, and early latent syphilis were treated with an injection of benzathine penicillin G 2.4 million units. Late latent syphilis is treated with an injection of benzathine penicillin G 2.4 million units 3 times on day 1, day 8, and day 15. Primary, secondary, and early latent syphilis who are allergic to penicillin or with a history of bleeding disorders can be given doxycycline 200 mg per day for 14 days, whereas latent syphilis is treated for 21-28 days.[2]

2. Case Presentation

A 28-year-old woman came for a pregnancy screening program. There were no clinical complaints in the patient. There is no history of genital lesions, spots on the palms of the hands and feet, no history of hair loss, or history of injuries to the extremities. The history of promiscuity was denied, the patient had VDRL and TPHA examination 5 years before hospital admission and the results were non-reactive. For the past 5 years, the patient has always used a condom

when having sex with her husband. STI history was denied. On examination, we found syphilis VDRL 1/4 and TPHA 1/320, non-reactive HIV, and non-reactive hepatitis B. The patient was advised to inject the antibiotic benzathine penicillin G but the patient refused. The patient has then treated with doxycycline 100 mg twice daily for 30 days.

Within 6 weeks, the patient underwent a follow-up laboratory examination. There were no clinical complaints in the patient. The results of the laboratory examination were RPR 1/64 and TPHA 1/640. The patient has then treated with azithromycin 500 mg twice daily for 30 days. The patient did not return for the follow-up.

One year after the last follow-up, the patient then performed an independent laboratory examination for pregnancy screening programs. The results of the VDRL 1/128 and TPHA 1/320 examination results were found without any clinical complaints. The patient was diagnosed with late latent syphilis and treated with benzathine penicillin G 2.4 million units per week for 3 weeks. On monitoring, there was an improvement in the patient's serological examination after being treated. The history of serological examination of the patient is shown in table 1.

Table 1. History of serological examination of the patient

Date	VDRL/RPR	TPHA	Note
March 20th 2020	1/4	1/320	
May 13th 2020	1/64	1/640	After treated with doxycycline
June 4th 2021	1/128	1/320	After treated with azithromycin
August 13th 2021	1/8	1/320	
September 23rd 2021	1/4	1/640	After being treated with benzathine penicillin G

3. Discussion

Syphilis has a major effect on some at-risk populations over time. It was later found that the incidence of primary and secondary syphilis among women is doubled between 2014 and 2018. The number of syphilis cases increased due to drug use or unprotected sex. All stages of syphilis in pregnant women can pose a risk of transmission to the fetus, but the risk is much higher in early syphilis than in later stages of the disease.[3] In this case, a woman was diagnosed with syphilis through a pregnancy screening program without any clinical symptoms.

There are several stages of syphilis, including primary syphilis, secondary syphilis, latent syphilis, and tertiary syphilis. The primary lesion of syphilis is a papule that appears at the site of contact, 10-90 days (mean 3 weeks) after exposure, sometimes accompanied by bilateral inguinal lymph node enlargement. Within weeks or months, systemic symptoms may develop, including low-grade fever, malaise, sore throat, headache, adenopathy, and skin or mucosal rash. The initial symptom of secondary syphilis is a copper-red macular rash on the body and extremities, sometimes with white scales. Another manifestation of secondary syphilis is condyloma lata. Latent syphilis is a patient who has positive serological results, has no clinical symptoms, and has never received treatment.[4] Latent syphilis is a patient who had a positive serological result for two years or more.[5]

The diagnosis of syphilis is made based on anamnesis, physical examination, laboratory, and sometimes radiological examinations. Laboratory tests available for the diagnosis of syphilis include direct detection methods, serology (treponemal and non-treponemal tests), and cerebrospinal fluid examination.[5] Serological tests are the standard to help establish the diagnosis of syphilis. The diagnosis of syphilis by serologic testing requires 2 tests, namely non-treponemal and treponemal. Non-treponemal and treponemal serological tests are used to avoid false positive or negative results, to determine the stage and success of therapy. The comparison between the results of the TPHA and RPR examinations can be used to determine the stage and course of the patient's

disease. The success of therapy was assessed by changes in PRP and TPHA titers.[6] In this patient, treponemal and non-treponemal serological examinations were performed, and the titers decreased from RPR 1/128 and TPHA 1/640 to RPR 1/4 and TPHA 1/640.

Syphilis treatment is classified according to the stage. The Center for Food Disease Control and Prevention in 2021 recommends the same dose of therapy for primary, secondary, and early latent syphilis, namely injection of benzathine penicillin G 2.4 million units intramuscularly (IM), a single dose. Meanwhile, late latent syphilis was treated with an injection of benzathine penicillin G in totals of 7.2 million units given in 3 divided doses.[7] Based on the 2016 World Health Organization (WHO) recommendation, the treatment for latent syphilis or whose stage is unknown, is an injection of benzathine penicillin G. 2.4 million units every week, for 3 weeks. Patients with penicillin allergy can be treated with doxycycline 100 mg twice daily for 30 days.[5] The response rate for latent syphilis treated with benzathine penicillin G is 56%-63%.[8]

Based on the European syphilis management guidelines 2020, doxycycline is one of the treatments for syphilis in patients who are allergic to penicillin antibiotics or patients who refuse parenteral treatment. Doxycycline in primary, secondary, and early latent syphilis, is given at 200 mg divided into 2 doses per day for 14 days, while late latent syphilis is given for 21 to 28 days.[2] Several studies have shown the effectiveness of administering doxycycline against latent syphilis with the same efficacy as administration of benzathine penicillin.[9] The study conducted by Dai T found that the effectiveness of doxycycline in latent syphilis was 79.2%.[10]

The use of azithromycin for syphilis remains controversial. In 2002-2003 there were reports of failure of treatment for syphilis treated with azithromycin due to mutations in the 23S rRNA gene (A2058G) identical to the Street 14 strain. The prevalence of the mutation increased over time.[11] *T. pallidum* Street Strain-14 (SS14) was isolated in 1977 in Atlanta, GA, from skin lesions of a patient with secondary syphilis who failed treatment with erythromycin. In vitro studies showing resistance to high levels of erythromycin and cross-resistance to azithromycin were confirmed in vivo. Resistance is caused by the changes in the target part of the 23S rRNA, due to the A2058/9G mutation. However, azithromycin continued to be used for the treatment of syphilis in the United States from 1999 to 2000. Genetic analysis of samples of patients with treatment failure revealed the SS14 A2058G mutation. The prevalence of mutations from various cities showed an increase over time.[12] The study found that administration of azithromycin failed to provide a cure effect in cases of primary and secondary syphilis. However, a randomized clinical study by Bai et al found a higher therapeutic efficacy with azithromycin. compared to benzathine G penicillin in long-term follow-up.[13]

In this patient, the treatment of choice was the administration of benzathine G penicillin, but the patient refused to receive injection therapy. Based on the patient's request, the patient's first choice of therapy was doxycycline for 30 days. The evaluation later found that there was no serological improvement in the patient. At that time the patient should be given benzathine G penicillin therapy, but the patient still refused so azithromycin was given. After 1 year of failure to follow-up, the patient came back again and was declared latent syphilis. The patient received benzathine G penicillin therapy for 3 weeks and showed serological improvement in monitoring in the form of a decrease in VDRL and TPHA by 4 times.

4. Conclusion

For a patient who refuses to be treated with penicillin injection, the alternative treatments are oral antibiotics. However, there is a reduced number of successful treatments for patients treated with oral antibiotics.

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