International Journal of Dermatology, Venereology and Leprosy Sciences

E-ISSN: 2664-942X
P-ISSN: 2664-9411
www.dermatologypaper.com
Derma 2022; 5(1): 33-38
Received: 19-01-2021
Accepted: 25-03-2021

Harry Gunawan
Department of Dermatology and Venereology, Faculty of Medicine, Udayana University, Bali, Indonesia

Prayogi Miura Susanto
Faculty of Medicine and Health Sciences, Atma Jaya Catholic University, Jakarta, Indonesia

Flora Anisah Rakhmawati
Department of Dermatology and Venereology, R. Syamsudin, SH Regional General Hospital, Sukabumi, Indonesia

Corresponding Author:
Prayogi Miura Susanto
Faculty of Medicine and Health Sciences, Atma Jaya Catholic University, Jakarta, Indonesia

Atypical palmoplantar lesion in relapsed advanced latent syphilis with HIV co-infection

Harry Gunawan, Prayogi Miura Susanto and Flora Anisah Rakhmawati

DOI: https://doi.org/10.33545/26649411.2022.v5.i1a.111

Abstract
Syphilis is a systemic infection caused by *Treponema pallidum* subspecies *pallidum*, which has a major and various manifestations on the skin (the great imitator). Its prevalence is frequently associated with Human Immunodeficiency Virus (HIV) prevalence. Atypical and aggressive presentation of syphilis is more commonly found in persons with syphilis and coinfection of HIV. We report a case of a 30-year-old male with erythematous plaques and desquamation on his palms and soles with neither pain nor pruritus, and also Beau's line on the hand and toe nails. HIV infection was detected. The diagnosis of the patient was relapse late latent syphilis with HIV co-infection. The diagnosis of syphilis was established based on clinical and serological testing. The clinical manifestations of syphilis in immunosuppressed patients are often atypical. In order to treat, the patient was prescribed with doxycycline 100 mg two times a day for a month and showed clinical improvement after three weeks course of medication. Serologic testing interpretation and treatment do not differ between syphilis patients with and without HIV coinfection.

Keywords: Atypical lesion, HIV co-infection, syphilis, *treponema pallidum*

Introduction
Syphilis is a systemic infection caused by the *Treponema pallidum* bacteria of the subspecies *pallidum*, where infection involves many organs with a significant clinical manifestation on the skin. The course of syphilis is divided into two periods, i.e., early syphilis (primary, secondary, and early latent syphilis) and advanced syphilis (advanced latent syphilis and tertiary syphilis). This classification is based on clinical manifestations with a certain time limit. Clinical manifestations on the skin can occur with a wide variation, similar to other skin diseases. Therefore, syphilis is known as "the great imitator" [1-4].

Syphilis is included in sexually transmitted infections and thus is often associated with Human Immunodeficiency Virus (HIV) incidence. Globally, WHO estimated 5.6 million new cases occur in the 15-49 years age group with a global prevalence reaching 18 million cases in 2012 [3]. Syphilis incidence begins to increase from 2000, especially in men who have sex with men (MSM) with various supporting factors [1, 5-7]. Around 58-75% cases of primary and secondary syphilis were reported in the MSM group [7-8]. Based on CDC, 30-74% of syphilis cases in MSM are estimated to be associated with HIV co-infection [1]. In Indonesia, the prevalence of syphilis in the MSM group increased from 4% in 2007 to 13% in 2011 with 23.8% of them associated with HIV co-infection [4]. Atypical and aggressive clinical manifestations of syphilis are often found in syphilis patients with HIV co-infection [1, 5, 9, 10].

Case Report
A 30-year-old male patient reported on December 23, 2018, with a complaint of thickening and peeling of the skin around both palms and soles. It started with red spots that appeared simultaneously on both palms and soles 2 months ago. The red spots extended to all the palms and soles within 2 weeks. The skin on that area also thickened and peeled. The patient denied feeling pain, heat, sting, and itchiness around the area. He complained of fever and lethargy 4 days before admission to the hospital. The fever was persistent. The patient has not married but had a history of sexual relationships with 3 people. The first sexual partner was a woman whom the patient knew.

He had a condom on and had sex once in January 2016. The second sexual partner was a woman whom the patient did not know of and had sex once without a condom in March 2016. The third sexual partner was a man that the patient knew of, had anal sex 6 times in a receptive role, and always used a condom from August 2016 to January 2017. The patient admitted to oral sex without a condom. He did not know the HIV status of his sexual partners and denied any skin abnormalities in the genitals of his sexual partners. The patient often consumed alcohol while visiting nightclubs in Jakarta around 2-4 times per month. The patient denied having a history of allergy, narcotics consumption, shared use of syringe, surgery, and blood transfusion. He had a history of pulmonary tuberculosis and human immunodeficiency virus (HIV) infection from July 2017. He admitted that he fully treated pulmonary tuberculosis for 6 months and routinely consume antiretroviral (ARV) medicine for 6 months from July 2017-December 2017. The patient did not continue routine ARV after because he thought he showed clinical improvements.

General physical examination showed 38.5ºC body temperature and other examinations were within normal limits. Skin lesion examination showed erythematous plaques with desquamation that spread through all palms and soles, not accompanied by itchiness or pain (Figure 1). Fingernails and toenails indicated horizontal indentations from the medial to the lateral edge of the nails (Beau's line) (Figure 2). No skin abnormalities were found in other parts of the body. Regarding laboratory examination, Venereal Disease Research Laboratory (VDRL) showed a 1:8 titer, and *Treponema pallidum* Hemagglutination Assay (TPHA) was reactive.

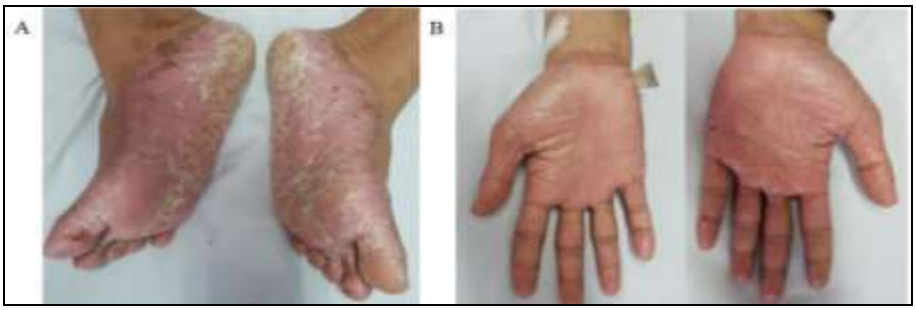

Fig 1: A) and B) Depicted erythematous plaques with desquamation throughout all palms and soles not accompanied by itchiness or pain

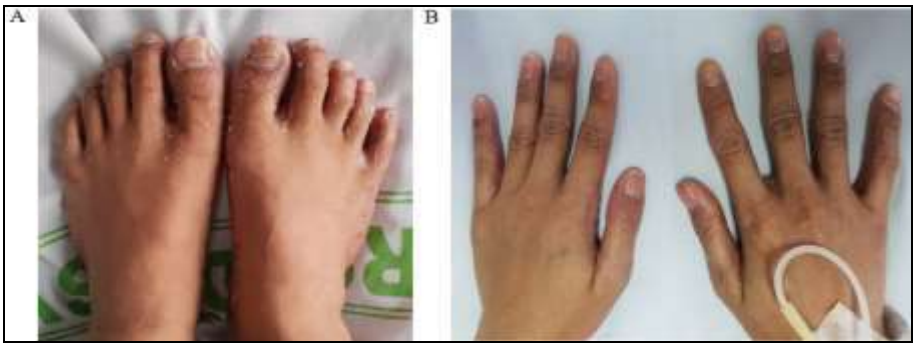

Fig 2: A) and B) Indicated horizontal indentations from the medial side to the lateral side of fingernails and toenails (Beau's line)

The patient was given 100 mg of doxycycline therapy two times a day and planned for 28 days. Three weeks follow-up showed clinical improvements (Figure 3).

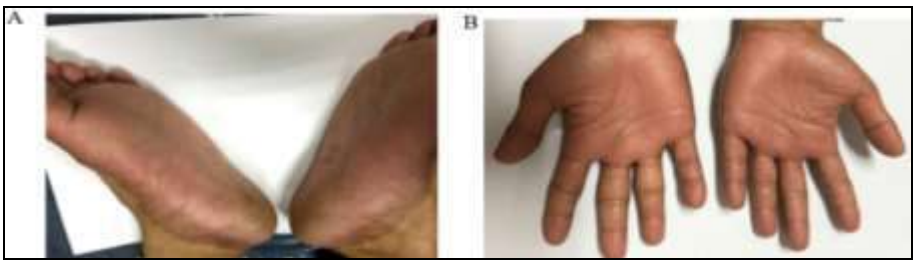

Fig 3 A) and B): Depicted clinical improvements in palmoplantar lesions after three weeks of doxycycline therapy

Discussion

Syphilis is a systemic sexually transmitted infection caused by *Treponema pallidum* of the subspecies *pallidum*. *T. pallidum* is included in the phylum *Spirochaetae*, spiral-shaped, motile, 5-16 µm in length and 0.2-0.3 µm in diameter [1, 6, 11-12]. The incubation period is between 10 days to three months, with an average of three weeks. Syphilis can be transmitted through direct contact with infectious syphilis lesions, tattoos, blood transfusions, or transplacental. Direct contact can occur through sexual contact (most common; the transmission can occur through oral, vaginal, or anal sex) and non-sexual contact. Infectious lesions in syphilis patients include chancre, condyloma lata, and mucous patches. Lesions on keratinized skin such as

palmoplantar lesions and maculopapular rash on the body usually do not contain many bacteria and are categorized as non-infectious [1, 11, 13, 26].

The prevalence of syphilis tends to increase since 2000, especially in the MSM group. Several factors contributing to the increase in syphilis prevalence include unsafe sexual practice, changing sexual partners, the use of the internet to look for a sexual partner, serosorting (having a sexual relationship based on similarity of HIV status), and the use of recreational drugs [1, 5-7]. The highest prevalence of primary and secondary syphilis cases is found in men in the 20-29 years age group. Syphilis is often associated with HIV co-infection. This is related to 2-9 times increased risk of HIV transmission and 2-4 times HIV acquisition from ulcers [4, 7, 10].

This patient had several syphilis risks, including a history of sexual practice without a condom, changing sexual partners, and being infected with HIV. Based on epidemiology, this patient is included in the MSM group and is a young adult. The MSM group might use a condom during anal sex, but not during oral sex because they are not aware that syphilis can be transmitted through oral sex. In around 20% of cases in MSM, syphilis is transmitted through oral sex [1, 5].

Based on clinical manifestation and time limit, syphilis is divided into two periods, i.e., early syphilis and advanced syphilis. The time limit refers to contact with the pathogen, where the early and latent period has a time limit of one year based on CDC and ECDC. However, WHO stated that the time limit is two years [2, 3, 8]. In Indonesia, the time limit was determined at one year.[4] Early syphilis consists of primary, secondary, and early latent stages. Advanced syphilis consists of advanced latent stage and tertiary stage [1-3].

Primary stage syphilis is characterized by the appearance of one or more chancre in the location of inoculation (usually around oral and anogenital areas) after passing the incubation period. Chancre lesions begin with ulcerated red papules for 3-12 weeks that can heal without therapy. The chancre is usually round or ovoid, two cm in diameter, well-defined with indurated edges, clean base, and usually painless. Patients might not be aware of primary stage syphilis, especially in hard-to-see locations [1, 2, 6, 12,14].

The secondary stage usually occurs 3-12 weeks after the appearance of chancre but can occur 6 months after exposure. Chancre can still be found in 25% of cases of secondary syphilis, more often in patients with HIV co-infection. Most secondary syphilis lesion (40-70% of cases) is erythematous macules (syphilitic roseola) or maculopapular rashes that spread throughout the body and extremities and usually are not accompanied by itchiness.[1,2,15] Secondary syphilis lesion is highly variated and can appear in the form of papules, papulosquamous lesions, and lichenoid. Skin lesions can be minimal and sometimes patients are not aware of secondary syphilis lesions. As many as 75% of cases had lesions reaching the hands and feet (palmoplantar), with brownish erythematous multiple papules that can spread to the lateral or posterior area of the plantar. Palmoplantar lesions are also varied, which can be in the form of macules or papules, discrete or diffused, and can be accompanied by squama or hyperkeratosis (syphilitic corn). The palmoplantar lesion is quite typical in syphilis [1, 2, 15, 16]. Other dermatologic manifestations include patchy non-scarring alopecia (moth-eaten), mucous patches in mucous membranes, and condyloma lata in intertriginous areas. Rare clinical manifestations include lichenoid, nodular, follicular, pustular lesions, and palmoplantar keratoderma. Nail manifestations include fissures, onycholysis, Beau's line, onychodystrophy, and onychomadesis. Patients usually have systemic symptoms such as fever, malaise, headache, muscle pain, vision impairment, tonsillopharyngitis, periostitis, and gastritis. Clinical manifestations of secondary syphilis will heal without therapy after 4-12 weeks and skin lesions usually do not leave scar tissues. Secondary syphilis is followed by a period without clinical manifestations (latent syphilis [1, 2, 6, 12].

Latent syphilis is diagnosed after excluding syphilis lesions and reactive serology as evidence of active infection. Latent syphilis is divided into three subcategories, i.e., early latent syphilis, advanced latent syphilis, and latent syphilis of unknown duration. Early latent syphilis is diagnosed in patients with one of the following criteria: a) documentation of seroconversion or increased non-treponemal titer $\geq$ 4 times; b) no primary and secondary syphilis symptoms; c) sexual partner is documented with primary, secondary, or early latent syphilis; or d) reactive non-treponemal and treponemal test in individuals that may be exposed within the last 12 months. Latent syphilis of unknown duration is a subcategory of latent syphilis in patients aged 13-35 years old with a non-treponemal titer of $\geq$ 32 and did not fulfill the early latent syphilis category. Advanced latent syphilis is diagnosed in patient infected more than 1 year ago and did not fulfill other latent syphilis subcategories [1, 8]. Tertiary syphilis is defined as advanced syphilis with clinical manifestations in various organ systems such as cardiovascular, skin, bone, and others. Neurosyphilis can occur in early syphilis, thus not specifically in tertiary syphilis. In the cardiovascular system, syphilis can cause syphilitic aortitis, coronary ostial stenosis, and saccular aneurysm. A typical clinical manifestation of the skin is the formation of gumma, nodular granuloma with central necrosis that can appear in the skin or mucous membrane [1, 2, 12].

Syphilis and HIV infection can be transmitted through sexual contact and are commonly found in the group of patients with similar risk factors, therefore co-infection of the two diseases often occurs. Syphilis can increase the risk of transmission and acquisition of HIV through epithelial damage due to ulceration and an increased number of T-cells as HIV targets [1, 3, 5, 12]. In general, clinical manifestations of syphilis in non-HIV patients are not significantly different from syphilis patients with HIV co-infection. However, aggressive and atypical clinical manifestations are more often found in syphilis patients with HIV co-infection [1, 2, 9, 10]. In patients with HIV co-infection, primary syphilis lesions are more often found multiple, deeper, and larger, and can be found together with secondary syphilis [1, 2, 10, 17].

The patient last had sexual contact in December 2016. Based on the time limit, he was categorized as advanced latent syphilis. This patient experienced systemic complaints of fever and skin clinical manifestations of palmoplantar erythematous plaques with desquamation that extended to the lateral side and were not accompanied by itchiness or pain. Beau's line was found as a manifestation in the nails. This clinical manifestation showed location predisposition of secondary syphilis lesion, even though erythematous plaques with desquamation were atypical. Latent syphilis

can be interspersed with relapse periods with secondary syphilis manifestations or advanced to tertiary syphilis. Relapse occurs in 25% of cases within 1-2 years after infection [2, 12]. Syphilis patients with HIV showed more atypical, ulcerative, or malignant clinical manifestations such as in secondary syphilis and erythematous plaques with thick squama around the palmoplantar areas resembling psoriasis that were reported by Bittencourt *et al.* [16], secondary syphilis case with multiple pustules surrounded by keratotic lesion and erythematous base in palmoplantar areas that were reported by Gianfaldoni *et al.* [18], and secondary syphilis case with whole-body ulcerative lesions with central necrosis to palmoplantar areas that were reported by Rajan *et al.* [9].

Syphilis can have various clinical manifestations. Therefore, an adjunctive examination is very helpful to establish a syphilis diagnosis. Adjunctive examinations in syphilis cases can be carried out by directly detecting *T. pallidum* infection, histopathological examination, and serological examination. A direct examination can be carried out using a dark-field microscope, direct fluorescence antibody test, and polymerase chain reaction (PCR) [1, 2, 19]. Samples that can be used for dark-field microscopy are chancre, condyloma lata, mucous patches, and rhinitis fluid from congenital syphilis. Other secondary syphilis lesions cannot be used as samples because they do not contain enough bacteria to be detected [1, 19]. In general, histopathological examination is not significant because syphilis diagnosis can be established from clinical examination, direct detection, and serology [1].

Serological examination is divided into non-treponemal and treponemal test. The non-treponemal test uses a reagent containing cardiolipin, cholesterol, and lecithin to detect antibodies on lipoidal materials from host cells that are possibly infected by *T. pallidum* [2, 10, 19]. The most common non-treponemal serological test is the Venereal Disease Research Laboratory (VDRL) and Rapid Plasma Reagin (RPR). VDRL and RPR become reactive 4-6 weeks after infection. The test will be non-reactive after adequate therapy in 25-30% of advanced latent syphilis cases. The non-treponemal serologic test can be used as a reference for successful therapy. However, several cases can have reactive non-treponemal serology in low titer for a long duration (serofast reaction) and are more often found in patients with HIV co-infection. The non-treponemal serologic test can provide a false-negative result during the early period of infection, latent syphilis, advanced syphilis, and the prozone phenomenon. The Prozone phenomenon is caused by a high antibody titer, thus inhibiting the reactivity of the test. However, this can be overcome by serum dilution. Around 1-2% of reactive tests can be due to biologic false-positive and usually have low titer under 1:8 with various causes [1, 2, 7, 19, 20].

The VDRL titer in this patient was 1:8, which indicated reactive with a relatively low titer. This finding was in line with the patient's diagnosis where a non-treponemal serologic test will decrease latent syphilis. Biologic false-positive can be caused by HIV co-infection, albeit very rare (1-2%) and with titer under 1:8.

Table 1: Cause of biologic false-positive of non-treponemal serological test[1]

	Acute	**Chronic**
Physiologic	Pregnancy	Advanced age
Spirocheta	Leptospirosis	Endemic syphilis
Infection	Lyme disease, Rat-bite fever, Relapsing fever	Pinta, Yaws
Viral infection	Cytomegalovirus, Infectious mononucleosis, Hepatitis, Herpes simplex, Herpes zoster-varicella infection, Measles, Mumps, Mycoplasma pneumonia, Toxoplasmosis, Viral sepsis	Human T-cell leukemia, HIV
Bacterial infection	Pneumonia	Lepromatous leprosy, Lymphogranuloma venerum, Tuberculosis, Brucellosis, Chancroid
Protozoic infection	Malaria	Kala azar, Trypanosomiasis
Autoimmune		Autoimmune hemolytic syndrome
Systemic disease		Autoimmune thyroiditis, ITP Polyarteritis, nodosa, Primary biliary cirrhosis, Rheumatoid arthritis, Sjogren's syndrome, SLE, Rheumatic heart disease, Ulcerative colitis
Other		Drug abuse, Immunization, Hepatic cirrhosis, Malnutrition, Malignancy, Lymphoproliferative disorder

Treponemal serologic test uses *T. pallidum* antigen to detect *T. pallidum* infection. This test can show a reaction 12 weeks after infection. Several treponemal serologic tests include TPHA (*Treponema pallidum* Hemagglutination Assay), TP Rapid (*Treponema pallidum* Rapid), TP-PA (*Treponema pallidum* Particle Agglutination Assay), and FTA-ABS (Fluorescent Treponemal Antibody Absorption). The treponemal serologic test will be reactive for a lifetime in patients with or who had syphilis, and thus cannot be used as a reference for successful therapy. This test can be used to confirm syphilis infection and exclude biologic false-positive results in non-treponemal serologic tests [1, 19]. Reactive non-treponemal serologic test accompanied by reactive treponemal serologic test confirm the diagnosis of syphilis [1, 10, 21]. (Table 1.)

In syphilis patients with HIV co-infection, the interpretation of adjunctive test results does not differ from common syphilis patients. Several things related to HIV co-infection include increased biologic false-positive frequency in non-treponemal serologic test, reduced or slower non-treponemal serologic titer, and increased prozone phenomenon frequency [10, 20].

This patient had a VDRL titer of 1:8, which was reactive with a relatively low titer. This finding was in line with the patient's diagnosis where a non-treponemal serologic test titer will decrease in advanced latent syphilis. Biologic false-positive can be caused by HIV co-infection, albeit very rare (1-2%) and a titer under 1:8. The VDRL test result in

this patient was confirmed by a TPHA test which was reactive. Based on clinical and laboratory examinations, the diagnosis of relapsed advanced latent syphilis with HIV co-infection can be established.

Syphilis treatment is given based on the stages of infection and involvement of the central nervous system. Treponemicidal levels from antimicrobial agents must reach serum and cerebrospinal fluid, especially in neurosyphilis patients. Antimicrobial agents with a long half-life are needed because the division time of Treponema pallidum is slow (around 30-33 hours) [1, 7, 12]. Centers for Disease Control and Prevention (CDC) 2015 [22], and World Health Organization (WHO) 2016, [3]. Recommend parenteral Penicillin G as the main choice of therapy for all stages of syphilis. There is no resistance tendency from penicillin detected in *T. pallidum*.

Penicillin preparation, dose, administration route, and treatment duration depending on the stages and clinical manifestations of syphilis and other management considerations (for example pregnancy, HIV status, and patient's age). Appropriate use of penicillin is important because *T. pallidum* can reach hard-to-reach locations (for example, the central nervous system, aqueous humor, synovial fluid). Penicillin level of more than 0.018 mg/l is considered a treponemicidal level. This level must stay in the serum for 10 to 14 days for early and advanced syphilis, and 21 days for neurosyphilis and cardiovascular syphilis. According to the working duration, there are three types of penicillin, which are penicillin G procaine in aqua (24 hours of working time), penicillin G in oil with aluminum monostearate (PAM) 32 hours of working time), and penicillin G Benzathine with a dose of 2.4 million units (stay in serum for two to three weeks). Penicillin is administered through intramuscular injection. Penicillin G benzathine has a long working time so that the drug can stay longer in serum and is more practical. Therefore, the patient does not need to be injected every day. Parenteral administration of penicillin G is effective to reduce clinical symptoms marked by lesion recovery and preventing sexual transmission and residual symptoms [1, 12, 23].

The 2017 Perdoski Clinical Practice Guideline in Indonesia recommends penicillin G benzathine as the main choice of treatment for syphilis. For primary and secondary syphilis, 2.4 million units of penicillin G benzathine is administered intramuscularly with a single dose, while latent stage syphilis was given for 2.4 million units intramuscularly weekly on days 1, 8, and 15. Syphilis therapy on individuals with HIV and without HIV is the same, which is an intramuscular injection of 2.4 million unit's single dose penicillin G benzathine [1, 24, 25].

Therapy evaluation is carried out clinically and serologically with more observation on syphilis patients with HIV every three months for the first year because of the higher risk of treatment failure and neurosyphilis. The criteria for therapy failure include persistent and recurrent signs and symptoms or four times increase of non-treponema titer. VDRL or RPR titer will decrease four times within 6-12 months after treatment in primary or secondary syphilis, and 12-24 months after treatment in latent syphilis patients. Titer that does not reduce four times after treatment must be considered for reinfection, therapy failure, or neurosyphilis [1, 25].

Other than penicillin, several antibiotics can be used for syphilis treatment. Alternative treatment is chosen if there is a history of allergy to penicillin, patient's rejection to injection, or unavailability of penicillin G benzathine. Other choices of antibiotics include 100 mg of doxycycline given twice a day orally for 14 days for primary and secondary stages or 28 days for latent syphilis. Xiao *et al.* [26] showed that doxycycline has the same effectiveness as penicillin G benzathine for syphilis therapy. Another antibiotic that can be given for primary or secondary stage syphilis is 500 mg of erythromycin given four times a day orally for 14 days or 30 days for latent syphilis. However, the effectiveness of erythromycin is still questionable because of the high resistance of *T. pallidum* on macrolides. Therefore, syphilis patients with allergies to penicillin should be desensitized and treated with penicillin. Macrolides are chosen as the last option if there is no penicillin or doxycycline. Cephalosporin drugs can also be used, such as 1-2 grams of ceftriaxone per day intramuscularly or intravenously for 10-14 days, which is effective for primary and secondary syphilis [1, 23-25]. Syphilis treatment is also given to the patient's sexual partner and intercourse is not permitted until the patient recovers [22, 24].

Syphilis therapy with penicillin can cause side effects, the Jarisch-Herxheimer reaction. This reaction is marked by fever, headache, flare from the mucocutaneous lesion, tender lymphadenopathy, pharyngitis, malaise, myalgia, and leukocytosis. The reaction occurs between 12 hours after therapy initiation and resolves within 24-36 hours. Yang *et al.* [27]. Revealed that Jarisch-Herxheimer occurs in 31.5% of syphilis patients who received penicillin (34.6% of co-infection with HIV and 25.2% without HIV co-infection). Patients should be educated on possible reactions after penicillin treatment and should be informed to rest, maintain fluid intake balance, and report to the hospital if the symptoms aggravate. The pathogenesis of the Jarisch-Herxheimer reaction is not clear but is estimated to be the result of hypersensitivity due to toxin and cytokine released from dead *T. pallidum*. Treatment of Jarisch-Herxheimer reaction uses corticosteroids such as prednisone or intravenous hydrocortisone [1, 27].

In this case report, the patient received 500 mg of doxycycline twice a day orally for 28 days. Doxycycline was chosen as an alternative because there was no penicillin G benzathine in the hospital pharmacy. The clinical observation was carried out on the third week after treatment. Clinical improvement was found in the cutaneous lesions on both arms and legs after receiving single-dose systemic doxycycline therapy.

Conclusion

Syphilis is a systemic disease with various clinical manifestations in the skin. In this relapsed advanced latent syphilis case with HIV co-infection in this patient, the skin lesion was located around the palmoplantar areas, which is often found in syphilis. However, erythematous plaques with desquamation were atypical. HIV co-infection can increase the frequency of atypical lesions. Therefore, the HIV status of the patient should be considered in the diagnosis of syphilis. The interpretation of serologic tests and syphilis treatment do not differ in patients with HIV co-infection.

Funding

No funding sources

Conflict of Interest
None declared

Ethical Approval
None required

References

1. Tuddenham SA, Zenilman JM. Syphilis. In: Kang S, Amagai M, Bruckner AL, Enk AJ, Margolis DJ, McMichael AJ, editors. Fitzpatrick's dermatology in general medicine. 9th ed. United States: McGraw-Hill. 2019, 3145-68.
2. Janier M, Hegyi V, Dupin N, Unemo M, Tiplica GS, Potočnik M, *et al*. 2014 European guideline on the management of syphilis. J Eur Acad Dermatol Venereol. 2014;28(12):1581-93. Doi: 10.1111/jdv.12734.
3. World Health Organization. WHO guidelines for the treatment of treponema pallidum (Syphilis) [Internet]. 2016 [cited 2019 Jan 24]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK384904/pdf/Bookshelf_NBK384904.pdf
4. Kementrian Kesehatan Republik Indonesia. Pedoman Tata Laksana Sifilis Untuk Pengendalian Sifilis Di Layanan Kesehatan Dasar [Internet]. 2013 [cited 2019 Jan 24]. Available from: https://siha.kemkes.go.id/portal/files_upload/PEDOMAN_TATALAKSANA_SIFILIS_PUSKESMAS___merah_ok.pdf
5. Lynn WA, Lightman S. Syphilis and HIV: a dangerous combination. Lancet Infect Dis. 2004;4(7):456–66. doi: 10.1016/S1473-3099(04)01061-8
6. Nyatsanza F, Tipple C. Syphilis: presentations in general medicine. Clin Med. 2016;16(2):184-8. Doi: 10.7861/clinmedicine.16-2-184
7. Clement ME, Okeke NL, Hicks CB. Treatment of syphilis: A systematic review. Jama. 2014;312(18):1905-17. Doi: 10.1001/jama.2014.13259
8. Centers for Disease Control and Prevention (CDC). Sexually Transmitted Diseases (STDs): syphilis [Internet]. [cited 2019 Jan 24]. Available from: https://www.cdc.gov/std/syphilis/default.htm
9. Rajan J, Prasad PVS, Chockalingam K, Kaviarasan P. Malignant syphilis with human immunodeficiency virus infection. Indian Dermatol Online J. 2011;2(1):19. Doi: 10.4103/2229-5178.79864
10. Hall CS, Klausner JD, Bolan GA. Managing syphilis in the HIV-infected patient. Curr Infect Dis Rep. 2004;6(1):72–82. Doi: 10.1007/s11908-004-0027-0.
11. LaFond RE, Lukehart SA. Biological basis for syphilis. Clin Microbiol Rev. 2006;19(1):29-49. Doi: 10.1128/CMR.19.1.29-49.2006.
12. Stary G, Stary A. sexually transmitted infections - syphilis. In: Bolognia JL, Schaffer JV, Cerroni L. Dermatology. 4th ed. United States: Elsevier. 2018, 1447-59.
13. Lewis DA, Young H. Syphilis. Sex Transm Infect. 2006;82:13–5. Doi: 10.1136/sti.2006.023085.
14. Kinghorn GR, Omer R. Syphilis and congenital syphilis. In: Griffiths CEM, Barker J, Bleiker T, Chalmers R, Creamer D, editors. Rook's textbook of dermatology. 9th ed. United Kingdom: Wiley-Blackwell. 2010;29:3-34
15. Marchand-Senécal X, Barkati S, Bouffard D, Martel-Laferrière V. A secondary syphilis rash with scaly target lesions. Oxf Med Case Rep. 2018;2:40-1. Doi: 10.1093/omcr/omx089
16. Bittencourt M de JS, Brito AC de, Nascimento BAM do, Carvalho AH, Nascimento MD do. A case of secondary syphilis mimicking palmoplantar psoriasis in HIV infected patient. A Bras Dermatol. 2015;90(2):16–9. Doi: 10.1590/abd1806-4841.20153399
17. Wahab AA, Rahman MM, Mohammad M, Hussin S. Case series of syphilis and HIV co-infections. Pak J Med Sci. 2013;29(3):856. Doi: 10.12669/pjms.293.3346
18. Gianfaldoni S, Tchernev G, Wollina U, Gianfaldoni R, Lotti T. Secondary syphilis presenting as palmoplantar psoriasis. Open Access Maced J Med Sci. 2017;5(4):445. Doi: 10.3889/oamjms.2017.087
19. Ratnam S. The laboratory diagnosis of syphilis. Can J Infect Dis Med Microbiol? 2005;16(1):45-51. Doi: 10.1155/2005/597580
20. Morshed MG, Singh AE. Recent trends in the serologic diagnosis of syphilis. Clin Vaccine Immunol. 2015;22(2):137-47. Doi: 10.1128/CVI.00681-14.
21. Henao-Martinez AF, Johnson SC. Diagnostic tests for syphilis: new tests and new algorithms. Neurol Clin Pract. 2014;4(2):114-22. doi: 10.1212/01.CPJ.0000435752.17621.48.
22. Workowski KA, Bolan GA. Sexually transmitted diseases treatment guideline 2015. Centers for Disease Control and Prevention Morbidity and Mortality Weekly Report (MMWR). 2015:64(3); 34-49.
23. Stamm LV. Syphilis: antibiotic treatment and resistance. Epidemiol Infect, 2014, 1-8. doi: 10.1017/S0950268814002830.
24. Widaty S, Soebono H, Nilasari H, Listiawan MY, Siswanti AS, Triwahyudi D, *et al*. Panduan praktik klinis bagi dokter spesialis kulit dan kelamin di Indonesia. Jakarta: PERDOSKI. 2017, 372-4.
25. Dewi VAP, Pudjiati SR. Sifilis sekunder, kondiloma akuminata anal, dan HIV pada pasien laki-laki biseksual: Sudut pandang lain, tinjauan waktu berdasar CD4 dan tatalaksana. Berkala Ilmu Kesehatan Kulit dan Kelamin – Periodical of Dermatology and Venereology. 2015;27(2):156-62.
26. Xiao H, Liu D, Li Z, Zheng R, Li Z, Hou J, *et al*. Comparison of doxycycline and Benzathine Penicillin G for the treatment of early syphilis. Acta Dermatovenerol Croat. 2017;25(2):107-11.
27. Yang CJ, Lee NY, Lin YH, Lee HC, Ko WC, Liao CH, *et al*. Jarisch-Herxheimer reaction after penicillin therapy among patients with syphilis in the era of the HIV infection epidemic: incidence and risk factors. Clinical Infectious Diseases. 2010;51(8):976-9. Doi: 10.1086/656419.