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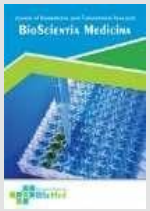

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The Jarisch-Herxheimer Reaction on Secondary Syphilis Patient with Roseola Syphilitica and Human Immunodeficiency Virus Co-Infection: A Case Report

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A B S T R A C T

Background: The Jarisch-Herxheimer reaction is an inflammatory reaction that occurs within 12 hours after administration of antibiotic therapy for spirochaeta species like *Treponema pallidum*. The reaction includes fever, headache, reappearing or worsening of skin lesions, lymphadenopathy, pharyngitis, malaise, and myalgias. **Case presentation:** We present a 27-year-old man complaining of high fever 4 hours after the injection of benzathine penicillin. The patient also complained of headaches, body aches and aches. There were no complaints of shortness of breath, itching, skin blisters, red eyes, or sores on the genitals. History of take any medication was denial by the patient. After treatment by giving antipyretics and corticosteroids and getting enough rest, in the 24 hours, the patient was improved. **Conclusion:** The Jarisch-Herxheimer reaction is an inflammatory reaction that occurs after the administration of antibiotic therapy for spirochaeta species like *Treponema pallidum*.

1. Introduction

Syphilis is a sexually transmitted disease (STD) caused by *Treponema pallidum*. Syphilis has a chronic disease course, has a latent phase, and can recur. This disease is invasive, can attack various organ systems of the body, and has clinical features resembling many other diseases.[1,2] Syphilis is most commonly transmitted through sexual contact and can also pass through the placenta from mother to fetus. Syphilis in patients with human immunodeficiency virus (HIV) infection has a similar clinical picture to syphilis in patients without HIV infection. The recommendations for treating syphilis in patients with HIV are the same as those for treating syphilis in patients without HIV.[3,4]

The Jarisch-Herxheimer reaction is an inflammatory reaction that occurs within 12 hours after administration of antibiotic therapy for spirochaeta, often occurring within 2-5 hours after therapy. The Jarisch-Herxheimer reaction includes fever, headache, reappearing or worsening of skin lesions, lymphadenopathy, pharyngitis, malaise, and myalgias. The pathogenesis of the Jarisch-Herxheimer reaction is not known with certainty but is thought to be due to the release of cytokines mediated by the release of lipoproteins from dead *Treponema pallidum*.[5]

The following is a reported case of the Jarisch-Herxheimer reaction in a case of secondary syphilis with manifestations of syphilitic roseola with human

immunodeficiency virus co-infection. This case is reported to provide an understanding of the Jarisch-Herxheimer reaction and to increase awareness of the risk of reactions after syphilis therapy.

2. Case Presentation

A 27-year-old male, Balinese, Indonesian citizen came to the dermatology and venereology polyclinic at Prof. Dr. I.G.N.G Ngoerah General Hospital division of sexually transmitted infections on January 10th, 2023, with complaints of high fever 4 hours after the injection of benzathine penicillin yesterday. The patient also complained of headaches and body aches. There were no complaints of shortness of breath, itching, skin blisters, red eyes, or sores on the genitals. There are no complaints of pain when urinating. The history of taking any medicine was denied by the patient.

The patient was diagnosed with syphilis and HIV at the end of December 2022. Initially, the patient went to the primary health care with complaints of red spots on the hands and soles of the feet and fever with diarrhea for 2 weeks. The patient admitted that 2 months before the appearance of the reddish spots (October 2022), genital sores such as chancre sores appeared; the wounds were painless and did not ooze pus or blood. The patient denied a history of painful urination, and the wound was said to heal naturally.

The patient also complained that his body felt very weak; he lost 6 kg in 1 month. The primary health care staff advised the patient to take the *Treponema pallidum* Haemagglutination Assay (TPHA) and anti-HIV tests. The results were reactive for both tests. The patient was referred to the sexually transmitted infections division of the dermatology and venereology department and voluntary counseling test (VCT) Department at Prof. Dr. I.G.N.G Ngoerah General Hospital for further examination and treatment. On admission day at Prof. Dr. I.G.N.G Ngoerah General Hospital (January 9th, 2023), the patient brought the result of quantitative VDRL and TPHA laboratory examination, and the result for VDRL titer was 1:128, and the TPHA titer was 1:5120.

On physical examination, the general condition of the patient was moderately ill and conscious of compos mentis. On vital signs examination, blood pressure was 110/70 mmHg, pulse was 88 times/minute, respiration was 18 times/minute, and axillary temperature was 38.1°C. On head and neck examination, no moth-eaten alopecia was found. There was no hyperemic conjunctiva in both eyes and icteric sclera. Examination of the ear, nose, and throat was not remarkable; no hyperemic mucosa was found. There were no enlarged lymph nodes in the patient's neck, armpits, or groin area. Examination of the patient's heart and lungs did not reveal any abnormalities on abdominal examination, normal bowel sounds, no distension or organomegaly. All four extremities are not edematous and warm. In dermatological status, at plantar pedis dextra et sinistra found hyperpigmented macules, multiple, indistinct borders, geographic shape, size 0.4x0.6cm, discretely configuration, bilateral distribution (Figure 2A-D).

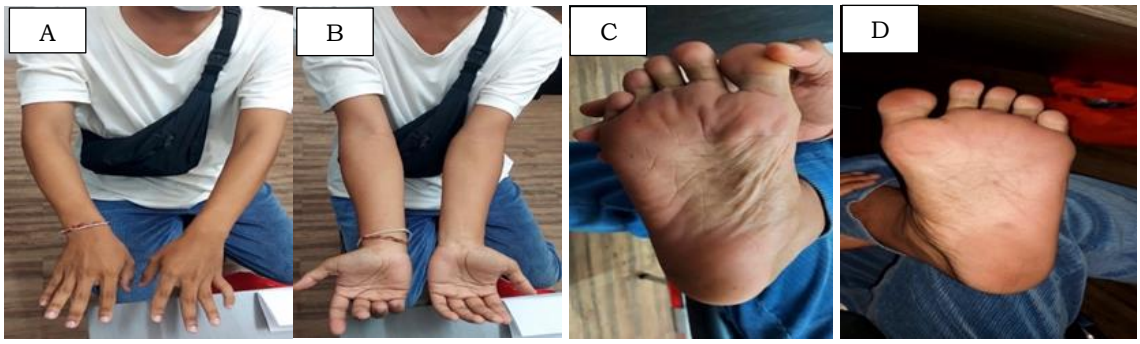

Figure 2A-D. At plantar pedis dextra et sinistra were found hyperpigmented macules, multiple, indistinct borders, geographic shape, size 0.4x0.6cm, discretely scattered, symmetrical distribution.

Based on history and physical examination, the patient was diagnosed with Jarisch-Herxheimer reaction in secondary syphilis with roseola syphilitica and HIV co-infection. The patient was given paracetamol 500 mg tablets every 8 hours intraorally and methylprednisolone 8 milligram tablets every 8 hours intraorally for 3 days. After three days, the patient did not have any complaints, and no aggravating skin lesions appeared.

3. Discussion

Syphilis is a systemic infection caused by the spirochaeta *Treponema pallidum*. This bacterium is invasive naturally by infecting almost all organs, and the clinical manifestation that arises can resemble other diseases. Syphilis infection is most often transmitted through sexual intercourse; it can also cross the placenta from mother to fetus through blood transfusions, accidental inoculation, or injury from contaminated instruments.[1,2]

The clinical course of syphilis can be divided into several stages, namely primary syphilis, secondary syphilis, early latent syphilis, late latent syphilis, and tertiary syphilis. Primary syphilis occurs due to the penetration of *T. pallidum* on the skin or mucous membranes, causing ulcers to appear at the inoculation site. Ulcers generally average 3 weeks after being infected with *T. pallidum*. The initial manifestation that appears is in the form of a papule, which then develops into an ulceration, forming a solitary ulcer that is round or elongated, 1-2 cm in diameter, with regular edges; the wound bed is clean without exudate and is painless. In addition, the lesions can also heal on their own without treatment within 1-6 weeks and generally heal without leaving scar tissue.[2,6] Secondary syphilis lesions occur due to the multiplication and spread of *T. pallidum* lymphatic and hematogenous from the primary lesion to various body tissues. Lesions in secondary syphilis generally appear within 3 to 12 weeks after the appearance of the ulcer, but in 15% of cases, may appear several months later. Secondary syphilis has various clinical manifestations and is difficult to distinguish from other diseases, so it is called the great imitator. Macular and/or maculopapular skin lesions are the most common form, accounting for 40%-70% of cases. The lesions are usually not itchy, but one study found itching in 40% of patients. In secondary syphilis, enlarged lymph nodes that are movable, symmetrical, and painless can also be found.[6,7]

In this case, the patient complained of red spots that had appeared a month ago (early December 2022) on both hands and the soles of feet. The patient denied complaints of itching. The patient admitted that 2 months before the appearance of the reddish spots (October 2022), genital sores such as chancre sores appeared; the wounds were painless and did not ooze pus or blood. The patient denied a history of painful urination. The wound was said to heal on its own. On physical examination, the location of the superior extremities right et left and plantar right left et left showed erythema-hyperpigmented macules, multiple, well-defined, geographic shape, size 0.4x0.6cm, discretely configuration, bilateral distribution. No enlarged lymph nodes were found.

The diagnosis of syphilis is established based on the clinical picture and investigations to detect infection due to *T. Pallidum* directly or indirectly.8 In primary syphilis, dark field microscopy (DFM) is a specific and easy method to establish the diagnosis of syphilis, but the method of sampling is very difficult to do, so this examination is rarely done. The serological examination is very important to help establish the diagnosis. Serological tests can be divided into non-treponemal tests and treponemal tests. Non-treponemal tests such as the venereal disease research laboratory (VDRL) and rapid plasma reagent (RPR) are commonly used for screening and monitoring therapy. This test detects immunoglobulins G and M that react to lipoidal material and are reactive within 4 to 5 weeks after infection. A high serological titer indicates active infection. Titers will decrease fourfold or more within 6 months post-therapy in primary or secondary and non-reactive syphilis within 12 to 24 months post-therapy.[9] Treponemal tests such as fluorescent

treponemal antibody absorption (FTA-ABS) and *Treponema pallidum* Haemagglutination Assay (TPHA) are used as diagnostic tests for confirmation of syphilis because they have higher sensitivity and specificity, but because the results of the examination lasting for a lifetime, these tests cannot be used to evaluate the successful rate of therapeutic.[10] The diagnosis of secondary syphilis in cases was established from the history, clinical examination, and supporting examinations.

The interaction between syphilis and HIV is complex. Several studies found that syphilis infection can increase HIV transmission up to four times. The disruption of the mucosal or epidermal barrier due to the chancre lesion in primary syphilis and the migration of inflammatory cells, which are the HIV target cells, are believed to increase HIV transmission. Several studies have also found that syphilis infection can increase viral load and decrease CD4, which then resolves after treatment. These changes may also increase HIV transmission in HIV-co-infected patients and syphilis. HIV infection can also affect the progression of syphilis and increase the risk of complications. The clinical manifestations of syphilis in patients coinfected with HIV are similar to those in syphilitic patients without HIV infection.[10,12]

The main goal of syphilis treatment is to prevent the transmission and complications of syphilis. The Centers for Disease Control and Prevention (CDC) recommends administering a single dose of benzathine penicillin G 2.4 million IU intramuscularly for the treatment of primary syphilis, secondary syphilis, and early latent syphilis.[7,14] Recommendations for the treatment of syphilis in patients with HIV are the same as those without HIV infection. Clinical monitoring and serological examination in patients with HIV were carried out at 3, 6, 9, 12, and 24 months after therapy.[9,12] In this case, the treatment given was a single intramuscular injection of benzathine penicillin G 2.4 million IU, the results of a quantitative VDRL examination 1 month after therapy obtained a titer of 1:64. Patients are advised to carry out follow-up serological examinations at 3, 6, 9, 12 and 24 months.

The Jarisch-Herxheimer reaction is an inflammatory reaction that occurs after the administration of antibiotic therapy due to spirochaeta infection. This reaction was first identified in 1895 by Adolf Jarisch, who reported an exacerbation of syphilitic roseola lesions after systemic antibiotics; 7 years later, Karl Herxheimer reported similar symptoms accompanied by systemic reactions in the form of fever, sweating, and anorexia within 24 hours after syphilis therapy. The Jarisch-Herxheimer can occur after the administration of various therapies that have sufficient anti-treponemal concentrations, such as penicillin, tetracycline, and sulfonamides.[13,14]

Until now, the pathogenesis of the Jarisch-Herxheimer reaction is not known with certainty but is thought to be through the activation of cytokines due to the release of lipoproteins from dead *T. pallidum* organisms. Systemic antibiotic therapy can make bacteria more susceptible to phagocytosis, which will trigger the release of cytokines such as tumor necrosis factor (TNF)-α, interleukins 6 and 8. Activation of these proinflammatory cytokines causes clinical symptoms in the form of fever, myalgia, tachycardia, and hypotension.[14,15]

The Jarisch-Herxheimer reactions most quickly appear within 2 hours after administration of therapy. This reaction begins with fever and is followed by other manifestations such as cephalgia, chills, lymphadenopathy, pharyngitis, malaise, and myalgias. Abnormalities in the skin can multiply and feel painful due to aggravating inflammatory processes. In some cases of the Jarisch-Herxheimer reaction, edema or ulcers can be found as clinical manifestations. Fever may peak within 6-8 hours after onset of illness, and body temperature ranges from 38°–42°C. Although most of the Jarisch-Herxheimer reactions can heal on their own within 24 hours, in some cases, life-threatening conditions can occur.[8,9,17] The Jarisch-Herxheimer reaction is most common in secondary syphilis (about 70-95% of all cases of the Jarisch-Herxheimer reaction) but can also occur in other stages of syphilis.[13,16] Patients with HIV infection or pregnant women have a higher incidence of the

Jarisch-Herxheimer reaction while on treatment for syphilis.[18,19]

There is no specific test to diagnose a JH reaction. Laboratory tests can find leukocytosis with an increase in neutrophils or a decrease in lymphocytes. Histopathological examination can reveal dermal edema and capillary dilatation as well as mononuclear cell infiltration.[14,17] JH reactions are often misdiagnosed as drug eruptions, especially in cases of penicillin therapy. Some literature states that prior syphilis therapy with penicillin reduces the risk of JH reactions, and patients with JH reactions after the first penicillin therapy do not experience reactions during the second and third penicillin therapy. This distinguishes between JH reactions and drug eruptions. Maculopapular drug eruption is the most common drug eruption reaction. Skin abnormalities found in the form of erythematous macules and papules to hyperpigmentation and desquamation can be found during the healing phase. Lesions that appear start from the body and then spread to the periphery. Pruritus is often complained of by patients, and there is a history of fever. Lesions usually appear within 1-2 days to 1 week post-therapy. Laboratory examination found lymphocytosis, eosinophilia, and histopathological examination found vacuolar changes, perivascular lymphocytic infiltrates, and spongiosis.

In the case of complaints of high fever 4 hours after the injection of benzathine penicillin. In addition, patients also complain of headaches and body aches. There were no complaints of shortness of breath, itching, skin blisters, red eyes, or sores on the genitals. There were no complaints of pain when urinating. Patients do not take drugs to deal with complaints that arise. A physical examination found the general condition of the patient looked moderately ill, with compost mentis awareness and an axillary temperature of 38°C. On dermatological examination, at plantar dextra et sinistra, hyperpigmented macular efflorescence, multiple, well-defined, geographic shape, size 0.4x0.6cm, discretely scattered, symmetrical distribution. There was no discharge or conjunctival hyperemia in the eye. No erosions were found in the mouth or genitalia. In this case, laboratory or histopathological examinations are not performed.

The Jarisch-Herxheimer reaction is a self-limiting reaction and is treated symptomatically. Patients should be given an explanation about the possibility of reactions related to spirochaeta infection after administration of systemic antibiotic therapy. The Jarisch-Herxheimer reaction was treated by giving antipyretic and corticosteroid medications, and the patient was suggested to have enough rest.[16,17,19] In this case patient received paracetamol 500 milligrams tablet every 8 hours intraorally and methylprednisolone 8 milligrams tablet every 8 hours intraorally for 3 days. After three days, the patient did not have any complaints, and no aggravating skin lesions appeared.

4. Conclusion

The Jarisch-Herxheimer reaction has been reported in this case of secondary syphilis with roseola syphilitica and human immunodeficiency virus co-infection in a 31-year-old man. Diagnosis was made on the history and physical examination. From clinical history, the patient complained of high fever, headache, and weakness that appeared 4 hours after the injection of benzathine penicillin. Physical examination obtained an axillary temperature of 38.1°C. There were no complaints of aggravating skin lesions. The treatment given was paracetamol 500 mg tablets every 8 hours intraorally and methylprednisolone 8mg tablets every 8 hours intraorally for 3 days. After three days, the patient did not have any complaints, and no aggravating skin lesions appeared.

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