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Indonesian Journal of Case Reports

Vol. 3, No. 1, 2025

Malignant Syphilis in HIV: A Diagnostic and Management Challenge

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Article History

Received 29 December 2024
Revised 19 February 2025
Accepted 27 February 2025
Available Online 5 March 2025

Keywords:
Lues maligna
Erythematous plaques
VDRL
Penicillin G
Jarisch-herxheimer reaction

Abstract

Malignant syphilis is a rare and severe form of secondary syphilis, often seen in immunocompromised individuals, including those with advanced HIV infection. We report a 29-year-old male with newly diagnosed Stage IV HIV who presented with widespread erythematous plaques and scales and systemic symptoms. Dermatological examination revealed generalized erythematous macules and plaques with scaling, erosion, and crusting. Ulcerative lesions with crusts were noted on the toes and soles. Venereological findings included erythematous to skin-colored macules on the scrotal and penile areas. Serological tests revealed high VDRL (1:128) and TPHA (>1:5120) titers, and histopathology confirmed secondary syphilis. The patient was treated with intramuscular benzathine penicillin G (2.4 million units) weekly for three weeks in conjunction with antiretroviral therapy (ART). Although the patient experienced a Jarisch-Herxheimer reaction, there was significant clinical and serological improvement, with a fourfold reduction in VDRL titers after nine months. This case emphasizes the need for early recognition of malignant syphilis in immunocompromised patients and highlights the effectiveness of benzathine penicillin G and ART in treatment. Regular follow-up is essential to monitor progress and prevent recurrence.

1. Introduction

Syphilis is a chronic sexually transmitted infection (STI) that can affect nearly all organs in the body. It is caused by *Treponema pallidum*, which enters the body through mucous membranes or skin and can be transmitted transplacental, via blood transfusions, or by sharing needles [1, 2]. According to data from the Ministry of Health of the Republic of Indonesia, the number of syphilis cases has increased by approximately 70% from 2018 to 2022, from 12,284 cases to 20,783 cases [1]. This rise in syphilis cases is linked to various social, economic, and healthcare system factors, such as changes in risky sexual behaviors, limited access to healthcare in rural areas, and gaps in preventive health education. Additionally, the higher prevalence of syphilis in individuals with HIV has contributed to this trend.

Syphilis is often referred to as the "great imitator" due to its wide range of clinical manifestations, one of which is malignant syphilis [1]. Malignant syphilis, or *lues maligna*, was first described by Bazin in 1859. In 1896, Huslund and Neisser classified malignant syphilis as a rare and severe variant of secondary syphilis [1]. Unlike the classic mucocutaneous lesions of secondary syphilis, malignant syphilis can present with papules, scales, or crusted plaques that may evolve into ulcers or necrotic lesions [1, 2]. These lesions, referred to as rupioid lesions, are often associated with high titers of nontreponemal serology and systemic symptoms [1, 2].

Secondary syphilis is characterized by diffuse mucocutaneous lesions (such as maculopapular rash, condyloma lata), alopecia syphilitica, and systemic symptoms (fever, lymphadenopathy). Lesions are typically non-ulcerative and do not exhibit extensive necrosis. Malignant syphilis is a more severe form, often occurring in immunocompromised individuals. Lesions are ulceronecrotic with rupioid-crusted plaques, tend to be more widespread, and exhibit marked serological reactivity. This condition is also associated with high fever, significant weight loss, and widespread organ involvement, distinguishing it from typical secondary syphilis [1, 2].

Malignant syphilis is frequently observed in immunocompromised patients, especially those infected with HIV/AIDS [3, 4]. Before the emergence of HIV, the prevalence of malignant syphilis was estimated to range from 0.12% to 0.36%, with most cases linked to chronic alcoholism or severe malnutrition [5]. However, with the AIDS pandemic, the incidence of malignant syphilis has increased, particularly among HIV-positive individuals [3]. HIV infection exacerbates the clinical course of syphilis by impairing the immune response, leading to more severe and aggressive manifestations that are difficult to treat [3, 6]. Studies have shown that syphilis in HIV-positive patients is more likely to present in severe forms and carries a higher risk of complications, including widespread tissue necrosis, organ damage, and a more rapid progression to AIDS.

Furthermore, the diagnostic challenges of malignant syphilis often lead to delayed or incorrect diagnoses. The atypical presentation of severe necrotic lesions and systemic involvement can result in misdiagnosis as other dermatological conditions, such as cutaneous leishmaniasis or pyoderma gangrenosum. As a result, clinical suspicion is essential, and the confirmation of diagnosis often requires histopathological examination and biopsy. Without proper treatment, malignant syphilis, especially in HIV-positive patients, can lead to high morbidity, with significant risks of mortality due to complications such as organ failure and secondary infections [3].

Globally, while malignant syphilis remains relatively rare, its prevalence has increased, particularly among immunocompromised individuals with HIV [7]. This growing incidence is particularly evident in regions with high HIV prevalence, such as sub-Saharan Africa and Southeast Asia. In Indonesia, the rise in syphilis cases can also be attributed to limited access to syphilis prevention and treatment, as well as insufficient sexual health education. These factors, combined with the increasing rate of HIV co-infection, make malignant syphilis a significant public health concern, highlighting the need for improved awareness, early detection, and better access to treatment [1].

2. Cases

A 29-year-old male, newly diagnosed with Stage IV HIV one week before presentation, visited the Dermatology and Venereology Clinic at Prof. Dr. R. D. Kandou Manado Central General Hospital with complaints of widespread erythematous plaques and scales across his body for one month. The lesions initially appeared on his palms and trunk before progressively spreading. Some lesions had ulcerated and formed crusts. He also experienced pruritus, fever, headache, and unintentional weight loss of 15 kg over two months. The patient reported a painless genital ulcer four months earlier that resolved spontaneously without treatment. He denied dysuria, urethral discharge, or hair loss. His history included high-risk sexual behavior, identifying as homosexual, with more than five sexual partners in the past month and engaging in unprotected oral and anal intercourse. There was no history of intravenous drug use or blood transfusion. The patient had no previous exposure to syphilis treatment.

The patient appeared cachectic on physical examination, with a body mass index (BMI) of 16.2 kg/m^2. He had a low-grade fever of 37.8°C but was hemodynamically stable. A dermatological examination revealed that approximately 70% of his body surface area was affected. The dermatological examination revealed multiple erythematous macules and plaques with well-defined edges, scaling, erosion, and crusting on the bilateral antebrachial to brachial regions, anterior and posterior thoracic regions, bilateral crural regions, palms, and soles. Multiple lenticular-sized ulcerations with irregular borders and crusted bases were observed on the third and fourth toes of the left foot as well as on both soles. The venereological examination showed multiple erythematous to skin-colored macules with scaling on the scrotal and penile regions (Figure 1).

Laboratory investigations were performed in a structured sequence. Routine blood tests showed a hemoglobin level of 10.2 g/dL, a leukocyte count of 6,500/mm^3, and a platelet count of 180,000/mm^3. The patient's CD4 count was 16 cells/μL, indicating advanced immunosuppression. Serological tests revealed a reactive Venereal Disease Research Laboratory (VDRL) titer of 1:128 and a Treponema pallidum Hemagglutination Assay (TPHA) titer of >1:5120, confirming syphilis. A histopathological examination of a skin biopsy demonstrated hyperkeratosis, parakeratosis, pseudoepitheliomatous hyperplasia, and inflammatory

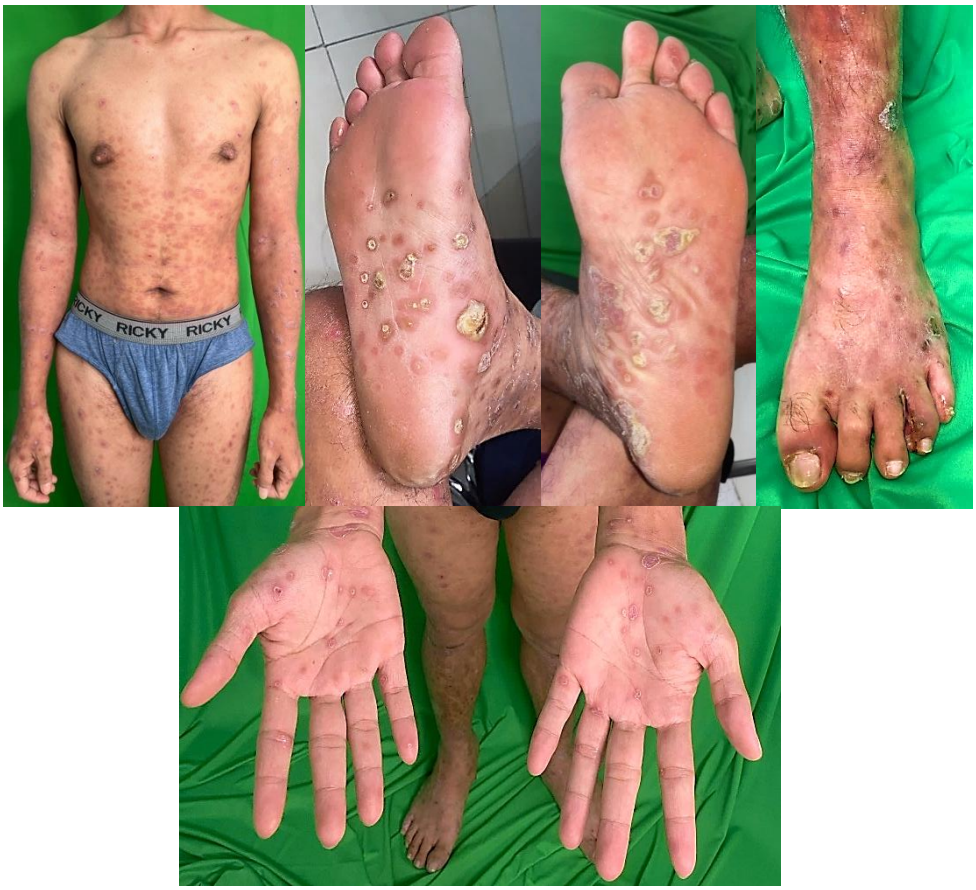

Figure 1. The efflorescence on the trunk, palms, and soles region.

cell infiltration in the dermis, consistent with secondary syphilis, particularly malignant syphilis. Based on clinical presentation, serological findings, and histopathology, the patient was diagnosed with malignant syphilis in advanced HIV infection (Stage IV).

The patient received three weekly intramuscular injections of benzathine penicillin G (2.4 million units) and was initiated on antiretroviral therapy (ART) consisting of tenofovir 300 mg, lamivudine 300 mg, and efavirenz 600 mg once daily. Supportive care included oral antihistamines for pruritus and topical antibiotics for ulcer edges. After the first injection, the patient experienced a Jarisch-Herxheimer reaction, presenting with transient fever, which resolved spontaneously.

Treatment response was closely monitored, showing significant clinical and serological improvements. By the first month, erythematous lesions had resolved, leaving hyperpigmented macules. The VDRL titer had decreased fourfold from 1:128 to 1:32. At three months, no active lesions were present, and the VDRL titer declined further to 1:16. Follow-up at six months showed continued improvement with a titer of 1:8. By the ninth month, complete resolution was observed, with no new lesions and a stable VDRL titer of 1:8, confirming successful treatment.

3. Discussions

Syphilis is a sexually transmitted infection (STI) caused by *Treponema pallidum*. It is a chronic disease that can affect multiple organ systems [1]. Data from the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) in 2022 indicate that the highest incidence of syphilis occurs in the 15–49 age group, with men who have sex with men (MSM) accounting for 45.1% of cases among all male syphilis patients [8]. This aligns with the age and sexual preference in this case, where the patient is a 29-year-old male identifying as MSM.

The interaction between HIV-related immunosuppression and the development of malignant syphilis is complex. HIV infection alters immune surveillance and disrupts normal inflammatory responses, particularly in advanced stages. A severely depleted CD4 count weakens the host's ability to mount an effective immune response against *T. pallidum*, allowing unchecked bacterial proliferation and increased tissue damage. Additionally, HIV-associated dysregulation of cytokines, including tumor necrosis factor-alpha (TNF-α) and interleukins, may contribute to the atypical ulceronecrotic manifestations observed in malignant syphilis [3]. This case supports these

mechanisms, as the patient had a CD4 count of 16 cells/μL, indicating profound immunosuppression, likely facilitating the severe and atypical disease presentation. Transmission occurs primarily through direct contact with infectious lesions during high-risk sexual activities (genito-genital, ano-genital, and oro-genital contact) [2, 9]. Vertical transmission, blood transfusion, and occupational exposure are less common routes [2]. In this case, the patient's history of multiple sexual partners without condom use strongly suggests direct sexual transmission. The absence of a history of intravenous drug use or blood transfusions further supports this mode of transmission.

Malignant syphilis, though rare, has been documented globally in both immunocompromised and immunocompetent individuals. A systematic review by Wibisono et al. analyzed 45 cases from 2014 to 2018, revealing that 73% occurred in HIV-positive individuals, while 27% affected HIV-negative patients, often with comorbidities such as diabetes, alcoholism, drug abuse, psoriasis, or hepatitis [10]. Several case reports further illustrate the diverse clinical presentations of malignant syphilis. Chen et al. described an HIV-negative woman with generalized condyloma lata and seborrheic dermatitis-like lesions, underscoring the necessity of considering this diagnosis even in immunocompetent patients [11]. Similarly, Dimnik et al. reported a 41-year-old immunocompetent female who developed malignant syphilis with systemic symptoms [12]. Jimenez et al. analyzed 74 cases, proposing new diagnostic criteria for "ulceronodular-rupioid syphilis" based on a case of a 28-year-old male with uncontrolled HIV who presented with extensive ulcerated lesions [13]. These studies highlight that while malignant syphilis is more common in immunocompromised individuals, it can also affect immunocompetent patients, necessitating early recognition and prompt treatment to prevent severe complications.

Syphilis is known as "the great imitator" due to its diverse clinical manifestations. Malignant syphilis, or *lues maligna*, is a rare, aggressive variant of secondary syphilis that occurs primarily in immunocompromised individuals, particularly those with HIV [3, 10]. This case exhibited clinical features consistent with those reported in the literature, including widespread ulceronecrotic skin lesions, systemic symptoms such as fever and headache, and high nontreponemal serologic titers [3, 4]. A review of similar cases demonstrates that malignant syphilis predominantly occurs in HIV-positive individuals with low CD4 counts, supporting the hypothesis that immunosuppression plays a key role in disease severity [3, 4].

Serological testing is essential for diagnosis. This patient exhibited a high VDRL titer of 1:128 and a TPHA titer of >1:5120, which aligns with previous reports of malignant syphilis cases showing significantly elevated titers [3, 11]. In HIV-positive patients, higher treponemal and nontreponemal titers have been associated with severe clinical manifestations, potentially due to impaired immune clearance of *T. pallidum* [1, 14]. However, a persistently high VDRL titer post-treatment does not necessarily indicate treatment failure, as immune dysregulation in HIV can lead to prolonged seroreactivity [1]. Histopathological examination of syphilis can demonstrate variable findings, including hyperkeratosis, psoriasiform changes, necrosis, and lymphoplasmacytic infiltrates [15]. This case demonstrated pseudoepitheliomatous hyperplasia with inflammatory cell exocytosis, findings consistent with secondary syphilis. The Warthin-Starry staining could not be performed due to limited facilities, but previous studies indicate that spirochetes are detectable in approximately one-third of cases [15].

Benzathine penicillin G remains the treatment of choice for all stages of syphilis. Several references recommend treatment for malignant syphilis using benzathine penicillin G 2.4 million IU via intramuscular injection every week for three consecutive weeks [6, 10, 11]. The patient in our case showed significant lesion improvement following this regimen. The response timeline was compared with standard secondary syphilis cases, which typically show lesion resolution within 2–4 weeks of treatment [1]. In malignant syphilis, complete resolution may take longer due to extensive tissue damage, particularly in immunocompromised hosts [3]. During treatment, the patient developed the Jarisch-Herxheimer reaction, characterized by fever and headache 16 hours after the first injection, consistent with the inflammatory cytokine response triggered by bacterial lysis [3, 16].

Given the high prevalence of syphilis-HIV co-infection, public health measures should focus on early screening, risk reduction counseling, and pre-exposure prophylaxis (PrEP) for high-risk individuals. Routine syphilis screening in HIV clinics is essential to detect early cases and prevent severe manifestations [1]. Community-based interventions, such as partner notification and educational campaigns, can help reduce transmission rates. Studies suggest that factors predisposing HIV patients to malignant syphilis include CD4 counts <200 cells/μL, high HIV viral loads, and delays in initiating ART [3, 4]. Additional predictive markers, such as elevated inflammatory cytokines and genetic predispositions, warrant further investigation.

Follow-up serological evaluation at 3, 6, 9, 12, and 24 months post-treatment is recommended. Successful therapy is defined by a fourfold decline in VDRL/RPR titers within 6–12 months [1, 17]. However, HIV-positive patients may exhibit a slower decline, necessitating extended follow-up. In this case, serial VDRL and TPHA tests demonstrated a fourfold decrease by month 9, confirming treatment success. Long-term management should include continued ART to improve immune function, routine STI screening every 3–6 months, and patient education on safer sexual practices. Persistent seropositivity should be monitored for potential reinfection or treatment failure.

This case illustrates the severe manifestations of malignant syphilis in an HIV-immunocompromised patient. A clear mechanistic link between immunosuppression and aggressive disease progression was established. Treatment with benzathine penicillin G was effective, with a slower resolution timeline compared to typical secondary syphilis. Enhanced screening and prevention strategies are critical to reducing morbidity and improving long-term outcomes in co-infected individuals. The prognosis for this case *quo ad vitam* is *bonam*, while *quo ad functionam* and *sanationam* are *dubia ad bonam*. Despite the therapeutic success in this case, the persistently low CD4 count highlights the ongoing challenges in managing HIV co-infection. Continued antiretroviral therapy and comprehensive care are necessary to improve immune function and reduce the risk of opportunistic infections.

4. Conclusions

This case highlights the importance of recognizing malignant syphilis as a rare but serious manifestation in individuals with advanced HIV. The atypical presentation, characterized by widespread ulceronodular lesions, systemic symptoms, and high serological titers, underscores the need for heightened clinical suspicion, especially in immunocompromised patients. Early recognition and timely treatment with benzathine penicillin G, alongside optimized antiretroviral therapy, can lead to significant clinical improvement. To enhance early detection, clinicians should maintain a high index of suspicion for malignant syphilis in HIV-positive patients presenting with unusual dermatologic findings. Routine syphilis screening in high-risk populations, particularly among individuals with advanced immunosuppression, is crucial for prompt diagnosis and treatment. Strengthening public health initiatives, including targeted screening programs and patient education, can help reduce delays in diagnosis and prevent complications associated with late-stage syphilis.

Author Contributions: Conceptualization, S.C.R. and N.J.N.; investigation, S.C.R.; writing—original draft preparation, S.C.R.; writing—review and editing N.J.N. All authors have read and agreed to the published version of the manuscript

Funding: This study does not receive external funding.

Ethical Clearance: Not applicable.

Informed Consent Statement: Written informed consent has been obtained from the patient to publish this paper.

Data Availability Statement: The article contains all the necessary data to support the results.

Acknowledgments: The author would like to sincerely thank the Department of Dermatology and Venereology, Faculty of Medicine, Sam Ratulangi University, and Prof. Dr. R. D. Kandou Manado Central General Hospital for their invaluable contributions in supporting this case report.

Conflicts of Interest: All the authors declare no conflicts of interest.

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