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Case Report

An Adult with Fever and Progressive Ulcerative Lesions: A Case of Malignant Syphilis

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Abstract: Background: Syphilis has recently reemerged as a significant public health concern, with rising incidence rates globally. Malignant syphilis is a rare and severe variant of secondary syphilis, often associated with immunocompromised states, particularly HIV infection. Methods: Here, we reported a rare case of malignant syphilis in a young man with well-controlled HIV. Case: A 35-year-old man with well-controlled HIV presented with disseminated ulcerated nodules and plaques, accompanied by fever, asthenia, and mild itching. Histopathology of the scapular ulcer revealed a granulomatous infiltrate. Cutaneous leishmaniasis, atypical mycobacteriosis, and T-cell lymphomas were excluded. Serological testing and polymerase chain reaction confirmed a diagnosis of malignant syphilis.

Keywords: malignant syphilis; HIV; granulomatous inflammation; cutaneous lesions; polymerase chain reaction diagnostics

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1. Introduction

Syphilis is a systemic, sexually transmitted infection caused by the spirochete *Treponema pallidum* [1]. The disease progresses through distinct stages (primary, secondary, latent, and tertiary), each with varying clinical manifestations, ranging from painless ulcers and systemic rashes to severe cardiovascular and neurological complications in later stages [1]. Although syphilis was once considered a largely controlled disease, it has recently reemerged as a significant public health concern, with rising incidence rates globally [1]. Malignant syphilis is a rare and severe variant of secondary syphilis often associated with immunocompromised states, particularly HIV infection [2,3]. Here, we reported a rare case of malignant syphilis in a young man with well-controlled HIV, where polymerase chain reaction (PCR) analysis of an ulcer biopsy confirmed the diagnosis.

2. Case

A 35-year-old man with HIV infection, virally suppressed via treatment with darunavir/tenofovir/emtricitabine, and a good immunological response (CD4+ T cell count of 603 cells/μL, CD4/CD8 = 2.3), presented with scattered ulcerated nodules and plaques distributed across the back, limbs, neck, and buttocks (Figure 1). The diagnosis of HIV was established 18 years previously, with a viral load of 700,000 copies/mL and a baseline CD4+ T cell count of 281 cells/μL. He had no recent travel history and was sexually active with men. He reported having occasional, apparently healthy sexual partners

with whom he sometimes engaged in unprotected sexual intercourse. The skin lesions had appeared three weeks prior and were associated with a fever (maximum temperature 39.5 °C), asthenia, and mild itching. The lesions initially manifested as papules, which progressively enlarged and ulcerated. Physical examination revealed a total of seven such lesions. Upon admission, his vital signs were as follows: a body temperature of 36.0 °C, blood pressure of 150/90 mm Hg, a heart rate of 99 beats per minute, oxygen saturation of 94% on room air, and a respiratory rate of 20 breaths per minute. Laboratory tests revealed a white blood cell count of 3700 cells/µL (reference range 4000–11,000 cells/µL) with 55.1% neutrophils (reference 40–70%), 27.8% lymphocytes (reference 20–48%), and 15% monocytes (reference 3–11%). Hemoglobin level was 13.1 g/dL (reference range 12–18 g/dL), aspartate aminotransferase 80 U/L, alanine transaminase 148 U/L (reference range 0–50 U/L), alkaline phosphatase (AP) 235 U/L (reference range 40–129 U/L), gamma-glutamyl transferase (GGT) 267 U/L (reference range 8–61 U/L), and C-reactive protein 34.9 mg/L (reference < 5 mg/L). Microbiological tests were conducted, and a biopsy of the lesion on the left scapula was taken for histopathological examination (Figure 2). Histopathological examination revealed a granulomatous inflammatory infiltrate characterized by a dense lymphohistiocytic infiltration rich in T cells (CD3+, CD20−) and giant cells, without the presence of atypical lymphocytes, and occasional plasma cells (CD138+). Giemsa staining, anti-CD1 immunostaining, and PCR for Leishmania species excluded cutaneous leishmaniasis. Ziehl–Neelsen staining did not reveal any mycobacteria, and staining for treponemes using a rabbit polyclonal antibody was negative. However, the rapid plasma reagin (RPR) titer was 1:32, which had been negative 6 months earlier, and the *T. pallidum* agglutination test based on the principle of enhanced chemiluminescence was positive. Furthermore, the polymerase chain reaction (PCR) for *T. pallidum* using primers specific for a conserved region of the 16S rRNA gene (VIASURE Treponema pallidum Real-Time PCR Detection Kit) on a skin biopsy was positive. Additionally, the patient reported a history of correctly treated primary syphilis three years prior. The clinical presentation, along with histopathological and microbiological findings, confirmed a diagnosis of malignant syphilis. Following premedication with 50 mg of prednisone, a single dose of intramuscular penicillin led to defervescence and progressive improvement, with complete resolution of the ulcers. At a six-month follow-up, the patient's repeat RPR test was negative.

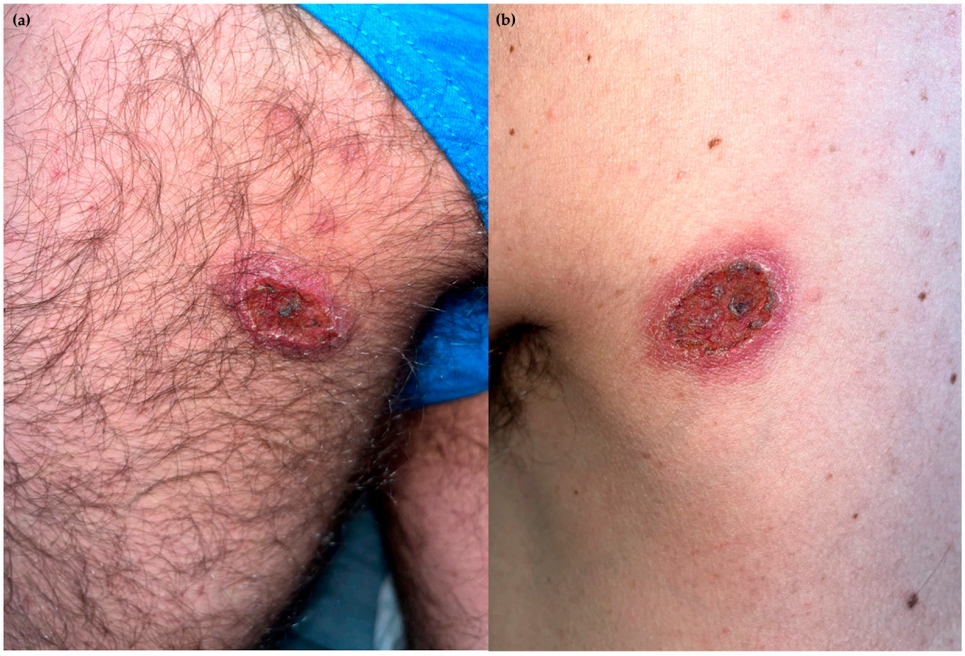

Figure 1. (**a**) ulcer on the left thigh; (**b**) ulcer on the left scapular area.

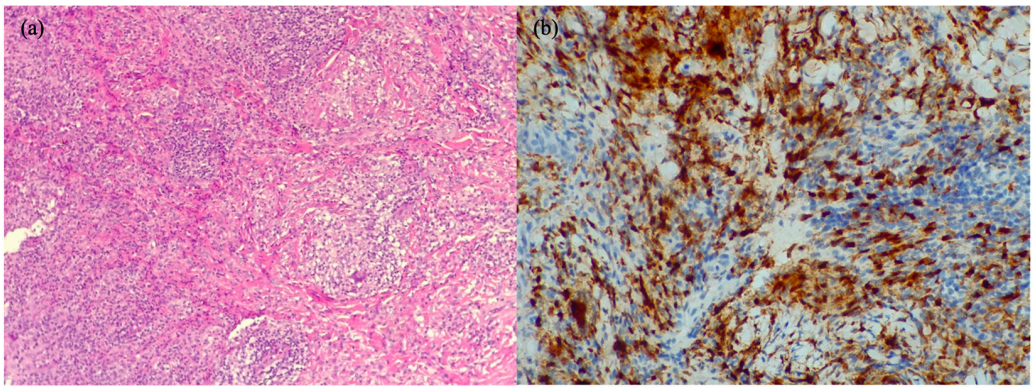

Figure 2. Histological examination of a cutaneous biopsy from the ulcer margin in the scapular area revealed the following: (**a**) hematoxylin and eosin staining (magnification ×10) demonstrated dermatitis with a dense lymphoplasmacytic infiltrate extending from the superficial to deep dermis. This infiltrate was predominantly composed of T cells, with no evidence of atypia, along with histiocytes; (**b**) CD68 immunostaining (magnification ×20) confirmed a dense granulomatous infiltrate, primarily consisting of CD68+ macrophages and T cells.

3. Discussion

Malignant syphilis is a rare and severe variant of secondary syphilis that predominantly affects immunocompromised individuals, particularly people living with HIV (PLHIV), who are 60 times more likely to develop the condition. Other at-risk groups include individuals with alcoholism, diabetes, and other immunocompromising conditions [2]. This form of syphilis is characterized by disseminated cutaneous and/or mucosal nodular and papular lesions that ulcerate, often progressing to central necrosis [2]. Cutaneous lesions with adherent oyster shell-like crusts and blackish-brown lamellated plaques are also suggestive of malignant syphilis [4]. Malignant syphilis can affect multiple organ systems, including the cardiovascular, central nervous, auditory, visual, gastrointestinal, musculoskeletal, and renal systems. Unlike typical secondary syphilis, malignant syphilis is frequently accompanied by systemic symptoms such as fever, malaise, and arthralgia [2]. The pathogenesis of malignant syphilis remains poorly understood [3]. The host's immune status seems to play a pivotal role in determining the pathogenesis and clinical progression of syphilis across its various stages. A robust delayed-type hypersensitivity response, primarily mediated by CD4+ T cells, is essential for controlling the infection. In this response, antigen-specific CD4+ T cells expand and release Th1 cytokines, which recruit and activate macrophages at the site of infection, leading to phagocytosis and pathogen clearance [5]. However, persistent localized antigenic stimulation can trigger excessive inflammation, resulting in plasma cell infiltration, granuloma formation, and tissue destruction [5]. In individuals with depleted CD4+ T-cell counts, such as those living with HIV or other immunodeficient states, a defective immunological response may predispose them to malignant syphilis [2,3,5]. Additionally, uncontrolled HIV viremia can impair CD4+ T-cell function [5]. Despite this, many reported cases of malignant syphilis in PLHIV have occurred in patients with normal CD4+ T-cell counts and well-controlled HIV viremia [2,3,5], as seen in our case. This finding suggests the involvement of other unidentified predisposing factors or conditions. Infection with a hypervirulent strain of *Treponema pallidum* has been hypothesized as a potential cause of malignant syphilis, potentially explaining its development in immunocompetent individuals. However, definitive evidence supporting this hypothesis is currently lacking, and no hypervirulent strains associated with malignant syphilis have been identified [2,3,5]. Histologically, malignant syphilis is characterized by a dense inflammatory infiltrate, which can include lymphocytes, plasma cells, macrophages, and neutrophils. This infiltrate is typically extensive, involving

both the dermis and subcutaneous tissue [2,3]. Additional features include epidermal hyperplasia, vasculitis, central necrosis, and the presence of *Treponema pallidum* spirochetes, which can be visualized within lesions using specialized staining techniques, such as silver staining and direct immunofluorescence. However, treponemes are often sparse or absent in the lesions, necessitating the use of sensitive detection methods, such as PCR, for diagnosis [2,3,6]. In our case, although immunostaining results were negative, PCR confirmed the presence of *Treponema pallidum*, and the RPR serology and clinical history further supported the diagnosis. Additionally, the disproportionate elevation of serum AP and GGT, accompanied by modest increases in hepatic transaminase levels, raised suspicion of syphilis. Cholestatic hepatitis is a well-known manifestation of early syphilis [7]. Regarding treatment, there is no consensus on the optimal approach for malignant syphilis [2,3]. In patients without central nervous system, ocular, or auditory involvement, some clinicians recommend weekly intramuscular injections of 2.4 million units of benzathine penicillin for three weeks, while others advocate a single dose as the treatment approach for secondary syphilis [2,3]. In our case, we opted for a single dose of benzathine penicillin, according to the current guidelines for secondary syphilis management [8]. In cases of malignant syphilis, the Jarisch–Herxheimer reaction may occur more frequently and with increased severity [3]. Therefore, in our case, we opted for premedication with prednisone. Diagnosing malignant syphilis can be challenging as it requires differentiating from conditions like cutaneous leishmaniasis, T-cell lymphoma, atypical mycobacterial infections, and other conditions. Cutaneous leishmaniasis is a global zoonotic infection caused by flagellate protozoa of the genus Leishmania transmitted by sandflies [9]. Histologically, lesions display a dense superficial dermal inflammatory infiltrate predominantly composed of macrophages, lymphocytes, and some epithelioid cells. Amastigotes, characteristic of Leishmania infection, can be observed within macrophages and detected using Giemsa staining or immunohistochemistry with specific antibodies [9,10]. Systemic symptoms are generally absent in cutaneous leishmaniasis, though they may appear in the disseminated form in some cases [11]. In our patient, Giemsa and anti-CD1a staining, along with PCR testing for Leishmania, were negative, effectively ruling out cutaneous leishmaniasis. CD1a, a dendritic cell marker, is regarded as an indirect marker for leishmaniasis, as amastigotes can acquire CD1a upon exiting dendritic cells [9,10,12]. Atypical mycobacteria are environmental pathogens that can cause skin and soft tissue infections, lymphadenitis, pulmonary infections, and disseminated infections [13]. PLHIV with CD4+ counts below 50 cells/μL are at elevated risk of atypical mycobacterial infections. Cutaneous lesions from these infections range from erythematous papules or nodules that may ulcerate to ecthyma-like presentations resembling cellulitis [13]. Histologically, atypical mycobacterial infections often elicit a granulomatous response with macrophages, neutrophils, and T cells at the infection site [13]. The Ziehl–Neelsen staining technique can identify mycobacteria, but in our case, the results were negative. Although some granulomatous inflammation was present, no granulomas were detected, making atypical mycobacterial infection unlikely, especially as these infections typically affect patients with severely compromised immunity (CD4+ counts below 50 cells/μL) [13,14]. Lastly, cutaneous T-cell lymphoma was excluded based on the absence of atypical lymphocytes and the patient's response to penicillin therapy, which resulted in symptom resolution.

4. Conclusions

This case underscores the importance of maintaining a high index of suspicion for malignant syphilis in PLHIV presenting with atypical skin lesions and systemic symptoms. Malignant syphilis can mimic other infectious and neoplastic conditions, and molecular

methods may help confirm diagnosis in challenging cases, especially when treponemes are not detected on histological examination.

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