CASE REPORT

Chronic non-healing ulcers as presenting sign of acquired immunodeficiency syndrome

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Abstract

Atypical forms of herpes simplex virus (HSV) infections, which indicate severe impairment of cellular immunity can be challenging to diagnose. In this paper, we report the case of an atypical HSV infection presenting as chronic nonhealing wounds, which are the first sign of HIV, in a 50-year-old female patient. The lesions had emerged as two large, chronic, and painful ulcerations on the left buttock and labia major 8 months prior. The skin biopsy revealed multinucleated keratinocytes with ground glass nuclei and intranuclear Cowdry type A viral inclusions. A serologic test for HIV-1 was positive. Her $CD4^+$ T-cell count was $42/mm^3$. Clinicians should be familiar with the dermatologic manifestations of HIV, as they are occasionally key to correctly suspecting an underlying HIV infection, allowing for early diagnosis and treatment.

Introduction

Herpes simplex virus (HSV) is a common and well-known viral skin disease. In cases of a typical lesion, the diagnosis is straightforward. However, atypical clinical manifestations of HSV can arise in immunocompromised patients presenting as chronic mucocutaneous ulcers and persist for more than a month.[1] Such an unusual presentation should lead the clinician to suspect immunodeficiency, acquired immune deficiency syndrome (AIDS) in particular.[2]

Since its 1981 discovery in the United States, AIDS has become an international crisis. The defective cellular immunity associated with AIDS puts infected persons at risk for a variety of opportunistic infections.[2] Individuals with HIV, including the one being discussed in this paper, often have more than one infection.[1] In an immunocompromised host, mucocutaneous lesions caused by infectious agents can be extensive, appear at unusual sites, and manifest atypically.[1]

Here, we present the case of a 50-year old female who presented with chronic non-healing HSV ulcers on her genitalia and buttock as well as tinea corporis on her trunk, which led to an HIV diagnosis.

Case presentation

A 50-year-old woman came to our dermatology clinic with an 8-month history of persistent, non-healing vulvar ulceration. The initial lesion was a tender papule that gradually progressed to form a large, painful ulcer. Three months after the emergence of the original lesion, she developed a similar ulcer on her left buttock which, similarly, grew worse through enlargement and increasing tenderness. A physical examination revealed swollen genitalia with superficial tender erosions on the patient's right labia major (**Fig 1**). On her left buttock was a shallow, well-demarcated erythematous ulcer 3–4 centimeters wide (**Fig 2**). Furthermore, a few erythematous annular plaques (**Fig 3**), which the patient was unaware of, were found in the left axillary region. The clinical differential diagnosis we considered for ulcers included skin malignancies, pyoderma gangrenosum, tertiary syphilis (gumma), deep mycosis, Crohn's disease, and chronic HSV and CMV infections.

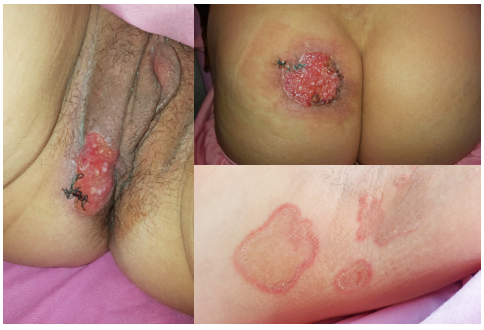

Fig. 1 (Left): Labia major superficial ulcer with a scalloped border

Fig. 2 (Top Right): Shallow, well-demarcated erythematous ulcer on the left buttock

Fig 3 (Bottom Right): Annular erythematous plaques with elevated borders on the axilla

The histopathological findings of punch biopsies taken from the patient's buttock and labia major lesions indicated that they were epithelial ulcer with severe infiltration of inflammatory cells, multinucleated giant cells with a ground glass appearance, and keratinocytes with slate-gray nuclei and intranuclear Cowdry type A viral inclusions, which are compatible with herpetic infection as well (**Fig 4,a,b**). Another skin biopsy taken from the patient's axillary lesions showed pseudoepitheliomatous hyperplasia with fungal hyphae in the stratum corneum layer, compatible with dermatophytosis (**Fig 5a,b**).

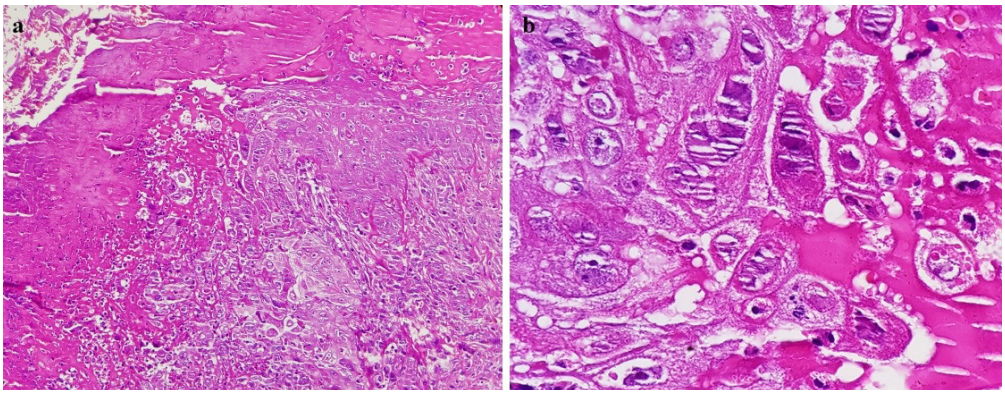

Fig. 4: Histologic examination showing ulcerated epidermis; keratinocytes with slate-gray nuclei and margination of chromatin containing eosinophilic intranuclear inclusion bodies surrounded by an artifact cleft (Cowdry type A inclusion). H&E (a):×20, (b):×100.

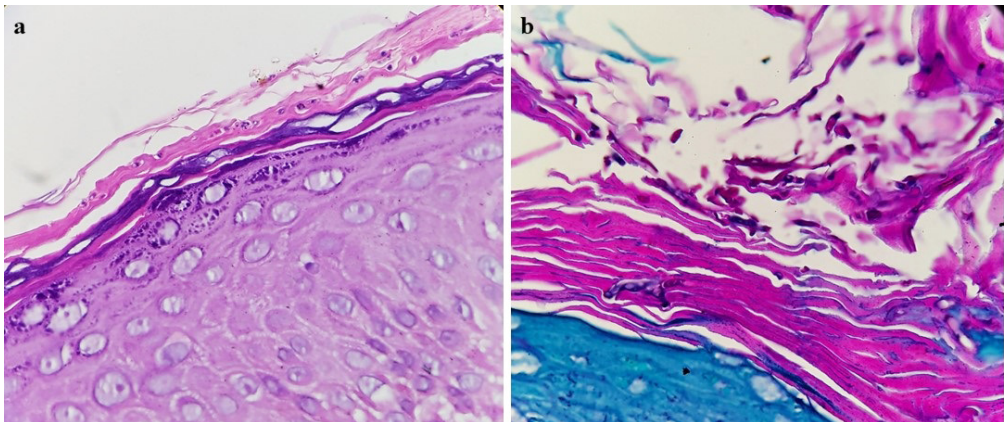

Fig. 5: Slightly hyperkeratotic stratum corneum containing numerous hyphae. (H&E stain ×40) (a); fungi are made more apparent by PAS (periodic acid Schiff) stain ×100 (b).

Given the unusual presentation of an HSV infection and the rarity of two concomitant skin infections in immunocompetent patients, we suspected an underlying HIV infection. ELISA testing revealed positive antibodies to HIV-1; the Western blot test confirmed the ELISA finding. The patient's total white blood cell count was 2.5 10^3/uL (with $CD4^+$ cell count 42/mm^3). The patient was treated with acyclovir 400 mg orally five times per day and terbinafine 250 mg once per day, which led to the complete resolution of the ulcers and annular plaques within two weeks. The patient was put on chronic daily suppressive therapy of acyclovir 400 mg twice per day for at least one year. The patient's husband was an IV drug user. He was tested for HIV-1 and HSV-2 infections and was found to be positive for both. After being counseled about HIV care and treatment, he agreed to be referred with his wife to an infectious disease specialist for further evaluation.

Discussion:

HSV is the most common sexually transmitted disease in patients infected with HIV. In relatively immunocompetent HIV-infected individuals, mucocutaneous HSV infections present in the typical fashion and severity with a recurrence rate similar to that of the general population.[1]

Lesions may appear as painful, grouped, and often umbilicated vesicles on an erythematous base; these may evolve into pustules, erosions, and/or ulcers with characteristic scalloped borders.[2]

However, in severely immunosuppressed HIV-infected persons, lesions may appear at a higher recurrence rate[2] as chronic, non-healing, and deep ulcers that favor the perianal region, genitalia, and tongue.

Several case reports of herpes simplex lesions in patients with AIDS described atypical presentations consisting of nodular, tumoral, or verrucous growth clinically simulating malignancies.[3]

Orofacial lesions associated with nasogastric tube use[4], periungual infections (herpetic whitlow)[5], and chronic herpetic foot ulcers[6] have been reported as presenting features of HIV infection.

Correlation has been found between certain HIV-associated cutaneous disorders and $CD4^+$ cell count.[7] For instance, large non-healing mucocutaneous HSV infections often emerge alongside $CD4^+$ cell counts under $50/mm^3$, as shown in our case.

The diagnosis of herpes in immunocompromised patients can be difficult.[8] Scrapings of the ulcer edge for Tzank smear has low sensitivity in HIV-infected patients. Multiple Tzank smears, a direct fluorescence assay (DFA), HSV Polymerase chain reaction (PCR) , or a viral culture may be required for confirmation. If these are negative, a skin biopsy from the edge of the ulcer should be performed. The characteristic histopathologic features of an HSV infection, would be an intraepidermal vesicle with ballooning degeneration of keratinocytes and multinucleated giant cells.[8]

The first-line agent for treatment of HSV infections in HIV-infected patients is Acyclovir (400 mg Po 5 times a day)[9]. In HIV-infected patients, antiviral therapy should be extended until clinical resolution is evident. When patients fail to respond to this medication, alternative drugs (e.g, Foscarnet and Cidofovir) should be prescribed.[9]

Long-term anti-HSV suppressive therapy should be considered in HIV-1-infected persons, as symptomatic recurrent HSV-2 infection can be more severe and asymptomatic shedding can be more frequent in these patients.[10] Treatment strategies for recurrent disease in HIV-infected persons include chronic suppressive therapy or episodic therapy based on frequency of recurrence and severity of outbreaks. According to 2015 guidelines on sexually transmitted disease[11], patients with recurrent genital herpes, especially those with frequent, painful, or prolonged recurrences, should receive one of the following daily suppressive therapies: acyclovir 400–800 mg two to three times daily; famciclovir 500 mg two times daily; valacyclovir 500 mg two times daily. For episodic therapy, the CDC[11] recommends one of the following regimens for a minimum duration of five to ten days or until the lesion has healed: acyclovir 400 mg three times daily; famciclovir 500 mg two times daily; valacyclovir 1g two times daily. Once the patient's $CD4^+$ count is ≥200 cells/mm, the ongoing need for suppressive antiviral therapy is evaluated annually based on disease activity.[10] It is worth noting that, based on current evidence, suppressive anti-HSV therapy in persons with HIV does not reduce the risk for either HIV transmission or HSV-2 transmission to susceptible sex partners.[12]

HIV-infected patients often have mixed infections on account of their immunocompromised state. In our patient, the combined infection of HSV and dermatophyte suggested immunosuppression and an HIV infection.

Dermatophyte infections are common in HIV-infected individuals.[13] Kaviarasan et al in a study on the prevalence and clinical variations in dermatophytosis in 185 HIV-infected patients found that more than 20% of all cases had a variant of dermatophytosis and Tinea corporis was the most common clinical form.[14] In Hiv-infected patients, dermatophytosis may manifest with unusual, multiple, or widespread lesions and may occur with less common etiologic agents.[14] Moreover, a noteworthy incidence of anergic skin lesions with little to no inflammation can be seen in HIV-infected individuals.[13]

Conclusion

This report emphasizes clinical indicators suggestive of underlying immunodeficiency, particularly AIDS. Atypical clinical manifestations of HSV may arise in immunocompromised patients as chronic mucocutaneous ulcers that persist for more than one month. Such an unusual presentation should lead clinicians to suspect HIV.

Since skin diseases brought about by opportunistic infections are common in HIV-infected patients, and these lesions can be the first manifestation of underlying immunodeficiency, clinicians must be aware of the characteristics and presentations of HIV in order to make early diagnoses and avoid delays in therapy initiation.

How does this paper make a difference to general practice?

- Atypical forms of herpes simplex virus (HSV) infections can be challenging to diagnose.
- Lesions may appear as chronic, non-healing, deep, nodular, tumoral, or verrucous ulcers.
- Unusual presentation should lead clinicians to suspect immunodeficiency, AIDS in particular.
- Clinicians must be familiar with HIV's dermatologic manifestations, as they can be key to suspecting an underlying HIV infection.
- The first-line agent for treatment of HSV infections in HIV-infected patientsis is acyclovir (400 mg /5 times per day).

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