

Manuscript title: “Successful treatment of hypertrophic herpes simplex genitalis in HIV-infected patient with topical imiquimod”

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Abstract

Hypertrophic herpes simplex genitalis is an atypical presentation of genital herpes described in the context of immunosuppression, particularly human immunodeficiency virus (HIV) -positive patients. This situation can become a diagnostic and therapeutic challenge. For this reason, alternative therapies are currently being discussed on the literature. We report a case of hypertrophic genital herpes in a HIV-positive patient who was successfully treated with topical 5% imiquimod after treatment failures with oral and intravenous antivirals.

Introduction

Herpes simplex virus (HSV) type 2 is the primary causative agent of genital ulcerations worldwide. The most common symptomatic presentation of genital herpes includes a prodromal period of pain, burning and tingling, followed by the development of painful vesicles on an erythematous base, which can progress to pustules and ulcerations.

Immunocompromised patients, particularly human immunodeficiency virus (HIV)-positive subjects, usually have an increased frequency of herpes reactivation, and clinical atypical features such as deep ulcerations, hypertrophic or pseudotumoral lesions or uncommon locations may be observed¹. In these atypical presentations, classical antiviral therapies are not always effective. We report a case of hypertrophic genital herpes in a HIV-infected patient who was successfully treated with topical 5% imiquimod after treatment failures with oral and intravenous antivirals.

Case report

A 45-year-old Guinean man was referred to our Department in 2013 for two painful and non-healing ulcers in the genital region of four month's duration. His past medical history included a secondary syphilis correctly treated in 2011 and HIV infection since 2008 on antiretroviral therapy (efavirenz, emtricitabine and tenofovir) with CD4 count of 232 cells/ μ L and a viral load of 126 copies/mL at the time of presentation.

Physical examination revealed two ulcerated lesions, both with exophytic- slightly infiltrated margins and verrucous and friable surface, one located in the left inguinal area extending 6 cm approximately and the other in the pubic area measuring 4 cm (Fig. 1). Painful bilateral inguinal lymphadenopathy was also noted. Due to the macroscopic appearance of the lesions and considering the clinical context, several skin biopsies specimens were obtained in order to exclude malignancy. Histopathological examination from the border of the ulcer revealed pseudoepitheliomatous hyperplasia associated with a dense dermal chronic inflammatory infiltrate with a predominance of plasma cells and eosinophils (Fig. 2A-B). After sectioning, an ulcerated epidermis with focal presence of multinucleated epithelial cells and acantholytic keratinocytes showing classic cytopathic effects of HSV infection was seen (Fig. 2C). These cells demonstrated unequivocal immunostaining for HSV type 2 (Fig. 2D). Bacterial, fungal and mycobacterial cultures and the polymerase chain reaction (PCR) for human papillomavirus, *Chlamydia trachomatis*, *Mycobacterium tuberculosis* and non-tuberculous mycobacterium yielded negative results. Immunohistochemistry performed on the skin biopsy for detection of *Treponema pallidum* and syphilis rapid plasma reagin test were also negative. A swab was tested for HSV DNA by PCR and was positive for HSV-2, confirming the diagnosis of hypertrophic herpes simplex genitalis.

Oral valacyclovir 1g twice a day for 14 days was prescribed with no clinical response. Intravenous acyclovir treatment (10mg/kg three times daily for 10 days) was also unsuccessful and a progressive worsening of the genital lesions was observed. Given the lack of improvement with the repeated isolation of HSV-2 from the PCR, an acyclovir-resistant HSV disease was suspected. Since it was not possible to perform in vitro susceptibility tests of HSV to antivirals, treatment with intravenous foscarnet 40mg/kg three times daily was started. After three weeks of antiviral therapy there were no signs of clinical improvement. At this time CD4 count remained at similar values (243 cells/ μ L). Treatment with topical 5% imiquimod cream three times weekly was initiated. On review eight weeks later, the genital lesions had achieved significant clinical improvement with partial resurfacing of both ulcerated lesions with a slight local redness. There was a complete reepithelialization of the ulcers after 15 weeks of treatment leaving residual hypopigmentation (Fig. 3). No further recurrence of the process has been observed after

five months of follow-up.

Discussion

Hypertrophic herpes simplex is an unusual and disfiguring condition often presenting with painful and exophytic tumoral nodules with or without ulcerated surface located predominantly in the anogenital region². This atypical presentation could be a diagnostic challenge and different disorders causing verrucous anogenital lesions in immunocompromised patients such as giant condyloma acuminatum (Buschke-Löwenstein tumor), secondary syphilis, mycobacterial infections, or even tumoral lesions (squamous cell carcinoma, lymphoma) should be ruled out.

From a histopathological point of view, most reported cases of hypertrophic herpes simplex genitalis show a dense dermal inflammatory infiltrate composed of plasma cells (usually more than 50% of the infiltrate), lymphocytes and eosinophils associated with variable degrees of epidermal hyperplasia, where multinucleated giant cells and cytopathic effects of HSV infection (like nuclear molding and clearing of chromatin) can be observed³. The presence of HSV in the lesion can be demonstrated either by immunohistochemistry, direct immunofluorescence, viral cultures or molecular biology techniques.

The cause of the evolution towards these hypertrophic forms remains unexplained. Probably the immune alteration secondary to HIV infection with the consequent imbalance in cytokine release could be responsible for an abnormal immune response to viral infection, stimulating TH2 immunological pattern and proliferation of keratinocytes and fibroblasts, leading to the formation of these exophytic lesions⁴.

This condition may pose therapeutic difficulties because it is often refractory to first-line systemic antiviral agents such as acyclovir (administered orally or intravenously), valacyclovir and famciclovir. The exact cause of the lack of response of this type of lesion for classic antivirals is not exactly known. Hypothesis of reduced or absent drug delivery to pseudotumor tissue or higher frequency of drug-resistant HSV strains in

immunocompromised patients has been proposed⁵⁻⁶. In the literature different alternative treatments have been used with variable results: drugs such as cidofovir and foscarnet, administered both topically and intravenous, or even surgical excision for affordable injuries. In the last decade some authors describe the effectiveness for treating these lesions with immunomodulators like thalidomide or imiquimod, given the possible pathogenic basis of the disease⁶⁻⁷.

Imiquimod is an imidazoquinoline amine with potent immunomodulatory properties. This molecule is a Toll-like receptors (TLR) agonist, particularly TLR-7. This activation would cause the release of endogenous proinflammatory cytokines such as interferon-alpha, interleukin-6 and tumour necrosis factor-alpha, stimulating both innate and adaptive immune response, explaining its antiviral and antitumor activity⁸. In our case, imiquimod 5% cream was used three times weekly, obtaining clinical improvement few weeks later without local complications, although a minimum local redness without bloating was noted. This treatment also avoids the need for hospitalization for intravenous treatment with substantial systemic toxicity. Furthermore, as imiquimod is an immune stimulator rather than a direct antiviral agent, it has no risk of generate drug resistance. In this case we found imiquimod to be a safe, tolerable and efficacious therapy, so it could be an alternative to consider in the treatment of these peculiar forms of genital herpes.

Conflict of interest. The authors declare that there are no conflicts of interest

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Figure legends

Figure 1. Hypertrophic ulcers located at the left inguinal and pubic area at the time of presentation.

Figure 2. Histologic sections of lesional skin. A. Pseudoepitheliomatous hyperplasia and exuberant inflammatory infiltrate in the dermis (hematoxylin & eosin, 40x). B. Dense dermal inflammatory infiltrate composed in its vast majority of plasma cells (hematoxylin & eosin, 400x). C. After sectioning, ulcerated epidermis and acantholytic keratinocytes with clear-cut cytopathic changes (nuclear molding, clearing of chromatin and multi-nucleation) were seen (hematoxylin & eosin, 400x). D. Herpes simplex virus type 2 immunostain showing strong positivity.

Figure 3. Complete reepithelialization of genital lesions after 15 weeks of treatment with topical 5% imiquimod cream.

Figures

Figure 1:



Figure 2:

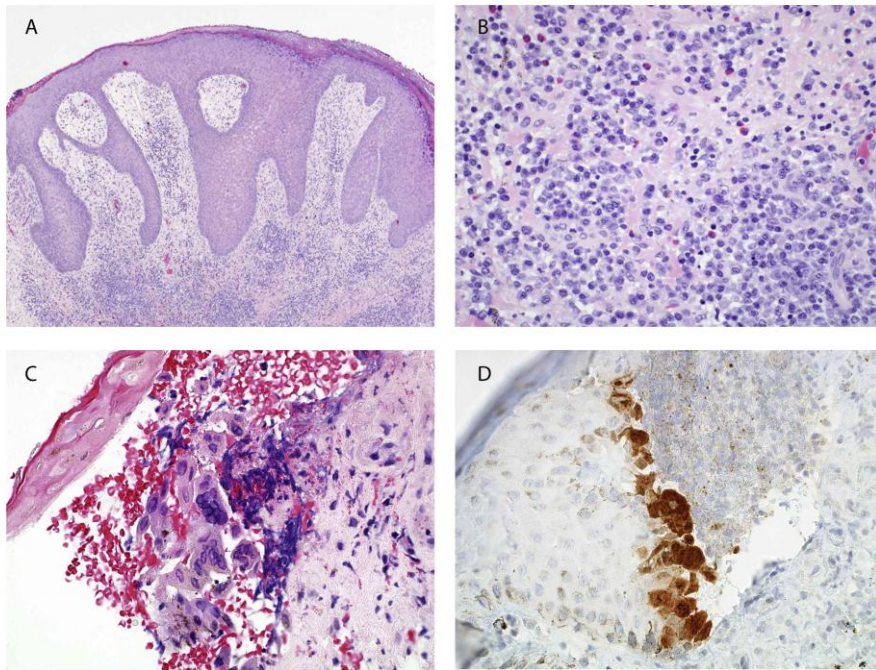


Figure 3

