

# Successful surgical treatment of hypertrophic genital herpes in HIV-infected patient

## Tratamento cirúrgico bem-sucedido de herpes genital hipertrófico em paciente infectado pelo HIV

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### Abstract

Genital herpes is mostly caused by the herpes simplex virus type 2 and is frequent in patients infected with the human immunodeficiency virus. In this setting, the disease may have atypical clinical presentations, including an unusual pseudotumoral hypertrophic form that may cause diagnostic and therapeutic problems, which usually shows an unsatisfactory response to first-line systemic antiretrovirals. The authors report a case of hypertrophic genital herpes refractory to oral acyclovir treatment and effectively treated with surgical excision, with no recurrence after the procedure.

**Keywords:** Herpes simplex. Herpes genitalis. Vulvar diseases. Human immunodeficiency virus infections. Surgical procedures.

### Resumo

O herpes genital é causado principalmente pelo vírus herpes simplex tipo 2, sendo frequente em pacientes infectados pelo vírus da imunodeficiência humana. Nesses casos, a doença pode ter uma apresentação clínica atípica, incluindo a forma hipertrófica, que pode passar despercebida ou ser confundida com outros diagnósticos mais prevalentes. Os antivirais sistêmicos de primeira linha apresentam resposta insatisfatória nessa rara forma de apresentação. Os autores relatam um caso de herpes genital hipertrófico refratário ao tratamento com aciclovir e efetivamente tratado com excisão cirúrgica, sem recidiva após o procedimento.

**Palavras-chave:** Herpes simples. Herpes genital. Doenças vulvares. Infecções por HIV. Procedimentos cirúrgicos operatórios.

### Introduction

Herpes simplex virus (HSV) infection is the leading cause of genital ulcers worldwide. HSV type 2 (HSV-2) is the most frequently associated serotype; however, genital lesions can also be caused by HSV type 1 (HSV-1), presenting with a less severe form and with

less chance of recurrence<sup>1-4</sup>. The incubation period of the virus can range from 2 to 12 days, with an average of 4 days<sup>1</sup>. Primo-infection is usually asymptomatic, with symptomatic patients showing multiple, widespread, and painful ulcerations on the genitalia<sup>2</sup>.

In recurrences, the most common presentation is characterized by 2-3 mm erythematous papules,

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Received: 07-06-2023

Accepted: 09-09-2023  
DOI: 10.24875/PJDV.23000050

Available online: 05-10-2023

Port J Dermatol and Venereol. 2023;81(4):285-288  
[www.portuguesejournalofdermatology.com](http://www.portuguesejournalofdermatology.com)



**Figure 1.** Pseudotumoral hypertrophic genital herpes simplex virus infection in the right labia majora.



**Figure 2.** Immediate post-operative image.

followed by formation of clustered vesicles with citrine content that break up and give rise to painful ulcerations<sup>1,4,5</sup>. However, in immunosuppressed patients, HSV infection may present in different forms such as generalized papular eruption, verrucous papules mimicking condyloma, and more rarely as a pseudotumoral hypertrophic form, which can simulate squamous cell carcinoma<sup>5-8</sup>.

These atypical presentations of HSV infection require a high degree of clinical suspicion, as well as knowledge of specific therapeutic modalities.

In this context, the authors report a case of hypertrophic genital herpes (HGH) in a patient with concomitant infection by human immunodeficiency virus (HIV), which was unsuccessfully treated with oral antivirals, and resolve after surgical excision.

### Case report

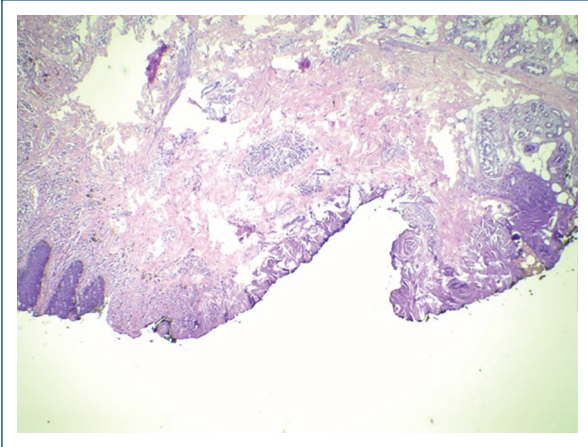
A 55-year-old female patient was referred to the Pathology of the lower genital tract Clinic of the Santa Casa de São Paulo Hospital (Brazil), by the primary health care unit. She reported a painful vulvar vegetating mass, with approximately 1 year of evolution and progressive growth. The patient was diagnosed with

HIV infection 22 years ago, with good adherence to the antiretroviral therapy, and an undetectable viral load (3 months before). She denied other comorbidities or chronic medication and reported that she was not sexually active for the past 20 years.

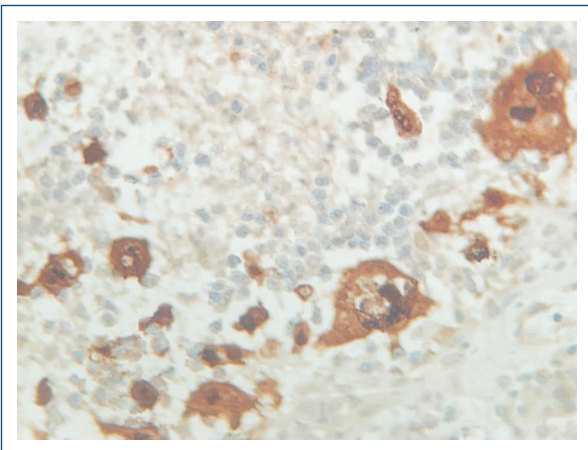
A lesional biopsy performed in primary healthcare suggested a herpes virus infection. Thus, she was treated with oral acyclovir at the maximum dose (800 mg 4/4 h) for about 3 months with continuous-lesional growth.

General physical examination was normal and vulvar examination revealed a rounded exophytic mass, with granulomatous appearance, ulcerated areas, and covered with purulent secretion, with approximately 4 cm, in the lateral face of the right labia majora (Fig. 1). In this context, the hypothesis of HGH was considered. Moreover, due to the failure of acyclovir therapy, the patient underwent surgical excision under local anesthesia (Fig. 2). Topical imiquimod was not part of the treatment of the patient reported in this case. The medication was unavailable in the service.

The final histopathological analysis revealed an ulcerated herpetic vulvitis with an intense acute inflammatory reaction and multinucleated cells (Fig. 3). Immunohistochemistry revealed immunoexpression of



**Figure 3.** Final histopathological result showing an intense acute inflammatory infiltrate and multinucleated cells in a microscopic magnification of  $\times 4$ .



**Figure 4.** Immunohistochemistry revealing immunoexpression of associated herpes simplex virus type 1 and herpes simplex virus type 2 (research of polyclonal antibodies to herpes simplex virus type 1, type 2, and treponema through the polymer amplification system ENVISION).

associated HSV-1 and HSV-2 (Fig. 4). Therefore, it was decided to maintain oral acyclovir (800 mg 4/4 h) for 30 days. After a follow-up of 12 months, the patient remains stable with no recurrences.

## Discussion

HGH is a rare presentation of HSV genital infection that has been described in immunocompromised patients<sup>7</sup>, especially in association with HIV infection<sup>6</sup>. The reason why this hypertrophic variant is more

prevalent in HIV-positive patients is uncertain, as it appears to have no relation with CD4+ T lymphocyte count, nor with the immunosuppression<sup>5,8</sup>. Possible immunological mechanisms for the development of hypertrophic lesions include increased production of tumor necrosis factor -alpha by factor XIII-positive plasmacytoid dendritic cells, promoting a growth of keratinocytes and consequent acanthosis and hyperkeratosis. Furthermore, the decreased production of interferon -gamma, which regulates the activity of keratinocytes, may also contribute to its development<sup>3,5</sup>.

This atypical manifestation is characterized by the presence of painful, well-defined exophytic masses with an irregular and ulcerated surface. The lesions are usually located in the perianal region, vulva, penis, and scrotum, but there are reports of similar extragenital lesions<sup>3,7</sup>.

The diagnosis depends on a high level of clinical suspicion with clinicopathological correlation, being fundamental for the exclusion of other infectious or non-infectious causes (genital condyloma and squamous cell carcinoma for example)<sup>6,7</sup>. Histopathology and virus identification support the diagnosis, but very small samples may be insufficient for diagnostic confirmation, due to the intense inflammatory response that can mask the diagnosis<sup>5</sup>. Histopathology shows a variable hyperplasia of the epidermis, with multinucleated epithelial cells and dense mixed inflammatory infiltrate composed of lymphocytes, plasma cells, and eosinophils. The identification of HSV in the lesion can be obtained by polymerase chain reaction or immunohistochemical methods<sup>9</sup>.

HSV infections in immune compromised patients should be treated with first-line systemic antivirals such as acyclovir (intravenous or oral) valacyclovir and famciclovir (foscanet and cidofovir can be used as a second-line treatment). However, atypical presentations of HSV infections, including HGH, are frequently resistant to antivirals. Thus, surgical excision may be considered, as in the present case<sup>8,10</sup>. A combined therapy of surgical excision with prophylactic antiretroviral drugs may also be an option. Finally, despite the lack of randomized studies, topical imiquimod and oral thalidomide have been described as an effective topical treatment for hypertrophic lesions in immunocompromised patients<sup>8,11,12</sup>.

## Conclusion

HGH is a rare presentation of HSV genital infection, which must be included in the differential diagnosis of vegetating anogenital lesions in immunocompromised

patients, especially in HIV infection. Biopsy is crucial to exclude other infectious and non-infectious causes. In the therapeutic approach, the likely resistance of this atypical form to antivirals must be considered, and additional topical imiquimod and surgical excision may be effective alternatives.

## Funding

None.

## Conflicts of interest

None.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that no experiments were performed on humans or animals for this study.

**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

## Use of artificial intelligence for generating text.

The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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