



Hypertrophic perianal herpes successfully treated with imiquimod *

Herpes hipertrófico perianal tratado eficazmente com imiquimod

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Abstract: Herpes simplex virus type 2 (HSV-2) infections are frequent in HIV (human immunodeficiency virus) infected patients. In those cases, genital herpes may have an atypical clinical presentation. Hypertrophic and vegetating variants are unusual. The authors describe a case of hypertrophic perianal herpes in an HIV patient with unsatisfactory response to acyclovir and valacyclovir, successfully treated with imiquimod. Hypertrophic genital herpes cases are frequently refractory to antiviral treatments. In our experience, imiquimod is an efficient, safe and well tolerated treatment that should be considered in therapeutic approach of these patients.

Keywords: Antiviral agents; Combined modality therapy; Efficacy; Herpes genitalis; Herpesvirus 2, human

Resumo: A infecção pelo vírus herpes simples tipo 2 (HSV-2) é frequente em pacientes infetados pelo vírus de imunodeficiência adquirida (VIH). Nestes casos, o herpes genital pode ter uma apresentação clínica atípica. As variantes hipertróficas e vegetantes são pouco habituais. Os autores relatam um caso de herpes hipertrófico perianal em paciente infetada pelo VIH, com resposta insatisfatória ao aciclovir e valaciclovir, tratado eficazmente com imiquimod tópico. O herpes genital hipertrófico é, frequentemente, refratário aos tratamentos antivirais. Na nossa experiência, o imiquimod é um tratamento eficaz, seguro e bem tolerado que deverá ser considerado na abordagem terapêutica destes pacientes.

Palavras-chave: Antivirais; Eficácia; Herpes genital; Herpesvírus humano 2; Terapia combinada

INTRODUCTION

Herpes simplex virus (HSV) infections are the main cause of genital ulcers worldwide, and HSV-2 is the serotype most frequently implicated in its etiology.¹ The synergism between the HSV-2 and the human immunodeficiency virus (HIV) infections has been demonstrated in several epidemiological and clinical studies, with increased frequency in reactivation of HSV-2 in HIV-positive individuals. On the other hand, HSV-2 infection increases the risk of acquiring HIV and hastens disease progression.² The ulcerative form is the most frequent clinical presentation of genital herpes, detected by the presence of small grouped vesicles that result in painful superficial ulcers, often accompanied by inguinal lymphadenopathies.¹ In individuals coinfecting by VIH, the clinical aspects are frequently atypical and extensive ulcers may be obser-

ved, which tend to be chronic, many times with bacterial suprainfection.³ More rarely, pseudo-tumoral hypertrophic forms that simulate squamous cell carcinoma or other viral infections have been described.^{4,5} In these cases, a high degree of clinical suspicion is required. The synergism between the HSV and HIV infections is also reflected in the therapeutic approach to genital herpes, particularly in individuals with low lymphocyte T CD4+ counts. In these patients, systemic antivirals are used in higher doses and for longer periods, and there is a higher prevalence rate of cases that are resistant to acyclovir.⁶ The onset of hypertrophic genital herpes usually occurs in the immunodepression context and it is often resistant to antiviral therapies, with frequent relapses.^{4,5,7} The authors report a case of hypertrophic perianal genital herpes

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in HIV- positive patient, where the utilization of topical imiquimod was found to be effective.

CASE REPORT

A 49-year-old female patient, black, from Guinea-Bissau, resident in Portugal (Lisbon) for eight years, was referred for a dermatology appointment in February 2010 with a painful vegetating tumor located in the left perianal region for two months, with progressive worsening.

This was a patient that had received HIV-1 infection diagnosis six months before. She had begun treatment with tenofovir/emtricitabine and nevirapine 1 month before (January 2010) due to low lymphocyte T CD4+ count ($197/\text{mm}^3$) and viral load of 32000 HIV/RNA copies per milliliter. There was no prior history of sexually transmissible or opportunistic infections.

Medical observation revealed a rounded, well-defined tumor with 4 cm diameter, located in the left perianal region (Figure 1). No other relevant alterations were detected in the physical examination. Considering the clinical context, diagnostic hypotheses of hyperthrophic perianal genital herpes, squamous cell carcinoma and genital condyloma were equated. An incisional cutaneous biopsy showed epidermal hyperplasia, multinucleate epithelial cells, focal ballooning epidermal degeneration and dense mixed dermal inflammatory infiltrate (Figure 2). Lesion investigation was also carried out by polymerase chain reaction (PCR) for HSV-1, HSV-2 and human papilloma virus (HPV), where only HSV-2 positivity was detected. The investigation of mycobacteria and deep fungi was also negative. The laboratory evaluation highlighted positivity for IgG HSV-2, while IgM HSV-2 was negative. The hemogram and biochemical tests were normal. Other active infections were excluded, mainly viral hepatites, infection by cytomegalovi-

rus (CMV), Epstein-Barr virus (EBV) and syphilis. Therapy with acyclovir at the maximum dose (800 mg 4/4h) was started, with good initial clinical response that resulted in visible decrease in lesion dimensions (Figure 3). However, as of the second month of treatment a loss of response was observed. Acyclovir was replaced by valacyclovir 1 g 12/12 hours during one month, with no satisfactory clinical improvement. As of the 4th month of treatment, topical imiquimod was associated with valacyclovir. Imiquimod was applied with occlusion, three times a week during the first two weeks and then on five consecutive days per week. The treatment was well tolerated by the patient, without any local and/or systemic significant adverse effect. The clinical response was excellent, which was particularly evident after the increase in frequency of application, with complete remission after 10 weeks of treatment (Figure 4).

After the clinical remission of the perianal lesion, the valacyclovir dose was reduced to 1g/day. At two months of follow-up, the patient continues clinically stable, with no signs of relapse, lymphocyte count CD4+ $310/\text{mm}^3$ and viral load lower than 20 HIV/RNA copies per milliliter.

DISCUSSION

In patients with HIV infection, the presence of anogenital vegetating lesions is common, possibly the infection or carcinoma clinical presentation form. HPV infection is the most frequent of anogenital verrucous lesions; however, infections caused by the Varicella-Zoster Virus, CMV, Molluscum Contagiosum and HSV should be considered in the differential diagnosis.⁸ The hypertrophic variant of genital herpes is rare and has been described in the context of immunodepression, particularly in patients with HIV infection and/or immune reconstitution inflammatory syndrome (IRIS).^{4,5,7} The reason why this hypertrophic

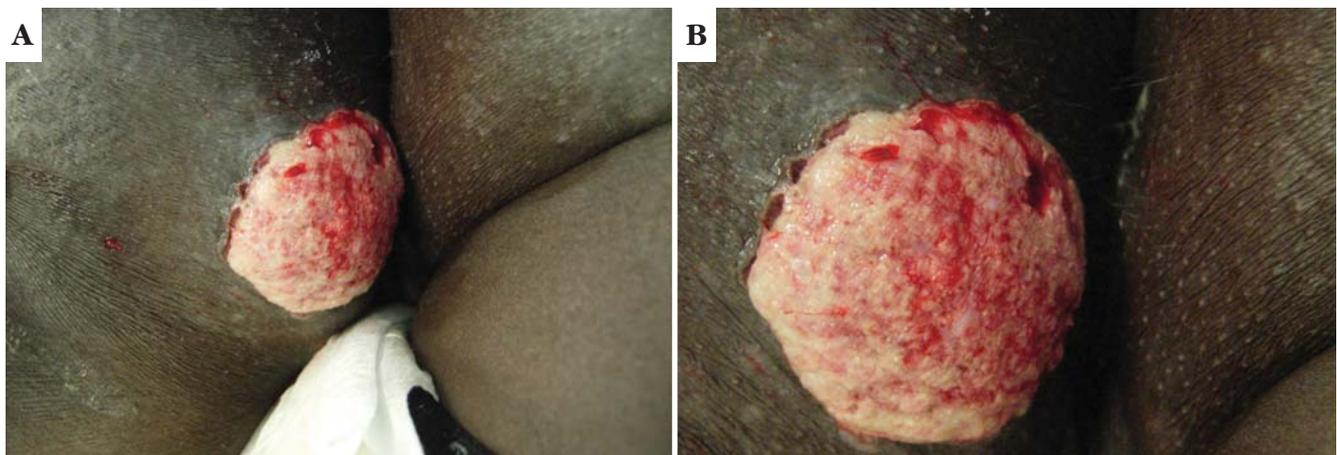


FIGURE 1: A. Tumor with well-defined limits in the left perianal region; B. Detail of tumoral lesion on plane, ulcerated and friable surface

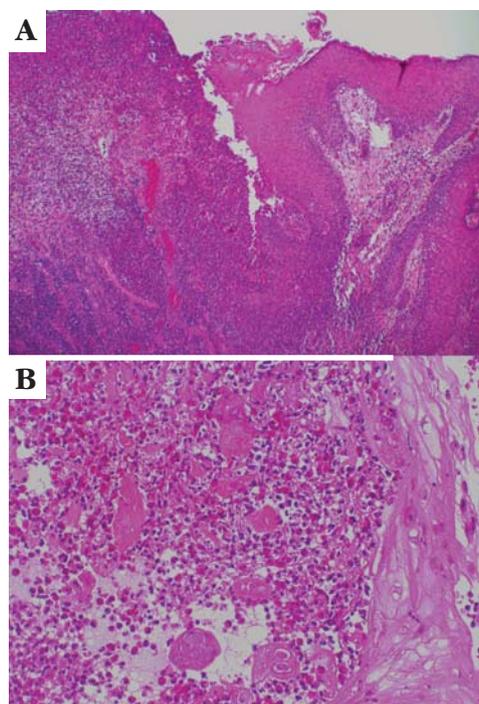


FIGURE 2: **A.** Epidermal hyperplasia with ulceration and necrosis. Dense inflammatory infiltrate on superficial and deep dermis, composed of lymphocytes, plasmacytes and eosinophils (hematoxylin-eosin; 40x); **B.** Larger size shows multinucleate epithelial cells (hematoxylin-eosin; 200x)



FIGURE 3: Clinical improvement after a 2-month treatment with acyclovir

variant appears almost exclusively in patients coinfecting by HIV is not totally clear, since there seems to be no correlation with the degree of immunodepression and/or lymphocyte count T CD4+.^{5,9,10} Nevertheless, the evolution into hypertrophic forms of genital herpes may be partially justified by immunological deregulation secondary to HIV infection, particularly by: 1) Production of TNF-alpha by an increased number of plasmacytoid dendritic cells factor XIII-positive, promoting the keratinocyte growth rate and consequent acanthosis and hyperkeratosis and 2) Diminution of IFN-gamma production, a cytokine that plays an important regulating role in keratinocyte activity.^{5,11}

In this case, the clinical evolution of HSV-2 infection does not seem to be related to the patient's immunodepression degree, as the antiretroviral therapy (ART) was started after the lesion onset, excluding the hypothesis of IRIS. On the other hand, the initial progression of the perianal tumor was not interrupted by immunological recuperation induced by ART.

This variante is clinically defined by the presence of exophytic and painful tumors, with well-defined limits and ulcerated surface, located on the perianal region, vulva, penis and scrotum. However, similar lesions have also been described in extragenital locations. The diagnosis is based on correlation between the clinical and histological data, supported by HSV isolation and exclusion of other infectious causes. Histologically, variable epidermal hyperplasia can be observed, with multinucleate epithelial cells and

dense mixed dermal inflammatory infiltrate composed of lymphocytes, plasmacytes and eosinophils.^{4,7} It is recommended to perform an incisional cutaneous biopsy, since small samples may be insufficient for diagnosis and masked by the intense inflammatory response to the virus.¹² The demonstration of the lesional HSV presence may be done through immunohistochemical methods or PCR.

The hypertrophic genital herpes is often refractory to first-line systemic antiviral agents, like acyclovir (oral and intravenous), valacyclovir and famciclovir. In such cases, foscarnet, interferon-beta and cidofovir have been used, despite variable effectiveness outcomes.^{9,10,13,14} Another therapeutic alternative to be considered is thalidomide, recently described by Holmes *et al.*¹⁴ Finally, surgical excision may be considered in small tumors.

Imiquimod is a topical immunomodulator with antitumoral and antiviral activity, inducing synthesis and liberation of several endogenous proinflammatory cytokines TH-1, namely interferon-alpha. Although there are no randomized studies, the efficacy of topical imiquimod in the treatment of chronic genital herpes in immunodepressed individuals has been described in the literature.¹⁵ In cases of genital herpes particularly resistant to medical therapies, such as the hypertrophic variant, the role of imiquimod is still not clear. Recently, it was used in the treatment of hypertrophic genital lesions caused by HSV-2 in two HIV-positive patients resistant to conventional medical treatments (oral acyclovir, intravenous acyclovir, valacyclovir and foscarnet).^{10,11} The first case was reported in 2007 and described a male patient with severe immunosuppression and vegetating lesions located on the penis and scrotum.¹¹ In 2008, Yudin and Kaul reported the second case in a female patient with persistent hypertrophic vulvar lesions after starting anti-

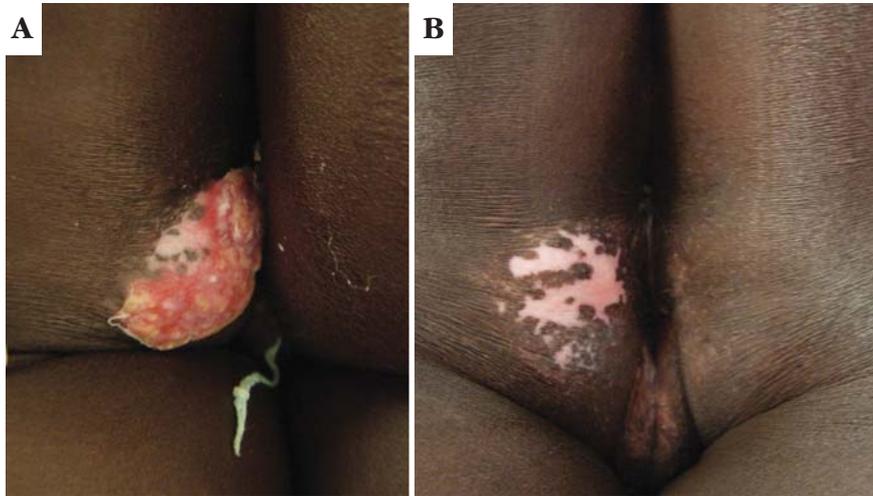


FIGURE 4: A. Therapeutic response after 2 weeks using imiquimod three times a week; B. Complete clinical regression after 10 weeks of treatment with imiquimod

retroviral therapy (ART) and full immunological recuperation.¹⁰ In both patients, the application of imiquimod three times a week was associated with systemic antiviral therapy (famcyclovir 500 mg twice a day and valacyclovir 1 g twice a day, respectively), resulting in complete lesion remission after 2 to 8 weeks of treatment. In the present case, we also observed excellent response to imiquimod, with full regression of the lesion after 10 weeks of treatment. As previously suggested by Bangsgaard and Skov, we verified that the increased number of weekly applications seems to be associated with faster response.¹⁵ In the case above

described, we chose to apply imiquimod with occlusion to para potentiate the efficacy of the treatment, which could be limited by the lesion location and size. This form of application is frequently badly tolerated, however, in our patient no significant local and/or systemic adverse effects were observed.

Hypertrophic genital herpes is a rare variant of genital herpes that should be equated in the presence of anogenital vegetating lesions in patients with HIV coinfection. Imiquimod should be considered in the therapeutic approach to these patients, as it is an effective, safe and well-tolerated treatment. □

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