

Association of oral acyclovir and imiquimod for the treatment of hypertrophic genital herpes simplex in HIV positive patients: report of two cases *

Associação de aciclovir oral e imiquimode no tratamento de herpes simples genital hipertrófico em paciente com sida: relato de dois casos

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Abstract: Chronic herpes simplex can present as exuberant clinical lesions, especially in HIV patients. The most probable mechanism of formation of these lesions is the invasion of the epidermal CD4 T cells by the herpes simplex virus. Due to the therapeutic difficulties and the high rates of treatment failure amongst these patients, new drugs are currently being discussed on the literature. Studies based on the immunopathology of these lesions have suggested that imiquimod might work as an adjuvant therapy to the antiviral drugs. Here we present two cases of excellent response to treatment with topical imiquimod as an adjuvant drug to acyclovir.

Keywords: Acquired immunodeficiency syndrome; AIDS-Related opportunistic infections; Herpes genitalis; Medication therapy management; Treatment failure

Resumo: Herpes simples crônico é doença capaz de gerar apresentações exuberantes, principalmente em pacientes com sida. O provável mecanismo da formação dessas lesões hiperplásicas consiste na invasão viral dos linfócitos T CD4 situados na epiderme. Diante das dificuldades terapêuticas e da grande taxa de insucesso do tratamento nesses pacientes, novas terapias têm sido citadas na literatura atualmente. O conhecimento da imunopatologia ratificou o mecanismo pelo qual o imiquimode poderia ser eficaz como terapia adjuvante aos antivirais. Relatamos aqui dois casos de pacientes tratados com aciclovir associado ao imiquimode tópico que obtiveram resposta clínica excepcional.

Palavras-chave: Conduta do tratamento medicamentoso; Falha de tratamento; Herpes genital; Infecções oportunistas relacionadas com a aids; Síndrome de imunodeficiência adquirida

Herpes simplex virus (HSV) is considered the most common cause of genital ulcer. In patients with AIDS it can present as chronic, clinically atypical and severe forms.¹ In this context much is being discussed nowadays in terms of new therapeutic trials, due to the increasing numbers of patients who do not

respond to the present treatments, as well as the emergence of HSV strains resistant to acyclovir. The following case is an example of the diagnostic difficulty of vegetative lesions in immunosuppressed patients, as well as to demonstrate therapeutic success with the use of topic imiquimod working as an adjuvant drug

Received on 09.05.2010.

Approved by the Advisory Board and accepted for publication on 13.07.2011.

* Work performed at the Dermatology Service of the Hospital Universitário Pedro Ernesto – Universidade do Estado do Rio de Janeiro (HUPE – UERJ) – Rio de Janeiro (RJ), Brasil.

Conflict of interest: None / *Conflito de interesse: Nenhum*

Financial funding: None / *Suporte financeiro: Nenhum*

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to the retrovirals, for the clinical improvement of these patients.²

CASE 1: 42 years old male patient came to the service complaining of painless, exudative lesion on scrotum which developed two years before (Figure 1). The patient reported HIV positive status for three years and he was taking Biovir and Efavirenz. According to him, many therapeutic modalities had been tried, including oral acyclovir for many months, as well as intravenous acyclovir, without satisfactory clinical improvement. During consultation it was noted that the patient had CD4 count of 150 cells/mm³ and a very high viral load. At dermatological examination a vegetative, exulcerated and exudative lesion was observed, measuring around 10cm, involving a great portion of the patient's scrotum. The histopathological examination confirmed the clinical hypothesis of chronic herpes simplex. At this point the patient was taken to hospital care and intravenous acyclovir at a dose of 10mg/Kg/ 3 times a day was started, for 10 days, and the lesion was surgically treated with shaving, in order to reduce the amount of hyperplastic tissue and therefore facilitate the penetration of the drug. When the patient left hospital the lesion was only partially improved. In view of the difficulty of performing sensibility tests of HSV to the nucleoside analogues, we decided to keep oral therapy with Valacyclovir and to associate topical imiquimod, based on its antiviral and antiproliferative effects. The patient was kept on the regimen for around three months, with complete clinical healing and with no evidence of relapse of the lesion after suspending the drugs (Figure 2).

CASE 2: 45 years old male patient with AIDS for



FIGURE 1: Lesion under treatment with oral acyclovir

nine years, with no antiretroviral therapy, presented with an exulcerated lesion, with raised borders, of approximately 12 cm, for one year. The lesion continued to grow despite the use of oral acyclovir. The patient was taken to hospital and treatment with intravenous acyclovir, for 10 days, was started. At this point the lesion was biopsied and the diagnosis was compatible with Chronic Herpes Simplex. The lesion improved, with partial healing. At this point antiviral therapy was initiated, which the patient took consistently (Lopinavir + Ritonavir, Lamivudine e Tenofovir). At the time he left hospital the patient's viral load was undetectable and the CD4 count was 315. He was kept on prophylactic acyclovir at a dose of 400 mg every 8 hours. However, despite the initial improvement the lesion still had vegetative and exudative borders. Due to the persistence of the condition, condition we decided to use imiquimod on the vegetative area, 3 times a week, as an adjuvant to oral acyclovir on the same initial dose. After around one month the patient had an excellent therapeutic response, with complete healing of the lesion. Therefore, we suspended the imiquimod and reduced the dose of oral acyclovir to 200mg every 8 hours, with no sign of relapse of the lesion after six months as outpatient follow-up.

Amongst the clinical indications of imiquimod its efficacy in treating genital and peri-anal HPV, superficial basal cell carcinoma (BCC) and actinic keratosis is confirmed. The frequency of application varies according to the pathology, therapeutic response, and local irritation. Amongst the "off-label" indications there are some reports on the literature about its use on Bowen's disease, bowenoid papulosis, erythroplasia of Queyrat, lentigo malignant melanoma, keloids, infantile hemangioma, mycosis fungoides and as an adjuvant in herpes simplex relapse.

Imiquimod in immunocompetent people has an immunomodulatory action, stimulating the production of TFN- α and others, as well as presenting anti-viral e anti-tumoral indirect effects. These cytokines have an activating role on the cell-mediated immunity or TH1, which justifies the antitumoral effect.³

Due to the increasing number of immunosuppressed patients by the HIV, we are now facing various new infection modalities by the HSV.^{3,4} The probable mechanism of formation of these hyperplastic lesions is the viral invasion of CD4 T lymphocytes and dendritic cells located on the epidermis which, when stimulated, are capable of responding with an TH2 immunological pattern, producing IL-4 and TNF-alpha, that are responsible for the proliferation of keratinocytes and fibroblasts, increase in collagenesis and anti-apoptotic activity.³

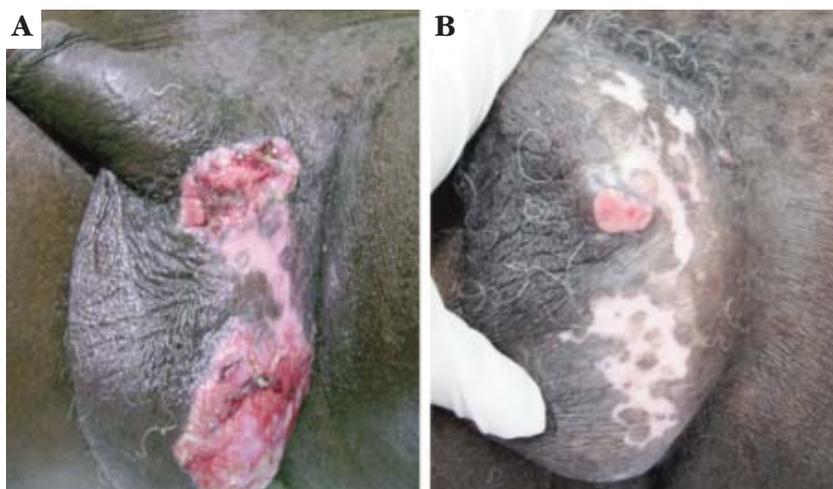


FIGURA 2: A. Lesion after surgical treatment and intravenous acyclovir; B. Lesion after use of topical imiquimod

It is important to emphasize that the two previously reported patients were already using oral acyclovir as monotherapy for a long time, with no satisfactory clinical response. According to the literature, if no clinical improvement is achieved with monotherapy with nucleoside analogues a viral resistance test to acyclovir should be performed and, if confirmed, the current medication must be changed or other adjuvant therapies should be added, like Foscarnet, 1-2% topical Cidofovir or imiquimod cream, with or without surgical resection.

As for imiquimod the knowledge of the immunopathology confirmed the mechanism by

which this medication would be able to control such conditions, considering its anti-proliferative effects and its ability to produce INF-gamma, the latter being very important on the defence against viral infections.⁵ In view of these advantages, imiquimod is considered an excellent topical adjuvant in cases of genital herpes resistant to conventional therapies.

It is important to emphasize the importance of constant diagnostic vigilance of this type of lesion, in view of the many differential diagnosis, such as squamous cell carcinoma, condyloma acuminatum, cutaneous leishmaniasis, and other contagious infection diseases.⁶ □

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How to cite this article/Como citar este artigo: Barbosa LN, Souto R, Furtado AL, Gripp AC, Daxbacher E. Association of oral acyclovir and imiquimod for the treatment of hypertrophic genital herpes simplex in HIV positive patients: report of two cases. *An Bras Dermatol*. 2011;86(5):1043-5.