Hypertrophic Herpes Simplex Infections: successful adjuvant treatment with topical imiquimod

Pichanee Chaweekulrat MD,

Charussri Leeyaphan MD.

ABSTRACT:

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DEPARTMENT OF DERMATOLOGY, FACULTY OF MEDICINE SIRIRAJ HOSPITAL, BANGKOK, THAILAND.

Genital hypertrophic herpes simplex infections, atypical presentations of herpes simplex virus infections, are commonly found in immunocompromised patients, particularly human immunodeficiency virus-infected patients, and hematologic disease patients. The first-line treatment for hypertrophic genital herpes infections is thymidine kinase-dependent antiviral drugs, such as acyclovir and valacyclovir. However, the clinical course of hypertrophic herpes is usually chronic with frequent relapses, and the disease is refractory to conventional treatment. Other medications for use with resistant herpes infections are foscarnet and imiquimod. We report a case of a male patient with human immunodeficiency virus infection who presented with a progressive hypertrophic genital herpes infection in the left scrotum, which improved after treatment with acyclovir and imiquimod.

Key words: Hypertrophic herpes simplex infection, HIV infection, imiquimod

From: Department of Dermatology, Faculty of Medicine, Siriraj Hospital Mahidol University, Bangkok, Thailand

Corresponding author: Charussri Leeyaphan MD, email: charussrilee@gmail.com

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Introduction

Herpes simplex virus (HSV) infections are common and have a worldwide distribution. HSV infections have a wide range of clinical presentations: they can be asymptomatic or present with primary or recurrent painful, grouped vesicles on an erythematous base. The infections occur mainly in the orolabial and anogenital areas. The lesions usually resolve within 2–6 weeks. In immunocompromised hosts (such as human immunodeficiency virus [HIV]-infected patients), the clinical manifestations may be atypical presentations and resistant to conventional treatment. In this study, we report a case of an HIV-infected patient with chronic hypertrophic genital herpes which was successfully treated with acyclovir and topical imiquimod.

Case history

A 48-year-old Thai male presented with a 2-month history of genital mass. The mass was painless and growing gradually, and no vesicles or pustules had developed in it. In addition, the patient had no signs of fever or other organ involvement. His underlying disease was acquired immune deficiency syndrome (AIDS), with a last CD4+ T-cell count of 187 cells/μl. He was being treated with antiretroviral combination therapy (zidovudine, tenofovir, lopinavir, and ritonavir) together with trimethoprim/sulfamethoxazole and fluconazole as primary prophylaxes for *P. jiroveci* pneumonia and fungal infection, respectively. The serology for syphilis was negative for VDRL but positive for TPHA.

Figure 1 Hypertrophic ulcerative mass at left scrotum at the time of presentation

A clinical examination revealed a well-defined erythematous ulcerative mass, 10 centimeters in diameter and covered with pus, on the left side of the scrotum (Fig. 1). There were no ulcerative lesions in other areas nor superficial lymphadenopathy. All other physical findings were normal. A Tzanck smear was positive for multinucleated giant cells. HSV antigen was also detected in the lesion. Based on the clinical examination and laboratory findings, the patient was diagnosed with hypertrophic herpes simplex infection. He was prescribed acyclovir (400 mg, three times a day) from January 2013 to March

2014, but he was then lost to follow-up for 7 months. The lesion minimally improved during the acyclovir treatment but significantly worsened after the patient was lost to follow-up. An incisional biopsy of the lesion was performed to exclude malignancy.

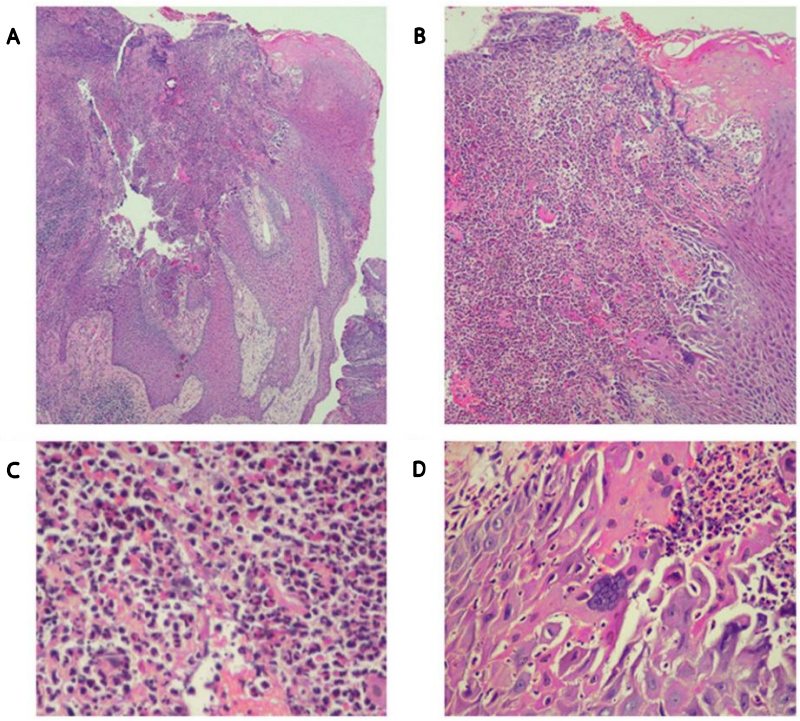

Figure 2 Histological sections of lesion.

A) Ulceration, pseudoepitheliomatous hyperplasia, and inflammatory infiltrate in epidermis and dermis (hematoxylin-eosin [HE], original magnification X10)

B) Dense inflammatory infiltration involving the entire epidermis (HE, X20)

C) Mixed cell infiltration with neutrophils, lymphocytes and plasma cells (HE, X40)

D) Multinucleated giant cells with ground glassy nuclei and marginal nuclear chromatin (HE, X40)

A histologic investigation revealed ulceration with pseudoepitheliomatous hyperplasia and a dense dermal inflammatory infiltrate composed of neutrophils, lymphocytes, plasma cells, and eosinophils (Fig. 2). Multinucleated giant cells with the cytopathic changes of an HSV infection (ground glassy nuclei and marginal nuclear chromatin) were observed (Fig. 2). There was no

vasculitis or dysplasia. An immunohistochemistry analysis showed positive staining for an HSV infection. The HSV antigen was also detected in a tissue specimen. Bacterial cultures of skin biopsy samples reported rare commensal flora, while PCR for TB complex had negative results. In view of the histologically confirmed diagnosis, topical 5% imiquimod cream was applied three times a week, and acyclovir (400 mg tablets, three times a day) were initiated. After 4 weeks of treatment, the lesion significantly reduced in size with no side effects.

Discussion

In HIV-infected patients, an HSV infection can present with varied clinical findings, ranging from a typical group of vesicles or erosions to atypical manifestations. Atypical lesions may be in the form of chronic ulcerations, verrucous plaques, a hypertrophic mass, or a pseudotumor, all of which need to be differentiated from giant condyloma acuminatum (Buschke–Löwenstein tumor), genital squamous cell carcinoma or other malignancies before a diagnosis is made. From previous studies, almost all patients who develop hypertrophic genital herpes are coinfected with HIV[1]. Additionally, hypertrophic herpes in extragenital areas, such as the eyelids and the nasal canals, have been observed[2,3]. The development of hypertrophic herpes results from dysregulation of the immune function and an abnormal cytokine response to the HSV, which stimulates the T-helper 2 immunological pattern, which enhances keratinocyte and fibroblast proliferation[4]. The atypical presentation of herpes infections may occur with other conditions associated with immunosuppression, including hematologic diseases and organ transplantations[5,6]. More severe, longer lasting, and recurring HSV infections are more frequently found in HIV-infected patients than immunocompetent individuals. A chronic herpetic ulcer lasting more than 1 month has been defined as an AIDS-defining condition if there is CD4+ count less than 200 cells/mm^3. From a previous study, a significantly longer duration has been reported for atypical lesions[1].

Depending on the treatment, hypertrophic herpes infections in HIV-infected patients are often refractory to first-line antiviral drugs. Moreover, several studies have reported refractory results with topical cidofovir and intravenous foscanet[5,7]. Imiquimod, an immune modulating agent, has become an alternative treatment for acyclovir resistant HSV. Imiquimod activates the toll-like receptor 7 (TLR-7) before stimulating production of pro-inflammatory cytokines (such as interferon-α, interleukin-12, tumor necrosis factor-α, and interferon-γ), which initiate and drive the T-helper 1 acquired immune response against virus-infected cells and provide immune memory to the HSV[8]. Many observational

studies and case series have reported favorable outcomes for the use of topical 5% imiquimod combined with antiviral drugs for the treatment of hypertrophic herpes, or as an additional treatment for acyclovir-resistant cases[1,5,7]. Imiquimod has also been reported to prevent the recurrence of HSV infections[5]. Most side effects of imiquimod are local and mild to moderate in intensity, such as erythema, excoriation, erosion or edema[9]. Severe local side effects from imiquimod that result in treatment interruption have been reported in only 2% of patients[10]. Systemic side effects rarely occur, and they include flu-like symptoms and symptoms mimicking acute meningitis; however, these improve without sequelae after drug cessation[9]. In the current case report, satisfactory outcomes without any side effects were achieved using a hypertrophic herpes treatment comprised of 5% imiquimod (three times a week) combined with oral acyclovir. The use of imiquimod is therefore considered a safe and efficacious therapy and an alternative treatment for hypertrophic herpes simplex genitalis.

In conclusion, genital hypertrophic herpes in HIV-infected patients may mimic other diseases such as giant condyloma acuminata and squamous cell carcinoma. Skin biopsy and viral antigen testing of the lesion will help to confirm diagnosis and rule out malignancy. For treatment, imiquimod is recommended for use either as an additional treatment for HSV-resistant cases or in combination with antiviral drugs to improve treatment outcomes and decrease recurrence of disease.

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