Chronic Genital Ulceration due to Herpes Simplex Infection Treated Successfully with Imiquimod

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Sir,

Genital herpes in immunocompromised patients can present as large, chronic, painful and disabling ulcerations, the infection is well-described but often overlooked. Treatment with acyclovir is not always effective. The lack of effect of this drug, especially in HIV-infected patients, is partly due to a growing number of acyclovir-resistant herpes simplex virus (HSV) strains isolated from such ulcers (1). However, even without acyclovir-resistant HSV strains, treatment can be difficult and new treatment modalities are therefore required.

Imiquimod is a novel synthetic molecule with potent immune-stimulatory activities. It is a well-documented and approved treatment for external genital and perianal warts caused by human papilloma virus, but its effect on herpes simplex infection is still debated (2).

A few clinical observations have reported dramatic responses to clinical signs and symptoms in patients with chronic ulcers after treatment with imiquimod (3–5).

We report here the successful treatment with imiquimod of a severe, long-standing genital ulcer in a patient with chronic lymphatic leukaemia.

CASE REPORT

A 79-year-old woman with chronic lymphatic leukaemia presented with a 7-month history of persistent, non-healing vulvar ulceration (Fig. 1a). During the 7 months the patient was seen by several doctors and various treatment regimens had been tried. She had been treated with topical clotrason (Clotrason, Schering-plough, Brussels, Belgium) and Ag-sulfadiazine and systemic fluconazole, metronidazole and diclocil (Dicillin, Sandoz, Odense, Denmark), all without effect. Due to the large ulceration, malignancy was suspected and several skin biopsies were taken. All biopsies were free from dysplasia, but positive for HSV type 2. The patient was treated with acyclovir 200 mg 5 times daily for 5 days, combined with topical acyclovir without effect. The herpes infection was considered secondary to the ulceration and the patient was referred to the dermatology clinic with suspected pyoderma gangrenosum.

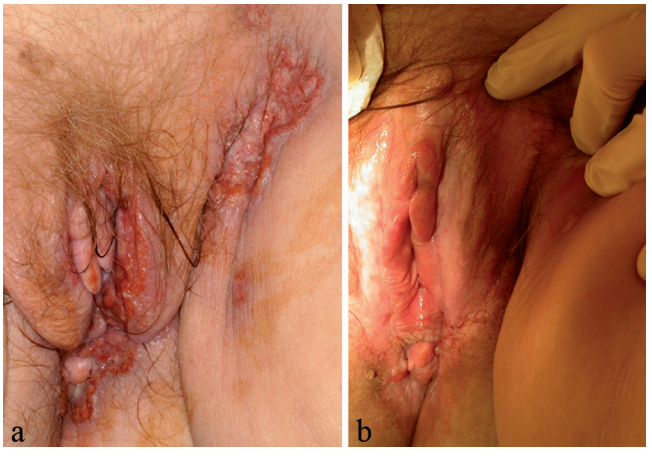

Fig. 1. Erosions (a) before and (b) 14 weeks after treatment with imiquimod.

The patient had a medical history of chronic lymphatic leukaemia since 1983, treated intermittently with chlorambucil and prednisolone. At the time of ulcer presentation her blood count was normal except for a slight anaemia. Because of this and secondary symptoms she was treated with chlorambucil 6 mg daily and allopurinol 300 mg daily.

The lesion was diagnosed as a chronic HSV infection. A long-term treatment with acyclovir and later famciclovir 500 mg 3 times daily was initiated. Acyclovir was first given per orally and later as an infusion. After 2 months of antiviral therapy there were no signs of improvement. The patient was still HSV-2 positive. *In vitro* testing of the HSV-2 strain demonstrated no resistance towards acyclovir.

Treatment with topical imiquimod 5% (Aldara, Meda, Sweden) was started, initially 3 times a week, then, when no adverse effects were noted, once daily. A low dose of acyclovir therapy was maintained. Following 4 weeks of treatment, the lesion had improved significantly, and after 14 weeks the ulcer had resolved completely (Fig. 1b).

DISCUSSION

In this case of an elderly woman with genital ulcerations, the diagnosis of HSV was not considered until rather late. When biopsy verified a HSV infection, it was considered to be secondary to the ulceration and therefore not paid much attention. The lack of improvement on acyclovir treatment reinforced this approach.

It is important to recognize HSV as a primary source of genital ulcerations, especially in immunocompromised individuals.

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When recognized, chronic HSV infection in the immunocompromised patient often poses a significant clinical problem. Treatment with acyclovir is not always effective and new treatment modalities are required.

Imiquimod is a novel synthetic molecule with potent immune-stimulatory activities. The molecule does not show any direct antiviral activity, but acts by inducing cytokine and chemokine secretion from monocytes/macrophages. The release of these cytokines and chemokines, including interferon-alpha, interleukin-12 and tumour necrosis factor-alpha leads to inhibition of viral replication and stimulation of local cell-mediated immunity. Imiquimod also stimulates natural killer cells and indirectly stimulates Th-1 cells to release interferon-gamma which plays a role in cytotoxic T-cell killing of viral infected cells (6).

Topical application of imiquimod has been shown to have an effect on genital HSV infection in a guinea pig model (7). Imiquimod treatment reduced virus shedding, virus in the spinal cord and primary genital lesions (7). In the guinea pig model imiquimod was unable to modify lesion development if treatment began after the appearance of the lesion 96 h after inoculation, unless combined with acyclovir treatment (8). Prolonged effect post-treatment is seen in guinea pig models and is thought to be due to the increased cellular immunity to HSV antigens and HSV-infected cells (9). However, in a randomized, double-blind, placebo-controlled study in humans topically applied imiquimod did not show any effect on recurrent herpes genitalis (2).

The effect of imiquimod in chronic HSV infection in the immunocompromised patient has been documented in only a few clinical cases (3–5). Our case report supports the results of these cases and demonstrates that treatment with imiquimod is effective in inducing remission of genital ulcers in patients with chronic HSV infection.

In this case no acyclovir-resistant strains were found, yet the ulcer resisted oral as well as parenteral long-term treatment with acyclovir. Imiquimod treatment once daily, combined with acyclovir treatment resulted in complete remission in 14 weeks.

In the clinical reports of imiquimod treatment for genital HSV published so far different treatment regimes have been used. Gilbert et al. (3) report on a 34-year-old, HIV-positive man with a genital HSV-2 infection. Treatment with imiquimod 5% 3 times weekly for just one week was enough to cause re-epithelialization of the erosion. Danielsen et al. (4) reported on a 28-year-old HIV-positive man with a large penile HSV erosion. The same treatment regime was used. Imiquimod 3 times weekly combined with antiviral therapy, but 10 weeks was required to heal the erosion. Martinez et al. (5) treated their young HIV and HSV-2 positive patient in the same way with good result after 4 weeks treatment. In our case, however, we increased the treatment from 3 times a week to every day after a few weeks due to slow improvement and no side-effects.

This case emphasizes the importance of recognizing HSV as the primary cause of genital ulcerations in the immunocompromised patient, and it provides evidence of the effect of imiquimod on such ulcerations.

Further clinical studies are required before final conclusions can be drawn regarding the best treatment regime and the efficacy of the treatment.

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