Published in final edited form as:

Infection. 2017 October ; 45(5): 705–707. doi:10.1007/s15010-017-1027-y.

Surgical excision for recurrent herpes simplex virus 2 (HSV-2) anogenital infection in a patient with human immunodeficiency virus (HIV)

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Abstract

Recurrent anogenital herpes simplex virus infections are common in patients with human immunodeficiency virus (HIV), of whom approximately 5% develop resistance to acyclovir. We present a case of a 49-year-old man with HIV who had an 8-year history of recurrent left inguinal herpes simplex virus type 2 ulcerations. He initially responded to oral acyclovir, but developed resistance to acyclovir and eventually foscarnet. The lesion progressed to a large hypertrophic mass that required surgical excision, which led to resolution without recurrences. Our case highlights the importance of surgical excision as a treatment option in refractory herpes simplex virus anogenital infections.

Keywords

Herpes simplex infection; HSV-1; HSV-2; Recurrent herpes simplex infection; Hypertrophic HSV herpes simplex vegetans

Introduction

Herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) infections are common in patients with human immunodeficiency virus (HIV). In the United States, approximately 95% of people with HIV are seropositive for either HSV-1 or HSV-2, while 70% are seropositive for HSV-2 [1]. HSV-2 is responsible for majority of genital herpes infections. Mild cases are treated with oral acyclovir, valacyclovir, or famciclovir. Intravenous acyclovir is recommended for severe disease until improvement of symptoms occurs, at which point oral therapy can be used. Acyclovir-resistant HSV strains are commonly seen in HIV-positive patients and the preferred treatment of choice is intravenous foscarnet [2]. Surgical excision has rarely been employed in the management of HSV infections.

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Conflict of interest The authors declare that there are no conflicts of interest.

Case report

A 49-year-old man was admitted with a recurrent painful ulcerative left inguinal lesion. He had a history of acquired immune deficiency syndrome that was diagnosed 14 years prior with a nadir CD4 count of 21 (1.9%) and HIV viral load of 196,710 copies/ml (CDC Stage 3 disease) [+ 3]. His initial antiretroviral therapy comprised of lamivudine, zidovudine, lopinavir, and ritonavir; which he took intermittently prior to transitioning to atazanavir, ritonavir, emtricitabine, and tenofovir disoproxil fumarate. He was also diagnosed with syphilis, for which he was treated. Eight years ago, he was diagnosed with ulcerative herpes simplex virus infection of the left groin. The lesion initially resolved with oral acyclovir. Due to multiple recurrences, he was transitioned to oral valacyclovir without significant response. Two years later, a skin biopsy of the ulcerative lesion was done. HSV-2 was detected by immunofluorescence. Further testing confirmed that the strain was sensitive to acyclovir. Resolution occurred after a 14-day treatment with intravenous acyclovir. He was subsequently transitioned to oral valacyclovir.

Over the next few years, he had multiple recurrences despite suppressive therapy, with varied responses to intravenous acyclovir. Resistance to acyclovir eventually occurred. There was initial clinical improvement noted with intravenous foscarnet. However, 10 months later, the lesion progressed in size to an approximately 5-cm erythematous, ulcerated nodule with prominent granulation tissue. Skin biopsy revealed epidermal ulceration with focal viral changes most consistent with herpes simplex virus infection. Drug sensitivity testing confirmed resistance to foscarnet, while acyclovir sensitivity was noted. Despite a 6-week course of intravenous acyclovir, the lesion progressed to a large hypertrophic papillomatous mass with significant erosions (Fig. 1a). Due to concerns for malignant transformation, a shave biopsy and tissue cultures were done. There was no evidence of malignancy on histopathology. Herpes simplex virus staining and cultures were positive. Intravenous acyclovir was continued for another 6 weeks with minimal improvement (Fig. 1b).

A positron emission tomography scan demonstrated 2-deoxy-2-[18F] fluoro-D-glucose uptake in the left groin, left pelvic and left inguinal lymph nodes. He was admitted and taken to the operating room for wide local excision of the ulcer and excisional biopsy of a left inguinal lymph node. Microscopic evaluation revealed multiple superficial ulcerations with viral cytopathic effect and abundant polytypic plasma cells within the dermis. Herpes simplex virus positivity was noted by immunohistochemistry (Fig. 2). Neither the skin nor lymph node showed evidence of malignancy. He was discharged on oral valacyclovir.

The patient did well after surgery. Four months later, the wound had completely healed (Fig. 3). Oral valacyclovir was continued for preventive therapy and HIV-RNA suppression has been achieved on abacavir, lamivudine, dolutegravir, darunavir, and cobicistat. There have been no recurrences of the left inguinal ulcer.

Discussion

Anogenital herpes simplex infections are most often caused by HSV-2. There are important interactions between HIV and HSV-2. Mucosal shedding of HSV-2 occurs at a higher rate in

patients co-infected with HIV and HSV-2 compared to HIV-uninfected patients. As a result, HIV-positive patients experience more frequent and severe anogenital HSV infections [4]. Furthermore, HSV-2 infection has been shown to be associated with a three-fold risk of HIV acquisition [5]. Acyclovir is the first line treatment for HSV infections. Acyclovir-resistant strains have been documented in 5% of HIV-positive patients [6]. When this occurs, resolution typically occurs with intravenous foscarnet. Intravenous and intralesional cidofovir have also been used successfully to treat resistant strains [7, 8].

A subset of immunocompromised patients, particularly those with HIV, do not respond to therapy and progress to chronic severe anogenital HSV-2 infections. The majority of these patients have CD4+ counts lower than 500 cells/mm³ and atypical presentations including herpes simplex vegetans and hypertrophic pseudo-tumors mimicking malignancies [9–12].

The role of surgery in the management of chronic severe herpes simplex infections was first documented in the 1970s, when there were no effective medical treatments for HSV. The rationale behind surgery was that epidermal denervation prevented the re-entry of the virus from the sensory neurons into the epidermis and thereby prevented recurrences. While the procedure was effective at preventing recurrences at the surgical site, new lesions erupted at adjacent sites [13]. With the discovery of acyclovir in 1974 and its clinical availability in 1982, surgical treatment became less desirable [14].

Despite the availability of highly effective antivirals, surgical management is sometimes necessary. Cury et al. described a case of a patient with hypertrophic anal and tonsillar herpetic lesions who failed valacyclovir, cidofovir, and thalidomide and eventually required surgical excision [11]. In their case report and literature review, Simonsen et al. found that surgical excision and prophylactic acyclovir or valacyclovir were an effective treatment strategy to ensure resolution and prevent recurrences in patients with chronic severe anogenital herpes simplex infections [12].

Our patient failed medical management of his chronic left inguinal ulcer, which progressed to a large hypertrophic mass that was concerning for malignancy. A combination of surgical excision and prophylactic valacyclovir resulted in complete resolution with no further recurrences.

In conclusion, surgical excision should be considered in immunocompromised patients with a history of chronic severe anogenital herpes simplex infections who fail to respond to antiviral therapy.

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Fig. 1.
a Progression to a hypertrophic mass despite 6 weeks of intravenous acyclovir. **b** Minimal improvement after an additional 6 weeks of intravenous acyclovir

Fig. 2.

Microscopic images of the inguinal lesions. **a** The epidermis demonstrates extensive reactive changes adjacent to the area of ulceration, including abundant acute (neutrophils) and chronic (plasma cells) inflammation. Many of the epidermal cells show extensive viral cytopathic effect (indicated by *arrows*), including nucleomegaly, multinucleation, and viral inclusions (H & E stain, 400 magnification). **b** In situ hybridization (ISH) shows positive staining for HSV-2 $\times$ (*brown*, cytoplasmic, granular staining) in the abnormal keratinocytes (HSV-2 ISH, $\times 1000$ magnification)

Fig. 3.
Complete resolution 4 months after surgery. Scar at the previous site of the mass (indicated by *asterisk*)