Treatment of acyclovir-resistant herpes simplex virus with intralesional cidofovir

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Key words: cidofovir; general dermatology; herpes simplex virus; infectious disease; intralesional.

INTRODUCTION

The prevalence of acyclovir-resistant herpes simplex virus (HSV) is a considerable burden in the HIV-infected population. Impaired cell-mediated immunity slows the normal clearing of HSV, allowing increased viral replication and more extensive ulcerating lesions to develop.[1] Prolonged and inconsistent use of antiviral therapy may lead to the selection of drug-resistant strains that are less responsive to standard therapies and result in more painful, disfiguring chronic lesions.[1,2] The presence of renal disease in some patients limits the use of intravenous non-guanosine-analog medications, such as foscarnet and cidofovir, given the risk of renal toxicity.[2] This case report describes the successful use of intralesional (IL) cidofovir injections for genital HSV in an HIV-infected individual with a history of end-stage renal disease (ESRD).

Abbreviations used:

ESRD:	end-stage renal disease
HSV:	herpes simplex virus
IL:	intralesional
TK:	thymidine kinase

CASE REPORT

A 69-year-old man with a past medical history of ESRD on hemodialysis and AIDS with intermittent adherence to antiretroviral therapy presented with condyloma and squamous cell carcinoma in situ of the scrotum and urethral meatus. Treatment with topical imiquimod 5% cream was initiated. The patient had an extensive history of recurrent genital and ocular HSV, for which 0.5 to 1 g daily valacyclovir for suppressive therapy had previously been prescribed but not consistently taken as per prescription refill records. The patient had responded well to imiquimod; however, at a follow-up visit 5 months after initial presentation, examination revealed an exquisitely painful 3.5 × 4.0 cm verrucous hyperkeratotic ulcerative plaque on the dorsal prepuce of the penis (Fig 1). This ulcer presented as a chronic, nonhealing lesion, although it was uncertain for how long it had been present. A biopsy revealed pseudoepitheliomatous hyperplasia with focal viral cytopathic effect consistent with verrucous HSV (Fig 2). Due to the suspicion of acyclovir

Fig 1. Verrucous herpes simplex virus (HSV) infection. A 3.5 cm × 4.0 cm ulcerative plaque on the dorsal prepuce of the penis.

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Funding sources: None.
IRB approval status: Not applicable.
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JAAD Case Reports 2021;13:86-9.
2352-5126

https://doi.org/10.1016/j.jdcr.2021.05.001

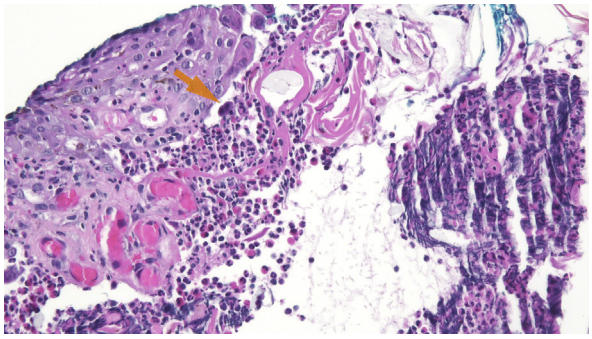

Fig 2. Biopsy of the penile ulcer demonstrated pseudoepitheliomatous hyperplasia with focal viral cytopathic effect (*orange arrow*) consistent with verrucous herpes viral infection. (Hematoxylin-eosin stain; original magnification ×20).

resistance given the history of poor adherence to antiviral therapy and the patient's absolute CD4 count being 9 cells/mm, viral culture and susceptibility testing was obtained. Viral culture of the ulcerated plaque revealed acyclovir-resistant, foscarnet-sensitive HSV.

Imiquimod was discontinued and intralesional cidofovir therapy was initiated. Pharmacy compounded cidofovir 15 mg/mL, the concentration published by Castelo-Soccio et al,[3] prior to each dose administration. The patient received 2 mL of the compounded cidofovir via intralesional (IL) injection for a total of 2 treatment sessions, which were 2 weeks apart. Lidocaine 5% ointment was applied 30 minutes prior to the procedure for pain control. On the first day of treatment, new ulcerated plaques on the left inguinal crease and right medial thigh were also identified and treated with IL cidofovir. Viral culture and susceptibility testing of these new lesions demonstrated acyclovir-sensitive HSV. The patient experienced significant improvement in both pain and size of all lesions within 1 week of the first injection (Fig 3) and near resolution within 2 weeks after the second injection (Fig 4). On day 28, there was complete resolution without any evidence of recurrence, which remained true at follow-up 7 months later. The patient did not experience any renal side effects or adverse events during or after treatment. Daily valacyclovir suppression therapy was discontinued due to the risk of future development of HSV resistance, as the patient continued to lack adherence to daily therapy.

DISCUSSION

Guanosine analogs including acyclovir, valacyclovir, and famciclovir require phosphorylation by HSV-thymidine kinase (TK) to function in viral chain termination during viral replication.[2] Strains of HSV

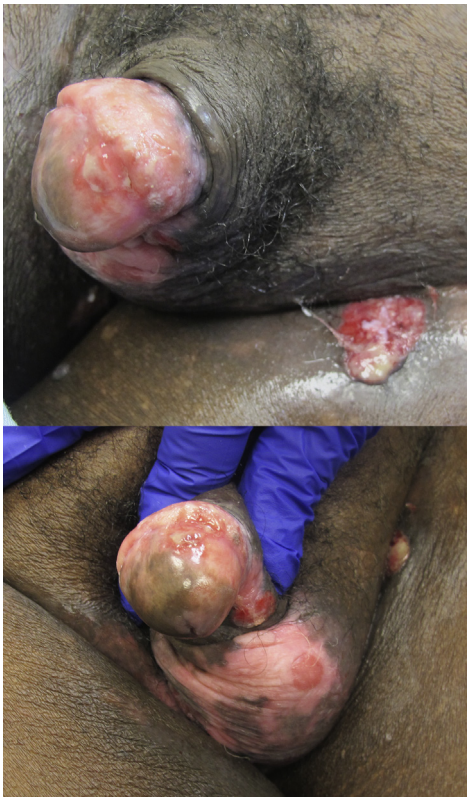

Fig 3. The penile lesion showed marked improvement in size 14 days after first intralesional cidofovir injection.

acquire resistance by eliminating TK, decreasing TK activity, or altering DNA polymerase affinity.[1,2] Decreased cell-mediated immunity permits the survival of these resistant strains.[1]

The prevalence of acyclovir-resistant HSV strains in immunocompromised patients ranges from 4.1%-7.1% versus 0.1%-0.7% in immunocompetent patients.[1] Unlike in immunocompetent hosts, whose cell-mediated immunity typically clears an HSV infection within 4-5 days,[1] the impaired host cell-mediated immune response delays the normal clearance of HSV, which permits increased viral replication, leading to more severe and chronic lesions. Our patient presented with a low CD4 count of 9 cells/mm^3 and intermittent use of antiviral therapy, which led to the disfiguring, painful, drug-resistant ulcers. The combination of acyclovir-sensitive and acyclovir-resistant strains suggested the relevance of continued use of acyclovir or valacyclovir for suppressive therapy. Nevertheless, in patients in whom adherence is not reliable, the risk of developing further resistance would typically outweigh the benefit of intermittent suppressive therapy.

Foscarnet and cidofovir are intravenous antiviral medications that do not require viral TK, making them the treatment of choice in acyclovir-resistant

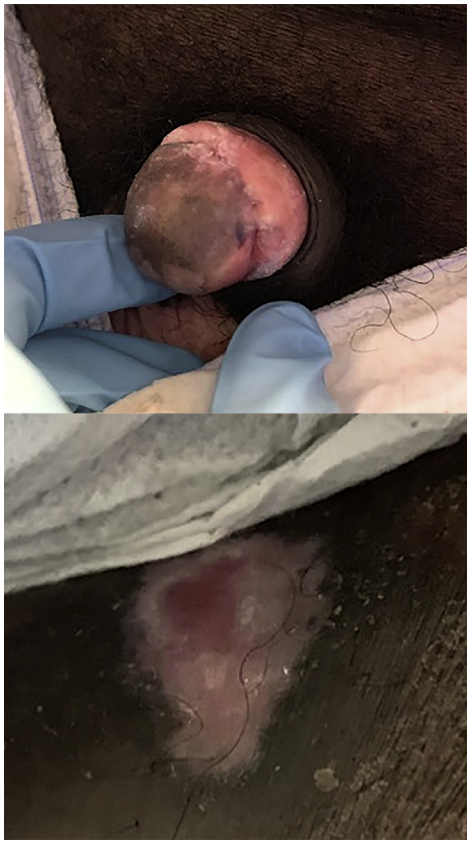

Fig 4. The penile and inguinal lesions showed complete resolution 28 days after first intralesional cidofovir injection.

HSV.[2] Their nephrotoxic side effects,[2] however, limit their use in patients with ESRD. Topical formulations of cidofovir for the treatment of acyclovir-resistant HSV in immunocompromised patients has been reported with varying success.[4,5] A report of 2 patients with vulvar and perianal herpes treated with cidofovir gel showed no improvement, along with intolerable irritation from the gel.[6] In another case, topical cidofovir induced acute kidney injury in 2 immunocompromised patients with multidrug resistant HSV.[7] Lastly, in a case of refractory genital HSV, topical cidofovir demonstrated success, but was used as an adjunct to systemic foscarnet, thus making its utility as monotherapy unclear.[8] Our patient's history of ESRD and unreliable adherence to treatment regimens made topical cidofovir an inappropriate option.

We found 3 cases of IL cidofovir in the successful treatment of guanosine-analog resistant HSV.[3,9,10] All cases obtained successful treatment, and, importantly, no nephrotoxicity was observed. Given the small sample of patients, however, close monitoring of renal function is recommended. The IL administration of cidofovir avoids reliance upon the patient for adherence, resulting in greater therapeutic success and avoidance of drug resistance. IL cidofovir can be painful; thus we used topical 5% lidocaine applied 30 min prior to injection with acceptable tolerance. Local regional lidocaine blocks, such as a penile ring block, have also been reported with success.[9]

Acyclovir-resistant HSV is significantly more prevalent in immunocompromised, specifically HIV-infected, patient populations. Aggressive treatment is often necessary given the increased severity of their lesions. Intravenous foscarnet and cidofovir are alternatives to guanosine-analog medications but should be avoided in patients with kidney disease. In this case of a patient with AIDS and ESRD, the marked improvement and resolution of HSV lesions with no adverse effects following IL cidofovir administration support it as a promising therapy for the treatment of acyclovir-resistant HSV lesions.

Conflicts of interest

None disclosed.

REFERENCES

1. Levin MJ, Bacon TH, Leary JJ. Resistance of herpes simplex virus infections to nucleoside analogues in HIV-infected patients. *Clin Infect Dis*. 2004;39(Suppl 5):S248-S257.
2. Kimberlin DW, Whitley RJ. Antiviral therapy of HSV-1 and -2. In: Arvin A, Campadelli-Fiume G, Mocarski E, et al., eds. *Human Herpesviruses: Biology, Therapy, and Immunoprophylaxis*. Cambridge: Cambridge University Press; 2007. Chapter 64. https://www.ncbi.nlm.nih.gov/books/NBK47444/
3. Castelo-Soccio L, Bernardin R, Stern J, Goldstein SA, Kovarik C. Successful treatment of acyclovir-resistant herpes simplex virus with intralesional cidofovir. *Arch Dermatol*. 2010;146(2):124-126.
4. Muluneh B, Dean A, Armistead P, Khan T. Successful clearance of cutaneous acyclovir-resistant, foscarnet-refractory herpes virus lesions with topical cidofovir in an allogeneic hematopoietic stem cell transplant patient. *J Oncol Pharm Pract*. 2013;19(2):181-185.
5. Lateef F, Don PC, Kaufmann M, White SM, Weinberg JM. Treatment of acyclovir-resistant, foscarnet-unresponsive HSV infection with topical cidofovir in a child with AIDS. *Arch Dermatol*. 1998;134(9):1169-1170.
6. Toutous-Trellu L, Hirschel B, Piguet V, Schiffer V, Saurat JH, Pechère M. Treatment of cutaneous human papilloma virus, poxvirus and herpes simplex virus infections with topical cidofovir in HIV positive patients [Article in French]. *Ann Dermatol Venereol*. 2004;131(5):445-449.
7. Saunders IM, Lahoti A, Chemaly RF, Trevino C, Westmoreland M, Hosing C. Topical cidofovir-induced acute kidney injury in two severely immunocompromised patients with refractory multidrug-resistant herpes simplex virus infections. *J Oncol Pharm Pract*. 2016;22(2):325-331.
8. Usoro A, Batts A, Sarria JC. Intravenous foscarnet with topical cidofovir for chronic refractory genital herpes in a patient with AIDS. *J Investig Med High Impact Case Rep*. 2015;3(4):2324709615621095.

9. Wanat KA, Gormley RH, Rosenbach M, Kovarik CL. Intralesional cidofovir for treating extensive genital verrucous herpes simplex virus infection. *JAMA Dermatol*. 2013;149(7):881-883.

10. Saling C, Slim J, Szabela ME. A case of an atypical resistant granulomatous HSV-1 and HSV-2 ulceration in an AIDS patient treated with intralesional cidofovir. *SAGE Open Med Case Rep*. 2019;7:2050313X19847029.