SAGE Open Medical Case Reports
Volume 7: 1–4

DOI: 10.1177/2050313X19847029
journals.sagepub.com/home/sco
SAGE

A case of an atypical resistant granulomatous HSV-1 and HSV-2 ulceration in an AIDS patient treated with intralesional cidofovir

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Abstract

We report a case of a granulomatous skin lesion in an AIDS patient whereby biopsy revealed both HSV-1 and HSV-2. This lesion was resistant to acyclovir and successfully treated with intralesional cidofovir without recurrence to date. This is the only known reported case of a granulomatous skin lesion in an HIV patient, whereby both HSV-1 and HSV-2 were isolated.

Keywords

Infectious diseases, dermatology, atypical HSV, exophytic HSV, HIV

Date received: 1 February 2019; accepted: 8 April 2019

Introduction

HSV types 1 and 2 are extremely prevalent worldwide. New studies compiling global prevalence data on this topic estimate that in 2012, there were as many as 3,709,000,000 individuals aged 0–49 years infected with HSV-1 and 417,000,000 individuals aged 15–49 years infected with HSV-2.[1,2] The classic dermatological presentation for HSV is recurrent clusters of small, often painful vesicular lesions that break and ulcerate.[1–4] HSV-1 more commonly affects the mucocutaneous regions around the mouth, while HSV-2 typically causes genital ulcers.[3] Further deviations from this typical presentation have been observed in immunocompromised patients, specifically those infected with HIV.[4] Research has already established a link between HSV-2 and HIV infection, claiming that HSV-2 infection increases the risk of acquiring HIV by three times, increases viral shedding of HIV in those already infected and may also augment HIV disease progression.[2] In turn, HIV increases HSV-2 viral load.[2] This positive reinforcement between HSV and HIV is a possible explanation for the higher incidence of atypical herpetic cutaneous lesions within the HSV-HIV co-infected patient population.

We report a case of an exophytic granulomatous hand lesion in an AIDS patient, whereby biopsy confirmed the presence of both HSV-1 and HSV-2. The lesion was resistant to acyclovir. The patient was treated successfully with intralesional cidofovir. This is the only known reported case of a granulomatous skin lesion in an HIV patient, whereby both HSV-1 and HSV-2 were isolated.

Case

A 51-year-old African American woman with past medical history significant for AIDS and herpetic whitlow of the right third finger with underlying osteomyelitis of the distal phalange, which was successfully treated in February 2001, presented to outpatient clinic for complaints of a progressively worsening painful right hand ulceration for 1 month duration. The lesion began as small and callous-like and increased in both diameter and induration. Two weeks prior, the patient received a 10-day course of amoxicillin–clavulanic acid with no improvement.

Physical exam revealed a tender, raised, hypertrophic lesion approximately 2.5 cm in diameter on the palmar aspect of the right hand. Figure 1 shows the lesion at presentation to

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Figure 1. Exophytic herpetic lesion of the right hand.

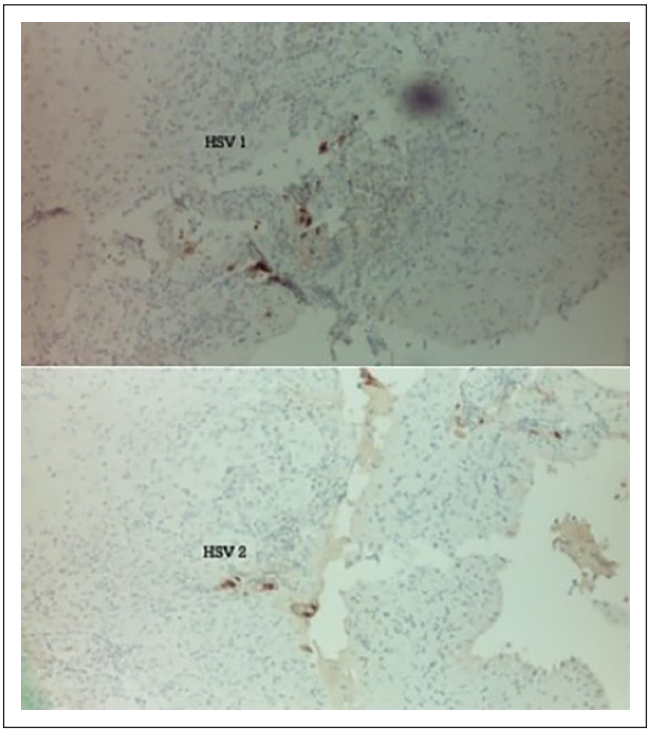

Figure 2. Pathology stain with immunoperoxidase analysis isolating both HSV-1 and HSV-2.

the clinic. Labs were significant for a $CD4^+$ count of 184, a $CD4^+/CD8^+$ ratio of 0.17, and an HIV viral load <20 copies/mL. The patient was started on valacyclovir 1 g three times daily. After 2 weeks of no improvement, a biopsy of the lesion was taken. Biopsy of the lesion with immunoperoxidase analysis confirmed HSV-1 and HSV-2. Pathology stains of the lesion showing HSV-1 and HSV-2 granulomatous formation are shown in Figure 2.

Therapy was switched to famciclovir 500 mg thrice daily plus imiquimod topical cream. The patient received 2 months of treatment with only mild improvement. She was then given three rounds of cidofovir intralesional injections. Cidofovir was dosed at 12.5 mg/cc. The initial injection was 25 mg (2 cc). 10 days later, the patient received a second injection of 50 mg (4 cc). A final cidofovir dose of 50 mg (4 cc) was given 1 month after the second dose. The ulceration completely resolved over a 6-week period from the final dose. The patient has been followed in the HIV clinic for 3 years since treatment and there has been no recurrence of the lesion.

Discussion

The documented atypical herpetic dermatological manifestations found within the literature are mostly hypertrophic and exophytic in nature.[4–8] Leeyaphan et al.[4] performed a retrospective observational study on the clinical characteristics of hypertrophic herpes simplex genitalis and found that hypertrophic lesions were only observed in HIV-positive patients. Furthermore, these findings were independent of $CD4^+$ count, which lead them to conclude that HIV infection itself may be the mechanism behind exophytic HSV.[4] A case study by Garib et al.[8] also documented exophytic lesions in immunocompromised patients. Upon biopsy of these lesions, HSV-2 and CMV were isolated together.[8]

It has been suggested that HSV-1 may be a contributing factor towards pyogenic granuloma formation.[9] In their case study, El Hayderi et al.[9] were able to detect HSV-1 in normal epithelium that surrounded pyogenic granuloma endothelium. Although the endothelial cells contained no HSV-1, both cell types stained positive for vascular endothelial growth factor (VEGF).[9] The pyogenic granuloma cleared after 2 weeks of treatment with oral valacyclovir, leading to the conclusion that HSV-1 may indirectly cause angiogenesis and pyogenic granuloma formation by up-regulating VEGF.[9]

Another proposed mechanism behind the formation of atypical hypertrophic herpetic lesions is HSV infiltration of epidermal CD4 and dendritic cells, resulting in a T-helper 2 response that activates tumour necrosis factor (TNF)-alpha and interleukin production.[5,10] This then signals fibroblast proliferation and collagen formation.[5,10] Many of these atypical lesions are also resistant to acyclovir.[4–8,10] Treatment with imiquimod cream has been shown to have good results

in these resistant cases of exophytic HSV, most likely due to its ability to stimulate T-helper 1 response and interferon production.[4,5,10] Due to an immunological induced response rather than direct anti-viral action, there is no chance for viral resistance against imiquimod.[4] Although there is documentation of hypertrophic HSV within the clinical setting, literature that contains evidence of actual granulomatous skin reaction from HSV infection is extremely scant. Nikkels et al.[11] did document one case of a granulomatous skin formation in an immunocompromised patient with HSV-1-positive antigens within the reticular dermis. Because no viral nucleic acids were isolated, they argued that viral envelope glycoproteins may induce granuloma formation following HSV skin infection.[11]

Castelo-Soccio et al.[12] reported the first use of intralesional cidofovir with concomitant intravenous cidofovir in the treatment of an exophytic herpetic nasal ulceration resistant to acyclovir in an HIV patient. Initially, the patient showed almost complete resolution of the lesion with intravenous (IV) cidofovir alone with 6 weeks of treatment.[12] However, due to rapid recurrence when stopping treatment and minimal response when restarting IV cidofovir, intralesional cidofovir was added to the regimen.[12] After 6 months of combined treatment (with only a brief 6-week interruption of intralesional injections) and then a three-time monthly dose of intralesional cidofovir alone, the herpetic lesion had resolved with no documented recurrence.[12] Sanchez et al.[13] also described dramatic improvement with three injections of intralesional cidofovir in a hypertrophic HSV-2 penile lesion in a person with HIV, but treatment had to be changed to the topical formulation due to poor toleration by the patient.

Literature documenting dual HSV-1 and HSV-2 isolation from a cutaneous lesion is practically non-existent. Perkins et al.[14] did report an HSV-1 and HSV-2 co-infected genital lesion confirmed via polymerase chain reaction (PCR) in a pregnant woman. However, this patient was HIV negative and was treated with acyclovir.[14] Furthermore, this lesion was not hypertrophic.[14] To our knowledge, there has been no reported case of an atypical exophytic herpetic cutaneous lesion where HSV-1 and HSV-2 were both isolated.

Conclusion

The documented atypical herpetic dermatological manifestations found within the literature are mostly hypertrophic in nature. Virtually all of these lesions are only observed in HIV-positive patients and seem to be independent of $CD4^+$ count. Many of these hypertrophic HSV lesions are resistant to acyclovir. However, literature describing the use of intralesional cidofovir in the treatment of these resistant atypical HSV lesions remains limited. This is the only known reported case of a granulomatous skin lesion in an HIV patient, whereby both HSV-1 and HSV-2 were isolated. A regimen consisting of an initial cidofovir intralesional injection of 25 mg followed by a 50 mg dose at 10 days and at 6 weeks resulted in complete resolution of the lesion. This response confirms the findings from the other few case reports on the subject that intralesional cidofovir is a viable option for resistant exophytic herpetic cutaneous lesions in the HIV-positive patient population. However, further studies examining the efficacy of intralesional cidofovir use in resistant hypertrophic HSV need to be conducted in order to formulate guidelines for ideal dosing and treatment duration in this setting.

Acknowledgements

The authors would like to thank Dr Eliezer Seguerra, Chief of Pathology at Saint Michael's Medical Centre, for providing figures for this manuscript.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Informed consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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