

# Acyclovir Resistant Anogenital Herpes Simplex in an HIV patient with Pseudoepitheliomatous Hyperplasia Resembling Squamous Cell Carcinoma

Jean Elizze Charles DO<sup>1</sup>, Stephen E. Weis DO<sup>1</sup>, Gregory A. Hosler MD, PhD<sup>2</sup>

1. Dermatology Residency, Medical City Weatherford, Weatherford, TX  
2. ProPath, Medical City Weatherford, Dallas, TX

## Introduction

Herpes simplex virus (HSV) infections are common. Among immunocompetent patients, HSV infections are controlled by the host's immune system and are commonly intermittent, self-limiting, and do not require antiviral therapy. While HSV usually causes mild infections in immunocompetent host, in the immunocompromised person, the virus reactivates frequently and might continue to replicate, forming large, slowly expanding, long-lasting ulcerative lesions. HSV lesions that persist longer than one month, particularly atypical presentations in unusual locations, are considered one of the AIDS defining illnesses. HSV infection is one of the most common opportunistic infections in the immunocompromised and can be seen in over 90% of HIV patients in countries where HIV is endemic.

The most commonly used anti-viral medication for prevention and treatment of HSV infections is acyclovir. Since its introduction in 1983, widespread use of acyclovir has led to the emergence of acyclovir-resistant HSV. While rare in immunocompetent patients (0-0.6% prevalence of resistance to acyclovir), it has increased prevalence in immunocompromised patients, varying from 3.5% to 7% in HIV-positive patients to 2.5-10% in solid organ transplant patients. The highest prevalence rates are seen in hematopoietic stem cells recipients ranging from 4.1 to 10.9%. The emergence of acyclovir-resistance poses difficulty in treatment and prevention, especially in cases of chronic HSV infection in HIV patients.

In this case report, we present a HIV patient's chronic skin lesions secondary to HSV that were acyclovir-resistant. Our patient presented with slowly enlarging ulcerated hyperplastic lesions that histopathologically revealed pseudoepitheliomatous hyperplasia (PEH). As we discuss this case report, we wanted to highlight how atypical presentations of HSV in immunocompromised patients with histopathological findings of PEH can be mistaken for other malignancies. We also wanted to see if there was a correlation with PEH and acyclovir resistance.

## Case Report

Patient is a 59-year-old African American female who presented in 2013 with complaints of vaginal discharge and erosions for several months associated with severe pain and itching that interfered with sleep. Patient has a complicated history, which includes diagnosis of HIV in 1990, history of substance abuse, and high-risk cervical human papillomavirus (HPV). Patient had recently resumed her antiretroviral therapy and her CD4 count had increased to 300 cells/mm<sup>3</sup> from 43 cells/mm<sup>3</sup>.

Patient had multiple exophytic ulcerations with serpinginous borders of varying sizes in the perianal region (Figure 1). Patient also had two large vulvar ulcers (Figure 2).



Figure 1



Figure 2

In 2016, patient's erosions and vulvodinia continued to persist despite increasing valacyclovir 1 gram from two times daily to three times daily. Specimens were again collected and revealed lesions to be acyclovir resistant. Biopsies were taken to rule out malignancy due to recalcitrant nature of patient's HSV lesions.

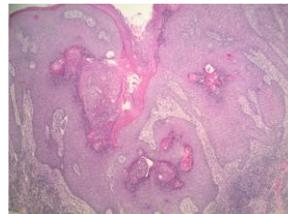


Figure 3

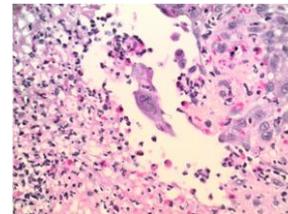


Figure 4

Histologic sections of skin revealed prominent pseudoepitheliomatous hyperplasia and a mixed inflammatory infiltrate in the dermis (Figure 3). There was viral cytopathic effect (Figure 4), but there was no dysplasia or acantholysis.

At one month follow up, patient's lesions have nearly healed after saucerization removal alongside prophylactic valacyclovir and application of topical imiquimod three times daily. At her three-month follow-up, patient had not noticed any new lesions and her physical exam revealed hypopigmented patches with complete re-epithelialization of previous lesions.

## Discussion

Atypical HSV presentations are common in immunocompromised patients. Atypical presentations include chronic ulcerations that may be large, and hypertrophic verrucous plaques. Chronic HSV are also atypical in that they can present in extragenital locations i.e. oral, endobronchial, facial, digits of hands and feet, buttocks or back. These presentations can be easily mistaken for malignancies such as squamous cell carcinomas.

Our patient's lesions had PEH pathology, a histologic pattern that can occur in a wide variety of situations where there is chronic inflammation. While PEH is a benign condition, the histopathological finding can often be misinterpreted as squamous cell carcinoma (SCC) and it is important to rule out malignancy in patients with HIV and chronic HSV lesions.

Misinterpretation clinically of atypical HSV lesions in conjunction with PEH on pathology can result in surgical and oncological overtreatment. Overtreatment can cause significant changes in patient quality of life. It is imperative to not overcall squamous cell carcinomas, but to have a level of suspicion of HSV especially in immunocompromised patients.

While literature review did not reveal a direct correlation between the presence of PEH changes and acyclovir resistance, acyclovir resistance should be considered a cause and patients should be tested for susceptibilities. Many of the patients who demonstrated PEH changes on histology had history of chronic, recurrent HSV lesions that were difficult to treat. Our patient did see her lesions nearly resolved after saucerization removal alongside prophylactic valacyclovir and application of topical imiquimod 5% three times daily. It can therefore be concluded that patients with PCE induced changes with HSV experience treatment difficulty if a single modality is used. These patients may benefit from use of adjunct therapies such as topical imiquimod, oral corticosteroids, and if still resistant, surgical excision.

## References

- Corey, L. and P.G. Spear, *Infections with herpes simplex viruses (2)*. N Engl J Med, 1986. 314(12): p. 749-57.
- Chilukuri, S. and T. Rosen, *Management of acyclovir-resistant herpes simplex virus*. Dermatol Clin, 2003. 21(2): p. 311-20.
- Schneider, E., et al., *Revised surveillance case definitions for HIV infection among adults, adolescents, and children aged <18 months and for HIV infection and AIDS among children aged 18 months to <13 years—United States, 2008*. MMWR Recomm Rep, 2008. 57(Rr-10): p. 1-12.
- Perkins, N., M. Nisbet, and M. Thomas, *Topical imiquimod treatment of acyclovir-resistant herpes simplex disease: case series and literature review*. Sex Transm Infect, 2011. 87(4): p. 292-5.
- Danve-Szatanek, C., et al., *Surveillance network for herpes simplex virus resistance to antiviral drugs: 3-year follow-up*. J Clin Microbiol, 2004. 42(1): p. 242-9.
- Cury, K., et al., *Bipolar hypertrophic herpes: an unusual presentation of acyclovir-resistant herpes simplex type 2 in a HIV-infected patient*. Sex Transm Dis, 2010. 37(2): p. 126-8.
- Zeyaur, M. and R. Lezova, *Pseudoepitheliomatous hyperplasia: a review*. Am J Dermatopathol, 2011. 33(2): p. 112-22; quiz 123-6.
- Strehl JD, Mehlhorn G, Koch MC, Harrer EG, Harrer T, Beckmann MW, et al. *HIV-associated hypertrophic herpes simplex genitalis with concomitant early invasive squamous cell carcinoma mimicking advanced genital cancer: case report and literature review*. International journal of gynecological pathology: official journal of the International Society of Gynecological Pathologists. 2012;31(3):286-93.
- Frimer, M., et al., *Pseudoepitheliomatous hyperplasia mimicking vulvar cancer in a patient with AIDS*. J Low Genit Tract Dis, 2011. 15(1): p. 66-8.
- Tangitgamol, S., et al., *Vulvar pseudoepitheliomatous hyperplasia associated with herpes simplex virus type II mimicking cancer in an immunocompromised patient*. J Obstet Gynaecol Res, 2014. 40(1): p. 255-8.
- Parsons, B.F. and N. Ryder, *Pseudoepitheliomatous hyperplasia causing a painful plaque in a HIV-infected female*. Int J STD AIDS, 2017. 28(7): p. 723-725.