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Case Report

Acyclovir-Resistant Anogenital Herpes Simplex Virus in an HIV Patient With Pseudoepitheliomatous Hyperplasia Resembling Squamous Cell Carcinoma

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Abstract

Background
Herpes simplex virus (HSV) is a common infection. However, it may present atypically when patients are immunocompromised, such as with slowly expanding, long-lasting ulcerative or hypertrophic lesions. The histopathologic finding of pseudoepitheliomatous hyperplasia (PEH) can occur in a variety of situations where there is chronic inflammation and can be seen in patients with chronic HSV. Atypical presentations of HSV, particularly hypertrophic lesions with histopathologic findings of PEH, can be misinterpreted as squamous cell carcinoma, create difficulty in diagnosis and hinder appropriate treatment.

Case Description
We report a case of a 59-year-old female with a past medical history of human immunodeficiency virus (HIV), who presented at a dermatology clinic with multiple exophytic ulcerations of varying sizes in the perianal region. The patient was diagnosed with HSV and was started on valacyclovir. Over a several-year period, the patient had multiple recurrences of her HSV lesions with persistent vulvodynia despite prophylactic treatment with valacyclovir. Specimens were collected for culture and sensitivities, which revealed acyclovir resistance. The patient's lesions were biopsied due to concern for possible malignancy. Biopsies revealed prominent PEH. The patient had improvement of her HSV with saucerization, topical imiquimod, and increased doses of prophylactic valacyclovir.

Conclusion
Atypical, chronic presentations of HSV are common in immunocompromised patients. Hypertrophic HSV is the least common clinical presentation and can be mistaken for squamous cell carcinoma, creating difficulty in diagnosis. Due to concerns for malignancy, our patient's lesions were biopsied, which revealed prominent PEH. While PEH is benign, it can be misdiagnosed as squamous cell carcinoma on histopathology, particularly when there is clinical suspicion for malignancy. In these cases, the clinician needs to alert the pathologist to the immunosuppressed status of the patient. Detailed evaluation for infectious causes, such as HSV, can avoid misinterpretation and potential surgical and oncological overtreatment.

Keywords
herpes simplex virus; HSV; simplex virus; herpes simplex; herpes genitalis; genital herpes; HIV; Human Immunodeficiency Virus; AIDS; acyclovir; valacyclovir; therapeutic use; drug resistance; hyperplasia; pseudoepitheliomatous hyperplasia; PEH; immunocompromised host

Introduction
Herpes simplex virus (HSV) infections are common and often present as mild infections that typically resolve in 7-14 days and heal without significant scarring.[1] Among immunocompetent patients, HSV infections are typically controlled by the host's immune system and are commonly intermittent, self-limiting, and do not require antiviral therapy.[2] However, HSV can present as a chronic disease in immunocompromised persons. In the immunocompromised patient, the virus reactivates frequently and might continue

to replicate, forming large, slowly expanding, long-lasting ulcerative lesions.[1] HSV lesions that persist longer than 1 month, particularly atypical presentations in unusual locations, are considered one of the acquired immunodeficiency syndrome (AIDS)-defining illnesses.[3] AIDS patients have a decreased interferon response, which is believed to be the cause of the chronicity of their HSV lesions.[4] HSV infection is one of the most common opportunistic infections in the immunocompromised, present in over 90% of human immunodeficiency virus (HIV) patients in countries where HIV is endemic.[5] Acyclovir is the most commonly used anti-viral medication for the prevention and treatment of HSV infections. Since its introduction in 1983, widespread use of acyclovir has led to the emergence of acyclovir-resistant HSV.[6-8] While acyclovir resistance is rare in immunocompetent patients (0% to 0.6% prevalence of resistance to acyclovir), there is increased prevalence in immunocompromised patients, with resistance ranging from 3.5% to 7% in HIV-positive patients and 2.5% to 10% in solid organ transplant patients.[8,9] The highest rates of acyclovir resistance are reported in hematopoietic stem cell recipients, with resistance ranging from 4.1% to 10.9%.[9] The emergence of acyclovir resistance in HIV patients poses difficulty in the treatment and prevention of chronic HSV infections.

In this case report, we present a patient with HIV infection who had chronic HSV skin lesions 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.

Case Description

The patient was a 59-year-old female who presented in 2013 having experienced vaginal discharge and erosions for several months, associated with severe pain and itching that interfered with sleep. She had a complicated history, which included HIV infection (diagnosed in 1990), history of substance abuse, and high-risk cervical human papillomavirus (HPV). The patient had recently resumed her antiretroviral therapy and her CD4 count increased from 43 cells/mm3 to 300 cells/mm^3.

The patient had multiple exophytic ulcerations with serpiginous borders of varying sizes in the perianal region (**Figure 1**). She also had two large vulvar ulcers (**Figure 2**). The patient's labia and buttocks were inflamed. She was clinically diagnosed with HSV infection and was started on valacyclovir, 1 g by mouth, twice daily. At the follow-up visit, she experienced an overall 75% improvement in discharge as well as clearance of erosions. The patient was seen in the clinic over 4 years from 2013 to 2016 with recurring HSV lesions, discharge, and severe vulvodynia that interfered with activities of daily living despite prophylactic valacyclovir, hydrocodone-acetaminophen, naproxen, nortriptyline, and topical lidocaine. She had multiple positive HSV-2 cultures and polymerase chain reaction (PCR) tests during this period.

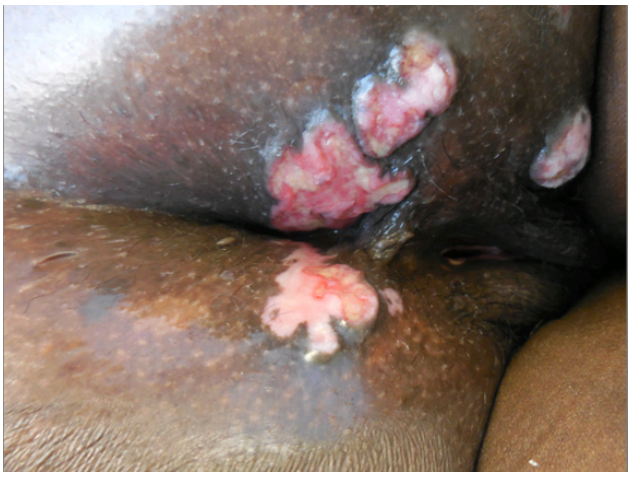

Figure 1. Multiple exophytic ulcerations of varying sizes are presented in the perianal region.

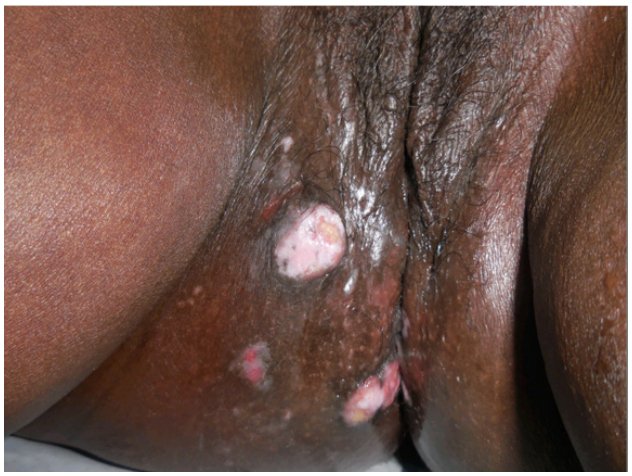

Figure 2. Exophytic ulcerations show involvement of the vulva.

In 2016, the patient's erosions and vulvodynia persisted despite valacyclovir being increased to 3 times daily. These lesions were also revealed to be acyclovir-resistant. Biopsies were taken due to concern for possible malignancy, which revealed chronic HSV infection with PEH changes. At the 1 month follow-up, the patient's lesions were nearly healed after saucerization removal alongside prophylactic valacyclovir and application of topical imiquimod cream (5%) 3 times daily. At her 3-month follow-up, she had not developed any new lesions and her physical exam revealed hypopigmented patches with complete re-epithelialization of previous lesions.

The patient's visits continued, with less frequent recurrence of lesions due to prophylactic valacyclovir (1 g by mouth twice daily) and daily application of topical imiquimod cream (5%). Despite acyclovir resistance, she stated that her ulcerations worsened each time she stopped valacyclovir. The patient's CD4 count was 928 cells/mm^3 and a viral load was undetectable in April 2019.

At that time, histologic sections of skin revealed prominent PEH. There was a mixed inflammatory infiltrate in the dermis, consisting of lymphocytes and scattered neutrophils. Under high power microscopy, there were several small foci of intraepidermal acantholysis. In these areas, there were few keratinocytes with nuclear molding and chromatin margination. Dysplasia was not observed (**Figure 3A-C**).

Discussion

HSV infection leads to a readily recognized clinical syndrome progressing from erythema, to grouped papules, to short-lived vesicles that burst and leave shallow painful ulcers. These ulcerations typically crust and heal within 2-3 weeks.[10] Atypical chronic presentations of HSV lesions can occur in immunocompromised conditions such as transplant recipients, long-term treatment with systemic immunosuppressants, lymphoma, or HIV. Atypical presentations include chronic ulcerations that may include large and hypertrophic verrucous plaques. Chronic HSV lesions may also present atypically in

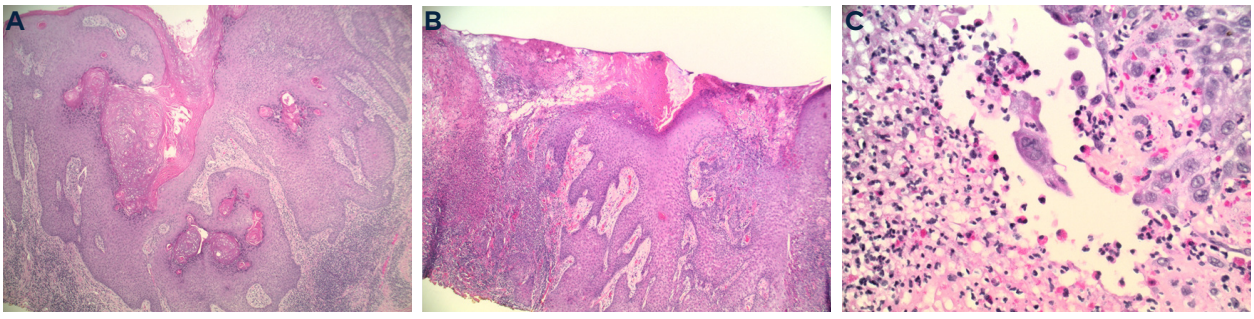

Figure 3. A) A 40X view showing pseudoepitheliomatous hyperplasia mimicking squamous cell cancer. **B)** A 40X view shows focal areas of ulceration. **C)** At high power, there were a few multinucleated keratinocytes with nuclear molding and chromatin marginization.

extragenital locations, ie, oral, endobronchial, facial, digits of hands and feet, buttocks, or back.[11] The severity and chronicity of these lesions often correlate with the degree of immunosuppression.

Hypertrophic HSV is the least common presentation.[12] In a chart review of 294 HIV patients from Thailand with genital herpes, 4.8% had hypertrophic HSV.[13] While rare, it is believed that hypertrophic herpes is a manifestation of immune reconstitution inflammatory syndrome (IRIS) as a result of initiating anti-retroviral therapy.[14] IRIS was observed in our patient, who initially presented with low CD4 counts prior to being restarted on anti-retroviral therapy. Many of these hypertrophic lesions can be mistaken for squamous cell carcinoma or other malignancies of the perineal region, creating difficulty in diagnosis and hindering the initiation of appropriate treatment.[15,16] Due to the clinical concern for malignancy our patient was biopsied, with histopathologic sections revealing prominent PEH.

The histopathologic pattern of PEH can occur in a wide variety of situations such as infections, trauma, neoplasia, or where there is chronic inflammation and presents as irregular acanthosis involving the epidermis and adnexal epithelium without cytologic atypia.[17] The PEH changes in the present case were likely a result of our patient' chronic HSV infection. Local inflammation in tissues infected by HSV creates overproduction of dermal dendritic cells in HIV-infected patients, resulting in tumor necrosis factor proliferation.[18] Antiretroviral therapy increases the number of T-helper cells, subsequently increasing interleukin-6, decreasing interferon-γ, and creating dysregulated keratinocytic activity.[18] As a result, keratinocyte proliferation and hyperkeratosis develop with a clinical and histopathological presentation of PEH.[19] While PEH is benign, it can be misinterpreted as squamous cell carcinoma on histopathology, especially in patients with hypertrophic lesions and a clinical suspicion for malignancy.[20] In these cases, it is important for the clinician to alert the pathologist to the immunosuppressed state of the patient. Detailed evaluation for infectious causes, such as HSV, can avoid misinterpretation and potential surgical or oncological overtreatment.

Once HSV diagnosis is confirmed, it is important to initiate treatment specific to immunocompromised patients. Immunocompromised patients have prolonged or severe HSV episodes due to frequent subclinical shedding despite antiretroviral therapy.[21] According to the Center for Disease Control and Prevention (CDC) in the 2010 "Update to CDC's Sexually Transmitted Diseases Treatment Guidelines", suppressive or episodic therapy with oral antiviral agents such as acyclovir is effective in decreasing HSV lesions among HIV patients.[22] Despite initiating appropriate treatment recommendations, acyclovir resistance can occur in patients receiving prolonged antiviral therapy. Clinical resistance is described as persistent lesions with chronic excretion and multiple clinical recurrences, which were observed in our patient.[8] Acyclovir resistance is rare even in immunocompromised patients; however, our patient had CD4 counts and viral loads not suggestive of immunosuppression. Several cases have been presented in the literature of patients diagnosed with HIV and HSV-induced PEH changes on histology.[15,16,23,24] One patient's vulvar lesions resolved after 21 days of acyclovir treatment, while other patients' vulvar lesions were unresponsive to high doses of oral acyclovir and/or valacyclovir.[15,16,23,24] Several treatment options have been employed including high doses of oral, topical, or intravenous acyclovir and foscarnet, or topical use of imiquimod.[5,13] Many patients' lesions resolved after resection due to concerns for malignancy because of the chronicity of their lesions.[19] Another patient experienced clinical resolution with the addition of a systemic oral corticosteroid.[24]

Conclusion

A direct correlation between the presence of PEH changes and acyclovir resistance has not been established; however, acyclovir resistance should be considered if PEH is seen histologically and these patients should be tested for susceptibilities. Many of the patients who demonstrated PEH changes on histology had a history of chronic, recurrent HSV lesions that were difficult to treat. Our patient's lesions nearly resolved after saucerization removal, prophylactic valacyclovir, and application of topical imiquimod. It can therefore be inferred that those patients with PEH-induced changes with hypertrophic HSV, experience treatment

difficulty if a single modality is used. These patients may benefit from the use of adjunct therapies such as topical imiquimod, oral corticosteroids, and surgical excision if still resistant. The details of this case illustrate the importance of a detailed evaluation of a patient's history and chronic HSV presentation to guide pathological diagnosis and treatment options.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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