Penile Herpes Vegetans in a Patient With Well-controlled HIV

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PRACTICE **POINTS**

- Maintain a high clinical suspicion for herpes vegetans (HV) in a patient who has a history of immunosuppression and presents with exophytic genital lesions.
- A history of resistance to acyclovir requires a multimodal approach to treatment of HV lesions, including medical and surgical therapies.

To the Editor:

Herpes vegetans (HV) is an uncommon infection caused by human herpesvirus (HHV) in patients who are immunocompromised, such as those who are HIV positive.[1] Unlike typical HHV infection, HV can present with exophytic exudative ulcers and papillomatous vegetations. The presentation of ulcerated genital nodules, especially in an immunocompromised patient, yields an array of disorders in the differential diagnosis, including condyloma latum, condyloma acuminatum, pyogenic granuloma (PG), and verrucous carcinoma.[2,3] Histopathology of HV reveals pseudoepitheliomatous hyperplasia, plasma cell infiltration, and positivity for HHV type 1 (HHV-1) and/or HHV type 2 (HHV-2). Herpes vegetans lesions typically require a multimodal treatment approach because many cases are resistant to acyclovir. Treatment options include the nucleoside analogues foscarnet and cidofovir; immunomodulators such as topical imiquimod; and the topical antiviral trifluridine.[1,4-6] We describe a case of HV in a patient with a history of well-controlled HIV infection who presented with a painful fungating penile lesion.

A 55-year-old man presented to the hospital with a painful expanding mass on the distal aspect of the penis of 3 months' duration. He had a history of HIV infection that was well-controlled by antiretroviral therapy, prior hepatitis B virus infection and acyclovir-resistant genital HHV-2 infection. Physical examination revealed a large, firm, circumferential, exophytic, verrucous plaque with various areas of ulceration and purulent drainage on the distal shaft and glans of the penis (Figure 1). The patient's most recent absolute CD4 count was 425 cells/mm^3 (reference range, 500–1500 cells/mm^3). His HIV viral load was undetectable at less than 30 copies/mL. Histopathology with hematoxylin and eosin staining of biopsy material from the penile lesion demonstrated pseudoepitheliomatous epidermal hyperplasia with focal ulceration and a mixed inflammatory infiltrate (Figure 2A). At higher magnification, clear viral cytopathic changes of HHV were noted, including multinucleation, nuclear molding, and homogenous gray nuclei (Figure 2B). Additional staining for fungi, mycobacteria, and spirochetes was negative. In-situ hybridization was negative for human papillomavirus subtypes. A bacterial culture of swabs of the purulent drainage was positive for *Staphylococcus aureus* and *Proteus mirabilis*.

Given the patient's known history of acyclovir-resistant HHV-2 infection, he received a 28-day course of intravenous foscarnet 40 mg/kg every 12 hours. He

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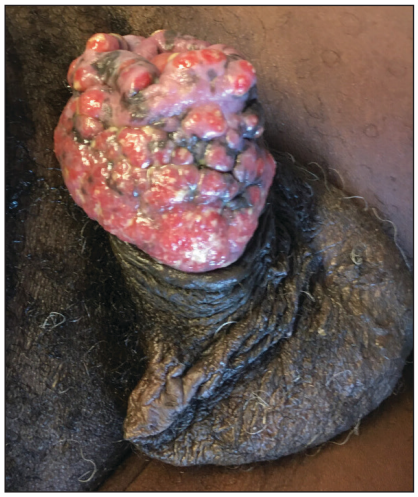

FIGURE 1. A large exophytic circumferential plaque on the distal shaft and glans of the penis with areas of ulceration and purulence characteristic of herpes vegetans.

also was given a 14-day course of intravenous ampicillin-sulbactam 3 g every 6 hours. The patient gradually improved during a 35-day hospital stay. He was discharged with cidofovir cream 1% and oral valacyclovir; the latter was subsequently discontinued by dermatology because of his known history of acyclovir resistance. Four months after discharge, the patient underwent a circumcision performed by urology to decrease the risk for recurrence and achieve the best cosmetic outcome. At the 6-month follow-up visit, dramatic clinical improvement was evident, with complete resolution of the plaque and only isolated areas of scarring (Figure 3). The patient reported that penile function was preserved.

Herpes vegetans represents a rare infection with HHV-1 or HHV-2, typically in patients who are considerably immunosuppressed, such as those with cancer, those undergoing transplantation, and those with uncontrolled HIV infection.[1] Few cases of HV have been described in an immunocompetent patient.[2] Our case is unique because the patient's HIV infection was well controlled at the time HV was diagnosed, demonstrated by his modestly low CD4 count and undetectable HIV viral load.

Patients with HV can present diagnostic and therapeutic challenges. Typically, a diagnosis of cutaneous HHV infection does not require a biopsy; most cases appear as clustered vesicular lesions, making the disease easy to diagnose clinically. However, biopsies and cultures are necessary to identify the underlying cause of atypical verrucous exophytic lesions. Other conditions with clinical features similar to HV include squamous cell carcinoma, condyloma acuminatum, and deep fungal and mycobacterial infections.[2,3] A tissue biopsy, histologic staining, and tissue culture should be performed to identify the causative pathogen and potential targets for treatment. Definitive diagnosis is vital to deliver proper

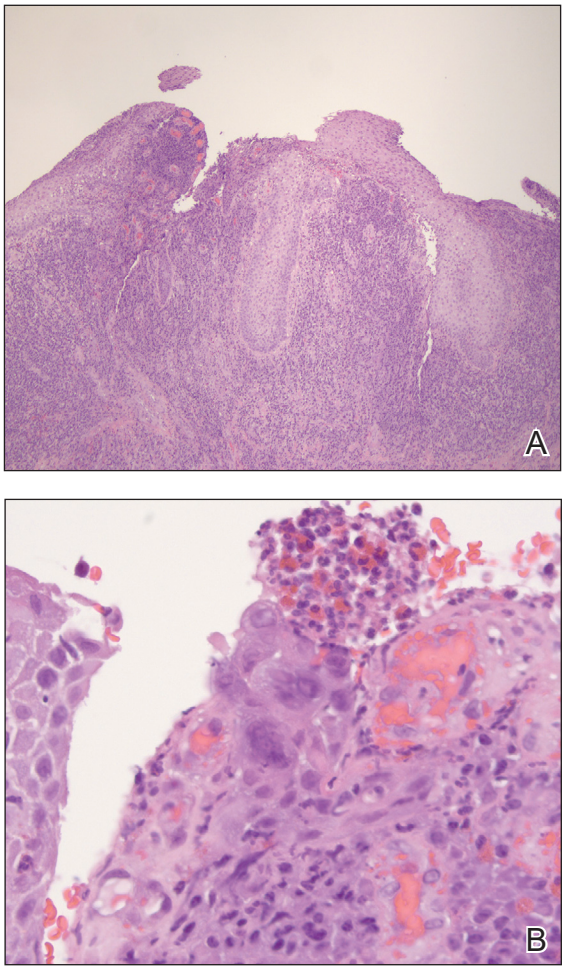

FIGURE 2. A, Histopathology revealed pseudoepitheliomatous epidermal hyperplasia with ulceration and a dense mixed inflammatory infiltrate (H&E, original magnification ×4). B, Multinucleation, nuclear molding, and homogenous gray nuclei were observed, all consistent with a herpesvirus infection (H&E, original magnification ×20).

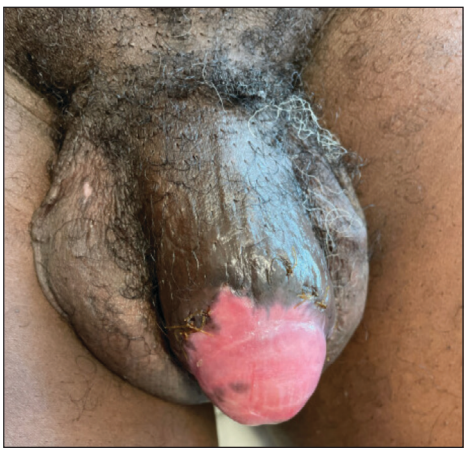

FIGURE 3. At 6-month follow-up, herpes vegetans lesions had completely resolved with good cosmetic outcome. The lesions were treated with intravenous foscarnet and ampicillin-sulbactam as well as cidofovir cream 1%. The patient also underwent a circumcision.

treatment modalities, which often involve a multimodal multidisciplinary approach.

Several pathogenic mechanisms of HV have been proposed. One theory suggests that in an immunocompetent patient, HHV typically triggers a lymphocytic response, which leads to activation of interferon alpha. However, in an immunocompromised patient, such as an individual with AIDS, this interferon response is diminished, which explains why these patients typically have a chronic and resistant HHV infection. HIV has an affinity for infecting dermal dendritic cells, which signals activation of tumor necrosis factor and interleukin.[6] Both cytokines contribute to an antiapoptotic environment that promotes continued proliferation of these viral cells in the epidermis. Over time, propagation of disinhibited cells can lead to the verrucous and hyperkeratotic-appearing skin that is common in patients with HV.[7]

Another theorized mechanism underlying hypertrophic herpetic lesions was described in the context of HHV-1 infection and subsequent PG. El Hayderi et al[8] reported that histologic and immunohistochemical examination of a patient's lesion revealed sparse epithelial cell aggregates within PG as well as HHV-1 antigens in the nuclei and cytoplasm of normal-appearing and cytopathic epithelial cells. Immunohistochemical examination also revealed vascular endothelial growth factor within HHV-1–infected epithelial cells and PG endothelial cells, suggesting that PG formation may be indirectly driven by vascular endothelial growth factor and its proangiogenic properties. The pathogenesis of PG in the setting of HHV-1 infection displays many similarities to hyperkeratotic lesions observed in atypical cutaneous manifestations of HHV-2.[8]

The management of patients with HV continues to be complex, often requiring a multimodal regimen. Although acyclovir has been shown to be highly effective for treating and preventing most HHV infections, acyclovir resistance frequently has been reported in immunocompromised populations.[5] Acyclovir resistance can be correlated with the severity of immunodeficiency as well as the duration of acyclovir exposure. Resistance to acyclovir often results from deficient intracellular phosphorylation, which is required for activation of the drug. If patients show resistance to acyclovir and its derivatives, alternate drug classes that do not depend on thymidine kinase phosphorylation should be considered.

Our patient received a combination of intravenous foscarnet and a course of ampicillin-sulbactam while an inpatient due to his documented history of acyclovir-resistant HHV-2 infection, and he was discharged on cidofovir cream 1%. Cidofovir is US Food and Drug Administration approved for treating cytomegalovirus retinitis in patients with AIDS. Although data are limited, topical and intralesional cidofovir have been used to treat acyclovir-resistant cases of HV with documented success.[1,9] In refractory HV or when the disease is slow to resolve, intralesional cidofovir has been documented to be an additional treatment option. Intralesional and topical cidofovir carry a much lower risk for adverse effects such as kidney dysfunction compared to intravenous cidofovir[1] and can be considered in patients with minimal clinical improvement and those at increased risk for side effects.

Our case demonstrated how a patient with HV may require a complex and prolonged hospital course for appropriate treatment. Our patient required an array of both medical and surgical modalities to reach the desired outcome. Here, a multitude of specialties including infectious disease, dermatology, and urology worked together to reach a positive clinical and cosmetic outcome for this patient.

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