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# Papillomatous Anogenital Lesions in a Patient With Human Immunodeficiency Virus

Omar E. Fernandez

Smitha Gudipati

Dayoung Ko

Alison Boucher

Indira Brar

*Clinical Infectious Diseases*

PHOTO QUIZ

Anthony Amoroso and Nancy E. Madinger, Section Editors

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## QUESTION

A 45-year-old African American man with history of human immunodeficiency virus (HIV) presented to the office complaining of a rash in his right groin for the past 7 weeks. He had a history of nonadherence to his combination antiretroviral therapy (cART), and at a previous visit, his HIV-1 load was noted to be >10 000 000 copies/mL. After that visit, the patient became adherent with his cART regimen. He presented to his primary care physician's office 3 weeks later, reporting a lesion in his right groin, and was treated with doxycycline for possible skin and soft-tissue infection. Blood work performed 2 weeks later showed an HIV-1 viral load of 1604 copies/mL. The patient was seen in the infectious disease clinic and reported that the rash had only gotten worse. He described it as "itchy but not painful." He denied fevers, chills, night sweats, unexplained weight loss, nausea, vomiting, and diarrhea.

At physical examination, the patient appeared well developed and well nourished. No oropharyngeal thrush was seen at oral examination. Findings of neurological, cardiovascular, respiratory, and abdominal examination were also unremarkable. Skin examination revealed multiple exophytic masses in the right inguinal and perineal areas, the largest measuring about 3 cm in diameter, and areas of hypopigmentation (Figure 1). There was no associated erythema or tenderness to palpation. The $CD4^+$ cell count was 59/μL, and the HIV load, 733 copies/mL. The patient was referred to dermatology for biopsy. What is your diagnosis?

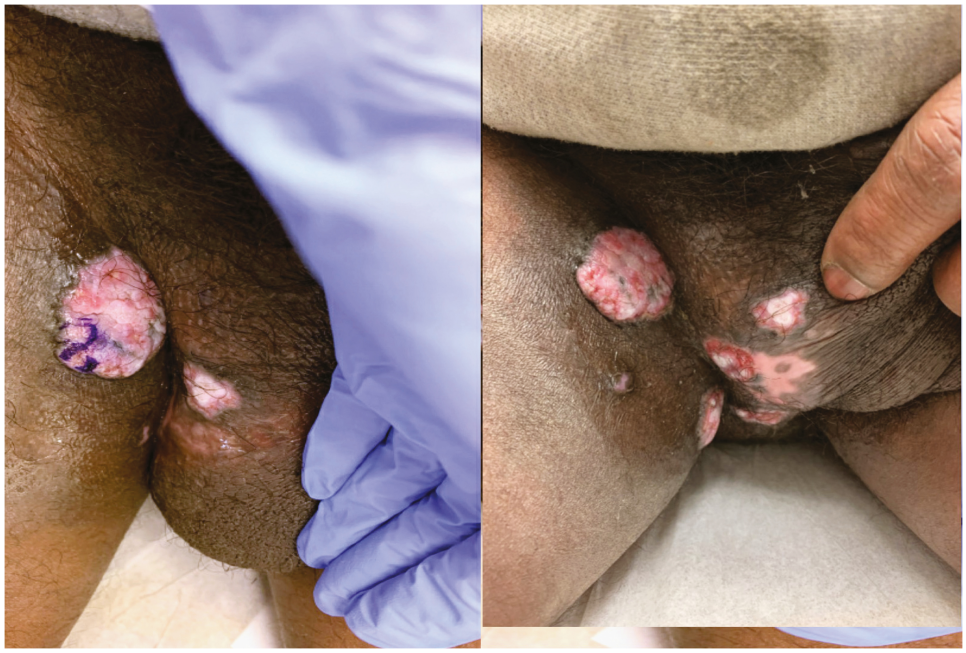

**Figure 1.** Images of the primary exophytic mass and associated lesions. *Left,* Right inguinal 3-cm exophytic mass marked in purple, with adjacent visible areas of hypopigmentation. *Right,* Elevation of scrotum revealing more areas of hypopigmentation and additional exophytic lesions in the right scrotum, medial thigh, and perineal area, each measuring about 1 cm in diameter.

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ANSWER TO THE PHOTO QUIZ

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Diagnosis: Verrucous herpes infection.

Two 4-mm punch biopsy specimens were taken from the patient's right thigh exophytic mass, one for histopathologic examination and one for tissue culture (marked in purple in Figure 1). Hematoxylin-eosin staining at scanning magnification showed verrucous hyperplasia with focal epidermal necrosis and acantholysis (Figure 2). Higher magnification at ×400 revealed multinucleated epithelial cells with nuclear molding, consistent with herpes virus. Immunohistochemical staining was performed and was focally positive for herpes simplex virus (HSV) and negative for treponema. Final tissue culture results were negative for all aerobic, fungal, and acid-fast bacilli positive organisms. Taken together, the diagnosis of verrucous HSV was confirmed.

Treatment was then started with acyclovir, 400 mg 3 times daily for 14 days. The patient's condition improved after treatment, although he reported difficulty with compliance. The patient was then started on valacyclovir, 1000 mg twice daily. Two months later, he presented with resolution of the exophytic masses and residual hypopigmented skin changes at the site of the original lesions (Figure 3). Procedural intervention was not required.

HSV is commonly transmitted by different routes and can affect various areas of the body, most frequently the orofacial and genital regions. The prevalence of HSV-2 serotype is even higher among individuals with human immunodeficiency virus (HIV), particularly those living in North America [1]. Genital infections typically present with grouped, shallow vesicles that cause significant pain and discomfort. They often last 8–10 days before spontaneously regressing [2]. In persons living with HIV, the clinical presentation of HSV infections can vary widely. Depending on the patient's immune status, HSV infections may last even longer and manifest more aggressively than they would in an immunocompetent patient [3, 4].

A subset of HSV- and HIV-coinfected patients develop verrucous growths, and the pathophysiology of these lesions is not

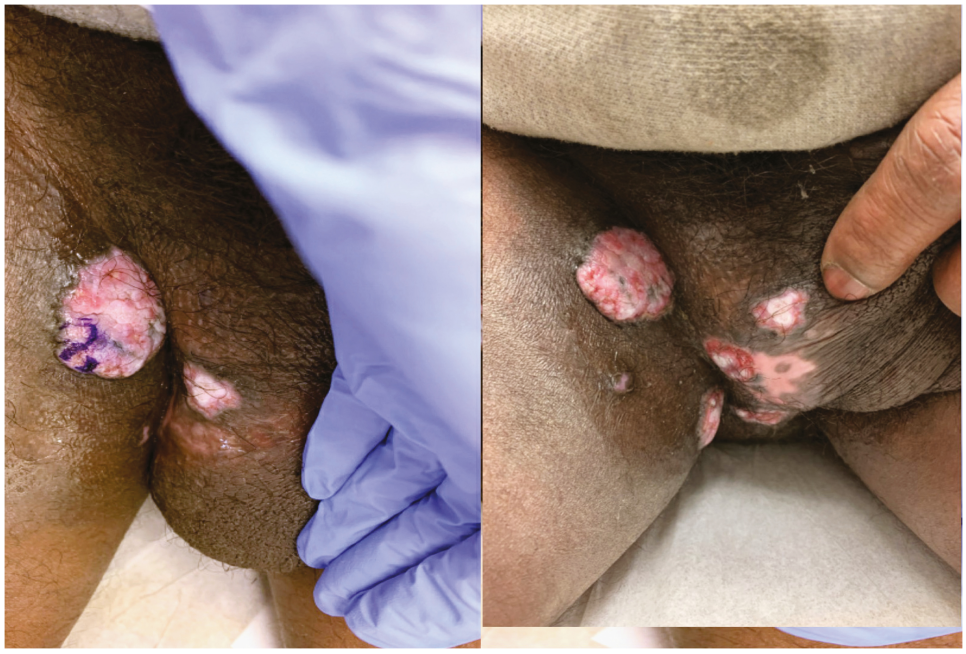

**Figure 1.** Patient images of primary exophytic mass and associated lesions. *Left,* Right inguinal 3-cm exophytic mass, marked in purple, with adjacent visible areas of hypopigmentation. *Right,* Elevation of scrotum revealing more areas of hypopigmentation and additional exophytic lesions in the right scrotum, medial thigh, and perineal area, each measuring about 1 cm in diameter.

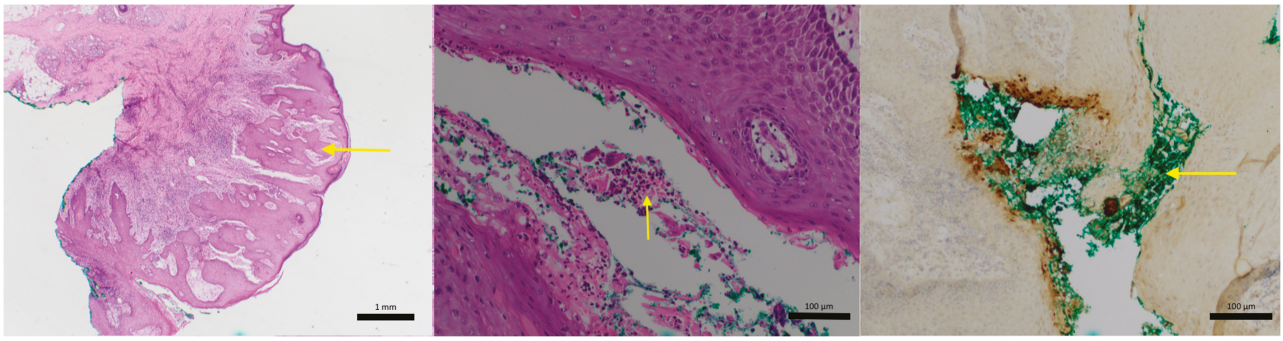


**Figure 2.** Histopathologic appearance of right thigh lesion. *Left,* Scanning magnification (×40) shows verrucous hyperplasia with focal acantholysis (arrow). *Middle,* Higher-power magnification (×400) reveals multinucleated epithelial cells with nuclear molding (*arrow*). *Right,* Immunoperoxidase stain (magnification ×400) for herpes simplex virus is positive, staining green (arrow).

completely understood [5–9]. The papillomatous lesions seen in our patient is a representative case of such atypical manifestations. It may be secondary to immune reconstitution inflammatory syndrome (IRIS) after the initiation of combination antiretroviral therapy (cART). In another proposed mechanism, HIV infection causes dendritic cells to produce antiapoptotic cytokines that create an environment favorable to tissue proliferation [5].

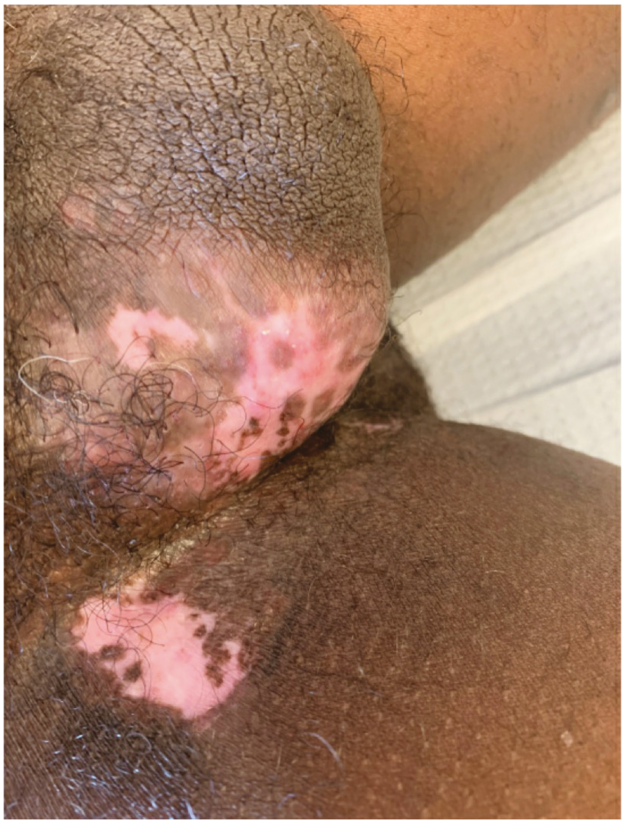

**Figure 3.** Patient's right inguinal area after treatment, demonstrating resolution of exophytic lesions with residual areas of hypopigmentation.

The appearance of warty, papillomatous lesions is often consistent with the presentation of condyloma acuminata, typically a manifestation of human papilloma virus (HPV) serotypes 6 and 11. Differential diagnosis for this type of clinical presentation may also include condyloma lata from secondary syphilis, lichen planus, and cancers such as squamous cell carcinoma, secondary to cancerous HPV serotypes. Like HSV infection, several of the causes leading to similar-appearing lesions, such as those caused by HPV, are more common in patients with HIV [10–12]. This highlights the importance of a broad differential diagnosis and appropriately inclusive testing.

Smith et al [6] first described the appearance of verrucous, hyperkeratotic lesions secondary to HSV infection in patients with HIV, suggesting that an increased presence of factor XIIIa–positive dendritic cells in these cases may be related to the pathogenesis of this presentation. Tong and Mutasim [5] later described a clinical presentation suggestive of condyloma accuminata in a patient with HIV. Further investigation revealed the absence of detectable HPV serotypes and the presence of HSV infection that was responsive to acyclovir treatment. Similar clinical presentations of HSV in individuals with HIV have been described elsewhere, although these cases have not always been responsive to medical therapy alone [7–9]. In such events, resection of the lesions is required in addition to acyclovir therapy.

The severe, atypical presentation of HSV in our patient was most consistent with IRIS due to viral shedding after the initiation of cART [13–16]. IRIS develops in approximately 16% of persons living with HIV who start antiretroviral therapy, which is called "unmasking" when occurring in the context of a previously unrecognized opportunistic infection and "paradoxical" when the opportunistic infection was previously recognized and being treated [17–20]. The rapid immune response after treatment initiation may cause a systemic or local inflammatory reaction, which can specifically target the sites of initial infection. Our patient had started cART only 3 weeks before presentation with new lesions. Hence, we propose that the verrucous

HSV in this case was most likely a manifestation of HSV IRIS. The patient's cART was continued, and the underlying infection was treated with acyclovir, leading to a resolution of his symptoms.

## Note

***Potential conflicts of interest.*** I. B. reports support from Gilead and ViiV for research, paid to their institution, and personal fees for serving on speakers bureaus for Gilead, ViiV, and Janssen, outside the submitted work. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

**Omar E. Fernandez,[1] Smitha Gudipati,[2] Dayoung Ko,[3] Alison Boucher,[3] and Indira Brar[2]**

[1]Wayne State University School of Medicine, Detroit, Michigan, USA; [2] Department of Infectious Disease, Henry Ford Hospital, Detroit, Michigan, USA; and [3] Department of Dermatology, Henry Ford Hospital, Detroit, Michigan, USA

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Correspondence: Smitha Gudipati, Henry Ford Hospital, 2799 W Grand Blvd, Detroit, MI 48202 (Sgudipa2@hfhs.org).

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