Malignant degeneration of diffuse intertriginous flat warts in a patient with AIDS

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INTRODUCTION
There are multiple dermatologic manifestations of human papilloma virus (HPV) infection in HIV-infected individuals including benign, premalignant, and malignant lesions of both anogenital and nongenital areas. 1 One uncommon example is acquired epidermodysplasia verruciformis (AEV) or epidermodysplasia verruciformis (EV)-like lesions, which features lesions that are histologically indistinguishable from the genetic condition, EV. 2 Patients of both inherited and acquired EV are susceptible to infection with β-HPV strains (particularly 3, 5, 8, 9, 10, 12, 14, 15, 17, 19-25, 27, 28, 29, 36, 46, 47, 49, and 50) leading to widespread flat warts, pityriasis versicolor-like lesions, and an increased risk for squamous cell carcinoma especially in sun-exposed areas. 2 With HPV infection rates higher among individuals with HIV, there has been a significant amount of reported cases of AEV or EV-like lesions in HIV patients in the literature. 3-6 One treatment trial of 38 children in Botswana indicates that this skin manifestation of HPV is quite common among HIV-infected children there and presents as diffuse flat warts in the typical sun-exposed distribution. 7 We report a rare case of a woman with AIDS who presented with diffuse intertriginous EV-like flat warts found to be HPV positive with the histopathologic findings of Bowen disease.

CASE REPORT
A 49-year-old woman recently diagnosed with HIV/AIDS (on HAART; CD4 count, 110) was seen in the dermatology clinic for an itchy rash in the bilateral inframammary and inguinal folds. She had been applying topical alcohol and triamcinolone 0.1% to the areas for the previous 2 weeks without relief. She did not report any systemic symptoms and recently had started on emtricitabine-tenofovir-alafenamide, dolutegravir, and atovaquone. Examination found flat-topped papules coalescing into broad plaques under both breasts and in the inguinal folds. The lesions appeared to koebnerize, and some were slightly excoriated (Fig 1). A 4-mm punch biopsy was performed in the left inframammary fold, which found Bowen disease. Atypia of the keratinocytes at all levels of the epidermis with associated maturation disorder was noted (Fig 2) in addition to strong staining of lesional epidermal keratinocytic nuclei using an HPV cocktail immunostain (HPV-1, 6, 11, 16, 18, and 31) and HPV 16 immunostaining (Fig 3). The tissue was sent for polymerase chain reaction testing, and both high-risk β-HPV 52—which has a closely related viral genome to HPV 16—and β-HPV 12 DNA were also detected. The patient was prescribed imiquimod 5% cream to be applied only to the right inframammary fold 3 times weekly to assess for efficacy and tolerance of the therapy.

At the 2-month follow-up appointment, the lesions under the right breast had resolved completely

Abbreviations used:
AEV: acquired epidermodysplasia verruciformis
EV: epidermodysplasia verruciformis
HPV: human papilloma virus
with imiquimod therapy, with only postinflammatory hyperpigmentation remaining (Fig 4). The examination findings were unchanged from those of the initial encounter under the left breast and inguinal folds. Given the response of the right inframammary fold to imiquimod therapy, she was instructed to treat the left inframammary and bilateral inguinal folds in the same manner.

**DISCUSSION**

This case is one of several reported cases of AEV in an AIDS patient but is unique in its clinical presentation and malignant transformation. In a review of 32 cases of EV-like lesions in HIV patients, only 4 had mention of lesions in the groin, axilla, or body folds. Most cases involve lesions in sun-exposed areas such as the face, neck, upper chest and back, and extremities. Several other similar case reports have been published since, none of which describe EV-like lesions in the intertriginous distribution. Non-EV HPV infections are more commonly seen in HIV patients and have a well-documented association with anogenital disease; however, the lesions in this patient were widespread in the bilateral inguinal folds with sparing of vulva and anal mucosa. Not only was the location and extent of lesions unusual in this patient, but biopsy also showed full-thickness keratinocytic atypia. HPV DNA polymerase chain reaction and immunostains detected high-risk types of HPV that have been associated with increased risk of malignancy in HIV-infected patients. HPV type 12, a member of the β-HPV genus, is known to be associated with EV and EV-like lesions and increased incidence of Bowen disease and invasive squamous cell carcinoma. These malignancies are typically caused by the compounded mutagenic effects of HPV infection and cumulative sun exposure on the skin, a 2-hit phenomenon. We posit that the co-infection of HPV 52 and HPV 12 in this immunocompromised patient’s intertriginous skin provided sufficient molecular biological alterations to cause malignant transformation in the absence of ultraviolet radiation. In the 2 most recent reviews of HIV-positive patients with EV-like lesions and in subsequent case reports, only 3 cases mention features of “ Bowenoid dysplasia” on biopsy. Multifocal or extensive Bowen disease has been described in the genitals and the periungual skin of HIV patients; however, these cases are not related to EV-like lesions. Thus, the case we present...
of widespread intertriginous EV-like lesions with development of Bowen disease in an immunocompromised patient does not have an established precedent in the literature.

Although not approved by the US Food and Drug Administration for the treatment of Bowen disease, imiquimod, a topical immunomodulator, was found in multiple small trials to be an effective therapy with cure rates ranging from 73% to 93%.\textsuperscript{10} Given this evidence and the extent of disease in this patient, imiquimod was preferred over surgical therapy. The right inframammary fold was treated first both to compare its response and assess for tolerability, given the risk of causing localized pain and erosion.\textsuperscript{10} There was a dramatic response on the right side after 2 months of treatment, whereas the left side remained unchanged on examination (Figs 1 and 4).

Patients with HIV/AIDS can present with unusual manifestations of common and uncommon diseases.

All patients should have a thorough history and physical examination to create a differential diagnosis, and there should be a low threshold for biopsy when cases are not clear cut. HPV-related malignancies continue to be an issue for HIV/AIDS patients, and creative treatment plans may be necessary to assist patients with widespread, refractory, or difficult disease.

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Fig 4. Only postinflammatory pigmentation under the right breast after treatment with imiquimod.