Recurrent fungating tumor and a chronic rash in an immunosuppressed transgender patient: a case of Buschke-Lowenstein condyloma and epidermodysplasia verruciformis

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Abstract

A transgender female in her 40s with history of HIV and testicular cancer status post-genital X-irradiation presented with a perianal mass and pruritic rash across her chest. Physical examination revealed a bulky, verrucous tumor protruding outward from the anus involving the medial buttocks. Examination of the chest and arms showed numerous guttate, pink, flat-topped papules coalescing into plaques. Clinically and histologically the lesions were consistent with Buschke-Löwenstein condyloma (BLC) and acquired epidermodysplasia verruciformis (AEDV). Buschke-Löwenstein condyloma incisional biopsy tested negative for common low- and high-risk human papillomavirus (HPV) subtypes, including 6, 11, 16, and 18, possibly implicating beta HPV subtype or a less common pathogenic subtype. The patient underwent abdominoperineal resection of the BLC, which tested positive for low-risk HPV subtypes, suggesting the possibility of multiple implicated HPV subtypes in the same tumor. This case demonstrates a possible role of beta HPV or rarer HPV subtypes in the pathogenesis of verrucous carcinoma, particularly in the setting of immunosuppression.

Keywords: acquired epidermodysplasia verruciformis, Buschke-Löwenstein condyloma, human papillomavirus, immunodeficiency virus

Introduction

Epidermodysplasia verruciformis (EV) is a rare autosomal recessive genodermatosis that increases susceptibility to cutaneous manifestations of human β-papillomavirus (β-HPV), [1,2], usually subtypes 5 and 8. Increased susceptibility to HPV may result from cell-mediated immunity defects [3]. Acquired epidermodysplasia verruciformis (AEDV) is an EV-like syndrome associated with human immunodeficiency virus (HIV) or other forms of immunosuppression [4]. Histologically, AEDV is characterized by epidermal acanthosis, a loose horny layer with a basketweave-like appearance, and large cells in the spinous and granular layers with blue-gray cytoplasm and a perinuclear halo [5]. Human papillomavirus subtypes 5 and 8 have been associated with the development of keratinocyte carcinomas, but to our knowledge, they have not been associated in "semi-malignant" verrucous carcinomas such as Buschke-Lowenstein condyloma (BLC).

Buschke-Lowenstein condyloma, or giant condyloma accuminata, is an HPV-associated verrucous carcinoma occurring in the anogenital region most commonly with low-risk HPV subtypes 6 and 11 [6]. Despite association with low-risk HPV subtypes, BLC has a high rate of malignant transformation, with about 30-56% transformation if excision is not performed [7]. Malignant transformation can also be seen in the setting of X-irradiation. Histologically, BLC is characterized by a well-differentiated squamous proliferation in addition to exo- and endophytic hyperpapillomatosis with acanthosis [8]. Invasion of the basement membrane indicates malignant transformation.

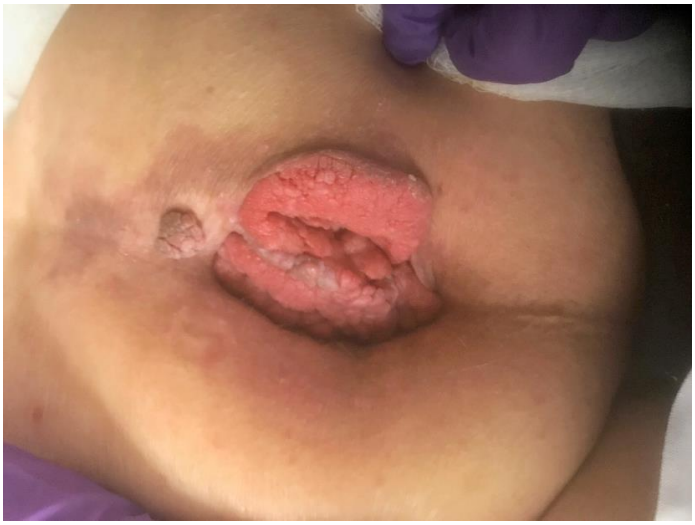

Figure 1. *Bulky, verrucous mass protruding outward from the anus and involving the medial buttocks.*

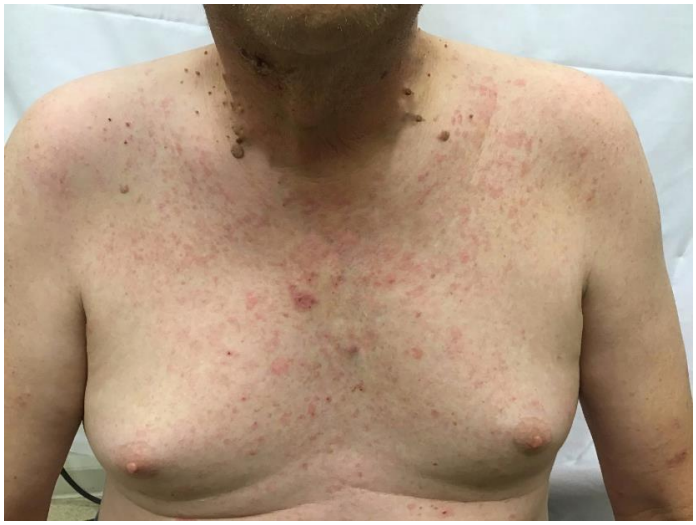

Figure 2. *Numerous guttate, pink, flat-topped papules coalescing into plaques on the chest and arms.*

We present a patient with BLC in the setting of AEDV that initially tested negative for common low risk and high risk HPV subtypes, with final excision testing positive for low-risk HPV subtypes.

Case Synopsis

A 46-year old transgender female with history of HIV (most recent CD4 count of 719. 25%) and a distant history of testicular cancer status post X-irradiation presented to the dermatology clinic for evaluation. The patient had a previously resected anal condyloma and a diffuse asymptomatic rash on the trunk and extremities. Physical examination of the perianal region revealed a bulky, verrucous tumor protruding outward from the anus and involving the medial buttocks (**Figure 1**). Examination of the chest and arms showed numerous guttate, pink, flat-topped papules coalescing into plaques (**Figure 2**). Incisional biopsy of the perianal mass showed classic viral cytopathic changes, including koilocytic perinuclear vacuoles and mitoses above the basal layer (**Figure 3**). Areas of full thickness dysplasia were not present. In-situ hybridization (ISH) for low risk (6, 11, 40, 42, 43, and 44) and high-risk (16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 58, 59, 66, 68, 73, and 82) HPV were negative in the lesion. The findings were consistent with BLC. Shave biopsy of the chest revealed epidermal acanthosis with coarse

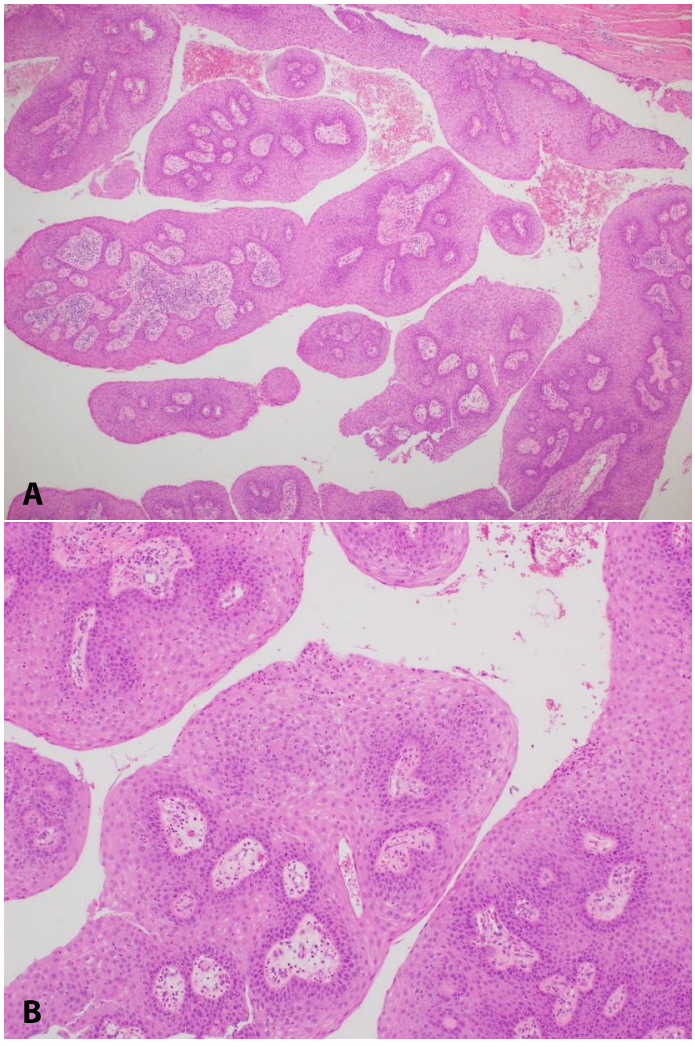

Figure 3. *Incisional biopsy of the perianal mass demonstrating viral cytopathic changes, including koilocytic perinuclear vacuoles and mitoses above the basal layer. H&E, 100× and 200×.*

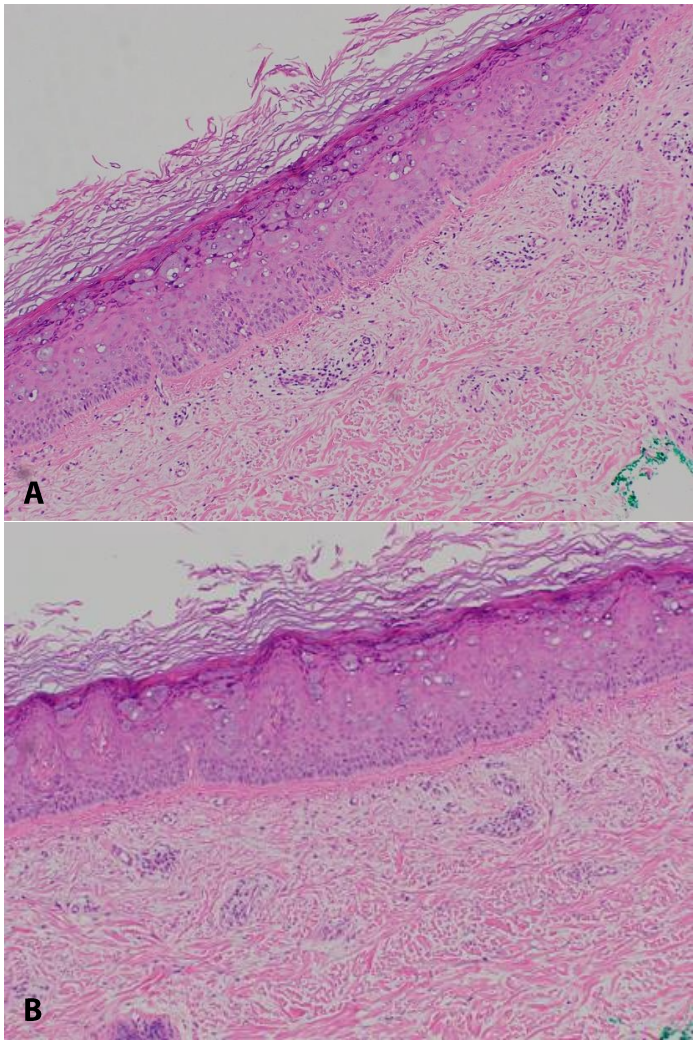

Figure 4. ***A)*** *Shave biopsy of the chest demonstrating epidermal acanthosis with coarse hypergranulosis and focal koilocytosis. H&E, 200×.* ***B)*** *Large keratinocytes with increased cytoplasm displaying a blue-gray hue within the epidermis. H&E, 200×.*

hypergranulosis and focal koilocytosis (**Figure 4A**). Within the epidermis were large keratinocytes with increased cytoplasm displaying a blue-gray hue (**Figure 4B**). These changes were diagnostic of AEDV. Abdominoperineal resection of the Buschke-Lowenstein condyloma tested positive for low-risk HPV subtypes through in-situ hybridization. Close surveillance of the AEDV lesions was recommended.

Case Discussion

Epidermodysplasia verruciformis represents a rare genodermatosis caused by homozygous inactivating mutations in *TMC6* (*EVER1*) and *TMC8* (*EVER2*) and presents in early childhood [1]. Acquired epidermodysplasia verruciformis, however, can relate to iatrogenic causes such as immunosuppressive drugs, infections (e.g., HIV, lepromatous leprosy), non-Hodgkin lymphoma, or lipoid proteinosis [2]. The appearance of the lesions in AEDV often coincide with HIV diagnosis. It classically presents as pink-red pityriasis versicolor-like macules, seborrheic keratosis-like lesions, and verruca-like papillomatous papules [1].

Both inherited EV and AEDV are associated with certain β-HPV subtypes (3, 5, 8, 9, 10, 12, 14, 15, 17, 19–25, 28, 29, 36, 46, 47, 49, and 50), with subtypes 5 and 8 being the most common [1]. β-HPV has been detected in squamous cell carcinomas (SCCs) and actinic keratosis [2-4]. The incidence of non-melanoma skin cancer in patients diagnosed with EV is believed to be 30-70% [5]. The pathogenesis of AEDV is believed to be similar to that of inherited EV and involves a defective cell-mediated immune response to HPV. There is no consensus in the literature for the treatment of EV, but surveillance is highly recommended because of the malignant potential.

Buschke-Lowenstein condyloma is described as a slow-growing and locally destructive cauliflower-like lesion occurring in the anogenital and perianal regions [6-9]. These tumors are typically driven by HPV subtypes 6 and 11 and the most common risk factor is immunosuppression with HIV [6,7,9]. Buschke-Lowenstein condyloma is more common in men with a male to female ratio of 2.7-3.5:1 [9]. The growth often begins as a keratotic plaque that expands into a long-standing condyloma and can reach 10-15cm in size over a period of 2.6 to 9.8 years [7]. When present in the anorectal region, it is often associated with abscesses, anal stenosis, and fistulas [10].

Given the high possibility of malignant transformation, wide surgical excision of the BLC is the gold standard of treatment, which alone results in a disease-free state in 46% of cases [11]. Topical and oral chemotherapeutic agents, cryotherapy, and photodynamic therapy can be used as adjuvants to surgery [7]. In recurrent or unresectable disease as well as BLC with SCC transformation, chemoradiation can be considered in addition to excision. However,

there have been reports of metastasis and more aggressive tumors after radiation [6]. Long-term follow-up is recommended for patients.

Conclusion

This report describes a patient with both AEDV and BLC in the setting of HIV. Interestingly, the initial BLC incisional biopsy tested negative for multiple HPV subtypes, including 6 and 11. Given the history of immunosuppression with HIV and previous genital X-irradiation, we postulate that HPV subtypes that can induce malignant transformation in AEDV (for example, β-HPV types 5 and 8) may have played a role in the development of BLC, which may suggest AEDV as a risk factor for other verrucous carcinomas [12]. Alternatively, less common pathogenic subtypes may lead to verrucous carcinomas in the setting of immunosuppression. Final resection of the BLC tested positive for low-risk HPV subtypes, suggesting that multiple HPV subtypes may be implicated in the pathogenesis of the same tumor.

Potential conflicts of interest

The authors declare no conflicts of interest.

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