Giant condyloma of Buschke-Lowenstein in a patient with pemphigus vegetans treated with intralesional and systemic human papillomavirus vaccine

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INTRODUCTION

Giant condyloma of Buschke-Lowenstein (GCBL) is often considered a low-grade verrucous carcinoma with the potential for local aggression, little risk of metastasis, and association with human papillomavirus (HPV) infection.[1-4] We report a case of GCBL in a patient with pemphigus vegetans receiving high-dose immunosuppressants who was treated with intratumoral and systemic HPV vaccine.

Abbreviations used:

GCBL: giant condyloma of Buschke-Lowenstein
HPV: human papillomavirus
WLE: wide local excision

CASE REPORT

A 63-year-old Indo-Caribbean man with a 1-year history of pemphigus vegetans presented to the dermatology clinic with a rapidly growing left groin nodule. His pemphigus was confirmed by biopsy and direct immunofluorescence (intraepidermal, intercellular IgG). It was of the Neumann type, beginning with typical flaccid blisters developing into vegetative plaques with prolonged time to resolution. The areas involved included the oral mucosa, trunk, flexures, and perineum. Medications included prednisone 60 mg daily and mycophenolate mofetil 1 g twice daily, and he had received a single course of ultra-low-dose rituximab (100 mg intravenously 2 weeks apart) 9 months earlier.[5] He was HIV negative.

Examination revealed a 4-cm, eroded, pedunculated nodule involving the left groin with a somewhat nodular surface (Fig 1, *A*). Shave biopsy revealed parakeratosis and marked exophytic (Fig 2, *A*) and deeply endophytic (Fig 2, *B*) epidermal hyperplasia (likely corresponding to the surface nodularity), along with bulbous rete ridges showing "pushing" borders (Fig 2, *B*). Glassy keratinocytes, subtle cytologic atypia, and occasional mitoses were identified (Fig 2, *C*). Koilocytes were focally present in the upper epidermis (Fig 2, *D*). These changes were consistent with GCBL. Microscopically, the tissue margins were involved, and there was residual tumor clinically (Fig 1, *B*).

The patient was referred for wide local excision (WLE) of the residual tumor. Because of concerns regarding delayed wound healing, the surgical team requested a reduction of the immunosuppressant dose. Prednisone was decreased to 40 mg daily, resulting in a pemphigus flare and re-escalation to 60 mg, and eventually 75 mg was required for disease control. WLE was delayed. Given the etiologic role of HPV in GCBL, as well as the observed koilocytosis, we trialed intratumoral and systemic HPV vaccine (off-label use) approximately 2 months after the initial biopsy. Because of financial

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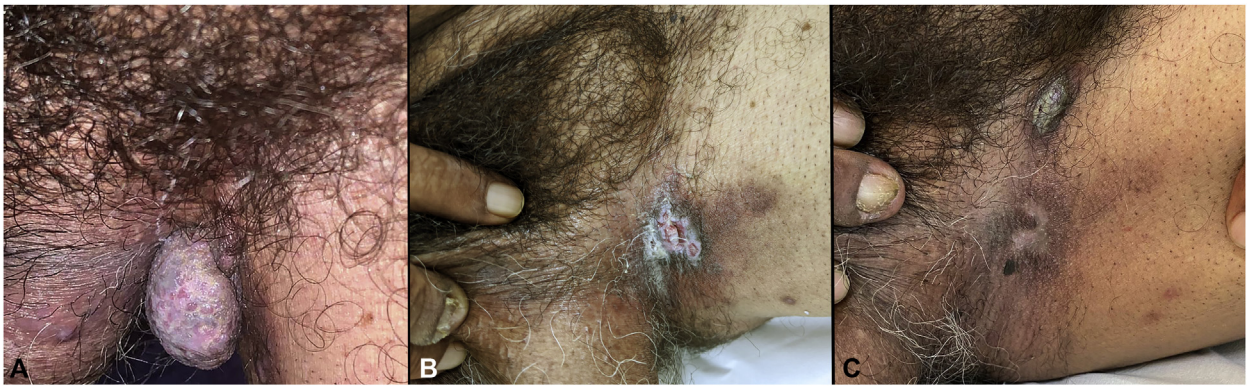

Fig 1. Giant condyloma of Buschke-Lowenstein treated with human papillomavirus vaccine. Giant condyloma of Buschke-Lowenstein of groin presenting as a pedunculated tumor with a lumpy/nodular surface (**A**). Note residual tumor at 2 months after biopsy (**B**). Clinical resolution at 12 weeks after two sessions of intralesional 9-valent and systemic 2-valent human papillomavirus vaccination. Note active pemphigus vegetans superiorly (**C**). Biopsy of this area showed scar tissue but evidence of residual carcinoma.

constraints, the 2-valent HPV vaccine (Cervarix; GlaxoSmithKline Pharmaceuticals Ltd) was used systemically, and the 9-valent vaccine (Gardasil-9; Merck & Co., Inc) was used intratumorally. We followed the standard immunization protocol of intramuscular administration at 0, 1, and 6 months. For intratumoral use, we diluted 0.5 mL of the 9-valent vaccine in 2.5 mL of saline and injected directly into the residual tumor and the subjacent dermis, using 0.2 to 0.5 mL per injection site.[6] Although the tumor decreased in size, there was still residual tumor 8 weeks after the initial injection, and the procedure was repeated at this time. Mild injection-site pain was the only adverse reaction. Twelve weeks after the initial treatment, the site was clinically disease free (Fig 1, *C*). A repeat biopsy revealed dermal fibrosis consistent with scar. At the time of writing (18 months after presentation), there has been no evidence of recurrence. Additional measures to reduce the risk of recurrence included switching from 2 g daily of mycophenolate mofetil to 17.5 mg of methotrexate weekly, but the patient still required between 50 and 75 mg of prednisone for disease control.

The patient consented to publication of the photographs and information presented in this article.

DISCUSSION

GCBL is considered by many to be a verrucous carcinoma variant with a propensity for local agression but which only rarely metastasizes.[4] Association with HPV infection, in particular HPV 6 and 11 and, rarely, high-risk subtypes, has been reported.[1-3] Although HPV subtyping on the tissue sample would have been ideal, it is not currently available in our setting. Nevertheless, the presence of koilocytosis, the characteristic architecture, and the bland cytology are strongly suggestive of a role for HPV (likely a low-risk subtype) in this lesion. WLE is the treatment of choice for genital verrucous carcinomas; however, this was a complex case.[7] First, the rapid onset of the lesion raises the possibility of a triggering role of the patient's immunosuppressants. Disease flare with dose reduction resulted in the reluctance of the surgical team to perform excision, resulting in the need for alternative therapies until a WLE could be performed. We opted for intratumoral and systemic HPV vaccination, given the role of HPV and the histopathologic identification of koilocytic change. Although this approach has not been used in GCBL or other verrucous carcinomas, it has been used in basaloid squamous cell carcinoma, another cutaneous malignancy sometimes associated with HPV.[6] Treatment resulted in both clinical and histopathologic clearance at 3 months, and the patient is disease free at the time of writing (18 months), obviating the need for excision at this time.

How intratumoral vaccination induces a therapeutic response is unknown, as is the relevance of simultaneous systemic vaccination. Direct antiviral, antitumor, and immunologic mechanisms have been suggested, but little research has been done in this area.[8] Although we acknowledge that systemic bivalent vaccination (HPV type 16/18) may not be ideal given its comparatively limited protection, in light of the need for long-term immunosuppression, we felt that high-risk subtype protection would be of some value in decreasing the risk of other HPV-associated cancers. Additionally, systemic bivalent

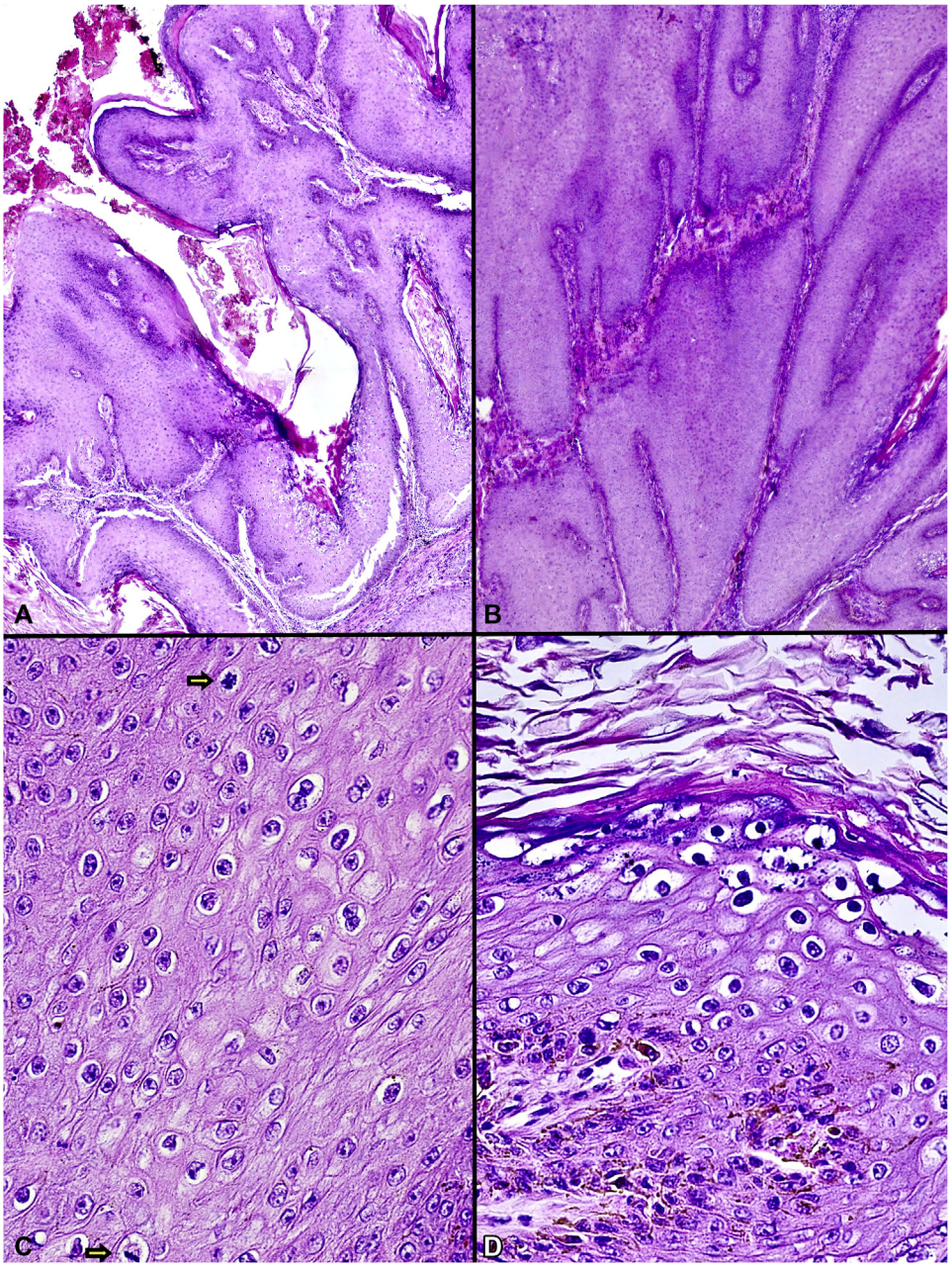

Fig 2. Giant condyloma of Buschke-Lowenstein. Because of its large size, the entire tumor could not be visualized at scanning magnification, and panels **A** and **B** show low-power views of the exo-endophytic hyperplasia. Note hyperkeratosis, with marked exophytic (**A**) and deeply endophytic (**B**) hyperplasia with bulbous rete ridges and deep, pushing borders (**B**). Glassy keratinocytes with only subtle atypia and occasional mitoses (**C**, *arrows*) are present. Koilocytic change is noted in the superficial portion of the tumor (**D**). These features are characteristic of giant condyloma of Buschke-Lowenstein. (Hematoxylin-eosin stain; original magnifications: **A**, **B**, ×40; **C**, **D**, ×200.)

HPV vaccination may induce an immunologic response against other alpha-papillomaviruses not specifically targeted by the vaccine, due to similarities in the L1 major capsid proteins shared by members of this genus, which potentially include the low-risk subtypes associated with GCBL.[9] This has clinically been demonstrated by the response of recalcitrant common warts (not typically caused by HPV types 16/18) to both intralesional and intramuscular bivalent vaccination.[8]

In conclusion, GCBL may occur in the setting of iatrogenic immunosuppression. Intratumoral and

systemic HPV vaccination may be considered as a therapeutic option in cases where excision is not immediately available or feasible. A potential extrapolation could also include the therapeutic use of intralesional HPV vaccines in HPV-driven lesions occurring in patients who have been fully vaccinated. Further studies should be performed elucidating the specific therapeutic mechanisms of vaccination immunotherapy.

Conflicts of interest

None disclosed.

REFERENCES

1. Lehn H, Ernst TM, Sauer G. Transcription of episomal papillomavirus DNA in human condylomata acuminata and Buschke-Löwenstein tumours. *J Gen Virol*. 1984;65(Pt 11):2003-2010.
2. del Pino M, Bleeker MC, Quint WG, Snijders PJ, Meijer CJ, Steenbergen RD. Comprehensive analysis of human papillomavirus prevalence and the potential role of low-risk types in verrucous carcinoma. *Mod Pathol*. 2012;25(10):1354-1363. https://doi.org/10.1038/modpathol.2012.91
3. Dias da Cunha e Silvaa JA, Lima L, De Georgea L, Araújo Sant'Ana T, Valadão M. Buschke-Lowenstein tumor in a patient with HIV and psoriasis. *J Coloproctol*. 2020;40(3):261-264. https://doi.org/10.1016/j.jcol.2019.11.491
4. Irshad U, Puckett Y. Giant Condylomata Acuminata of Buschke and Lowenstein. In: *StatPearls*. StatPearls Publishing; 2021.
5. Alaibac M. Ultra-low dosage regimen of rituximab in autoimmune blistering skin conditions. *Front Immunol*. 2018;9:810. https://doi.org/10.3389/fimmu.2018.00810
6. Nichols AJ, Gonzalez A, Clark ES, et al. Combined systemic and intratumoral administration of human papillomavirus vaccine to treat multiple cutaneous basaloid squamous cell carcinomas. *JAMA Dermatol*. 2018;154(8):927-930.
7. Jo DI, Han SH, Kim SH, Kim HY, Chung H, Kim HS. Optimal treatment for penile verrucous carcinoma: a systematic literature review. *BMC Urol*. 2021;21(1):13. https://doi.org/10.1186/s12894-020-00777-1
8. Nichols AJ, De Bedout V, Fayne RA, Burke GW, Kirsner RS, Ioannides T. Systemic and intratumoral 9-valent human papillomavirus vaccine treatment for squamous cell carcinoma in situ in a renal transplant recipient. *JAAD Case Rep*. 2020;6(4):289-291. https://doi.org/10.1016/j.jdcr.2020.02.002
9. Nofal A, Marei A, Ibrahim AM, Nofal E, Nabil M. Intralesional versus intramuscular bivalent human papillomavirus vaccine in the treatment of recalcitrant common warts. *J Am Acad Dermatol*. 2020;82(1):94-100. https://doi.org/10.1016/j.jaad.2019.07.070