"The Vaccine" by Louis Léopold-Boilly. Courtesy National Gallery of Art, Washington.

Beyond Prophylaxis: Could the HPV Vaccine be Repurposed in Skin Cancer Treatment?

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Counseling patients—in pediatrics, sometimes their parents—on human papillomavirus (HPV) vaccination frequently includes a turn of phrase believed to be so persuasive that not only is there an entire CDC webpage dedicated to it, but it has practically become a commandment on infographics for patients on cancer prevention—one has only to peruse WebMD for moments to find dozens of examples (1, 2). Medical students across the country are taught to lean in and say, "this is one of two vaccines that can prevent cancer."

Papillomaviridae is a family of mucosal and cutaneous epitheliotropic viruses that cause hyperproliferative lesions. For over four decades, the causative link between high risk (HR) mucosal HPV and malignancies, particularly cervical cancer, has been robustly established. HPV is currently the most common sexually transmitted infection worldwide and represents a tremendous disease burden, with up to 5% of cancer diagnoses attributable to HPV infection (3, 4). Hence the importance of counseling on the vaccines (bivalent, quadrivalent, and nonavalent) that exist against a number of HR HPV types in order to prevent both benign and malignant diseases. The high risk mucosal types of HPV all fall within the alpha genus of papillomaviridae. Their mechanism of mucosal carcinogenesis is

dependent on continuous expression of oncoproteins E6 and E7, often following a DNA integration event (5). During HR HPV chronic infection, these oncoproteins interact with various cellular targets to prevent apoptosis and promote unchecked growth.

Viruses from the beta, gamma, mu, and nu genera (and some alpha HPV types), colonize the epidermis, with hair follicle stem cells representing a natural reservoir of persistent infection (6). Cutaneous HPVs are ubiquitous on human skin and have been increasingly implicated in the development of non-melanoma skin cancer (NMSC), particularly β-HPVs and squamous cell carcinomas (SCC). However, up to 90% of healthy individuals test positive for cutaneous β-HPVs (5). In contrast to mucosal HR HPV carcinogenesis, it appears that E6 and E7 expression is only required at the beginning of skin carcinogenesis. The expression of these oncoproteins facilitates the accumulation of UV-induced mutations by preventing apoptosis in skin cells with high mutation burdens, known as the "hit-and-run" mechanism (5). The high prevalence of HPV in healthy people combined with a lack of evidence for an integration event as in mucosal carcinogenesis and an absence of active virus expression in cutaneous tumor samples support the hypothesis of synergism between UV radiation and HPV in the early pathogenesis but not maintenance of cutaneous SCC (7).

Currently, the FDA-approved HPV vaccines contain virus-like particles (VLP) of L1 major capsid proteins. This protein is not conserved among HPV types, with only 60% sequence homology between α- and β-types, and the resulting antibodies after vaccination are thus theoretically highly type-specific to α-HPV (8, 9). Though these vaccines were developed to prevent mucosal infection, there have been numerous reports of complete resolution of disseminated, treatment-resistant verruca vulgaris after quadrivalent HPV vaccination, even when the HPV type isolated from the lesions did not match the quadrivalent vaccine, which covers types 6, 11, 16, and 18, suggesting the existence of cross-protection against heterologous types (10).

Further, there exist in the literature five recent reports of a novel use of the quadrivalent and nonavalent HPV vaccines in patients with cutaneous squamous cell carcinoma. Nichols et al. offered two patients with SCC and BCC three systemic doses of the quadrivalent vaccine for prophylaxis for skin cancer. Sixteen months after the first dose, the male patient's new cancerous lesion rate had a 62.5% reduction in new SCC (12 to 4.4 per year) and 100% reduction in BCC (2.25 to 0) and at 13 months, the female patient had a 66.5% reduction in SCC (5.5 to 1.84) and 100% reduction in BCC (0.92 to 0) (11).

The third case is the first documented therapeutic use of HPV vaccination and involves a 90-year-old immunocompetent patient with multiple inoperable cutaneous squamous cell carcinomas, biopsy-proven to be basaloid SCC, a rare SCC characterized by invasive growth, high recurrence rate after resection, and a propensity for metastasis. The patient underwent Mohs surgery on the largest tumor but given the severity of the tumor burden and the patient's advanced age, additional surgery and radiation were deemed infeasible; the patient subsequently declined systemic chemotherapy. She was treated with a series of systemic and intratumoral nonavalent HPV vaccines (2 doses intramuscularly, 4 doses intratumorally in the largest 3 tumors over 10 months) to complete resolution of her tumors, including the non-injected ones. At eleven months after the first intratumoral dose, a small papule at the site of a previous large tumor was biopsied and showed no histologic evidence of residual disease. At 24 months after her first

intratumoral dose, the patient remained with a complete response to treatment, with no clinical evidence of SCC (12). The same research team performed the treatment—two intramuscular and two intratumoral injections with the nonavalent vaccine—on an 87-year-old immunosuppressed renal transplant recipient with inoperable SCC in situ who elected to forego radiation. His lesion resolved with biopsy-proven histologic cure (13). The final case currently reported is from Geizhals and Lebwohl, who treated an 84-year-old immunocompetent patient with multiple invasive cutaneous keratoacanthoma-type SCC with 2 intramuscular and 3 intratumoral injections of the nonavalent vaccine. Ten months after the first injection, there was neither clinical nor histologic evidence of residual carcinoma (14).

The current understanding of the cofactor-like hit-and-run relationship between cutaneous β-HPV and early squamous cell carcinogenesis would not suggest cross-protectivity and immunogenicity of highly α-type-specific L1-based vaccines for established SCC. However, the growing body of observational data of the efficacy of the vaccine as a therapeutic treatment for a number of cutaneous HPV-related conditions, from verruca vulgaris to, rather strikingly, aggressive squamous cell carcinomas implies that the reality of immunologic treatment based on specific HPV serotypes is complicated.

As with any case report, there are significant limitations to their conclusions, not least that there are currently only 5 patients with cutaneous carcinomas known to be treated with this modality. A major question stemming from the lack of controls is whether the possible immunogenic effects of the vaccines were due to the VLP contents or the vaccine adjuvants. While regression of non-injected tumors suggests systemic effects beyond local adjuvant augmentation, a broader downstream adjuvant-activated immunologic cascade cannot be ruled out. The lack of HPV testing is also a hindrance to broader conclusions being drawn from these reports, as understanding cross-protectivity is rendered impossible without knowing the serotypes present. Another distinct possibility, particularly given the small sample size, is that the observed regressions were spontaneous.

There are a number of ongoing investigations aimed at creating papillomavirus vaccines based on the more broadly conserved but less immunogenic L2 minor capsid proteins to broaden protection to include heterologous HPV types, including cutaneous (15). However, these anecdotal studies raise the possibility of an already available alternative to the current orthodoxy of physical destruction (resection, ablation, topical/intralesional chemotherapeutics) for treatment of HPV-related cutaneous SCC. Further exploration and controlled experimentation is warranted into whether the commercially available HPV vaccines may be used as therapeutic, not just prophylactic, cancer vaccines. More robust and durable data must be collected and validated, and several questions must be answered, the most important being what the immunologic mechanism of action is; whether there are predictors of outcomes such as HPV vaccination status, serotype, and tumor type; and the safety profile of using the vaccine as a therapeutic agent.

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