Successful Treatment of Perianal Giant Condyloma Acuminatum in an Immunocompromised Host With Systemic Interleukin 2 and Topical Cidofovir

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Report of a Case

A 46-year-old man presented for evaluation of large recurrent growths around the anus and rectum. He had been diagnosed as having chronic lymphocytic leukemia at age 36 years and was treated with fludarabine phosphate, cyclophosphamide, and rituximab at age 42 years, with successful induction of remission. His disease returned 3 years later, and while undergoing chemotherapy with the same regimen, he developed perianal and penile skin lesions. The penile lesions cleared with serial treatment with cryotherapy, imiquimod, and sinecatechins, to which the perianal lesions were refractory. He underwent 2 surgical debulking procedures for the rapidly progressive perianal lesions, which exhibited aggressive regrowth within 2 weeks of each debulking.

Physical examination revealed a large (>10 cm in diameter), circumferential (but not occluding the rectum), exophytic, friable perianal mass with punctate bleeding, consistent with giant condyloma acuminatum (GCA). An adjacent 3-mm papule with corymbiform surface consistent with a common wart was also noted (Figure 1). The patient reported considerable rectal pain and bleeding due to the anal condyloma. The perianal mass demonstrated severe squamous dysplasia, with focal areas concerning for squamous cell carcinoma in situ on histopathologic examination. The remaining findings from examination were unremarkable.

Therapeutic Challenge

Surgical excision often plays a central role in the treatment of the GCA; however, more than 50% of patients will experience regrowth following excisional or debulking procedures. Poor wound healing, fecal contamination of the operative site, and extensive removal of soft tissue contribute to considerable postoperative morbidity and mortality. Malignant transformation has been reported in up to 56% of anorectal GCA cases, and combinations of surgery, radiation therapy, and chemotherapy have been attempted to treat these lesions. Topical therapies reported in the literature including podophyllin, fluorouracil, and imiquimod have been investigated, with efficacy limited by recurrence. Intralesional administration of bleomycin sulfate, interferon alfa-2b, and systemic treatments with various chemotherapy regimens including bleomycin, cisplatin, fluorouracil, mitomycin, and methotrexate have also been attempted. Unfortunately, no therapeutic modality, alone or in combination, has been established as definitively superior to others. For our patient, 2 prior surgical procedures had both met with full, rapid recurrence. He was deemed ineligible for bone marrow transplant for his relapsed chronic lymphocytic leukemia while the perianal tumor remained refractory to treatment.
Solution to the Problem

Given the evidence of human papillomavirus (HPV)-mediated infectious etiology underlying GCA and the functional immunodeficiency seen in patients with underlying hematologic malignancy, we hypothesized that our patient might benefit from increased recognition of viral particles by the cellular immune system as well as targeted antiviral treatment to enhance clearance of his perianal skin lesions. After completing his chemotherapy regimen, he had remained persistently leukopenic with sustained lymphopenia and neutropenia, during which time the GCA remained refractory to treatment. His peripheral blood flow cytometry analyses revealed markedly decreased proportions of CD8+ T cells relative to CD4+ T cells, suggestive of sustained diminished cellular-mediated immunity.

Our patient underwent a third surgical resection, consisting of simple excision with base fulguration, and findings from pathologic examination again showed severe squamous dysplasia with focal squamous cell carcinoma in situ; HPV typing was not performed. He was started on treatment with high-dose interleukin 2 consisting of $5 \times 10^6$ units injected subcutaneously once daily. In addition, he was started on treatment with topical cidofovir, 3%, cream applied twice daily to the perianal area.

He was seen at a follow-up examination 3 weeks after his surgical procedure. Anal skin showed evidence of granulation tissue without gross evidence of condyloma acuminatum. There were no new warts, no bleeding, no itching, and no irritant reaction observed. While our patient was receiving high-dose interleukin 2 therapy, low-grade fevers were responsive to acetaminophen. After 3 months of therapy, the patient experienced moderate irritation at the perianal site, which was thought to be due to cidofovir use. Treatment was withheld for 2 weeks, and hydrated petroleum jelly was used for symptomatic relief. Physical examination revealed a small subcentimeter recurrence of condyloma, for which he restarted therapy with focal topical cidofovir, applied every other day, with subsequent resolution.

Four months after initiation of systemic high-dose interleukin 2 and topical cidofovir therapies, the patient underwent successful allogeneic stem cell transplant for underlying chronic lymphocytic leukemia with subsequent cessation of interleukin 2 treatments. He remained free of anal condylomata during induction and immune reconstitution. He has since been maintained on weekly topical cidofovir as prophylactic field treatment; focal areas of recurrence have been successfully treated with liquid nitrogen cryotherapy, followed by daily application of topical cidofovir. Sixteen months after initiating high-dose interleukin 2 and topical cidofovir therapies, 2 slow-growing, perianal condylomata (Figure 2) were treated successfully with fulguration and continued topical cidofovir therapy. He remains without evidence of recurrence 2 months later, with a total of 21 months of follow-up.

Discussion

Giant condyloma acuminatum, also known as Buschke-Lowenstein tumor or giant condyloma of Buschke-Lowenstein, is a rare tumor of the skin most commonly reported in the penile or anogenital region. Characteristic findings on histologic examination include an exophytic tumor with compact hyperkeratosis, extensive epidermal hyperplasia, vacuolated keratinocytes, and a tendency toward dermal invasion. It is characteristically associated with HPV types 6 and 11, though other HPV types have rarely been implicated in the development of such tumors. Giant condyloma acuminatum may represent a variant of verrucous carcinoma.

The HPV-mediated infectious etiology of GCA is reflected in an increased incidence in immunocompromised and immunosuppressed populations; those with immune incompetence are particularly susceptible to treatment-refractory disease, with associated morbidity resulting from aggressive local tissue invasion and destruction, occlusion of the rectum, and malignant transformation into squamous cell carcinoma.1-2 Treatment failure is common with both surgical and nonsurgical modalities, often necessitating a combined approach. Previously reported immunotherapies for GCA include topical imiquimod, 5%, and intralesional interferon alfa as monotherapies, or combined with surgical resection or carbon dioxide laser vaporization for debulking of tumor mass and...
enhancing topical agent contact, with varying results. Maintenance of surgical clearance by optimizing the immunologic response and simultaneously addressing the viral basis of the disease by topical means has not been reported.

Human papillomaviruses are double-stranded DNA viruses associated with the development of mucosal and cutaneous conditions ranging from common warts to oropharyngeal, penile, and cervical cancers. The viruses initially proliferate intracellularly within basal keratinocytes and are amplified as the keratinocytes migrate to the upper layers of the epidermis. Topical and intralesional treatments for viral warts are thought to preferentially damage infected keratinocytes, giving rise to 2 mechanisms of wart clearance: (1) direct cell death and elimination of infected cells and (2) exposure of infected cell contents to the body’s natural immune surveillance system, resulting in immune-mediated clearance of remaining HPV infection in immunocompetent individuals. A nucleotide analog of deoxycytidine monophosphate, cidofovir selectively competitively inhibits viral DNA polymerase. It is approved by the Food and Drug Administration for the treatment of cytomegalovirus infection in patients with AIDS and is traditionally administered as an intravenous infusion. Notable adverse effects of systemic administration include nephrotoxicity and neutropenia. Compounded topical cidofovir has been successfully used in the management of condyloma acuminatum and other HPV-mediated diseases; however, its use in GCA is novel. Interleukin 2 is a cytokine known to regulate the development and proliferation of lymphocytes and stimulate inflammatory activation of the body’s immune system. It may be administered intravenously or subcutaneously. Adverse effects associated with interleukin 2 administration include influenza-like syndromes of fevers and chills. High-dose interleukin 2 regimens were first introduced for immunotherapeutic effects in the treatment of aggressive metastatic cancers and continue to play a role in the management of select cases of melanoma and renal cell carcinoma. More recent development of lower dose interleukin 2 regimens have posited a selective or preferential enhancement of T-regulatory cells in vivo and explored such regimens as a treatment for chronic graft-vs-host disease.

Previous anecdotal reports have noted improvement of verrucae vulgaris in patients receiving interleukin 2 therapy. The theoretical benefit of high-dose interleukin 2 in this patient may lie in its ability to expand the T-effector cell population with subsequent regulation of the immune response in a patient with both leukemia and virally mediated disease. We postulate a synergistic effect between the immune up-regulation by interleukin 2 such as in T-effector cell function and the antiviral properties of cidofovir in achieving a multifaceted targeted approach to elimination of the HPV in this patient with sustained defects in cell-mediated immunity. Whether the administration of interleukin 2 achieved disease remission and the addition of topical cidofovir was able to maintain it, or whether the cidofovir achieved viral clearance and the immunotherapeutic effect of high-dose interleukin 2 treatment was able to sustain this, is an area warranting future basic and clinical investigation.

Our case highlights the potential role of topical cidofovir in maintaining remission of GCA, used in conjunction with surgical excision and high-dose interleukin 2 immunotherapy. Notably, this treatment allowed our patient to undergo definitive bone-marrow transplant treatment for his chronic lymphocytic leukemia, which was otherwise deferred due to GCA, as well as remain recurrence-free during periods of iatrogenic immunosuppression during induction and immune reconstitution.