The management of numerous carcinomatous sequelae of human papilloma virus in an allogeneic stem cell transplant patient with chronic graft versus host disease

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INTRODUCTION
The clinical manifestations of human papilloma virus (HPV) infection are vast, ranging from common warts to squamous cell carcinomas (SCCs). Immunodeficient populations are particularly susceptible to HPV infection in part because of deficiencies of cell-mediated immunity and diminished production of neutralizing antibodies.1 In particular, recipients of allogenic stem cell transplantation (allo-SCT) exhibit an increased risk for cutaneous SCC (cSCC) development, with a 20-year posttransplant incidence of 3.4%.2 Patients that have chronic graft versus host disease (cGVHD) are even more dramatically affected, with a risk of cSCC 5 times higher than that of the general population.3

CASE
A 53-year-old, nonsmoking, white (Fitzpatrick type II, blue eyes), heterosexual, HIV-negative man had AML diagnosed in 2003. He underwent induction and consolidation chemotherapy with high-dose cytarabine followed by single-antigen—mismatched unrelated peripheral stem cell donor transplant in his first remission. His conditioning regimen included total body irradiation and cyclophosphamide. His posttransplant course was complicated by acute gut, liver, oral, and cutaneous GVHD managed with oral corticosteroids and cyclosporine. Two years after transplant he had widespread chronic, sclerotic GVHD (maximum Rodnan score of >13) for which he was treated successively with combinations of cyclosporine, mycophenolate, prednisone, methotrexate, rituximab, imatinib, tacrolimus, azathioprine, and intermittent extracorporeal photopheresis. His skin sclerosis finally stabilized 5 years after transplant with a combination of extracorporeal photopheresis, tacrolimus, prednisone, and cyclophosphamide. A decade later, he continued to have contractures and intermittent ulcerations of the lower extremities and was maintained on low-dose (5 mg daily) prednisone monotherapy without the need for further immunosuppression.

The patient presented in April of 2012 for evaluation of numerous verrucous papules on the hands and feet (Figs 1 and 2). He had no history of administration of HPV vaccination. Multiple biopsies
were performed. SCC in situ (SCCIS) was detected on the left ring finger (Fig 3) and was successfully treated with topical 5% 5-fluorouracil. Biopsy from the right middle finger found subungual invasive SCC, which was treated with radiotherapy (64 Gy in 32 fractions); subsequent local recurrence was successfully eradicated with topical 5-fluorouracil under occlusion.

In November 2015, the patient had an oral lesion of the left alveolar ridge with mandibular invasion. He had no history of smoking or using smokeless tobacco products. He underwent surgical resection, revealing stage T4a, N0, M0 SCC with strong p16 expression (Fig 5). His surgical management was later followed by adjuvant radiotherapy (63 Gy in 30 fractions).

In May 2016, he had an eroded perianal plaque for which a biopsy found SCCIS with follicular extension and strong p16 expression (Fig 6). Staging included magnetic resonance imaging of the pelvis, which highlighted a contrast-enhancing lesion at the right anal verge with involvement of the right external sphincter. Surgical resection was considered; however, the patient was thought to be at risk for significant anal stenosis, and he instead underwent definitive treatment with radiotherapy (60 Gy in 30 fractions). He continued to have surveillance examinations, including colonoscopy, and remained without evidence of recurrence for more than 2 years after radiation treatment.

**DISCUSSION**

We report on a patient with numerous, serious manifestations of HPV infection ranging from destructive warts to cutaneous and mucosal SCCs.
Allo-SCT, male sex, GVHD, and subsequent treatment of GVHD with immunosuppressive therapies have all been found to increase the risk of SCC. More specifically, we believe that our patient's history of severe cGVHD particularly contributed to his development of HPV-associated malignancies. An international case control study investigating the impact of cGVHD therapy on the development of SCC after allo-SCT by Curtis et al in 2005 found that immunosuppression for greater than 24 months resulted in a 6-fold increase in occurrence of SCC. Immunosuppression with azathioprine, cyclosporine, and steroids increased the risk 18-fold. Proposed mechanisms for this increased risk include the hindered repair of tissue damaged via cGVHD-mediated mechanisms within the context of superimposed immunosuppression. Notably, the patient did receive a short course of voriconazole before transplantation, which has been linked to an increased risk of squamous cell carcinoma.

Given increased susceptibility to HPV16- and HPV18-associated SCCs of the cervix, vulva, vagina, penis, anus, oral cavity, and pharynx in post-allo-SCT patients, some have proposed off-label use of the quadrivalent HPV vaccine. HPV vaccination may also have a role as an intratumoral chemotherapeutic agent. Our patient did receive the full schedule of the quadrivalent HPV vaccine after transplant but nonetheless went on to have multiple HPV-associated SCCs, highlighting the importance of further investigation of the proper timing of the administration of these vaccinations and effectiveness in this patient population.

Determining the presence or absence of HPV infection in SCCs can provide important prognostic information, as survival for some HPV-associated SCCs is superior to HPV-negative SCCs. In particular, p16 detection can serve as a surrogate marker for HPV infection and has been found to correlate with HPV positivity in various SCCs including vulvar, penile, cervical and oropharyngeal subtypes. P16 acts as a tumor-suppressing, cyclin-dependent, kinase inhibitor that prevents hyperphosphorylation of pRB and eventual progression through the G1 phase of the cell cycle. Expression of HPV viral oncogenes E6 and E7 also results in inhibition of pRB ultimately leading to subsequent overexpression of the p16 regulator. Relevant to our patient, p16 appears to be useful in evaluating for the presence of HPV in anal intraepithelial and oral intraepithelial neoplasia. Walts et al found that for anal intraepithelial neoplasia, band-like p16 expression correlates strongly with the presence of HPV by in situ hybridization. Similarly, periungual SCC is frequently associated with the oncogenic, high-risk α-HPVs, and the presence of HPV correlates with p16 expression.
The utility of p16 immunostaining in nonmucosal, cutaneous SCC is less clear. In a study that explored the correlation between overexpression of p16 and HPV positivity in patients with extragenital and extranongal Bowen disease, only 28% of 121 samples evaluable for HPV DNA status were found to both strongly express p16 and exhibit of HPV DNA positivity suggesting that other mechanisms resulting in loss of functional pRB independent of HPV may drive p16 expression.14 The determination of p16 status in such clinical scenarios may still prove useful, however, as this molecular profile is thought to confer a similar phenotype to HPV-positive cancers ultimately resulting in better outcomes.8

Surgical management yields the highest rate of clearance for HPV-associated SCC.15 Although radiotherapy in general has been found to be inferior to surgical management for cSCC with 4-year local-regional control rates estimated at 58%, radiotherapy was used for both the perianal SCCIS and periangual SCC in our patient because of the presence of several comorbidities complicating management.16 Our patient continued to be without evidence of local recurrence or loco-regional spread of his perianal SCCIS, although he did ultimately die from recurrence of his head and neck SCC. Literature on the use of radiotherapy for periangual SCC is sparse.17 Our patient had local recurrence of periangual invasive SCC and SCCIS after radiotherapy, both of which were subsequently treated with topical 5-fluorouracil without evidence of recurrence at more than 2 years.

Chemoprevention may also be a consideration for select patients at high risk for cSCC. Acitretin has been used as chemoprevention for cSCC in several high-risk populations, including (but not limited to) those patients with multiple (>5) cSCCs in a year, xeroderma pigmentosum, solid organ transplant,18 and more recently in those with cSCC arising in the setting of BRAF inhibitor use.19 There is no literature on using acitretin for chemoprevention of oropharyngeal or periangual SCC, and given the potential side effects, acitretin was not used in our patient. Nicotinamide (vitamin B3) has protective effects against ultraviolet damage and was found in a phase 3 trial to reduce the incidence of new squamous cell carcinomas by 30% after 12 months.20 As with acitretin, no literature exists for the use of nicotinamide in chemoprevention of noncutaneous SCC.

Our case reinforces the need for early detection of SCC in allogeneic stem cell transplant patients. Yearly follow-up should emphasize the avoidance of high-risk behaviors known to increase the development of HPV-associated malignancies such as alcohol use, tobacco use, and excessive ultraviolet exposure.

Close monitoring of the oral and pharyngeal mucosa should be emphasized in those with GVHD.2 Based on our patient’s experience, we also recommend close monitoring of the genital and perianal areas, particularly in those with other manifestations of HPV infection, and further investigation of the role for HPV vaccination after allogeneic stem cell transplant.

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