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Human papillomavirus reactivation following treatment of genital graft-versus-host-disease

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Abstract

Vaginal chronic graft-versus-host-disease (cGVHD) is a common complication of stem cell transplantation. Human papillomavirus (HPV) disease can reactivate after transplantation, presumably because of immune factors affecting systemic immunity, such as waning antibody titers, impaired T- and B- lymphocyte responses, and the use of immunosuppressive therapies. However, a relationship between the use of local immunosuppressive agents and HPV reactivation and spread has not been previously described, to our knowledge. A 30-year-old woman, 2 years post transplant receiving systemic cyclosporine for cGVHD, was treated with vaginal dilators, topical corticosteroids, and estrogen for vaginal cGVHD. Colposcopy and biopsy for abnormal cytology revealed condylomatous cervicitis. Over the next 4 months, while continuing dilator therapy, linear verrucous lesions developed in the vagina and vulva, and were successfully treated with laser therapy. Use of local immunosuppression and dilators for genital GVHD can enhance spread of HPV infection. Integration of HPV screening and treatment into the care of women with genital cGVHD and development of strategies to manage both conditions simultaneously is warranted.

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Keywords

human papillomavirus; graft-versus-host-disease; immunosuppression; stem cell transplantation; genital GVHD

Allogeneic hematopoietic stem cell transplantation (SCT) is the treatment of choice for hematological diseases such as aplastic anemia, especially in those patients who do not respond to medical treatment. Reduced-intensity regimens have been developed to enable treatment of older patients and those with co-morbidities (1). However SCT has its drawbacks, including acute and chronic graft-versus-host-disease (cGVHD). Female genital GVHD affecting the vulva and vagina has been reported in 25–49% of allogeneic hematopoietic SCT survivors (2). Vaginal symptoms include dyspareunia, dryness, burning, itching, and pain to touch, along with signs including scars forming in the vagina. Recommended treatment of vaginal GVHD may involve the use of dilators with topical corticosteroids and topical estrogen (2).

Human papillomavirus (HPV) infection is the most common sexually transmitted infection worldwide, with immunosuppression being an important risk factor. In a healthy reproductive-aged female population, an estimated 20–46% of women harbor the virus (2). Women after SCT have an increased risk of reactivation of HPV, with 43% having an abnormal Papanicolaou smear and 20% having high-grade squamous intraepithelial lesions (3). We report a case of spread of HPV along the sides of the vagina when treatment of genital GVHD continued in a patient who underwent colposcopy and biopsy of HPV cervical infection, and highlight important measures that can be taken to prevent such complications.

Case report

A 30-year-old woman, 2 years post SCT for aplastic anemia, complained of severe dyspareunia and post-coital bleeding, and was referred to the Gynecology Consult Service for evaluation. She had been diagnosed with aplastic anemia at the age of 8, and underwent reduced-intensity, non-myeloablative chemotherapy before peripheral blood SCT with a human leukocyte antigen-matched sibling donor at the age of 28. As part of her immunosuppression regimen post transplant, she received 150 mg cyclosporine daily. No acute GVHD was reported, but cGVHD in the mouth and eyes began a year later. She was then started on prednisone, which was eventually tapered and discontinued.

She had been advised to postpone pregnancy until 5 years post transplant, and was prescribed a combined oral contraceptive for contraception and to lessen menses. Her symptoms of dyspareunia and bleeding occurred the first time she had attempted intercourse after her transplant 2 years earlier.

On speculum and bimanual examination, the patient had vaginal synechiae consistent with genital GVHD. Fine linear scarring in the form of 4 ridges, each 3–4 cm in length, was felt on the left vaginal wall, at the level of the levator ani muscles. As pain was elicited on palpation of the scarred vaginal areas, the patient's dyspareunia likely was caused by these narrowed areas. She was given instructions to use a pea-sized amount of clobetasol propionate cream and 1 inch (2.54 cm) of conjugated estrogens cream (Premarin®; Pfizer, New York, New York USA) on the tip of vaginal dilators, and to use the dilators twice a week for 10 min for treatment of the vaginal synechiae.

Cytology testing also revealed low-grade intraepithelial neoplasia and high-risk HPV types were detected. The patient underwent colposcopy and cervical biopsy, which indicated

condylomatous changes. Cervical cytology testing with HPV typing in 1 year was recommended.

In a follow-up visit 4 months later, the patient reported that she had continued to use the prescribed therapy of dilators with topical estrogen and corticosteroids. On examination, the patient's HPV disease was found to have spread substantially. Verrucous lesions were found on the posterior fourchette and the left labia near the urethral opening. A linear ridge of HPV lesions extended from the fornices along both left and right sides of the vagina (Fig. 1). Vaginal biopsy indicated vaginal intraepithelial neoplasia Grade I and vulvar biopsy showed condyloma. Given the linear distribution of HPV lesions within the vagina and the use of dilators and topical clobetasol propionate for the treatment of genital GVHD, the patient was advised to stop using the dilators and topical steroids immediately. The verrucous lesions were successfully treated with laser therapy.

On follow-up 1 month later, her vulva was healing well and there was no evidence of HPV disease. However, marked atrophy of the laser-treated vaginal epithelium and a denuded area on the left side of the vagina was noted. Epithelial fragility did not improve with intravaginal estrogen tablets, but did lessen with use of an ultralow-dose estrogen vaginal ring.

Discussion

Our case illustrates a possible relationship between use of local immunosuppressive therapy for genital GVHD and rapid spread of HPV-associated condyloma. Although this particular relationship has not been reported previously, to our knowledge, studies have reported reactivation of HPV in the setting of immunosuppressive treatment of lichen planus and lichen sclerosus. Von Krogh et al. (4) report an otherwise healthy 51-year-old man with penile erosive lichen planus, who was treated repeatedly over 5 years with topical mild-to-moderately potent corticosteroids at intervals of up to 10 weeks. During that time he suffered a total of 9 clinical outbreaks, each occurring after a period of treatment, of condylomata that showed the presence of low-risk HPV. Secondly, Bilenchi et al. (5) present 2 patients who received tacrolimus ointment for genital lichen sclerosus. Both patients experienced genital condylomata that were positive for low-risk HPV. None of these patients reported a history of condylomata, multiple sexual partners, or a change in sexual partners. These cases suggest that long-lasting topical immunosuppressive therapy may be associated with reactivation of a latent HPV infection. Furthermore, glucocorticoid steroid hormones have been shown to induce HPV transcription *in vitro* by exerting a direct influence on hormone response elements in the viral genome (6).

Studies have shown an increase in HPV disease and related cytological abnormalities in the immunocompromised, including renal allograft recipients and human immunodeficiency virus (HIV)-infected individuals. Although most immunocompetent hosts clear HPV infection with no sequelae, women infected with HIV have 1.8–8.2 times higher rates of HPV reactivation and recurrent dysplasia compared with HIV-uninfected women (7).

In the setting of SCT, changes in T-cell immunity to HPV or the loss of antibody titers along with the use of immunosuppression to treat GVHD may all contribute to HPV reactivation (8), leading to the development of widespread condylomata. Our patient was using topical corticosteroids as well as systemic cyclosporine at the time of her HPV disease outbreak. Cyclosporine was initiated for GVHD prophylaxis and continued at 1 year when she developed cGVHD, but not increased when her HPV spread. HPV worsened only when corticosteroids and dilators were used after colposcopically directed biopsy. Before that, she had no obvious condyloma when she was on her post-transplant immunosuppressive

regimen. Consequently, it is most likely that the use of topical immunosuppressive therapy, coupled with dilators after genital tract biopsies, led to this presentation.

Abnormal cervical cytology reports and reactivation of HPV disease post transplant illustrate the importance of routine cervical cytology and HPV testing, and, if necessary, colposcopy, in women. Such testing and allowing time for healing after biopsies may be especially important before treatment is initiated in patients with genital GVHD, given their potential risk for HPV disease-associated cervical, vaginal, and vulvar intraepithelial neoplasia.

Several approaches can be used to limit the spread of pre-existing HPV. First, when biopsies are performed to diagnose HPV, biopsied regions should heal before initiating topical steroids and dilator use. Treating visible HPV lesions with topical imiquimod, before genital GVHD treatment is implemented, is also important. To limit spread of cervical and vaginal HPV once vaginal treatment is initiated, vaginal dilators can be cleansed after each use with dilute bleach, to prevent the dilators acting as a mode of dissemination for the virus. Limiting use of topical immunosuppression and initiating treatment of genital GVHD after systemic immunosuppression is optimized or, in some cases, discontinued may also limit HPV reactivation. However, in this case, active cGVHD precluded tapering of cyclosporine. An additional strategy may be use of a low-dose estrogen vaginal ring instead of dilators (2), which can mechanically open opposing sides of the upper vagina, preventing vaginal stenosis. Finally, topical estrogen alone may be tried, to improve the integrity of the vulvar and vaginal mucosa.

In conclusion, this report highlights the possibility of HPV reactivation after topical corticosteroid treatment for genital GVHD in women post SCT. This observation underscores the importance of HPV screening and treatment in the care of women after SCT, especially those with genital GVHD. Implementing strategies to manage both conditions simultaneously is warranted.

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Fig. 1.
Vulvar and linear vaginal condyloma on the left side of the vagina.