SAGE Open Medical Case Reports

SAGE Open Medical Case Reports
JCMS Case Reports
Volume 8: 1–3

DOI: 10.1177/2050313X20904542
journals.sagepub.com/home/sco
SAGE

Refractory extensive vulvar high-grade squamous intraepithelial lesion in an immunosuppressed transplant patient treated with topical cidofovir: A case report

Darosa Lim[1], Annie Belisle[2] and Deana Funaro[1]

Abstract

High-grade squamous intraepithelial lesion of the vulva is a premalignant condition which may be especially resistant to treatments among immunosuppressed patients. We present our experience with the use of topical cidofovir in a refractory case of extensive vulvar high-grade squamous intraepithelial lesion in a 37-year-old transplant patient. Eighteen cycles of cidofovir over a 2-year period led to a sustained significant improvement, mainly of the mucosal lesions and was well tolerated. To our knowledge, we have not seen this therapy described in transplant patients with extensive high-grade squamous intraepithelial lesion.

Keywords

High-grade squamous intraepithelial lesion, vulva, cidofovir, immunosuppressed, transplant

Introduction

Vulvar intraepithelial neoplasia (VIN) is a premalignant condition with an incidence of 5 cases per 100,000 women in the United States and affects mainly premenopausal women.[1] Risk factors include high-risk human papillomavirus (HPV), smoking, and immunodeficiency.[2] In 2015, the International Society for the Study of Vulvovaginal Disease (ISSVD) revised the terminology system. It classifies VIN as follows: vulvar low-grade squamous intraepithelial lesion (LSIL), vulvar high-grade squamous intraepithelial lesion (HSIL) and VIN differentiated type (dVIN).[3] HSIL and dVIN have a 2%–15% risk of progression to invasive squamous cell carcinoma.[2] Before this classification, the term VIN was used in previous publications.

Therapy is individualized for each case and is aimed to completely remove lesions, relieve symptoms and prevent malignant progression, while preserving vulvar function and anatomy.[4] Treatments include surgical options such as excision, electrosurgery and CO_2 laser, and medical options such as topical imiquimod, cidofovir and photodynamic therapy. HSIL in immunosuppressed patients may be especially resistant to treatments.[5]

We present a case of refractory extensive vulvar HSIL in an immunosuppressed transplant patient treated with topical cidofovir.

Case report

A 37-year-old woman was referred to the Vulvar Disease Clinic for recurrent extensive HSIL of the vulva. She was known for cystic fibrosis and had lung transplantation 11 years ago. She was under immunosuppressive therapy including systemic tacrolimus, mycophenolate mofetil and prednisone. The lesions were resistant to numerous treatments tried over several years including imiquimod, topical fluorouracil, CO_2 laser and photodynamic therapy. The patient presented diffuse papillomatous papules involving the vulva, pubic area, clitoral hood, perianal region and intergluteal cleft (see Figure 1). Multiple vulvar and perianal biopsies demonstrated HSIL (see Figures 2 and 3) and were positive for HPV 58.

Cidofovir 1% cream was initiated with daily application for 5 days followed by a 9-day rest period which was

[1]Division of Dermatology, Centre Hospitalier de l'Université de Montréal (CHUM), Montreal, QC, Canada
[2]Department of Pathology, Centre Hospitalier de l'Université de Montréal (CHUM), Montreal, QC, Canada

Corresponding Author:
Deana Funaro, Division of Dermatology, Centre Hospitalier de l'Université de Montréal (CHUM), 1051 Sanguinet Street, Montréal, QC H2X 3E4, Canada.
Email: rouleaufunaro@videotron.ca

extended up to 16 days in case of a strong inflammatory reaction. After eight cycles of cidofovir over a 6-month period, the patient showed for the first time significant improvement with almost complete resolution of lesions, mainly of the vulvar mucosa (see Figure 4). Clearance was based on physical examination only. Local irritation, although considerable at first, lessened over time with the decrease of lesions. Liquid nitrogen was added to treat recalcitrant lesions on hair-bearing portion of labia majora, groins and buttocks leading to a satisfying response. Laboratories and urinalysis were monitored monthly and did not show any sign of toxicity. At 2-year follow-up, no recurrence of vulvar mucosal lesions was observed after 18 cycles of treatment. Remaining lesions on hair-bearing portion of labia majora, groins and buttocks are still being treated will liquid nitrogen.

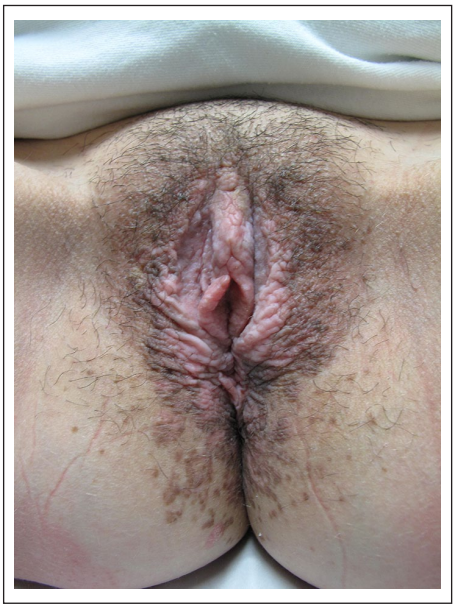

Figure 1. View of vulvar and perianal regions showing diffuse papillomatous lesions before cidofovir was initiated.

Discussion

Among immunocompromised patients, treatment has been mostly described in HIV women while transplant patients have rarely been specifically addressed.[5] In this population, VIN develops at a younger age (37 vs 44 years old) and is more often multifocal and multicentric with a higher risk of recurrence and progression. There is no consensus for vulvar HSIL management in immunosuppressed patients. Because of their often ongoing condition and/or recurrent issues with HPV-related lesions, pharmacologic therapies may be preferred over surgery to avoid sometimes extensive procedures.

In the present case of refractory HSIL in an immunosuppressed transplant patient, topical cidofovir was a tolerable effective treatment. Cidofovir is a nucleoside analogue with antiviral activity which induces apoptosis of HPV-infected cells.[6] It also reduces oncoproteins E6 and E7 expression, while increasing tumor suppressor proteins p53 and pRb.[7] In 2005, Tristram et al.[8] first described its use in vulvar HSIL among 12 women with unknown immune status, with at least a partial response (⩾50% reduction of lesions) in 58% of patients after 16 weeks of therapy. In 2014, Stier et al.[9] included in their study eight HIV women with vulvar HSIL treated with cidofovir 1%, leading to at least a partial response in 50% of cases after six cycles. Our patient's regimen was based on this study. Finally, a prospective multicentric study comparing cidofovir 1% to imiquimod 5% randomly assigned to 180 women over 24 weeks showed 46% of complete response in both groups.[10] Among immunocompromised cases, one patient out of two responded to cidofovir, while two patients out of six responded to imiquimod. At 18-month follow-up after treatment, 94% and 72% of complete responders remained free of disease in cidofovir and imiquimod groups, respectively.[11]

Topical cidofovir is usually well tolerated and main side effects include local irritation and ulcerations, which decrease over time. Complete blood count and renal function should be monitored regularly because of the

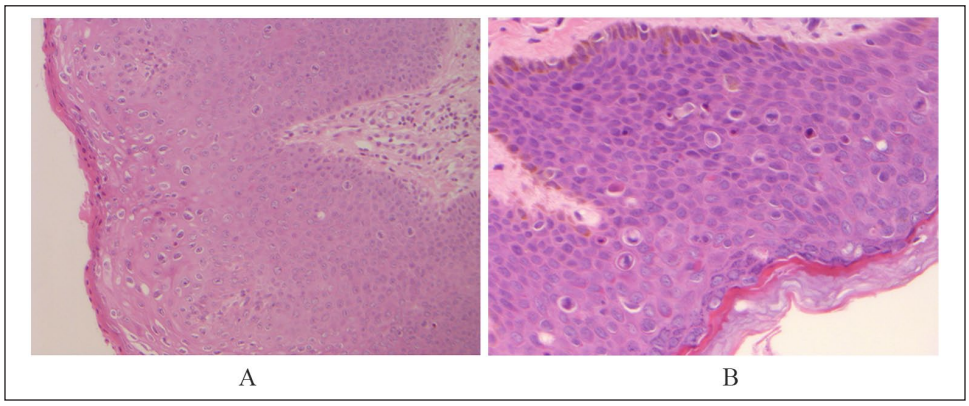

Figure 2. (a) and (b) A hematoxylin and eosin-stained section at 20× (a) and 40× (b) magnification shows vulvar and perianal HSIL with full-thickness atypia, loss of maturation, increased mitotic index and basal hyperplasia with basaloid appearance.

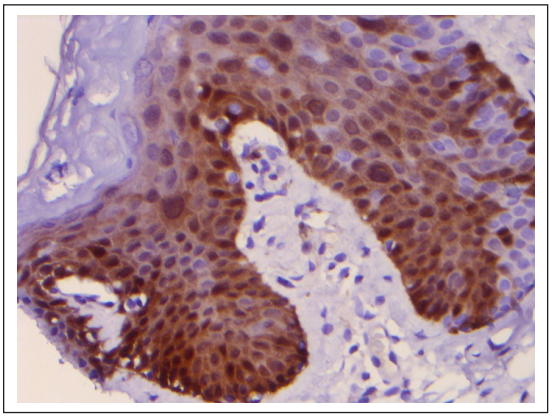

Figure 3. Staining with p16 at 40× magnification highlights high-risk HPV-related HSIL.

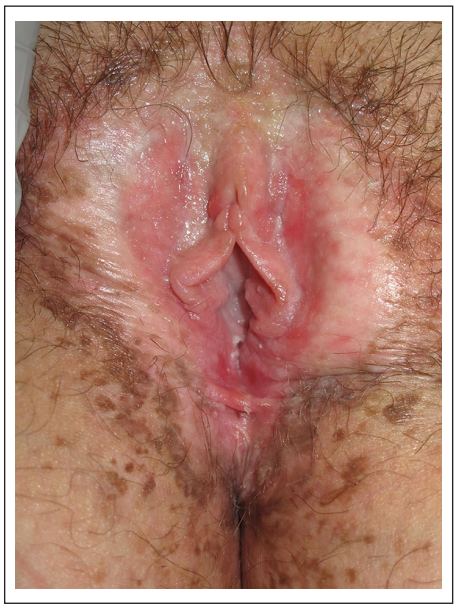

Figure 4. Significant improvement was sustained after 11 cycles or 14 months of topical cidofovir, mainly of the vulvar mucosa. Liquid nitrogen was added on cutaneous regions.

theoretical risk of hematological and renal toxicity described with systemic cidofovir.[12] Topical cidofovir bioavailability in humans is not known, but systemic absorption may not be negligible as proteinuria was reported in 23% of cases in one study.[10]

In this case occurring in the Province of Quebec, a request for topical cidofovir as an "exceptional medication" for the Quebec Medical Insurance Board (*Régie de l'assurance maladie du Québoc* (RAMQ)) was obtained through the hospital pharmacological committee. The Committee accepted the request supported by previously cited articles on topical cidofovir as a treatment for vulvar HSIL. Cidofovir 1% cream was obtained from the manufacturing company and compounded by the hospital pharmacy.

Topical cidofovir hence represents an interesting pharmacologic option for vulvar HSIL. The present case features that it is an effective tolerable treatment among immunosuppressed transplant patients with extensive refractory disease.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Informed consent

The patient provided written consent for publication of the case report.

References

1. Bodelon C, Madeleine MM, Voigt LF, et al. Is the incidence of invasive vulvar cancer increasing in the United States. *Cancer Causes Control* 2009; 20(9): 1779–1782.
2. Nelson EL, Bogliatto F and Stockdale CK. Vulvar intraepithelial neoplasia (VIN) and condylomata. *Clin Obstet Gynecol* 2015; 58(3): 512–525.
3. Bornstein J, Bogliatto F, Haefner HK, et al. The 2015 International Society for the Study of Vulvovaginal Disease (ISSVD) terminology of vulvar squamous intraepithelial lesions. *J Low Genit Tract Dis* 2016; 20(1): 11–14.
4. Preti M, Scurry J, Marchitelli CE, et al. Vulvar intraepithelial neoplasia. *Best Pract Res Clin Obstet Gynaecol* 2014; 28(7): 1051–1062.
5. Bradbury M, Cabrera S, Garcia-Jimenez A, et al. Vulvar intraepithelial neoplasia: clinical presentation, management and outcomes in women infected with HIV. *AIDS* 2016; 30(6): 859–868.
6. Andrei G, Snoeck R, Schols D, et al. Induction of apoptosis by cidofovir in human papillomavirus (HPV)-positive cells. *Oncol Res* 2001; 12(9–10): 397–408.
7. Abdulkarim B, Sabri S, Deutsch E, et al. Antiviral agent cidofovir restores p53 function and enhances the radiosensitivity in HPV-associated cancers. *Oncogene* 2002; 21(15): 2334–2346.
8. Tristram A and Fiander A. Clinical responses to cidofovir applied topically to women with high grade vulval intraepithelial neoplasia. *Gynecol Oncol* 2005; 99(3): 652–655.
9. Stier EA, Goldstone SE, Einstein MH, et al. Safety and efficacy of topical cidofovir to treat high-grade perianal and vulvar intraepithelial neoplasia in HIV-positive men and women. *AIDS* 2013; 27(4): 545–551.
10. Tristram A, Hurt CN, Madden T, et al. Activity, safety, and feasibility of cidofovir and imiquimod for treatment of vulval intraepithelial neoplasia (RT3VIN): a multicentre, open-label, randomised, phase 2 trial. *Lancet Oncol* 2014; 15(12): 1361–1368.
11. Hurt CN, Jones S, Madden TA, et al. Recurrence of vulval intraepithelial neoplasia following treatment with cidofovir or imiquimod: results from a multicentre, randomised, phase II trial (RT3VIN). *BJOG* 2018; 125(9): 1171–1177.
12. Lea AP and Bryson HM. Cidofovir. *Drugs* 1996; 52(2): 225–230.