



Successful Use of Combination 5% Fluorouracil and 0.005% Calcipotriene Cream for Peri-Anal HSIL and SCCIS in an HIV-Positive Patient

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Abstract

Purpose: The management of multifocal perianal high-grade squamous intraepithelial lesion (HSIL) and squamous cell carcinoma in situ (SCCIS) remains challenging, especially in immunosuppressed populations such as individuals with HIV. Current treatments are often invasive and associated with high recurrence rates. This case report explores the use of combination 5% fluorouracil and 0.005% calcipotriene cream (5FU/C) as a non-invasive therapeutic alternative for recurrent perianal HSIL and SCCIS.

Methods: We present a case of a 57-year-old HIV-positive male on antiretroviral therapy with recurrent HSIL and SCCIS involving the perianal, gluteal, perineal, and inguinal regions. After failing multiple surgical excisions, the patient was treated with 5FU/C cream applied topically twice daily for 8 days.

Results: The patient experienced a strong inflammatory response and discontinued therapy prior to the recommended 10-day course. However, at 1-month follow-up, there was complete clinical resolution of external lesions. Four months later, internal recurrence was detected via digital rectal exam and high-resolution anoscopy, but external lesions remained clear. Biopsies confirmed HSIL without invasive disease.

Conclusion: This case illustrates the potential of 5FU/C as a non-invasive treatment option for extensive external HSIL and SCCIS in immunocompromised patients. While external lesion resolution was achieved, internal disease recurrence at 4 months after 5-FU/C treatment emphasizes the importance of comprehensive internal evaluation. These findings support further investigation of 5FU/C as an adjunct or alternative to surgical treatment in the multidisciplinary management of anal neoplasia.

Introduction

Perianal high-grade squamous intraepithelial lesion (HSIL) and anogenital squamous cell carcinoma in situ (SCCIS) are frequently encountered in immunosuppressed patients, particularly those with human immunodeficiency virus (HIV).¹⁻³ Immunosuppression predisposes these patients to persistent viral infections, such as human papillomavirus (HPV), leading to recurrent dysplastic and neoplastic lesions that can be persistent and difficult to treat. HSIL refers to a high-grade precancerous lesion typically characterized by HPV infection, whereas SCCIS is a localized carcinoma confined to the epithelium. These lesions are characterized by disordered epithelial cell maturation and atypia, often presenting as multifocal, erythematous or verrucous plaques with potential to progress to invasive squamous cell carcinoma if left untreated. Multifocal SCCIS/HSIL in immunosuppressed patients is challenging to

treat with no standard of care and has the propensity to develop into invasive peri-anal squamous cell carcinomas that have 5-8% risk of developing metastatic disease.⁴ Current management strategies for multifocal HSIL and SCCIS include surgical excision, topical therapies, and ablative procedures; however, no standardized treatment approach exists, and recurrence rates remain high^{5,6,7}. Additionally, very few studies have evaluated the use of topical 5% fluorouracil and 0.005% calcipotriene (5FU/C) in immunosuppressed populations. In a randomized controlled trial of 131 participants evaluating 5FU/C versus Vaseline plus 5-FU, only one immunosuppressed patient was included and subsequently excluded from the final analysis. Notably, this patient, who was in the 5FU/C arm, demonstrated lower reduction in facial actinic keratoses than the rest of the cohort⁸. This case represents a novel report highlighting the successful use of 5FU/C to treat recurrent HSIL and SCCIS in the perianal, perineum, inguinal, and gluteal areas in HIV-positive patient on antiretroviral therapy (ART).

Case Report

A 57-year-old male diagnosed with HIV in 2004 on ART with an undetectable viral load, but persistently low CD4 count, presented with recurrent HSIL and SCCIS. He had multiple lesions localized to the perianal area, gluteal crease, right perineum, and left groin (scrotum, inguinal crease, and upper inner thigh) (Figure 1).

Clinically the lesions appeared to be confined to the epidermis and several biopsies confirmed SCCIS with no invasive disease. The patient was previously treated with multiple surgical excisions over several years. Notably, in May and December of 2019, he underwent excision of multiple HSIL and SCCIS lesions in the perianal and perineal regions, with pathology consistently demonstrating positive peripheral margins and subsequent recurrence at the same sites. Further excisions in November 2022 again revealed HSIL and SCCIS involving the perianal



Figure 1: Lesions of perianal, inguinal, and scrotal regions presenting as velvety, pink-to-brown papules with a hyperpigmented hue, indicative of recurrent HSIL and SCCIS

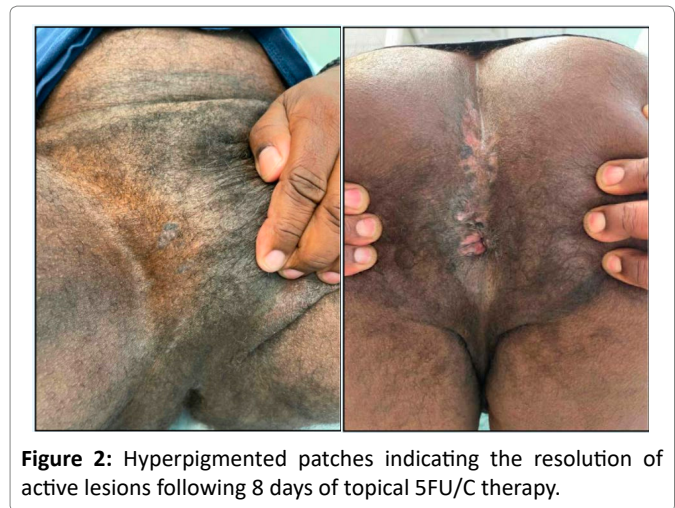


Figure 2: Hyperpigmented patches indicating the resolution of active lesions following 8 days of topical 5FU/C therapy.

skin, left groin, and left gluteus, with repeated positive margins. Despite undergoing more than twelve excisions, he experienced persistent regrowth of lesions. In light of these outcomes a topical regimen of combination 5FU/C was recommended as a non-invasive treatment to reduce the lesion burden and alleviate symptoms.

In April 2024, the patient completed 8 days of topical 5FU/C to all involved regions. The therapy induced a strong inflammatory response within 8 days, leading the patient to discontinue the treatment prior to the recommended 10 days. At 1 month, there was no evidence of residual disease (Figure 2).

In August 2024, the patient reported perianal discomfort for over 1 week and on exam by his general surgeon a new firm mass concerning for malignancy was noted on digital rectal exam (DRE) and high-resolution anoscopy (HRA). Findings showed dysplastic tissue in the anterior midline and a larger dysplastic lesion in the left posterolateral location extending distal to the dentate line. Biopsies in October 2024 confirmed high-grade squamous intraepithelial lesion of both clinical areas. The plan was to also perform HRA; however, the patient could not tolerate this in an office-based setting and received the HRA in the operating room in April of 2025. HRA revealed areas of acetowhite, Lugol's-negative tissue in the left posterolateral, right lateral, and left lateral regions, consistent with HSIL. These areas were ablated using electrocautery during the procedure. The patient is scheduled for a follow-up visit in the HRA clinic in 9 months.

Discussion

Treatment options for anal HSIL and SCCIS include both ablative and topical approaches. Office-based ablative procedures, such as electrocautery ablation and infrared coagulation, and surgical excision under anesthesia, are commonly used. A retrospective study of 246 patients followed over 10 years showed that 78% had no evidence

of HSIL at their last visit after HRA-guided electrocautery ablation, however 57% experienced recurrence and 18.7% had persistent disease in the follow up period⁹.

Topical treatments, including 5-fluorouracil (5FU), imiquimod, cidofovir, and trichloroacetic acid (TCA) have increasingly been used in practice.⁶ In a randomized controlled trial involving 148 HIV-positive men who have sex with men, researchers compared the efficacy of imiquimod, topical 5-fluorouracil (5-FU), and electrocautery for the treatment of anal intraepithelial neoplasia¹⁰. The study found complete response rates of 24% for imiquimod, 17% for 5-FU, and 39% for electrocautery. Additionally, recurrence rates at 72 weeks post-treatment were 71% for imiquimod, 58% for 5-FU, and 68% for electrocautery, indicating a high likelihood of lesion recurrence across all treatment modalities. In a separate multicenter trial involving 33 HIV-positive men and women with high-grade perianal and vulvar intraepithelial neoplasia, topical cidofovir 1% gel applied once daily for five consecutive days every two weeks over six cycles resulted in a complete response in 15% of participants and partial regression in 36%¹¹. Combination of 5-FU/C has been used off-label for SCCIS. In a pilot study, histological clearance of SCCIS was achieved in 83.3% and 87.5% of patients in the 7-day and 14-day treatment groups, respectively, compared to no clearance in the placebo group, though immunosuppressed patients were excluded from participation.¹² A retrospective cohort study from 2 academic centers of 163 patients using 5FU/C for biopsy proven superficial keratinocyte carcinoma (SKC) showed 91% achieving a complete response (CR) with 89% of immunosuppressed patients achieving CR¹³. Challenges to using topical 5FU include temporary local inflammation and irritation which can be particularly difficult for patients with sensitive or extensive lesions. In our case, the patient experienced significant discomfort from inflammation, ultimately leading to early discontinuation of therapy despite clinical response.

To our knowledge, there are no prior reports of peri-anal HSIL/SCCIS being treated with this combination regimen.

One important consideration highlighted by the case presented herein is the potential for internal HSIL. This underscores the importance of internal examinations, particularly in immunosuppressed patients, with peri-anal HSIL and SCCIS.

This case demonstrates the utility of combination 5FU/C as a non-invasive treatment option for extensive and recurrent perianal HSIL and SCCIS. Although these findings are limited by the single patient nature of the report and a relatively short follow-up duration, the successful resolution of external lesions following topical therapy suggests that this approach may be a valuable alternative to surgical excision in select patients, particularly those

with a history of multiple procedures and high recurrence risk.

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Patient Consent

The authors obtained written consent from patients for their photographs and medical information to be published in print and online and with the understanding that this information may be publicly available. Patient consent forms were not provided to the journal but are retained by the authors.

Conflict of Interest

ESR: Serves as a consultant Regeneron Inc., Checkpoint Therapeutic, Feldan Pharmaceuticals, Merck Pharmaceuticals. She serves as a Principal Investigator/Co-Investigator for the following companies: Regeneron (PI/Co-I), Merck (Co-I), Castle Biosciences (PI/Co-I). She is on the Board of Directors of Skin Cancer Outcomes Consortium (SCOUT).

Abbreviations used

HSIL (High-grade squamous intraepithelial lesion), SCCIS (Squamous cell carcinoma in situ), HIV (Human immunodeficiency virus), HPV (Human papillomavirus), ART (Antiretroviral therapy), SCJ (Squamocolumnar junction), HRA (High-resolution anoscopy){Citation}

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