The patient was subsequently treated with IVIG, 0.4g/kg/d, for 5 consecutive days for her newly diagnosed CVID, while local application of paraffin gauze dressing (Jelonet; Smith & Nephew) was maintained. Surprisingly, 3 weeks after this single cycle, all ulcerations had healed (Figure 2), and complete resolution of pain was reported. The immunoglobulin levels remained stable 3 months after IVIG treatment, and no further ulcerations were detected during a 2-year follow-up, and so the patient did not require additional therapy.

Discussion | In our case, no significant success was observed in reduction of NL ulcers after administration of currently accepted treatments, the efficiency of which was known to be limited. Interestingly, treatment of the patient’s CVID with IVIG appeared to heal the ulcers within 3 weeks. As the IVIG treatment showed a similar dramatic ulcer reduction within 2 weeks in a previous case (where no investigation of associated hypogammaglobulinemia was performed), the immunologic aspect of NL appears of major importance in these patients. Because of its strong association with diabetes, NL has been postulated to arise due to microangiopathic vascular changes. Therefore, NL might be due to immunologically mediated vascular changes.4,5 In this context, measures of serum immunoglobulin levels and direct immunofluorescent histologic study might be recommended in NL.

Our findings suggest that IVIG can be a successful option in the treatment of NL, particularly in patients with CVID, while a broader approach in NL without underlying CVID requires further investigations.

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Intralesional Cidofovir for Treating Extensive Genital Verrucous Herpes Simplex Virus Infection

Verrucous herpes simplex viral infections in immunocompromised patients can be a therapeutic challenge, and we present a case of successful treatment with intralesional cidofovir.

Report of a Case | A 55-year-old man with human immunodeficiency virus (HIV) and hepatitis C virus coinfection presented with new lesions on his scrotum and perianal area. He noted mild tingling and slow growth over the prior 2 months. His medications included darunavir, ritonavir, emtricitabine/tenofovir, and trimethoprim-sulfamethoxazole. His CD4 count was stable at 350 cells/μL, and he had an undetectable HIV viral load. Findings of a comprehensive metabolic panel and complete blood cell count were normal, and rapid plasma reagin was nonreactive. Physical examination was notable for exophytic, verrucous, and ulcerated plaques on his right inferior scrotum and perianal area (Figure 1A and B). Biopsy and tissue culture were performed. Histopathologic analysis demonstrated full-thickness epidermal ulceration with adjacent pseudoepitheliomatous hyperplasia (Figure 2A and B). Multinucleated keratinocytes with peripheral rimming of nuclear chromatin were present at the edge of the ulceration (Figure 2B and C), and immunostaining for herpes simplex virus (HSV) was positive, confirming HSV infection (Figure 2D). Gram and periodic acid-Schiff stainings and Treponema pallidum immunostaining were negative. Tissue culture had no growth, and viral resistance testing could not be performed.

The patient began treatment for HSV, and despite successive 1-month courses of high-dose oral acyclovir, valacyclovir, and famiciclovir, his lesions progressed. A repeated tissue culture for viral resistance testing was not successful in growing virus. A repeated biopsy confirmed the original diagnosis of verrucous HSV. Given concern for acyclovir-resistant HSV, oral therapy was discontinued, and intravenous (IV) cidofovir treatment was initiated, with improvement noted after 3 doses. This treatment was complicated by elevations in serum creatinine levels and discontinued. Intralesional cidofovir was then initiated every other week, as previously reported,6 with resolution of his scrotal lesion and dramatic improvement in his perianal lesion after 6 treatments (Figure 1C and D).

Discussion | Herpes simplex virus infections cause significant morbidity in immunocompromised patients, and active HSV infection increases HIV transmission.7 Infection with acyclovir-resistant HSV strains is about 10-fold higher in patients with HIV than in immunocompetent individuals and appears related to the degree of immunosuppression and duration of antiretroviral therapy.7 Treatment options for acyclovir-resistant HSV are limited and include foscarnet, cidofovir, imiquimod, and immunomodulating dipeptides.8-10 Foscarnet and cidofovir are not dependent on phosphorylation of viral thymidine kinase for activation and can therefore be used in acyclovir-resistant cases; however, both have limited formulations, and drug-induced nephrotoxic effects are potentially serious complications. Topical and intralesional admin-

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istrations of cidofovir have also been used for acyclovir-resistant disease.1,5

In this case, acyclovir resistance was not confirmed with viral resistance testing but inferred from lack of treatment response. Given the disease extent, treatment with IV cidofovir was first attempted than discontinued owing to nephrotoxic effects. Topical cidofovir was considered but not pursued, to avoid the significant potential for local irritation and burning in the setting of ulcerated plaques. Intralesional cidofovir was ultimately used because of previously reported success in the treatment of facial acyclovir-resistant HSV.1 Since increased sensation is known to occur in the genital area, a ring block with lidocaine and epinephrine followed by a 1:4 dilution of cidofovir (75 mg/mL) was used, with 5 mL infiltrated into the scrotal lesion and 5 mL into the perianal lesion. The patient tolerated the injections well, requiring no additional pain medication, and had remarkable improvement without laboratory abnormalities (Figure 1C and D).

This report highlights the successful use of intralesional cidofovir in a patient with verrucous HSV infection of the scrotum and perianal area. Given its low risk of adverse effects and ease of use in the outpatient setting, it should be considered in this patient population.

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Concerns Regarding Results of a Randomized Controlled Trial to Promote Skin Self-Examination and Sun Protection Behaviors

To the Editor We write regarding 2 articles by Aneja and colleagues describing results of a randomized trial to promote skin self-examination (SSE) and sun-protection behaviors among individuals attending dermatology clinics. A key concern is that imbalance in baseline levels of each behavioral outcome (ie, performance of SSE, use of sun-protective clothing, and sunscreen use) may explain or attenuate treatment arm differences at follow-up. For example, use of sun-protective clothing at the follow-up was significantly higher among intervention than control group participants. However, 40.2% of intervention group participants reported always or frequently using sun-protective clothing at baseline compared with 28.6% of control group participants. A prudent approach should include sensitivity regression analyses (akin to those summarized in Table 3 and the Table) estimating intervention effects on behavioral outcomes at the 3-month follow-up after controlling for the baseline levels. If baseline adjustments yielded nonsignificant results, then intervention effects would need to be interpreted with more caution.

An additional major concern pertains to the handling of missing data. Of 210 individuals who completed the baseline assessment and were randomized, 78 (37%) did not complete the 3-month follow-up assessment (although Figure 1 incorrectly indicates that 76 individuals were lost to follow-up). However, the outcomes in both articles were analyzed using a complete-case approach focusing on the 132 individuals with data available from the baseline and follow-up assessments. This approach commonly produces biased results, which can be mitigated using intent-to-treat analytic methods (eg, model-based strategies or imputation).

There are also issues related to the reporting and interpretation of the study results. In both articles, the authors misinterpreted odds ratios as relative risks and thus overstated the impact of the intervention. For example, an odds ratio of 2.40 is described as showing that “[t]hose in the intervention group were 2.4 times more likely to wear sun-protective clothing.” Calculation demonstrates that with a rate of 0.35 among the controls, this odds ratio would be equivalent to a relative risk of 1.61.

Additionally, based on the reported odds ratios, the authors claim that their intervention produced a greater increase in SSE than a study by Glazebrook and colleagues. However, the authors did not demonstrate that the odds ratio of 2.36 obtained in their study is statistically significantly greater than the odds ratio of 1.67 reported by Glazebrook et al. Moreover, the fact that the 2 studies used different approaches to measure SSE limits the ability to compare their relative impact on SSE.

A, Acanthotic epidermis at the edge of an ulceration with acute inflammation (hematoxylin-eosin, original magnification ×100) with prominent multinucleated giant cells (B and C, hematoxylin-eosin, original magnification ×200 and ×400, respectively). D, Herpes viral infection was confirmed with positive immunoperoxidase staining of multinucleated giant cells (herpes simplex virus immunohistochemical staining, original magnification ×200).