Thalidomide Therapy for the Treatment of Hypertrophic Herpes Simplex Virus–Related Genitalis in HIV-Infected Individuals

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Hypertrophic genital herpes is a disfiguring manifestation of a common infection seen in immunocompromised hosts that can be clinically mistaken for malignancy. We review the literature and describe hypertrophic genital herpes in a human immunodeficiency virus–positive patient receiving antiretroviral therapy. Treatment with valacyclovir, cidofovir, and foscarnet failed, but thalidomide treatment was successful.

Genital infection with herpes simplex virus (HSV) classically presents with $\geq 1$ vesicles evolving into shallow, painful ulcers and is most commonly caused by HSV-2. The virus remains latent in local sensory ganglia and periodically reacti- vates. Herpetic ulceration of $\geq 1$ month’s duration is an AIDS-defining illness [1]. Atypical presentations of HSV infection have been described, including the development of hypertrophic lesions, particularly in immunocompromised patients [2–11]. Patients with HIV infection may experience more frequent and more severe recurrences of genital herpes and are more likely to have resistance to standard antiviral agents [12]. We describe the case of an HIV-infected patient who presented with hypertrophic herpetic genital ulceration.

**Case report.** The patient was a 30-year-old black man from the Democratic Republic of Congo who had recurrent, painful genital ulceration of many years’ duration. The patient first received a diagnosis of HIV infection when he initially presented at the sexual health clinic of St. James’s Hospital (Dublin, Ireland) in 2001 for assessment of these ulcers. Baseline and nadir CD4 cell count was $119 \times 10^3$ cells/L (CD4 cell percentage, 8%). He initiated a HAART regimen consisting of zidovudine, lamivudine, and neviripine. After 3 months of receiving HAART, his HIV load was undetectable. By 6 months after initiation of HAART, his CD4 cell count exceeded $200 \times 10^3$ cells/L. Zidovudine-related anemia required a switch of this drug to stavudine. The patient also received treatment for pulmonary tuberculosis for a duration of 1 year.

A presumptive diagnosis of HSV-related genital ulceration was made during the patient’s first visit, on the basis of his condition’s clinical appearance and the high prevalence of this infection in sub-Saharan Africa. Cultures of vesicular fluid samples, performed on several occasions, were negative for HSV; despite this, our suspicion that the patient had HSV infection remained high. As such, the patient was initially treated episodically with valacyclovir; he later received ongoing valacyclovir at prophylactic doses. Eighteen months after receipt of a diagnosis of HIV infection, 17 months after initiating HAART, and 1 year after restoration of his CD4 cell count to $>200 \times 10^3$ cells/L, the patient developed persistent genital ulceration while receiving valacyclovir prophylaxis. These ulcers progressed to become nodular in 3 areas: the pubis, penile shaft, and perineum (figures 1A and 1B). There was no palpable inguinal lymphadenopathy. Sexually transmitted infection screening, which included culturing of a urethral swab specimen for gonococcus, testing of a urine sample for detection of *Chlamydia* species ligase chain reaction, and serum sample testing for detection of syphilis, all had negative results. High-dose valacyclovir therapy (1 g 3 times daily for 2 weeks) was ineffective. The patient’s lesions were subsequently biopsied.

**Results.** Punch skin biopsies of the perineal and pubic lesions revealed ulceration with very prominent eosinophilic and, to a lesser extent, neutrophilic inflammatory infiltrate in the residual intact epidermis and epithelium of the hair follicles. A heavy inflammatory infiltrate composed of neutrophils, eosinophils, lymphocytes, and plasma cells was present in the dermis. Florid HSV infection was present, with numerous herpetic inclusions in multinucleated keratinocytes. The classic cytopathic effects of HSV infection were observed: nuclear molding and clearing of chromatin (figure 2). No dysplasia or vasculitic changes were observed. Immunohistochemical analysis revealed HSV infection. There was no evidence of cytomegalovirus or human papilloma virus infection.

*Treponema pallidum* EIA and rapid plasma reagin tests...
yielded negative results. Serological analysis for varicella zoster virus, Epstein-Barr virus, and cytomegalovirus identified evidence of previous exposure to all 3. Bacterial cultures of skin biopsy samples grew scanty commensal organisms. Electron microscopy of biopsy samples had normal findings, and viral cell, mycobacterial, and fungal cultures had negative results. Viral cell cultures of ulcer swab specimens repeatedly had negative results from 2001 until 1 month after the patient underwent the skin biopsy in 2004, when HSV-2 was cultured from 1 of 4 swab specimens. No thymidine kinase mutations were identified.

With a culture-proven, histologically confirmed diagnosis of HSV-2 infection, the patient was admitted to the hospital to receive intravenous foscarnet therapy; he experienced no improvement in his condition. Intravenous cidofovir therapy, administered weekly for 3 weeks, also failed. In light of the success of thalidomide therapy in the treatment of recurrent aphthous ulceration in HIV-infected patients [13] and the clinical interpretation of the pathophysiology of the patient’s presentation, a trial of thalidomide therapy (100 mg twice daily) was commenced. Confirmation of appropriate use of contraception by the patient and his wife was documented. Within 1 week of initiation of thalidomide therapy, notable improvement was observed in all lesions, with reepithelization and, in subsequent weeks, shrinkage of nodular tissue.

The valacyclovir dosage was decreased to 500 mg daily after 5 weeks, and thalidomide therapy was discontinued after 8 weeks. There was continued improvement observed, with evidence of minimal, residual scarring and hypopigmentation up to 7 months after discontinuation of thalidomide therapy (figure 3A). A large scar on the patient’s perineum was subsequently removed by a plastic surgeon, with good results (figure 3B). Histological examination of this tissue revealed early keloid formation without ulceration, dysplasia, herpetic inclusions, conspicuous eosinophilic infiltrate, or vasculitis.

**Discussion.** The differential diagnosis of verrucous genital lesions includes condylomata acuminata and lata, squamous cell carcinoma, varicella zoster virus infection, cytomegalovirus infection, molluscum contagiosum virus infection, and HSV infection. Hypertrophic genital herpes is unusual; in our cohort of 1700 patients with HIV infection, we have seen 4 cases, all
involving patients of sub-Saharan African origin. A second male patient from Zimbabwe who received a diagnosis of HIV infection in 2003 had proven HSV-2–related penile ulceration at that time. His CD4 cell count remained high and, as such, he did not initiate HAART. This patient developed nodular penile ulceration refractory to receipt of valacyclovir therapy, and analysis of a biopsy sample of this tissue had findings that were suggestive of HSV infection. Thalidomide and valacyclovir therapy were recently initiated in this patient, with a slow response; initiation of HAART is being considered. Two female patients received diagnoses of HSV infection after analysis was performed of tissue biopsy samples. Both case patients experienced treatment failure with valacyclovir and intravenous cidofovir. One also received intravenous foscarnet therapy, but underwent a vulvectomy when dysplastic changes were identified by analysis of biopsied vulval tissue samples.

Nodular or verrucous forms of HSV infection of the tongue and genital mucosa have been described in immunosuppressed, HIV-negative patients [2, 3]. There are several case reports in the literature of hypertrophic, HSV-related lesions in patients with HIV infection, regardless of immune status [4–11]. These cases frequently respond to treatment with thymidine analogues, such as valacyclovir, but may require treatment with other agents, such as foscarnet or cidofovir.

The mechanism of this unusual presentation of a very common condition remains unexplained, although the immune dysregulation of HIV infection is likely to have a pivotal role in this patient’s case. Immune reconstitution inflammatory syndrome was postulated as the cause of 3 cases of refractory penile erosion observed in black Ugandans with AIDS in London, England [14]. Each had a prior history of genital herpes, and after a variable duration of receipt of HAART ranging from 4 weeks to 6 months, each developed florid genital lesions that were unresponsive to previously effective antiviral treatments. These patients were treated with, among other agents, intravenous foscarnet and topical cidofovir. Thalidomide was used unsuccessfully in 1 case. We do not believe that immune reconstitution inflammatory syndrome occurred in our patient, because the hypertrophic lesions developed later than 1 year after restoration of his CD4 cell count to $>200 \times 10^3$ cells/L; nor would this syndrome explain the development of hypertrophic lesions in the other 3 patients in our cohort.

A genetic predisposition to the development of hypertrophic lesions may be a factor. In a population-based study of herpesvirus infection and human leukocyte antigen (HLA) phenotype that was conducted from 1977 to 1979 (Framingham Study cohort [15]), HLA-Cw2 was found more often in individuals who had histories of herpes labialis, as was a higher mean antibody titer of HSV-1, although no strong association was found with HSV-2 antibody titers. The 3 individuals from London described above [14] shared the class I molecules HLA-B72 and HLA-Cw0202 and the class II allele DRB-4. HLA-B72 is relatively common among African populations; only 0.9% of white British individuals carry the marker [14]. All 4 patients in our cohort who had hypertrophic genital herpes are of sub-Saharan origin, and although we did not perform HLA typing in our patients, this may support a theory of genetic predisposition to the hypertrophic response, perhaps exacerbated by immunocompromisation in the setting of chronic symptomatic HSV infection.

Carrasco et al. [16] suggest a treatment algorithm for HSV-related disease that includes performing susceptibility testing in cases of thymidine analogue failure and the use of intravenous foscarnet or topical cidofovir therapy in cases of resistance or failure of response. Topical cidofovir was shown to

Figure 3. A, Minor residual scarring and hypopigmentation of the penile lesions 7 months after completion of thalidomide therapy. B, Improved appearance following resection of residual perineal scar tissue.
significantly improve or heal mucocutaneous herpetic lesions in 50% of patients with HIV infection in a small, randomized, placebo-controlled trial of the treatment of acyclovir-unresponsive lesions [17]. Equivalent herpetic lesions on the tongue in patients with HIV infection have responded to brivudine, a novel nucleoside analogue [18].

Thalidomide is a synthetic derivative of glutamic acid that was widely used in the 1950s as an antiemetic and a sedative. It became notorious following the realization of its teratogenic effects. It is now used in the treatment of a wide range of diseases associated with immune dysregulation, although its mode of immunosuppression remains unclear. It is known to be antiangiogenic [19] and to reduce TNF-α levels by 50%–80%. It reduces phagocytosis and chemotaxis in neutrophils and monocytes [20, 21]. Well-established as a treatment for recurrent aphthous ulceration associated with HIV infection [13], it is also used in the treatment of prurigo nodularis, AIDS wasting syndrome, Castleman disease, refractory microsporidiosis, and AIDS-associated proctitis [22]. There is 1 report in the literature of the success of thalidomide therapy in a case of refractory, HSV-related genital ulceration in a female patient [23]. Documented adverse effects include neuropathy, rash, constipation, neutropenia, and sedation. It is contraindicated in cases of pregnancy. Its use is carefully monitored and requires patient-signed consent. Standard dosing is 50–200 mg per day. Patients with HIV infection warrant increased care with its administration, because conditions such as peripheral neuropathy have the potential to be worsened by thalidomide use.

Although uncommon, hypertrophic herpes genitalis is a painful, disfiguring condition, with lesions that are clinically suspicious for malignancy. Here, we describe an HIV-infected male patient who was receiving HAART and who had a CD4 cell count >200 × 10^3 cells/L and a chronic HSV-2 infection that initially manifested as recurrent genital ulcers that responded to episodic valacyclovir therapy and progressed to refractory, HSV-related genital ulceration that initially manifested as recurrent genital ulcers that responded to episodic valacyclovir therapy and progressed to HSV-related genital ulceration in a female patient [23]. Documented adverse effects include neuropathy, rash, constipation, neutropenia, and sedation. It is contraindicated in cases of pregnancy. Its use is carefully monitored and requires patient-signed consent. Standard dosing is 50–200 mg per day. Patients with HIV infection warrant increased care with its administration, because conditions such as peripheral neuropathy have the potential to be worsened by thalidomide use.

Although uncommon, hypertrophic herpes genitalis is a painful, disfiguring condition, with lesions that are clinically suspicious for malignancy. Here, we describe an HIV-infected male patient who was receiving HAART and who had a CD4 cell count >200 × 10^3 cells/L and a chronic HSV-2 infection that initially manifested as recurrent genital ulcers that responded to episodic valacyclovir therapy and progressed to extensive, painful, hypertrophic lesions without evidence of acyclovir resistance. Furthermore, the infection was refractory to established therapies of foscarnet and cidofovir. In this case, we found thalidomide to be a safe, tolerable, and efficacious therapy. We recommend the consideration of its use in patients who have hypertrophic genital herpes.

Acknowledgments

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References