



Original Research

Vulvar pseudotumoral acyclovir-resistant herpes in an HIV-negative, non-immunosuppressed patient: A therapeutic challenge^{☆☆☆☆}



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ABSTRACT

Background: Vulvar pseudotumoral herpes infections have been reported in HIV-positive patients. A 32-year-old HIV-negative woman presented with a 6-month history of a vulvar pseudotumor that had been unresponsive to oral acyclovir and valacyclovir, as well as topical imiquimod.

Objective: This study aimed to evaluate the therapeutic efficacy of a multidrug regimen for vulvar pseudotumor herpes infection in an HIV-negative patient.

Methods: Histology revealed multinucleated giant cells, consistent with a herpes infection. The patient's herpes simplex virus type 2 was resistant to acyclovir. Immunomodulatory agents (thalidomide and topical imiquimod) were started.

Results: The lesion enlarged after 6 weeks of treatment. Topical cidofovir 1% gel was added. There was gradual decrease in the pseudotumor size. After 7 months, the Pseudotumor had resolved.

Conclusion: This is the first reported case of vulvar pseudotumoral herpes in an immunocompetent, HIV-negative patient. Oral thalidomide, in association with topical imiquimod and topical cidofovir, was effective in treating acyclovir-resistant pseudotumoral herpes of the vulva.

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Introduction

Herpes simplex virus type 2 (HSV-2) infection of the female genital tract is a common sexually transmitted infection worldwide. The HSV-2 seroprevalence in the United States is 12.1% (McQuillan et al., 2018). Immunocompromised patients, especially with HIV infection, are at an increased risk for acyclovir-resistant HSV infection, which has been reported to cause anogenital pseudotumors in this population (Tandon et al., 2017; Ranu et al., 2011; Sbidian et al., 2013). However, HSV-2 acyclovir resistance is rare in immunocompetent individuals. Similarly, an HSV-related pseudotumoral herpes infection in these patients is unexpected.

Methods

We report a case of vulvar pseudotumoral HSV-2 herpes in an immunocompetent patient. Written patient consent was obtained for publication. The chart review was approved by the institutional review board at the University of Michigan.

Patient history

A 32-year-old nulligravida woman was referred to the University of Michigan Center for Vulvar Diseases with a 6-month history of vulvar irritation, itching, and an erosive vulvar tumor. An initial biopsy 4 months before referral excluded malignancy and showed a cytopathic effect of herpes virus infection. At that time, the patient was treated with oral acyclovir (400 mg three times daily for 10 days) and later switched to valacyclovir (1 g twice daily for 10 days) with no improvement. Given the persistent tumor and failure of prior treatments, the vulvar lesion was excised. Histopathology consisted of ulceration and pseudoepitheliomatous hyperplasia with underlying polypoid granulation tissue; cytologic abnormalities indicative of HSV infection were also present (Fig. 1). The

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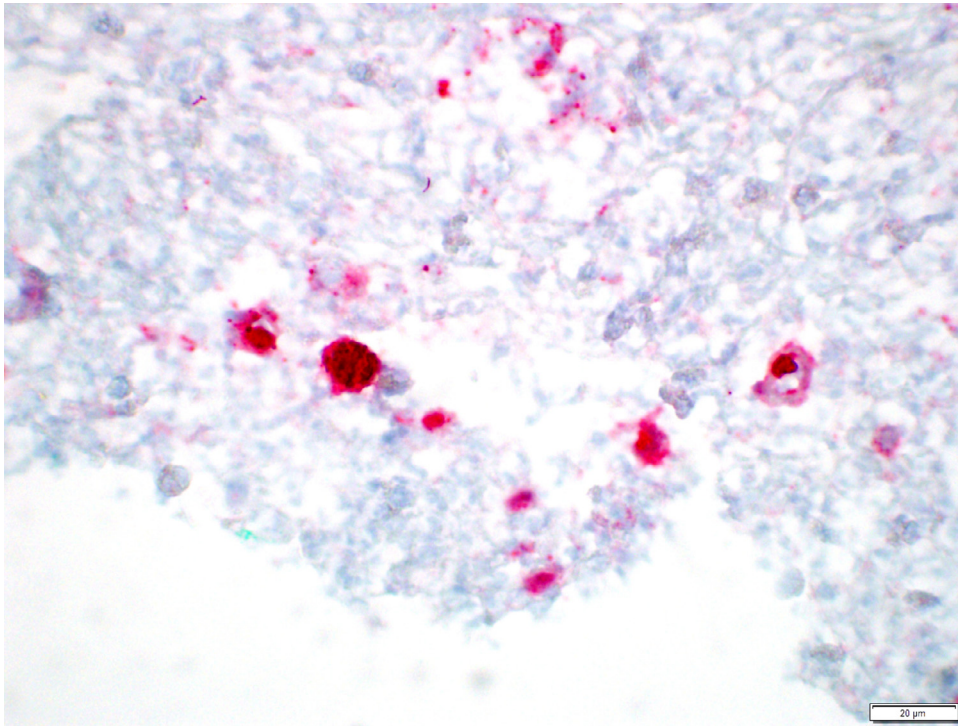


Fig. 1. Immunohistochemical stain specific for herpes simplex virus type 2 antibody with alkaline phosphatase method.



Fig. 2. Initial presentation at our clinic. Extensive erosions of the inner labia minora with a pseudotumoral lesion of the posterior aspect of the left labium majus.

patient received antibiotics to prevent infection after excision of the vulvar pseudotumor. The lesion began to regrow within 7 days of excision. She was restarted on valacyclovir with no improvement and was therefore referred to our clinic.

Treatment

When the patient initially presented, she reported itching, irritation, and copious vaginal discharge. Her medical history included HSV-2 infection with occasional outbreaks. She denied tobacco use and had no history of diabetes or immunodeficiency. On physical

examination, the inner aspects of both labia minora were eroded and a 2 cm × 2 cm lesion with an irregular, erosive surface was present along the posterior left labium majus (Fig. 2). There was significant purulent exudate from the lesion. Given prior treatment failure, an additional biopsy was obtained. The pathology results confirmed the findings of her previous biopsies. A polymerase chain reaction from the left posterior labium majus was positive for HSV-2.

Because pseudotumoral herpes is known to be associated with immunodeficiency, particularly HIV-related, a variety of tests were performed to assess the patient's immune status

Table 1
Laboratory tests involving the immune status of the patient

Tests	Laboratory methods	Results
HIV serology	Fourth-generation HIV antibody/antigen screen	Negative
	HIV viral load	Not detectable
Complete blood count	White blood cell count	7500/uL
Immunoglobulin profile	Immunoglobulins G, A, and M	1650/188/82 mg/dL
	Cutaneous immunofluorescence testing	Negative
Flow cytometry	Initial CD4 count and percent	272 cells/mm ³ ; 27.2%
	Repeat CD4 count and percent	871 cells/mm ³ ; 48.4%
NK cell function	NK cell function	Normal

NK, natural killer

(Di Lucca-Christment et al., 2012; Leevaphan et al., 2015). The results of the tests are shown in Table 1. The patient had a low initial CD4 count (272/mm³), which was attributed to recent steroid treatment, but the follow-up CD4 count 4 days later was normal (871/mm³). In addition, testing for syphilis by serum rapid plasma regain; gonorrhea, chlamydia, and trichomonas by endocervical swab with DNA amplification; and yeast infection via vulvo-vaginal culture were all negative.

The patient previously failed to respond to oral acyclovir; thus, she was admitted to our inpatient gynecology service and treated with intravenous acyclovir 5 mg/kg every 8 hours based on Centers for Disease Control and Prevention (CDC) Sexually Transmitted Diseases Treatment Guidelines (acyclovir 5–10 mg/kg intravenously every 8 hours for 2–7 days; CDC, 2015). She was also started on several medications to treat the significant vulvar inflammation,

including oral prednisone, intravenous clindamycin, and ampicillin/sulbactam, which were chosen for their anti-inflammatory properties. Wound cultures to rule out superinfection were also obtained, and testing of the cultures revealed no growth. The patient was also started on fluconazole for *Candida* infection prevention. The patient remained in the hospital for 6 days and was discharged with slight relief of her vulvar symptoms. She was placed on oral valacyclovir (1 g daily) and topical imiquimod (5% cream three times a week).

Results

After 6 weeks of treatment with valacyclovir and topical imiquimod, the left labium majus/perineum perineal pseudotumor was noted to have enlarged (Fig. 3). HSV-2 resistance testing by



Fig. 3. Increased pseudotumoral lesion after initial therapy. The pseudotumoral herpes of the left labium majus increased in size from initial appearance after 6 weeks of treatment with valacyclovir and topical imiquimod.



Fig. 4. Partially healed lesion. After 3 months of treatment with oral thalidomide, 5.5 months of topical imiquimod, and 1 month of topical cidofovir, the pseudotumoral herpes of the left labium majus/perineum, started to flatten. Here, the lesion is partly healed.



Fig. 5. Lesion resolution after treatment. After treatment with oral thalidomide, topical imiquimod, and topical cidofovir, the pseudotumoral herpes lesion was completely healed. Only a depigmented scar of the posterior left labium majus/perineum was observed.

phenotype showed acyclovir resistance (result: 2.53 u/mL; reference interval: sensitive <2.00; resistance >1.90), and valacyclovir was subsequently discontinued. Topical imiquimod was continued for an additional 10 weeks, and although the patient reported less pain, there was no significant improvement in lesion appearance.

A review of the literature on immune modulators showed that thalidomide had been used previously for this condition with good results (Charles et al., 2016; Sbidian et al., 2013; Verberkmoes et al., 1996). Therefore, double contraception (intrauterine device and oral contraception) was started prior to prescribing oral thalidomide (150 mg daily). She was also continued on topical imiquimod for potential synergistic effects, given the report of improved ef-

ficacy of pseudotumoral HSV treatment when used sequentially (Sbidian et al., 2013). Consequently, thalidomide was well tolerated, with no leukopenia, peripheral neuropathy, or fatigue observed. After 3 months on this regimen, however, there was no significant change to the lesion.

In an effort to optimize treatment, compounded topical cidofovir 1% in VersaBase cream (once daily) was started while the patient continued thalidomide and topical imiquimod. Six weeks later, the left labium majus/perineum pseudotumor was noticeably flatter, although still with significant exudate (Fig. 4). Given the persistent exudate and slow clinical response to treatment, along with the knowledge that an HSV infection could coexist with a ma-

lignancy, the care team maintained a high index of suspicion for malignancy. Therefore, biopsy was performed to rule out a neoplasm, and showed acute lymphoplasmocytic inflammation with no features of malignancy. Improvement in the lesion occurred after the addition of topical cidofovir; thus, oral thalidomide associated with topical imiquimod and cidofovir were continued for a total of 7 months. After 7 months of this treatment regimen, the lesion healed completely, leaving only a depigmented scar on the left labium majus/perineum (Fig. 5). Twelve months after completion of treatment, there was no recurrence of the vulvar lesion.

Discussion

We report a case of vulvar pseudotumoral acyclovir-resistant herpes in a patient who was HIV negative and had no immunodeficiency. The lesion responded to a treatment regimen consisting of 7 months of oral thalidomide, topical imiquimod, and topical cidofovir.

Vulvar herpes is usually characterized by the presence of acute vesicles and erosions. However, atypical presentations including pseudotumoral herpes, also designated as tumor-like (Ranu et al., 2011) or hypertrophic (Holmes et al., 2007; Leevaphan et al., 2015; Tandon et al., 2017) lesions, have been reported. Chronic genital pseudotumoral herpes has only been described in immunocompromised—mainly HIV positive—male or female patients. In a retrospective study of 294 patients with herpes simplex genitalis in Thailand, hypertrophic pseudotumoral lesions were noticed in 14 patients (7 female and 7 male patients), all of whom were infected with HIV (Leevaphan et al., 2015). Other immunosuppressive conditions associated with pseudotumoral herpes are reported more rarely, including lymphoid leukemia, orthotopic liver transplantation, and Hodgkin's disease (Di Lucca-Christment et al., 2012). However, no pseudotumoral herpes has ever been reported in a nonimmunosuppressed patient.

In our patient, immunologic investigations and evaluation by an immunologist were unrevealing. The initial low CD4 count ($272/\text{mm}^3$) was attributed to steroid treatment prescribed to address the inflammation associated with the pseudotumoral lesion. The CD4 count normalized on follow-up testing, but the pseudotumoral lesion remained. Therefore, this is the first case to reflect pseudotumoral vulvar HSV in an immunocompetent individual, based on our literature search.

Pseudotumoral herpes is often resistant to acyclovir (Tandon et al., 2017; Ranu et al., 2011; Sbidian et al., 2013). Reduced drug delivery to pseudotumoral exophytic lesions or increased chances of infection with acyclovir-resistant HSV strains in immunocompromised patients have been hypothesized to be the mechanism of drug resistance (Sbidian et al., 2013). By contrast, HSV-2 acyclovir resistance is rare among immunocompetent individuals, even those who have had extensive acyclovir exposure (Ziyaeyan et al., 2007).

Treatment of pseudotumoral genital HSV-2 is challenging because conventional antiviral therapy is often ineffective due to acyclovir resistance (Barde et al., 2011; Di Lucca-Christment et al., 2012). Given this, therapies other than antivirals, including imiquimod and thalidomide, have been investigated as alternative treatments (Tandon et al., 2017). Imiquimod, a topical agent reported in the treatment of HSV pseudotumoral disease, is a toll-like receptor agonist that evokes cell-mediated immunity and downregulation of viral replication. Imiquimod also stimulates natural killer cells, causing a cytotoxic effect. Used for its immunomodulatory effects, imiquimod has been reported to be effective in the treatment of acyclovir-resistant HSV disease (Barroso dos Reis et al., 2020; Tandon et al., 2017).

The successful use of thalidomide to treat acyclovir-resistant pseudotumoral HSV-2 in HIV-infected patients, first described by Verberkmoes et al. (1996), has been confirmed by further studies

(Charles et al., 2016; Sbidian et al., 2013). Thalidomide is known to downregulate proinflammatory cytokines and to be antiangiogenic, anti-proliferative, and proapoptotic. The effectiveness of thalidomide could be related to its effects on the immune system (Sbidian et al., 2013). In the HIV-positive population, it has been suggested that thalidomide should not be considered as a last-line therapy; instead, it should be considered early in the course of the disease (Charles et al., 2016).

Other agents that have been proposed in the treatment of acyclovir-resistant pseudotumoral herpes include ganciclovir (Gouveia et al., 2014), foscarnet (Levin et al., 2004; Safrin et al., 1991) and intravenous cidofovir (CDC, 2015). These agents are associated with significant potential adverse effects, including cytopenia (valganciclovir), nephrotoxicity and electrolyte abnormalities (foscarnet), and nephrotoxicity (intravenous cidofovir). There is also a high rate of cross-resistance with acyclovir and ganciclovir in HSV (Andrei et al., 2000).

Due to an incomplete response to imiquimod after 10 weeks of treatment, we added thalidomide. This combined treatment was not effective after 3 months, so topical cidofovir (Epstein et al., 2016; Perkins et al., 2011) was added to the regimen. The use of topical cidofovir required special compounding by the pharmacy and was well tolerated in this patient. There was a complete response to this therapeutic association after 7 months. Although we cannot comment on the individual effects of each of these three treatments, we hypothesize that their ultimate efficacy could be related to the combination of their immunomodulatory (thalidomide, imiquimod) and antiherpetic (cidofovir) effects.

Conclusion

An HIV-negative patient with acyclovir-resistant pseudotumoral herpes of the vulva was successfully treated with a combination of immunomodulators, as well as antiviral agents. This rare condition requires a multidisciplinary approach to diagnosis and treatment.

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