Chronic Ulcerative Herpes Simplex Virus Infection of the Vulva

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Abstract
Herpes simplex virus infections in HIV-infected individuals can be clinically unusual and difficult to treat due to underlying problems with cell-mediated immunity and the occurrence of antiviral resistance. Additionally, partial or incomplete restoration of immune function may result in chronic ulcerations that require rotational treatments. In this report, we describe the case of a 38-year-old HIV-positive woman who developed the ulcerative form of chronic herpes simplex infection despite highly active antiretroviral therapy and valacyclovir prophylaxis. Repeated intravenous courses of foscarnet and topical cidofovir finally controlled her erosions as her cell-mediated immunity was slowly restored. This case highlights the challenges that still exist in diagnosing and managing this rare presentation of herpes simplex virus

Introduction

Mucocutaneous herpes simplex virus (HSV) infections are among the most common sexually transmitted diseases in HIV-infected individuals [1]. Typical acyclovir-responsive vesicular outbreaks as seen in HIV-uninfected individuals are the norm, although severity and number of recurrences can increase when host immunity is poor [2]. Additionally, classic outbreaks of genital HSV also increase after starting highly active antiretroviral therapy (HAART) as part of the well-described immune reconstitution inflammatory syndrome (IRIS) [3]. Uncommonly, HSV infections may become chronic and recalcitrant to treatment. These persistent infections are rare in the literature but have recently been grouped into ulcerative and pseudo-tumoral (hypertrophic or granulomatous) variants [4, 5]. While increased acyclovir resistance is a contributing factor, poorly understood complications and/or defects during and after...
immune recovery are other likely contributors to chronic outbreaks. We report a case of chronic ulcerative HSV infection of the vulva in a patient with HIV developing almost 1 year after initiating HAART and continuing even after significant improvement in her CD4 cell count. This emphasizes the fact that these chronic HSV recurrences may start or persist outside of the normal 6-month window of IRIS and despite partial or complete restoration of immunity.

Case Report

A 38-year-old HIV-1-infected African American woman presented in September 2009 with several weeks of a painful vulvar ulcer. Her HIV disease was diagnosed in 2003 and she had been on HAART (lamivudine, zidovudine and atazanavir) since 2006, although with poor compliance. After another lapse in treatment for 1 year, she resumed therapy in 2008 with a prompt improvement in immune status 2 months later (viral load drop from >1,000,000 to 390 copies/ml and concomitant rise in CD4 count from 3 to 64/mm³). Her HAART regimen was changed to emtricitabine, tenofovir, atazanavir and ritonavir, and approximately 8 months later (11 months after resuming HAART) she developed the painful erosion on the inner left labia minora. Her viral load was still detectable at 240 copies/ml and her CD4 count had risen to 194/mm³. She had a history of genital herpes simplex and was on valacyclovir 500 mg twice-daily prophylaxis up to this time with no clinical symptoms. Lesional culture did not detect HSV but she experienced some symptomatic relief with empiric increase in her valacyclovir dosing to thrice daily. However, the erosion persisted and by 6 months later had enlarged to involve both labia with painful ulceration and yellowish adherent exudates (fig. 1). HAART therapy was again changed to abacavir, lamivudine, atazanavir and ritonavir due to nausea. On this regimen, viral activity dropped to <50 copies/ml with a rise in CD4 count to 265/mm³. Again HSV was not detected on culture so a biopsy was obtained to confirm the suspicion and exclude the possibility of fixed drug reaction, erosive lichen planus, syphilis, or malignancy. The result was non-diagnostic, revealing diffuse mixed dermatitis with neutrophils, plasma cells, and numerous eosinophils. Immunohistochemistry did not detect HSV-1 or -2, and special stains for spirochetes were negative. The rapid plasma reagin was non-reactive as well. Supportive care with triamcinolone 0.1% ointment and topical lidocaine were started, and valacyclovir was continued. With spread of the ulceration to the perineal region 2 months later, another skin biopsy was performed showing similar findings (fig. 2), but the presence of HSV was confirmed by immunohistochemistry (fig. 3). IgG antibodies to HSV-1/-2 were detected at high titer in the serum confirming past exposure to HSV. There was no evidence of treponemal organisms and the rapid plasma reagin was again negative, no cytomegalovirus was detected by immunohistochemistry or PCR, and direct immunofluorescence was negative.

Acyclovir-resistant HSV was assumed and intravenous foscarnet was initiated at 40 mg/kg twice daily. After 3 weeks, her vulvar lesions had completely resolved and her perineum was greatly improved. Topical cidofovir 1% gel was then started twice daily with prompt worsening, so she resumed foscarnet for another 4 weeks. Ulcerations persisted again, so her dose of foscarnet was increased to 60 mg/kg twice daily for an additional 3 weeks. At follow-up, she showed improvement; however, she still had small persistent erosions. Her total CD4 count was still low at 168/mm³. She then resumed topical cidofovir and had slow but gradual improvement over the next 9 months. Valacyclovir prophylaxis was added and by 5 months later she was almost completely healed and comfortable. Her total CD4 count was now at 330/mm³. She continues to maintain control with this regimen.

Discussion

HSV infections are a common cause of morbidity in individuals infected with HIV and occur throughout the course of their infection and as part of immune reconstitution. Chronic HSV ulcers (those lasting more than 4 weeks) on the contrary had been primarily a consequence of advanced HIV/AIDS, yet the introduction of HAART has not completely abolished their occurrence [6]. This case is another example of the
溃疡性亚型的慢性生殖器HSV和是类似文献中报道的少数几例慢性HSV病例，在发生IRIS期间或之后 [7–11]。类似Fox et al. [7]报告的那些患者，我们的患者也发展了严重的溃疡性生殖器HSV，很难在体文化和检测，对阿昔洛韦衍生物，foscarnet和cidofovir反应差。类似报告中1例患者和Yudin and Kaul and Lanzafame，我们的患者显然不在IRIS的正常窗口 [7–9]。

慢性HSV爆发的机制尚不清楚。抗病毒耐药性当然在最近的一项研究中起着作用，其中7例慢性HSV病例中有5例在体外对阿昔洛韦，cidofovir和/or foscarnet有临床和/或体外耐药性 [4]。但是，无论使用不同的治疗方案，还是初始抗病毒治疗的缺乏，所有这些病例仍然需要数月甚至数年才能治愈。抗病毒耐药性不能在我们的病例中被证明，因为病毒没有被培养，但她的不良反应重复的治疗和剂量的增加foscarnet可能暗示，因为HSV据报平均在foscarnet治疗后6天内愈合 [12]。

由于慢性HSV病变中存在炎症浸润，另一种可能的解释是，免疫不足以抑制病毒活性，导致在免疫不充分的炎症途径失衡 [7, 8]。这类似于IRIS期间的初始过度免疫反应，但过程在免疫部分和完全恢复的个体中被延迟。我们的患者CD4计数在她的病程中一直低于300/mm³，尽管她一直在逐渐恢复，但病情仍在持续。一种有趣的病理学特征是，这种异常的浆细胞和嗜酸性粒细胞，不是在复发性HSV爆发中通常看到的 [13]。这也已在Fox et al. [7]的病例中报道，并在文献中不明确描述的炎症浸润中被忽视。

在结论中，慢性溃疡性HSV感染在HIV感染个体中是一个罕见的实体，诊断和治疗都是挑战性的。更好地理解HSV-特定的免疫缺陷和炎症反应的模式，部分和完全免疫重建将有助于更好地理解慢性HSV爆发的病理性机制或疾病进程，将有助于改善管理。
Fig. 1. Vulvar ulceration with adherent fibrinous exudates and scalloped borders.

Fig. 2. Histopathology from the edge of the ulceration shows epidermal hyperplasia, mild papillary dermal edema, fibrosis in the upper lamina propria, and a diffuse, deeply extending mixed infiltrate of lymphocytes, neutrophils, and numerous eosinophils. Scattered plasma cells are also present. HE, 10× (40× inset).
Fig. 3. Immunohistochemistry staining showing positive keratinocytes containing HSV-1/-2 antigens.

References

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