Case Report

Herpes Simplex Virus Type 2 and Cytomegalovirus Perigenital Ulcer in an HIV Infected Woman

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Abstract

We report a case of mucocutaneous Herpes Simplex Virus (HSV)-2 and Cytomegalovirus (CMV) infection in a 39-year-old female with acquired immunodeficiency syndrome, who presented with a perigenital ulcer. The patient was receiving antiretroviral treatment (ART) for 3 months before presentation. Scraping from the perigenital ulcer was positive for HSV-2 and *Treponema pallidum* using polymerase chain reactions (PCR). The extent and duration of the lesions led us to consider the possibility of coinfection with CMV. The patient also tested positive for CMV by PCR. On subsequent follow-up after 8 weeks, the genital lesions had healed completely. This is possibly ascribable to the ART, which led to significant immune reconstitution.

Keywords: Cytomegalovirus, herpes simplex virus, human immunodeficiency virus

Introduction

Genital Herpes (GH) is the most common cause of genital ulcer disease (GUD) worldwide, and its association with Human Immunodeficiency Virus (HIV) is well established.[1] GUD increases the risk of HIV-1 acquisition, by increasing the genital shedding of HIV-1 during clinical and subclinical herpetic episodes. In patients infected with HIV, GH can result in severe and atypical clinical presentation, with severity and duration of the ulcers correlating with the degree of immunosuppression. There are few reports of GH ulcers in HIV-infected patients being coinfected with other pathogens especially cytomegalovirus (CMV).

CMV is an important opportunistic agent in immunosuppressed states, particularly in HIV infected, manifesting as ocular and visceral involvement.[2] Although cutaneous manifestations are rare, there are growing number of reports of concurrent HSV and CMV infections in genital and perigenital ulcers of immunocompromised individuals. These ulcers described are generally chronic and painful, similar to those caused by HSV.

Herein, we report a case of mucocutaneous HSV-2 and CMV infection in a woman with acquired immunodeficiency syndrome, who presented with a perigenital ulcer.

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Case Report

A 39-year old HIV-1 positive woman presented to us in June 2017 with a 9-month history of a single, painful, non-healing ulcer over the left labia majora. On clinical examination, the patient had a single, tender, non-indurated, exuberant ulcer of size ~3 cm^2 with overlying adherent yellowish slough over the left labia majora [Figure 1]. There was bilateral inguinal lymphadenopathy in the form of multiple, firm, non-tender nodes of size 1–2 cm. On per speculum examination, scant, mucoid, non-foul-smelling cervical discharge was noted, which on Gram-staining revealed >10 polymorphonuclear cells/oil immersion field, but no Gram-negative diplococci.

The patient was receiving antiretroviral treatment (ART) with tenofovir, lamivudine and efavirenz (the TLE regimen), along with cotrimoxazole for 3 months before the presentation. Her HIV-1 serology was positive, with a CD4+ lymphocyte count of 34 cells/mm^3 and an undetectable viral load. The Venereal Disease Research Laboratory Test (VDRL) and *Treponema*

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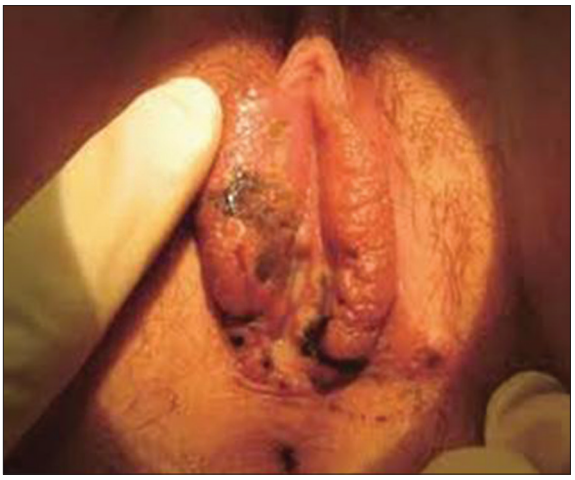

Figure 1: Irregular perigenital ulcer, measuring ~1.5 × 2.0 cm^2 with a yellowish adherent exudate with viral co-infection with herpes simplex virus-2 and cytomegalovirus

pallidum haemagglutination assay for syphilis were positive. Different primers and probes were used for detection of *Haemophilus ducreyi and T. pallidum* by polymerase chain reaction (PCR).[3] Scrapings from the perigenital ulcer were positive by PCR for HSV-2, CMV and *T. pallidum* but tested negative for *H. ducreyi*.

The patient was treated appropriately for syphilis (injection benzathine penicillin, 2.4 mega units and single dose) and GH (acyclovir 1200 mg/day). She was told to continue her ART (TLE regimen) and report after a week, which she did not. However, after several reminders, she reported after 8 weeks, when it was found that her genital lesions had healed completely. A repeat VDRL was negative, and the CD4 count had increased to 275 cells/mm^3.

Discussion

Sexually transmitted coinfections are common among patients with HIV. In our patient, the presence of an ulcerative perigenital lesion against the background of HIV infection raised a suspicion of GH. However, the knowledge of a recent report of coinfection with CMV and HSV in a persistent exuberant perigenital ulcer prompted us to subsequently send our patient's sample for CMV testing also. It was only 7 days after she first reported to us that we received the patient's CMV report. Interestingly, when the patient eventually reported back after 8 weeks, the ulcer had healed completely.

In CMV infection, mucocutaneous lesions are very rare in contrast with the high frequency of ocular and visceral involvement and occur when the CD4+ lymphocyte count is below 50 cells/mm^3, usually due to the reactivation of previous latent CMV infection.[4] The lesions manifest as chronic, painful ulcers, preferentially located in anogenital region, often coexisting with HSV.[5]

CMV seroprevalence in the reproductive age group in India is nearly 100%.[6] Reactivation of this virus can present with cutaneous disease in immunocompromised individuals, which may even reflect systemic involvement. Systemic CMV disease is associated with higher morbidity and mortality and can significantly affect patient care.

Awareness of the possibility of atypical presentation of HSV infection with verrucous forms and of the possibility of concurrent CMV infection is essential for a correct clinical and pathologic diagnosis to be rendered in a timely fashion. Gouveia *et al*.[7] reported a case of HSV and CMV coinfection presenting as exuberant genital ulcer in a woman infected with HIV. The presence of exuberant and persistent HSV genital ulcer in patients with HIV should also raise suspicions of the presence of coinfection with other organisms such as CMV. Their case highlighted the difficulties in the diagnosis of genital ulcer in patients infected with HIV.

In India, diagnostic tests for the detection of the aetiological agents of genital ulcer disease, namely sexually transmitted HSV, CMV, *H. ducreyi* and *T. pallidum* are currently not routinely used in clinical settings, and the frequency of these sexually transmitted diseases (STIs) remain an enigma. Thus, diagnostic tests for their detection should be implemented in the clinical settings in India. The gold standard for the diagnosis of tissue-invasive HSV and CMV infection is histologic examination with immunohistochemistry staining. However, in the present case, PCR amplification of DNA from the scraping of the ulcer was used to detect HSV and CMV because of its high sensitivity and specificity as reported in previous studies.[8]

The sexual history of the patient does not allow us to determine whether HSV-2 and CMV infection were acquired before or after HIV infection, or to infer causality in the coinfection relationship. Sexual behaviour was assessed through self-report, and there may be inaccuracies due to recall bias. Furthermore, sexual behaviour during the previous few months may not represent that at the time of HIV acquisition or prove relevant for long persistent pathogens such as the herpes viruses.

It was noted that though acyclovir was given for GH, no specific antiviral treatment could be initiated for CMV (in the form of ganciclovir or valganciclovir) since she did not return immediately for review. Nevertheless, the mucocutaneous lesion had resolved completely when she came for follow-up after 8 weeks. This is possibly ascribable to the completion of 5 months on ART by that time, which led to significant immune reconstitution (from 34 cells/mm^3 to 275 cells/mm^3). This highlights the close interaction between these three viruses and the level of immunodeficiency in the patient. Since the lesion had resolved clinically, we neither attempted to determine the cervicovaginal HIV-1 ribonucleic acid (RNA), CMV DNA and HSV-2 DNA loads nor the plasma HIV-1 RNA load. Had the lesion persisted, it would have been particularly important to assay the CMV DNA load in the blood, to rule out systemic reactivation of CMV

and to decide on initiation of specific antiviral treatment for this virus.

Our patient did not test positive for any bacterial STI other than syphilis. However, given the availability of effective antibiotic treatment for these pathogens, and the fact that many of these infections resolve without treatment, the current status of our patient does not reflect any infections that could have occurred in the past.

In conclusion, this case underscores the importance of maintaining a broad differential diagnosis for genital ulcers in immunocompromised patients. Any genital or perigenital ulcer should be investigated to rule out CMV in an immunocompromised patient as its recognition could reflect systemic involvement and significantly affect patient care.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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