Genital Ulcer in a HIV-infected Man

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In January 1998 the genital ulcers recurred, but this time they remained chronic for months. Initially he was treated empirically with various antibiotics like erythromycin, doxycycline and minocycline for suspected chancroid. Later the ulcers progressed to become two rapidly enlarging exophytic masses. A surgical opinion was sought for the possibility of malignancy.

**CASE SUMMARY**

**History**

A 54-year-old Chinese male with stage 3 HIV infection presented with preputial swelling and ulcerations for a few days in November 1996. He denied any sexual intercourse since his HIV infection was diagnosed in mid-1996. He didn't take any medication other than the anti-retrovirals for his HIV infection. These ulcers healed spontaneously after 1 week though they recurred several times in the following 2 years.

**Physical examination**

Two fleshy, exophytic masses with sizes 4x2 cm and 2x2 cm respectively were present on the prepuce (Figure 1). There was no inguinal lymphadenopathy.

**Investigations**

Tests for syphilis (dark ground examination, VDRL, FTA, TPHA) as well as bacterial and viral (herpes) cultures were performed. They were all

![Figure 1: Two fleshy, exophytic masses on the prepuce](image-url)
negative. His CD4 cell count was 321/ul in 1996 and ranged between 400-600/ul in the following years. His plasma HIV-1 load was 4 logs when first checked in 1998. It has remained rather stable till now.

In view of the persistent ulcers, punch biopsies were performed twice, with special staining for acid fast bacilli, syphilis, fungus and cytomegalovirus. However no pathogen could be identified and the pathological findings were inconclusive. Lastly excisional biopsy with local flap was performed by surgeons. A dense band of inflammatory cells including plasma cells, lymphocytes, neutrophils and eosinophil was present. Herpes inclusions were identified at the edge of the ulcer. Therefore a diagnosis of herpes virus infection was made.

Progress
With the diagnosis of genital herpes, oral acyclovir was given accordingly with resolution of the genital lesions.

The patient had two episodes of genital herpes relapse in October and November 1999 respectively. The disease responded to oral acyclovir.

REVIEW ON GENITAL HERPES IN IMMUNOCOMPROMISED HOST

The immune defense mechanism involves close interplay of various components at different levels of the immune system. Individuals with a defect in the T-cell mediated response are more susceptible to viral infections and atypical manifestation of these infections. For genital herpes, the atypical clinical features include chronicity (up to 1 year) and excessiveness of lesions both in primary and reactivated infection. Individual lesions tend to be more necrotic, painful and persistent. Also the site involved can be outside the genitalia such as over the buttocks, low back or in the rectum. Moreover, the affected patients usually have more systemic upset.

Other presentations include a papular eruption, a hyperkeratotic verrucous lesion or an eroded vegetative plaque. Therefore warty genital lesions in HIV-1 infected patients should be interpreted with caution, since besides genital wart other diseases can present atypically in this group of patients (Table 1).

Nevertheless, ulceration is still the most common presentation among all other atypical manifestations of herpes simplex virus (HSV) infection. On the other hand, not all herpes simplex infection with atypical presentations is associated with immunocompromised states.

Effect of herpes simplex type 2 on HIV-1 infection
HSV-2 and HIV-1 can coinfect and replicate in the same T lymphocyte. The interaction between HIV-1 and HSV-2 was unidirectional; there is accelerated replication of HIV-1 but not HSV-2. Plasma viral load is increased by a median of 3.4 fold during an acute outbreak of herpes simplex infection. The magnitude of this response is related to the size, extent and length of time that HSV lesions are present, and to any concomitant anti-herpetic or antiretroviral therapy taken. The post-outbreak levels (30-45 days after the appearance of lesions) remain above the pre-outbreak baseline levels in some subjects. The long-term clinical implication of this phenomenon is not known.

Laboratory diagnosis of HSV infection
The sensitivity of laboratory tests for detecting

| Table 1. Diseases with genital verrucous presentation in HIV-1 infected individuals |
|-----------------------------------|---------------------------|-----------------------------|
| Common diseases                   | Typical presentation      | Atypical presentation       |
| Viral wart, secondary syphilis    | Herpes simplex, Herpes zoster, molluscum contagiosum, tuberculosis |
| Bowen's disease, squamous cell carcinoma | Cytomegalovirus infection  |
HSV depends on: 1) the stage of the disease - the yield is usually higher in the first episode; 2) the type of lesion - vesicular and ulcerative lesions are usually better than erosion; and 3) the immune status of the patient - positive finding is more common in immunocompetent patients than in the immunocompromised.

Various investigative methods can help the diagnosis of HSV infection. Culture of the virus is still the gold standard for diagnosing HSV. It also allows typing and antiviral sensitivity testing. But this test is relatively time-consuming.

Cytology (Tzanck preparation) is a simple test with rapid result, but it is not able to differentiate between HSV-1 and HSV-2. Moreover, the cytopathic changes may resemble those produced by varicella-zoster virus. This is a potential problem in HIV infected patients since varicella-zoster infection is rather common in this group. The sensitivity of this method is variable, about 30-80%.

Electron microscopy is a highly specific but insensitive method, besides this facility is not widely available.

Antigen detection/DNA detection technique have sensitivity around 75% and specificity around 85%. The yield is lower for asymptomatic shedding. It is costly and expertise is required to interpret the result.

Polymerase chain reaction (PCR) is a highly sensitive method and enables us to detect minute amount of nucleic acid materials in the specimen. Unfortunately false positive is a problem when there is contamination of the specimens. Also the test is quite time-consuming. Thus it is not widely available.

Although skin biopsy is a traumatic procedure, it is the only way to exclude other pathologies especially when malignancy is suspected. It can also differentiate between CMV and HSV infection.

In clinical practice, differentiation among chancre, chancroid and herpes ulcer may not be straightforward. Therefore dark ground microscopy, Tzanck preparation, bacterial and viral cultures are often performed at the same time. If the tests are repeatedly negative, detection of the antigen by immunofluorescence staining or skin biopsy should be considered (Figure 2).

**Treatment**

Treatment of genital herpes is broadly divided into topical and systemic therapies.

**Topical treatment**

Patients can be treated conservatively by antiseptics. Topical acyclovir is not useful. Sack et al found that topical cidofovir (1, 3, 5%) was useful in shortening the course of disease and viral shedding. Topical foscarnet was also found to be beneficial in treating acyclovir-resistant cases.

**Systemic treatment**

Oral antivirals like acyclovir are commonly used in treating patients with genital herpes. It was found that atypical HSV infections are more commonly unresponsive or resistant to acyclovir therapy. The incidence of acyclovir-resistant infection in HIV-positive patients is estimated to be 5%. Foscarnet is the only drug with proven success in the treatment of acyclovir-resistant HSV infection. However, foscarnet-resistant HSV infections have also been reported.

Interferon alpha-2 given by subcutaneous injection (3x10^6 IU, 3x/wk for 4 weeks and follow-up for 2 years) decreased the healing time from 8.5 days to 2.5 days and there was a reduction in the number of recurrence during the study period.

Different types of genital herpes vaccines are still under development. The effectiveness of inactivated virion derived vaccines have not been proved. Adjuvant subunit vaccines, nucleic acid vaccines and replication-limited live viral vaccines are under clinical trial. Genetically attenuated live viral vaccines and vectored vaccines are still in preclinical development.
Figure 2: Algorithm for the investigation of genital ulcer in immunocompromised host

Genital Ulcer

- Syphilis:
  - Painless, indurated clean-based ulcer
- HSV:
  - Multiple, shallow, tender ulcers
- Chancroid:
  - Deep, undermined purulent ulcer

<table>
<thead>
<tr>
<th>Dark ground microscopy</th>
<th>Viral Culture +/- Tzanck smear</th>
<th>Gram Stained smear +/- Bacterial culture</th>
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<tr>
<td>Syphilis serology</td>
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<tr>
<td>Bacterial culture</td>
<td>Dark ground microscopy</td>
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<tr>
<td>Tzanck smear &amp; viral culture</td>
<td>Bacterial culture</td>
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- Positive
  - Treat accordingly
  - Direct Immunofluorescence staining/PCR if available

- Negative
  - Tzanck smear & viral culture
  - Bacterial culture
  - Dark ground microscopy
  - Syphilis serology

- Skin biopsy
  - Treat accordingly
Learning points:
Genital herpes can present atypically in immunocompromised patient and a high index of clinical suspicion is needed. Tzanck smear is a simple and non-invasive method to enable an early diagnosis of herpes infection.

References