Genital Ulcers: Etiology, Clinical Diagnosis, and Associated Human Immunodeficiency Virus Infection in Kingston, Jamaica

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The prevalence of genital ulcers among patients attending Jamaican public clinics for sexually transmitted diseases (STDs) increased from 6.8% in 1983 to 12.8% in 1990 [1]. Genital ulcers have been reported as a risk factor for the rising prevalence of HIV type 1 infection in STD clinic attenders in Jamaica [2]. Thus, adequate case management is crucial to control classic STDs as well as to reduce the transmission of HIV.

Traditionally, treatment of genital ulcers is based on etiology. However, determining the etiology of genital ulcers is costly, technically sophisticated, time-consuming, and thus is rarely affordable, available, or accessible in developing countries. Clinical diagnosis has been shown to be often inaccurate [3–5], and, recently, laboratory diagnosis by means of conventional techniques such as culture for Haemophilus ducreyi and herpes simplex virus (HSV) has also been found to have less-than-optimal sensitivity [6].

The World Health Organization has recommended syndromic management of genital ulcer disease (GUD) based on local epidemiological data rather than individual diagnosis. A study was initiated to determine the causal agents of genital ulcers in Jamaica, by using state-of-the-art diagnostic techniques, and to review the existing national guidelines for the routine management of genital ulcers. At the same time, HIV infection was assessed. The study was conducted at the Comprehensive Health Clinic in Kingston, which is the largest STD care facility in Jamaica. Section 3 of this clinic provides care to people from disadvantaged neighborhoods who present with symptoms suggestive of STDs, as well as to patients referred by other health care providers for STD care.

Methods

Individuals presenting consecutively at the Comprehensive Health Clinic in Kingston, Jamaica, with GUD from 5 March 1996 through 30 August 1996 were enrolled in the study after informed consent was obtained. A brief structured questionnaire was administered by one of two study clinicians (one physician and one registered nurse, both senior health care...
providers with extensive training and experience in STD care) who also performed a physical examination, recorded a clinical diagnosis, and collected a clinical specimen after cleansing the ulcer. In this study, the clinicians made a clinical diagnosis solely based on findings of physical examination and history without knowledge of results of laboratory testing. Criteria utilized by these health care providers to determine clinical diagnosis, as outlined in the Jamaican Practical Case Management of Common STD Syndromes [7], were not individually documented. Treatment and clinical follow-up conformed to the national STD treatment guidelines. A sterile swab was used to collect material from the clean ulcer base, which was expressed into Amplicor specimen transport medium (Roche Molecular Systems, Alameda, CA).

The ulcer material was frozen at −20°C until analysis at the Centers for Disease Control and Prevention (CDC) by means of multiplex PCR (M-PCR) testing (Roche Molecular Systems) for H. ducreyi, Treponema pallidum, and HSV following previously described techniques [8].

Blood specimens were obtained from the study subjects through venipuncture. Syphilis serology was performed by the nonTreponemal antigen toluidine red unheated serum test (TRUST) [9] (New Horizons Diagnostics, Columbia, MD) at the laboratory of the Comprehensive Health Clinic following the manufacturer’s instructions. Reactive serum samples were diluted to determine end point reactivities, and the results were confirmed at the Kingston-based National Public Health Laboratory by means of the microhemagglutination test for T. pallidum (MHA-TP) (Fujirebio; Miles, Elkhart, IN). Titters of antibodies to HIV were determined at the National Public Health Laboratory by EIA (HIVAB HIV-1/HIV-2 [rDNA] EIA; Abbott Laboratories, Abbott Park, IL). Repeatedly positive serum samples were tested by using a second EIA (Enzygnost HIV-1/2 Plus; Behring Diagnostics, Marburg, Germany). Serum samples that were consistently reactive by both EIAs were considered HIV-positive. Discordant serum samples that were positive for HIV types 1 and 2 by HIV-SPOT (Genelabs Diagnostics, Singapore) were considered HIV-positive, and those that were negative by this test were evaluated by using western blotting (Genelabs Diagnostics). Western blotting was considered positive when antibody reactivity to two envelope bands (gp110, 120, 160) was observed with or without the presence of antibodies to gag (p17, 24, 39, 42, 55) or pol (p31, 51, 66).

A subset of frozen serum samples were sent to the Chlamydia Laboratory, University of California, San Francisco, for detection of IgG and IgM antibodies to Chlamydia by microimmuno-fluorescence testing [10, 11].

The collected data were entered twice in a database, cleaned, and analyzed by using Epi Info version 6.02 (Centers for Disease Control and Prevention). Not all patient records contained complete information. Records with missing data for variable(s) under specific analysis were excluded; therefore, denominators varied. Differences in rates were assessed by using the Mantel-Haenzel χ² or Fisher’s exact test. Means were compared by means of analysis of variance for normally distributed data; the Kruskal-Wallis test was used to compare two groups with nonhomogeneous variances.

**Results**

**Demographic, behavioral, and clinical characteristics.** A total of 304 patients, 252 men (82.9%) and 52 women (17.1%), were enrolled in the study. The mean age of the women was 27.0 years (median, 25.0 years); the mean age of the men was 30.7 years (median, 28.0 years) (P = .05). Five (2.0%) of the 252 male patients were circumcised. The clinicians observed an average of 5.1 ulcers (median, 2.0 ulcers) per patient; the mean diameter of the largest ulcers was 12.9 mm (median, 6.0 mm). Of the male patients, 76.2% had genital lesions located on the foreskin; 25.4%, coronal sulcus; 22.6%, frenulum; 15.5%, glans; 13.5%, shaft; 2.0%, scrotum; and 1.6%, urethral meatus. Of the female patients, 61.5% had genital lesions located on the labia majora; 28.8%, labia minora; 25.0%, posterior fornix; 13.5%, shaft; 2.0%, scrotum; and 1.6%, urethral meatus.

On average, the patients reported to have first noticed their genital sore(s) 17.6 days (median, 10.0 days) before attending the clinic and to have had their most recent sexual contact 37.4 days (median, 14.0 days) earlier. The lesions were reported as painless by 229 (75.8%) of 302 individuals. One hundred fifty-four (50.7%) of the 304 patients reported having had a prior episode of genital sores or “haircut.”

For treatment of their current genital lesion(s), 83 patients (27.3%) used self-medication, 30 (9.9%) used medication prescribed by another clinician, 13 (4.3%) had purchased drugs on the street, and 10 (3.3%) had purchased drugs in a drug store. Reported self-medication included a few unspecified “capsules” taken orally and/or used locally, as well as alcohol, ointments, creams, black dressing, olive oil, castor oil, dettol, lime, salt water, petroleum jelly, gentian violet, merbromin, zinc oxide ointment, “left over drugs,” erythromycin, “red and black” (ampicillin), and “yellow and orange” (tetracycline).

A clinical diagnosis of chancroid was made in 111 (36.5%) of the 304 subjects. Genital herpes was clinically diagnosed in 109 patients (35.9%); syphilis, 45 (14.8%); granuloma inguinale, 21 (6.9%); traumatic lesions, 21 (6.9%); lymphogranuloma venereum, 8 (2.6%); and candidiasis, 8 (2.6%). Other recorded clinical diagnoses included cancer (2 cases [0.7%]), folliculitis (2 [0.7%]), scabies (2 [0.7%]), secondary syphilis (1 [0.3%]), and HIV infection (1 [0.3%]; this case had been previously diagnosed).

**M-PCR testing.** Of the 304 genital ulcer specimens analyzed by M-PCR, 158 (52.0%) contained HSV DNA; 72 (23.7%), H. ducreyi DNA; and 31 (10.2%), T. pallidum DNA (table 1). Twenty-two genital ulcer specimens (7.2%) contained DNA from two of these agents, and one contained DNA from all three. Specimens from 67 patients (22.0%) were negative by M-PCR analysis. The prevalence of lesions positive for
was positive for positive syphilis screening and a positive confirmation test). (5.5%) who had positive M-PCR tests compared with eight

\[
P \text{T. pallidum}
\]

had positive nontreponemal and treponemal antigen tests associated with a negative M-PCR test. Patients who reported

\[
T. pallidum
\]

TRUSTs (OR, 19.5; 95% CI, 7.2–60.6; \( P < .001 \)). Secondary syphilis was diagnosed by M-PCR analysis and 41 (15.0%) of the 273 patients who were positive for \( T. pallidum \) by M-PCR analysis had reactive TRUSTs; results of 64 (87.7%) of these tests were confirmed by MHA-TP. Twenty-five (80.6%) of the 31 patients who were positive for \( T. pallidum \) by M-PCR analysis and 48 (17.6%) of the 273 patients who were negative for \( T. pallidum \) by M-PCR analysis had reactive TRUSTs (OR, 19.5; 95% CI, 7.2–60.6; \( P < .001 \)). Twenty-three (35.9%) of 64 patients for whom both nontreponemal and treponemal antigen tests were positive were HIV-seropositive compared with 44 (18.3%) of 240 \( T. pallidum \)–seronegative patients (OR, 2.5; 95% CI, 1.3–4.8; \( P = .002 \)). Eight (40.0%) of the 20 patients who had positive serological tests for syphilis and had palmar, plantar, or truncal rash were HIV-seropositive compared with 59 (20.8%) of 284 patients who had no signs of secondary syphilis (OR, 2.5; 95% CI, 0.9–7.1; \( P = .05 \)).

**Antibodies to Chlamydia.** Of the 91 serum samples evaluated for antibodies to \( C. trachomatis \), 85 (93.4%) had IgG antibodies to \( C. trachomatis \) (average titer, 1:483; median titer, 1:128). Eleven serum samples (12.1%) had titers of IgG antibody of \( \geq 1:2,048 \); the highest titer observed was 1:4,096. Three (3.3%) of the 91 serum samples had IgM antibodies to \( C. trachomatis \), all with an end point titer of 1:8 and corresponding titers of IgG antibody of \( < 1:512 \). No associations were found between titers of IgG antibody of \( \geq 1:2,048 \) and a clinical diagnosis of lymphogranuloma venereum or ulcers negative by M-PCR analysis.

**M-PCR analysis—determined etiologies and associations with clinical diagnoses and behavioral characteristics.** The sensitivity, specificity, and predictive values of clinical diagnosis compared with M-PCR analysis are shown in table 2. Granuloma inguinale was a more frequent clinical diagnosis in patients for whom no etiology was determined by M-PCR analysis than in those with positive M-PCR tests: nine (13.4%) of 67 vs. 12 (5.1%) of 237, respectively (OR, 2.9; 95% CI, 1.1–7.9; \( P = .03 \)).

A clinical diagnosis of lymphogranuloma venereum was not associated with a negative M-PCR test. Patients who reported taking medication for treatment of their current genital ulcer(s) were not more likely than those who did not to have negative M-PCR tests. Traumatic lesions were found in 13 patients (5.5%) who had positive M-PCR tests compared with eight patients (11.9%) who had negative M-PCR tests, but this difference was not significant (\( P > .05 \)). The category “other diagnoses” (including candidiasis, cancer, and scabies) was recorded for 13 (5.5%) of 237 patients whose ulcer specimens were positive by M-PCR analysis compared with six (9.0%) of 67 patients whose ulcer specimens were negative by M-PCR testing, but this difference lacked statistical significance.

Lesions that were positive for HSV by M-PCR testing were not associated with a reported history of genital ulcer(s) nor with HIV infection, but were more common in patients who reported that their lesion had started as a “water blister” than in those who did not: 50 (73.5%) of 68 vs. 103 (45.0%) of 229 patients, respectively (OR, 3.4; 95% CI, 1.8–6.47; \( P < .001 \)). Sixteen (44.4%) of 36 men who reported sexual contact with a prostitute during the 3 months preceding the consultation were positive for \( H. ducreyi \) by M-PCR analysis vs. 47 (23.6%) of 199 men who did not report sex with a prostitute (OR, 2.59; 95% CI, 1.16–5.77; \( P = .009 \)). Lesions positive for \( T. pallidum \) by M-PCR analysis or clinically diag-

### Table 1. The etiology of genital ulcers in Jamaican patients as determined by multiplex PCR analysis.

<table>
<thead>
<tr>
<th>Etiology</th>
<th>No. (%) of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herpes</td>
<td>138 (45.4)</td>
</tr>
<tr>
<td>Chancroid</td>
<td>54 (17.8)</td>
</tr>
<tr>
<td>Syphilis</td>
<td>22 (7.2)</td>
</tr>
<tr>
<td>Herpes and chancroid</td>
<td>14 (4.6)</td>
</tr>
<tr>
<td>Herpes and syphilis</td>
<td>5 (1.6)</td>
</tr>
<tr>
<td>Chancroid and syphilis</td>
<td>3 (1.0)</td>
</tr>
<tr>
<td>Herpes, chancroid, and syphilis</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>No diagnosis</td>
<td>67 (22.0)</td>
</tr>
<tr>
<td>Total</td>
<td>304 (99.9*)</td>
</tr>
</tbody>
</table>

* Due to rounding, the total does not add up to 100%.

\[ T. pallidum \] or HSV by M-PCR analysis did not vary significantly by gender. However, \( H. ducreyi \) was detected by M-PCR analysis in specimens from six (11.5%) of 52 female patients compared with 66 (26.2%) of 252 male patients (OR, 0.37; 95% CI, 0.1–1.0; \( P = .02 \)).

**Syphilis serology.** Seventy-three (24.0%) of the 304 study participants had reactive TRUSTs; results of 64 (87.7%) of these tests were confirmed by MHA-TP. Twenty-five (80.6%) of the 31 patients who were positive for \( T. pallidum \) by M-PCR analysis and 48 (17.6%) of the 273 patients who were negative for \( T. pallidum \) by M-PCR analysis had reactive TRUSTs (OR, 19.5; 95% CI, 7.2–60.6; \( P < .001 \)). Twenty-three (74.2%) of the 31 patients who were positive for \( T. pallidum \) by M-PCR analysis and 41 (15.0%) of the 273 patients who were negative for \( T. pallidum \) by M-PCR analysis had positive nontreponemal and treponemal antigen tests (OR, 16.3; 95% CI, 6.4–42.8; \( P < .001 \)).

Twenty (6.6%) of the 304 study subjects had evidence of secondary syphilis (i.e., palmar, plantar, or truncal rash with a positive syphilis screening and a positive confirmation test). Of these 20 individuals, 11 (55.0%) had an ulcer specimen that was positive for \( T. pallidum \) by M-PCR analysis compared with 20 (7.0%) of 284 patients who did not have clinical signs and serological evidence of secondary syphilis (OR, 16.1; 95% CI, 5.4–48.8; \( P < .001 \)). Secondary syphilis was diagnosed in 13 (5.2%) of 252 male patients compared with seven (13.5%) of 52 female patients (OR, 0.35; 95% CI, 0.1–1.0; \( P = .05 \)).

**HIV serology.** Antibodies to HIV were detected in 67 (22.0%) of the 304 study subjects. The HIV seroprevalence rates did not statistically differ by gender. HIV serostatus did not correlate with the presence of herpetic, syphilitic, or chancroid ulcers as determined by M-PCR testing. A clinical diagnosis of granuloma inguinale, however, was made in 10 (14.9%) of 67 HIV-seropositive patients compared with 11 (4.6%) of 237 HIV-seronegative patients (OR, 3.6; 95% CI, 1.3–9.8; \( P = .003 \)). Ingual lymphadenopathy was observed in 54 (80.6%) of 67 patients infected with HIV compared with 129 (54.4%) of 237 HIV-seronegative patients (OR, 3.5; 95% CI, 1.7–7.1; \( P < .001 \)).
nosed granuloma inguinale were not associated with reported sexual contact with prostitutes; however, 12 (33.3%) of the 36 men who reported sexual contact with a prostitute during the 3 months preceding the consultation had lesions that were positive for HSV by M-PCR testing compared with 104 (52.3%) of 199 men who did not report this behavior (OR, 0.46; 95% CI, 0.2–1.03; P = .04). Of the 36 men who had sexual contact with a prostitute, 14 (38.9%) were HIV-seropositive compared with 37 (18.6%) of 199 men who did not report this contact (OR, 2.79; 95% CI, 1.21–6.39; P = .007). Twelve (33.3%) of these 36 men had reactive serological tests for syphilis compared with 31 (15.6%) of the 199 men who did not report sex with a prostitute (OR, 2.71; 95% CI, 1.14–6.4; P = .011).

Discussion

Most of the genital ulcers in these Jamaican patients were caused by HSV. Genital herpes has been reported as an increasingly important cause of genital ulcers in studies conducted in Lesotho, Uganda, Rwanda, and South Africa [6, 12–14]. To our knowledge, this is the first report from the Caribbean region. Chancroid was more prevalent than syphilis in these patients: 23.7% vs. 10.2% of patients, respectively. Although the most advanced diagnostic techniques were used, 22% of the ulcers remained without definite etiology. Granuloma inguinale was diagnosed clinically more frequently in patients with ulcers negative by M-PCR analysis, and it is thus likely that some of these ulcers were indeed a result of infection with Calymmatobacterium granulomatis. Other causes hypothesized by the clinicians included cancer, candidiasis, scabies, and trauma.

As observed elsewhere, most patients with a genital ulcer who were attending this clinic were men. M-PCR analysis–proven chancroid was found less frequently in females than in males, whereas palmar, plantar, or truncal rash was more often observed in female patients. In a study in Durban, South Africa, secondary syphilis was the commonest diagnosis in Zulu women with genital ulcers [14]. Although awareness may play an important role in seeking health care, other factors are also likely to influence this behavior. For instance, opening hours of a public clinic might limit access for sex workers.

Our findings confirm the inadequacy of clinical diagnosis as shown in other studies using nucleic acid amplification assays as well as those employing traditional laboratory tests [3, 5, 6]. We also demonstrated the limited utility of syphilis serology for the diagnosis of GUD: if TRUST and MHA-TP alone had been used for the detection and management of syphilitic ulcers, 26% of the cases would have been missed. A slightly higher sensitivity has been found with the fluorescent treponemal antibody absorption test than with MHA-TP: 84% (range, 70%–100%) vs. 76% (range, 69%–90%), respectively [15]. Furthermore, 15% of the patients who had ulcers that were negative for T. pallidum by M-PCR testing had reactive syphils serologies.

Patients with genital ulcers are at increased risk for transmitting or acquiring HIV infection [16]. Besides providing prompt and effective treatment, novel approaches are needed to stimulate patients with GUD to avoid self-medication, to seek early and adequate treatment, to refrain from sexual intercourse while infected, and to consistently use condoms to minimize the spread of STDs and HIV infection. The associations found between sexual contact with a prostitute and increased risk for chancroid and T. pallidum as well as HIV seropositivity underline the need for further action.

Other investigators have reported that prostitutes are a primary source of infection for chancroidal ulcers [17]. Prostitutes in Nairobi, Kenya, were found to be a major reservoir of STDs, and genital ulcers including chancroid were more common in female sex workers of middle and lower social classes [18]. Ronald and Plummer [19] concluded that “The control of chancroid in prostitutes and their clientele will substantially slow the heterosexual transmission of HIV-1.” In a study in Abidjan, Ivory Coast, Ghys et al. [20] inferred that genital ulcers may be an opportunistic infection in female sex workers, since higher prevalence rates of genital ulcers were associated with increasing severity of immunosuppression. Targeted interventions should provide commercial sex workers with reproductive health information, timely and efficient STD treatment, and barrier prevention including female condoms.

As advocated by the national STD and HIV infection control program genital ulcers should clearly be managed syndromically with use of algorithms based on the local etiology of GUD, since clinical diagnosis proved to be unreliable and local laboratory diagnosis was restricted to syphilis serology with the described limitations. Our results confirm the validity of
the national guidelines, which stipulate that genital ulcers not caused by HSV should be treated for both chancroid and syphilis. Because clinicians are often reluctant to rely on simple decision trees instead of clinical and laboratory diagnoses, these local data need to be utilized to promote syndromic management of GUD among clinicians working in private as well as public settings.

Acknowledgments

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References