Lymphogranuloma Venereum Causing a Persistent Genital Ulcer

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Abstract: Lymphogranuloma venereum (LGV) is a sexually transmitted cause of inguinal lymphadenopathy and proctocolitis. We report a patient with a persistent genital ulcer due to LGV (serovar L2b), an unusual presentation among US men who have sex with men. Lymphogranuloma venereum should be considered when evaluating persistent genital ulcers, and LGV-specific testing should be sought.

CASE REPORT

Lymphogranuloma venereum (LGV) is a sexually transmitted disease caused by serovars L1, L2, L2a, L2b, and L3 of the bacterium *Chlamydia trachomatis* (*CT*). Lymphogranuloma venereum classically begins with a self-limiting, transient, painless lesion at the site of inoculation after an incubation period of 3 to 30 days.[1] This is followed several weeks later by either an inguinal syndrome with lymphadenopathy and abscess formation or an anorectal syndrome presenting with proctocolitis. Lymphogranuloma venereum invades lymphatic tissue and, without treatment, can progress to cause abscesses, lymphatic fibrosis and obstruction, elephantiasis of the genitalia, anal strictures, and fistulae.[1]

Lymphogranuloma venereum is endemic in parts of Africa, Asia, South America, and the Caribbean, where it typically presents as a painless ulcer followed by inflammation and swelling of the inguinal lymph nodes, but it is rare in Western countries.[2] Since 2003, there have been multiple reports of LGV among men who have sex with men (MSM) in Europe, most of whom are HIV infected and have presented with proctocolitis.[3] Most cases have been caused by serovar L2b.[4] Although some data suggest that LGV has been endemic in San Francisco since the 1980s,[5] there is no systematic surveillance for LGV in the United States, and access to diagnostic assays specific for LGV is limited.[6] We describe here an unusual presentation of LGV disease in an HIV-infected man with a persistent genital ulcer and minimal inguinal lymphadenopathy.

A 45-year-old HIV-positive man presented to his primary care provider with a penile lesion. He reported that the lesion had been present for 1 week and was painful and enlarging in size. One week before the onset of the lesion, he had insertive anal sex with a partner whom he suspected had anal herpes simplex virus (HSV). He denied fever, chills, fatigue, rash, urethral discharge, dysuria, or rectal symptoms.

The patient's medical history was significant for well-controlled HIV (plasma HIV RNA level was undetectable and recent $CD4^+$ T-cell count was 832 cells/μL while taking a fixed-dose combination of efavirenz, tenofovir, and emtricitabine), chronic hepatitis C virus infection, depression, anxiety, and a self-reported history of genital herpes. He had no known history of syphilis. He reported regular use of intravenous methamphetamines, was sexually active exclusively with men, did not use condoms, had both insertive and receptive anal sex, and reported engaging in commercial sex work years prior. He was abstinent from alcohol and tobacco.

Genitourinary examination revealed a 4-mm penile ulcer at the coronal sulcus. The lesion was slightly indurated and was tender to palpation. There was no inguinal lymphadenopathy. The remainder of the physical examination was unremarkable. A swab of the penile lesion was sent for HSV culture and varicella zoster virus polymerase chain reaction (PCR), and rectal and pharyngeal swabs were sent for *Neisseria gonorrhea* (*GC*) and *CT* nucleic acid amplification tests (NAATs). A serum rapid plasma reagin (RPR) was sent; dark-field microscopy was not available. The patient was empirically treated for a possible HSV ulcer with valacyclovir 1000 mg twice daily for 10 days. Both HSV culture and varicella zoster virus PCR were negative, and serum RPR was nonreactive. The *CT* NAAT result from the rectal swab was positive, but pharyngeal *CT* NAAT result was negative. *GC* NAAT results from both the rectum and the pharynx were negative. The patient was treated for rectal *CT* with a single 1-g dose of azithromycin.

The patient returned to clinic 4 weeks later with persistence of the painful ulcer. On examination, the lesion was unchanged in size and appearance. A swab of the lesion was sent for routine bacterial culture and *Haemophilus ducreyi* culture. The patient was treated with clindamycin 300 mg 3 times daily for 7 days for a possible pyogenic bacterial infection. Bacterial culture of a swab of the lesion showed that rare *Staphylococcus aureus* (sensitive to both methicillin and clindamycin), group B *Streptococcus*, and *Haemophilus parainfluenzae*. *H. ducreyi* culture was negative.

Approximately 6 weeks later (11 weeks from the onset of symptoms), the patient returned to clinic reporting persistence of the penile ulcer. Physical examination revealed a 1-cm ulcer with scant white exudate that was tender to palpation, 2- to 3-cm surrounding induration (Fig. 1A), and new bilateral shotty inguinal lymphadenopathy. Repeat serum RPR and HSV culture were negative. *N. gonorrhea* and *CT* NAATs were sent from

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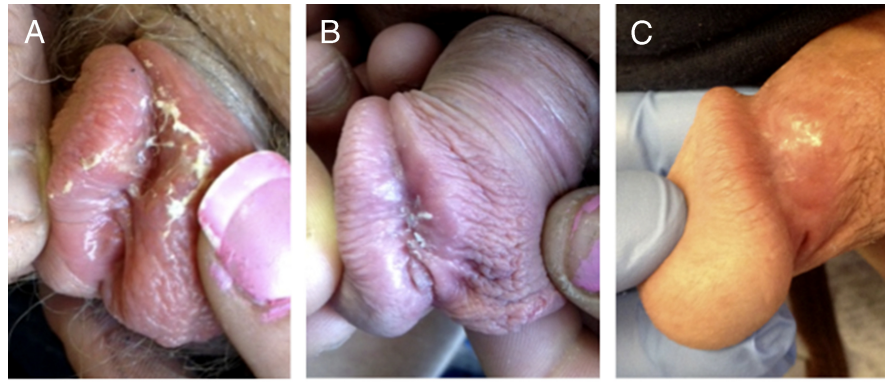

Figure 1. Pretreatment, early posttreatment, and late posttreatment appearance of persistent LGV ulcer.

swabs of the penile ulcer, rectum, and pharynx. Although all *GC* test results and the pharyngeal *CT* NAAT result were negative, the *CT* NAAT results from both the ulcer and the rectum were positive.

Suspecting LGV, the department of public health was consulted and recommended collecting an additional sample from both the penile ulcer and rectum for LGV testing, and recommended treating the patient empirically for LGV. The rectal sample was positive for *CT* but negative for LGV. The penile ulcer swab was positive for *CT* and for L-serovar *C. trachomatis* by PCR. The patient was treated with doxycycline 100 mg twice daily for 21 days. On clinical follow-up, one week after the completion of doxycycline, the patient reported no pain, and the penile ulcer was substantially improved (Fig. 1B). Eight weeks after therapy, the lesion was completely resolved (Fig. 1C), and results from both serum RPR and TPPA remained negative.

All specimens for *GC* and *CT* were processed and tested on a Tigris DTS Automated Analyzer, which used the APTIMA Combo 2 Assay (Hologic Gen-Probe, San Diego, CA). Gen-Probe's Tigris DTS assay is Food and Drug Administration approved for the diagnosis of *GC* and *CT* from urethral, endocervical swabs and from urine specimens. The San Francisco Public Health Laboratory has validated this test for use on rectal and pharyngeal swabs.

Swab samples from the penile ulcer and rectum were tested for LGV as follows: samples were placed into 3 mL of BD Universal Viral Transport medium (UVT; Becton Dickinson, Franklin Lakes, NJ). To purify *CT* DNA, 200 μL of each UVT sample was extracted on the automated sample prep QIAcube using the QIAamp DNA Mini kit (Qiagen, Germantown, MD). A real-time PCR assay, based on the method developed by Morre et al.,[7] was used to detect LGV-specific DNA using a Roche LightCycler 2.0 instrument (Roche Applied Science, Indianapolis, IN). The target sequence of this assay is the polymorphic membrane protein H gene (*pmpH*), a highly specific region for the detection of L-serovar *C. trachomatis* due to a specific 36-base pair deletion found in this gene in L-serovar, LGV-associated strains.[7]

Lymphogranuloma venereum–specific DNA was detected in the penile ulcer swab sample but not in the rectal swab sample. To confirm the presence of *C. trachomatis* in the penile ulcer sample, subsequent molecular analysis was performed to amplify and sequence the *omp*1 gene, which encodes the major outer membrane protein, the immunodominant antigen of *C. trachomatis*.[8] Amplification of *omp1* was performed as previously published.[9] Sequencing results were processed using the MEGA 5.1 genetic analysis method, then genotyped by BLAST (http://www.ncbi.nih.gov/projects/genotyping/formpage.cgi) and found to have 99.9% homology to *C. trachomatis*, serovar L2b.

This patient's clinical course was unusual for several reasons. First, the genital ulcer was painful, which is uncharacteristic of the ulcerative stage of LGV. Second, it had already been present more than 7 days when first evaluated and persisted for 3 months, both unusually long periods. Third, the patient did not develop enlarged or painful inguinal lymphadenopathy. The patient has a history of HSV and was tested with HSV culture, which is less sensitive than HSV PCR. It is possible that concurrent HSV reactivation played a role in his unusual clinical course. Although there have been reports of LGV presenting as genital ulcer disease in MSM in Europe,[10,11] most of LGV in MSM has presented as proctocolitis.

Also of note is the patient's non-LGV rectal *CT* infection concurrent with his ulcerative LGV penile infection. After his initial presentation, he was appropriately treated for asymptomatic rectal *CT* with 1 g of azithromycin.[6] This did not result in any improvement in his penile ulcer. Current sexually transmitted disease treatment guidelines recommend a longer course of treatment of LGV than for non-LGV *CT* (21 days of doxycycline for LGV) due to the more invasive nature of LGV[6]; limited data suggest that azithromycin 1 g weekly for 3 weeks may also be effective.[11]

Whether the positive result from non-LGV rectal *CT* NAAT at his follow-up visit was secondary to treatment failure or reinfection is unclear. Ensuring adequate partner treatment and repeat testing at 3 months are both important cornerstones of management of patients diagnosed as having *CT*, *GC*, or syphilis.[6] Recent reports based on observational data have suggested that doxycycline 100 mg twice daily may be more efficacious than a single 1-g dose of azithromycin for the treatment of rectal *CT*,[12] and a controlled trial to address this question is needed.

This case demonstrates that clinicians should consider the possibility of LGV in the differential diagnosis of persistent genital ulcer disease, particularly in HIV-infected MSM. It also illustrates the value of PCR as a diagnostic tool for differentiating LGV from non-LGV serovars of *CT*. However, there are no commercially available assays that simultaneously detect and differentiate LGV from non-LGV serovars of *CT*, and few facilities have the capability to identify LGV by PCR-based methods. Therefore, in the absence of an LGV-specific test, clinicians should consider administering empiric LGV treatment in MSM who present with non-HSV, nonsyphilitic genital ulcer disease, or who have severe proctitis.

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