Lymphogranuloma venereum presenting as genital ulceration and inguinal syndrome in men who have sex with men in London, UK

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ABSTRACT
Objectives: To describe a series of lymphogranuloma venereum (LGV) cases presenting as inguinal syndrome and/or genital ulceration seen among men who have sex with men (MSM) in London, UK.

Methods: Collaborative retrospective case note review. Clinicians from three London genitourinary medicine (GUM) clinics accessed by large populations of MSM within the current LGV outbreak collected clinical data from confirmed cases of LGV inguinal syndrome or genital ulcer. LGV was confirmed by the detection of LGV-specific DNA from specimens such as bubo aspirates, ulcer swabs, urethral swabs, first void urine and rectal biopsy material.

Results: There were 13 cases detected overall: 5 cases of urethral LGV infection with inguinal adenopathy, 3 cases of genital ulcer with LGV inguinal adenopathy, 3 cases of isolated LGV-associated inguinal buboes, 1 case of a solitary LGV penile ulcer and 1 case with a penile ulcer and bubonulosis. Only 6 of the 13 were HIV positive and all tested negative for hepatitis C. The majority of cases reported few sexual contacts in the 3 months preceding their diagnosis.

Conclusions: Clinical manifestations of LGV in MSM have not been confined to proctitis in the current outbreak in the UK and a small but significant number of inguinalgonital cases of LGV have been observed. Epidemologically, many of the cases described seem to have occurred at the periphery of the current MSM LGV epidemic. Clinicians need to be vigilant for these less common presentations of LGV among MSM and specific diagnostic tests should be done from the relevant lesions.

Lymphogranuloma venereum (LGV) is caused by Chlamydia trachomatis serovars L1–L3.1 These serovars display tropism for the lymphatic system in contrast to serovars A–K that affect mucocutaneous tissue.1 Endemic in Africa, the Caribbean and parts of Asia,1 the classical presentation of LGV is inguinal lymphadenitis and abscess formation sometimes preceded by anogenital ulceration. Since 2004 there has been a resurgence of LGV proctitis affecting predominantly men who have sex with men (MSM) who are HIV positive in the UK, Western Europe and the USA.2–4 Detected cases have had high rates of co-infection with other sexually transmitted infections (STIs), including hepatitis C.5 Anogenital ulceration and/or lymphadenitis has been reported rarely in the current MSM LGV epidemic.2–5

We describe 13 recent cases of LGV that presented with “classical” inguinocecal manifestations. LGV was detected, usually in the absence of other STIs, and symptoms resolved after treatment with long-course regimens of doxycycline or azithromycin.

METHODS
Clinicians from three inner London genitourinary medicine (GUM) clinics servicing large populations of MSM collected clinical data from confirmed cases of LGV inguinal syndrome or genital ulcer. Case histories were anonymised and relevant data were collated and compared. Written informed consent was obtained from all cases that provided clinical images for this paper. As this was a retrospective anonymised case note review, ethics committee approval was not sought from the participating centres.

Initial tests for C trachomatis and other STIs were performed at the respective hospital laboratories using commercially available assays performed according to the instructions of the manufacturer. All 13 cases described had specimens confirmed as LGV using molecular tests performed at the Sexually Transmitted Bacteria Reference Laboratory (STBRL), Health Protection Agency, Colindale, UK. DNA was extracted from clinical specimens (ulcer swabs, urethral swabs, first void urine) using the MagNA Pure total NA kit (Roche Diagnostics GmbH, Mannheim, Germany) according to the manufacturer’s instructions. In instances where limited clinical specimen was available (bubo aspirates and rectal biopsies), manual DNA extractions were performed using the QiAamp Viral Mini Kit (Qiagen, Crawley, UK). The chlamydia status of all referred specimens was confirmed initially using a plasmid-based real-time PCR method. The presence of LGV DNA was then detected using a LGV-specific pgmH real-time PCR assay.

RESULTS
Clinical records
The characteristics of the 13 cases are summarised in table 1.

All were MSM with a median age of 36 years (range 21–61). Ten were of white ethnicity; only six were infected with HIV and none tested positive for hepatitis C antibodies. Twelve cases presented with unilateral or bilateral inguinal adenopathy, four of whom had concurrent genital ulceration, and one patient presented with penile ulceration only. Five of the twelve men with inguinal adenopathy appear to have had urethral...
<table>
<thead>
<tr>
<th>Case number, date &amp; clinic</th>
<th>Ethnicity &amp; age</th>
<th>Clinical presentation</th>
<th>Urethritis symptoms</th>
<th>HIV IgG status</th>
<th>Number of sexual contacts in last 3 months</th>
<th>Negative STI tests performed</th>
<th>LGV-specific PCR result</th>
<th>LGV serology</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1* Dec 2003 STH</td>
<td>White British 54</td>
<td>Tender unilateral 4 cm by 5 cm inguinal lymphadenopathy, subsequent ruptured bubo</td>
<td>Nil</td>
<td>Positive CD4 615 VL&lt;50</td>
<td>&gt;5</td>
<td>Urethral, rectal and pharyngeal GC culture</td>
<td>Positive (rectal biopsy specimen from subsequent LGV proctitis)</td>
<td>CGAb CFT negative (titre &lt;20 in Feb 2005)</td>
<td>Doxycycline 100 mg twice daily for 3 weeks</td>
</tr>
<tr>
<td>2 Sept 2005 C&amp;W</td>
<td>White British 56</td>
<td>0.5 cm scrotal and perianal ulcers with subsequent unilateral inguinal lymphadenopathy and 4 cm by 3 cm bubo formation</td>
<td>Nil</td>
<td>Positive CD4 523 VL&lt;50</td>
<td>1</td>
<td>Urethral swab and rectal swab GC/CT (SDA)</td>
<td>Positive (scrotal ulcer swab and swab of fluid from ruptured bubo)</td>
<td>Pittacosis/LGV CFT negative (titres 1:20 twice, 2 weeks apart)</td>
<td>Doxycycline 100 mg twice daily for 17 days then azithromycin 1 g daily for 12 days then azithromycin 500 mg daily for 5 days</td>
</tr>
<tr>
<td>3 Jan 2006 C&amp;W</td>
<td>White British 46</td>
<td>Penile ulcer and unilateral inguinal lymphadenopathy</td>
<td>Nil</td>
<td>Positive CD4 470 VL&lt;50</td>
<td>10</td>
<td>Urethral swab and rectal swab GC/CT (SDA)</td>
<td>Positive (penile ulcer swab)</td>
<td>Not done</td>
<td>Doxycycline 100 mg twice daily for 3 weeks</td>
</tr>
<tr>
<td>4 April 2006 STH</td>
<td>White British 61</td>
<td>0.7 cm painless solitary penile ulcer. No lymphadenopathy</td>
<td>Nil</td>
<td>Negative</td>
<td>1</td>
<td>Urethral swab GC/CT (SDA)</td>
<td>Positive (penile ulcer swab)</td>
<td>Positive: CGAb titre 1:320 (STH); CGAb/LGV CFT titre 1:512 (HPA); CT WIF (L2 strain) titre 1:3000 (HPA, Bristol)</td>
<td>Doxycycline 100 mg twice daily for 3 weeks</td>
</tr>
<tr>
<td>5 Dec 2006 STH</td>
<td>White Irish 24</td>
<td>Bilateral inguinal buboes and preputial ulcer</td>
<td>Nil</td>
<td>Negative</td>
<td>1</td>
<td>Preputial ulcer swab darkground microscopy</td>
<td>Positive (bubo aspirate)</td>
<td>Positive CGAb CFT (titres 1:320 and 1:1280 2 weeks apart)</td>
<td>Doxycycline 100 mg twice daily for 3 weeks</td>
</tr>
<tr>
<td>6 April 2007 STH</td>
<td>White British 34</td>
<td>Bilateral tender 2 cm by 3 cm ruptured buboes</td>
<td>Nil</td>
<td>Positive CD4 787 VL&lt;40</td>
<td>1</td>
<td>Rectal and pharyngeal GC culture</td>
<td>Positive (swab of bubo pus)</td>
<td>Not done</td>
<td>Doxycycline 100 mg twice daily for 3 weeks</td>
</tr>
<tr>
<td>7 July 2007 MMC</td>
<td>White other 36</td>
<td>Tender right 12 cm by 8 cm and left 4 cm by 2 cm inguinal lymphadenopathy</td>
<td>Nil</td>
<td>Negative</td>
<td>4</td>
<td>Rectal swab CT (PCR)</td>
<td>Positive (urethral swab PCR and chlamydial culture)</td>
<td>Positive CGAb (1:400)</td>
<td>Doxycycline 100 mg twice daily for 3 weeks</td>
</tr>
</tbody>
</table>

**Table 1** Characteristics of 13 confirmed cases of lymphogranuloma venereum (LGV) presenting with inguinal syndrome and/or genital ulceration

infection as their primary LGV lesion and none of the five reported any preceding anogenital ulceration, although such symptoms might have been transient and unnoticed. Six of the men reported only solitary sexual contacts in the previous 3 months, three of whom were their HIV positive regular male partners.

### Notable features of cases

Of note, case 1 was first seen in December 2003 when he developed a tender right inguinal swelling. He reported regular unprotected insertive and receptive anal sex with anonymous male partners in London in the preceding months. On examination there was a single fluctuant 4 cm by 5 cm right
inguinal swelling. Fine needle aspiration biopsy showed reactive lymphoid hyperplasia; Gram stain, microscopy and culture of the aspirate were negative for bacterial pathogens including mycobacteria. Oral amoxicillin 500 mg three times daily and flucloxacillin 500 mg four times daily were prescribed with no improvement in the mass, which ruptured spontaneously and discharged pus periodically for several months. The patient then began to pass red blood per rectum, developing tenesmus and showing weight loss. Colonoscopy in October 2004 showed an “unusual, chronic-looking fissure” in the anal canal and a purulent proctitis, biopsies of which showed acute and chronic inflammation with crypt abscesses and focal granuloma formation, consistent with LGV. A rectal swab specimen (ProbeTec, Becton Dickinson, Sparks, Maryland, USA) tested positive for *C. trachomatis* by strand displacement amplification (SDA). The inguinal and rectal symptoms resolved completely after 3 weeks of doxycycline treatment. LGV-specific DNA was detected retrospectively from rectal biopsy material using techniques described previously.\(^8\)

Case 2 also had a complicated clinical course after first presenting in September 2005 with a week’s history of a 5 mm tender ulcer over the right hemiscrotum and a healing perianal ulcer. He was prescribed a course of aciclovir and flucloxacillin but a swab from the ulcer tested negative for both herpes simplex virus (HSV) and *C. trachomatis* (urethral swab and urethra). The patient re-presented 2 weeks later with worsening of the ulcer that was now indurated with granulation tissue evident in the base (see fig 1). This time an ulcer swab specimen tested positive for *C. trachomatis* by SDA subsequently confirmed to be LGV. Five days after testing the patient was recalled and by this time had developed an enlarged firm right inguinal node and was thus commenced on doxycycline 100 mg twice daily for presumed LGV. After 10 days he had developed further lymphadenopathy above the inguinal ligament despite compliance with treatment. After 17 days of doxycycline, the swelling had progressed to a hot, fluctuant, 4 cm by 3 cm bubo confirmed with ultrasound. Treatment was switched to azithromycin 1 g daily but despite the change in antibiotic treatment the bubo continued to enlarge. Surgeons were reluctant to incise the lesion due to extensive overlying cellulitis but the abscess ruptured spontaneously 2 weeks after starting azithromycin. A sample of fluid draining from the sinus also tested positive for *C. trachomatis* and was later confirmed to be LGV. Symptoms improved on azithromycin, reduced to 500 mg daily for the last 5 days. The lesions resolved completely without rupture after a 3 week course of doxycycline.

Case 8 was admitted to hospital for investigation of bilateral inguinal lymphadenopathy with a differential diagnosis including lymphoma. His urine had tested positive for *C. trachomatis* by SDA 4 days before and he was reviewed in the GUM clinic where a diagnostic aspirate was performed from the non-fluctuant lymph node mass measuring 0.5 ml normal saline (see fig 2) and the blood-stained material obtained was deposited onto a ProbeTec female swab. *C. trachomatis* was detected using SDA and was confirmed to be LGV as was the DNA extract from his initial chlamydia-positive urine specimen. His symptoms and lesions resolved after 5 weeks of doxycycline treatment.

Case 9 also had a diagnostic aspirate performed from non-fluctuant inguinal lymphadenopathy and was started on doxycycline treatment. He returned the following day after the mass had doubled in size to 8 cm by 4 cm but it was still non-fluctuant. Urgent ultrasound assessment showed a cluster of enlarged lymph nodes up to 3 cm each in size with...
surrounding cellulitis and oedema but only a small 1.4 cm by 0.5 cm abscess situated deeply and not amenable to drainage. Doxycycline treatment was continued for 3 weeks and the symptoms and mass resolved without further suppuration.

Case 11 presented with a non-tender, non-fluctuant, lymph node swelling, yet 1 ml of frank pus was aspirated from the node and this tested positive for *C. trachomatis* and confirmed to be LGV (fig 3).

Case 12 presented with a 3 cm by 5 cm right inguinal lymph node mass and asymptomatic LGV urethritis yet the non-purulent lymph node aspirate tested negative for *C. trachomatis* by SDA.

Case 13 presented with a penile ulcer and subsequently developed unilateral inguinal lymphadenopathy as well as a penile bubonulus—only the second case to be described in the recent MSM LGV epidemic. His new male partner was asymptomatic but had LGV detected from a rectal swab specimen.

**DISCUSSION**

The cases described in this series differ epidemiologically from the typical MSM LGV proctitis cases seen thus far in the UK epidemic. Less than half was HIV positive compared with 74% of proctitis cases and other concurrent STIs were not detected. Half of the cases appear to have contracted LGV from relatively isolated episodes of sexual risk with far fewer recent sexual contacts than reported from most proctitis cases, particularly those seen early in the epidemic. Notably, most of the present cases reported no downstream sexual contacts following the onset of their symptoms and thus were unlikely to have transmitted LGV to subsequent partners. The prompt symptomatology and management seen in cases 2–13 suggests that they are unlikely to have been a source of onward transmission of LGV. In case 13, the index case’s asymptomatic partner was diagnosed subsequently with rectal LGV, reminding us that asymptomatic LGV exists in the MSM population. This is in accordance with findings from the Netherlands where 40% of men with LGV proctitis reported few complaints and/or had no physical abnormality. Nevertheless, a recent UK case finding exercise failed to demonstrate a significant reservoir of asymptomatic infection to explain persistent transmission and further work is needed to define true differences in LGV epidemiology between Dutch and British MSM.

While patient 1 was not diagnosed with LGV inguinal syndrome contemporaneously, his inclusion in the present series serves to demonstrate the consequences of missed diagnosis. He presented in an era when LGV was not recognised as a prevalent pathogen in the UK MSM population and much morbidity and onward transmission could have been averted by early diagnosis and treatment. It is not possible to determine if his eventual LGV proctitis was due to progression of his inguinal syndrome or from newly acquired anorectal infection.

Diagnosis of LGV is dependent on the detection of a LGV-associated serovar of *C. trachomatis* from the site of pathology; however, serology may be helpful should this fail and the clinical suspicion is high. Only three of five cases in our series showed typical serological responses and more work is needed to assess the diagnostic value of serology in this population.

The LGV genital ulcers seen in this series showed non-specific clinical features and clinicians should consider obtaining suitable specimens for *C. trachomatis/LGV* when assessing anogenital ulceration in MSM. Swabs from ulcers and diagnostic aspirates of scant material from non-fluctuant inguinal lesions produced suitable specimens for the successful detection and typing of *C. trachomatis* using standard nucleic acid amplification assays and we recommend this approach for investigation of suspicious lesions.

Urethral *C. trachomatis* appears to have been the primary LGV lesion in five of the present cases. Variability in symptomatology and urethral smear microscopy findings in the present cases suggest that this might not simply represent LGV-associated urethritis and that other primary endourethral lesions such as ulceration may occur. We do not believe that routine LGV typing of *C. trachomatis*-positive urethral isolates from MSM is currently indicated, based on the rarity of urethral LGV seen in the UK case-finding exercise (Ward H, in press). Nevertheless, in the presence of additional clinical signs such as ulceration or lymphadenopathy, or in LGV contacts, then referral of *C. trachomatis*-positive specimens for detection of LGV serovars is warranted.

The presence of persistent anogenital ulceration and severe proctitis can enhance HIV and possibly hepatitis C transmission. Although no new diagnoses were made within the present case series, incident HIV and hepatitis C infection may not have been detected by testing performed at the time of LGV diagnosis and follow-up serology beyond the relevant window periods is indicated.

Treatment with doxycycline for 3 weeks achieved resolution of symptoms and signs in 11 of 12 patients and azithromycin in 2 patients using multiple-dose regimens. As demonstrated in patient 2, diagnosis of LGV can be challenging and patients with large buboes may require longer courses of treatment than the recommended 3 weeks. Adjuvant drainage of fluctuant abscesses may hasten the resolution of such lesions and prevent spontaneous rupture and sinus formation. There were no signs of tertiary sequelae such as chronic lymphoedema reported in any of the present cases although some local scarring was seen.

![Figure 3](clinical.png) Figure 3 Clinical images from case 11 demonstrating right-sided non-tender, non-fluctuant lymphadenopathy. Despite this, 1 ml of frank pus (see inset) was aspirated from the node and this tested positive for lymphogranuloma venereum DNA.
The present cases demonstrate that clinical manifestations of LGV have not been confined to proctitis in the current outbreak in MSM in the UK despite the predominance of anorectal disease reported. Clinicians who see MSM patients should familiarise themselves with the clinical features and diagnostic pathways illustrated in this series. The striking clinical signs seen in some of these cases, especially in those who were systemically unwell, led to provisional diagnoses of incarcerated herniae and lymphoma. In addition, there has been a recent report of two heterosexual LGV cases: further evidence that the epidemic is spreading beyond its initial core group.

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Patient consent: Obtained.

Contributors: GS and JW conceived the paper, collected data on cases seen at St Thomas’ Hospital, co-ordinated the multicentre collaboration and wrote the final draft; EA-J, JR, NTA and DH each contributed cases from their respective clinics and edited the manuscript; AE wrote the early first draft; SA was responsible for the molecular typing and verification of LGV results as well as editing the manuscript.

REFERENCES
practice it would seem logical to prescribe PDE5i in order to produce good erections that MSM can be confident will be sustained even while putting on a condom. Unfortunately, the current data do not support this contention, rather showing an association between PDE5i usage and HIV prevalence. Recent quantitative and qualitative studies strongly suggest that the likelihood of MSM having unsafe sex and having HIV is significantly higher in those with current depression, fatigue, past and current sexual assault and regular users of recreational drugs to counteract the psychological sequelae of these psychosocial issues. Many of the recreational drugs used such as crystal meth and cocaine are profound peripheral vasoconstrictors as well as cerebral stimulants. Hence the need for PDE5i to counteract the erectile dysfunction produced by them. Furthermore, there is suggestive evidence that the use of PDE5i itself can reverse low mood, cause aggression and amnesia and enhance sensation for the receptive partner at anal sex. Enhanced engorgement of penile and anal areas with PDE5i may themselves predispose to HIV transmission. Other factors associated with erectile dysfunction in MSM with HIV are the use of antiretroviral drugs, particularly protease inhibitors and accelerated penile arterial pathology.

Most of the studies showing an association between unsafe sex, HIV and PDE5i use in MSM show that these men do not acquire PDE5i from medical practitioners, but rather via the internet or other local contacts. With this in mind it would seem prudent for all MSM who attend for STI or HIV screening or therapy to be asked about erectile dysfunction at partnered sex, as well as other relevant clinical issues, as delineated above. Management should include the whole spectrum of the clinical disorders these men present with, including the prescribing of PDE5i medication, along with advice about appropriate condom and lubrication use and the minimalisation of recreational drug use and management of other psychosocial issues. Asking about these issues in busy STI/HIV clinics may not be easy, not least because of lack of time but also because of health practitioner and patient embarrassment in bringing up these issues. Some of the health issues related to PDE5i use, such as depression, are crucial to recognise, because they are associated with poor antiretroviral compliance.

In spite of these complex interactions between PDE5i and other conditions, MSM are ethically entitled to receive these medications when there is clinical necessity.

REFERENCES