Lymphogranuloma venereum: what does the clinician need to know?

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It has been surprising to see that lymphogranuloma venereum (LGV), caused by the L-serovars of *Chlamydia trachomatis*, a sexually transmitted infection (STI) previously rare in industrialised countries, has emerged as a significant disease among homosexual men over the past three years.[1,2] Following the recognition of a large number of cases of LGV proctitis among homosexual men in the Netherlands in 2004,[3] an epidemic is now well established in the UK,[2,4] Western Europe and the USA. Thus far, the infection has been confined almost exclusively to the homosexual male population, especially those coinfected with HIV,[2] hepatitis C[5] and other STIs, most cases presenting with severe proctitis.

Diagnostic delays have occurred, commonly due to the non-specific nature of the clinical presentation. Even inguinogenital manifestations of LGV such as buboes and genital ulcers, usually seen in regions of the world where LGV is endemic, are beginning to be recognised.[2] Prompt antibiotic treatment is effective and curative, yet broader awareness among a wide range of clinicians is needed to enable appropriate investigation and management and the interruption of onward spread.

Clinical presentation

In contrast to the D-K serovars of *C. trachomatis* responsible for genital mucosal disease, the LGV-associated serovars are lymphotropic and thus capable of regional dissemination and systemic disease. The clinical course of LGV is classically divided into three stages.

Primary stage

The primary lesion is usually transient and often unnoticed. It may appear at the site of inoculation as a painless papule, pustule or ulcer, most likely in the anogenital region. Incubation periods from 3–30 days after sexual contact have been observed. Proctitis in homosexual men can occur as a primary manifestation of infection following direct inoculation of the rectal mucosa. Symptoms of proctitis may arise within days of anoreceptive sexual exposure.

Secondary stage

The secondary stage of LGV involves the subsequent spread of *C. trachomatis* to regional lymph nodes, which leads to inflammation and swelling, and the entire chain can become matted with considerable periadenitis. Suppuration and bubo formation can ensue, which may then ulcerate and discharge pus from multiple points creating chronic fistulae. Rectal involvement at this stage may develop in both men and women, presenting as an acute haemorrhagic proctitis with symptoms of mucopurulent discharge, pain, bleeding, tenesmus and constipation. Systemic symptoms such as fever and malaise can accompany this stage.

Tertiary stage

Untreated infection may then progress to chronic inflammation and destruction of tissue in the involved areas, including:

- chronic proctocolitis mimicking inflammatory bowel disease (IBD)
- fistulae
- strictures
- chronic granulomatous conditions of the external genitalia, including lymphoedema and elephantiasis.

These tertiary sequelae tend not to reverse with antibiotic therapy alone.

Presentation of lymphogranuloma venereum in homosexual men

LGV detected among homosexual men in the UK has so far largely presented as overt proctitis (Fig 1), possibly as either a primary or a secondary manifestation of disease, in many cases with severe local and systemic symptoms. Some cases were misdiagnosed with ulcerative colitis or Crohn's disease and long delays occurred before LGV was recognised and treated appropriately. Endoscopic appearances and histopathological findings from rectal biopsies in LGV show severe inflammatory changes in common with IBD (Fig 2), and no pathognomonic features have yet been described that can be attributable to LGV. A small number of men have presented with inguinogenital

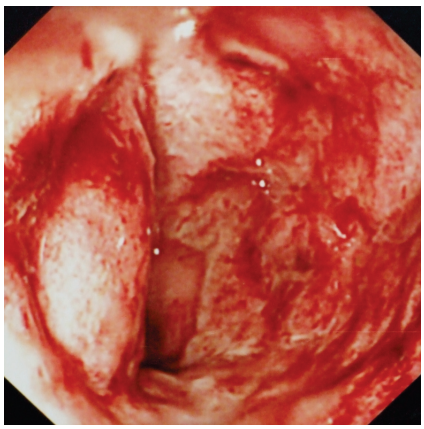

Fig 1. Endoscopic view of the rectum in a 42-year-old HIV-positive homosexual man with a nine-month history of intermittent diarrhoea and constipation associated with blood, mucus and pain on defecation. Rectal biopsy showed severe non-specific inflammation and the patient was treated empirically with steroid suppositories for possible irritable bowel disease. Following genitourinary medicine review, a rectal swab specimen tested positive for *Chlamydia trachomatis*, subsequently typed as the L2 strain. Symptoms abated completely after three weeks' treatment with doxycycline.

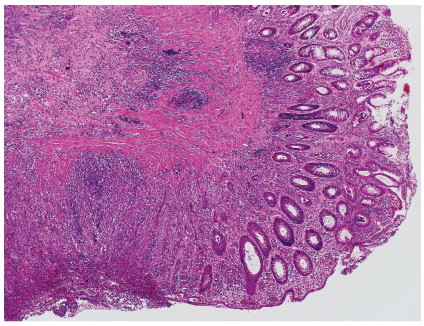

Fig 2. Rectal biopsy specimen from an HIV-positive homosexual man with a six-month history of purulent anal discharge, bleeding and constipation. Histological features included rectal mucosal ulceration and non-specific inflammatory changes within the lamina propria, including both cryptitis and crypt abscesses.

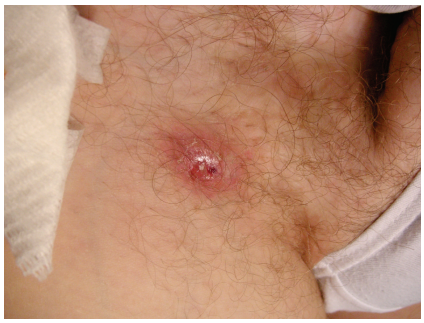

Fig 3. Ruptured inguinal bubo in a homosexual man who had presented with a three-week history of painful bilateral inguinal swellings. Lymphogranuloma venereum-associated *Chlamydia trachomatis* DNA was isolated from aspirated pus.

syndrome including anogenital ulceration and buboes (Fig 3). Less common presentations have been described such as urethritis[6] and bubonulus[7] (primary stage of disease with large tender lymphangial nodule and lymphangitis of dorsal penis). Asymptomatic rectal infections have been detected only rarely within a large case-finding exercise in the UK, suggesting that a large reservoir of 'silent' infection is unlikely.[8]

Differential diagnosis

The differential diagnosis of proctitis among homosexual men includes rectal gonorrhoea, which is usually less severe clinically and often asymptomatic. Anorectal herpes simplex virus-1 or -2 infection, especially if a primary infection, can cause severe anorectal pain often out of proportion to other proctitis symptoms and may also cause regional neurological symptoms including urinary retention and constipation. Non-LGV rectal *C. trachomatis* infection caused by serovars D-K is usually asymptomatic but can occasionally show clinical features of overt proctitis. Syphilis infection is on the rise again among homosexual men, and in its role as 'the great imitator' can cause clinical proctitis.

Excellent clinical and microbiological responses have been observed in LGV infection with the recommended treatment of oral doxycycline 100 mg bid for three weeks.[9,10]

Laboratory diagnosis

The laboratory diagnosis of LGV requires the detection of *C. trachomatis* belonging to serovars L1, L2 and L3 from clinical samples. Historically, growth in tissue culture cells has been the only 'approved' method. However, this facility is available in very few laboratories in the UK, is technically difficult and has a low sensitivity even in the most experienced laboratories. Alternative methods include direct immunofluorescence, a test licensed for detection of *C. trachomatis* from rectal swabs from symptomatic patients, but again technically demanding and with low sensitivity. Enzyme immunoassays (EIAs) and nucleic acid amplification tests (NAATs) have been widely used but neither is licensed for use with rectal specimens.

The lack of an available licensed commercial test to detect *C. trachomatis* in rectal specimens may have prevented the true extent of the outbreak being recognised. Many microbiologists have been reluctant to use an unlicensed test as it may compromise their accreditation. In addition, no diagnostic service has been available for genotyping *C. trachomatis* to identify the L-serovars.

Detection of lymphogranuloma venereum in rectal specimens

In October 2004, the Sexually Transmitted Bacteria Reference Laboratory (STBRL) at the Health Protection Agency (HPA) Centre for Infections established a testing algorithm for the detection of LGV in rectal specimens. This includes confirmation of the presence of *C. trachomatis* using a real-time polymerase chain reaction (RT-PCR) that uses primers different from any commercial assay.[11] Residual samples from both NAATs and EIAs or dry swabs can be tested. Any specimens giving a negative result are confirmed using the Qiagen RT-PCR (which is not used extensively in the UK) and a report issued. All samples confirmed to contain *C. trachomatis*-specific DNA are then tested to determine whether this belongs to an LGV serovar (L1, L2 or L3), using an RT-PCR which detects a deletion in the *pmp* gene present only in L-serovars of *C. trachomatis*.[12]

This test gives a positive result for LGV-associated serovars and a negative result for other serovars and provides a timely result allowing a positive report to be issued. All positive specimens are then confirmed using a nested PCR that amplifies the *omp1* gene which is present in single copy, followed by digestion with restriction endonucleases.[13,14] The pattern obtained is compared with control strains and can be confirmed by DNA sequencing.

STBRL has now tested over 4,000 specimens and identified over 600 LGV positive results in the UK. All LGV positive specimens were found to belong to the serovar L2 where full genotyping was possible (S. Alexander; personal communication). Only 36% of the specimens originally tested positive for *C. trachomatis* by EIA were confirmed compared with 92% of those originally tested by NAATs.[15] This highlights the lack of specificity of EIA for detection of *C. trachomatis* from rectal specimens. It also provides robust validation that NAATs can – and should – be

Key Points

- Lymphogranuloma venereum (LGV) is a common cause of severe proctitis among homosexual men
- LGV may also present as anogenital ulceration or inguinal lymphadenitis/abscesses
- Nucleic acid amplification tests for *Chlamydia trachomatis* from swab specimens are the most appropriate diagnostic tools, but specific molecular typing of the sample is needed to confirm LGV
- Cases respond well clinically to three weeks' doxycycline therapy
- Clinicians outside genitourinary settings need to be vigilant for clinical presentations consistent with LGV occurring among male homosexual patients

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used as the test of choice for detecting *C. trachomatis* in rectal specimens.

Diagnostic material for LGV confirmation has also been obtained from needle aspirates from inflamed lymph nodes and buboes, ulcer swabs from anogenital ulcers and first void urine from men with urethritis. Some complicated cases presented to gastroenterologists and detected by retrospective testing of biopsy samples[16] have resolved following treatment for LGV. Local genitourinary medicine clinics in the UK have managed most clinical cases of LGV to date and welcome referred patients for a full diagnostic work-up.

Epidemiology

Enhanced surveillance data are requested on all laboratory confirmed cases as part of the alert issued in October 2004 by the HPA. Epidemiological and behavioural data on 423 cases detected between October 2004 and the end of April 2007 showed LGV in the UK follows a similar pattern to Europe: cases are found predominantly among homosexual men of white ethnicity who are often coinfected with HIV (78%) and other STIs including hepatitis C, gonorrhoea, and syphilis.[2] Cases have been distributed widely across the UK, but the highest number has been seen in London and Brighton. Most cases of LGV have been symptomatic, usually presenting with proctitis, with a few cases as contacts. LGV in the UK has seldom presented with urethral or inguinal symptoms and only two known cases occurred in heterosexuals. The largest number of cases was seen in 2005, but cases continue to be identified. Homosexual men with LGV report a large number of contacts, most of whom are untraceable, with most men reporting high-risk sexual behaviour, including meeting new sexual partners at sex on premises venues, sex parties or on the internet.

Conclusions

An established epidemic of LGV exists among homosexual men in the UK causing many cases of severe proctocolitis and rarer inguinogenital syndromes. LGV may also be contributing to the epidemics of HIV and hepatitis C among homosexual men by facilitating transmission. Further control efforts are required, including awareness campaigns, continued detailed surveillance and expanded chlamydia testing among homosexual men. All clinicians should be aware of the current epidemiological and clinical features of LGV infection in the UK. Appropriate testing and referral should be initiated promptly when confronted with the relevant clinical scenarios among homosexual male patients.

Further information

Please see the Health Protection Agency website, www.hpa.org.uk/cfi/stbrl/lgv_surveillance.htm

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Syphilis: an update

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Syphilis is caused by infection with the spirochaete bacterium *Treponema pallidum*. Transmission from one person to another is by direct contact with an infectious lesion (usually occurring during sexual contact), during pregnancy from mother to child or via infected blood products. *T. pertunue* and *T. carateum*, organisms almost identical to *T. pallidum*, cause yaws and pinta, respectively. They are indistinguishable microscopically and all three give positive results on standard serological tests for syphilis. However, yaws and pinta affect skin and bone almost exclusively and are generally found only in patients from endemic areas.

Epidemiology

Syphilis remains common worldwide. Social disruption, mobility, lack of medical services and changing sexual behaviours have contributed to epidemics. Early syphilis has re-emerged in Western Europe since the late 1990s.[1]

Most sexually acquired infectious syphilis in the UK is among men who have sex with men (MSM). New diagnoses of all sexually transmitted infections (STIs) in MSM have risen consistently for the last 10 years. This indicates a resurgence in sexual risk taking by MSM which has probably led to continuing HIV transmission within this population in the UK. In parallel with the outbreak of syphilis in MSM, clusters of early syphilis among heterosexual men and women have been reported.[2,3]

Clinical presentation

Entry of *T. pallidum* probably occurs through areas of 'microtrauma', usually in mucous membranes, and most sexual transmission of syphilis probably occurs from the genital and mucous membrane lesions of primary and secondary syphilis.

Syphilis is classified as:

- *acquired*: early (primary, secondary and early latent <2 years of infection) and late (late latent >2 years of infection)
- *congenital*: early (diagnosed in the first 2 years of life) and late (presenting after the age of 2 years).

Acquired syphilis

Primary syphilis

Primary syphilis is characterised by an ulcer (the chancre) and regional lymphadenopathy. The incubation period is 9–90 days, but the primary lesion most often appears about three weeks after transmission. The chancre is classically in the anogenital region, is single, painless and indurated with a clean base discharging clear serum. However, chancres may be multiple, painful, purulent, destructive, extragenital (most frequently oral) and may cause the syphilitic balanitis of Follman. There may also be mixed aetiology.

Secondary syphilis

Secondary syphilis is characterised by multisystem involvement within the first two years of infection, the manifestations first appearing about eight weeks after transmission. The rash of secondary syphilis is initially roseolar or macular, with more long-standing lesions becoming papular or nodular. This skin rash is typically non-irritant but may be associated with itch in dark-skinned persons. There are often condylomata lata, mucocutaneous lesions, generalised lymphadenopathy and, less commonly, patchy alopecia, anterior uveitis, meningitis, cranial nerve palsies, hepatitis, splenomegaly, periosteitis and glomerulonephritis.