Genital-inguinal *Lymphogranuloma venereum* in men taking HIV Pre-Exposure Prophylaxis

Making the diagnosis: a report of two cases

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Lymphogranuloma venereum

• One of three invasive Chlamydia trachomatis serovars (L1, L2, L3) → lymphatic infiltration

• **Endemic in countries in our region**: South East Asia and India (as well as in Sub-saharan Africa, Caribbean)

• In Australia—outbreaks in sexual networks of MSM with HIV
  LGV associated **proctitis in MSM with HIV** (symptomatic anorectal infection)
  **Genital (ulcerative) LGV exceedingly rare**

UK/European evidence:

• Asymptomatic rectal infection relatively common in MSM in Netherlands but not UK

In all groups: genital (ulcerative) LGV uncommon


LGV: Clinical course

Primary stage (Acute infection: incubation period 3-30 days)

Clinically 2 forms:

1) Proctitis - rectal pain, bleeding, discharge, tenesmus, constipation +/- fever, malaise

2) Primary lesion: on coronal sulcus of penis, vulva, posterior fourchette, cervix

Transient self-resolving papule $\rightarrow$ ulcer (+/- pain) +/- fissuring, lymphadenopathy
LGV: Clinical course

Secondary stage (Lymphatic spread: 10-30 days after resolution of primary lesion)

unilateral inguinal & femoral lymphadenopathy

+/- ‘buboe’ formation: ‘groove sign’

fever, malaise, arthralgia

sexually acquired reactive arthritis

LGV: Clinical course

Tertiary advanced disease (Chronic tissue destruction, inflammation, fibrosis, scarring)

- persistent / relapsing proctocolitis
- rectal fistulae
- genital tract / rectal strictures
- lymphoedema
- vulval fibrosis, scarring
- SCC risk

Case 1-History

35 year old man

Pre-Exposure Prophylaxis (PrEP)

10 day history of a painful penile ulcer and an enlarging left inguinal mass

Systemically well

condomless insertive penile-anal sex (casual male partner) 18 days earlier in Thailand.

6 male partners in the previous 3 months (Thailand, Australia)

Had early latent Syphilis treated 9 months previously
Case 1- Examination

10mm non-indurated ulcer (left coronal sulcus-peripheral erythema, slough to ulcer base)

30x30mm tender, left inguinal mass (no erythema or fluctuance)

Normal vital signs

No other signs of active Syphilis elsewhere
Case 1- Progress in consult

Tests sent:

*Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG) Nucleic-Acid Amplification Tests (NAAT-throat, rectal, first-void urine)

HIV, Hepatitis C, Syphilis Rapid Plasma Reagin

Herpes (HSV) and Syphilis NAAT/PCR (ulcer base)

CT NAAT (ulcer base)

Management: intramuscular benzathine penicillin 1.8g statim
Case 1- Progress 3 days later

Penile ulcer unchanged.

New, second ulcer-2x2mm, superficial-right coronal sulcus.

Inguinal mass larger (60x70mm)-remained non-fluctuant.

Test results:

*Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG) Nucleic-Acid Amplification Tests (NAAT-throat, rectal, first-void urine) all non-reactive

HIV, Hepatitis C, Syphilis Rapid Plasma Reagin non-reactive

Herpes (HSV) and Syphilis NAAT (ulcer base) non-reactive.

**CT NAAT (ulcer base)=REACTIVE: referred for LGV PCR.**

Management: Oral doxycycline (100mg, 12-hourly, 21 days) commenced
Case 1- Progress 7 days later

Ulcers receding, mass unchanged but now painful

LGV PCR (ulcer case)=REACTIVE

Inguinal mass aspiration (day 6 Doxycyline):

- Granulomatous inflammation (histopathology)

- CT NAAT non-reactive

- Bacterial culture no growth

Followed to treatment completion
Symptoms resolved at treatment completion
Case 2-History

37 year old man taking PrEP

4 day history of a painful, swollen penile shaft

Systemically well.

Multiple episodes of condom-less insertive penile-anal sex previous 4 weeks

5 male partners over the preceding month

No recent travel. No new or regular medications. No trauma. Otherwise well
Case 2-Pre-consult

Penile ultrasound (with referring doctor) revealed soft tissue oedema (no collection or vascular/lymphatic changes)

First-void urine CT NAAT (with referring doctor)=REACTIVE

Had already commenced oral doxycycline (100mg, 12-hourly, 7 days) 2days prior to consult.

All else negative/non-reactive (CT & NG-rectal, pharyngeal NAAT, and Syphilis, Hepatitis C & HIV serology)
Case 2- examination

3mm superficial, non-indurated ulcer inside urethral meatus, adjacent to piercing (potential entry)

Markedly swollen, red, tender, non-fluctuant penile tissue (dorsal mid-shaft extending to penile base)

No inguinal lymphadenopathy.

Vital signs normal.

No signs of active Syphilis elsewhere

Case 2 - Progress in consult

Tests sent:

- Bacterial culture, HSV, Syphilis, NG and CT (ulcer base)

Management:

- Transferred to Emergency Department for presumed cellulitis
- 2 day admission
- Intravenous piperacillin/tazobactam 4/0.5g 8-hourly then oral amoxicillin/clavulanate 875/125mg 12-hourly 5 days
- Also continued on Doxycycline to 7 days.
Progress 5 days later

Seen 5 days later (day 3 post-discharge, day 7 doxycycline)

Only reactive/positive microbiological investigation before or during hospital admission was CT→reflex LGV reactive (result available 3 days after post-discharge).

All changes had significantly receded.

Management:

Doxycycline was extended to 21 days with resolution of symptoms at completion of treatment

Partner notification completed
LGV Diagnosis and Management

**Diagnosis**

- **Risk Factors for LGV:**
  - MSM, Bacterial, STIs, HIV, Contact, ?Travel, ?Behavioural, ?Immunological

- **Symptoms**
  - proctitis
  - ulcer
  - inguinal mass

- **Chlamydia**
  - esp Rectal

- **Tissue / Specimens**
  - >10-20 x PMNLs / HPF
  - NOT culture, serology
  - LGV DNA (PCR):
    - Rectal, FVU, throat ulcer, buboe material
  - Tissue biopsy

**Management**

- **Presumptive VS Confirmed**

- **Aspirate** fluctuant lesions/buboes

- **Doxycycline**
  - PO 100mg 12 hrly for 21 days
  - Pregnancy / lactation use macrolide eg Azithromycin PO
  - 1g wkly/3wk

  - Resolution: 2-6 wks (dep. stage)

- **Abstain on Rx/ until TOC**

- **Notify PHU**

- **Contact tracing:**
  - -4 weeks if sympts
  - -3 months if A-Sx

- **Test of cure** 2 weeks post Tx completion

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LGV DNA (PCR)

- Limited testing sites
- In-house assays at reference laboratories. At ICPMR (Westmead): Roche Light Cycler 2.0
- Reflex/automatic referral (by request) of samples reactive for Chlamydia trachomatis or recollection of LGV PCR

- Clinicians with high sexual health & HIV caseloads should ensure there is a specimen referral pathway (reflex/automatic referral of samples reactive for Chlamydia trachomatis or recollection of LGV PCR)

**LGV PCR can take up to two weeks to return result but:**

- Chlamydia trachomatis NAAT (ulcer base) has a quicker turnaround -> reflex LGV if positive
- Syphilis serology can help rapidly rule out Syphilis - but use with caution
Genital-Inguinal LGV: Other approaches to Diagnosis from Australian Cases in Sexual Health Clinics

*Read P, McNulty AM (MJA 2013)*

LGV test rationale: buboes after self-resolving genital ulcer (Dx & Rx as ‘chancre’). Longstanding HIV infection

LGV test method: aspiration from buboes LGC DNA PCR

*Davies SC, Shapiro J, Comninos NB, Templeton DJ (Int J STD&AIDS 2019)*

Case 1:

LGV test rationale: large ulcer with concurrent inguinal mass. On PrEP

LGV test method: Ulcer base CT → LGV PCR

Case 2:

LGV test rationale: persisting genital ulcer and inguinal mass (Syphilis and HSV PCR negative, empirical Rx for both) + Chlamydia contact. On PrEP

LGV test method: Ulcer base LGV DNA PCR


Davies SC et al. Lymphogranuloma venereum presenting as penile ulcer in two HIV-negative gay men. *Int J STD & AIDS* 2018
Conclusions

We may be missing LGV genital ulcers → risk of disease progression

Consider LGV in the differential diagnosis of genital ulcers in at-risk groups (consider testing at first presentation)

Carefully consider LGV in genital ulcers testing negative for Herpes and Syphilis

Surveillance of genital LGV is key- in the age of increasing STIs, ‘sero-mixing’ and PrEP

Travel histories alongside sexual histories- learning more about STIs in our region

Impact of changes in antimicrobial use (eg Doxycycline STI Prophylaxis)- watch this space


Davies SC, Shapiro J, Comminos NB, Templeton DJ. Lymphogranuloma venereum presenting as penile ulcer in two HIV-negative gay men. Int J STD & AIDS 2019;30(5):-095646241882157

Acknowledgements and Thanks

**Patients:** informed consent

**Project collaborators**
Dr Suzanne Rix
Dr Rick Varma
A/Prof Anna McNulty

**Clinicians involved in care**
Dr Dick Quan (Holdsworth House)
Department of Infectious Diseases and Microbiology, Prince Of Wales Hospital NSW

**Sexual Health Clinic**
All of the Staff at Sydney Sexual Health Centre

**Pathology services**
SEALS and ICPMR Pathology