Lymphogranuloma venereum in an Italian MSM: concurrent pharyngeal and rectal infection

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SUMMARY

An Italian HIV-positive man having sex with men (MSM) attended the STIs Outpatients Clinic of Sant'Orsola Hospital in Bologna complaining of anal pain and constipation. According to patient's sexual history and repertoires, NAAT testing for *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (GC) was performed. Pharyngeal and anal swabs resulted positive for CT DNA detection and the following molecular genotyping identified a L2 serovar, coming to the final diagnosis of pharyngeal and rectal lymphogranuloma venereum (LGV) infection. After an antibiotic therapy with doxycycline 100 mg twice a day for 3 weeks, the patient completely recovered and the test of cure was negative for LGV infection.

KEY WORDS: Lymphogranuloma venereum, *Chlamydia trachomatis*, Pharyngeal infection, MSM, HIV.

Received December 13, 2013 *Accepted* April 8, 2014

INTRODUCTION

Lymphogranuloma venereum (LGV) is a systemic sexually transmitted infection (STI) caused by *Chlamydia trachomatis* (CT) serovars L1-L3 (Stary *et al.,* 2008). In the last decade, a new outbreak of LGV infection has been reported in Western Countries, mainly in men who have sex with men (MSM) (Nieuwenhuis *et al.,* 2004). In the recent epidemic, LGV infection was characterized by an anorectal primitive syndrome, showing anal ulceration, anal pain and mucous or bloody discharge (Nieuwenhuis *et al.,* 2004). LGV infections are often associated with other STIs, and in particular a strong connection with HIV infection has been reported in MSM (Rönn *et al.,* 2011). LGV's ulcerative nature and similar risk behaviour could explain this association (Van der Bij *et al.,* 2006; Kalichman *et al.,* 2011).

If LGV is already a well-established cause of proctitis, only few cases of pharyngeal LGV infection have been described so far (Dosekun *et al.,* 2013). Since pharyngeal localization could be asymptomatic or characterized by non-specific symptoms, it can remain unnoticed or misdiagnosed in many cases. Hence, untreated pharyngeal LGV may act as a reservoir for infection among MSM (Vall-Mayans *et al.,* 2009; Dosekun *et al.,* 2013). Nucleic acid amplification tests (NAATs) are recommended for the detection of rectal and oropharyngeal infections caused by CT and *Neisseria gonorrhoeae* (GC). Although rectal and pharyngeal swabs have not been cleared for use with NAATs, many laboratories have performed their own validation studies, proving that NAATs are characterized by the best performance in terms of sensitivity and specificity (Association of Public Health Laboratories 2009; CDC 2010).

The main laboratory critical aspect of commercial NAATs regards their inability in discriminating LGV from non-LGV serovars; for that reason, further investigations for CT molecular

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typing are needed. The gene encoding the major outer membrane protein (MOMP), *omp1*, or genes encoding for the polymorphic protein family have been widely used for this purpose, with different molecular techniques as PCR-RFLP, RT-PCR or nested PCR followed by sequencing. The first Italian case of LGV was described by Cusini *et al.* (Cusini *et al.,* 2008), involving a proctitis case observed in Milan in 2006. Here we report the first Italian case of pharyngeal LGV in a MSM with a concurrent rectal LGV infection.

CASE REPORT

In July 2013, a 36-year-old Italian MSM attended the STIs Outpatients Clinic of St. Orsola Hospital in Bologna complaining of a one-week history of anal pain and constipation in the absence of rectal discharge. Neither systemic symptoms nor urethral and oropharyngeal disorders were noticed.
He reported unsafe receptive anal and oral intercourse with an occasional male partner, one month previously. His past clinical history for STIs included HIV, syphilis, genital HSV and genital warts.
At clinical examination, a perianal ulcerated lesion with local skin inflammation was noticed. Inguinal adenopathy was absent and no remarkable signs were observed at genital or pharyngeal inspection.
According to patient's history and sexual behaviour, anorectal and pharyngeal swabs as well as a urine sample were collected for CT and GC DNA detection by a duplex Real-time PCR (Versant CT/GC DNA 1.0 Assay; Siemens Healthcare Diagnostics, Terrytown, USA).
Moreover, microbiological investigations for the main STIs (syphilis, HIV, HCV, HBV) and a serological screening for anti-*Chlamydia* antibodies (Chlamydia IgG and Chlamydia IgA, Virion/Serion GmbH, Wurzbug, Germany) were performed.
Pharyngeal and anal swabs resulted positive for CT DNA. Molecular genotyping, based on *omp1* gene semi-nested PCR (Marangoni *et al.,* 2012), followed by RFLP analysis (Sayada *et al.,* 1991; Lan *et al.,* 1994), identified a L2 serovar, coming to final diagnosis of pharyngeal and rectal LGV.
A previously treated syphilis was confirmed by serological results, while HIV status revealed 155,400 RNA copies/ml, 741 CD4 cells/ml and CD4/CD8 of 0.38 ratio in the absence of HAART therapy. Finally, *Chlamydia* IgG value was 30 Arbitrary Units/ml (normal value <12 AU/ml), while IgA value was 7 AU/ml (normal value <12 AU/ml).
An antibiotic therapy with doxycycline 100 mg twice a day for 3 weeks was established. Three months after treatment, at follow-up visit, the patient had completely recovered and the test of cure was negative for LGV infection.

DISCUSSION

In the MSM population, unsafe anal and pharyngeal intercourse is common, leading to the emergence of selective high-risk networks for STIs transmission. In this way, in addition to the well-known proctitis, LGV infection can be characterized by a pharyngeal localization, although only few cases have been described in literature to date (Dosekun *et al.,* 2013; Haar *et al.,* 2013).
Here we describe the first Italian case of pharyngeal LGV in a MSM with concurrent LGV proctitis. As observed in our case, LGV anorectal infections are usually symptomatic and in more than 90% of cases they occur as a moderate or severe ulcerative proctitis with rectal pain, anal discharge and rectal bleeding (Martin-Iguacel *et al.,* 2010). Pharyngeal localization could be asymptomatic or characterized by non-specific symptoms such as cervical adenopathy, odynophagia and tongue ulcer (Thorsteinsson *et al.,* 1976; Dosekun *et al.,* 2013). For that reason, pharyngeal LGV could easily remain untreated and act as a reservoir for the infection among MSM (Vall-Mayans *et al.,* 2009; Dosekun *et al.,* 2013).
LGV infection is often associated with other STIs and in particular with high HIV co-infection rates among MSM (Rönn *et al.,* 2011). A high number of sexual partners, unsafe anal intercourse and sex toy use have been reported by LGV-infected patients (Van der Bij *et al.,* 2006; Ward *et al.,* 2007). Similar risk behaviour and LGV ulcerative lesions can explain the high prevalence of other STIs found in LGV patients

(Van der Bij *et al.,* 2006; Kalichman *et al.,* 2011). In our case, the patient was HIV-positive and his clinical history revealed syphilis, HSV and HPV infections in the past, suggesting high-risk sexual behaviour.

Laboratory investigations have a crucial role in LGV diagnosis but a few aspects remain critical. In particular, although NAATs are the most sensitive tests for laboratory CT diagnosis (CDC, 2010), no commercial assays are available to differentiate L from non-L serovars. For this purpose, LGV identification requires specific 'in-house' molecular genotyping. Therefore it is very likely that the true LGV incidence is greatly underestimated (ECDC, 2010).

In our experience, Versant CT/GC DNA 1.0 Assay showed a good performance in CT detection on rectal and pharyngeal swabs and the following RFLP analysis of CT positive samples seemed to be a reliable and inexpensive method for CT genotyping.

Besides molecular techniques, serological methods are not recommended for LGV laboratory diagnosis (Association of Public Health Laboratories, 2009; CDC, 2010). Nevertheless, in our case, a significant elevation of anti-Chlamydia IgG was found, suggesting a potential additional role for LGV diagnosis in the appropriate clinical and epidemiological context.

In Italy, extragenital CT testing and CT molecular typing are not routinely performed but they should be recommended in high-risk sexual populations, even in the absence of symptoms. Testing of only symptomatic cases can lead to miss pharyngeal infection and promote further transmission (Dosekun *et al.,* 2013). Sexual history and repertoires are crucial for testing the pharyngeal site (Peters *et al.,* 2011).

LGV proctitis is usually treated with doxycycline 100 mg orally twice a day for 21 days (CDC, 2010). Although guidelines for pharyngeal LGV therapy are not available, antibiotic treatment with a 3-week regimen of doxycycline could be effective, regardless of HIV status, as observed in our experience.

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