Lymphogranuloma venereum proctitis mimicking inflammatory bowel diseases in 11 patients: a 4-year single-center experience

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Lymphogranuloma venereum (LGV) is a sexually transmitted disease caused by *Chlamydia trachomatis* (CT) serovars L1–L3. Our study wants to underline the similarities between rectal LGV and idiopathic inflammatory bowel diseases (IBD), which can share clinical, endoscopic and histopathological findings.

Key Words: lymphogranuloma venereum, inflammatory bowel diseases, proctitis, MSM

INTRODUCTION

Lymphogranuloma venereum (LGV) is a systemic sexually transmitted disease caused by *Chlamydia trachomatis* (CT) serovars L1–L3. It invades and destroys the lymphatic tissue and typically presents as genital ulceration and/or painful erythematous inguinal lymphadenopathy that can suppurate and rupture (buboes).[1,2] When the rectum is the site of primary inoculation, as happens among men and women who practice anoreceptive sexual intercourses, LGV can cause muco-hemorrhagic proctitis usually without inguinal lymphadenopathy. However, the most common symptomatic form of the rectal localization presents as a nonspecific low proctitis characterized by abdominal discomfort, anal pain, diarrhea or constipation, blood, and mucus and pus discharge.[1–3]

Proctitis, an inflammation of the distal 15 cm of the colon, is a diffuse problem often caused by idiopathic inflammatory bowel diseases (IBD), including Crohn's disease and ulcerative proctitis. However, in the last decades, proctitis has been more and more associated with sexually transmitted infections (STIs), due to the diffusion of receptive anal sex.[4] Since 2003, indeed, a new outbreak of LGV infection with rectal localization has been described in Europe, mainly in men who have sex with men (MSM).[5] These patients, conducting high-risk sexual behavior, are often coinfected with other STIs, especially HIV.[6,7] LGV clinically presents with a wide range of nonspecific symptoms suggestive of other intestinal conditions, including tenesmus, constipation, and mucopurulent anal discharge; systemic symptoms like fever, malaise, and weight loss are also relatively common.[6,8] However, even if rectal LGV usually presents as a symptomatic proctitis, some studies have reported asymptomatic reservoirs of infection that probably represent a pre-symptomatic transient condition preceding classic clinical manifestations of LGV.[6]

Besides clinical manifestations and symptoms, LGV proctitis may mimic IBDs in endoscopic findings and histological features. Therefore, a high index of suspicion is necessary to carry out the specific examinations for a correct diagnosis.[6,8] Laboratory investigations have a fundamental role in LGV diagnosis, but some aspects are still critical. Even if nucleic acid amplification tests (NAATs) represent the most sensitive method, commercial assays are not able to differentiate L from non-L serovars. For this purpose, LGV identification requires CT-molecular genotyping. The reliability of serological methods has not been established yet; therefore, they are not recommended for LGV laboratory diagnosis. However, a significant elevation of anti-*Chlamydia* IgG and IgA can suggest LGV diagnosis in the appropriate clinical and epidemiological setting.[5,7] The diagnosis of IBD must be questioned when IBD therapy fails, additional components of sexual history emerge, *Chlamydia* tests are positive and antibiotics

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effective against *Chlamydia* lead to a clinical improvement.[8] Moreover, if specific LGV diagnostic testing is not available, patients with a clinical profile consistent with LGV should be presumptively treated with doxycycline 100 mg orally twice a day for 3 weeks.[5–7] These precautions allow to prevent high-risk complications such as chronic anal lesions, genital fistulae, infertility, and elephantiasis but also widespread transmission of HIV and other STIs.[2,6,8]

Herein we report our experience of 11 patients affected by LGV that had performed an endoscopy with or without endoscopic biopsy in the suspicion of IBD before the *Chlamydia*-positive rectal swab. The aim of this study was to underline the necessity of a high index of suspicion to carry out the specific examinations for a correct LGV diagnosis. A prompt LGV diagnosis can prevent complications of the disease and avoid invasive procedures such as colonoscopy.

METHODS

We performed a retrospective study among all the patients (18–100 years) with a clinical and molecular diagnosis of LGV referring to the STI Unit of the University of Bologna between the 1 January 2013 and the 31 December 2017. We investigated their previous medical history and enrolled all the patients who had performed an endoscopy with or without endoscopic biopsy in the suspicion of IBD before the *Chlamydia*-positive rectal swab. For each enrolled patient, we considered the following risk factors: age, gender, sexual orientation, HIV infection if present, and symptoms.

RESULTS

During the period from 2013 to 2017, 69 diagnoses of LGV were made. We enrolled 11 out of the 69 patients (15.9%), who had performed an endoscopy with or without an endoscopic biopsy in the suspicion of IBD before the *Chlamydia*-positive rectal swab. The mean age was 43.0 years (range 34–63 years). All the patients were MSM (11/11, 100%) and 7/11 (63%) were HIV positive. Regarding the symptomatology, 9/11 patients (81.8%) complained of tenesmus and anal discharge, thus representing the most common symptoms, while 8/11 patients (72.7%) experienced rectal hematic and mucosal secretions. Of the 11 patients, 5 (45.5%) presented an anal external ulceration and only 3 patients (27.3%) presented a modification of bowel habits (Table 1).

Regarding previous medical history, 8 of 11 patients (72%) had already been treated for IBD after a rectal suggestive biopsy for an average time of 5 months (range from 1 month to 37 months). These 8 patients had experienced no improvement or a minimal improvement of symptoms after previous treatments. Of the 11 patients, 2 (18.1%) had already undergone proctological surgery for perianal Crohn's disease before the *Chlamydia*-positive rectal swab. All our enrolled patients achieved a complete recovery in terms of symptoms and laboratory findings within some weeks after treatment with minocycline 100 mg twice a day for 21 days.

DISCUSSION

In accordance with currently available data, our study confirmed that LGV proctitis is a relatively common infection in MSM and generally involves middle-aged men.[9] Moreover, a higher prevalence of HIV co-infection (63%) was observed in our cohort compared with the general population, probably enhanced by the ulcerative nature of LGV proctitis.[10] Whether HIV co-infection represents a risk factor itself or just a high-risk sexual behavior marker is still under discussion.[10–13] However, concomitant HIV infection or HAART therapy did not influence the clinical presentation of rectal LGV.[12]

In our cohort, all patients were symptomatic, showing the typical rectal LGV syndrome in MSM, characterized by severe rectal pain, mucoid and/or hemorrhagic rectal discharge, tenesmus, constipation, and other features of lower gastrointestinal inflammation.[10,14] It is important to point out that tenesmus represented the most frequent symptom reported by our patients,

TABLE 1: Clinical features of the cohort of the 11 LGV patients misdiagnosed with IBD.

Age	HIV coinfection	Tenesmus and anal discharge	Rectal secretion	Modification in bowel habits	Anal ulceration
50	+	+	−	−	−
44	−	−	+	−	+
42	+	+	+	+	−
37	+	−	+	−	+
43	−	+	+	+	−
34	+	+	+	−	−
35	+	−	−	−	+
63	−	+	+	−	−
40	+	+	−	−	+
40	+	+	+	−	+
52	−	+	+	+	−

in line with the literature.[15–19] Indeed, in previous studies, MSM with tenesmus and/or constipation showed a 7-times higher risk of LGV compared with other sexually transmitted proctitis.[6]

The performance of an invasive instrumental examination such as colonoscopy in the suspicion of IBD before the *Chlamydia*-positive rectal swab is another noteworthy result (Fig. 1). Moreover, 8 of 11 patients (72% of cases) had undergone a rectal biopsy in the suspicion of IBD before the *Chlamydia*-positive rectal swab. The histology of LGV proctitis shows lymphoplasmacytic infiltrates, lymphohistiocytic colitis, cryptitis with focal crypt distortion, and crypt abscesses, which are often interpreted as similar to Crohn's-type IBD (Fig. 2).[1,3,8,20,21]

Misdiagnosis of LGV with IBD has been previously described in several studies as a consequence of the nonpathognomonic features of clinical presentation, endoscopic appearance, and histopathological findings from rectal biopsies and unnecessary endoscopic investigations.[20,22–27] Therefore, diagnosis may be delayed, therapies may be noneffective, and invasive surgical approaches may be inappropriately chosen.[20,22–29]

Clinical diagnosis of LGV proctitis is still challenging and until now few studies have investigated the specific symptoms and signs of this infection. It has been suggested that patients complaining of tenesmus and constipation, alone or in combination, are more likely to have LGV and, therefore, should be carefully examined.[6]

As rectal symptoms and signs may be caused by several factors (infections, hemorrhoids, diverticular disease, inflammatory bowel disease, neoplasia, etc.), long-lasting examination, misdiagnosis or useless gastroenterological referrals have been frequently reported. Since rectal bleeding, pain, tenesmus, mucoid discharge, constipation, or hematochezia are nonspecific symptoms, IBD often represents the first diagnostic hypothesis. Thus, a previous medical history of endoscopy with biopsy execution, subsequent IBD pharmacologic treatment, or even radical surgery without response or improvement of symptoms are not rare in patients with LGV.[12,28,30,31]

Our study wants to shed light on the similarities between LGV and IBD, which share chronic severe inflammation as the main endoscopic and histopathological finding. Until now, no pathognomonic features have been described to differentiate LGV from IBD. What is more, some reports of LGV show anoscopic or endoscopic nonpathological findings.

Nonspecific clinical presentation, nonspecific endoscopic findings, nonpathognomonic histopathological features, insufficient awareness of the disease in both patients and clinicians, a lack of recommended diagnostic tests for LGV serovars, and the shame in seeking care may explain the frequently delayed diagnosis and misdiagnosis of LGV proctitis. Therefore, physicians should carefully collect information about the patient's sexual risk behavior and should be aware that both HIV-negative and HIV-positive MSM, as well as heterosexuals who practice anal intercourse, complaining of unspecific anorectal symptoms, should be tested for LGV and presumptively treated.[20,27,32] The recommended approach to patients with suspected IBD who are at risk of LGV includes a rectal swab for NAATs, currently representing the most sensitive method for LGV detection. However, commercial assays are not able to differentiate L from non-L serovars and CT-molecular genotyping is required for this purpose. Serological tests play a secondary role in LGV diagnosis because their reliability has not been established yet. However, a significant elevation of anti-*Chlamydia* IgG and IgA can suggest LGV diagnosis in the appropriate clinical and epidemiological setting, especially when NAATS are not available. Moreover, serological tests can be very useful in the follow-up period after specific LGV therapy to verify its effectiveness.[5,7]

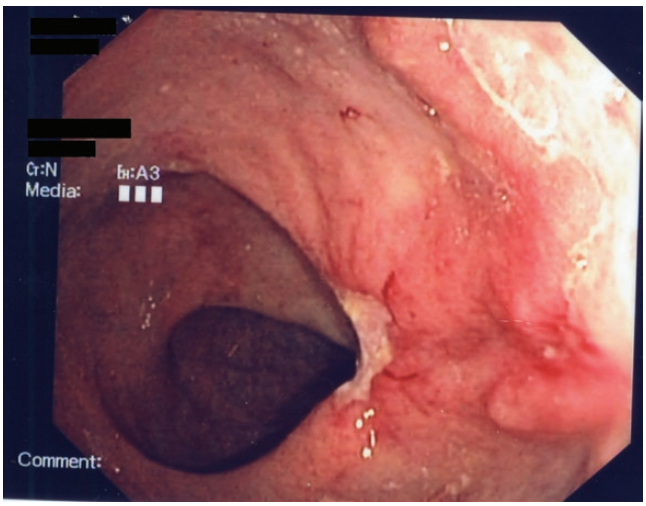

FIGURE 1. Endoscopic image of a large ulcer in the distal rectum of a patient with LGV-proctitis. The lesion is partially covered by fibrin and surrounded by edematous and friable mucosa.

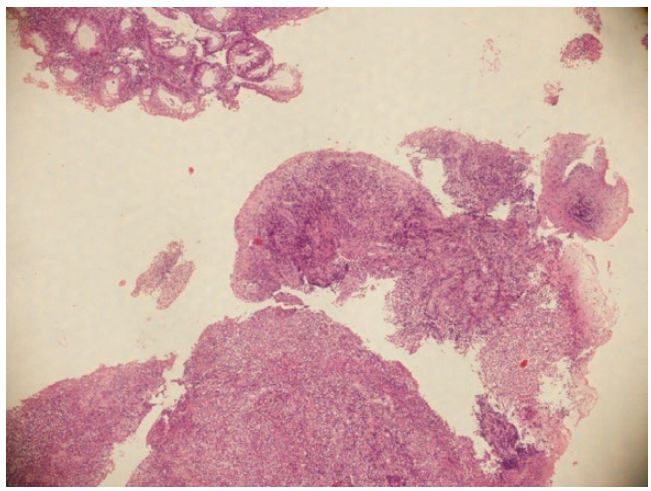

FIGURE 2. Histology of a fragment of colic mucosa in a patient with LGV-proctitis: ulceration and lymphoplasmacytic infiltrate are suggestive for both IBD and LGV-proctitis.

Histopathologists should consider LGV in the differential diagnosis when analyzing inflammatory colorectal biopsy specimens, as MSM sexual history may have been improperly investigated.[28]

Even if LGV patients show significantly higher anti-*Chlamydia* IgG values compared with LGV-negative subjects, serologic tests for lymphogranuloma venereum are still not routinely performed due to the frequent cross reactions with other *Chlamydia* species. Moreover, low anti-*Chlamydia* IgG titers do not rule out LGV diagnosis.[33]

A high index of suspicion is therefore necessary to carry out the specific examinations for a correct LGV diagnosis and prevent avoidable complications.

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