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**Lymphogranuloma venereum masquerading as
Inflammatory Bowel Disease in 12 homosexual men**

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5 1 **Lymphogranuloma venereum proctitis masquerading as inflammatory bowel**
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7 2 **disease in 12 homosexual men.**

8
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33 13 **Running title:** LGV proctitis masquerading as IBD.

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54 22 **Keywords:** lymphogranuloma venereum, proctitis, inflammatory bowel disease,
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56 23 histology

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4 25 **SUMMARY**
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6
7 26 Background: Lymphogranuloma venereum(LGV) is a recognised cause of proctitis.
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9 27 Symptoms, endoscopy and histology findings are similar in IBD and LGV proctitis.
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11 28 Aims: To characterise the clinical, endoscopic and histological features seen in men
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13 29 diagnosed initially with IBD and subsequently with LGV proctitis. To attempt isolation
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15 30 of *Chlamydia trachomatis* DNA from the stored rectal biopsy specimens of these
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17 31 patients using real-time PCR.
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19 32 Methods: Clinical data were collated from confirmed or suspected cases of LGV
20

21 33 proctitis where endoscopy and biopsy had been performed as part of the
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23 34 investigation of clinical symptoms. LGV was confirmed by the detection of LGV-
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25 35 specific DNA from rectal swab specimens, with supportive evidence from Chlamydial
26

27 36 serology. Stored histological specimens from rectal biopsies were analysed
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29 37 retrospectively for LGV-specific DNA with molecular techniques.
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31 38 Results: Rectal biopsies had been obtained from twelve cases of LGV proctitis.
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33 39 Mucosal ulceration, cryptitis, crypt abscesses and granulomas were common
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35 40 histological findings. Extraction of LGV-specific DNA from rectal biopsy specimens
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37 41 enabled confirmation of three suspected cases.
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39 42 Conclusions: During the recent LGV proctitis epidemic among UK men who have sex
40

41 43 with men, it has become apparent that this infection may closely resemble IBD.
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43 44 Gastroenterologists should remain alert to LGV as a cause of proctitis in this group.
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46 INTRODUCTION

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48 Proctitis has several infectious and non-infectious aetiologies. In men who have sex
49 with men (MSM) rectal infection with sexually transmitted pathogens such as herpes
50 simplex virus (HSV), *Neisseria gonorrhoeae* (GC), *Treponema pallidum* and
51 *Chlamydia trachomatis* (CT) are more common and important to consider.
52 Lymphogranuloma venereum (LGV) proctitis is caused by L1, L2 and L3 serovars of
53 CT and has evaded detection in recent decades in developed countries.

54
55 Following the report of an outbreak of LGV proctitis among MSM in the Netherlands
56 in 2004 (1), the Health Protection Agency (HPA) in the UK introduced a national
57 surveillance program and diagnostic support service in an attempt to enhance case
58 ascertainment and to help control the spread of this sexually transmitted infection
59 (STI) in the UK (2). Prior to October 2004, routine rectal Chlamydia testing had not
60 been recommended in the UK for patients describing symptoms of proctitis. By
61 December 2008, 849 UK cases of LGV had been confirmed (3). Where full
62 genotyping has been possible, all cases have been confirmed as the L2 serovar of
63 CT (4). This epidemic has been characterised by a preponderance of proctitis, rather
64 than the classical LGV genital ulcer-adenopathy syndrome seen in tropical regions
65 and affecting primarily heterosexuals. In the UK, LGV proctitis has been detected
66 almost exclusively among men who have sex with men (MSM), many of whom are
67 both HIV-positive and report high risk anal sexual practices with multiple and
68 anonymous partners (5).

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4 70 Rectal STIs can lead to histological changes of proctitis that may mimic IBD (6). The
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7 71 severe inflammatory changes seen with chlamydial infection are usually caused by
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9 72 the LGV-associated serovars (L1-3) whereas the oculogenital strains of CT (A-K)
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11 73 tend to produce milder proctitis histologically (7), and this infection is usually
12
13 74 asymptomatic. Histological diagnosis of infective-type colitis, particularly in the acute
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15 75 phase, relies heavily on the lack of features usually seen in IBD, especially the crypt
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17 76 architectural distortion and the presence of a prominent increase in the cellularity of
18
19 77 the lamina propria. Yet these features that usually predominate in IBD biopsies are
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21 78 also seen with LGV infection, including the development of well-formed granulomas.
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23 79 With more advanced LGV infection, transmural inflammation can ensue, further
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25 80 resembling Crohn's disease (8).
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33 81
34 82 The aims of this study were firstly, to characterise the clinical, endoscopic and
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36 83 histological features seen in men diagnosed initially with IBD and subsequently with
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38 84 LGV proctitis, and secondly, to describe attempts to detect the causative organism
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40 85 from stored histological specimens with the use of advanced molecular techniques.
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45 87 **MATERIALS AND METHODS**

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47 88 106 cases of LGV proctitis were identified between October 2004 and August 2009
48
49 89 at our centre, a combination of Genitourinary medicine (GUM) clinic and HIV clinic
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51 90 patients. 78/106 (73.6%) were HIV-positive. All patients had rectal swab specimens
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53 91 taken for detection of *C. trachomatis* and *N. gonorrhoeae* DNA by strand
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55 92 displacement amplification (ProbeTec, Becton Dickinson, Sparks, MD) as well as
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57 93 culture for *Neisseriae*. After retrospective case note review of all HIV clinic patients it
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4 94 was noted that 12 of these men had been referred to either gastroenterologists or
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6 95 colorectal surgeons for evaluation of their symptoms and had undergone rectal
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8 96 biopsy at some stage prior to their eventual diagnosis of LGV. None of these patients
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10 97 had undergone rectal testing for CT beforehand since this was not routine clinical
11
12 98 practice outside of GUM clinics. Initial histological reports were reviewed and these
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14 99 stored slides were re-read by an expert pathologist experienced in reporting IBD
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16 100 specimens (SBL). Endoscopic findings were also reviewed. It is possible and likely
17
18 101 that some HIV-negative men similarly may have undergone endoscopy and biopsy
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20 102 but such referrals would have been made through primary care and these reports
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22 103 would not be available to our GUM department.
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30 105 Recently, Martin *et al.* described a technique of DNA extraction and identification of
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32 106 L2 serovar from biopsy specimens (8). They confirmed the presence of LGV DNA in
33
34 107 one rectal biopsy specimen and one lymph node from two patients whose diagnoses
35
36 108 had been uncertain but in whom LGV had been suspected (8). We approached the
37
38 109 Sexually Transmitted Bacteria Reference Laboratory (STBRL) to attempt isolation of
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40 110 CT DNA from the stored rectal biopsy specimens of our 12 patients to help confirm
41
42 111 our four suspected LGV diagnoses and explore further the validity of this technique.
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44 112 Rectal tissue was excised from 20 histology specimen blocks (sourced from 12
45
46 113 patients) and excess paraffin removed by heating at 56°C. The tissues were then
47
48 114 digested using proteinase K and the DNA subsequently extracted using the DNeasy
49
50 115 Blood & Tissue Kit (Qiagen). The presence of CT DNA (all serovars) was confirmed
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52 116 using a plasmid-based real-time polymerase chain reaction (PCR) assay (9). Any
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4 117 specimen confirmed as CT-positive was then examined using an LGV-specific real-
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6 118 time PCR assay (10).
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12 122 **RESULTS**

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18 123 Median age of cases was 41.5 yrs (range 27-55). Two of the 12 had newly-
19 124 diagnosed hepatitis C infection and four men had concurrent rectal GC. Median time
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21 125 to LGV diagnosis from time of initial rectal biopsy was 6 months (range 0-23).
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27 28 127 **Clinical symptoms and endoscopic findings**

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30 128 All 12 men described altered bowel habit and 11 described mucous discharge per
31
32 129 rectum; further details regarding the presenting symptoms are listed in table 1. All
33
34 130 underwent lower gastrointestinal endoscopy (either colonoscopy or flexible
35
36 131 sigmoidoscopy). The findings at endoscopy are also listed in table 1: these varied
37
38 132 from normal mucosal appearances to a moderately active proctitis (figure 1). In one
39
40 133 case there was mucosal inflammation extending to the distal sigmoid colon.
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46 47 135 **Treatment**

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49 136 All cases were seen in either gastroenterology or colorectal surgical outpatient clinics
50
51 137 where initial diagnoses of IBD proctitis or “non specific” proctitis were made. Table 1
52
53 138 summarises the different treatments that patients were initially and subsequently
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55 139 prescribed. Three patients were initially treated with metronidazole and 5 patients
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59 140 were commenced on oral 5-aminosalicylates and hydrocortisone enemas prior to
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4 141 diagnosis of LGV proctitis, all with no effect on symptoms. Two patients were given
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6 142 reducing courses of oral prednisolone, leading to a transient partial improvement in
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9 143 symptoms. Longer times to LGV diagnosis were associated with increased numbers
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11 144 and types of treatments prescribed. Once their LGV diagnoses were made all
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13 145 patients were treated with doxycycline 100mg bd for three weeks with prompt and
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15 146 complete resolution of symptoms in all cases and at 12-month follow-up only one
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17 147 patient was having recurrent symptoms and was undergoing further investigations
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19 148 for possible irritable bowel syndrome.
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150 **Histology**

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28 151 Cryptitis and crypt abscesses were common histological findings but distortion of the
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30 152 crypt architecture was not prominent, more consistent with an infective aetiology
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33 153 (11). Granulomas were seen in biopsies from 5 of the 12 cases. Table 2
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35 154 summarises the histological features and the diagnostic timeline for each case.
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37 155 Where biopsies from the same patient were obtained on more than one occasion for
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39 156 the same symptomatic episode the histological findings have been combined (in
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41 157 most cases the biopsy findings were identical). Representative images
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44 158 demonstrating some of the histological features are presented (figure 2).
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161 **Confirmation of LGV cases**

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52 162 Eight of the 12 men had the diagnosis of LGV confirmed by detection of CT DNA
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54 163 from rectal swab specimens, confirmed to be L-serovar DNA by the STBRL. In the
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56 164 remaining cases, LGV was suspected on the basis of clinical proctitis in the
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58 165 presence of a positive CT DNA test from a rectal swab specimen (not forwarded for
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4 166 LGV typing) and/or a high titre anti-Chlamydial group antibody response detected
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7 167 with the use of either Chlamydia Group antibody serology or a Whole
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9 168 Immunofluorescence (WIF) test that employs LGV L2 strain as the source antigen
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11 169 (12).

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14 170
15 171 In total, 17 biopsy specimens from the 12 patients were submitted to STBRL.
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17 172 Evidence of LGV-specific CT DNA was found in 7 of 17 biopsy specimens from 5
18
19 173 different patients, 3 of whom had suspected but unconfirmed diagnoses of LGV. Of
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21 174 the remaining 10 specimens, 7 tested negative for CT plasmid DNA and hence did
22
23 175 not undergo further testing for LGV-specific DNA. Two specimens gave equivocal
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25 176 results on initial CT plasmid DNA testing, which is consistent with low CT DNA
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27 177 concentrations and therefore testing for LGV was not performed. One specimen was
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29 178 repeatedly inhibitory thus further molecular analysis was not possible.
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35 36 180 **DISCUSSION**

37
38 181 The clinical, endoscopic and histological findings in LGV can be indistinguishable
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40 182 from those of IBD. The potential for misdiagnosis of LGV and subsequent
41
42 183 inappropriate management has been well described (13-17). At our centre between
43
44 184 2002 and 2006, twelve HIV-positive men underwent extensive investigation for
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46 185 symptoms of proctitis, including lower gastrointestinal endoscopy and biopsy. Some
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48 186 patients were treated for IBD, with repeated courses of metronidazole, 5-
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50 187 aminosaliclates and topical and oral steroids to which they failed to respond either
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52 188 clinically or histologically.
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4 190 Rectal biopsy specimens from these 12 patients with LGV proctitis demonstrated
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7 191 features of acute and chronic inflammation with less distortion of crypt architecture
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9 192 than is usually seen in IBD, though there were no other distinguishing features or
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11 193 patterns. Granulomas and ulceration were present in 5 of 12 and 7 of 12 biopsy
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13 194 samples, respectively. These findings serve as a reminder that histologically LGV
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15 195 can be confused with IBD as well as other infective and non-infective causes of
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17 196 proctitis.
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23 198 De la Monte *et al.* commented on the distribution of lesions in the colons of 28
24
25 199 subjects at autopsy in whom LGV had been diagnosed previously (18). They
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27 200 observed that the rectum was uniformly involved and colonic lesions in LGV were
28
29 201 likely to affect the distal left side whereas Crohn's colitis can have a more varied
30
31 202 colonic distribution. Other attempts have been made to distinguish between LGV and
32
33 203 Crohn's or ulcerative colitis but often a considerable degree of overlap between the
34
35 204 two is found histologically (11,18,19) and thus far, no pathognomonic features of
36
37 205 LGV have been described. Recognition of the disease has relied on clinical
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39 206 suspicion in a patient with risk factors, though formal molecular or microbiological
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41 207 identification of the causative organism remains the only definitive diagnostic
42
43 208 technique. Although not currently licensed for use at extra-genital sites (throat and
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45 209 rectum), commercially available nucleic acid amplification tests (NAATs) have shown
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47 210 high sensitivity and specificity for the detection of CT in the rectum and are now used
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49 211 routinely in most GUM clinics (20).
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4 213 We were able to confirm LGV in three of our patients with suspected diagnoses by
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6 214 extracting DNA from rectal biopsy specimens and identifying the presence of LGV-
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8 215 specific CT DNA. This technique may provide a useful way of confirming LGV
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10 216 retrospectively in cases where isolation of the organism prior to treatment was not
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12 217 performed yet the diagnosis was suspected based on sexual history, clinical
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14 218 presentation and/or histological findings. In one case of LGV (case 4), the diagnosis
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16 219 was based on a typical clinical presentation and a high titre of anti-Chlamydial
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18 220 antibody, though treatment was commenced prior to the attempted detection of CT
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20 221 through molecular testing. Although serology cannot provide a definitive diagnosis of
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22 222 LGV, in our experience, a high WIF titre of 1:4000 has only been observed in
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24 223 confirmed cases of LGV infection.
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32 225 Notably, the majority of LGV diagnoses made at our centre were in HIV-positive
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34 226 individuals, many with concomitant STIs and hepatitis C and some testing positive
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36 227 for HIV at the same time, reflecting a pattern seen across Western Europe within the
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38 228 present LGV epidemic. The exact route of transmission and mechanism of spread of
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40 229 LGV remain unclear; however MSM with untreated LGV remain at risk of infecting
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42 230 others or being infected with HIV and hepatitis C due to the inflammation and
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44 231 ulceration associated with the condition. Targeted interventions in this group are
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46 232 warranted.
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53 234 After reaching a peak in mid-2005, symptomatic cases of LGV proctitis and
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55 235 occasional ulcer adenopathy disease continue to be diagnosed in the UK. Once
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57 236 established among MSM populations, infections such as gonorrhoea and syphilis
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4 237 have remained endemic in recent years and it is likely that LGV will follow a similar
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6 238 course. From Table 2 it is evident that, at least in our GUM/HIV clinics, diagnosis and
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8 239 treatment of affected individuals has become timelier since the first cases were seen.
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10 240 Nevertheless, affected individuals may not consider their symptoms to be sexually-
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12 241 related and thus may present to gastroenterology and colorectal surgery clinics,
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14 242 many via general practice or emergency department referrals. During the last twelve
15
16 243 months we have encountered patients in our GUM clinic with sexually transmitted
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18 244 proctitis who have reported prior referral to gastrointestinal specialists via general
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20 245 practice. Relevant clinicians should remain alert to the possibility of LGV as a cause
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22 246 of proctitis, particularly in the presence of MSM sexual risk behaviour and HIV-
23
24 247 positivity. Where NAAT-based testing is available through local laboratories, we
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26 248 recommend that all relevant clinicians send a rectal swab specimen for CT testing if
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28 249 suspicion of LGV is high and refer to GUM clinic for onward management, full STI
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30 250 screening and HIV testing. Histopathologists should also remember to include LGV
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32 251 in the differential diagnosis when reporting on inflammatory colorectal biopsy
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34 252 specimens, as MSM risk behaviour might not be provided in the clinical history
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36 253 accompanying the specimen.
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Figure 1: Endoscopic images from one patient with LGV proctitis demonstrates mild patchy colitis, with inflamed mucosa.

Figure 2: a and b) Rectal biopsies from Cases 7 and 1 showing multinucleate giant cells seen a) within a ruptured crypt abscess and b) between crypts – these were rarer findings. c) Rectal biopsy from Case number 6 showing surface ulceration with underlying densely inflamed granulation tissue. The large bowel mucosa shows crypt hyperplasia and the lamina propria is fibrotic and contains some smooth muscle fibres. There is acute and chronic inflammation with crypt abscesses and focal granuloma formation.

Case No	Age & CD4 count (cells/mm ³) at diagnosis	Date of Onset of symptoms	Symptoms					Endoscopic findings	Treatment (Tx)			
			Per rectal bleeding	Mucous	Altered bowel habit	Tenesmus	Anal pain		Tx initiated	Tx response	Tx change	Tx response
1	41yrs, 856	Sep 2002	■	■	■			Moderate proctitis -circumferentially inflamed granular mucosa	MTZ, Ciprofloxacin	Nil	ASA, HC enema	Nil
2	41 yrs, 432	Jan 2003		■	■	■	■	Moderate proctitis -patchy mucosal inflammation & small ulcers	ASA, HC enema	Nil	Oral pred.	Partial
3	42 yrs, 335	Dec 2002		■	■	■		Mild proctitis patchy mucosal inflammation	MTZ x3 courses	Nil	ASA, HC enema	Nil
4	45 yrs, 849	Aug 2003	■	■	■	■	■	Moderate proctitis inflamed granular mucosa and multiple ulcers	Acyclovir and Ciprofloxacin	Nil	Doxy.	Full
5	27 yrs, 156	Mar 2004			■		■	Moderate proctitis -inflamed, granular and ulcerated mucosa	Erythromycin & fluconazole	Nil	MTZ, Doxy	Full
6	55 yrs, 651	Aug 2004	■	■	■			Normal endoscopic findings	Doxy.	Full		
7	54 yrs, 487	Apr 2004		■	■	■		Moderate proctitis inflamed, granular and ulcerated mucosa	ASA, HC enema	Nil		
8	34 yrs, 572	Dec 2004	■	■	■			Moderate proctitis -patchy mucosal inflammation, small ulcers in rectum and distal sigmoid colon	Oral pred.	Partial		
9	42 yrs, 625	Jun 2005		■	■			Mild proctitis -inflamed, granular mucosa	Doxycycline	Full		
10	41 yrs, 625	Nov 2005	■	■	■		■	Normal endoscopic features	MTZ x3 courses	Nil	ASA, HC enema	Nil
11	42 yrs, 600	Oct 2005	■	■	■			Mild proctitis -inflamed mucosa	Antibiotics x 2 courses	Nil		
12	39 yrs, 497	Aug 2006		■	■		■	Not recorded	Penicillin	Nil		

Table 1. Patient demographics, clinic symptoms, endoscopic findings and therapy commenced. MTZ = metronidazole, ASA = 5-aminosalicylate, HC = hydrocortisone, Pred = prednisolone.

Case No.	Time between biopsy & LGV diagnosis (months)	Histological features							Diagnosis		
		Mucosal Ulceration	Cryptitis	Crypt abscess	Crypt Distortion	Granuloma	Plasma Cell infiltrate	Giant Cells present	Initial Histological Diagnoses/ Suggestions	Mode of initial LGV diagnosis	LGV DNA results from biopsy(date of biopsy)
1	23		■	■	■ mild			■	Uncertain aetiology Possible IBD	Rectal swab LGV Positive	LGV Positive (Sept 04) Negative (Dec 2002 & June 2003)
2	22		■	■		■			?IBD ?infective	Rectal swab LGV Positive	LGV Positive (May 03)
3	23		■		■ mild				?Due to prolapse ?IBD	Rectal swab LGV Positive	Negative
4	12	■	■				■		Uncertain aetiology	Clinical & Serology WIF titre = 1:4000	Negative (Sept 2004) Inhibitory (Dec 2003)
5	12	■				■	■		?Infective ?Crohn's	Rectal swab LGV Positive	Positive
6	3	■		■		■			Exclude LGV	Clinical Rectal swab CT detected, not sent for LGV testing	LGV Positive
7	9		■	■	■ minimal			■	Favours infective aetiology	Rectal swab LGV Positive	Negative (Sept 2004 and Jan 2005)
8	2	■	■	■	■ mild				?IBD. Exclude CT/LGV	Clinical & Serology CFT titre = 1:512 WIF titre = 1:4000	LGV Positive (Mar 2005) Negative (Jun 2005)
9	4	■	■	■		■	■		?Crohn's	Clinical & Serology CFT titre = 1:1280	LGV Positive (Nov 2005) Aug 2005 not tested
10	0	■					■		Diagnosed Crohn's 1999, thought to be recurrence	Rectal swab LGV Positive	Negative (Nov 2005)
11	0	■	■		■ mild	■			?IBD. Exclude LGV Concurrent Anal SCC present	Rectal swab LGV Positive	Negative (Nov 2005) Dec 2005 not tested
12	6		■				■		?Early ulcerative colitis	Rectal swab LGV Positive	Negative

Table 2. Summary of histological features of rectal biopsies and diagnostic timeline from 12 HIV positive men subsequently diagnosed with LGV proctitis

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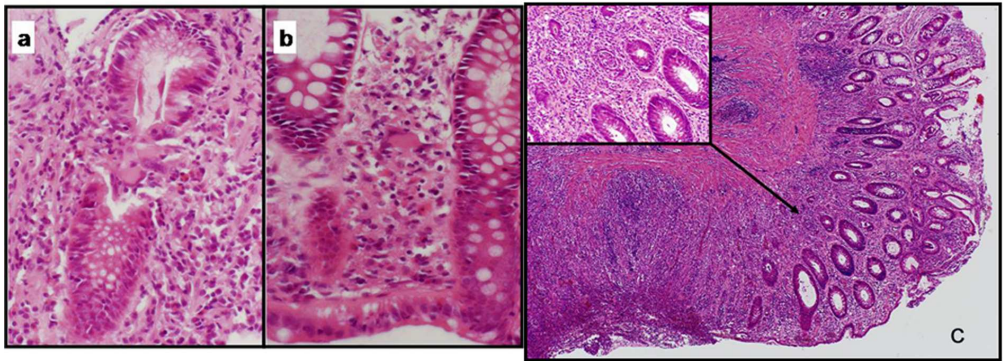
For Peer Review

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Peer Review