Open Forum Infectious Diseases

MAJOR ARTICLE

Lower Gastrointestinal Syphilis: Case Series and Literature Review

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Background. Syphilis infections are increasing globally. Lower gastrointestinal syphilis (LGIS) is a rare manifestation of early syphilis transmitted through anal sexual contact. Misdiagnosis of LGIS as inflammatory bowel disease may result from clinician underawareness.

Methods. We searched the literature for articles describing cases of LGIS, and identified additional cases diagnosed within our institution. Data were extracted from the articles and medical records and analyzed to provide a summative account.

Results. Fifty-four cases of LGIS were identified in 39 articles published between 1958 and 2020. Eight additional cases were diagnosed at our institution between 2011 and 2020, totaling 62 cases. All cases were described in men and transwomen aged 15–73 years. Fifty (93%) individuals reported having sex with men. In 26 cases (52%), the individuals were human immunodeficiency virus (HIV) coinfected. LGIS presented most commonly with hematochezia (67%) and anal pain (46%). The most common physical examination findings were rectal mass (38%), lymphadenopathy (31%), and rash (26%). Nontreponemal titers ranged from 1:2 to 1:1024. Of the 52 cases in which endoscopy was reported, 22 (42%) showed anorectal mass and 18 (35%) showed anorectal ulcer. In 44 cases (75%), histopathology revealed a chronic inflammatory infiltrate with a prominent lymphocyte component (45%) and/or plasma cells (36%). Seventy-eight percent of specimens to which a tissue stain was applied were positive for spirochetes.

Conclusions. LGIS should be suspected in men and transwomen presenting with a lower gastrointestinal symptom or mucosal abnormality. A sexual history must be elicited and guide testing. Misdiagnosis can delay treatment and threatens patient and public health.

Keywords. syphilis; proctitis; anal; rectal; colitis.

Rates of syphilis infection are rising globally in high-income countries and remain endemic in low- and middle-income ones [1]. In the United States, for example, syphilis infections have increased 71% since 2014, with at least half of infections occurring in men and transwomen who have sex with men [2]. Furthermore, people of minority race and those living with human immunodeficiency virus (HIV) are also disproportionately represented among patients acquiring syphilis infections [1, 3]. Lower gastrointestinal syphilis (LGIS), a rare manifestation of early syphilis, can present with a wide variety of symptoms and signs. These include symptoms of chancre or condyloma lata such as anal ulcer or mass, symptoms of proctocolitis such as hematochezia and tenesmus, or asymptomatic/incidentally discovered lower gastrointestinal mucosal abnormalities. LGIS is transmitted most often through anal sexual contact, including penis-, mouth-, and fingers-to-anus contact. Case series document misdiagnosis of LGIS as inflammatory bowel disease [4] with associated delay in treatment and increased risk for ongoing transmission and development of complications such as rectal fissure, fistula, and stricture. Health provider underawareness may be 1 possible explanation for misdiagnosis. With the global rise in syphilis infections, providers are likely to encounter more cases of LGIS. The aim of this report is to expand understanding of the demographics, behaviors, range of presenting symptoms, and laboratory, endoscopic, and histopathologic findings associated with LGIS in order to increase provider knowledge and awareness and to prompt consideration of this often-misdiagnosed entity. Herein, we describe a series of 8 cases of LGIS diagnosed at our institution and have added these to previously published cases to describe a total of 62 cases of LGIS.

METHODS

In this review and case series, LGIS is defined as *Treponema pallidum* infection occurring in the colon, rectum, or anal canal. This definition encompasses 2 scenarios. In the first scenario, a lower gastrointestinal syndrome such as anal mass or hematochezia is accompanied by serologic and/or histopathologic evidence of *T. pallidum* as a causative agent. In the second scenario, an asymptomatic/incidental finding

Received 31 December 2020; editorial decision 24 March 2021; accepted 26 March 2021.

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Open Forum Infectious Diseases®2021

DOI: 10.1093/ofid/ofab157

of a lower gastrointestinal mucosal abnormality is likely to be secondary to *T. pallidum* as demonstrated by positive syphilis serologies and biopsy staining. Articles were retrieved from Medline and Scopus databases. We searched these databases using search terms "anal syphilis," "rectal syphilis," "syphilis proctitis," and "syphilis colitis." For range of years searched, no lower limit was defined. All resulting abstracts were reviewed, and those describing cases of lower gastrointestinal syphilis consistent with our definition as outlined above were selected for further study. The text of these references was then read in entirety. Articles were included in the final review if they met 1 of the 2 following sets of criteria: Either they described a lower gastrointestinal syndrome accompanied by positive syphilis serologies and/or positive syphilis staining of lower gastrointestinal biopsied tissue, or they described an asymptomatic/incidental finding of a lower gastrointestinal mucosal abnormality accompanied by positive syphilis serologies and positive syphilis staining of biopsied tissue. We defined a lower gastrointestinal syndrome as symptoms of diarrhea, constipation, hematochezia, mucous discharge per rectum, tenesmus, painful defecation, anal pain, or anal ulceration. Articles written in languages other than English or presenting cases in which the diagnosis of LGIS was of uncertain reliability were excluded from the review. Demographic and historical data, presenting symptoms, physical examination findings, laboratory results, and endoscopic and histopathologic findings were extracted from each article, tabulated, and analyzed.

For the case series portion of this study, institutional review board (IRB) approval to conduct medical record review was obtained. Our institution is a combined primary and tertiary care referral center serving a predominantly urban population. Five hospitals and numerous outpatient clinics (generating 2.4 million outpatient encounters in 2018) contribute to its electronic medical record. With the help of the Joint Data Analytics Team, we searched this health system's electronic medical record database, which comprises >4 million patient records, for cases of LGIS. The database was searched for medical records within which both an *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* code for a syphilis diagnosis (A51.1–A51.4, A51.9, A51.31, A51.49, A52.0, A52.7, A52.9, A52.79, or A53.9), as well as a colonic, rectal, or anal surgical pathology biopsy specimen, was present. The resulting records were reviewed for presence of at least 1 of the 2 sets of inclusion criteria described above. Pertinent data were extracted from the charts selected for inclusion in the final review and added to tables describing the literature review findings to provide a summative account of observations. Hematoxylin and eosin–stained slides were reviewed by 2 pathologists (A. B. and M. C. O.) to complete the tabulated histopathologic data. A rabbit polyclonal immunoglobulin G (IgG) antibody directed to *T. pallidum* (1:100 with low pH antigen retrieval; Biocare Medical, Pacheco, California) using the Ventana BenchMark Ultra system (Roche Diagnostics, Indianapolis, Indiana) had been applied to all slides to identify spirochetes.

Each case from the literature and case series was analyzed independently by 2 physician members of the research team (D. D. and E. F.) with the goal of assigning a stage of syphilis where possible. Stages of syphilis were assigned according to the Centers for Disease Control and Prevention (CDC) syphilis staging definitions [5]. For example, primary syphilis was defined as *T. pallidum* infection characterized by 1 or more ulcerative lesions with supportive laboratory criteria such as a reactive Venereal Disease Research Laboratory (VDRL) or rapid plasma reagin (RPR) test. Secondary syphilis was defined as infection characterized by localized or diffuse mucocutaneous lesions, often with generalized lymphadenopathy, as well as a reactive VDRL or RPR and a reactive treponemal serologic test. Late syphilis was defined as characteristic abnormalities or lesions of the cardiovascular system (eg, aortitis, coronary vessel disease), skin (eg, gummatous lesions), bone (eg, osteitis), or other tissue, in the absence of other known causes of these abnormalities, supported by laboratory findings of a reactive VDRL or RPR and a reactive treponemal test.

Ethical Considerations

The procedures followed by our research team were in accordance with the ethical standards of the Helsinki Declaration of the World Medical Association. Our team obtained the approval of the Yale University and Yale–New Haven Hospital IRB to conduct medical records review. The IRB determined that the research protocol presented minimal risk to subjects. The IRB further determined that informed consent could be waived for the entire study. In accordance with the Yale–New Haven Hospital and Yale Medical Group reporting request process, requests for medical records were made through the Joint Data Analytics Team.

RESULTS

The literature search yielded 2492 references published between 1885 and 2020. After applying the inclusion criteria outlined in the Methods to this yield, 39 articles describing 54 cases of LGIS published between 1958 and 2020 were identified for inclusion in the final review (Supplementary Table). Eight cases of LGIS from our institution were also identified and included, totaling 62 cases. Most articles (31 [79%]) were published after the year 2000. The 8-case series from our institution is detailed in Table 1. The remaining results and tables were derived from the total 62 cases.

Demographic Characteristics

All 62 cases of LGIS were described in individuals of male sex assignment at birth. The age at diagnosis ranged from 15 to 73 years. In 50 cases (93%), individuals reported having sexual contact with men. In 4 cases (7%), individuals described themselves as heterosexual and/or denied sex with men.

Table 1. Yale New Haven Health System Case Series (N = 8)

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Age, y	57	26	37	53	25	47	73	30
Year of diagnosis	2016	2019	2015	2010	2019	2019	2012	2020
Gender identity	Man	Man	Man	Man	Man	Man	Man	Man
Sex at birth	Male	Male	Male	Male	Male	Male	Male	Male
Reported sexual activity	MSM	MSM	Unknown	MSM	MSM	Heterosexual, denies MSM	MSM	MSM
Recent anal-receptive intercourse	Yes	Yes	Unknown	Unknown	Yes	No	Yes	Yes
HIV serostatus	Negative	Negative	Positive	Positive	Negative	Negative	Positive	Negative
CD4 cell count	NA	NA	732 cells/μL	Unknown	NA	NA	502 cells/μL	NA
RPR	Not done	1:128	1:32	Unknown	1:32	1:16	Not done	1:64
VDRL	1:128	Not done	Not done	Unknown	Not done	Not done	1:2	Not done
Other testing	TPPA reactive	FTA-Abs reactive	Not done	Unknown	*T. pallidum* Ab reactive	*T. pallidum* Ab reactive	TPPA reactive	*T. pallidum* Ab reactive
CT/GC testing	Not done	Positive rectal CT-LGV PCR, negative rectal GC PCR	Negative CT immunostain of rectal biopsy	Unknown	Positive rectal CT-LGV PCR, negative rectal GC PCR, and negative oropharyngeal and urine CT/GC PCR	Negative urine CT/GC PCR	Negative rectal CT/GC PCR	Negative rectal GC/CT PCR
Presenting symptoms	Asymptomatic	Abdominal pain, hematochezia, constipation	Unknown	Rectal bleeding	Anal pain, tenesmus, hematochezia	Abdominal pain, bloody diarrhea	Rectal bleeding initially; diarrhea, constipation, and fecal incontinence subsequently	Anal mass for 1 y, genital rash
Examination	Diffuse erythematous papules on back and chest, 1 wk later	Suprapubic tenderness	Unknown	Unknown	Faint maculopapular rash on upper thorax and back, 2 ulcers with raised edges, 1 scrotal and 1 perianal	Raw, tender abrasion at 6 o'clock below the anus	Unremarkable	Perianal skin with posterior raised and fleshy lesion with some sloughing and fibrinous changes
Endoscopic findings	Small raised ulcer in distal rectum	Area of nodular mucosa at the anus extending into the rectum. The nodules were hard and had erosions/ulcers	Unknown	Unknown	Severe ulcerative proctitis	Congested mucosa at the anus	Rectal ulcers initially, slight loss of vascular pattern in the rectum subsequently	Not performed

Table 1. Continued

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Histologic findings	Colonic mucosa with acute and chronic inflammation and focal ulceration	Moderately active colitis on anorectal specimen, severe syphilitic chronic gastritis on the stomach specimen	Expansion of the lamina propria including the subcryptal space by excess lymphocytes, plasma cells, and neutrophils. Only 1 or 2 branched crypts. A single epithelioid collection is noted. Acute cryptitis is seen	Dense chronic inflammatory infiltrate in the lamina propria with a prominent component of plasma cells. The background reveals spindle cell (likely fibroblasts) proliferation with fibrosis. No granulomatous inflammation is identified	Marked expansion of the lamina propria by a mixed inflammatory infiltrate with prominent plasma cells and lymphocytes. There is cryptitis and crypt abscesses and ulceration and granulation tissue	Markedly inflamed fragments of rectal type mucosa with numerous plasma cells and features suggestive of ulceration	Moderate expansion of the lamina propria with lymphoplasmacytic infiltrate and multiple foci of cryptitis and crypt abscess formation. Granulomatous inflammation is not seen. The crypt architecture distortion is minimal	Squamous mucosa with acute erosive and chronic inflammation
Treponema immunostain	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive
CDC stage on presentation	Secondary	Secondary	Unclear	Unclear	Secondary	Primary	Primary	Secondary

Abbreviations: Ab, antibody; CDC, Centers for Disease Control and Prevention; CT, *Chlamydia trachomatis*; FTA-Abs, fluorescent treponemal antibody test; GC, *Neisseria gonorrhoeae*; HIV, human immunodeficiency virus; LGV, lymphogranuloma venereum; MSM, men who have sex with men; NA, not applicable; PCR, polymerase chain reaction; RPR, rapid plasma reagin; TPPA, *Treponema pallidum* particle agglutination test; VDRL, Venereal Disease Research Laboratory.

In 26 of 50 cases (52%), individuals were coinfected with HIV. HIV staging information was inconsistently described, but where described (8/26 cases [30%]), CD4 cell counts ranged from 67 to 732 cells/μL and averaged 388 cells/μL. In 6 cases (n = 22 [27%]), individuals tested positive for chlamydia by rectal swab. Of the 6 individuals coinfected with rectal chlamydia, 2 were confirmed to have lymphogranuloma venereum (LGV) and the remaining 4 were presumptively treated for it. One individual (n = 21 [5%]) tested positive for gonorrhea by rectal swab.

Clinical Characteristics

LGIS presented most commonly with hematochezia (41/61 cases [67%]) and anal pain (28/61 cases [46%]). Other common symptoms included abdominal pain, tenesmus, mucous discharge, diarrhea, and constipation. Four individuals (n = 61 [7%]) were asymptomatic at presentation. Two of these individuals were found to have abnormalities on screening colonoscopy. A third individual had abnormal screening syphilis serologies at a routine HIV follow-up visit and reported anal receptive intercourse, but apparently failed treatment for early latent syphilis, ultimately developing fulminant proctitis, colitis, and gastroparesis 3 months later with anorectal biopsy immunostain and serologies strongly suggestive of persistent syphilis infection. No further details were available regarding the circumstances of the diagnosis of the fourth individual for whom presentation was asymptomatic. Three of the 4 individuals who were asymptomatic at presentation were people living with HIV (Table 2).

The most common physical examination findings reported were rectal mass (16/42 cases [38%]), lymphadenopathy (13/42 cases [31%]), and rash (11/42 cases [26%]). Six individuals (n = 42 [14%]) had unremarkable physical examinations. In 20 cases (n = 62 [32%]), authors did not comment on physical examination findings, or findings were unknown (Table 3).

In 61 cases (n = 62 [98%]), serologic testing for syphilis was performed and reported positive. Given the literature time span, serologic testing strategies and types varied. Treponemal tests were performed and reported positive in 45 cases (n = 61 [74%]). The most common assay was fluorescent treponemal antibody absorption test followed by *T. pallidum* hemagglutination assay. Nontreponemal tests (majority RPR and/or VDRL) were performed and reported positive in 56 of 61 cases (92%). The VDRL and RPR titer modes were 1:64 and 1:128, respectively, and the range for both was 1:2–1:1024. In 4 of the 61 cases (7%) for which serologic testing was performed and reported positive, the type of test was not specified (data not shown).

A staging analysis was performed and showed that 17 cases (n = 62 [27%]) were consistent with the CDC definition of primary syphilis. Twenty-six cases (n = 62 [42%]) were consistent with the CDC definition of secondary syphilis. Eight cases (n = 62 [13%]) were consistent with either primary or secondary

Table 2. Presenting Symptoms

Presenting Symptom	No. of Subjects/Total (%)[a]
Hematochezia	41/61 (67)
Anal pain	28/61 (46)
Abdominal pain	17/61 (28)
Tenesmus	15/61 (25)
Mucous discharge	14/61 (23)
Diarrhea	14/61 (23)
Constipation	8/61 (13)
Weight loss	6/61 (10)
Fever	5/61 (8)
Anal ulceration	4/61 (7)
Rash	3/61 (5)
Myalgia	3/61 (5)
Arthralgia	3/61 (5)
Anal mass	2/61 (3)
Anorexia	2/61 (3)
Headache	2/61 (3)
Pruritus	1/61 (2)
Lymphadenopathy	1/61 (2)
Unknown/authors did not comment	1/62 (2)
Asymptomatic	4/61 (7)

[a]Sum of all listed percentages does not equal 1, as some cases presented with multiple symptoms.

syphilis but lacked the information necessary to assign a more definitive stage. One case (n = 62 [2%]) had features of early and late (tertiary) syphilis and was therefore of uncertain stage. In 10 cases (n = 62 [16%]), available information was so limited that a probable syphilis stage could not be assigned.

Table 4 summarizes the most common endoscopic findings, which were anorectal mass (22/52 cases [42%]) or anorectal ulcer (18/52 cases [35%]). In 15% of cases, endoscopic findings were described in nonspecific terms such as proctitis (4/52 cases [8%]), colitis (3/52 cases [6%]), or sigmoiditis (1/52 cases [2%]).

Table 3. Physical Examination Findings

Physical Examination Finding	No. of Subjects/Total (%)[a]
Rectal mass	16/42 (38)
Lymphadenopathy	13/42 (31)
Inguinal	9/13 (69)
Generalized	4/13 (31)
Rash	11/42 (26)
Unremarkable	6/42 (14)
Perianal ulceration	3/42 (7)
Anal fissures	2/42 (5)
Rectal tenderness	2/42 (5)
Rectal ulceration	1/42 (2)
Perianal lesions	1/42 (2)
Perianal condyloma acuminata	1/42 (2)
Abdominal tenderness	1/42 (2)
Suprapubic tenderness	1/42 (2)
Unknown/authors did not comment	20/62 (32)

[a]Sum of all listed percentages does not equal 1, as some cases presented with multiple physical examination findings.

Histopathology

In 44 cases (n = 59 [75%]), documented histopathology findings or the reviewed slides revealed features of chronic inflammation. This included prominent lymphocytic infiltrate with lymphoid aggregates (20/44 cases [45%]), prominent plasma cells (16/44 cases [36%]), basal lymphoplasmacytosis (9/44 cases [20%]), and prominent histiocytes (7/44 cases [16%]). Acute inflammation, including cryptitis and crypt abscesses, was reported in 27 cases (n = 59 [46%]). These and other less frequently reported findings are presented in Table 5.

In 79% of cases (26/33), *T. pallidum* immunostain performed on histologic specimens revealed spirochetes. Other organism-specific staining and microscopy techniques included Warthin-Starry stain (9/50 cases [18%]), darkfield microscopy (7/50 cases [14%]), and Steiner stain (1/50 cases [2%]). Overall, 78% (39/50) of histologic specimens were positive for spirochetes by at least 1 type of stain. It should be noted that darkfield microscopy is not a recommended technique for identification of *T. pallidum* in the gastrointestinal tract given its inability to isolate this species from commensal gut treponemes. In this review, the 4 cases in which darkfield microscopy was the only organism-specific technique employed for identification of *T. pallidum* within biopsied tissue were also cases in which a convincing syndrome of proctocolitis was accompanied by lower gastrointestinal mucosal abnormality and positive syphilis serologies, strongly suggesting a diagnosis of LGIS.

DISCUSSION

This review of 62 cases of LGIS, the largest to date, contributes depth to the current understanding of this infectious entity through 5 key findings. First, consistent with existing literature, clinical experience, and route of transmission, we found that LGIS is almost exclusively observed in adolescent boys, men, and transwomen who report engaging in sex with men [4]. While unsurprising, this is significant given its implications for testing and diagnosis: A thorough and emotionally skillful sexual history remains the most powerful tool for estimating the pretest probability of LGIS. Here we note that cisgender women are also at risk for LGIS, and while they have rarely been observed to suffer from it, the medical community should remain vigilant for such a possibility. Second, the rate of sexually transmitted coinfection among those diagnosed with LGIS is high. Half of individuals with LGIS were coinfected with HIV, and 27% of those tested for rectal chlamydia were positive. This redemonstration of a known epidemiologic trend represents an important reminder for medical providers to test broadly for sexually transmitted infections when LGIS is suspected. Furthermore, the CDC

Table 4. Endoscopic Findings

Endoscopic Finding	No. of Subjects/Total (%)[a]
Anorectal mass(es)	22/52 (42)
Unifocal anorectal mass	17/22 (77)
Multifocal anorectal masses	5/22 (23)
Anorectal ulcer(s)	18/52 (35)
Unifocal anorectal ulcer	9/18 (50)
Multifocal anorectal ulcers	9/18 (50)
Edematous mucosa	2/52 (4)
Anorectum	1/2 (50)
Colon	1/2 (50)
Nodular areas in the distal anorectum	2/52 (4)
Colonic erosions (transverse, descending, sigmoid)	2/52 (4)
Colonic ulcers (location not specified, presumed >12 cm from the anal verge)	2/52 (4)
Fissure	2/52 (4)
Fistula	1/52 (2)
Abscess	1/52 (2)
Sigmoid erythema	1/52 (2)
Unknown/authors did not comment	8/62 (13)
Not performed	2/62 (3)

[a]Sum of all listed percentages does not equal 1, as some cases presented with multiple endoscopic findings.

recommends that those with a clinical syndrome consistent with LGV (ie, proctocolitis or tender femoral lymphadenopathy) be treated presumptively for it at the time of initial visit, even prior to the results of chlamydial diagnostic testing [2]. Concern remains high that cases of LGV are frequently missed, given lack of routine testing for it and its co-occurrence with other infections. Third, while LGIS presents most commonly with hematochezia, the range of presenting symptoms is broad, with some individuals developing anal pain or ulcer only, others manifesting symptoms of florid proctocolitis, and still others presenting with an asymptomatic/incidentally noted lower gastrointestinal mucosal abnormality. This reinforces the importance of maintaining a high level of suspicion for LGIS in adolescent boys, men, and transwomen presenting with a lower gastrointestinal symptom or mucosal abnormality. Fourth, we found that 27% of cases were likely primary syphilis, 42% of cases were likely secondary syphilis, and 13% of cases were likely primary or secondary syphilis. These findings, significant for their impact on treatment, are congruent with existing literature suggesting that LGIS is most commonly a manifestation of early syphilis [6]. It is important to note that signs and symptoms of secondary syphilis may appear before the chancre of primary syphilis has fully healed, and that both stages are known to not infrequently co-occur. Fifth, analysis of histopathology reports and slides supports the presence of morphologic overlap between LGIS and inflammatory bowel disease. Consistent with prior studies, this observation suggests that when a chronic and/or active inflammatory infiltrate in the lower gastrointestinal tract is identified, pathologists and clinicians should work together to exclude sexually transmitted proctocolitis through a combination of clinic-based tests and immunohistochemical staining of biopsy specimens [7]. Health professionals should be aware that *T. pallidum* immunostain is not 100% sensitive, and that gummatous lesions are especially likely to stain negative for syphilis given the paucity of organisms typically found in these late-stage growths, hence the importance of multiple testing modalities.

Table 5. Histopathological Findings

Histopathological Finding	No. of Specimens/Total (%)[a]
Chronic/lymphoplasmacytic inflammation	44/59 (75)
Prominent lymphocytes/ lymphoid aggregates	20/44 (45)
Prominent plasma cells	16/44 (36)
Basal lymphoplasmacytosis	9/44 (20)
Prominent histiocytes	7/44 (16)
Acute inflammation/ cryptitis/crypt abscess	27/59 (46)
Ulcer/erosion	22/59 (37)
Crypt distortion	13/59 (22)
Granuloma	13/59 (22)
Vascular inflammation[b]	5/59 (8)
Paneth cell metaplasia	1/59 (2)
Unspecified inflammation	8/59 (14)
Not applicable/not available[c]	3/62 (5)

[a]Sum of all listed percentages does not equal 1, as some cases presented with multiple histopathologic findings.

[b]Vascular inflammation included perivascular inflammation, endarteritis, and vasculitis.

[c]Designates cases in which biopsies were not obtained (n = 1) or in which histopathologic results were unavailable (n = 2).

Since small case series had suggested significant morphologic overlap with inflammatory bowel disease as a possible "clue" to syphilis as the etiology, we felt it important to undertake a more focused discussion of histopathology. The most frequent finding reported was chronic inflammatory infiltrates (75% of cases), which is well-known to occur in syphilis. This included lymphocytic inflammation and lymphoid aggregates, prominent plasma cells, basal lymphoplasmacytosis, and/or histiocytes. Chronic inflammatory infiltrates may be underreported in this series due to 14% having "unspecified inflammation." Acute inflammation, as well as ulcerations and erosions, were also frequently reported, usually in association with chronic inflammation, but not exclusively. These findings, with or without other uncommon features (granulomas, mild architectural distortion, Paneth cell metaplasia), have histomorphologic overlap with the more routinely encountered inflammatory bowel disease (Crohn disease and ulcerative colitis), which is a diagnostic pitfall. Previous literature has explored distinguishing morphologic features between these 2 entities [8], but has been limited to a small series. A study to characterize the chronic

inflammatory infiltrate of syphilis in more detail has also shown its varied nature with other potential diagnostic pitfalls, such as IgG4-related diseases, fungal and mycobacterial infections, and lymphoma [9]. In the current study, *T. pallidum* immunostain was positive in most (79%) cases, and showed superior sensitivity to Warthin-Starry stain, which is in keeping with previous literature [9].

This study is limited by the retrospective nature of the case series, case reports, and medical record review and resultant quality of the data, pooled from multiple sources lacking standardized language and reporting. No information was routinely reported regarding number of sex partners, use of protection during intercourse, and screening for concomitant sexually transmitted pathogens, for example. More importantly, the serologic, examination, and historical data needed to accurately stage syphilis infections were not uniformly reported. In multiple cases, authors did not report a probable syphilis stage. In several cases, the stage reported by the authors conflicted with the stage assigned by this study's reviewers based on CDC staging guidelines. We highlight these failures to draw attention to a crucial point: The stage of syphilis infection has implications for treatment of the patient and exposed partners, risk of complications from treatment, and risk of mother-to-child transmission. It has significant patient-level and public health–level consequences, and therefore should be established clearly by clinicians at the point of care.

Prompt diagnosis and staging of LGIS is needed to reduce patient morbidity, and minimize community spread. Understanding the spectrum of presenting symptoms (or lack thereof) and endoscopic and histopathologic findings of LGIS can help clinicians make more timely diagnoses. Our analysis confirms that pathognomonic features of LGIS are scarce and that infectious disease practitioners, primary and urgent care providers, and gastroenterologists who see patients with a lower gastrointestinal symptom or mucosal abnormality must routinely elicit a sexual history to assess risk for a sexually transmittable etiology. Our analysis of this largest literature review to date suggests that relying on a specific histopathologic pattern to prompt staining and reflex serologic testing for syphilis would miss a significant number of cases. Current epidemiology reinforces the importance of including LGIS on the differential for adolescent boys, men, and transwomen of any age presenting with a lower gastrointestinal tract symptom or asymptomatic/incidentally noted mucosal abnormality. A detailed sexual history may further support workup to evaluate this diagnostic possibility. In addition to serologic testing for syphilis, *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and herpes simplex virus, polymerase chain reaction testing should be obtained from rectal swabs given significant rates of coinfection. Organism-specific staining for *T. pallidum* should be performed on biopsied tissue. Last, patients diagnosed with LGIS (or any sexually transmitted pathogen) should be tested for HIV, reported to the health department, and referred for partner notification services.

CONCLUSIONS

No single clinical or histopathologic finding is clearly diagnostic of LGIS. LGIS should be included on the differential for adolescent boys, men, and transwomen of any age presenting with a lower gastrointestinal tract symptom or asymptomatic/incidentally noted mucosal abnormality. A detailed sexual history must be obtained at first presentation. A missed or delayed diagnosis can significantly impact individual and public health.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Potential conflicts of interest. All authors: No reported conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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