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Delayed diagnosis of colorectal sexually transmitted diseases due to their resemblance to inflammatory bowel diseases

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ABSTRACT

Objective: Sexually transmitted diseases (STDs), mainly lymphogranuloma venereum (LGV), induce colorectal symptoms that may be misdiagnosed as inflammatory bowel disease (IBD). This study describes patients who presented with STDs masquerading as IBD in order to improve understanding of missed diagnosis of colorectal STDs and their association with LGV in Israel.
Methods: This retrospective, descriptive study characterized the clinical, endoscopic, and pathological findings of 16 patients who were diagnosed with a colorectal STD after erroneously being diagnosed with IBD. Molecular genotyping was used to characterize some of the *Chlamydia trachomatis* isolates.
Results: All patients were men who have sex with men (MSM), mostly HIV-1-positive, and had clinical and endoscopic findings compatible with IBD. The STD was diagnosed 1–36 months after the initial diagnosis: 14 were positive for *Chlamydia trachomatis*, of which three were of the LGV2b (ST58) serotype and one was ST 108 serotype. Five were positive for gonorrhea and four were positive for syphilis. Several pathogens were diagnosed in six episodes.
Conclusions: Colorectal STDs may resemble IBD and therefore their diagnosis may be delayed. IBD symptoms in MSM who engage in non-protected anal sex should prompt at least syphilis and anal PCR for STD testing. If *C. trachomatis* is diagnosed but LGV subtyping cannot be done, doxycycline 100 mg twice daily for 21 days should be recommended.

Introduction

Proctitis and proctocolitis are emerging diseases, especially in men who have sex with men (MSM) who engage in unprotected anal sex (Bissessor et al., 2013). With the introduction of pre-exposure prophylaxis (PrEP) for HIV, the incidence may increase even further. The etiology may either be infectious, usually sexually transmitted, including *Chlamydia trachomatis* (mainly lymphogranuloma venereum (LGV)), gonorrhea, syphilis, and herpes simplex virus (HSV), or non-infectious, i.e., inflammatory bowel disease (IBD). Symptoms, signs, and endoscopic findings may be similar in both groups (Arnold et al., 2013, 2015; Gallegos et al., 2012; Soni et al., 2010), leading to delayed diagnosis, the administration of inappropriate treatment, and transmission of the pathogen to sexual partners. In the last 15 years, the incidence of both LGV (Blank et al., 2005; Nieuwenhuis et al., 2004) and syphilis (Health Protection, 2009; Brosh-Nissimov et al., 2012) among MSM has increased, leading to increasing numbers of cases of STD-associated proctitis/proctocolitis misdiagnosed as IBD.

The main aim of this study was to describe the authors' experience with 16 cases of sexually acquired proctocolitis in MSM who were misdiagnosed as having IBD in order to increase awareness of this delayed diagnosis.

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Methods

This was a retrospective descriptive study. A central institutional review board approved the study. Due to the retrospective nature of the study, the ethics board exempted informed consent.

Study population

Nineteen patients who were diagnosed with IBD by a gastroenterologist in the outpatient setting during the years 2010–2018 were identified, of whom 16 were subsequently diagnosed with sexually acquired proctitis/proctocolitis.

Clinical, endoscopic, and pathological findings were obtained from the medical records. The treating physician obtained rectal samples using the technique described by Bachmann et al. (Bachmann et al., 2010). Three rectal swabs (Dacron) were collected from each participant. The collection tubes were stored according to the manufacturer's instructions.

Laboratory work-up

Tests for STDs were performed at the Sheba Medical Center Microbiology Laboratory. *Neisseria gonorrhoeae* and *C. trachomatis* were diagnosed using a commercial real-time PCR kit (Anyplex II STI-7; Seegene). Although the test has not been validated for rectal samples, many centers have reported its good performance (van der Helm et al., 2009). Syphilis was diagnosed by a positive chemiluminescent microparticle immunoassay (CMIA) test; if positive, this was followed by a rapid plasma reagin (RPR) or Venereal Disease Research Laboratory (VDRL) test and Treponema pallidum hemagglutination assay (TPHA).

Multilocus sequence typing (MLST) analysis was performed at the National Public Health Laboratory in Tel Aviv. A newly developed and improved in-house MLST was used that is based on the scheme of Bom et al. (Bom et al., 2011) (manuscript in preparation). In short, a nested PCR was used for amplification for the five genes of the scheme *hctB* (CT046), CT058, CT144, CT172, *pbpB* (CT682), and *ompA*. Sequencing was performed from both sides by dedicated sequencing primers that did not participate in the amplification steps. The Chlamydia MLST database of Uppsala University, Sweden (http://mlstdb.bmc.uu.se/) was used to assign the allele number and sequence type (ST) for each isolate.

For molecular serotyping, a Blastn search was run for *ompA* against the nr database (https://blast.ncbi.nlm.nih.gov/Blast.cgi?PROGRAM=blastn&PAGE_TYPE=BlastSearch&LINK_LOC=blasthome).

Results

Sixteen patients (17 episodes) were erroneously diagnosed with IBD (Table 1). The median age of the patients was 35 years (range 23–66 years). All included patients were MSM. All except one were HIV-1-positive. At the time of STD diagnosis, HIV viral load in those positive for HIV-1 was undetectable (less than 40 copies/ml), except for one patient who had a viral load of 170 500 copies/ml and a median CD4 cell count of 782 cells/mm^3 (range 451–1588 cells/mm^3). All patients reported participating in unprotected anal intercourse.

Presenting symptoms included diarrhea and abdominal or rectal pain, as well as rectal bleeding and tenesmus. Seven patients had systemic symptoms including fever and malaise, and two had arthralgia. With the exception of one patient, none had inguinal lymphadenopathy. Endoscopic examinations demonstrated varying degrees of inflammatory changes. Rectal/colonic ulcers were found in 10 patients. Histopathology findings included cryptitis, crypt distortion, or crypt abscess in six of 12 (50%) available examinations. All patients were diagnosed as having IBD, and nine out of 17 (53%) patients were initially treated for their IBD with anti-inflammatory drugs. One patient was treated with infliximab when his symptoms did not respond to first- and second-line anti-inflammatory drugs including steroids. Nevertheless, none of the patients was 'cured'.

A sexually transmitted infection was subsequently diagnosed in all patients: *C. trachomatis* was detected in 14 out of the 17 episodes (82.3%). Unfortunately, *C. trachomatis* molecular serotyping and genotyping was introduced only recently, therefore only five sequences were examined. LGV2b (ST58) was diagnosed in three of them and ST108 in one.

N. gonorrhoeae was detected in five patients; this was concomitant with chlamydia in four. Four patients were diagnosed with syphilis that was clinically and serologically assumed to be active; this was concomitant with chlamydia in two of them. In 15 episodes the diagnosis was made by the HIV treating physician, and in two episodes by the gastroenterologist after his attention was drawn to previous missed cases. The median time elapsed between the misdiagnosis of IBD and diagnosis of the STD was 2 months (range 1–36 months).

All patients with *C. trachomatis* were treated with doxycycline for 21 days due to a presumed diagnosis of LGV. Patients with gonorrhea and syphilis were treated according to the US Centers for Disease Control and Prevention guidelines. All patients were cured without sequelae. The health authorities performed contact tracing.

Discussion

This study describes 16 patients (17 episodes) with severe sexually acquired proctitis/proctocolitis among MSM who were misdiagnosed as having IBD for a period ranging from 1 to 36 months. As expected, the most commonly detected pathogen was *C. trachomatis*, followed by *N. gonorrhoeae* and *Treponema pallidum*. In at least three cases, the diagnosis of LGV was laboratory-confirmed.

In this study, histopathological findings indistinguishable from those described in IBD, such as mucosal ulcers (found in 7/12 samples), cryptitis (5/12), granuloma (2/12), and plasma cell infiltrate (2/12), resulted in a mistaken histopathological diagnosis of IBD. Rectal STDs can lead to histological changes that mimic IBD (Arnold et al., 2013; Surawicz et al., 1986). The severe inflammatory changes seen with chlamydial infection are usually caused by the LGV-associated serovars (L1–3), whereas the oculogenital strains of *C. trachomatis* (A–K) tend to produce milder proctitis, which is usually asymptomatic (Quinn et al., 1981).

Classically, LGV is characterized by genital ulcers, followed by the appearance of tender unilateral inguinal lymphadenopathy with a characteristic 'groove sign'. Over the past decade, LGV has emerged in Europe and North America as the leading cause of proctitis and proctocolitis in MSM.

All patients in this study experienced a significant delay and several visits to their general practitioner, gastroenterologist, or proctologist before testing for the STD diagnosis was performed. In all of these encounters, an STD was not looked for despite the patient's known history of being MSM or HIV-positive.

In 2010, Soni et al. (Soni et al., 2010) reported that during the recent LGV proctitis epidemic among UK MSM, it had become apparent that the infection may closely resemble IBD. In a retrospective study, they found that 12 out of 106 patients (11.3%) with LGV proctitis had been misdiagnosed with IBD. Most patients had been treated with metronidazole, 5-aminosalicylates, and steroid enema without improvement. The median time between wrong IBD diagnosis and correct STD diagnosis was 6 months, ranging between 2 and 36 months. Colonoscopy findings