Clues to uncommon and easily overlooked infectious diagnoses affecting the GI tract and distinction from their clinicopathologic mimics CME

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There are a myriad of causes that may result in GI tract inflammation. Whether the cause is autoimmune, iatrogenic, ischemic, infectious, or idiopathic, the alimentary canal responds to injury in a limited number of ways. As a result, endoscopic and histologic evaluation of these patients may result in a great deal of frustration to both gastroenterologists and pathologists. Infections can be particularly challenging because (1) only a limited number of organisms provoke a specific endoscopic and/or histologic appearance and (2) whereas some organisms may be present on biopsies, the findings may be so subtle or organisms so few that they are missed easily if the reviewer is not performing a specific search for the culprit. To narrow the differential diagnosis, clinicians rely on a thorough clinical history and pertinent laboratory studies, whereas pathologists depend on identifying patterns of inflammation and tissue injury. Establishing definitive diagnoses requires an integrated and systematic approach that depends largely on an open dialogue between the gastroenterologist and pathologist. This review aims to illustrate some challenging entities that can be encountered in daily practice and to provide helpful endoscopic and pathologic clues to clinicians and pathologists alike. The emphasis is on the topic of sexually transmitted infection (STI) proctitis because world-wide outbreaks are being reported. The United States is no exception, and we have identified several of these cases in recent years.

STIs

STIs represent an ever-increasing cause of GI tract inflammation. This discussion is limited to infectious proctitis, because it is predominantly in the rectum that STIs often are mistaken for other conditions, most notably inflammatory bowel disease (IBD). The bacterial pathogens implicated most frequently are *Chlamydia trachomatis, Neisseria gonorrhoeae,* and *Treponema pallidum*.

Proctitis is defined as inflammation involving, although not necessarily restricted to, the rectum.[1] Causes of proctitis include IBD, radiation, diversion of the fecal stream (diversion colitis), ischemia, and sexually and non–sexually transmitted infections.[2] The increased prevalence of infectious proctitis secondary to sexually transmitted pathogens has been widely documented in men who have sex with men (MSM).[1,3-6] Although as many as 10% of women report having anal-receptive intercourse on a regular basis,[7] sexually transmitted infectious proctitis is overlooked frequently in female patients.[8] A review of proctitis in MSM implicated *Neisseria* as the causative organism in 30%, *Chlamydia* in 19%, herpes simplex virus in 16%, and *Treponema* in 2%.[9,10] Patients with infectious proctitis are at higher risk for HIV infection because of shared risk factors. In addition, the presence of rectal inflammation facilitates the transmission of HIV.[11]

Although there are no pathognomonic findings to definitively diagnose these infections on histologic grounds alone, there are morphologic clues that pathologists can

Abbreviations: CDC, Centers for Disease Control and Prevention; CMV, cytomegalovirus; FDA, U.S. Food and Drug Administration; FTA-ABS, fluorescent treponemal antibody-absorption; HAART, highly active antiretroviral therapy; H&E, hematoxylin and eosin; IBD, inflammatory bowel disease; Ig, immunoglobulin; LGV, lymphogranuloma venereum; MSM, men who have sex with men; NAAT, nucleic acid amplification testing; PAS, periodic acid–Schiff; PCR, polymerase chain reaction; STI, sexually transmitted infection; VDRL, Venereal Disease Research Laboratory.

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identify in order to suggest this as a diagnostic possibility and avoid misdiagnosis and mismanagement.

CHLAMYDIAL PROCTITIS

C trachomatis serovars L1, L2, and L3 are the causative agents of lymphogranuloma venereum (LGV), an invasive infection that has tropism for the lymphatic system. Serovars D through K are typically responsible for cases of genital tract infection (urethritis, cervicitis) limited to the mucosal surfaces. An obligate intracellular gram-negative bacterium, this organism replicates inside membrane-bound vacuoles in endothelial and epithelial cells via a process that requires 2 morphologic forms, namely, the infectious but metabolically inactive elementary body and the noninfectious metabolically active reticulate body. In vitro studies have demonstrated a reversible persistent state for this organism, which is defined as "viable but non-cultivable chlamydiae," characterized by large, abnormal, non-dividing reticulate bodies. This persistent, in vitro state may be triggered by several factors, namely, exposure of infected cells to penicillin, interferon-γ, nutrient–amino acid starvation, iron deprivation, and herpes virus infection.[12,13] Whether this persistent state exists in vivo is unknown but certainly possible and could explain cases of reactivation in patients in whom infection resolved after antibiotic treatment (assuming re-exposure has been excluded). This is an interesting proposition, given that *Chlamydia* proctitis preferentially affects individuals infected with HIV, which induces production of several inflammatory cytokines, among them, interferon-γ.[14]

Lymphogranuloma venereum proctitis outbreaks largely have been associated with serovar L2 (genovariant L2b) in Europe, Canada, and Australia.[15-18] On the other hand, studies from Seattle and China were unable to identify LGV-associated serovars. Instead, the most prevalent genotypes in these groups were G, D, and J.[19,20] Virulence factors responsible for the chronic inflammatory response are largely unknown. A *Clostridium difficile*–like cytotoxin has been demonstrated in vitro in *Chlamydia* serovar D but not in serovar L2.[21] Recombination may play a role in the emergence of new, hypervirulent strains of *C trachomatis*. For example, a unique recombinant strain of L2 and D strains (L_2c) recently was isolated from the rectum of an MSM who presented with severe hemorrhagic proctitis. This particular strain is the only LGV strain that so far demonstrates an in vitro cytotoxic phenotype.[22]

Clinical presentation

Although endemic to parts of Africa, Asia, the Caribbean and South America, LGV has been identified increasingly over the past decade among MSM in Western industrialized countries.[23-26] From 67% to 100% of MSM with LGV infections also have concomitant HIV.[27] The progression of LGV is divided into 3 stages. The primary stage occurs after an incubation of 3 to 30 days and presents as a painless, ulcerating papule at the inoculation site, which goes unnoticed by 58% of patients and resolves spontaneously.[26,28] The secondary stage occurs several weeks later and is characterized by painful and typically unilateral inguinal and/or femoral lymphadenopathy.[2,26] Lymphadenopathy is not, however, a sine qua non for LGV. Proctitis is common in the secondary stage, occurring in 96% of patients.[29] LGV proctitis presents as rectal pain, tenesmus, bloody or purulent rectal discharge, and constipation, along with systemic symptoms such as fever and weight loss.[5,26,30] Tertiary-stage LGV presents strictures, fistulas, and disfiguring lesions of the anogenital region.[30,31] Non-LGV *Chlamydia* also can cause proctitis in individuals engaging in receptive anal intercourse. Although as many as half the patients may be asymptomatic,[32,33] symptoms can include anorectal pain, tenesmus, mucosanguinous discharge, abdominal pain, constipation, and fever.[2,34]

Endoscopic appearance

There is significant overlap in symptoms and morphology between *Chlamydia* proctitis and IBD. This mimicry extends to endoscopic appearance. On endoscopy, *Chlamydia* proctitis has protean manifestations (Figs. 1A), with mucosal hyperemia, mucopurulent discharge, friability, and multiple ulcers; strictures may be seen in LGV-associated proctitis.[30,35-37] Aside from the endoscopic resemblance to IBD, LGV proctitis also can present as a mass lesion, mimicking a neoplasm.[38]

Treatment

Antimicrobial treatment cures LGV and prevents progression of tissue damage. First-line therapy consists of doxycycline 100 mg orally twice a day for 21 days. Alternative regimens are erythromycin 500 mg orally 4 times a day for 21 days or azithromycin 1 g daily for 21 days. Antibiotic regimens for non-LGV *Chlamydia* consist of doxycycline 100 mg twice daily for 7 days or a single dose of azithromycin 1 g given orally.[39] All sexual partners of the patient during the 60 days before onset of symptoms should be tested for *Chlamydia* and offered treatment.[40]

SYPHILITIC PROCTITIS

T pallidum, a gram-negative, motile spirochete, is the causative agent of syphilis. Research on this organism is limited because this metabolically challenged bacterium obtains most necessary macromolecules from its host and cannot survive in vitro for more than a few generations. Despite its slow doubling time (30-33 hours)[41] and oxygen and heat sensitivities, *T pallidum* thrives in the human body, invading and disseminating to a wide variety of tissues.[42] Latent or persistent infection in asymptomatic persons has been demonstrated in vivo.[42,43] The organism's lack of virulent factors (eg, cytotoxins) suggests

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