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Case Report

Human intestinal spirochetosis and proctitis in the context of acute cytomegalovirus infection: a case report and review of the literature

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Abstract

Introduction: Prevalence of sexually transmitted infections, including those affecting the rectum and presenting as proctitis, is increasing worldwide. Diagnostic evaluation may be particularly challenging when serological findings are negative or when concomitant infections are present.

Case Presentation: A 44-year-old man who has sex with men presented with persistent fever and watery diarrhea. Initial evaluation revealed elevated inflammatory markers, hepatosplenomegaly, lymphocytosis, mild hepatocellular injury, and computed tomography findings suggestive of rectosigmoid colitis. Extensive microbiological, immunological, and hematological investigations supported the diagnosis of acute cytomegalovirus infection. Serological testing for syphilis was negative. Since the patient was immunocompetent and gastrointestinal symptoms could not be fully explained by cytomegalovirus (CMV) infection alone, flexible sigmoidoscopy with biopsies was performed. Endoscopy showed edematous rectosigmoid mucosa without ulcerations. Histopathological examination revealed superficial epithelial injury with preserved crypt architecture, focal cryptitis, occasional crypt abscesses, and mixed inflammatory infiltrates. Immunohistochemical staining was strongly positive for *Treponema pallidum*. However, in the context of negative syphilis serology and compatible histopathological features, this finding was interpreted as cross-reactivity associated with human intestinal spirochetosis. The patient was treated with intramuscular benzathine penicillin G, followed by normalization of bowel habits.

Conclusions: This case illustrates the diagnostic complexity of proctitis in an immunocompetent MSM patient with acute CMV infection and human intestinal spirochetosis. It emphasizes that positive anti-*Treponema pallidum* immunohistochemistry should not be interpreted in isolation, as cross-reactivity with intestinal spirochetes may lead to overdiagnosis of gastrointestinal syphilis. Careful clinicopathological correlation remains essential when routine diagnostic findings are inconclusive or potentially misleading.

Key words: CMV; proctitis; sexually transmitted infection; human intestinal spirochetosis.

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Introduction

Cytomegalovirus (CMV) is a widespread pathogen that persists lifelong in a latent form after primary infection. Primary CMV infection in immunocompetent individuals is usually asymptomatic; when clinically apparent, it most commonly presents as unexplained fever or a mononucleosis-like syndrome, reflecting effective T-cell-mediated control of viral replication [1,2].

Human intestinal spirochetosis (HIS) is an uncommon but clinically relevant condition in infectious diseases and pathology. HIS is reported more frequently among people living with HIV (PLWH) and men who have sex with men (MSM), suggesting the importance of specific epidemiological and behavioral risk patterns [3].

Syphilitic colitis is considered a “great imitator” in gastroenterology [4,5]. Although mucocutaneous and neurological manifestations of syphilis are well described, gastrointestinal involvement is rare and may mimic inflammatory bowel disease, infectious colitis, or malignancy [6,7]. Although gastrointestinal syphilis and HIS are both spirochetal infections, they represent distinct clinicopathological entities with different causative agents, mechanisms of mucosal injury, histopathological patterns, clinical implications, and treatment approaches [8]. Recognizing these differences is essential, particularly because histopathological and immunohistochemical findings may overlap and create diagnostic uncertainty.

Case Report

A 44-year-old MSM patient presented to the Clinic for Infectious and Tropical Diseases, University Clinical Center of Serbia, on January 16th, 2025, because of persistent fever and watery diarrhea. He denied abdominal pain, tenesmus, nausea, vomiting, weight loss, respiratory symptoms, and urinary complaints. His past medical history was unremarkable. He was unmarried, lived alone in adequate housing

conditions, and denied recent international travel, contact with animals, illicit drug use, blood transfusions, or piercings. His history included two tattoos, the most recent seven months before admission, and a dental procedure one month before fever onset. He was a non-smoker and reported occasional alcohol consumption.

Symptoms had started approximately 15 days before admission, on January 2nd, 2025, initially as low-grade fever that later increased to 39.4°C, predominantly in the afternoon and evening. Fever was accompanied by up to four daily episodes of watery, non-bloody, non-mucoid diarrhea. He did not report abdominal pain, weight loss, nausea, vomiting, or respiratory symptoms.

During outpatient evaluation on January 8th, laboratory findings showed elevated lactate dehydrogenase, elevated D-dimer, mildly increased transaminases, and elevated C-reactive protein (CRP). The complete blood count was initially unremarkable; however, lymphocytosis became evident during subsequent follow-up. Between January 13th and January 19th, relative lymphocyte counts ranged from 46.2% to 63.1%, while absolute lymphocyte counts ranged from 3.96 to 5.94 × 10^9/L, peaking on January 19th.

Chest radiography showed bilateral reticulonodular infiltrates. A chest computed tomography (CT) scan suggested sequelae of varicella pneumonia, pulmonary alveolar microlithiasis, or pulmonary alveolar proteinosis. Clarithromycin was prescribed empirically for seven days, but fever persisted. The pulmonologist considered that the pulmonary findings were unlikely to explain the febrile illness, and bronchoscopy was planned for further evaluation. Respiratory polymerase chain reaction (PCR) panel, as well as serological testing for HIV, HBV, HCV, and *Treponema pallidum*, including both non-treponemal VDRL and treponemal TPHA assays, were negative.

On January 13th, repeated laboratory testing showed thrombocytopenia, markedly elevated D-dimer, increased CRP and ferritin, and further elevation of transaminases. CT pulmonary angiography ruled out pulmonary embolism but confirmed calcified micronodules with traction bronchiectasis and interstitial thickening, again raising suspicion for pulmonary alveolar proteinosis. An autoimmune and granulomatous disease workup, including serum angiotensin-converting enzyme (ACE) and chitotriosidase, was requested. CT of the abdomen and pelvis performed on January 16th revealed hepatosplenomegaly and segmental thickening of the rectosigmoid colon with mucosal hyperenhancement, suggestive of inflammatory colitis. No significant lymphadenopathy was detected. The patient was subsequently referred to the Clinic for Infectious and Tropical Diseases and admitted to the hepatology department.

On admission, he remained febrile, but was in good general condition. Initial laboratory evaluation showed an elevated CRP of 58.7 mg/L, ferritin of 1,255 µg/L, and LDH of 1,037 U/L, with mild thrombocytopenia (143 × 10^9/L), absolute lymphocytosis (4.40 × 10^9/L; 50.0%), moderate hepatocellular injury (AST 84 U/L and ALT 139 U/L), and mild renal impairment (serum creatinine 117 µmol/L; eGFR 59 mL/min/1.73 m^2). During follow-up, these abnormalities progressively improved: by February 12, 2025, CRP had decreased to 1.8 mg/L, LDH to 190 U/L, platelet count was 199 × 10^9/L, AST 26 U/L, ALT 56 U/L, and the absolute lymphocyte count 2.32 × 10^9/L. At long-term follow-up on June 12, 2026, CRP was < 0.5 mg/L, ferritin 90.7 µg/L, LDH 183 U/L, platelet count 185 × 10^9/L, absolute lymphocyte count 1.84 × 10^9/L, AST 28 U/L, and ALT 26 U/L.

Given the clinical picture of fever of unknown origin with gastrointestinal involvement, an extensive diagnostic workup was performed. Repeated stool cultures, blood cultures, and testing for *Clostridioides difficile* and gastrointestinal PCR multiplex panel were negative. Serological testing was positive for CMV IgM and IgG, supporting the diagnosis of acute CMV infection presenting with fever, lymphocytosis, hepatosplenomegaly, and mild hepatitis. EBV testing indicated previous exposure, with negative IgM and positive IgG antibodies.

Further investigations, including ANA, ANCA, ENA, ASCA, and QuantiFERON-TB Gold, were negative. Serum ACE was elevated, but there was no radiological or clinical evidence to support sarcoidosis. Thyroid function tests and thyroid autoantibodies were within normal limits. Transthoracic echocardiography was unremarkable, while abdominal ultrasound confirmed hepatosplenomegaly.

Because diarrhea and CT signs of rectosigmoid colitis could not be attributed to acute CMV infection alone, flexible sigmoidoscopy was performed. It showed edematous mucosa of the rectum and sigmoid colon with loss of the normal vascular pattern, but without ulcerations, erosions, or pseudomembranes. Multiple biopsies were obtained.

The patient was treated supportively with low-molecular-weight heparin and proton pump inhibitors, without antimicrobial therapy. Despite persistent low-

grade fever and two to three loose stools per day, he left the clinic against medical advice after five days, shortly after receiving the positive CMV serology result (IgM positive, IgG negative), together with positive qualitative CMV DNA PCR. At discharge, laboratory findings had improved, with lower CRP, normalization of creatinine and estimated glomerular filtration rate (eGFR), improved LDH and transaminases, and persistent lymphocytosis.

Ten days after biopsy, histopathological examination revealed superficial epithelial damage with preserved crypt architecture, focal cryptitis, occasional crypt abscesses, and an edematous lamina propria infiltrated with lymphocytes, plasma cells, eosinophils, and scattered neutrophils. A characteristic basophilic fringe was present along the luminal surface of the colorectal epithelium. Immunohistochemical staining for *Treponema pallidum* showed strong positivity confined to the luminal epithelial surface, without evidence of invasion into the epithelium or lamina propria. In the context of negative syphilis serology and compatible histomorphological findings, the diagnosis of human intestinal spirochetosis was established. No additional histochemical stains or molecular methods were performed. Figure 1.

The patient was treated with three weekly doses of intramuscular benzathine penicillin G (2.4 million units), as the final histopathological evaluation was still pending at the time treatment was initiated. Following therapy, the patient showed clinical improvement, with normalization of bowel habits. At the last follow-up visit, liver transaminase levels were within the normal range.

Discussion

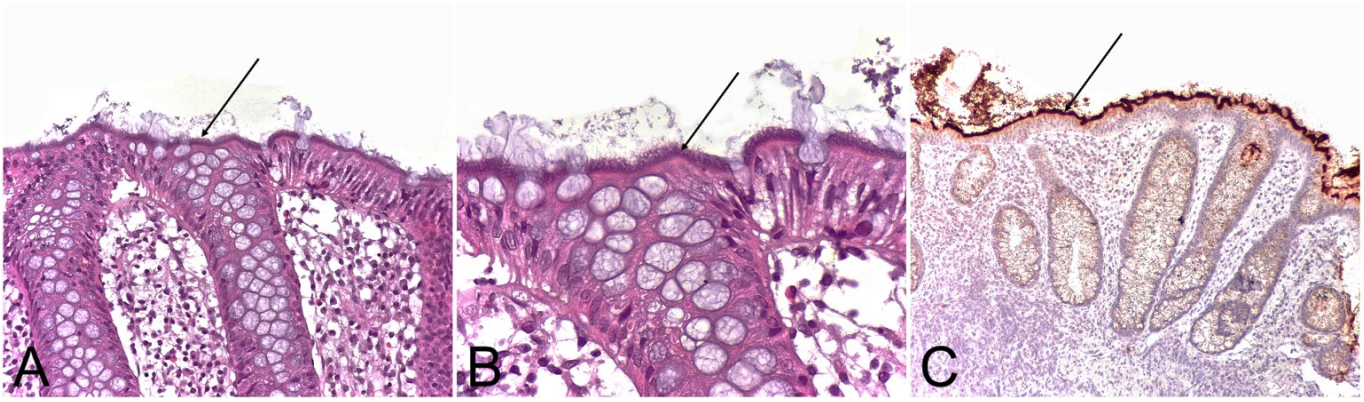
Sexually transmitted infections remain a major global public health concern, with their true burden underestimated because many infections are asymptomatic and therefore remain undiagnosed [9,10].

Syphilis is a systemic sexually transmitted infection that may involve the gastrointestinal tract, including the rectum, where it can present as proctitis with non-specific clinical and endoscopic findings, often leading to delayed diagnosis. Although syphilitic proctitis should be considered in the differential diagnosis, it is far less common than proctitis caused by *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, or herpes simplex virus [4,5,11–13].

In the present case, the central diagnostic challenge was the interpretation of strongly positive anti-*T. pallidum* immunohistochemistry in a patient with negative syphilis serology. Rectal biopsy alone may be insufficient to diagnose syphilitic proctitis, because anti-*T. pallidum* immunohistochemistry lacks specificity and may be positive in HIS due to cross-reactivity with intestinal spirochetes [14].

HIS is characterized by colonization of the colorectal mucosal surface by anaerobic spirochetes of the genus *Brachyspira*, predominantly *Brachyspira aalborgi* and *Brachyspira pilosicoli* [15]. Although it is often considered an incidental histopathological finding, HIS may be clinically relevant in selected patients, particularly those presenting with chronic diarrhea, abdominal pain, rectal bleeding, or proctitis. Symptomatic cases have been described more frequently in PLWH and MSM [16].

Figure 1. Histopathological features of intestinal spirochetosis.



A: H&E staining showing a characteristic basophilic fringe along the luminal surface of the colonic epithelium (arrows) (× 200). **B:** Higher magnification highlighting the dense basophilic fringe (arrows) (× 400). **C:** Treponema pallidum immunohistochemistry demonstrating numerous spirochetes along the luminal epithelial surface (arrows) (× 100).

Acute CMV infection was diagnosed early during hospitalization, based on positive CMV IgM and IgG serology in the presence of fever, lymphocytosis, hepatosplenomegaly, and mild hepatitis [17]. The patient was not treated with ganciclovir because he was immunocompetent and showed spontaneous clinical and laboratory improvement. However, the diarrheal syndrome and rectosigmoid colitis were not sufficiently explained by CMV infection alone, which justified endoscopic evaluation with biopsy.

The diagnosis of HIS is primarily histopathological. On hematoxylin and eosin-stained sections, HIS classically appears as a basophilic fringe, approximately 2–5 μm thick, along the luminal surface of the colorectal epithelium, creating the characteristic "false brush border." The organisms adhere to the apical membrane of enterocytes, while the underlying mucosa often shows minimal or no significant inflammation [18].

Anti-*T. pallidum* immunohistochemistry may serve as a sensitive ancillary stain for detecting intestinal spirochetes, but it should not be regarded as specific evidence of syphilis. Graham *et al.* demonstrated that anti-*T. pallidum* immunohistochemistry was positive in all examined cases of HIS, indicating that this stain can identify intestinal spirochetes but cannot reliably distinguish HIS from syphilitic infection [14]. This cross-reactivity represents an important diagnostic pitfall, especially when immunostaining is interpreted without adequate clinical and serological correlation.

Histological distinction between syphilitic proctitis and human intestinal spirochetosis is therefore crucial. Syphilitic proctitis is typically characterized by dense chronic inflammation rich in plasma cells, often accompanied by cryptitis, crypt abscesses, ulceration, architectural distortion, and occasionally obliterative endarteritis or granulomatous inflammation [19]. In addition, immunohistochemistry for *Treponema pallidum* in syphilitic proctitis typically demonstrates invasion of spirochetes into the epithelium and lamina propria. In contrast, human intestinal spirochetosis usually presents as superficial epithelial colonization with a false brush border pattern and only minimal associated mucosal inflammation. In these cases, positive *Treponema pallidum* immunostaining is typically confined to the luminal surface of the colorectal epithelium [20].

In this patient, negative non-treponemal and treponemal syphilis tests, the absence of typical serological evidence of syphilis, and the known cross-reactivity of anti-*T. pallidum* immunohistochemistry supported HIS as the most consistent diagnosis. However, caution remains necessary, as syphilitic proctitis may show diverse endoscopic and histological features, and serological testing can be negative during the window period or in severely immunosuppressed patients [4,11–13,21]. The symptomatic presentation of proctitis in an MSM patient is also consistent with published observations on HIS in this population [16,22].

There are currently no standardized treatment guidelines for HIS. Asymptomatic individuals often do not require therapy, whereas symptomatic patients may benefit from antimicrobial treatment. Metronidazole is the most commonly used agent and has been associated with clinical improvement in reported cases [15,23]. Benzathine penicillin G was used because of its known activity against spirochetes, including *T. pallidum* and other related organisms.

This case highlights the diagnostic complexity of HIS proctitis in an immunocompetent MSM patient with concomitant acute CMV infection. Its main message is that positive anti-*T. pallidum* immunohistochemistry does not establish the diagnosis of gastrointestinal syphilis when interpreted in isolation. Awareness of cross-reactivity with intestinal spirochetes, together with careful clinicopathological correlation, is essential to avoid misdiagnosis and guide appropriate management.

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Conflict of interest
No conflict of interest is declared.

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