Colonic Spirochetosis in a 60-Year-Old Immunocompetent Patient: Case Report and Review

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Abstract
Spirochetes, a genetically and morphologically distinct group of bacteria, are thin, spiral-shaped, and highly motile. They are known causes of several human diseases such as syphilis, Lyme disease, relapsing fever, and leptospirosis. We report a case of colonic spirochetosis in a healthy patient presenting for surveillance colonoscopy. The diagnosis of intestinal spirochetosis was made accidentally during the histological examination of colonic polyps, which were removed during colonoscopy. We also performed an extensive review on intestinal spirochetosis with a focus on clinical presentation and outcomes of reported cases from the past two decades.

Keywords
Spirochetosis, Colon, Immunocompetent host

Introduction
Spirochetes are a genetically and morphologically distinct group of bacteria. Morphologically, they are thin, spiral-shaped, and highly motile.¹ Spirochetes are known causes of several human diseases such as syphilis, Lyme disease, relapsing fever, and leptospirosis. Intestinal infestation by spirochetes has long been recognized.² Clinical presentations vary, ranging from asymptomatic to gastrointestinal (GI)-related symptoms such as bleeding or diarrhea.³ We report a case of colonic spirochetosis in a healthy patient who initially presented for surveillance colonoscopy. Additionally, we also perform an extensive review of previously reported cases in the literature.

Case Report
A 60-year-old asymptomatic man with no significant past medical history underwent a surveillance colonoscopy due to a previous history of a 1.8-cm hyperplastic polyp at the ileocecal valve. He denied weight loss and any GI symptoms, such as abdominal pain, diarrhea, or rectal bleeding. Colonoscopy revealed 2 tubular adenoma polyps in the cecum and 6 hyperplastic polyps in the rectosigmoid junction, ranging from 2 to 4 mm. The hematoxylin and eosin (H&E) stain of these polyps showed several filamentous structures on the colonic epithelium (Figures 1 and 2). A Warthin-Starry stain was subsequently performed and confirmed the diagnosis of intestinal spirochetosis (Figure 3). He also tested negative for HIV (human immunodeficiency virus) infection.

Discussion
Intestinal spirochetosis (IS), first described by Harland and Lee in 1967 using electron microscopy,⁴,⁵ is an uncommon disease in humans defined by colonization of the luminal surface of colonic epithelial cells with anaerobic spirochetes of the Brachyspiraceae family, which include Brachyspira aalborgi (measuring 2-6 µm in length) and Brachyspira pilosicoli (measuring 4-20 µm in length).⁶,⁷

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The prevalence of IS varies from 2.5% to 32%, depending on geographic locations and diagnostic modalities. The reported prevalence of human IS found in rectal biopsy specimens ranges between 2% and 7% in Western countries, whereas the prevalence is considerably higher in patients from India and other parts of Asia. Of note, the overall prevalence is much lower when the diagnosis is made using stool culture (1.2% to 1.5%) compared to that from mucosal biopsies. The highest prevalence of IS was previously reported in homosexual men (30% to 60%) as well as in HIV-positive patients. However, in a recent study from Japan including 5265 consecutive colorectal biopsies from 4254 patients, the authors found that 5.5% of those with HIV seropositivity had IS compared to 1.7% in those with negative serology. The lengths of the spirochetes were also significantly longer in HIV-positive patients.

IS is found primarily in the colon, though there have been reported cases in the stomach and small intestine from the early 1900s. Similar to the case we present, most cases of IS are an incidental finding discovered during a screening/surveillance colonoscopy. The clinical as well as prognostic significance of IS are debatable. Given the lack of association between the presence of IS and GI symptoms, current theory suggests IS has a commensal relationship with the human host and is part of normal flora. However, spirochetes can become pathogenic and invasive in a subset of patients, due to diminishing host defenses or a pathologic factor favoring the virulence of the microorganism. In symptomatic cases, IS most commonly presents with chronic watery diarrhea and abdominal pain. Most cases are mild. However, some may present with an invasive and rapidly fatal course.

Using PubMed, we searched the English-language literature published between January 1996 and May 2016. The terms utilized in the search were “intestinal spirochetosis” and “human subjects.” Reference lists of the identified articles were also reviewed to find additional cases. The baseline characteristics, clinical presentations, as well as outcomes of these cases are presented in Table 1.

One crucial observation in our case is that the presence of colonic spirochetosis is found on mucosa adjacent to colonic polyps. This leads to the question of whether there is any association between IS and colonic polyps. Omori
Table 1. Clinical Characteristics of Reported Cases With IS From 1996 to 2016a.

| Year (Reference) | Age (Years)/ Sex | Underlying Condition/ Risk Factor | Clinical Presentation | Endoscopic Findings | Histologic Findings | Treatment | Outcome |
|------------------|------------------|-----------------------------------|-----------------------|---------------------|---------------------|-----------|---------|
| Adult population (18 years of age and older) | | | | | | | |
| 20151 | 39/male | HIV | Watery, nonbloody diarrhea, abdominal distention | Normal | IS | Penicillin (2 weeks) | Initially, responded well but then developed toxic megacolon 2 years later requiring total colectomy |
| 20152 | 63/male | Healthy | Asymptomatic, + FOBT | Intestinal stricture of transverse colon | Chronic infective colitis consistent with IS | Metronidazole (2 weeks) | Not effective, pathology showed mucinous adenocarcinoma associated with IS requiring subtotal colectomy |
| 20140 | 37/male | 15-year history of pancolitis | Diarrhea 2-3 times per day, occasional bloody stools | Mild erosive mucosa in both sigmoid colon and rectum; longitudinal ulcer in transverse colon | IS | Mesalazine + prednisolone | Responsive to mesalazine and prednisolone but difficult to taper prednisolone; improvement after metronidazole |
| 20141 | 61/male | 20-year history of distal ulcerative colitis | Diarrhea 4-5 times per day, occasional bloody stools | Irregularly shaped ulcer in rectum | IS | Metronidazole | No resolution of ulcer with prednisolone; improvement with metronidazole |
| 20142 | 60/male | Hepatitis C cirrhosis | Progressive weight loss | Sessile polyp in ascending colon | IS | Metronidazole | No treatment | No follow-up information |
| 20113 | 34/male | Healthy | Abdominal pain, diarrhea | Not performed; CT showed colocolic intussusception | IS: florid lymphoid hyperplasia in submucosa of terminal ileum and ileocecal valve | Right hemicolecotomy | Resolution |
| 20104 | 60/male | Healthy | Lower abdominal pain, loose stools | Mild erythema of cecum and ascending colon | IS | Metronidazole (400 mg x10 days) | Improvement |
| 20095 | Middle-aged | HIV | Soft stools, occasionally bloody | Small polyp in cecum | Tubular adenoma with IS on luminal epithelium | Amoxicillin | No follow-up information |
| 20086 | 23/male | Healthy | Diarrhea | Patchy edema with areas of erythema and small erosions | Patchy mucosal inflammation and IS | Clarithromycin (800 mg/day x10 days) | Improvement |

(continued)
| Year (Reference) | Age (Years)/Sex | Underlying Condition/ Risk Factor | Clinical Presentation | Endoscopic Findings | Histologic Findings | Treatment | Outcome |
|-----------------|-----------------|----------------------------------|-----------------------|---------------------|---------------------|-----------|---------|
| 2010 <sup>25</sup> | 68/male | Healthy | Persistent diarrhea | Normal | IS | Metronidazole (750 mg/8 h ×10 days) | Resolution |
| 2007 <sup>26</sup> | 26/male | Healthy and those with HIV | Diarrhea, abdominal discomfort, abdominal pain, iron deficiency anemia | All cases with mucosal erosions/hyperemia | Inflammatory cells infiltrate | Metronidazole | Resolution except for one died from pulmonary embolism and one lost to follow-up |
| 2007 <sup>27</sup> | 31/male | Healthy | Abdominal pain, watery diarrhea | Edematous mucosa with erythematous spots in ascending and transverse colon; sigmoid sessile polyp | IS | Metronidazole (1000 mg/day ×7 days) | Resolution |
| 2006 <sup>28</sup> | 11 cases in the series/age 29-87 | Healthy and those with HIV | Diarrhea and abdominal pain | Normal to extensive area of inflammation | Normal mucosa to inflammatory cells infiltrate and mucosal ulceration | Metronidazole (500 mg PO 4 times per day) | Resolution except 2 with persistent diarrhea, and one subject with abdominal pain but without reported outcome. Some cases received benzathine penicillin 2.4 million units IM single dose |
| 2005 <sup>29</sup> | 62/male | HIV | Flatulence, intestinal hemorrhage | Pan-colonic hypotonic diverticular disease | IS | Penicillin G | Resolution |
| 2004 <sup>30</sup> | 41/male | HIV, neuropathy, GERD, depression | Abdominal pain, loose stools, hematochezia | Nonspecific inflammation without colitis | IS | Metronidazole | Resolution |
| 2004 <sup>31</sup> | 57/female | Rectal prolapse | Asymptomatic | Not performed | IS and pneumatosis coli; IS within pneumatic cysts | No information on treatment | No follow-up |
| 2002 <sup>32</sup> | 78/male | Non-Hodgkin lymphoma | Severe bloody diarrhea, abdominal pain | Not performed | IS | No information on treatment | No follow-up |
| 2001 <sup>33</sup> | 50/male | Healthy | Diarrhea, abdominal cramping | Normal | IS | Metronidazole | Resolution |
| 2000 <sup>34</sup> | 57/male | Healthy | Asymptomatic | Two polyps in descending and sigmoid colon | IS | No information on treatment | No follow-up |
| 2000 <sup>35</sup> | 32/male | Healthy | Bloating, lower abdominal pain, watery diarrhea | Normal | IS | Metronidazole (500 mg 4×/day for 10 days) | Improvement |

(continued)
| Year (Reference) | Age (Years)/Sex | Underlying Condition/Risk Factor | Clinical Presentation | Endoscopic Findings | Histologic Findings | Treatment | Outcome |
|-----------------|----------------|----------------------------------|-----------------------|---------------------|---------------------|-----------|---------|
| 1998            | 65/male        | Presumed healthy (HIV test not performed) | Weight loss | Red spot on mucosa of cecum, small polyps in descending colon | IS | No treatment | No follow-up |
| 1996            | 21/female      | Healthy; heterosexual             | Rectal bleeding      | Active proctitis, mild erythema of rectal and colonic mucosa | IS | Hydrocortisone 1% rectal foam | Resolution |
| 28/male         | Healthy; heterosexual | Intermittent nausea and lassitude, weight loss | Patchy erythema in sigmoid colon, intense erythema, mucosal nodularity and friability in distal rectum | IS in rectal biopsy; lymphocytes and plasma cells within lamina propria, no spirochetes on sigmoid biopsy | High fiber diet (unsure etiology of symptoms and thought to have post-infectious IBS) | Improvement |
| 45/male         | Healthy; heterosexual | Colicky pain in left iliac fossa, flatulence, diarrhea | Normal | IS | No treatment (diagnosed with IBS due to uncertain significance of intestinal spirochetosis at that time) | No follow-up |

Pediatric population (0-18 years of age)

| Year (Reference) | Age (Years)/Sex | Underlying Condition/Risk Factor | Clinical Presentation | Endoscopic Findings | Histologic Findings | Treatment | Outcome |
|-----------------|----------------|----------------------------------|-----------------------|---------------------|---------------------|-----------|---------|
| 2012            | 13/male        | Recurrent aphthous stomatitis    | Blood-stained diarrhea, urgency, weight loss | Mucosal edema in sigmoid and rectum | IS | Amoxicillin (2 weeks) | Cessation of rectal bleeding but continuous mucous diarrhea with amoxicillin; resolution with metronidazole |
| 2012            | 14/female      | Healthy                          | Intermittent generalized abdominal pain | Normal | IS | Metronidazole (10 days) | No follow-up |
| 2010            | 11/female      | HSV, psoriasis, upper airway disease | Intermittent abdominal pain, hematochezia | Normal | IS | Metronidazole (250 mg 3x/day) | No improvement after repeated courses of metronidazole and vancomycin, spirochetes found on repeat endoscopy |
| Year (Reference) | Age (Years)/Sex | Underlying Condition/ Risk Factor | Clinical Presentation | Endoscopic Findings | Histologic Findings | Treatment | Outcome |
|-----------------|-----------------|-----------------------------------|----------------------|--------------------|----------------------|-----------|---------|
| 2005<sup>41</sup> | 9/male Healthy   | Blood mixed in stool, diarrhea    | Normal               | IS                 |                      | No therapy | Resolution, spirochetes eradicated |
| 2004<sup>42</sup> | 9/male Healthy   | Abdominal pain, diarrhea, hematochezia | Mild erythema of rectal mucosa | IS                       | Erythromycin (40 mg/kg/day × 10 days) | Resolution |
| 2002<sup>43</sup> | 5/female Enterobiasis | Diarrhea, abdominal pain, occasional blood | Edema in rectum | IS                  | Erythromycin 40 mg/kg/day × 10 days | Rectal bleeding ceased, recurrent abdominal pain; no follow-up |
|                  | 7/male Healthy   | Abdominal pain, diarrhea          | Slight proctitis     | IS                 | Doxycycline (200 mg for 1 day, then 100 mg/day for 8 days) | Persistent abdominal symptoms, eradication of spirochetes |
|                  | 4/female Healthy | Mucus and bloody stools           | Proctitis, juvenile polyps | IS                 | Clarithromycin (50 mg/kg/day × 10 days) | Improvement |
|                  | 10/female Healthy | Blood-stained diarrhea           | Hyperemic membranes on rectoscopy | IS                 | Clarithromycin | Resolution |

(continued)
| Year (Reference) | Age (Years)/Sex | Underlying Condition/Risk Factor | Clinical Presentation | Endoscopic Findings | Histologic Findings | Treatment | Outcome |
|-----------------|----------------|---------------------------------|----------------------|---------------------|---------------------|-----------|---------|
| 13/male         | Healthy        | Abdominal pain, nausea, weight loss, blood-stained stools | Slight inflammation of rectum | IS and HP-positive gastritis | Omeprazole | No improvement |
|                 |                |                                 |                      |                     |                     |           |         |
|                 |                |                                 |                      | Clarithromycin, amoxicillin, omeprazole | Improvement with relapse |
|                 |                |                                 |                      | Clarithromycin, metronidazole, omeprazole | Sustained improvement |
| 8/male          | Healthy        | Abdominal pain                  | Juvenile polyp       | IS                  | Penicillin V        | No improvement |
|                 |                |                                 |                      | Erythromycin (40-50 mg/kg/day × 10 days) | Resolution |
| 15/female       | Healthy        | Abdominal pain, blood-stained stools | Normal               | IS                  | Clarithromycin 500 mg, BID for 2 weeks | Relieved discomfort, bleeding persisted; spirochetes eradicated |
| 14/female       | Healthy        | Abdominal pain                  | Normal colonoscopy, HP-positive gastritis | IS                  | Ranitidine + amoxicillin | No improvement |
|                 |                |                                 |                      | Metronidazole       | No improvement of symptoms, IS eradicated |
| 2001^44         | 12/male        | Healthy                         | Vomiting, diarrhea, weight loss | Normal              | IS with mild focal colitis | Metronidazole and amoxicillin for 1 week | Resolution |
| 12/male         | Healthy        | Abdominal pain                  | Normal               | IS                  | Penicillin V and metronidazole (1 week) | Symptoms persisted |
|                 |                |                                 |                      |                     | Metronidazole (800 mg 3×/day for 1 week) | Improvement |
| 16/female       | Healthy        | Right upper quadrant pain       | Normal               | IS                  | Metronidazole (10 days) | Resolution |
| 9.5/female      | Healthy        | Diarrhea, bright rectal bleeding | Normal              | IS                  | Amoxicillin and metronidazole (10 days) | Resolution |

Abbreviations: IS, intestinal spirochetosis; FOBT, fecal occult blood test; CT, computed tomography; PO, per os; IM, intramuscular; GERD, gastroesophageal reflux disease; IBS, irritable bowel syndrome; HSV, herpes simplex virus; BID, twice a day.

^Cases were limited to nonsyphilitic spirochetosis.
et al conducted a retrospective case-control study to determine the prevalence of IS in sessile serrated adenomas/polyps (SSA/Ps) in 19 SSA/P cases and 172 controls. They found that the rate of IS was significantly higher in the SSA/P cases (52.6%, 10/19 cases) compared to that in controls (8.1%, 14/172), suggesting the potential association between IS and SSA/Ps. The finding from this study is similar to results from an Italian study in which the authors also proposed an association between IS and hyperplastic/adenomatous colonic polyps. Further studies are needed to determine the implications of IS and the presence of colonic polyps.

The histological appearances of IS on biopsy specimens using H&E stain is normal in 6 subjects and nonspecific in the remaining cases (7 with polypoid lesions, 1 with erythematous mucosa, and 1 with questionable lesion). In general, IS cannot be detected with routine colonoscopy. However, a recent study showed the potential of in vivo diagnosis of IS using confocal endomicroscopy with fluorescein sodium as a contrasting agent and Acriflavine hydrochloride, as a topical agent to highlight superficial cell borders and nuclei. Using this technique, the spirochetes become visible as bright ring-like bands within the lumina of the crypts. Of note, in clinical practice, IS is normally found coincidentally in biopsies taken from areas of intestinal mucosa with an irregular appearance. However, in the majority of cases, it is discovered during random biopsies of normal appearing colonic mucosa. The histological appearances of IS on biopsy specimens using H&E stain is a diffuse blue fringe, approximately 3 to 6 μm thick, along the border of the intercryptal epithelial layer (Figures 1 and 2). The presence of spirochetes can be confirmed with Warthin-Starry stain (Figure 3).

The decision on whether to treat IS should be tailored to the clinical presentation, the severity of the patients’ symptoms, and their immune status. IS can either present asymptptomatically, as the organisms responsible are thought to have a commensal relationship with normal gut flora, or symptomatically with associated GI symptoms, as the organisms can also have an invasive, pathogenic form (Table 1). For the former presentation and in a patient such as the one we present, a “wait-and-see” observational approach without any interventions is appropriate. For symptomatic patients, medical treatment with metronidazole (500 mg 4 times a day for 10 days) has been shown to be beneficial.

In conclusion, IS can be found accidentally from colonic biopsies, and, in most cases, there is no correlation with clinical symptoms. The association of IS and the presence of colonic polyps has been reported, though further investigation is required to confirm these anecdotal findings. Most cases can be followed without specific treatment. For symptomatic cases, metronidazole is an effective treatment of choice.

Authors’ Note
Authors Taiwo Ngwa and Jennifer L. Peng share co-first authorship. Informed consent was obtained for this case report.

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