Colonic Spirochetosis in Children and Adults

Ayman Koteish, MD,1 Rajesh Kannangai, MD,2 Susan C. Abraham, MD,3 and Michael Torbenson, MD2

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Abstract

We undertook a retrospective analysis of colonic spirochetosis in 14 cases: females, 3; males, 11; children, 4; adults, 10. Two men had HIV infections. All children and both HIV-infected men had abdominal complaints, diarrhea, or both. Most other adults underwent colonoscopy for polyp screening (n = 4) or follow-up of Crohn disease (n = 1) or had other indications (n = 2) or diarrhea (n = 1). Histologically, spirochetosis was identified in all parts of the colon and was not strongly associated with active inflammation, mucosal injury, or changes of chronicity. Genotype analysis of 13 cases showed that 11 resulted from Brachyspira aalborgi and 2 from Brachyspira pilosicoli infections. Only 2 patients were treated specifically with antibiotics, with complete resolution of abdominal symptoms in 1 patient with follow-up. Follow-up biopsy result were available for 2 patients who did not receive treatment; one showed persistent spirochetosis, and the other was negative. Spirochetosis in this series had a male predominance, was generally caused by B aalborgi, and occurred in 2 distinct clinical settings: children who often have abdominal symptoms and adults who typically are asymptomatic. While treatment information remains limited, treatment can lead to resolution of symptoms in some cases.

Spirochetosis of the colon was first reported in 1967 in a patient with chronic diarrhea.1 Since this first description, however, the clinical significance of spirochetosis has been controversial, as its relationship with human disease has remained unclear. Spirochetosis has been associated with abdominal pain, appendicitis, chronic diarrhea, and rectal bleeding in some cases,2,3 but in the majority of cases, spirochetosis is an incidental finding with no clear clinical correlates.

The anaerobic intestinal spirochetes Brachyspira aalborgi and Brachyspira pilosicoli seem to be responsible for most cases of spirochetosis. B aalborgi was cultured from a case of colonic spirochetosis in 1982,4 and most subsequent cases diagnosed via surgical biopsy specimens were assumed to be B aalborgi based on similar morphologic features. However, a role for B pilosicoli also seemed likely because B pilosicoli colonizes the intestinal tract of many animal species, especially pigs,5 and can be found in approximately 30% of feces from persons in developing countries.6-8 Subsequent studies seemed to confirm a major role for B pilosicoli, as it was the predominant species cultured from stool.9 In contrast, after the initial report associating B aalborgi with spirochetosis, B aalborgi was cultured from only 1 additional patient.10 Thus, the recent results of retrospective studies using polymerase chain reaction (PCR)-based assays on paraffin-embedded tissue samples were of interest when they showed that most cases from several Western countries (predominantly Scandinavia and Australia) were associated with B aalborgi, not the expected B pilosicoli.11-14

We undertook a retrospective analysis of colonic spirochetosis at a tertiary care center to provide additional clinical
Pathologic information on this entity and determine the genotype of the spirochete species in a US cohort using a PCR-based assay.

Materials and Methods

Case Selection

Computer files at the Johns Hopkins Hospital, Baltimore, MD, were reviewed retrospectively to identify all cases diagnosed as spirochetosis from January 1994 to January 2002. All identified cases had paraffin blocks available and were included in the study. The study was conducted with approval from the Johns Hopkins Medical School Institutional Review Board.

DNA Analysis

Ten-micrometer sections of paraffin-embedded tissues were microdissected under ×40 magnification with a 27½-gauge needle, and genomic DNA then was extracted with Proteinase K digestion, 1 mg/mL at 56°C for 16 hours. The primers for PCR were designed to anneal to conserved regions of the 16S ribosomal RNA gene and amplify a nonconserved 241-base-pair region, permitting species identification based on sequence alignment. The genomic DNA sequences of B aalborgi and B pilosicoli used for primer design were GeneBank accession numbers Z22781 and AY155458, respectively. PCR was performed in 50 µL volumes using an 0.8 µmol/L concentration of both 5’ (5’-GCGAACTGGTGAGTAACACG-3’) and 3’ (5’-GAGTCTGGGCCGTATCTCAG-3’) oligonucleotides. The following conditions were used: 94°C for 1 minute, 58°C for 1 minute, and 72°C for 1 minute for 40 cycles. Amplicons were detected by electrophoresis in 1% agarose gels with ethidium bromide and then were purified (QIAquick-spin PCR purification kit, Qiagen, Valencia, CA) and directly sequenced.

Results

Clinical Findings

Fourteen cases were identified, including 3 females and 11 males. Four cases were found in children (median age, 12 years), and 10 cases in adults (median age, 50 years). Only 2 of the men had HIV infections. None of the non-HIV infected adults were clinically immunosuppressed, although 1 had colon carcinoma and another a history of active alcohol abuse.

All children and both HIV-infected men sought care because of complaints of abdominal pain, diarrhea, or both. In contrast, only 1 of the remaining adults had gastrointestinal symptoms, and most underwent colonoscopy for other reasons. Treatment and follow-up information was not available for most cases. Two patients were treated, with resolution of symptoms in case 1; case 10 was lost to further follow-up. Follow-up biopsy specimens also were available for 2 patients who did not receive treatment: one case showed persistent spirochetosis, while the other was negative.

Histologic Findings

A median of 5 colorectal sites were sampled for each patient (range, 1-9). Silver stains obtained at the time of original

<table>
<thead>
<tr>
<th>Case No./ Sex/Age (y)</th>
<th>Symptoms</th>
<th>Other History</th>
<th>Genotype</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/9</td>
<td>Abdominal pain</td>
<td></td>
<td>Brachyspira aalborgi</td>
<td>Benzathine; symptoms resolved</td>
</tr>
<tr>
<td>2/M/12</td>
<td>Abdominal pain</td>
<td></td>
<td>B aalborgi</td>
<td></td>
</tr>
<tr>
<td>3/F/12</td>
<td>Gastrointestinal bleeding;</td>
<td>Abdominal pain</td>
<td>B aalborgi</td>
<td></td>
</tr>
<tr>
<td>4/M/12</td>
<td>Abdominal pain</td>
<td>Unexplained hypergammaglobulinemia</td>
<td>Brachyspira aalborgi</td>
<td></td>
</tr>
<tr>
<td>5/M/34</td>
<td>Chronic diarrhea, 1 y</td>
<td>HIV; CD4 count, 150/µL (150 × 10^6/L)</td>
<td>Brachyspira pilosicoli</td>
<td>Diarrhea treated symptomatically; symptoms resolved</td>
</tr>
<tr>
<td>6/M/36</td>
<td>Abdominal pain</td>
<td>HIV; CD4 count, 383/µL (383 × 10^6/L); colonic lymphoma in 1997</td>
<td>B aalborgi</td>
<td></td>
</tr>
<tr>
<td>7/M/40</td>
<td>Follow-up of known Crohn disease</td>
<td></td>
<td>Did not amplify</td>
<td></td>
</tr>
<tr>
<td>8/M/47</td>
<td>Polyp screening</td>
<td></td>
<td>B aalborgi</td>
<td></td>
</tr>
<tr>
<td>9/M/48</td>
<td>Back pain</td>
<td></td>
<td>B aalborgi</td>
<td></td>
</tr>
<tr>
<td>10/M/50</td>
<td>Colon mass</td>
<td>Stage T3 cecal carcinoma</td>
<td>B pilosicoli</td>
<td>Flagyl; no follow-up</td>
</tr>
<tr>
<td>11/F/52</td>
<td>Polyp screening</td>
<td></td>
<td>B aalborgi</td>
<td></td>
</tr>
<tr>
<td>12/M/57</td>
<td>Polyp screening</td>
<td>Active alcohol abuse</td>
<td>B aalborgi</td>
<td></td>
</tr>
<tr>
<td>13/M/66</td>
<td>Diarrhea</td>
<td></td>
<td>B aalborgi</td>
<td></td>
</tr>
<tr>
<td>14/F/65</td>
<td>Polyp screening</td>
<td></td>
<td>B aalborgi</td>
<td></td>
</tr>
</tbody>
</table>
diagnosis were available for 6 cases. Histologically, spirochetosis was characterized by a uniform 2- to 3-µm-thick layer of basophilic organisms adherent to the surface epithelium [Image 1]. Spirochetosis was identified in all parts of the colon [Table 2] and typically involved all tissue fragments and all specimen locations. However, rectal biopsy specimens occasionally were negative. Likewise, the terminal ileum was biopsied in 2 patients, and both had negative results for spirochetosis. While 4 of 14 cases had cryptitis, the active inflammation was focal and mild and not clearly associated with the spirochetes. In 1 case with tubular adenomas and 1 with cecal carcinoma, the spirochetes were present only on the nonadenomatous epithelium. In contrast, spirochetes were present on the adenomatous epithelium in another case with tubular adenomas. One additional case had hyperplastic polyps with adherent spirochetes.

### DNA Analysis

Spirochete DNA was amplifiable in 13 of 14 cases. Two cases were classified as *B pilosicoli* based on sequence comparison, while the remaining 11 cases were classified as *B aalborgi*. No clear association was evident between species and clinical or pathologic findings.

### Discussion

The prevalence of spirochetosis varies from 2.5% to 16% in Western countries and is significantly higher in the developing world and in homosexual men, with prevalence as high as 50%, based on stool culture and biopsy findings. Spirochetosis is identified histologically as a densely packed layer of organisms attached to the luminal surface of colonic epithelium. Most cases can be identified readily on H&E-stained sections, although silver stains also can be used to highlight the organisms and can detect cases not evident on routine H&E stains.

Our study confirms the male predominance previously reported, as well as the ability of spirochetes to colonize adenomatous epithelium. In addition, our results highlight the diffuse colonic distribution of the organisms. Similarly to the findings of Surawicz et al., our results indicate rectal sparing in several cases, although others have reported a higher frequency of rectal involvement. Furthermore, the results of the present study extend our understanding of the species distribution, highlighting the predominance of *B aalborgi* as the major causative agent of spirochetosis in the United States. Perhaps ironically, the species associated with spirochetosis has come full circle, from an assumption that most cases are *B aalborgi* based on report of an initial culture result, to associating most
cases with *B. pilosicoli* based on culture of biopsy specimens,\(^9\) back to *B. aalborgi* based on genotypic analysis. In this regard, *B. aalborgi* is reportedly much more difficult to culture than *B. pilosicoli*.\(^{10,20}\)

We observed no significant clinical or histologic differences between the 2 species. However, the number of *B. pilosicoli* cases in this study was small, and our results do not exclude the potential for real differences in the clinicopathologic import of these 2 species, in particular given multiple lines of evidence from other sources. For example, in poultry, *B. pilosicoli* causes colonic disease, while *B. aalborgi* does not.\(^{20}\) *B. pilosicoli* also is a recognized cause of diarrhea in farm animals.\(^3\) It is interesting to note that *B. pilosicoli* also has been cultured from the blood of several critically ill humans.\(^{21}\)

This study is limited partially because of its retrospective nature, in which reliance on previously diagnosed specimens is likely to miss a proportion of cases, in particular because silver stains were not performed routinely.\(^{17,18}\) However, this limitation does not detract substantially from our findings because our goal was not to establish the overall prevalence. Also, our observations are limited by the lack of clinical follow-up for most cases, reflecting the prevailing opinion that the diagnosis of spirochetosis is clinically irrelevant. In fact, much of the literature has not supported treatment for colonic spirochetosis. For example, in a study of 15 patients by Nielsen et al.,\(^{22}\) treatment effectively eliminated the organisms but did not lead to clinical improvement. However, our findings of clinical improvement in 1 case after treatment adds to a growing number of case reports and case series associating treatment with resolution of symptoms in some cases,\(^12,23,24\) especially children.\(^{12,24}\) Thus, while many cases might not require therapy, especially those that are incidental findings, treatment in symptomatic cases might be effective in selected people. Both specific and nonspecific treatments (for diarrhea) alleviated symptoms in the cases in the present study. Both specific and nonspecific treatments (for diarrhea) alleviated symptoms in the cases in the present study. Thus, while many cases might not require therapy, especially those that are incidental findings, treatment in symptomatic cases might be effective in selected people. Both specific and nonspecific treatments (for diarrhea) alleviated symptoms in the cases in the present study.

While all 4 children in the present study had clinical symptoms, it is unclear whether pediatric spirochetosis is associated specifically with clinical symptoms, as essentially all pediatric colonoscopy studies are performed in the setting of abdominal complaints, while a large proportion of adult colonoscopies are performed as screening procedures. Thus, the association noted in the present study between symptoms and children also is likely to be encountered in the practice of diagnostic surgical pathology but might be due to “referral bias.” Specific epidemiologic studies would be required to further clarify this issue.

Spirochetosis in the present series had a male predominance and a diffuse colonic distribution and predominantly was due to *B. aalborgi*. While treatment information remains limited, treatment leads to resolution of symptoms in some cases.

From the Departments of \(^1\) Medicine and \(^2\) Pathology, the Johns Hopkins University School of Medicine, Baltimore, MD; and \(^3\) Pathology, Mayo Clinic, Rochester, MN.

Address reprint requests to Dr Torbenson: Johns Hopkins University School of Medicine, Room B314, 418 N Bond St, Baltimore, MD 21231.

**References**


