Immunoproliferative Small Intestinal Disease Associated with Campylobacter jejuni

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BACKGROUND
Immunoproliferative small intestinal disease (also known as alpha chain disease) is a form of lymphoma that arises in small intestinal mucosa-associated lymphoid tissue (MALT) and is associated with the expression of a monotypic truncated immunoglobulin α heavy chain without an associated light chain. Early-stage disease responds to antibiotics, suggesting a bacterial origin. We attempted to identify a causative agent.

METHODS
We performed polymerase chain reaction (PCR), DNA sequencing, fluorescence in situ hybridization, and immunohistochemical studies on intestinal-biopsy specimens from a series of patients with immunoproliferative small intestinal disease.

RESULTS
Analysis of frozen intestinal tissue obtained from an index patient with immunoproliferative small intestinal disease who had a dramatic response to antibiotics revealed the presence of Campylobacter jejuni. A follow-up retrospective analysis of archival intestinal-biopsy specimens disclosed campylobacter species in four of six additional patients with immunoproliferative small intestinal disease.

CONCLUSIONS
These results indicate that campylobacter and immunoproliferative small intestinal disease are associated and that C. jejuni should be added to the growing list of human pathogens responsible for immunoproliferative states.
Immunoproliferative small intestinal disease, also known as alpha chain disease, is a mucosa-associated lymphoid-tissue (MALT) lymphoma characterized by infiltration of the bowel wall with a plasma-cell population that secretes a monotypic, truncated immunoglobulin $\alpha$ heavy chain lacking an associated light chain.\textsuperscript{1-3} Lymphoid infiltration leads to malabsorption and protein-losing enteropathy. The disease can cause a spectrum of histopathological changes, ranging from seemingly benign lymphoid infiltration to malignant diffuse large-B-cell lymphoma.

Since its initial description,\textsuperscript{1} immunoproliferative small intestinal disease has largely been reported in the Mediterranean basin, the Middle East, the Far East, and Africa. In the Middle East, the most common site of extranodal lymphoma is the gastrointestinal tract: immunoproliferative small intestinal disease accounts for approximately one third of gastrointestinal lymphomas.\textsuperscript{4} The restricted geographic distribution of the disease has led to the hypothesis that environmental factors may have a pathogenic role.

Remarkably, early-stage immunoproliferative small intestinal disease typically responds to antibiotics, suggesting that it may be triggered by bacterial infection.\textsuperscript{5,6} However, previous attempts to identify a causative agent with the use of standard culture methods have failed.\textsuperscript{5-7} Immunoproliferative small intestinal disease shares histopathological features with gastric MALT lymphoma associated with \textit{Helicobacter pylori} infection,\textsuperscript{2,3} and a case report suggested that \textit{H. pylori} may be a potential causative agent.\textsuperscript{8} However, this proposal was not supported by the results of a subsequent retrospective study of 21 patients with immunoproliferative small intestinal disease.\textsuperscript{9} We used a molecular strategy similar to that used to identify the causative agents of bacillary angiomatosis (\textit{Bartonella henselae})\textsuperscript{10} and Whipple’s disease (\textit{Tropheryma whipplei}),\textsuperscript{11} in order to determine whether immunoproliferative small intestinal disease could be linked to specific bacterial species.

### Case Reports

**Index Patient**

A 45-year-old woman from Cameroon was hospitalized for a 12-month-long illness characterized by chronic diarrhea and wasting. Histologic examination of endoscopic biopsy specimens from her duodenum and proximal jejunum revealed massive infiltration of the lamina propria, with a dimorphic population of plasma cells located in the superficial mucosa and centrocyte-like lymphocytes proliferating deeper in the mucosa, mostly around crypts (Fig. 1A, 1B, 1C, and 1D). Infiltration of the lamina propria was less pronounced in antral-biopsy specimens.

Immunohistochemical studies of these biopsy specimens showed that the plasma cells were negative for CD20, whereas the centrocyte-like lymphocytes were positive for CD20 (Fig. 1E and 1F). The cytoplasm of both plasma cells and centrocyte-like lymphocytes showed intense staining for immunoglobulin $\alpha$ heavy chain, with no detectable expression of light chains or surface immunoglobulin in these cells (Fig. 1G, 1H, 1I, and 1J). Centrocyte-like lymphocytes were responsible for the lymphoepithelial lesions that are typical of MALT lymphomas (Fig. 1D, 1E, and 1F).

Staining of gastric- and intestinal-biopsy specimens with Giemsa and silver stains and serological assays were all negative for \textit{H. pylori}. Tissue and stool cultures were negative for salmonella, yersinia, shigella, and campylobacter. An enzyme-linked immunosorbent assay and Western blot assays of serum were positive for \textit{Campylobacter jejuni} (data not shown).

Analysis of blood samples disclosed 7560 lymphocytes per cubic millimeter, with the vast majority having morphologic features of lymphoplasmacytes. Analysis with the use of a fluorescence-activated cell sorter established that 82 percent of peripheral-blood lymphocytes were CD19+, CD20−, CD38+, CD138−B cells. Immunocytochemical studies of the sorted cells revealed high levels of cytoplasmic $\alpha$ heavy chains without detectable light chains or surface immunoglobulin. Bone marrow biopsy disclosed extensive infiltration with lymphoplasmacytes. Evidence of the clonality of this population was provided by Southern blot analysis of peripheral-blood lymphocyte DNA, which showed discrete rearrangements of the genes for the immunoglobulin heavy-chain and $\kappa$ light-chain loci (data not shown). The serum IgA level was increased to 10.9 g per liter (normal range, 0.76 to 3.90), whereas IgG and IgM levels were decreased (to 5.81 and 0.22 g per liter, respectively). Immunoelectrophoresis of serum, aspirated jejunal luminal contents, and urine from the patient showed a prominent arc of $\alpha$ heavy chain precipitin (Fig. 2A). Western blot analysis of serum revealed the presence of a truncated monotypic $\alpha$ heavy chain.

On the basis of these clinical, histopathological-
Immunoproliferative small intestinal disease associated with *Campylobacter jejuni*

The immunologic findings, a diagnosis of immunoproliferative small intestinal disease was made. Given the gastric extension of the disease, the phenotypic similarities between the disease and *H. pylori*-associated gastric MALT lymphoma, and a previous case report of regression of immunoproliferative small intestinal disease in a patient after the eradication of *H. pylori* infection, triple antimicrobial therapy was initiated (1 g of amoxicillin twice daily, 500 mg of metronidazole twice daily, and 500 mg of clarithromycin twice daily) in combination with a proton-pump inhibitor (20 mg...
of omeprazole twice daily). The diarrhea subsided within a week, the leukemic component disappeared within 10 weeks (Fig. 2B), and there was progressive resolution of the paraproteinemias (Fig. 2A and 2C) and intestinal lymphoplasmacytic infiltrate (data not shown). Treatment was stopped after five months because the patient was asymptomatic, the leukemic and serum paraprotein abnormalities had disappeared, and lymphoplasmacytic infiltration of the intestine was barely detectable in follow-up endoscopic biopsy specimens from the jejunum. One year after the diagnosis had been established, the results of clinical examination and laboratory studies were normal.

**SIX ADDITIONAL PATIENTS**

Immunoproliferative small intestinal disease is rare. Frozen intestinal samples from other patients with untreated immunoproliferative small intestinal disease were not available to us. Therefore, we retrieved archival paraffin-embedded excisional jejunal-biopsy specimens obtained at the time of laparoscopy 8 to 27 years earlier from six additional patients in whom immunoproliferative small intestinal disease had been diagnosed at a single hospital according to established histopathological and immunologic criteria.1,5,6,12

**METHODS**

**TISSUE SAMPLES**

We analyzed tissue specimens from six sources. Frozen and formalin-fixed, paraffin-embedded specimens were obtained from gastric, duodenal, and jejunal biopsies performed endoscopically in the index patient one day before and eight days after the initiation of antimicrobial therapy. Archival jejunal-biopsy specimens, which had been fixed in Bouin’s fluid and embedded in paraffin, were obtained from six additional patients who had received a diagnosis of immunoproliferative small intestinal disease. Formalin-fixed, paraffin-embedded jejunal-biopsy specimens were obtained endoscopically from a patient infected with human immunodeficiency virus (HIV) who had acute C. jejuni enteritis. Formalin-fixed, paraffin-embedded stomach samples were obtained from a patient with H. pylori gastritis. Frozen duodenal-biopsy specimens were obtained from 10 patients with chronic diarrhea of unknown origin (as defined by negative cultures for known enteropathogens). Formalin-fixed, paraffin-embedded duodenal-biopsy specimens were obtained from 10 patients who were being evaluated for anemia.
Bacterial Strains and Antibodies

We obtained C. jejuni reference strain CIP 70.2, H. pylori reference strain CIP 103995, and Escherichia coli reference strain CIP 7624 from the Institut Pasteur collection. Two mouse monoclonal antibodies were used for immunohistochemical studies: IgG2b NCL-C-JEJUNI (Novocastra), which recognizes a flagellar immunologic determinant common to C. jejuni and H. pylori, and IgM CPI/HIG10 (Biotrend), which is directed against a 43-kD, non–rDNA amplicon. Primers specific for belonging to the same species.

Polymerase Chain Reaction

Universal primers PB (5’TAAACATGCAAGTCGAGAAG3’) and DG74 (5’AGGAGGTATCACAACCGCAAG3’) were used to amplify bacterial 16S ribosomal DNA (rDNA). Established primers directed at C. jejuni (CCCJ609F 5’AATCTAATGGCTTGACCC3’) and CCJ1442R, 5’GAATAGATTATGATTCTCCCG3’) were used to generate an 852-bp 16S rDNA amplicon. Primers specific for H. pylori (5’flaA909/1025R (5’ACATTCTCATCTCTGAAAACTTCG3’) and 3’flaB2132/2153F (5’AATCTAATGGCTTAACC3’) — were designed to amplify a 401-bp fragment from the flaB gene. Two pairs of primers — 72/96F (5’ACAGGAAGACTTAACCTCCCG3’) and 455/477F (5’GAGCAGCTTGCTTCTTTGC3’) and 455/477R (5’GAGCAGCTTGCTTCTTTGC3’) were used to generate amplicons from the 16S rDNA genes of most phyla in the bacteria superkingdom. Cycling conditions for all polymerase chain reactions (PCRs) were as follows: 7 minutes at 95°C, 35 cycles of denaturation for 30 seconds at 95°C, annealing for 20 seconds at 55°C, and 2 minutes of extension at 72°C.

The specificity of the PCR assays was initially established by means of epifluorescence microscopy. All tissue samples studied were collected as part of routine care. The National Ethics Committee of France requires neither approval by institutional review boards nor informed consent for this type of research to be conducted.

Identification of C. jejuni DNA

DNA was extracted from frozen jejunal- and gastric-biopsy specimens from the index patient. Initial PCR assays of these DNAs were performed with the use of well-established universal primers known to generate amplicons from the 16S rDNA genes of most phyla in the bacteria superkingdom. Amplicons were produced in assays in which the DNA template was extracted from frozen jejunal samples harvested one day before treatment was initiated. In contrast, no amplicons were produced with the use of DNA prepared from material harvested eight days after therapy was started.

The nucleotide sequences of 8 of 12 cloned amplicons generated from the pretreatment preparation of jejunal DNA were 99.6 percent identical to 16S rDNA amplified from DNA of the C. jejuni reference strain. Computer searches of GenBank with the use of the BLAST program (http://www.ncbi.nlm.nih.gov/blast/) and the 16S rDNA data base (http://greengenes.lnl.gov/16S/) showed that the four remaining sequences were from abiotrophia, neisseria, lactococcus, and haemophilus. Members of these four genera are part of the normal oropharyngeal microbiota in humans.

Follow-up PCR studies with the use of primers
directed at *C. jejuni* 16S rDNA yielded amplicons of the expected size from antral, jejunal, and fecal DNAs prepared from material obtained before the initiation of antimicrobial therapy (Table 1). Assays of the same DNAs with the use of primers directed at *H. pylori* 16S rDNA or primers that recognize 16S rDNA from members of the Enterobacteriaceae family were all negative (Table 1). In addition, the PCR assay was negative with the use of primers directed at *C. jejuni* and DNA prepared from jejunal- and gastric-biopsy specimens obtained from the index patient eight days after the initiation of antibiotic treatment and from DNA extracted from frozen proximal intestinal-biopsy specimens from 10 control patients with diarrhea of unknown origin (i.e., not associated with cultivatable enteropathogens) (Table 1).

The results of sequencing 16S rDNA amplicons obtained with universal bacterial 16S rDNA primers and the *C. jejuni*–directed PCR assays of endoscopic biopsy specimens from the index patient and controls provided initial evidence of an association between this campylobacter species and immunoproliferative small intestinal disease.

### DETECTION OF CAMPYLOBACTER JEJUNI IN SMALL INTESTINAL TISSUE

To provide further evidence of the presence of *C. jejuni* in the index patient, we developed a fluorescence in situ hybridization (FISH) assay using an oligonucleotide probe directed at *C. jejuni* 16S rRNA. The sensitivity and specificity of the FISH assay were established as follows: staining with the Cy3-labeled oligonucleotide was readily detectable in a smear of cultured *C. jejuni* (Fig. 3A), intraluminal *C. jejuni* were detected in a jejunal-biopsy specimen from an HIV-infected patient with culture-documented *C. jejuni* enteritis (Table 2), and no signal was noted in gastric-biopsy specimens from a patient with *H. pylori* gastritis (Table 2 and Fig. 3B).

Subsequent FISH analysis with the *C. jejuni* probe revealed the organism in sections of jejunal- and stomach-biopsy specimens obtained from the index patient before the initiation of antimicrobial therapy. The organism was most prominent in the lamina propria, often in the vicinity of capillaries (Fig. 3D, 3E, 3F, and 3G), a finding consistent with the observed tropism of this organism in an animal model of infection.

A control *H. pylori*–specific FISH probe (Fig. 3C) did not produce a signal (Table 2), a finding that is consistent with the negative Giemsa and silver staining and the PCR results (Table 1).

Finally, immunohistochemical methods were used to confirm the presence of *C. jejuni* in the index patient. Two well-characterized, commercially available preparations of monoclonal antibody were used: one recognizes a flagellar immunologic determinant shared by *C. jejuni* and *H. pylori* (NCL-C-JEJUNI), and another is specific for an *H. pylori* epitope (CP1/IIG10). Control experiments that used sections of jejunum from an HIV-infected patient

<table>
<thead>
<tr>
<th>Specimen</th>
<th>PCR Results</th>
<th>Bacterial 16S rDNA Primers</th>
<th>Campylobacter Primers</th>
<th>Helicobacter Primers</th>
<th>Enterobacteriaceae Primers</th>
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<tbody>
<tr>
<td><strong>Controls</strong></td>
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<td></td>
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<tr>
<td>Reference strain</td>
<td></td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
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<tr>
<td><em>Campylobacter jejuni</em></td>
<td></td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
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<tr>
<td><em>Helicobacter pylori</em></td>
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<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
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<tr>
<td><em>Escherichia coli</em></td>
<td></td>
<td>+</td>
<td>-</td>
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<td>+</td>
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<tr>
<td>Duodenum from 10 controls with diarrhea of unknown origin</td>
<td>ND</td>
<td>-</td>
<td>-</td>
<td>ND</td>
<td>ND</td>
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<tr>
<td><strong>Index patient</strong></td>
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<tr>
<td>Stomach and jejunum before antimicrobial treatment</td>
<td>+</td>
<td>+</td>
<td>-</td>
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<tr>
<td>Stomach and jejunum on day 8 of antimicrobial treatment</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Stool before antimicrobial treatment</td>
<td>ND</td>
<td>+</td>
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<td>ND</td>
<td>ND</td>
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with culture-positive acute *C. jejuni* enteritis disclosed a prominent signal with NCL-C-JEJUNI and no signal with the *H. pylori*–specific monoclonal antibody (Fig. 3H and Table 2). Assays of sections prepared from jejunal- and gastric-biopsy specimens obtained before the index patient started antimicrobial therapy disclosed readily detectable signals in the lamina propria with NCL-C-JEJUNI but not with the *H. pylori*–specific antibody (Fig. 3I and Table 2). Together, these results support the conclusion that *C. jejuni* was present at the sites of gut abnormalities in the index patient and rule out the possibility of concomitant *H. pylori* infection.

**ANALYSIS OF ARCHIVAL TISSUES**

We were unable to recover amplifiable DNA from any of the archival samples from six patients with immunoproliferative small intestinal disease — that is, the PCRs for the human β-actin gene as well as for *C. jejuni* 16S rDNA were all negative. This failure most likely reflects the method of fixation together with the age of the samples. However, because ma-
Terrestrial fixed with Bouin’s fluid is known to be suitable for FISH,22,23 these biopsy specimens were analyzed with the use of three probes: a universal bacterial 16S rDNA oligonucleotide (positive control for the presence of bacteria), the probe directed at C. jejuni, and the specific probe for H. pylori. The bacterial FISH probe was positive in samples from five of the six patients (Patients 1 through 5 in Table 2). The C. jejuni–directed probe produced a positive signal in three of the six biopsy specimens from these patients (Patients 1, 2, and 3 in Table 2).

In addition, the two monoclonal antibodies were used to confirm that C. jejuni immunologic determinants were present in all three FISH-positive samples (Fig. 3J, 3K, and 3L), as well as in one FISH-negative sample (Fig. 3M and Table 2). No signal was detected with these monoclonal antibodies in the 10 control duodenal samples. Moreover, the H. pylori–specific FISH probe and monoclonal antibody did not detect this species in any of the archival jejunal-biopsy specimens from the six patients with immunoproliferative small intestinal disease (Table 2).

**DISCUSSION**

Previous attempts to link a bacterial species to immunoproliferative small intestinal disease with the use of culture-based approaches have failed.5-7 We used a molecular approach to establish a link between immunoproliferative small intestinal disease and C. jejuni infection in an index patient. This association is based on three observations. First, a PCR assay with the use of universal bacterial 16S rDNA primers and DNA templates prepared from biopsy specimens of the proximal small intestine obtained before the initiation of antimicrobial treatment in the index patient yielded amplicons encompassing the entire 16S rDNA gene that were identified as C. jejuni by sequencing. No other enteropathogen was detected by PCR. Second, FISH and immunohistochemical analyses showed C. jejuni in diseased biopsy specimens of the small intestine. Third, the eradication of C. jejuni with antimicrobial therapy was associated with rapid remission of the immunoproliferative small intestinal disease (i.e., resolution of both diarrhea and lymphoplasmacytic infiltration of the intestine and the disappearance of the leukemic component and the monotypic truncated immunoglobulin α heavy chain in serum).

Further support for an association between C. jejuni and immunoproliferative small intestinal disease is provided by four additional observations. Our retrospective study of a monocentric series of archival biopsy specimens yielded four additional cases of campylobacter-associated disease among six patients with immunoproliferative small intestinal disease. Puri et al. described a patient in whom

### Table 2. Results of Fluorescence in Situ Hybridization and Immunohistochemical Assays of Biopsy Specimens from the Index Patient, Six Other Patients with Immunoproliferative Small Intestinal Disease, and Controls.*

<table>
<thead>
<tr>
<th>Group and Diagnosis</th>
<th>FISH Results</th>
<th>Immunohistochemical Results</th>
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<tbody>
<tr>
<td></td>
<td>Bacterial 16S rDNA Probe</td>
<td>Campylobacter jejuni Probe</td>
</tr>
<tr>
<td>Controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C. jejuni enteritis</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>H. pylori gastritis</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Normal duodenum from 10 patients</td>
<td>ND</td>
<td>–</td>
</tr>
<tr>
<td>Patients†</td>
<td></td>
<td></td>
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<tr>
<td>Index patient, IPSID stage A</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Patient 1, IPSID stage A</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Patient 2, IPSID stage A</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Patient 3, IPSID stage B</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Patient 4, IPSID stage A</td>
<td>+</td>
<td>–</td>
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<tr>
<td>Patient 5, IPSID stage A</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Patient 6, IPSID stage B</td>
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<td>–</td>
</tr>
</tbody>
</table>

* Plus signs indicate positive results, and minus signs negative results. FISH denotes fluorescence in situ hybridization, rDNA ribosomal DNA, ND not done, and IPSID immunoproliferative small intestinal disease.
† The IPSID stage was defined according to the criteria of Galian et al.12 Archival biopsy specimens were analyzed from Patients 1 through 6.
culture-positive C. jejuni diarrhea developed two to three days after the initiation of antineoplastic chemotherapy for immunoproliferative small intestinal disease—a sequence of events that suggests that chemotherapy exacerbated a preexisting C. jejuni infection. Immunoproliferative small intestinal disease occurs almost exclusively in developing countries where C. jejuni infection is hyperendemic, often chronic, and asymptomatic. Finally, antimicrobial regimens reported to be effective in treating the disease are also active against C. jejuni infection.

Our FISH and immunohistochemical studies detected C. jejuni in biopsy specimens of the small intestine and stomach from the index patient but not in biopsy specimens of the intestinal lumen. This result is in agreement with the negative stool cultures and may account for the failure of previous studies to link immunoproliferative small intestinal disease with this organism with the use of standard culture-based studies. Moreover, C. jejuni is microaerophilic and may exist in a viable but noncultivable state.

Our results do not allow us to conclude that C. jejuni is the only bacterial species associated with immunoproliferative small intestinal disease. Nonetheless, C. jejuni should be added to the growing list of human pathogens responsible for chronic infection that are also implicated in antigen-driven immunoproliferative states. The association of C. jejuni with immunoproliferative small intestinal disease is reminiscent of the link between H. pylori infection and gastric MALT lymphoma. However, in contrast to a previous case report and in agreement with a more recent study based on a series of 21 cases, we found no evidence that H. pylori is involved in the development of immunoproliferative small intestinal disease.

C. jejuni has been shown to persist in Peyer’s patches and mesenteric lymph nodes in a gnotobiotic mouse model and to secrete a toxic, CdtB, that mediates DNA damage. These properties could be critical in the pathogenesis of immunoproliferative small intestinal disease. C. jejuni can elicit a strong IgA mucosal response, and chronic infection with C. jejuni leads to sustained stimulation of the mucosal immune system. This persistent stimulation could eventually lead to the expansion of IgA-secreting clones and to the selection of a clone that secretes heavy chains that has eluded antibody-antigen Fc-dependent down-regulation. Eradication of the antigenic source with antimicrobial treatment may stop the proliferation of this lymphoplasmacytic population.

As is true for H. pylori-associated gastric MALT lymphomas, a better understanding of the role of C. jejuni in the pathogenesis of immunoproliferative small intestinal disease will require further analysis of mechanisms and the development of suitable animal models. The identification of an association between C. jejuni and immunoproliferative small intestinal disease may lead to improvements in the diagnosis, management, and prevention of this disease, at least in a subgroup of patients.

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REFERENCES