Two for one: Coexisting ulcerative colitis and Crohn’s disease

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Three cases of coexisting ulcerative colitis and Crohn’s disease are presented. In the first case, the patient had a long-standing history of ulcerative proctitis before developing Crohn’s colitis. In the two remaining cases, the patients presented initially with Crohn’s disease of the ileum and, subsequent to resection, developed ulcerative colitis. Well-documented cases of patients diagnosed with both ulcerative colitis and Crohn’s disease are rare. The literature on such cases is reviewed, and the controversy over whether ulcerative colitis and Crohn’s disease are two distinct diseases is explored.

Key Words: Antineutrophil cytoplasmic autoantibodies; anti-Saccharomyces cerevisiae mannan antibodies; Crohn’s disease; Ulcerative colitis

Crohn’s disease (CD) and ulcerative colitis (UC) are chronic inflammatory bowel diseases (IBDs) of unknown etiologies. The epidemiology, genetics and immunology of both diseases overlap, which can make them difficult to distinguish. Originally, UC and CD were distinguished on the basis of anatomical location. With the widespread acceptance of Crohn’s colitis as an entity distinct from ulcerative colitis in the 1950s (1), differentiating the two diseases in cases in which inflammation was confined to the colon became an issue.

Because the cause of these diseases is unknown, these two forms of colitis are distinguished based on a combination of clinical, radiological, endoscopic and pathological characteristics. For many years, the Lennard-Jones classification of IBD provided guidelines that facilitated the separation of UC and CD (2). The recent development of serological testing for perinuclear antineutrophil cytoplasmic autoantibodies (pANCA) and anti-Saccharomyces cerevisiae mannan antibodies (ASCA) has refined our ability to distinguish between the two diseases (3). At a histological level, a further refinement has been proposed (4,5).

Several pathognomonic characteristics of CD allow a definitive diagnosis to be made in many, but not all, patients. These characteristics include perianal disease, small bowel
involvement, fistulas, aphthoid erosions, segmental disease, transmural inflammation and granulomas, among others. UC lacks such precise diagnostic features, leaving physicians to rely on certain typical features coupled with an absence of any of the CD-specific identifiers (1). These features include bloody diarrhea and endoscopic findings of rectal disease, including granularity, friability and circumferential inflammation in continuity (in the absence of prior treatment). Histologically, confinement of the process to the mucosa, diffuse mucosal involvement with architectural distortion, and inflammation including basal plasmacytosis and goblet cell depletion, strongly supporting the diagnosis of UC.

Tanaka’s group (4) has suggested that a combination of crypt atrophy and severe chronic inflammation points strongly to UC.

Although UC and CD are presented here as two distinct entities, familial and genetic studies indicate that they are, in fact, interrelated and perhaps even two manifestations of a single basic disease process. A MEDLINE literature review revealed rare instances of well-documented UC and CD diagnosed in the same patient. We present three patients in whom both diagnoses were made. The first patient initially presented with UC and subsequently developed coexisting Crohn’s colitis. In the other two patients, surgical resection of ileal CD was followed by the development of UC.

**CASE PRESENTATIONS**

**Case 1**

A 24-year-old man was referred in 1981 for a second opinion with a two-year history of intractable ulcerative proctitis involving the distal 6 to 12 cm of the rectum. The chief complaint, and only symptom, was rectal bleeding with a normal bowel habit. When he was first seen, he was taking prednisone 20 mg daily, nightly betamethasone enemas (Betnesol, Roberts Pharmaceutical Canada, Inc) and sulfasalazine tablets (Salazopyrin, Pharmacia & Upjohn Inc, Canada), 1 to 2 g daily. There was no history of diarrhea, anorexia, weight loss, fever or chills. Past medical history was unremarkable. Family history was significant for two aunts who had an unknown form of ‘colitis’. The patient had a Cushingoid appearance, but the physical examination was otherwise normal. Rigid sigmoidoscopy revealed mild but typical UC, limited to the distal 5 cm of the rectum. A barium enema, including views of the terminal ileum, was normal. A distal rectal biopsy taken at that time demonstrated diffuse mucosal changes, including architectural abnormalities (mainly crypt atrophy) and severe chronic inflammation, with basal plasmacytosis and goblet cell depletion, strongly supporting the diagnosis of UC (Figure 1). Hydrocortisone suppositories (Cortiment Forte, Hoechst Marion Roussel Canada Inc, Canada), 40 mg at bedtime, were substituted for the betamethasone enemas. Sulfasalazine 2 g daily was continued, and the prednisone was tapered and stopped. There was no change in the bleeding. He was then treated with one sulfasalazine suppository (Salazopyrin, Pharmacia Inc, Sweden) twice daily. Within a few days, the bleeding subsided.

Over the next eight years, he was generally well with occasional episodes of bleeding that resolved with sulfasalazine suppositories. No other treatment was given. Throughout this period, his hemoglobin concentration, white blood cell count, platelet count and erythrocyte sedimentation rate remained normal. In 1989, during a typical exacerbation with daily rectal bleeding, a flexible sigmoidoscopy to 30 cm revealed moderate ulcerative proctitis in the distal rectum only. He was given 5-aminosalicylate (5-ASA) suppositories (Salofalk, Axcan Pharma Inc, Canada) with no response. He was switched back to the sulfasalazine enemas. Sulfasalazine 2 g daily was continued, and the prednisone was tapered and stopped. There was no change in the bleeding. He was then treated with one sulfasalazine suppository (Salazopyrin, Pharmacia Inc, Sweden) twice daily. Within a few days, the bleeding subsided.

In 1990, 11 years after his initial presentation, he developed painful red nodules on his legs; these were diagnosed as erythema nodosum and treated with a course of prednisone. In August 1991, he presented with three months of nonbloody diarrhea, oral aphthous ulcers, weight loss and abdominal cramps that were generally relieved by bowel movements. There was no urgency or tenesmus. He also experienced an exacerbation of his erythema nodosum.

**Figure 1** A biopsy specimen from the rectum of case 1 taken in 1981 shows prominent crypt atrophy, severe chronic inflammation (top) and basal plasmacytosis (bottom) consistent with ulcerative colitis. Hematoxylin and eosin stain, original magnification ×100 (top) and ×600 (bottom)
Ulceration in the caput of the cecum was seen on colonoscopy; the ileal orifice was obscured by ulceration and edema, and could not be entered. There were serpiginous ulcerations in the region of the hepatic and splenic flexures, and a long segment of continuous disease extending down the descending colon and into the sigmoid. The distal sigmoid and proximal rectum were spared, but there was a distal proctitis, identical with that seen repeatedly since 1981. Crohn’s colitis was diagnosed on the basis of the endoscopic findings – segmental disease, skip areas and linear ulcers – and the clinical picture. Symptoms did not improve with oral 5-ASA or metronidazole (Flagyl, Rhône-Poulenc Rorer Canada Inc) but subsided with prednisone 40 mg daily.

In December 1991, he presented with left mid-abdominal pain radiating to the back and a sore leg with a limp. A positive left psoas sign was found. A computed tomography scan of the abdomen and pelvis illustrated a thickened descending colon wall, a possible fistula into the retroperitoneum and a 1.5 cm abscess in the left psoas muscle, with a focal enlargement of the left psoas. Rectal and sigmoid thicknesses were normal. He was treated with metronidazole, and the prednisone dose was tapered. He improved somewhat, and ciprofloxacin (Cipro, Bayer Inc, Canada) was added, but there was no further improvement.

In March 1992, he underwent a left hemicolectomy and drainage of the abscess. Examination of the resection specimen showed typical features of Crohn’s disease, with a thickened bowel wall, segmental crypt distortion and full-thickness inflammation of the bowel wall, including scattered lymphoid aggregates (Figure 2).

The postoperative course was unremarkable. Five months after surgery, he presented with intermittent rectal bleeding typical of his previous ulcerative proctitis. This was controlled with 5-ASA suppositories. Nine months after surgery, the patient presented with pain and swelling of his left ankle, abdominal pain, decreased appetite, mild weight loss and sores in the mouth. Colonoscopy revealed gross nodularity, mild stricturing and ulceration in two segments of the proximal colon. Although there were no granulomas, both the endoscopic findings and the biopsies were in keeping with recurrent Crohn’s colitis. Imaging studies continued to show normal rectal and distal sigmoid wall thicknesses. The patient subsequently sought alternative treatments and was lost to follow-up. At the authors’ request, he agreed to provide a blood sample for pANCA and ASCA testing (Prometheus, Inc, USA) (Table 1). At the time of testing, his ulcerative proctitis was clinically quiescent; however, his Crohn’s colitis was moderately active.

**Case 2**

A 36-year-old man was referred for ongoing management of previously diagnosed IBD. In 1981, at age 21 years, he presented with abdominal cramps and diarrhea; Crohn’s ileitis was diagnosed. He was treated medically until 1986, when he was hospitalized with acute right lower quadrant pain that was unresponsive to steroids and signs of peritonitis. Laparotomy revealed free pus and an abscess in the pelvis, approximately 30 cm of ileitis, and a grossly normal cecum and appendix. An ileocecal resection was performed, with a side-to-side ileocolic anastomosis. Gross pathological examination revealed typical features of CD, with thickening of the ileum and cecum, and marked narrowing of the ileal lumen. Microscopic features

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**Table 1**

<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Reference range</th>
</tr>
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<tr>
<td>ANCA</td>
<td>&lt;12.1</td>
<td>14.7</td>
<td>&lt;12.1</td>
<td>&lt;12.1 EU/mL</td>
</tr>
<tr>
<td>ASCA IgA</td>
<td>&lt;12.5</td>
<td>19.1</td>
<td>125.3</td>
<td>&lt;20.0 EU/mL</td>
</tr>
<tr>
<td>ASCA IgG</td>
<td>13.5</td>
<td>44.0</td>
<td>116.4</td>
<td>&lt;40 EU/mL</td>
</tr>
</tbody>
</table>

All tests were performed by Prometheus, Inc (USA). Prometheus’ interpretations of the test results are as follows: “Does not rule out ulcerative colitis (UC) or Crohn’s disease (CD): 157% of patients with this test result combination have CD and 23% have UC; 196% of patients with this test result combination have CD and 11% have UC. Ig Immunoglobulin; EU Elisa units

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included segmental crypt distortion, transmural granulomatous inflammation with fissure formation, marked submucosal fibrosis, prominent lymphoid aggregates and perforation with abscess formation.

He remained well for seven years and in 1993 presented with bloody diarrhea, false urge and tenesmus. Flexible sigmoidoscopy done elsewhere was said to show typical features of UC to 40 cm above the anal verge, and normal mucosa beyond. Symptoms were controlled with 5-ASA enemas (Salofalk) and oral 5-ASA (Asacol, Proctor & Gamble Pharmaceuticals, Canada). He remained on maintenance therapy with oral 5-ASA 1.2 g twice daily, and 5-ASA suppositories as needed for intermittent urgency.

In 1996, when he was first seen at the authors’ institution, the physical examination was normal, except for the surgical scar. Colonoscopy into the neoterminal ileum was normal down to 25 cm; from that point to the anal verge, the typical changes of chronic UC (circumferential, continuous inflammation, with erythema, granularity, friability and complete absence of the vascular pattern) were present. Random biopsies taken from the right colon, transverse colon and left colon at 35 cm were all normal. Biopsies from the distal 25 cm were consistent with chronic UC, showing diffuse crypt atrophy and distortion, and severe chronic inflammation with basal plasmacytosis and mucus depletion (Figure 3). During four-and-a-half years of follow-up, the patient remained well, except for one minor flare of his colitis in 1999, which responded promptly to rectal 5-ASA. Tests for pANCA and ASCA (Table 1) were performed in August 2000; at that time, the patient was in remission.

Case 3
A 28-year-old woman was referred in 1997 for ongoing management of ulcerative proctitis. She had been healthy until 1993, when she was diagnosed with Crohn’s ileitis at another institution. She was treated with prednisone; sev-

DISCUSSION
The patient described in case 1 initially presented with distal UC (ulcerative proctitis). After a decade of exacerbations and remissions, he developed a more proximal colitis typical of CD. While no granulomas were ever seen histologically, the clinical and pathological features (see case presentation) of CD were apparent. The rectal disease remained constant as typical UC (see case presentation), and imaging studies continued to show a normal rectal and distal sigmoid wall thickness. This case represents the extremely rare occurrence of UC and CD simultaneously coexisting in the same patient.

Cases 2 and 3 developed apparent UC following resection of ileal CD. This pattern of sequential coexistence of CD and UC, while still very uncommon, has been recognized more often.

A MEDLINE literature review contains only six well-documented cases of coexisting CD and UC (6-11). In three cases, Crohn’s ileitis was the initial diagnosis (6-8), and UC developed following resection at varying time...
intervals. In the three remaining reports, UC was the initial diagnosis, and when CD was subsequently diagnosed, both diseases were thought to be present concurrently (9, 10, 11). Table 2 summarizes the cases found in the literature and those described in this paper.

In case 1, UC appeared first and CD developed a decade later. Following surgery for the CD, the ulcerative proctitis continued to follow the previous clinical pattern, and the Crohn's colitis recurred nine months after the operation. In cases 2 and 3, the intervals between resection of the CD and subsequent appearance of the UC were seven years and six months, respectively.

A case has been described in which a patient with UC treated with a prolonged course of steroids 'converted' to CD (12). The purpose of that report was to suggest that the two diseases are just parts of a single disease spectrum. We believe that the clinical and pathological evidence in our cases supports the existence of two distinct diseases.

Clinical and pathological features are still the mainstay of both the diagnosis and differentiation of UC and CD, and while tests for pANCA and ASCA are thought to be helpful, the overall utility of these tests in clinical practice has yet to be determined (13-15). Results of the pANCA and ASCA tests in our cases are summarized in Table 1. In case 1, the results were negative when the patient's recurrent CD was clinically active. In case 2, it is difficult to attach any definite significance to the borderline values. Vasiliauskas et al (16) showed that 100% of CD patients with a UC-like clinical phenotype are pANCA positive. Case 3 in the present report had the 'typical' serological pattern of CD. She was negative for pANCA, yet she clearly developed a UC-like clinical phenotype. Because 30% to 40% of UC patients are pANCA negative, and 100% of CD patients with UC-like features are pANCA positive, one interpretation is that this patient has both UC and CD.

The controversy over whether UC and CD are one or two separate conditions has been long debated (17-19). Eyer et al (9), using the prevalence rates of UC and CD, calculated that between 15 and 60 patients in the United States have both diseases. This creates a large discrepancy between the number of reported cases and the estimate. Given this situation, previous reporters have argued that this can be explained if the two diseases are distinct entities, because the chance that a patient has two uncommon and distinct diseases at the same time is low (8, 10). However, others have argued that this result may be explained if the two diseases are different manifestations of a single disease process and that the clinical presentation and evidence is the result of the individual patient's response to the underlying disease process (7). The situation may be further confounded by the possibility that patients with UC may be genetically predisposed to developing CD and vice versa. Lastly, this may simply be a situation of under-reporting.

The evidence that genetics plays a role in IBD is overwhelming. This evidence comes from studies of families, monozygotic versus dizygotic twins, ethnic groups and genetic markers. First-degree relatives of a proband have a 10- to 15-fold increased risk of developing IBD compared with the general population (20). With the characterization of the human genome, it is expected that significant advances will be achieved soon (21).

Reports of coexisting UC and CD suggest that it is a very rare occurrence. Reaching such a conclusion is difficult because both diagnoses rely on similar clinical, radiological, endoscopic and pathological criteria (2, 22). Testing for pANCA and ASCA, and more detailed histological analysis (4, 5) allow additional levels of refinement. We have provided evidence for these two separate diagnoses in each of these three patients by combining the Lennard-Jones classification of IBD (2), recent specific histological criteria

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age at first diagnosis (years)</th>
<th>First diagnosis</th>
<th>Interval to second diagnosis (years)</th>
<th>Second diagnosis</th>
<th>Author (reference)</th>
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<tbody>
<tr>
<td>Female</td>
<td>38</td>
<td>Ileocecal CD</td>
<td>10</td>
<td>Pancolonic UC</td>
<td>Voitk et al (6)</td>
</tr>
<tr>
<td>Male</td>
<td>33</td>
<td>Terminal ileal CD</td>
<td>4</td>
<td>UC (ileotransverse anastomosis to rectum)</td>
<td>McDermott et al (7)</td>
</tr>
<tr>
<td>Female</td>
<td>30</td>
<td>Ileocolonic CD</td>
<td>13 months</td>
<td>UC (recto-sigmoid)</td>
<td>White et al (8)</td>
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<tr>
<td>Male</td>
<td>20</td>
<td>Terminal ileal CD</td>
<td>8</td>
<td>Terminal ileal CD</td>
<td>Eyer et al (9)</td>
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<tr>
<td>Male</td>
<td>30</td>
<td>'Granular' proctitis</td>
<td>46 years</td>
<td>Terminal ileal CD</td>
<td>Jones et al (10)</td>
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<tr>
<td>Male</td>
<td>3</td>
<td>UC (rectum-sigmoid)</td>
<td>16 years</td>
<td>Jejunal CD</td>
<td>Mendelsohn and Korelitz (11)</td>
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<tr>
<td>Male</td>
<td>22</td>
<td>Ulcerative proctitis</td>
<td>11 years</td>
<td>Crohn's colitis</td>
<td>Chen et al*</td>
</tr>
<tr>
<td>Male</td>
<td>21</td>
<td>Crohn's ileitis</td>
<td>12 years</td>
<td>UC (sigmoid-rectum)</td>
<td>Chen et al*</td>
</tr>
<tr>
<td>Female</td>
<td>24</td>
<td>Crohn's ileitis</td>
<td>6 months</td>
<td>UC (sigmoid-rectum)</td>
<td>Chen et al*</td>
</tr>
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*Patients described in the present article
Chen et al

(4,5) and serological testing (3). The paucity of reported cases of co-existing disease compared with the calculations of Eyer et al (9) highlights the controversy over whether UC and CD are the same disease or two separate entities. Further genetic studies will hopefully give us more clues and allow us soon to determine the definitive relationship between CD and UC.

REFERENCES
