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Case Report

Sprue-Like Intestinal Disease Following Colectomy for Inflammatory Bowel Disease

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ABSTRACT

After an initial index case of post-colectomy sprue-like intestinal disease or enteritis from our hospital in a patient with ulcerative colitis in 2012, a retrospective examination of over 3000 patient records with either ulcerative colitis or Crohn's disease was done to determine if this post-colectomy sprue-like disease could be defined retrospectively in earlier patients. After review of records from a intestinal diseases clinic from 1979 to 2012, three more cases of post-colectomy sprue-like intestinal disease were discovered complicating the clinical course of inflammatory bowel disease. All of these patients were defined prior to 1990. All were females and had emigrated to Canada. Clinical onset of severe sprue-like intestinal disease developed within 2 years of surgery in all patients. One patient had already completed a pelvic pouch reconstruction procedure elsewhere before onset of the disease. Two patients had colectomies for ulcerative colitis, but after pathological review, the diagnosis was changed to Crohn's colitis. All had small intestinal biopsies characteristic of untreated celiac disease and repeated biopsies failed to demonstrate a response to a gluten-free diet. Treatment in these early patients usually consisted of added systemic and topical steroids as well as azathioprine. Studies are needed to elucidate the immunopathologic development of this unusual entity following colectomy in patients with inflammatory bowel disease.

INTRODUCTION

Sprue-like intestinal disease (or unclassified sprue) may be associated with diarrhea, sometimes severe, and weight loss accompanied by inflammatory pathological features including crypt hyperplastic villus atrophy or a moderate to severe "flat" mucosal lesion, typically reported in the small intestinal mucosa in patients with untreated celiac disease [1,2]. In contrast to celiac disease, however, the small intestinal mucosa in sprue-like intestinal disease fails to improve with a gluten-free diet [3]. Occasionally, serum antibodies to tissue transglutaminase may also be present, potentially leading to diagnostic confusion. An increasingly long list of sprue-like intestinal disorders are now appreciated including tropical sprue, a variety of infections and different immunodeficiency syndromes [3]. All of these share some histopathological features of untreated celiac disease, but do not improve with a gluten-free diet. Several medications also may cause similar pathological features in the small intestinal mucosa, particularly non-steroidal anti-inflammatory drugs [4]. Recently, others like olmesartan, a commonly prescribed anti-hypertensive drug, have also been recognized to cause a profound sprue-like enteropathy [5].

In recent years, an unusual form of enteropathy, sometimes even fatal, has been recognized after colectomy for severe ulcerative colitis [6-11]. The pattern seems unique in some patients with severe symptoms, a form of small intestinal enteritis with marked architectural disturbance extending distally for variable distances from the most proximal small intestine following surgical treatment for colitis (i.e., specifically, total colectomy). Importantly, *Clostridium difficile* enteritis after total abdominal colectomy has also been described in this setting and so there is a need to consider other causes [12]. Subsequent to discovery of our own initial case in 2012 [11], a retrospective review was conducted by the author using over 3000 personal patient records from an intestinal diseases clinic seen over a period of 33 years from 1979 to 2012. This was done to further explore historically this distinctive clinical entity among patients with a prior colectomy antedating formal recognition of this "new" entity in the literature and the advent of new and emerging biological and immunosuppressive agents for treatment. Three added cases were identified during this record review and are described here. Likely, although seemingly rare, this entity is more common in clinical practice than currently appreciated.

CASE STUDIES

The index case for this series from our hospital was previously reported and is summarized below as Case 1 [11]. Another 3 cases were detected in 2019 during a formal retrospective review of over 3000 chart records during 33 years dated 1979 to 2012 from a focused intestinal diseases clinic.

Case 1

In 2009, a 43-yr old Caucasian female was initially evaluated in Washington State for abdominal pain and diarrhea. Endoscopic studies and biopsies of the upper and lower gastrointestinal tracts showed changes of extensive ulcerative colitis in the colon. Serologic studies for anti-tissue transglutaminase (tTg), anti-neutrophil cytoplasmic (ANCA) and anti-Saccharomyces cervesiae (ASCA), anti-CMV (cytomegalovirus) and anti-HIV (human immunodeficiency virus) antibodies were negative. Fecal studies for bacterial (including *Clostridium difficile*) and parasitic agents were negative. Initial drug treatment included mesalamine, prednisone and azathioprine, and later, biologic agents, infliximab and certolizumab. In 2011, because of continued and refractory symptoms, she had a colectomy with ileostomy with a plan for later pouch reconstructive surgery. During early 2012, approximately 3 months after surgery, however, severe epigastric cramping pain and weight loss developed. In our hospital, computerized tomography, upper endoscopy and push enteroscopy with biopsies revealed gastritis and a diffuse enteritis. Biopsies of duodenum and jejunum were reported to show moderate to severe active inflammatory changes. No mucosal granulomas were seen. There was no history of alcohol, salicylate, non-steroidal anti-inflammatory drug or other drug use (including olmesartan). Further treatment with steroids and parenteral nutrition did not alter symptoms and further enteroscopy and biopsies of the duodenum showed a severe extensive inflammatory process. After a course of oral tacrolimus, 6 mg daily, her symptoms improved with resolution of pain permitting oral intake and hospital discharge as earlier reported with this pharmaceutical agent [10,13,14]. Later push enteroscopy in another hospital showed improvement and, after 6 months, she remained clinically improved.

Case 2

A 48-yr old female was referred from a rural community hospital with a history of surgical treatment for colitis. In 1969, she had emigrated to Canada from India (Punjab). In 1981, she developed diarrhea, rectal bleeding and weight loss. A limited endoscopic examination revealed changes of a non-specific and diffuse colitis thought to be typical of ulcerative colitis. In 1988 and 1995, colonoscopies and multiple biopsies during symptomatic flares with diarrhea and rectal bleeding also showed inflammatory features indicative of severe and extensive pancolitis. Despite treatment with aminosalicylates and repeated courses of steroids, she remained symptomatic. In 1996, proctocolectomy and ileostomy were done at another hospital. The resected specimen showed features typical of Crohn's colitis with fissuring and transmural inflammatory change along with skip lesions. Following the colectomy, she continued to have increased ileostomy output up to 10-15 times daily. Exam was otherwise normal, except for surgical scars and an ileostomy. Ileostomy fluid studies for enteric pathogens, including parasites and *Clostridium difficile* toxin, were negative. Upper gastrointestinal endoscopy, gastric and multiple duodenal biopsies were normal. A barium study of

her small bowel was normal. Ileoscopy and biopsy were normal.

Because of continued symptoms and weight loss, she was referred for review in 1997. Her upper endoscopic study was repeated and diffuse severe duodenal hyperemia without ulceration was present. Biopsies showed moderate to severe architectural disturbance with "flattening" of duodenal mucosa and increased intra-epithelial lymphocytes but no granulomas. Anti-gliadin antibodies were negative. She was treated with a gluten-free diet, but this had no symptomatic effect on her ongoing ileostomy diarrhea. She was treated with added enteric coated 5-aminosalicylate and added budesonide 3 mgm bid with partial resolution of her diarrhea and weight gain. In 1998 and 2003, additional biopsies of her duodenum showed no improvement, despite an ongoing gluten-free diet and the same pharmacologic treatment.

Case 3

A 32-yr old female was first seen in 1993. She had emigrated from South Africa in 1988. In 1979, rectal bleeding and diarrhea led to a diagnosis of ulcerative colitis treated with steroids. In 1987, a total colectomy and pelvic pouch reconstruction was done in Capetown followed by closure of a loop ileostomy. Her immediate post-operative clinical course was complicated by a left leg deep venous thrombosis necessitating treatment with anti-coagulants. In September 1989, now in Canada, she suddenly developed abdominal cramping pain with liquid stool every 2-3 hours, day and night. Fecal studies for enteric organisms, including *Clostridium difficile*, and parasites were negative. Endoscopic evaluation in another hospital confirmed pouchitis with focal inflammatory changes. No other studies were done and a course of metronidazole was administered with symptomatic improvement. In June 1990, she presented to a surgical service in our hospital with an acute abdomen and emergency laparotomy revealed shallow ulceration (0.6 cm) with perforation in the distal jejunum. In addition, severe, but non-specific, inflammatory changes were evident thought then to be consistent with "ischemic" injury in the small intestine. The distal resection margin was measured to be approximately 80 cm proximal to the pouch and the proximal resection margin 152 cm from the ligament of Trietz. A proximal small bowel enterostomy was created. There was no evidence of neoplasia or vasculitis in the resected specimen. Her subsequent clinical course in hospital was complicated by systemic candidiasis, a right-sided pulmonary embolic event and renal failure attributed to amphotericin neprotoxicity. After 3 months of hospitalization, she was discharged on oral coumadin, taken over 6 months. Over the next year, she required repeated outpatient visits for dehydration associated with high output stomal drainage. This was treated with courses of intravenous fluid replacement. In May 1991, her enterostomy was finally closed with the small bowel mucosa in the anastomotic region reported to show non-specific inflammatory changes with villous blunting. She continued to have 4 to 5 loose bowel motions per day, controlled with codiene. By March 1993, severe anemia developed (i.e., hemoglobin of 80 g/L with iron deficiency) but there was no overt clinical evidence of blood loss. She was transfused to a hemoglobin of 144 g/L and pouchoscopy now showed scattered focal erosions limited to the pouch. Biopsies showed only non-specific inflammatory changes. However, her upper endoscopy showed marked and extensive duodenal hyperemia and biopsies showed focally severe inflammatory change in the duodenum with marked architectural change including severely "flattened" mucosa. No granulomas were seen. She was empirically treated with omeprazole and a gluten-free diet. Over the next year, she remained stable with a hemoglobin between 120 and 130 g/L. Repeat small bowel biopsies showed no improvement. Pouchoscopy and biopsies showed changes of pouchitis that was treated with intermittent metronidazole. In 1999, she moved to another city and no follow-up information could be obtained.

Case 4

A 26-yr old Indo-Canadian female was born in the Fijian Islands, emigrated to Canada in 1982 and later developed intermittent abdominal pain, diarrhea and weight loss. In 1989, after a severe episode, ulcerative colitis was diagnosed and treated by a suburban hospital gastroenterologist with steroids. In July 1991, she presented with an acute abdomen from a perforated cecal ulcer. Urgent sub-total colectomy with creation of an end ileostomy was done. Initial pathological evaluation reported chronic active and extensive colitis, but with multiple discrete ulcers. Following discharge, she suffered from depression and chronic abdominal pain and high ileostomy output, treated in part with anti-depressants and

narcotics. In November 1991, small bowel biopsies were done showing severe crypt hyperplastic villous atrophy with intra-epithelial lymphocytosis, consistent with untreated celiac disease. In spite of a gluten-free diet, pain symptoms persisted including diarrhea. In 1993, her rectum was resected, a cholecystectomy was done for cholelithiasis and repeat duodenal biopsies showed no change. Over the next decade, she was independently reviewed by at least 4 different gastroenterologists from 3 hospitals. Limited compliance to the gluten-free diet was considered. Chronic abdominal pain requiring chronic narcotics persisted. Diarrhea continued and repeated small bowel biopsies showed severe villous atrophy. Immunohistochemical stains and gene re-arrangement studies to explore for a monoclonal lymphocyte population were negative. Studies for luminal microbial pathogens including *Clostridium difficile* and parasites were negative. Anti-gliadin antibodies and IgA antibody to tissue transglutaminase were positive suggesting the possibility of associated celiac disease. In addition to her gluten-free diet, however, treatment courses of added prednisone and azathioprine were not effective.

In 2003, she was first reviewed in our clinic along with her pathological specimens. She was now chronically requiring narcotics every 3 to 4 hours and anti-depressants along with a gluten-free diet despite her history of ongoing and refractory symptoms. She was believed to have celiac disease as reflected in a case series report by others, however, a response to a gluten-free diet was not observed [15]. Review of small bowel biopsies confirmed features of severe and total villous atrophy while her colectomy specimen confirmed cecal perforation and multifocal ulcers. However, numerous granulomas were now identified in the resected colon, but not her small bowel. Blood studies were normal except for a hemoglobin of 101 g per L (normal, 115 to 160) with a low MCV of 56 fL (normal, 80 to 100), consistent with thalassemia trait. CT scans of the abdomen and pelvis were normal with no adenopathy. Endoscopic studies of the upper gastrointestinal tract and ileum showed a diffusely abnormal duodenum with a thickened nodular mucosal appearance and biopsies showed a severely abnormal diffuse lesion with villous atrophy. Ileal biopsies were normal. A course of added budesonide was provided to supplement the gluten-free diet. Repeated biopsies of her duodenum remained unchanged. Subsequently, until 2011, pain management remained the main focus her treatment. Repeated duodenal biopsies continued to show changes of sprue-like intestinal disease, now for over 20 years and remained unchanged.

DISCUSSION

Ulcerative colitis and Crohn's disease are two largely distinctive patterns of idiopathic inflammatory bowel disease, usually differentiated by their clinical and pathological features. Over the past 20 years, however, an unusual form of diffuse enteritis has occasionally been described, particularly in the most proximal small bowel following colectomy in patients with severe colitis. This "new" entity, especially if clinically severe and sometimes extensively present through the entire small intestine, is unusual, and, occasionally, the disorder has even been fatal [9,13]. This syndrome consists of severe abdominal pain, diarrhea and weight loss post-colectomy. A diffuse inflammatory process results that extends distally within the small intestine. Pathologic evaluation of the small bowel, particularly in the duodenum, reveals a severe but non-specific inflammatory process, including severe alterations in villous structure. As with other sprue-like intestinal disorders, there has been no response to a gluten-free diet.

Table 1: Cases of Post-colectomy Sprue-like Intestinal Disease.

	Patient 1	Patient 2	Patient 3	Patient 4
Origin (country)	USA	India	South Africa	Fiji
Sex	Female	Female	Female	Female
IBD Diagnosis	UC	CD	UC	CD
Pouch reconstruction completed	No	No	Yes	No
Age in Canada (years)	44	21	33	26
Age dx of colitis (years)	41	33	24	33
Age of colectomy (years)	44	48	31	35
Age dx of sprue-like disease (years)	45	49	34	36
Positive celiac serology (> 20 IU)	No	No	No	Yes

Reports indicate that this disorder follows colectomy in patients with either ulcerative colitis [6-11,13] or Crohn's disease [16], but not after colectomy for other colonic inflammatory or non-

inflammatory disorders. In present series, shown in Table 1, 3 added patients with a diffuse post-colectomy enteritis were detected with severe non-specific inflammatory duodenal mucosal changes extending into the distal small intestine. In these 3 patients, there was no histological response to a gluten-free diet. In addition, use of antibiotics, anti-inflammatory agents, corticosteroids, immunosuppressive agents, including azathioprine, were, at best, only partially clinically effective. In this retrospective series of post-colectomy patients from a single practice seen over 3 decades, the possibility of other diagnoses (i.e., Crohn's disease) were also considered and further pouch reconstructive surgery was not done. In 1 patient here, construction of a pelvic pouch preceded onset of recurrent and severe symptoms and ischemia with perforation was thought to be present leading to an emergency partial mid-small bowel resection. Later, diffuse disease was detected proximally in the duodenum indicating a different and far more extensive small bowel mucosal inflammatory process. Except for the initial case in this series, all presented at a time when use of drug treatments for inflammatory bowel disease, including some more modern immunosuppressive agents and biological agents, was limited. Interestingly, all of these patients were female and the clinical onset developed within 2 years of their colectomy, similar to observations in another centre [7]. Recently, 1 report on long-term treatment suggested that the enteritis may be more responsive with immunosuppressive agents after colectomy than before this surgical procedure [8]. While this series could not confirm that impression here, further studies related to the long term natural history of this entity are needed.

The final case in the series was initially reported elsewhere as celiac disease associated with ulcerative colitis. Subsequent pathological review of her resected colon, however, showed deep colonic ulceration with multiple granulomas in the colon more characteristic of Crohn's colitis. She also had a positive anti-tTG assay with biopsies typical of untreated celiac disease. For some, this might be sufficient for diagnosis of celiac disease. However, the pitfall of an incorrect diagnosis of celiac disease has long been recognized in patients with duodenal Crohn's disease [17]. And, repeated biopsies over more than 2 decades failed to show improvement with a gluten-free diet and so the typical gluten-dependent nature of celiac disease could not be confirmed.

Previous studies have also shown that abnormalities in biopsies should improve within 1-2 years, if celiac disease is present [18]. This did not occur here. Small intestinal involvement with Crohn's disease was also considered but numerous duodenal biopsies over the course of her disease did not reveal granulomas and the clinical behaviour of her disease did not lead to either stricture formation or penetrating disease complications over 2 decades. Previous studies have indicated that this would be highly unusual in patient with extensive Crohn's disease of the small bowel [17]. A separate, presumably, immune-mediated, small bowel disorder seemed to evident. Further immunological studies are needed to elucidate the nature of this intriguing immune-mediated post-colectomy sprue-like intestinal inflammatory process.

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