

# Sprue-Like Intestinal Disease Following Crohn's Disease

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**Abstract** A 48-yr old female was reviewed for ongoing symptoms of diarrhea and weight loss following a total colectomy for colitis. Pathological review of the surgical specimens revealed changes of Crohn's colitis. Subsequent investigations after the colectomy revealed endoscopic evidence of duodenal mucosal scalloping, negative celiac serological studies and moderate to severe changes in villous architecture including crypt hyperplasia with complete villus atrophy and increased numbers of intra-epithelial lymphocytes. No changes were present in the distal small intestine. Over the course of almost a decade, measures directed towards symptom relief were effective. However, in spite of a strict gluten-free diet, repeated endoscopic biopsies of the proximal small bowel remained severely abnormal with persistent crypt hyperplastic villus atrophy. "Sprue-like" intestinal disease occurs in Crohn's disease limited to the duodenum, mimicking biopsy changes of celiac disease and may represent a post-colectomy complication in Crohn's disease.

**Keywords:** *celiac disease, Sprue-like intestinal disease, Crohn's disease, gluten-free diet*

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## 1. Introduction

Crohn's disease of the duodenum was first recognized over 40 years ago, also termed regional enteritis of the duodenum [1,2]. Initially, the disorder was believed to occur with other sites of involvement in the intestinal tract. Now, however, it is appreciated that Crohn's disease may sometimes be recognized in isolation in the duodenum, but this is exceedingly rare, in 1 large study occurring in 7 of 877 patients, or less than 1% [3]. Changes described in the duodenum in Crohn's disease have included severe ulceration and fibrotic stricturing disease, frequently resistant to most forms of pharmacological treatment [4]. In recent years, however, endoscopic and histopathologic features in the duodenum along with the clinical course and natural history of the disease have become better described in both children and adults [5,6].

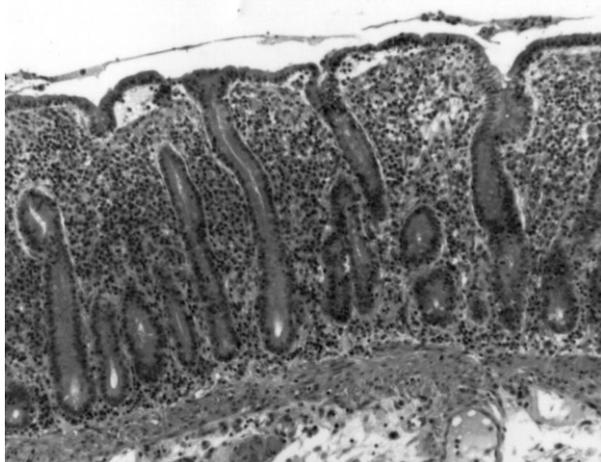
A histopathological "footprint" of duodenal Crohn's disease has included detection of granulomas in endoscopic biopsies. Unfortunately, these are often detected in less than 15%, even after examination of multiple serially-sectioned biopsies. In contrast, a spectrum of other mucosal biopsy changes have been detailed in the absence of granulomas in Crohn's disease, some being prominent but not well appreciated, including partial or total villus atrophy with hyperplastic crypts [7] and intra-epithelial lymphocytosis [8,9]. It is well recognized that biopsy changes typical of untreated celiac disease may be detected in other sprue-like intestinal disorders [10], such as tropical sprue, some infections, HIV disease and use of some medications (eg., olmesartan) [11]. The present report documents late development of sprue-like intestinal disease localized only

in the duodenum and following prior surgical treatment for ileo-colonic Crohn's disease. Despite endoscopic and histopathologic changes in the duodenum typical of untreated celiac disease, a prolonged gluten-free diet had no effect in normalizing the endoscopic or histopathologic abnormalities in the small bowel mucosa.

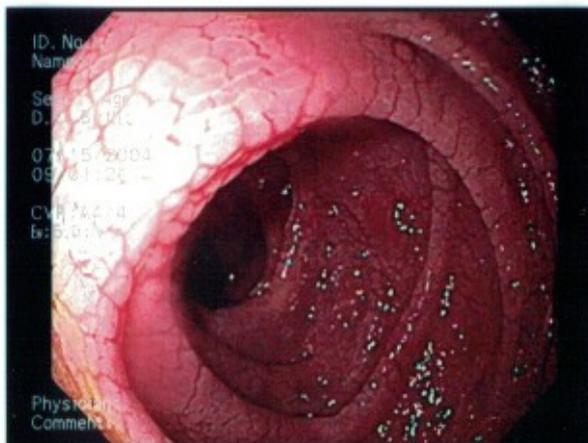
## 2. Case Description

A 48-yr old female had been referred from a rural community hospital for review. She emigrated to Canada from India (Punjab region) in 1969. In 1981, she developed diarrhea, rectal bleeding and weight loss. A limited sigmoidoscopic exam by her physician revealed changes of diffuse colitis and she improved with steroids. In 1988 and 1995, colonoscopies and multiple biopsies in another center during symptomatic flares with diarrhea and rectal bleeding were reported to show inflammatory features thought to be consistent with ulcerative colitis. Despite treatment with 5-aminosalicylates and repeated courses of steroids, she remained symptomatic. In 1996, a proctocolectomy was done with a long-term plan to perform restorative pouch surgery. However, the resected specimen showed features attributed to Crohn's colitis with deep fissuring and transmural inflammatory change along with skip lesions discouraging further surgical treatment. Following colectomy, she continued to have increased ileostomy output and frequency up to 10-15 per day. Exam was otherwise normal, except for surgical scars and an ileostomy. Ileostomy fluid studies for enteric pathogens, including parasite and *Clostridium difficile* were negative. Anti-gliadin antibodies and ANCA serological studies were negative [12]. Blood studies, including iron

studies and serum proteins were normal. Upper gastrointestinal endoscopy, gastric and duodenal biopsies were normal. A barium study of her small bowel was normal. Ileoscopy to 60cm and multiple ileum biopsies were also normal. Some diarrhea relief was achieved with oral codeine.



**Figure 1.** Distal duodenal endoscopic biopsy showing moderate-to-severe “flat” mucosal lesion with reduced to absent villi, hyperplastic crypts with an increased mitotic index and increased intra-epithelial lymphocytes



**Figure 2.** Endoscopic view of duodenal mucosa showing hyperaemia and prominent “scalloped” mucosal folds. Re-biopsy showed histologic features similar to [Figure 1](#)

Because of continued symptoms and weight loss, she was referred to our hospital for further review in 1997. Her upper endoscopic study was repeated and now showed diffuse duodenal hyperemia without ulceration. In addition, “mucosal scalloping”, often noted during endoscopy in celiac disease, but also reported in Crohn’s disease [13], was seen. Biopsies taken from multiple duodenal sites showed moderate to severe “flattening” of mucosa and increased intra-epithelial lymphocytes, but no granulomas ([Figure 1](#)). She was treated with a gluten-free diet, but her ileostomy diarrhea persisted. She was empirically treated with enteric coated 5-aminosalicylate preparation (Pentasa) and, later, added budesonide (3 mg bid). Further resolution of her diarrhea and weight gain resulted. In 1998, additional biopsies of her duodenum showed no improvement, despite a continued gluten-free diet and her medication. She was reviewed periodically over the next 6 years. Additional duodenal biopsies during

this time were unchanged. Immunohistochemical and gene rearrangement studies to define an abnormal subset of monoclonal lymphocytes were negative [14,15]. Her medications were reduced and eventually discontinued. She was having 4-6 semi-fluid ileostomy motions per day and her weight was stable on a gluten-free diet alone. She required occasional codeine tablets. In 2004, upper gastrointestinal endoscopy was repeated. Scalloping of the mucosa was still present ([Figure 2](#)) and multiple duodenal biopsies showed no change with moderate to severe “flattening”, increased intra-epithelial lymphocytes but no granulomas.

### 3. Discussion

Celiac disease is an immune-mediated small intestinal mucosal disease that responds to a gluten-free diet. Most often, it is believed that failure to show a dietary response to gluten restriction may be suggestive of poor compliance to a gluten-free diet, a ubiquitous or unrecognized dietary source of gluten, an associated disorder (eg., microscopic colitis), a complication (eg., lymphoma) or another disorder [10]. In recent years, different medications have been increasingly recognized as a cause of sprue-like intestinal disease (eg., olmesartan) [11]. In sprue-like intestinal disease [10], another form of treatment may be needed, or removal of the offending agent or medication, not a gluten-free diet. If a histological small bowel response results from a gluten-free diet and then, later, relapse is documented, some of these patients may represent a subset that are highly sensitive to gluten, or alternatively, a form of refractory disease unresponsive to a gluten-free diet, including the insidious development of a cryptic lymphoma.

This report confirms that small bowel mucosal changes of untreated celiac disease may be mimicked by Crohn’s disease involvement of the duodenum. This includes macroscopic changes, like mucosal “scalloping”, previously reported in Crohn’s disease [13] and documented in the present case, as well as microscopic features that are well recognized. As in a previous report [7], serially-sectioned mucosal biopsies did not show granulomas typical of Crohn’s disease, but other “non-specific” pathologic biopsy features shared with untreated celiac disease were evident. These are described elsewhere by others [16,17,18] and have included atrophic changes in the duodenal mucosa, collections of polymorphonuclear leukocytes in surface epithelium or the lamina propria, or increased numbers of intra-epithelial lymphocytes. Crohn’s disease of the duodenum is uncommon, even if other sites (ileum, colon) are involved. In recent years, however, recognition of a wider spectrum of mucosal inflammatory change in Crohn’s disease of the duodenum has widened [17]. In part, this may be related to greater reliance on direct endoscopic visualization and biopsy compared to other less direct radiologic imaging methods.

The patient also had a prior colectomy for a presumed diagnosis of ulcerative colitis. Occasionally, as occurred here, this diagnosis must be revised to Crohn’s colitis after detailed pathological review of the entire surgical specimen, and in this patient, discouraged further surgical treatment. The development in this patient of post-colectomy

inflammatory disease of the small bowel is reminiscent of the severe and extensive enteritis reported after colectomy in patients with ulcerative colitis [19,20]. Whether a similar form of post-colectomy enteritis could occur in patients with Crohn's colitis after colectomy has not been previously reported. Here, an indolent and ongoing "sprue-like" inflammatory process developed in the proximal small bowel "isolated" from evidence of recurrent disease elsewhere in the intestinal tract. Clinical, but not histopathological improvement occurred after symptomatic treatment measures, but the gluten-free diet *per se* had no effect on the histopathological features present in the proximal small bowel.

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