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Intra-epithelial Lymphocytosis of the Ileum: A Pathological Clue to Clinically Occult Adult Celiac Disease

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Abstract A 39-yr-old male presented with diarrhea, weight loss and rectal bleeding. Hemorrhoids were present but the colon and distal ileum were macroscopically normal. Random mucosal biopsies of the ileum and multiple sites in the colon revealed extensive ileal and focal cecal intra-epithelial lymphocytosis. Subsequent duodenal mucosal biopsies confirmed the suspicion of adult celiac disease. Later endoscopic biopies done after gluten-free diet treatment were normal. This report demonstrates that intra-epithelial lymphocytosis in the ileum may be an important pathological clue to underlying clinically occult adult celiac disease.

Keywords: *celiac disease, intra-epithelial lymphocytosis, ileal biopsy, colonic biopsy, lymphocytic colitis, microscopic enteritis, lymphocytic ileitis*

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1. Introduction

Adult celiac disease is an immune-mediated disorder usually causing diarrhea and weight loss along with characteristic small intestinal biopsy changes that include variable degrees of architectural disturbance and increased numbers of intra-epithelial lymphocytes [1]. Treatment with a strict gluten-free diet usually results in resolution of symptoms, the inflammatory mucosal process and altered architecture. Most severe changes, typical of untreated celiac disease, may be detected in the duodenum and upper endoscopic biopsies are usually employed for diagnostic evaluation [2]. Characteristic architectural changes of adult celiac disease include hyperplastic and elongated crypts with flattened or atrophic villi, sometimes associated with changes elsewhere in the gastrointestinal tract, including intra-epithelial lymphocytosis in gastric [3], ileal [4,5] and colonic biopsies [6].

The case reported here further illustrates that these pathological changes, specifically increased numbers of intra-epithelial lymphocytes, not only may be detected in the ileum but, from a practical clinical perspective, emphasizes their relevance as a presenting pathological clue to subsequent clinical detection of unrecognized adult celiac disease that completely resolves with a gluten-free diet.

2. Case History

A 39-yr-old male was referred in 1996 for evaluation of diarrhea and a 10 kg weight loss. Blood studies, including a haemoglobin and iron studies, were normal and fecal studies for infectious causes of diarrhea were negative. Endoscopic evaluation of the lower intestinal tract revealed macroscopically normal mucosa of the distal ileum and colon. Biopsies of the ileum and multiple sites within the colon were done to exclude a microscopic cause for diarrhea. These showed increased numbers of intra-epithelial lymphocytes in the ileum (Figure 1 and Figure 2) along with focal collections of intra-epithelial lymphocytes in the cecum alone (Figure 3), while biopsies distally in the rest of the colon were normal. Because of continued diarrhea with these ileal biopsy findings showing increased numbers of intra-epithelial lymphocytes, the possibility of occult celiac disease was considered. At that time, serological studies were not available in our hospital, so upper endoscopic biopsies were done. These revealed typical features of untreated celiac disease in the duodenal mucosa with severe "flat" biopsy lesion (i.e., crypt hyperplastic villous atrophy, Marsh 3) (Figure 4 and Figure 5). A strict gluten-free diet was initiated. In 1997, he was reviewed. He was compliant with his gluten-free diet. Diarrhea had resolved and his weight had returned to his prior pre-illness level. In 2001, he was reviewed. Blood studies were normal along with serological studies, including immunoglobulin A quantitation and anti-IGA tissue transglutaminase (tTG) antibodies of 8 units (normal, less than 20 units). Endoscopic studies were normal and biopsies of the stomach and duodenum were normal. He continued on a strict gluten-free diet. In 2008, his tTG was 4.7 units. In 2010, he developed vague left lower quadrant abdominal pain. A colonoscopy showed a small adenoma that was resected. Added biopsies of the

ileo-colonic mucosa were normal. His pain spontaneously resolved. In 2011, he had additional endoscopic studies of the upper and lower gastrointestinal tracts and biopsies of the stomach, small intestine and colon remained normal.

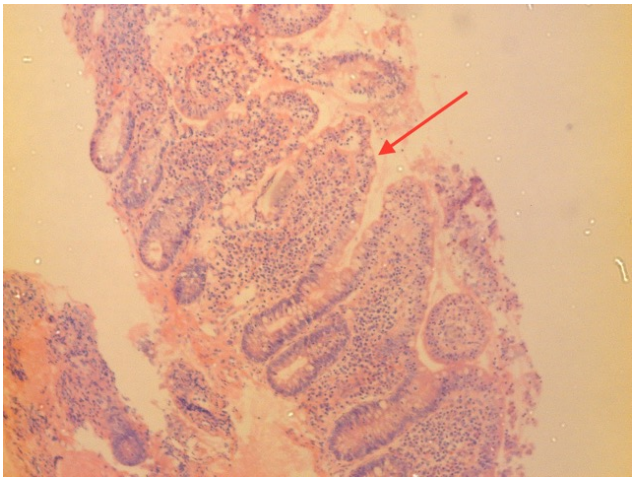

Figure 1. Biopsy of distal ileum showing slight architectural mucosal disturbance with intra-epithelial lymphocytosis (see arrow). Hematoxylin & Eosin, 100X

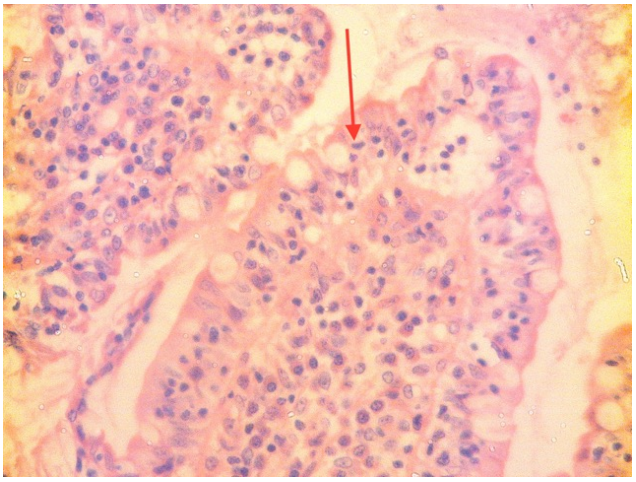

Figure 2. Biopsy of distal ileum showing higher power view of increased intra-epithelial lymphocytes (over 40 per 100 enterocytes; normal less than 20) (see arrow). Hematoxylin & Eosin, 400X

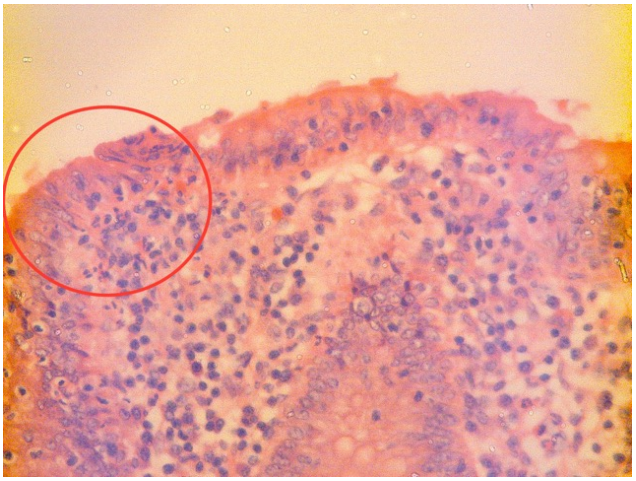

Figure 3. Cecal biopsy showing focal collection of intra-epithelial lymphocytes. More distal colonic biopsies (not shown) were normal. Hematoxylin & Eosin, 400X

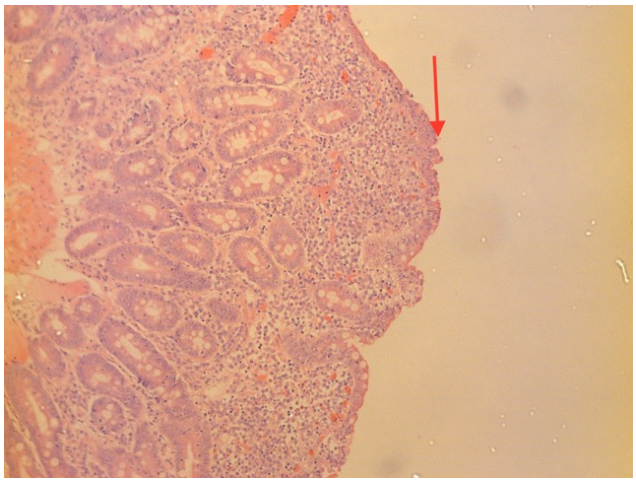

Figure 4. Duodenal mucosal biopsy showing a severe "flat" mucosal biopsy lesion with "crypt hyperplastic villus atrophy" (i.e., Marsh 3) and intra-epithelial lymphocytosis characteristic of untreated celiac disease. Hematoxylin & Eosin, 100X

Figure 5. Higher power photomicrograph showing increased numbers of intra-epithelial lymphocytes (over 40 per 100 enterocytes; normal less than 20). Hematoxylin & Eosin, 400X

3. Discussion

Celiac disease is an immune-mediated disorder that causes characteristic histopathologic findings in the proximal small bowel mucosa and these are now usually detected with endoscopic duodenal biopsies. In untreated celiac disease, these changes include significant architectural alterations, often severe, including "flattening" or atrophy of the villi and elongation and hyperplasia of the crypts, a prominent inflammatory

response in the lamina propria region along with increased numbers of intra-epithelial lymphocytes [1,2]. Although these mucosal changes are not specific for celiac disease and can have other causes, including medications, such as olmesartan [5], only in celiac disease, do these histopathologic mucosal changes normalize with treatment using a gluten-free diet. In recent years, increased numbers of intra-epithelial lymphocytes, while not specific for celiac disease, have also been detected in other sites, including gastric, ileal and colonic mucosa in adult celiac disease [3,4,5,6].

Because histopathologic changes of adult celiac disease are most severe in the proximal small bowel, likely a reflection of higher luminal concentrations of ingested toxic gluten peptides in the duodenum compared to more distal small intestinal sites, such as the ileum. However, earlier small bowel infusion studies demonstrated that the distal ileal mucosa is also highly sensitive to tube-infused gluten [7]. It is not surprising, then, that ileal lymphocytosis may occur in patients with celiac disease [4,5]

Interestingly, in a prior report [8], a patient with an ileal pouch-anal anastomosis was found to have ileal pouch intra-epithelial lymphocytosis. Later, a diagnosis of celiac disease was suggested. Interestingly, however, later studies by the same group emphasized the high frequency of ileal lymphocytosis in pouch patients and the concomitant failure to detect serological markers of celiac disease in this setting [9].

4. Conclusion

In the present patient noted here, intra-epithelial lymphocytosis was detected in ileal biopsies in a patient with diarrhea and weight loss. These changes served as a distinctive pathological clue that clinically occult celiac disease might be present, and later endoscopic duodenal biopsies confirmed the characteristic changes of untreated celiac disease. A strict gluten-free diet led to resolution of diarrhea and weight loss, complete histological resolution of the prior pathological changes and confirmed that a gluten-sensitive enteropathy was present.

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