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Adenocarcinoma in the Small Intestine in Celiac Disease over more than 30-years

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Abstract A variety of malignancies may complicate the clinical course of adult celiac disease. In a cohort of 154 patients with celiac disease (55 males, 99 females, aged over 30 years) also defined by a single case of cecal cancer, 4 males were observed to have small bowel adenocarcinoma in the duodenum or jejunum during a period of more than 30 years. This far exceeded the cumulative rate for this cancer in the background population (8.6 males per 100,000 over 10 years) indicating that patients with celiac disease, even after treatment with a gluten-free diet, remain at risk for development of small intestinal adenocarcinoma.

Keywords: *small bowel cancer, epithelial carcinogenesis, celiac disease, gluten-free diet*

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1. Introduction

The incidence of specific malignant disorders may be increased in celiac disease, particularly a complicating or superimposed small intestinal lymphoma [1] [2] [3]. This occurs most often, but not exclusively, in elderly patients, especially if initially diagnosed with celiac disease at an advanced age [3]. Many lymphomas in celiac disease prove to be T-cell in type, although B-cell types have been recorded. In addition, further evidence for this linkage comes from patients with lymphoma who, only later, prove to have occult underlying celiac disease [4]. Moreover, reports of unusual patients with T-cell lymphoma that have arisen in non-intestinal sites (eg., liver, thyroid) in celiac disease provides further evidence for this critical relationship between adult celiac disease and intestinal lymphoma [5].

Subsequent studies [6] [7] have also suggested an increased risk for small intestinal adenocarcinoma in adults with celiac disease. In 2004, data was reported from over 20 years of a personal clinical practice experience demonstrating that 3 patients (all males) with biopsy-defined celiac disease had small bowel adenocarcinoma (1.4%). This far exceeded the combined cumulative age-standardized rates for the local British Columbia population over a 10-year period at that time (males, 8.4 per 100,000; females, 6.2 per 100,000) [3].

Now, additional data has been accumulated representing over more than an added decade of clinical practice to further explore the rates of small intestinal adenocarcinoma in biopsy-defined celiac disease. In this study of small intestinal adenocarcinoma, the same cohort evaluated was previously studied for colon cancer and reported earlier in this journal [8].

2. Patients and Methods

A total of 154 patients with adult celiac disease (55 males, 99 females) were seen directly by the investigator. Office and hospital records for all patients were reviewed, including medication history. As noted elsewhere [8], patient records were extracted from a previously reported group of 182 patients [9]. In the present study, small intestinal mucosal biopsies were required to permit diagnosis of biopsy-defined disease. The macroscopic appearance of the duodenal mucosa and detection of reported descriptive features, such as scalloping, were considered non-specific, not sufficient for diagnosis of celiac disease. Although serological studies were performed in some (eg., endomysial antibodies, tissue transglutaminase antibodies), particularly in recent years, a positive serologic test alone was not used for diagnosis. In many, serologic studies were actually only done after biopsies were positive for celiac disease, negating any role for serological screening. Endoscopic biopsies were routinely obtained from the stomach and small intestine, but prior to 1985, biopsies were also done with a 4-hole multipurpose tube or a Quinton hydraulic suction multi-site intestinal biopsy instrument. Subsequently, biopsies were done under direct vision through Olympus fiberoptic gastroscopes (Olympus, Tokyo, Japan), and later, Olympus video-gastroscopes with large size forceps. Fiberoptic colonoscopes and later video-colonoscopes were used for colonic evaluations, including ileum. As previously noted [10], epithelial lymphocytosis in the ileum may have been used as a pathological clue to a possible celiac diagnosis, but diagnosis was only defined by subsequent duodenal mucosal biopsies. As noted, repeated duodenal biopsies

were usually done to define mucosal recovery and mucosal healing in biopsy-defined celiac disease [9].

3. Results

Altogether, there were 4 patients with small bowel adenocarcinoma associated with celiac disease in this series over more than 3 decades. In 3 patients, histologically-defined celiac disease was followed years later with an adenocarcinoma of the small bowel. In 1 patient, adenocarcinoma was initially diagnosed followed by later histological recognition of celiac disease [11].

Case 1. A 55-yr old male real estate broker presented to another hospital in 1980 with watery diarrhea and the passage of malodorous stools over 2 years. A macrocytic anemia was defined. Barium studies suggested possible malabsorption. Barium enema was normal. Colonoscopy was normal, but small bowel biopsies could not be done due to instrument failure. He was treated with a gluten-free diet, parenteral iron and vitamin B12. Diarrhea improved and resolved. In 1982, diarrhea recurred and persisted, up to 6 to 8 times daily so he was referred to our hospital. He estimated a weight loss of 6 to 8 kg. He was receiving iron and vitamin B12. He admitted to sporadic consumption of gluten-containing foods. Blood studies revealed a normal hemogram, iron, calcium, albumin, folate, vitamin B12, liver chemistry tests and immunoglobulins. A serum carotene was 0.3 mg per L (normal, 1.0 to 1.5). All prior treatments were terminated. A small bowel barium study showed a malabsorption pattern. Small intestinal biopsies in May 1982 showed typical features of untreated celiac disease (i.e., severe lesion with crypt hyperplastic villus atrophy, Marsh 3). Gastric biopsies were normal. A strict gluten-free diet was initiated with monitoring by a specialty dietitian providing support. Diarrhea resolved with weight gain. In September 1982, a gluten-free diet response was documented in repeated small bowel biopsies with reappearance of villi and only mild mucosal changes with intra-epithelial lymphocytosis.

In 1988, an acute onset small bowel obstruction resulted in referral to his original hospital and hospitalization. A surgical resection of an annular constricting adenocarcinoma of the proximal jejunum was done. Regional nodes were negative for metastases. Repeated blood studies, including serum iron and ferritin, folate and vitamin B12 were normal. In October 1991, he was referred for further evaluation because of recurrent diarrhea. Blood and fecal studies were normal. A small bowel barium study showed no abnormal change. Colonoscopy appeared normal. Repeat small intestinal biopsies showed persistent, mild changes and he remained on his gluten-free diet.

In October 1993, he was reviewed. Blood studies remained normal. In February 1994, increased fecal frequency up to 5 to 6 times daily in spite of his gluten-free diet was reported. Blood and fecal studies were normal. Colonoscopy appeared normal but colonic mucosal biopsies showed changes of lymphocytic colitis. No added treatment was provided and his diarrhea spontaneously resolved without added treatment. Endoscopic follow-up in 1996 was done and blood and biopsy studies were normal.

Case 2. An 85-yr old male was hospitalized in October 1989 with post-prandial abdominal pain, vomiting and weight loss (10 kg). Gastrograffin contrast studies suggested obstruction of the duodenal loop. Endoscopic biopsies of nodular duodenal mucosa revealed adenocarcinoma while more proximal duodenal mucosal biopsies showed moderately severe villus flattening with hyperplastic crypt epithelial cells. Biopsies from small bowel distal to the carcinoma were normal. Gastric biopsies showed epithelial lymphocytosis consistent with lymphocytic gastritis. Computerized tomography with contrast showed a mass in the third portion of the duodenum and a laparotomy showed a circumferential duodenal tumor mass confirmed histologically to be an adenocarcinoma. A bypass gastrojejunostomy was done. Subsequent surgical conference review of this case in 1992 led to consideration of possible celiac disease.

He was referred in April 1993 with no symptoms. Biopsies of the small bowel showed similar changes to those done over 3 years earlier, typical of untreated celiac disease (Marsh 3). He was treated with a strict gluten-free diet. After 6 weeks, repeated biopsies were improved and showed reappearance of villi and persistent mild to moderate inflammatory changes.

Case 3. A 48-yr old male labourer with intermittent burning epigastric abdominal pain and loose stools was seen in March 1994. Symptoms started a month or so earlier, appeared to resolve on omeprazole, but recurred after drug cessation. A barium study in May 1994 suggested a duodenal bulbar deformity but no ulcer. Interestingly, his 19-yr old son died from intestinal lymphoma, but there was no known familial celiac disease. Blood studies were normal. Ultrasound and upper GI endoscopy were normal in May 1994, however, gastric biopsies showed lymphocytic gastritis and small bowel biopsies showed severe crypt hyperplastic villus atrophy (Marsh 3) consistent with untreated celiac disease. He was treated with a strict gluten-free diet. His symptoms resolved with a weight gain of 5 kg.

In February 1995, he was first reviewed in the emergency room because of the development of acute abdominal pain, nausea and vomiting. After initial symptom resolution, symptoms promptly recurrred with re-introduction of oral intake. UGI endoscopy was normal, but radiographs suggested proximal jejunal obstruction. Laparotomy with proximal jejunal resection was done. A high grade poorly differentiated adenocarcinoma was present with extension to the serosa surface. Regional lymph nodes (7 of 13) were involved with metastatic cancer. A liver biopsy was normal, negative for metastatic cancer. Sections of small intestine distant from the resected tumor showed re-development of villus structure consistent with treated celiac disease. Following surgery, he was treated with adjuvant chemotherapy consisting of 5-fluorouracil and folinic acid from February to July 1995. Follow-up CA19.9, carcinoembryonic antigen, hemograms and liver chemistry tests were normal. Radiographic studies, including chest and abdominal computerized tomography were normal. In December 1997, upper GI endoscopy was normal. Gastric biopsies were normal while biopsies from multiple duodenal sites showed only mild changes with intraepithelial lymphocytosis.

In January 2000, he was referred for colonoscopy. He remained asymptomatic. Blood studies were normal except for a serum IgA of 0.13 g per L (normal, 0.7 to 4). Tissue transglutaminase was 1.2 U (normal, 0 to 20 U). Colonoscopy and colon biopsies were normal. Later colonoscopies and biopsies in 2006 and 2011 were normal.

Case 4. A 67-yr old university professor complained of bloating, intermittent loose stools and weight loss of 5 kg over 3 to 4 months. Blood studies in March 2008 revealed a normal hemogram and albumin with antibodies to IgA tissue transglutaminase of 33 U (normal, less than 20 U). A barium enema showed diverticulosis. Fecal studies were negative. Endoscopic evaluation in September 2008 showed patchy mucosal scalloping and a small tubular adenoma in the duodenum (< 5 mm) that was resected. A focal area in the resected polyp showed a non-invasive adenocarcinoma. Gastric biopsies were normal. Duodenal mucosal biopsies showed mild to moderate architectural changes, crypt hyperplastic villus atrophy (Marsh 2 to 3) with intraepithelial lymphocytosis consistent with celiac disease. He was treated with a strict gluten-free diet. Repeat endoscopic evaluation in February 2009 appeared to be normal and additional duodenal biopsies were improved with reappearance of villi, but no other polyps. A repeat tissue transglutaminase was normal (16 U). Colonoscopy in October 2010 showed a small tubular adenoma (< 5 mm) in the sigmoid colon. Added biopsies revealed mucosal inflammatory changes with intra-epithelial lymphocytosis consistent with lymphocytic colitis. Further colonoscopy in December 2011 revealed a small tubular adenoma, measuring about 6 mm, removed by snare polypectomy. Colonoscopy in 2014 revealed no additional polyps and a sigmoid biopsy was normal.

3. Discussion

This report adds to striking findings from a previous study [8] on this same cohort with biopsy-defined celiac disease that documented the rarity of a single colonic adenocarcinoma. Here, in contrast, 4 of 154 (or about 2.6%) patients, all male, had their celiac disease complicated by a small bowel adenocarcinoma over a period of 30 years. This far exceeds the small bowel adenocarcinoma rate for males in the general population of British Columbia over a 10 year period (8.4 per 100,000) [8] and further emphasizes the predisposition for development of small bowel adenocarcinoma in celiac disease in a cohort largely "protected" from a complicating colon cancer, a far more commonly diagnosed malignancy.

The first case of adenocarcinoma of the small intestine was recorded in the case records of the Massachusetts General Hospital in 1958 [12]. Later, several cases were described, and recently, reviewed [13], usually with cancer in the proximal small intestine, most often as a solitary malignancy, but occasionally in the ileum [14] and multifocal [15]. A number of mechanisms have been hypothesized predisposing the celiac mucosa to malignant change, in particular, increased crypt epithelial cell proliferation with higher rates of epithelial cell turnover. This occurs particularly in the proximal small intestine representing a premalignant change in celiac disease, especially since the proximal small intestine is the principal site of involvement in celiac disease. Carcinogens or co-carcinogens may more readily penetrate the damaged epithelial cell surface, already deficient in carcinogen-detoxifying enzymes, and, hypothetically, this could predispose to malignancy not only in the small intestine, but elsewhere in other extra-intestinal sites.

In this study, a small bowel carcinoma was defined after celiac disease was already defined in 3 patients (after long-term treatment with a gluten-free diet). In 1 elderly asymptomatic patient (case 2) with suspected celiac disease, a diagnosis of celiac disease could be confirmed histologically with proximal duodenal biopsies even in the presence of an advanced cancer. Taken together, these observations demonstrate that in celiac patients treated long-term with a strict gluten-free diet, a malignant cancer may still develop and may not be prevented by the long-term dietary treatment. Other confounding factors may play a role. Interestingly, in the single very elderly patient presenting with a cancer, biopsies proximal to the cancer failed to improve after surgical bypass but did improve with a gluten-free diet. This finding further suggests that the mucosal biopsy changes in the proximal duodenum were not caused by the cancer, and, even in the presence of the cancer, were still responsive to a gluten-free diet. This observation in a single cancer patient with a small intestinal enteropathy that responded to a gluten-free diet contrasts with previous reports of a sprue-like disorder in patients with cancer, or so-called "cancer enteropathy" [16,17] and concurs with a previous study [18] demonstrating that flattened small intestinal biopsies are not caused by malignancies, including intestinal and non-intestinal sites. Similar improved histopathological observations with a gluten-free diet were previously reported in celiac disease complicating a small intestinal lymphoma [4]. As hypothesized earlier [4], detection of celiac disease in the presence of malignancy may have similar important nutritional consequences associated with improved absorption. Further studies are needed to address this issue.

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