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Mini Review

Intestinal Adenocarcinoma in Biopsy-Defined Celiac Disease

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Abstract

Different intestinal malignancies develop in celiac disease, particularly lymphoma. In this study, the records of 154 patients with celiac disease followed during a 30 year period with an initial small bowel biopsy and a histopathological response to a gluten-free diet were retrospectively reviewed for development of adenocarcinoma. Four males were observed with a small bowel adenocarcinoma as well as 1 elderly female with colon cancer. Other sites, including esophagus, stomach, hepatobiliary tract and pancreas, had no adenocarcinomas detected. Patients with biopsy-defined celiac disease had an increased rate of small bowel adenocarcinoma, at least in males, but a reduced rate of colonic adenocarcinoma. These long-term clinical results from published studies in a well-defined population of celiac disease have important implications for further investigative endeavour related to celiac disease and intestinal malignancies.

Keywords: Celiac Disease; Small Bowel Cancer; Colon Cancer; Epithelial Carcinogenesis; Gluten-free Diet; Cancer Enteropathy

Introduction

Many different types of malignancy may occur in the small intestine of patients with celiac disease, particular lymphoma [1]. Adenocarcinoma has also been described, not only in the small intestine complicating the clinical course of celiac disease [2], but also, very rarely in the colon [3]. Indeed, prior studies by other investigators with prospective or retrospective methods of meta-analyses have included a total of less than 100 cases of small intestinal cancer in celiac disease, a normally uncommon malignancy [4-12] in the general population, while others have noted that the risk for colonic cancer is not increased [13,14].

Celiac disease is an immune-mediated disorder associated with ingestion of dietary gluten. From a practical perspective, celiac disease has been defined in different ways among different physicians in clinical practice as well as basic clinician scientist investigators. In some, it is believed, that a small intestinal biopsy consistent with the disease may be sufficient to define the presence of celiac disease. Complementary serological screening studies, usually with IgA antibodies to tissue transglutaminase, may be an added requirement for diagnosis. In some studies, this may be the only diagnostic test. It is also becoming increasingly appreciated by gastrointestinal mucosal pathologists that the biopsy typically seen in untreated celiac disease is neither specific nor diagnostic for this gluten-sensitive disease. Other causes of a sprue-like enteropathy have been reported. In particularly, a number of medications may cause similar sprue-like biopsy changes that do not respond to a gluten-free diet [15].

In our long-term follow-up studies of celiac disease, however, focus has been related to histopathologically-defined disease requiring small intestinal biopsy before and after treatment with a gluten-free diet in order to confirm evidence of a long-term mucosal response to treatment [16].

Adenocarcinoma in celiac disease

In studies from our center, a single cohort of 154 biopsy-defined adult celiac disease patients (55 males, 99 females) was studied over 30 years and these were retrospectively evaluated for a diagnosis of adenocarcinoma, particularly small bowel and colon cancer. All patients in this cohort were adults over 30 years of age.

In 4 males from this cohort, a small intestinal adenocarcinoma was found in either the duodenum or jejunum.

Surgical resections of a jejunal segment for obstructive symptoms were done in 2 with long-standing and established celiac disease, while 1 celiac patient underwent endoscopic polypectomy for a duodenal adenoma with a focal area of invasive carcinoma. In 1 of the celiac disease patients with cancer localized to the jejunum that was surgically resected, positive nodal disease led to further adjuvant chemotherapy. A final male patient had a duodenal cancer resected with creation of a bypass gastro-enterostomy. After subsequent pathological review of the resected bowel at a clinical conference, 3 years after the initial surgical treatment, biopsies of the bypassed proximal duodenum showed changes of celiac disease that responded to a gluten-free diet.

A single female was discovered with a cecal adenocarcinoma during the course of investigation of an iron deficiency anemia. After surgical resection of a pathologically-defined early stage colon cancer, iron deficiency anemia persisted and further studies revealed the presence of celiac disease. Treatment with a gluten-free diet alone resulted in improved small bowel biopsies and a normal hemoglobin level.

In this biopsy-defined cohort of adult celiac diseae, no epithelial cancers were noted elsewhere in the gastrointestinal tract in this cohort, specifically, esophagus, pancreas or hepatobiliary tract.

Discussion

For the purposes of these clinical research studies, only biopsy-defined celiac disease patients were evaluated. Biopsy-defined disease has been arbitrarily described as disease with an initial biopsy showed classical histopathological features of celiac disease, and then, after a gluten-free diet, a demonstrated histopathological response to a strict gluten-free diet occurs with normalization of a second biopsy [4]. Clinical and/or serological results may also be improved, but are not critical to the definition.

In this cohort of 154 patients with biopsy-defined celiac disease, studied over a 30 year period, there were 4 with small bowel cancer, or about 2.6%. In all of these patients (except 1 noted above), there was evidence for celiac disease prior to the cancer diagnosis, and in each case, a biopsy-defined small intestinal mucosal response to a gluten-free diet occurred. This rate far exceeded the small bowel adenocarcinoma rate in the general population of British Columbia over a previously reported 10-year period (i.e., 8.4 per 100,000), further emphasizing the predisposition in adults with biopsy-defined celiac disease for small bowel cancer. Moreover, the study suggests that gluten-free diet treatment *per se* is not absolutely protective for this complicating cancer. Moreover, this study did not define the role, if any, of duration of gluten-free diet administration in the pathogenesis of intestinal adenocarcinoma. This result appears to be similar and extend prior published nationwide registry results in celiac disease patients, but defined only by initial reported biopsy changes of celiac disease without definition of gluten-free diet treatment effects [17]. Finally, in the single elderly patient with a bypass gastroenterostomy done for a duodenal cancer, the enteropathy proximal to the cancer resolved with a gluten-free diet, consistent with a diagnosis of celiac disease, not a so-called "cancer induced enteropathy" either caused directly by cancer or indirectly as a paraneoplastic phenomenon [18].

Also in this cohort of 154 patients with biopsy-defined celiac disease, a single colon cancer was detected in the cecum initially investigated because of the presence of an iron deficiency anemia. Only later, because of the persistence of the anemia despite surgical resection of the cancer was celiac disease defined as the cause of the anemia. Information on the co-occurrence of colon cancer and celiac disease is limited. In most reported studies, the development of colon cancer in celiac disease patients is uncommon, particularly from European studies [13,14]. Additional studies are needed to elucidate this apparent celiac disease "protective effect" for colon cancer, and, conversely, the role of a gluten-free diet *per se* in playing a possible role in colon cancer pathogenesis. Importantly, in a recent cancer prevention study conducted over more than a decade [19] using food frequency questionnaires to evaluate grain intake and measurements of protein content of grain products to define gluten intake, higher whole grain intake was associated with a lower colorectal cancer risk in older men, not women. In addition, however, a positive, but unexplained, association with gluten intake

and proximal colon cancer risk was noted. This strongly suggests that further study is needed to evaluate the effects of a gluten-free diet on the intestinal tract, immune system and intestinal luminal microbiome.

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