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OBSERVATION

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Malignancy in adult celiac disease

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Abstract

Prior studies have suggested that the incidence of some neoplastic disorders, particularly malignant lymphoma and small intestinal adenocarcinoma, are increased in celiac disease. Earlier studies from the United Kingdom have also suggested a link between celiac disease and esophageal carcinoma, although this has not been confirmed in North America. The risk of other gastrointestinal cancers seems to be limited. Gastric cancer does not appear to be detected more frequently, although direct endoscopic visualization of the upper gastrointestinal tract is now very common in patients with celiac disease. Colon cancer also appears to be limited in celiac disease, even in patients first diagnosed with celiac disease late in life. This has led to the hypothesis that untreated celiac disease may be protective, possibly owing to impaired absorption of fat or fat-soluble agents, including hydrocarbons and putative co-carcinogens implicated in the pathogenesis of colon cancer, which may be poorly absorbed and rapidly excreted.

Key words: Adult; Celiac disease; Adenocarcinoma; Lymphoma; T cell enteropathy

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INTRODUCTION

Malignant disease is a serious concern in celiac disease[1] and recently has been reviewed in detail[2,3]. Some patients may even present with lymphoma[4,5] or a small-intestinal adenocarcinoma[6], and the celiac disease is only detected later. In others, malignancy, particularly lymphoma, complicates the clinical course of well established celiac disease, but may be especially difficult to diagnose[7]. The precise risk of malignant disease in adult celiac disease is difficult to evaluate, but about 8%-10% with severe biopsy changes develop lymphoma[8], and this figure has remained remarkably constant over several years[9]. Age of first diagnosis of celiac disease seems to be a critical factor. In those first diagnosed late in life (and presumably, initiating a protective gluten-free diet much later), detection of lymphoma may be much higher[8].

Mechanisms involved in development of malignant disease in celiac disease require elucidation. Significantly, however, the small-intestinal mucosa that is involved, with changes caused by celiac disease, may still pathologically respond to a gluten-free diet, even after lymphoma is detected[4,5]. There are likely to be many potential confounding variables that alter the pathogenesis of lymphoma in a celiac population and influence risk measurements for various malignancies in different populations. These include genetic, geographic, infectious, and other epidemiological factors. Finally, the duration of gluten restriction and the degree of compliance with the gluten-free diet are specific factors that may be difficult to measure precisely, but seem crucial to malignant change in celiac disease.

DIAGNOSTIC DIFFICULTIES

Most lymphomas are detected in the small intestine, usually the jejunum, but ileal localization may also occur[2]. Gastric or colonic lymphoma also occurs[2]. Lymphomas are usually ulcerating lesions, or stenosing and obstructing tumors[3]. Occasionally, the lymphoma may be multifocal or diffuse and localized only in the mucosa[5]. Often, concomitant nodal involvement is present[2]. The diagnosis may be especially difficult if small-intestinal (including duodenal) erosions and ulcers are present, as neoplastic cells may be more difficult to identify pathologically if significant superimposed inflammatory changes are present[4]. In some, benign

ulcers may lead to a mistaken diagnosis of Crohn's disease or a label of "ulcerative jejunoileitis"[4]. Some of these ulcers may contain frankly neoplastic lymphoma cells. Free perforation of the small intestine is a condition that should lead the clinician to a high level of suspicion of lymphoma in a patient with known or suspected celiac disease[10]. Even if there is a very high degree of suspicion, lymphoma may be notoriously difficult to diagnose, despite multiple endoscopic or suction small-intestinal biopsies[7]. In some patients that eventually prove to have lymphoma, even full thickness biopsies of the small intestine may not yield a definitive pathological diagnosis, especially if only mucosal disease is present. Additional tissue may be helpful for immunohistochemical labeling or PCR may be helpful in showing an altered binding pattern of antigen expression or a monoclonal cell population.

TYPES OF LYMPHOMA

Lymphoma may be classified based on pathological and immunophenotypical features. B-cell and T-cell lymphomas both occur in celiac disease. However, detection of a T-cell type more often leads to suspicion of underlying celiac disease. Primary intestinal T-cell lymphoma is recognized under the WHO classification as enteropathy-associated T-cell lymphoma (ETL or EATL). They are very uncommon and represent an estimated 5% of all gastrointestinal lymphomas[3,11]. Previously, these were thought to be histocytic in origin (and labeled malignant histiocytosis) but their origin now appears to be from T cells, specifically intra-epithelial lymphocytes[3,11]. In celiac disease (without lymphoma), the intra-epithelial lymphocytes express the following antigens (among others): surface CD3 and CD8. In a subset of patients that seem clinically refractory to a gluten-free diet, intra-epithelial lymphocytes have a different form of T-cell phenotypic expression: CD3 shows intra-cytoplasmic expression while CD8 expression is absent. Some believe this may reflect a specific form of refractory celiac disease (type 2) with a poor prognosis and a possible precursor lesion for the development of lymphoma[12-15].

Even lymphomas with T-cell immunophenotypic features have been detected in extra-intestinal sites, which complicates the clinical course of celiac disease. These may be very rare and include lymphoma diffusely involving the liver and spleen (i.e. hepatosplenic type T-cell lymphoma) without evidence of small-intestinal involvement[16], or lymphoma in other embryologically related or gut-derived sites, such as the thyroid gland or broncho-pulmonary and pleural sites[17].

Recent studies have also provided evidence for an increased risk of other lymphoma types. In a pathological review of tumor materials from celiac disease patients, there was an apparent aggregation of autoimmune disorders, female sex and B-cell lymphoma[18]. More than double the risk for B-cell lymphoma was recorded, with the most common type classified as a diffuse large B-cell lymphoma. In the same study, T-cell lymphomas had an approximately 50-fold risk along with a poorer prognosis (reflected in mean survival time after diagnosis and 5-year survival rate)[18].

Recent studies have also evaluated risk of lymphoma in celiac disease. While the risk of lymphoma in celiac disease, especially of the T-cell type, is increased, the risk appears not to be as significant. The relative risk has been estimated to be close to 3 and likely is lower in clinically silent disease[19].

OTHER GASTROINTESTINAL CANCER

Also intriguing are studies related to malignant disease elsewhere in the gastrointestinal tract. Small-bowel adenocarcinoma is increased in celiac disease. Normally, this is a rare tumor. Some have suggested that this carcinoma may be related to an adenoma-carcinoma sequence[2], but the risk of duodenal adenoma may not be increased in celiac disease[20]. Most patients appear to present with proximal small-intestinal localization, usually with small-bowel obstruction or bleeding. If complete surgical resection of a small-intestinal adenocarcinoma can be accomplished, the prognosis is better than if lymphoma is present[21].

Some European studies have shown that there may be an increased risk of esophageal and pharyngeal carcinoma[1,22]. However, these findings have not been confirmed in America. In one report[8], only a single terminal hypopharyngeal squamous cell carcinoma was detected in a celiac disease patient with lymphoma. No esophageal or gastric cancer was detected, despite repeated endoscopic studies during the course of diagnosis and treatment of celiac disease. Interestingly, however, Barrett's esophagus, a known precursor lesion of esophageal adenocarcinoma was frequently detected[8]. It may be that exposure to different environmental factors in different geographic areas or other confounding variables are important in cancer etiology and pathogenesis in celiac disease.

In a population-based cohort of celiac disease patients, overall colorectal cancer risk was marginally increased, owing to an increased risk in the ascending and transverse colon[23], but not in dermatitis herpetiformis[23]. However, others have noted that colorectal cancer may not be increased[9], especially in celiac disease patients with a diagnosis established late in life[9]. Possibly, untreated celiac disease is protective; dietary fat or fat soluble agents, including hydrocarbons or other putative co-carcinogens, may be implicated in the pathogenesis of colon cancer if poorly absorbed and rapidly excreted. Alternatively, immunological changes (e.g. increased intraepithelial lymphocytosis) in celiac disease may inhibit the development of epithelial malignancies at other gastrointestinal sites. Additional studies are needed to further clarify this information for celiac disease patients.

TREATMENT

Treatment of lymphoma associated with celiac disease to date has not substantially differed from lymphoma in the absence of celiac disease, and generally involves a combination of surgical treatment, radiation and chemotherapy. Most believe that the best treatment results occur in those diagnosed early[24]. Biological agents are also being evaluated.

In newly diagnosed lymphoma patients with chronic diarrhea and weight loss, underlying celiac disease should be excluded, preferably prior to lymphoma treatment (since both radiation and chemotherapy may structurally alter the small intestine), because concomitant recognition of celiac disease may have important nutritional implications.

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