

Celiac Disease and Cancer – Are There Potential Links? Is the Vigilance of Immune System in Celiac Disease a Double-edged Sword?

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Abstract Celiac disease (CD) is a chronic immune – mediated inflammatory intestinal disorder with prevalence about 1% of the West European population. The emergence of the disease is dependent on presence of grain storage proteins from wheat, barley, and rye (collectively called gluten) and genetic predisposition. After diagnosis is immediately deployed lifelong gluten free diet (GFD) to promote villous healing. In the case of CD - like other autoimmune disease, additional complications are observed especially if dietary compliance is poor. The most serious complications are malignancies including predominantly various types of lymphomas. On the other hand recent studies indicate lower risk of colon cancer in contrast to cutaneous malignant melanoma where the results are contradictory.

Keywords: celiac disease, malignancies, lymphomas

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1. Introduction

Celiac disease (CD) is a chronic immune – mediated inflammatory intestinal disorder and it is ranked among the autoimmune disease. Typical symptoms are seemingly unrelated complaints, such as diarrhea, flatulence, cramps, weight loss, fatigue, decreased bone density, unexplained iron deficiency and infertility. CD can occur at any time during childhood and adulthood with different manifestations. Unfortunately, nowadays celiac disease is causally incurable and the only treatment option is a gluten free diet (GFD). However, GFD causes very rapid alleviation of symptoms and promotes villous healing. Diagnosis is determined primarily by biopsy from the intestinal mucosa and on the results of specific serological tests, which especially include the level of enzyme transglutaminase. This enzyme is directly involved in the pathogenesis of the disease - binds to glutamine residues in gliadin molecule, a major component of gluten.

Like other autoimmune diseases CD have a genetic basis and therefore almost exclusively occurs in people having HLA - DQ2 or DQ8 antigens. CD incidence is higher in families where the CD has already been diagnosed. Trigger of CD in susceptible individuals is gluten, contained in some cereals, which is then digested in the digestive tract into smaller peptides. They bind to specific lymphocytes CD4⁺ and CD8⁺ thus triggering cell response in the mucosa of the small intestine [1], leading

to the typical histological changes of the damaged mucosa, which can appear in a wide range from a minimum damage of the mucosa (increased numbers of intraepithelial lymphocytes) to total villous atrophy with crypt hyperplasia and increased inflammation of lamina propria [1,2]. All these changes may regress in compliance with GFD. Recent studies in Western Europe countries report prevalence of CD about 1 % of all population, with a higher rate in female gender (ratio of 2:1) [1,3,4,5].

In addition to the active form of CD, which is characterized by the presence of increased levels of specific antibodies and typical pathology in intestinal mucosa, in the population occur also other forms of CD. Subclinical form is without presence of symptoms, but with typical findings in the small intestine. GFD is fully indicated also in this case. In latent form occurs only positive serological test, but during the examination of the small intestine is not present any pathology [6].

The CD is associated with a lot of complications, and this review is focused on the relationship between CD and malignancy, particularly lymphoma. The objective of this paper is to perform a study of recent literature on CD and cancer.

2. Material and Methods

A review for the potential links between CD and cancer was performed. Only relevant papers were included and the topic was discussed interesting form.

3. Results

3.1. Celiac Disease and Cancer

One of the most serious complications in CD is the development of malignancy. Celiac patients have higher risk of malignancy than healthy population (incidence observed / expected = 1,2 - 1,5). Compared with expected rates the risk of lymphomas was increased significantly, but in other cancers results are inconclusive. CD is also associated with a higher incidence of autoimmune diseases particularly with type 1 diabetes and autoimmune thyroiditis [4,7,8].

3.2. Link to Lymphomas

Gastrointestinal lymphomas are the most frequently occurring neoplasms in the celiac population, but the diagnosis of lymphoma may be difficult, because the most of lymphomas occurs in small intestine. Basic classification divides lymphomas into Hodgkin's lymphomas and non-Hodgkin's lymphomas. Non-Hodgkin's lymphomas are further divided according to their origin into two major group T-cell type and B-cell type. Both of them occur in CD. However, the presence of a T-cell type is more frequent [9].

By the WHO classification is primary intestinal T-cell lymphoma recognized as enteropathy-associated T-cell lymphoma (ETL or EATL) with prevalence about 5 % of all gastrointestinal lymphomas [10]. In 2008, the WHO has introduced EATL classification into two types according to morphological, immunohistochemical and genetic differences [11]. Both of them can affect any part of the gastrointestinal tract. The most commonly affected parts are jejunum and proximal ileum, but EATL can occur also in the stomach, duodenum and colon. Extra-intestinal manifestation is rare [12].

The original type or type I EATL represents the majority of EATL, and its incidence is strongly linked to CD. The tumour cells in type I EATL are medium-to-large with a pleomorphic appearance and an increased mitotic index. Morphologically these are seen as a prominent inflammatory background composed of histiocytes and eosinophils, which in some cases can obscure the population of neoplastic cells [12,13].

The monomorphic variant of EATL, also called type II, is defined as an intestinal tumour composed of small-to medium-sized monomorphic T-cells and comprises approximately 10 - 34% of cases [14]. Unlike type I is observed a lateral spread of tumour within the mucosa, and the absence of an inflammatory background. This type of EATL also may occur in the CD, but only in the isolated cases [12].

EATL may precede refractory celiac disease (RCD), which is a form of CD that is resistant to GFD. Type I RCD is very similar to CD, except for persistence of inflammatory processes in the intestine and there are less than 20% of intraepithelial lymphocytes with normal phenotype [12,13]. However, a significant influence on development of EATL has RCD type II. RCD type II is characterized by an increase of aberrant intraepithelial lymphocytes above 20 % [12,15].

In patients with CD were also observed Burkitt-like lymphoma (BLL) and mucosa-associated lymphoid tissue

(MALT) lymphoma [16,17]. The first observation of BLL was in a patient with CD in his eight decade of life. This high grade B-cell lymphoproliferative disorders is probably caused by chronic inflammation, profound immunosuppression and nutritional deficit [16].

MALT lymphoma is quite rare disease, but it was described a case, in which a celiac patient had synchronous gastric and colonic MALT lymphoma with re-evaluation in 3 years. Usually gluten withdrawal generally leads to disappearance of acquired gastric MALT, probably due to disappearance of the antigenic stimulation [18]. Unfortunately, the patient refused a new colonoscopic evaluation, so the reasons for the return of disease are only speculative, but it is possible, that one of the reasons was the failure of GFD diet, as confirmed by the patient [17].

In the case of Hodgkin's lymphoma is 9 – fold increased risk in patients afflicted by CD [8]. Other study reports 5-fold increased risk in non-Hodgkin's lymphoma and 10-fold increased risk in Hodgkin's lymphoma [4].

3.3. Link to CRC

One of the most common types of cancer is colorectal cancer (CRC), but in the population of patients with celiac disease is the risk of colorectal carcinoma lower than in the healthy population, as it is evidenced by recent studies [9,19,20].

3.4. Link to Other Malignancies

Except lymphoma, patients with CD are further threatened by small-bowel adenocarcinomas (SBA). Even though it is a rare tumour, CD patients have an 80-fold greater risk than the general population [21,22,23]. Most common location of SBA is duodenum. If the disease is detected in time, surgical resection follows. Unfortunately early diagnosis of SBA is not easy despite significant radiological and endoscopic progress. The main prognostic factor after surgical resection is node invasion. Increase in the risk of SBA in the event of CD is the lymphocytic infiltration, which induces damage to intestinal epithelial cells [24].

Previous publications demonstrated that the CD is also associated with an increased risk of cutaneous malignant melanoma (CMM), but recent studies have not confirmed this phenomenon, on the contrary, they found no association between CD and the incidence of CMM [25].

3.5. Immune System Function in Cancer Predisposition

According to previously mentioned data, there are mentioned links with lymphomas rather than CRC where links are not proven or more precisely the risk of CRC is noted to be decreased [19]. It is even mentioned that CD can act as a protective condition against other cancers than lymphomas [9]. It is hypothesized that an extreme immune response elicited from damaged intestinal mucosa results in depletion of cellular components of lymph nodes manifesting as involution or cavitation and hyposplenism in CD patients [26]. This is evidence that immune system is persistently alert. Maybe alertness of immune system could be also the mechanism underlying protection against

cancer in CD, because lymph nodes are known to be effective barrier in cancer spreading in organism.

Concerning lymphomas various types are described as was already mentioned above [9,16,17,27,28]. Underlying mechanisms are still poorly understood. Immunological mechanisms are obviously predominantly involved in pathogenesis. There is suggested link with lymphocytic infiltration of gastric and colonic mucosa. Increased numbers of these lymphocytes are responding to gluten exposure probably due to cytokine-dependent mechanisms [28]. The chronic antigenic stimulation by gluten can result to an increased risk of lymphoproliferation [17]. Previously mentioned facts show that the vigilance of immune system may be in CD patients a double-edged sword. Thus, it is worth to pay attention to immune system functions in CD in further studies.

4. Conclusions

CD is a worldwide disease with permanently increasing prevalence. CD patients are more prone to some types of cancer, but on the other hand CD seems to be protective for other types. Mechanisms involved in the pathogenesis of malignancies in CD are not completely known, but alertness of immune system is probably the reason why CD patients are more predisposed for concrete malignancies and contrary less to another ones. Concrete mechanisms contributing to these outcomes have to be revealed thoroughly, but we can conclude that immune system actions may be a double-edged sword in cancer predisposition of CD patients.

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