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CELIAC DISEASE AND RISK OF LYMPHOMA

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MINI REVIEW

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Abstract

Celiac disease (CD) is a popular autoimmune systemic defect producing from consumption of gluten that stores a protein of barley, wheat and rye. A few numbers of individual's celiac disease continuous atrophy of villous with a raise of mucosa intraepithelial lymphocytes (IELs) in an intestine, regardless of a rigorous gluten free diets GFD termed refractory celiac disease (RCD). Precocious detection and treatment could be related to avoid disease problems as a malignant lymphoma. The purposes of this research are to epitomize the accessible facts on the (CD) history related to lymphoma, the lymphoma kinds associated with CD , the methods that gluten excite enteropathy-associated T-cell lymphoma and celiac disease molecular grounds associated with lymphoma

INTRODUCTION

Natural history of celiac disease associated with lymphoma

The linkage between malignant tumor and celiac disease (CD) is determined in for a prolonged of time. Fairley and Mackie, were the first researchers to observe this linkage in 1937 who diagnosis 6 cases of steatorrhoea presented with lymphoma of the small bowel [l]. Sleisenger, Almy, and Barr (1953) after ten years of study and reported four cases believed to be suffering from secondary steatorrhoea.

Six cases suffering from reticulum cell sarcoma have been seen between June 1955 and March 1963, five of whom presented with steatorrhoea in late middle life, while the sixth case in all chances had celiac disease from infancy. These cases confirm the need to consider the potential reticulosis in this age group, illustrate the difficulties in the affirmative the clinical doubt of its presence, and, even with the information offered by biopsy or necropsy, reveal the problems in deciding whether the primary injury was idiopathic steatorrhoea or reticulosis [2]. Gough et al in 1962, recorded 5 patients of small bowel lymphoma presented with CD for a long time and propose that celiac disease was a pre-cancer condition [3].

The study of a large concatenation can only aid in the demonstration of the aetiological linkage of bowel lymphoma and sprue-like atrophy of the bowel mucosa accompanied or unaccompanied symptoms and clinical manifestations of malabsorption.

O'Farrelly et al (1986) introduced the expression "enteropathy-associated T-cell lymphoma" (EATL), that closely utilized for qualifying the scare arrangement of high-stage, T-cell non-Hodgkin lymphoma (NHL) of the superior small bowel, especially related to CD [4]. It was not obvious at that time if the celiac disease was exclusively linked with enteric lymphoma or it might give rise to a raise risk of NHL of any initial location, as obliquely propose by diagnosis of individuals with dermatitis herpetiformis (DH), which are considered as one of the potential clinical appearance of gluten sensibility (as well -termed "skin CD") [5,6]. Then the relation between lymphoma and celiac disease has been introduced in many studies [7-17].

Epidemiology of the association of celiac and lymphoma

The epidemiologic studies have shown that celiac disease influence about 1% of the population of the Western world [18-22], but the prevalence alters between countries 0.3% in Germany (0.1-0.4) and 2.4%[18] in Finland (2.0-2.8)[18,23]. The reports of previous study demonstrates that CD spread in the Italian inhabitance is about 0.7% [18] where in another study found that spread in an Italian individuals about 4.9 for each 1000, rising above to 5.7 for each 1000 with the thoroughness of possibility cases [24]. It is found to be prevalent among the Sahrawi children of North Africa and in Mexico, which is about 2% to 5% [23,25] and there are only four cases of celiac disease accompanied with malignant tumor have been reported in Europe until 2001. However they found that it has reached to 21 patients of celiac disease related to malignant tumor in children of Europe. Celiac disease and malignant tumor in children are under reported [26].

The celiac-cancer relation has therefore enticed modern attention since this possibility treatable_defect could be accountable for a great load of NHL, which is considered as the fifth extreme popular malignant tumor in America [27]. Celiac disease is comparatively repeated amongst the poorer category of the Middle East [28-31].

Types of lymphoma concerning with celiac disease

Most recent facts propose that a 3-6 fold increased risk of lymphoproliferative disease with CD [26,27,32]. The reports of previous study found that the large number (n=32, 57%) of lymphomas presented with celiac disease in the group study [21]and also another study found that CD was determined in 6 (0.92%) of 653 cases with lymphoma[13]. Also ,there is a report shows that there is no relation between positive celiac disease serology and malignancy without performing of biopsy [33,34] and also another recent study found by a case report of a 41 years old female presented with EATL [35]. Another report shows the relative risks in all types of malignant lymphoma related to celiac disease and they are equal in woman and men [21]. There are a few reports of the association between myeloid leukemia and celiac disease in 15 years old boy [36].

The most popular kind of lymphoma to be related to CD is non-Hodgkin's lymphoma (NHL). The previous study did not notice any association between CD and NHL [9] while other study found the risks of NHL malignancy associated with the latent type of CD is rare[32]. Also other studies found an increasing risk of NHL in individuals with CD [37, 38, 39] and there is 5-fold expansion of the risks in NHL in individuals with a hospital discharge presented with a celiac disease [40].

The reports of studies found that the risk of T-cell non hodgkin lymphoma was raised in individuals with CD [13,36,33] where in another study found that there were 6 individuals with malignant lymphoma accompanied with celiac disease and three of them with B cell and another three with T cell origin[13]. The analysis of another study found that the individuals which were diagnosed with T-cell lymphoma and CD have a lesser prediction in contrast to individuals diagnosed with B-cell lymphoma and celiac disease. Non enteropathy-Type T-Cell (NETL) had an especially weak prognosis, and the prognosis of whole T-cell lymphomas combined was significantly lesser than B-cell lymphomas. The low volume of individuals with enteropathy-type T-cell lymphoma (ETL) prevents differentiation of existence between the kinds of lymphomas and ETL. The survivors of patients with ETL were unfamiliar and there was 2 from 8 ETL individuals had a strong reaction to the therapy [41]. Despite the fact that B-cell lymphoma is scared, it was found particularly in female cases with refractory celiac disease and permanent symptoms [42].

Gluten excites enteropathy-associated T-cell lymphoma

In a small number of individuals presented with celiac disease, a gluten-free diet did not suffice to get rid of the disease. Those individuals are categorized as undergo from refractory celiac disease (RCD), which influences 2-5 % of celiac disease patients [43].The disease is defined as persistent VA and symptoms [44,45] which include diarrhea, reduce of weight, anemia, malabsorption, and abdominal pain [46] regardless of adherence to a rigorous gluten-free diet and not considered for by other causes than CD[44].

Refractory sprue have two subtypes, with thither is a normal intraepithelial lymphocyte phenotype in type 1(RCDI) [46] and type 2 (RCDII), is the existence of abnormal intraepithelial lymphocyte phenotype. In several cases with refractory celiac disease, the patients may internally have responded to a GFD or may have recrudesced in spite of commitment and response to the GFD at the first time. RCDI progressed after remediation together with incorporation of attacker nutritional backing, different pharmacological therapies and commitment to GFD. On the contrary, clinical response in (RCD II) to different therapies is less confirmed and the diagnosis is weak [47].

T cells are a kind of immune cell that dominates the organism's inflammatory reaction to gluten [43]. With other types of inflammatory cells such as mesenchymal cells, neutrophils released a large domain of mediators arranged the inflammatory response and exert various functions in preserving inflammation [43, 48]. Among the mediators, cytokines play serious roles in diversifying the inflammatory process which created when they uncover the protein [14], and catalyse the other type of immune cells [43,49,50]. This leads to the highly inflammatory and painful response idealistic of celiac disease. The tumor necrosis factor (TNF), interleukin 1 (IL -1) and interleukin 6(IL-6), are considered to be the major cytokines for inflammation and cancer evolution [49,50]. The cytokines IL-21, and IL-2 can also make reproduction of cancer cells. The onset of malignant lymphoma rely on the cytokine IL-15, which increases the number of cancer cells [43,51], is very offensive form of white blood malignant cell is termed enteropathy-associated T-cell lymphoma (EATL) [43].

EATL is a serious-stage, T-cell non-Hodgkin lymphoma (NHL) found in the superior small bowel that related to CD [52]. There are two subtypes of disease (EATL-I and EATL-II) that differ in pathological characteristic and clinical quality [53]. These types of non-Hodgkin lymphoma appears in individuals with either formerly or diagnosed accompany with celiac disease. In a sub collection of individuals, there is gradual retrogradation of (RCD) of a celiac disease. EATL comes from intraepithelial lymphocytes clonal reproduction [52]. Modern phenotypic test, in vitro molecular and studies on mice in vivo, proposed that the source of RCD II is from natural IELs (NK/T cell precursors). The immune micro-circumference of the small bowel mucosa in CD reinforces the growing of enteropathy associated T-cell lymphoma, through a many step passageway [54]. In addition to bowel, (EATL) are found also in skin, brain, liver, nasal sinus, spleen and thyroid [52].

Molecular mechanisms of lymphoma associate with CD

The individuals with CD have the molecules of HLA-DQ8 [55-57] and/orHLA-DQ2 [57]. Inflammatory T cell response to HLA-DQ2-bound gluten peptides and this is causing the disease. There are two molecules form of HLA-DQ2 [56,57]; HLA-DQ2.2 and HLA-DQ2.5. The HLA-DQ2.5 increase risk of CD, whereas HLA-DQ2.2 has a minimize risk [58-60] because the stably binding between gluten peptides and HLA-DQ2,2 is fewer [60]. However recent study found that the DQ2.5/2.5,DQ2.5/DQ8 genotype are risk for evolving to CD and the genotype DQ2.5/DQ2.2 also causing an increased risk for growing CD[61, 62]. HLA-DQA1*05 and DQB1*02, encoded for HLA-DQ2 for

more than 90% of celiac disease cases [63,64] and that gliadin reactive T cells from small bowel specimen only found in CD cases [65]. Another study has found that CD4 (+) T cells of glutin from small bowel specimen are limited to HLA-DQ2; the Th1 cytokines that distinguish peptides of gluten and deamidated by cellular enzyme transglutaminase [63].

It is hypothesized that the response time between malignant tumor and celiac disease is a multi-stride procedure require the sequential piling up of a few carcinogenic mutations and that RCD is robustly accompanied with an incomplete trisomy of the 1q region. The reports also demonstrate that 16% of EATL would lead to lymphomagenesis [66]. A recent paper addressed EATL genetic aspects during whole-exome sequencing of 69 patients with EATL cancers and found that the most repeatedly quite gene in EATL in about 32% of patients was *SETD2* and found that *SETD2* silencing play important role on T cell development and lymphomagenesis in mice [67]. Another paper found that in EATL there is a repeated of the wastage of heterozygosity at chromosome 9 p21 and the lack of gene within this position lead to the evolution of ETL [68]. The progression and development of lymphomas is associated with deletions or genetic alteration at chromosome 9p21, which harbors the cancer suppressor genes p14/ARF, p15/INK4b, and p16/INK4a, and 17p13 in the location of p53 [68,69,70].

CONCLUSION

Celiac disease is a chronic enteropathy excites through intake of gluten in hereditary inclined patient and is an autoimmune turmoil; impacting on ~1% of general population of the world. The disease leads to refractory celiac disease in 2-5% of patients and if there is in type 2 (RCDII), T-cell, epithelial and mesenchymal cells would release a large domain of mediators of inflammatory response that lead to the malignant development. The presence of the cytokine IL-15 is the first step of lymphoma which leads to increased cancer cells and cause EATL. The silence of *STED2* gene and deletion of many tumor suppressor genes that are located at chromosome 9p21 as well as loosing of heterozygosity in this chromosome in EATL is hypothesized the reasons of lymphoma associated with celiac disease.

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