Celiac Disease

Subjects: Oncology
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Celiac disease (CD) is a chronic enteropathy that develops in genetically susceptible individuals after the ingestion of gluten. There has been a substantial increase in CD prevalence in the last 50 years, and it is now estimated that this disease affects approximately 1% of the population in the Western world. In the large majority of cases, CD is a benign disease, characterized by the complete resolution of symptoms and a normal life expectancy after the onset of a gluten-free diet (GFD). However, failure to adhere to a strict GFD bears the risk of adverse events and increases mortality. A considerable number of studies have considered the possible association between CD and neoplasms. In particular, an increased risk of malignancies, such as cancers of the gastrointestinal tract and intestinal lymphomas, has been reported. In this review, we summarize and discuss the current evidence on the possible association between CD and cancer.

Keywords: small bowel adenocarcinoma ; T-cell lymphoma ; colorectal cancer ; gluten ; refractory celiac disease ; HLA-DQ2 ; HLA-DQ8 ; gluten-free diet.

1. Introduction

The first association between CD and lymphoma goes back to 1937 when Fairley and Mackie described six patients with intestinal lymphoma and steatorrhea [1]. Since then, other reports followed and in 1986 the term enteropathy-associated T cell Lymphoma (EATL) was firstly used to identify the rare form of high-grade T-cell NHL of the upper small intestine, specifically associated with CD [2]. EATL is a rare form of cancer that predominantly occurs in patients in the seventh decade of age. Usually, EATL arises in patients with a diagnosis of CD, either pre-existing or made concomitantly [3][4]. EATL has an incidence rate of approximately 0.10 cases per 100,000 inhabitants/year, with a large prevalence in males compared to females [5]. The tumor is more frequently localized in the jejunum compared to the ileum and it is often multifocal with ulcerative lesions. EATL immune phenotype is characterized by the clonal proliferation of intraepithelial lymphocytes TCR α/β positive [6][7]. Several histological varieties are described, but most cases consist of medium-to-large-sized cells with a pleomorphic appearance and an increased mitotic index [8]. In many cases, but not necessarily, EATL is the end stage of RCD type 2. Since 2008, the World Health Organization (WHO) has identified a minority (<20%) of EATL that meets specific molecular criteria (for example, the expression of CD56) and is less often associated with CD [9].

A large study on CD-associated malignancy demonstrated that CD-associated lymphoma risk may not be as high as previously noted [10] (Table 1).

Table 1. Studies examining lymphoma risk in CD patients.

Cancer Type	Cohort	First Author	Year	Ref.
NHL	British	Holmes	1989	[11]
Malignant lymphoma	British	Logan	1989	[12]
NHL	Finnish	Collin	1994	[13]
NHL	Italian	Corrao	2001	[14]
Malignant lymphoma Small-intestinal lymphoma	Swedish	Askling	2002	[10]
NHL	US	Green	2003	[15]
B cell NHL Non-intestinal lymphoma	Swedish	Smedby	2005	[16]
NHL	British	Goldacre	2008	[17]

Cancer Type	Cohort	First Author	Year	Ref.
NHL Hodgkin lymphoma	Swedish	Elfstrom	2011	[18]

However, despite the magnitude of risk remain debatable, the unequivocal association between CD and lymphoma remains. This same study gives information on the positive role of GFD in the prevention of EATL development. Many studies provided evidence that prompt diagnosis and strict adherence to GFD may decrease cancer risk and mortality [10][11][12][13][14]. However, both EATL and other malignancies have been described in patients on a GFD as well [15]. This latter finding, which apparently denies the beneficial effect of a GFD, could be explained by the fact that these patients have been exposed for too many years to a gluten-containing diet in face of few years of GFD, and this could be insufficient to revert the effect of longstanding gluten exposure.

Some patients have disseminated disease at diagnosis, with extra-intestinal localizations. Symptoms include abdominal pain, diarrhea, weight loss, fever, lymphoadenopaty, hepatomegaly, and palpable abdominal mass. Upper and lower endoscopy, enteroscopy, and CT and MR enterography are part of the diagnostic work-up to diagnose and stage EATL. In some patients, laparoscopy can be necessary to reach a final diagnosis. The therapeutic management of EATL is particularly difficult and survival is poor (13% at 30 months) [3][19].

Some authors suggest that CD patients are at increased risk of malignant lymphomas other than EATL. In a large prospective cohort of CD patients, a six-fold increase in overall lymphoma risk was observed [10]. Histopathological analysis of 58 patients included in this study demonstrated that non-intestinal B cell and T cell NHLs constituted the majority of CD-associated malignant lymphomas [16]. Larger studies are, however, needed to confirm these observations.

2. CD-Associated Small Bowel Carcinoma

SBC is an extremely rare neoplasm that accounts for less than 5% of all gastrointestinal cancers [20]. It may occur either as a sporadic tumor or associated with predisposing inflammatory conditions. In Europe, SBC has an estimated incidence rate of 3600 new cases/year, with a median age in the seventh decade [20].

Many epidemiological studies and meta-analysis suggest that CD patients have a higher risk to develop SBC compared to the general population [15][21] (Table 2).

Table 2. Studies examining small bowel carcinoma risk in CD patients.

Cancer Type	Cohort	First Author	Year	Ref.
Small bowel	British	Kenwright	1972	[22]
Small bowel	British	Howdle	2003	[3]
Small bowel	US	Green	2003	[15]
Small bowel	Swedish	Elfstrom	2012	[23]
Small bowel	Meta-analysis (17 studies)	Han *	2015	[21]

Accordingly, among all SBC, 13% are associated with a diagnosis of CD [3]. The first case of SBC in CD was described in 1972 and, from that on, many other reports followed up [22].

CD patients with a diagnosis of SBC usually have a median age between 53 to 62 years old. Risk factors for CD-associated SBC are not completely clear, but strict adherence to the GFD seems to have a protective role. In a large cohort study conducted in Sweden, the increased risk to develop gastrointestinal cancers in CD patients was completely abolished after one year from the diagnosis, suggesting a beneficial role of controlling intestinal inflammation [23]. On the other hand, SBCs have also been described in CD patients on a strict GFD, thus highlighting the importance of other predisposing factors in the development of this complication. It is noteworthy that the median age at diagnosis for CD patients with SBC was significantly higher than the median age at diagnosis for CD patients without malignancies [24][25]. This observation suggests that the diagnostic delay could play a role not only in the development of refractoriness and intestinal lymphoma but also in CD-associated SBC. Overall, apart from the age at diagnosis, a delay in the identification of CD, and poor adherence to the GFD, there are no other identified risk factors for the development of CD-associated SBC.

Considering the rarity of this tumor, molecular data are scarce. However, Vanoli and co-workers identified specific features of CD-related SBC in a large case series [24]. Compared to sporadic SBC and Crohn's disease-associated SBC, CD-SBC was characterized by frequent microsatellite instability (MSI) and high density of tumor-infiltrating T lymphocytes [24]. The same group recently reported that two main molecular subtypes characterize CD-related SBC, the MSI-immune subtype, and the mesenchymal subtype, with the latter associated with prominent TGF-β production and matrix remodeling [26].

Some reports suggest that CD-associated SBC arise from the classic "adenoma-to-carcinoma sequence", although this hypothesis is still highly debated [27]. In CD patients, the most frequently affected site is the jejunum as compared to the duodenum and ileum [28]. Time of onset and clinical presentation are largely variable. Some cohort studies reported a median onset time ranging from 1.4 to 17 years from CD diagnosis, whereas in some cases SBC and CD can be diagnosed at the same time [24]. Patients can present with direct or indirect signs of intestinal bleeding, such as overt hemorrhage, melena, coffee ground vomiting, and anemia, with obstructive symptoms (e.g., nausea, vomiting, abdominal pain), or with intussusception or perforation [29]. In patients with known CD, in the presence of the abovementioned symptoms, SBC (together with other CD-related complications) must be suspected and investigated. Esophagogastroduodenoscopy with biopsy is usually the first exam to perform to identify lesions proximal to the Treitz ligament. However, since most CD-associated SBC are localized in the jejunum, other techniques, such as enteroscopy, CT enterography, and MR enterography, are often required [30]. On the other hand, small bowel capsule endoscopy is not recommended due to the risk of capsule retention and the impossibility to collect mucosal samples.

SBC prognosis is generally extremely poor. A retrospective study analyzing the records of 491 patients with a diagnosis of SBC, both sporadic and associated with predisposing conditions such as CD, showed a median overall survival of 20.1 months, with a 5-year overall survival of 26% [31]. Age at diagnosis, stage of the disease, and the presence of lymph nodes or distant metastases were the factors that most correlated with a poor outcome [32][33]. When CD-associated SBC was specifically assessed, survival was better compared both to sporadic SBC and to Crohn's disease-associated SBC: two separate cohorts demonstrated a 5-year overall survival of 64.2% and 83% for CD-associated SBC [24][34]. Patients with diffuse-, mixed-, and solid-type histology tended to have a worse prognosis compared to glandular-type and medullary-type cancers [35][36]. Molecular subtypes have also been associated with prognosis: SBC with microsatellite instability are more likely indolent, whereas mesenchymal subtypes present worse tumor behavior [26]. Considering the rarity of CD-associated SBC, all therapeutic recommendations derive from the treatment of sporadic SBC. Surgery is the mainstay and can be curative only in the early stages of the disease, while surgery plus adjuvant chemotherapy is reserved for advanced stages. There is a large variety of medical therapies (e.g., classic chemotherapy, novel immune- and molecular-targeted therapies) used to treat solid tumors including SBC for which the reader is directed toward excellent reviews [37][38]. Among the possible therapeutic target in SBC, there is the programmed cell death protein-1 (PD-1)/programmed cell death ligand 1 (PD-L1) pathway. This pathway was recently evaluated in a large series of SBC. PD-L1 was highly expressed in CD SBC compared to sporadic SBC, and PD-1-positive immune cells were largely present in CD SBC compared to the sporadic ones [39]. These findings further support the possibility of the use of checkpoint inhibitors in CD-associated SBC.

3. Other CD-Associated Malignancies

Although the aforementioned studies clearly indicate that the risk to develop EATL and SBC is higher in CD patients as compared to the general population, whether CD patients are more susceptible to develop other malignancies is still under debate. In this context, some authors reported an increased risk for CD patients to develop pharyngeal and esophageal carcinomas [40][41] (Table 3).

Table 3. Studies examining the risk of developing other malignancies in CD patients.

Cancer Type	Cohort	First Author	Year	Ref.
Large intestine	Swedish	Askling	2002	[10]
Colonic adenoma	US	Lebwohl	2010	[42]
Colon Rectal	Swedish	Elfstrom	2012	[23]
Colorectal	Argentine	Pereyra	2013	[43]
Colon	Italian	Volta	2014	[44]
Esophageal	Swedish	Askling	2002	[10]

Cancer Type	Cohort	First Author	Year	Ref.
Esophageal	US	Green	2003	[15]
Esophageal	Swedish	Elfstrom	2012	[23]
Esophageal	Meta-analysis (17 studies)	Han *	2015	[21]
Breast	Swedish	Askling	2002	[10]
Breast	British	Card	2004	[45]
Breast	Swedish	Ludvigsson	2012	[46]
Papillary thyroid	US	Kent	2006	[47]
Papillary thyroid	Italian	Volta	2011	[48]
Thyroid	US	Ludvigsson	2013	[49]
Pancreatic	Swedish	Askling	2002	[10]
Pancreatic	Swedish	Elfstrom	2012	[23]
Melanoma	US	Green	2003	[15]
Melanoma	Swedish	Lebwohl	2014	[50]
Oropharyngeal Hepatobiliary	Swedish	Askling	2002	[10]
Gastric Liver	Swedish	Elfstrom	2012	[23]
Endometrial Ovarian	Swedish	Ludvigsson	2012	[46]

Using a Swedish registry of around 12,000 CD patients, Askling and colleagues reported an increased risk to develop malignant lymphoma, SBC, oropharyngeal, esophageal, large intestinal, hepatobiliary, and pancreatic carcinoma [10]. In the same paper, the authors reported that CD patients had a decreased risk of breast cancer, a finding confirmed by other population studies [45]. The protective role of CD toward breast cancer has been reported by many different studies, although the reasons for this negative association are not clear. A large study by Ludvigsson confirmed the protective effect of CD, but with borderline significance [46].

As already mentioned above, in a more recent Swedish cohort study of CD patients, the risk of any gastrointestinal (GI) cancer decreased over time: during the first year after diagnosis and initial biopsy, CD was associated with a 5.95-fold increase in risk of incident GI cancer of any type, whereas one year after the diagnosis, patients were not at increased risk [21]. Overall, after the first year of diagnosis, CD patients seemed to have a lower absolute risk to develop cancer [23]. The highest relative risk for GI cancer in CD was seen for SBC and pancreatic adenocarcinoma [23]. There was an 8-fold increase in colorectal cancer (CRC) in the first year of diagnosis that was abolished after one year [23]. Misdiagnosis of CD in patients that eventually resulted to have cancer is a possible explanation for the increased risk observed within the first year of diagnosis. Indeed, the overall risk of CRC in CD is comparable to the general population [23]. A case-control study conducted in 2010 found no association between colonic adenomas and CD [42]. Another multicenter, retrospective case-control study, within four community hospitals, demonstrated that CD was not associated with an increased risk of CRC [43]. Finally, a population study conducted in Italy reported that CD patients have even a lower risk to develop CRC as compared to the general population [44].

The literature regarding the risk of melanoma in CD is conflicting. Two studies found no association [10][45], while an increased risk of melanoma was described in a cohort of US patients affected by CD [15]. In a population-based study conducted in 2014 in Sweden, in which 29,028 CD patients were each matched with 5 controls, no association between these two diseases was reported [50]. Considering these results, it is likely there is no causal relationship between melanoma and CD.

The studies on the risk of developing thyroid cancer in CD are conflicting as well. In 2006, Kent and co-workers identified an increased risk of papillary carcinoma of the thyroid (standard morbidity ratio of 22.52) in a US cohort of CD patients [47]. According to these data, an Italian study population including 1757 patients diagnosed with CD between 1982 and 2006

demonstrated a 2.5-fold increased risk of papillary cancer of thyroid [48]. However, only 6 thyroid cancers were identified during the study. On the other hand, Ludvigsson identified 15 thyroid cancers out of 29,074 patients with CD (HR 0.6) [49]. Collectively, these data are still inconclusive and no formal association between CD and thyroid cancer can be made.

4. Conclusions

The available data suggest that adults with CD have an overall risk of developing intestinal lymphoma and SBC slightly increased as compared to the general population. Besides these two neoplasms, there is not sufficient evidence so far to suggest a higher prevalence of other malignancies in CD patients. Data on malignancies in children with CD are scarce. Two large studies did not find any increased risk of malignancy in children diagnosed with CD [10][51]. Only the study by Solaymani-Dodaran and colleagues found an excess of mortality due to cancer in children with CD [52]. However, given the low number of events reported (5 deaths), data must be taken with caution.

Overall, the risk of developing EATL and SBC is very small in humans. Despite that, as these types of cancer bear a poor prognosis, strategies aimed at reducing their incidence should be followed. So far, only adherence of CD patients to a GFD would seem to reduce the risk of these rare, though very aggressive, forms of cancer. In support of this hypothesis is the fact that children with CD do not have an increased risk of cancers in later life, further underlining the beneficial effect of a GFD [10][53]. Nevertheless, the effect of a GFD in preventing/reducing the risk of developing malignancies in CD patients is still debated. As the non-adherence and/or non-responsiveness to a GFD may lead to chronic inflammation of the small bowel, it is tempting to speculate that a gluten-containing diet in CD patients may promote the activation of immune/inflammatory signals and ultimately favor the onset/progression of lymphomas and SBCs. On the other hand, as CD patients drastically modify their dietary habits following the diagnosis of the disease, such changes could someway influence the risk of developing malignancies.

In conclusion, diversely to the increase of the awareness about CD pathogenesis that occurred in the last decade, as well as the reduction of the diagnostic delay, we still have poor knowledge about the risk factors/biological links that may contribute to the development of CD-associated neoplasms. Further mechanistic studies in experimental models as well as multicenter observational cohort studies, conducted not only in Western and/or westernized countries, would help clarify these issues.

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