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Colonic neoplasia and celiac disease: A systemic review

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Abstract

BACKGROUND

Celiac disease (CD) is a chronic inflammatory disease that affects multiple systems in genetically predisposed individuals. The only known treatment for CD is adherence to a gluten-free diet. Gluten has been found to exert deleterious immune-inflammatory effects beyond the small bowel, involving several genetic, cellular, and paracellular mechanisms in the context of chronic inflammation, leading to colorectal carcinoma (CRC) in CD patients. Several neoplasms, including adenocarcinoma and lymphoma, are associated with CD. Despite strong evidence of an association between CD and small intestinal malignancies, CRC is less common and underdiagnosed in patients with CD. In practice, most CD patients are only monitored for small bowel complications despite mild lower gastrointestinal symptoms; thus, colonoscopy is underused, with a greater focus on upper endoscopy and small bowel biopsy, a major hindrance in early diagnosis. Delayed diagnosis and poor prognosis have also been linked to nonspecific symptoms and late presentations. The lack of screening guidelines appears to be a critical gap. Educational gaps regarding the connection between CD and celiac neuropathy and heterogeneous disease expression and risk further add to the diagnostic delay.

AIM

To critically evaluate and synthesize existing evidence on the association between CD and CRC to encourage early-stage detection through lower gastrointestinal screening in CD patients and suggest individual-specific management strategies.

METHODS

The Scopus, Web of Science, and PubMed databases were searched *via* Medical Subject Headings words related to the criteria pertinent to CD and colon cancer/neoplasm, with a focus on pathophysiological mechanisms and clinical presentations, and the literature was reviewed.

RESULTS

A total of 4028 citations related to CD and neoplasia were initially identified. Following a critical review and exclusions, 134 citations were suitable for inclusion in this study. Despite its low incidence, a clinically significant association was found between CRC and CD that could impact the overall patient survival rate, suggesting early screening investigations, individual-specific interventions, and further longitudinal studies.

CONCLUSION

A low incidence of colon lymphoma and adenocarcinoma has been revealed. The clinical presentation of colon lymphoma and adenocarcinoma is indolent and nonspecific, with late presentation in the form of adhesions and perforation. A modest but statistically significant increase in CRC risk among CD patients was noted. Several overlapping factors, including individual variability, genetic and environmental factors, diagnostic delays and duration of gluten exposure, compliance with a gluten-free diet, lack of educational awareness, and complex immune-inflammatory interactions, were found to contribute to the overall incidence of CRC in CD patients. However, the true incidence may be underestimated due to the iceberg phenomenon, where limited clinical suspicion, poor screening, and underreporting may mask the underlying burden. This study highlights the need for increased clinical awareness and early screening, especially in noncompliant patients.

Key Words: Celiac disease; Gluten; Colon; Lymphoma; Cancer

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Core Tip: Celiac disease (CD) involves proinflammatory mechanisms that predispose untreated ³ patients who adhere to a gluten-free diet to the development of neoplastic complications. Gluten peptides have known direct effects on several levels of cell

structure, and they increase proinflammatory potential and oncogenesis. Neoplastic complications of the colorectum are considered rare among the neoplasias that are induced by CD. Intestinal lymphoma is a recognized and well-known long-term complication of CD; however, little is known about its role in colorectal cancer. The unfavorable outcomes related to colorectal lymphoma and adenocarcinoma associated with CD require further evaluation to inform possible screening initiatives.

INTRODUCTION

³Celiac disease (CD) is an immune-mediated disease with several gastrointestinal and extragastrointestinal manifestations ²triggered by gluten intake in susceptible individuals with the histocompatibility molecules human leukocyte antigen (HLA)-A1 and HLA-A8[1]. Gluten is recognized by CD4 HLA-DQ1 and HLA-DQ8 cells through a heterogeneous group of γ/δ T-cell receptors (TCRs) in the lamina propria[2]. In contrast, noncoeliac wheat allergy is an entity with a different presentation of wheat-related intolerance that poses no immunological sequelae, with no antibody response against the gluten. The characteristic microscopic RNA signature hsa-miR-30e-5p distinguishes noncoeliac wheat allergy from CD, as observed in CD3+ intraepithelial lymphocytes (IELs) and CD45+ immunocytes in the duodenal lamina propria[3,4].

With a global incidence of 1%, interest in the pathogenesis of CD and its complications, especially neoplastic complications, is increasing. Small bowel neoplasia is thought to be the prevailing pathology and includes adenocarcinoma and lymphoma (due to chronic intestinal inflammation) in addition to carcinoids and leiomyosarcoma[5]. Notably, intestinal lymphoma is an aggressive neoplasm associated with CD; colon neoplasms are frequently associated with but less commonly reported neoplasms in CD[6]. The rarity of colorectal carcinoma (CRC) in confirmed CD could be explained by possible immune-mediated protective effects within the colon[7]. CD triggers a surge of IELs, which results in increased tumor immune surveillance and inhibits epithelial malignancies in the colon at the cost of chronic inflammation[8]. Additionally, malabsorption associated with CD leads to decreased dietary fat- and fat-soluble carcinogen intake, which could also explain

the possible protective mechanisms in the colon[8]. More specifically, the colon has far less direct gluten exposure. Its mucosal immune system, which is supported by gut-associated lymphoid tissue and a robust microbiome, provides stronger surveillance and relative protection[9]. These factors may contribute to a higher diagnostic threshold for initiating large bowel screening investigations in patients with established CD, potentially leading to delayed diagnosis and underrecognition.

MATERIALS AND METHODS

The Scopus, Web of Science, and PubMed databases were searched *via* Medical Subject Headings words related to the criteria pertinent to CD and colon cancer/neoplasm, with a focus on pathophysiological mechanisms and clinical presentations, and the literature was reviewed.

RESULTS

A total of 4028 citations related to CD and neoplasia were initially identified. Following a critical review and exclusions, 136 citations were ¹⁷ suitable for inclusion in this study (Figure 1 as shown in PRISMA flow diagram). Despite its low incidence, a clinically significant association was found between CRC and CD that could impact the overall patient survival rate, early screening investigations are advocated with consideration of individual-specific decisions. Further longitudinal studies of global nature will help in structuring a precise recommendation.

DISCUSSION

Intestinal protective factors

Within the dynamic milieu of the gastrointestinal tract (GIT), several key factors operate in concert to maintain the integrity of the intestinal barrier during periods of chronic inflammation. These factors include cytoskeletal proteins[10], cellular factors[11], microbial factors[12], and immune cells[13,14], all of which play critical roles in maintaining barrier function (Table 1).

Gluten effects on the bowel

Gliadin peptides exert systemic and local effects. Among those that affect the bowel wall are the induction of oxidative stress, the disruption of the intestinal barrier, and damage to the intestinal mucosa[16] (Figure 2). The deleterious effects occur at the onset of the initial humoral reaction with the recruitment of CD8+ $\alpha\beta$ and $\gamma\delta$ T cells expressing TCRs, which interact with the natural killer group 2, member D ligand on enterocytes, a class Ib molecule, and the major histocompatibility complex (MHC) class 1 chain-related genes A and B, which act as activating receptors. In contrast, gluten-free diet (GFD)-adherent CD patients exhibit CD8 $\alpha\alpha$ TCR $\gamma\delta$ IELs that express the inhibitory natural killer cell receptor group II member A receptor[2].

Glutathione enzymes (glutathione reductase, glutathione S-transferase, and reduced glutathione peroxidase) that combat reactive oxygen species (ROS) are markedly decreased after treatment with gliadin peptides[17]. Furthermore, a high prevalence of proapoptotic signals is observed in immune-mediated diseases such as CD[18]. The expression of MHC class 1 chain-related genes A and B, which is recognized by the natural killer group 2, member D receptor on enterocytes and mediates apoptosis, is greater in untreated CD patients than in control subjects, and these genes are broadly expressed in CD7+, CD20+, CD138+, and CD68+, as is the mouse monoclonal antibody HAM56[19].

Effects of a long-term GFD on colorectal neoplasia

Compared with data on outcomes in other malignancies, such as lymphoma, little is known about the outcomes of patients with colorectal cancer and strict adherence to a GFD. Available evidence is limited by differing methods of assessment of adherence and inherent recall bias. Additionally, factors such as inability to reverse prior gluten exposure during study assessment, inability to comply strictly with a GFD and the absence of a noninvasive assessment method for a GFD are factors used to assess long-term effects decisively[20]. The physiological basis attributed to a lower risk of colon

cancer in CD patients adherent to a GFD is thought to be a balanced healthy diet and the limitation of high-calorie food items with a lean body mass index as well as a decreased fat absorption capability, hence attenuating most of the main inflammatory risk factors involved in gastrointestinal tumorigenesis[21]. Conversely, patients who are not adherent to a gluten diet would theoretically be protected from CRC due to impaired absorption of fat- and fat-soluble agents[8]. Patient-specific risk modifiers, including older age at CD diagnosis, prolonged untreated disease, and nonadherence to a GFD, likely exacerbate inflammation-driven epigenetic changes and genomic instability, increasing CRC susceptibility[21,22]. These factors likely explain the variable risks of CRC in CD patients. Conversely, early diagnosis and strict adherence to a GFD may maintain mucosal barrier (MMR) integrity and mitigate this risk, as found in a study by Pereyra *et al*[39]. Low GFD adherence increased adenoma risk nearly sevenfold. Regarding precancerous lesions of CRC, such as adenoma and advanced neoplasia, low adherence to a GFD is significantly associated with adenoma (odds ratio = 6.78, confidence interval: 1.39-33.20) according to multivariate analysis, as reported by Pereyra *et al*[39], when adherence was evaluated by a Biagi score of 0-1. For CRC, long-term studies investigating the association between CD diagnosis and the development of new diagnoses of CRC are rare, and a case series by Volta *et al*[41], who adhered to a strict GFD on the basis of a food diary assessment, eventually developed CRC. Additionally, Marafini *et al*[22] reported that late CD diagnosis and delayed treatment increase overall cancer risk.

ONCOGENIC PATHWAYS IN CD

The influence of gluten exposure is discussed in a multilayered classification to understand the toxic effects of gluten that target several body compositions on the basis of observations at the de novo and cell culture levels, starting from the gene level to the organ level.

Gene level

At the gene level, hypermethylation induces high-frequency ¹⁴microsatellite instability (MSI) and ¹⁰deficient mismatch repair, as shown by the loss of expression of the repair genes human mutL homolog 1 and human mutS homolog 2 in CD. CD-associated CRC is distinct from Lynch syndrome. Although MMR deficiency and MSI are common in both CD-associated CRC and Lynch syndrome, in CD, they arise largely from age- or inflammation-driven epigenetic silencing [MutL homolog 1 (MLH1) promotes hypermethylation] rather than germline mutations[24]. This silencing adds microsatellite mutations to genes ¹⁵[transforming growth factor-beta (TGF-β) receptor type II, B-cell lymphoma ¹(BCL) 2-associated X protein, and insulin-like growth factor 2 receptor], promoting malignant transformation[25]. Furthermore, genomic instability at the tumor protein 53 gene locus, which acts as a tumor-suppressor gene with a specific short tandem repeat in untreated patients, is observed with a high frequency in CD[21].

Molecular level

Although the significant risk of CRC in patients with CD has been explored, the counter-association, *i.e.*, whether CRC patients have a higher incidence or altered immune profiles suggestive of latent or undiagnosed CD, has not been studied in detail. Some studies suggest the potential underdiagnosis of CD in patients with CRC due to overlapping symptoms and masking by cancer-associated immunosuppression. However, evidence is limited, warranting exploration of shared immunopathogenic pathways. Hence, genome-wide and biopsy-based studies are needed to determine whether the CRC-induced tumor microenvironment (TME) can mimic CD-like mucosal changes.

Several complex and integrated ²⁴mechanisms have been described to explain the association between CD and CRC at the molecular level. CD results in the overexpression of interleukin-15 (IL-15) in intestinal epithelial cells, which then ⁴activates the Janus kinase/signal transducer and activator of transcription 3/5 ²³and phosphatidylinositol 3-kinase/protein kinase B signaling pathways, leading to the overexpression of BCL-2 and BCL-extra large and the survival of genetically damaged epithelial cells, promoting tumorigenesis[26]. Moreover, IL-15 suppresses TGF-β/Sma and Mad related protein 3,

which is responsible for epithelial cell homeostasis and anti-proliferative signaling[27]. Chronic inflammation in CD activates ²² nuclear factor- κ B (NF- κ B), which upregulates cyclooxygenase-2 (COX-2), a proinflammatory and procarcinogenic enzyme that contributes to overall DNA damage, angiogenesis, and immune evasion[28]. Studies have shown that chronic epithelial turnover and chronic inflammation in CD may promote Wnt pathway dysregulation, which is central to CRC tumorigenesis, leading to beta-catenin accumulation and unchecked proliferation[29]. As discussed previously, MSI and MMR play key roles in CRC tumorigenesis by increasing mutation rates in oncogenes. Additionally, elevated IL-6 levels in active CD lead to the ⁴ activation of signal transducer and activator of transcription 3 (an oncogene present in several gastrointestinal cancers), which supports survival, angiogenesis, and the proliferation of intestinal cells[30]. These diverse signaling mechanisms highlight overlapping pathways in the TME in the context of chronic inflammation leading to colorectal tumorigenesis in CD patients.

Cell level

At the cell level, activated lymphocytes lead to respiratory bursts and the release of ROS, affecting the prooxidant-antioxidant balance. There is evidence that gliadin has a direct effect on cytoplasmic mitochondria: When mitochondria are disrupted and cell viability is reduced, as observed in Caco cell lines exposed to gliadin, increased mitochondrial biogenesis and a reduced mitochondrial antioxidant response occur. Gliadin peptide-driven dendritic cells (ijCD80/83/83/HLA-DR) *via* mitogen-activated protein kinases and NF- κ B signaling lead to elevated cytokines (IL-6, IL-8, TNF- α) and enhanced T-cell priming[31]. Gliadin also promotes NF- κ B-mediated TNF- α and IL-8 release from HLA-DQ2+ monocytes and macrophages[32]. Moreover, gliadin interacts with C-X-C chemokine receptor 3 on enterocytes and peripheral blood mononuclear cells, driving zonulin-mediated permeability and IL-8 secretion[33]. These proinflammatory cytokines alter the TME, promoting the maturation of antigen-presenting cells (enhancing the T helper 1 cells response), supporting CD8+ cell cytotoxic activity, and interferon secretion,

creating a cytokine-rich environment that can promote antitumor immune surveillance and may cause immunosuppression in the long-term[34,35]. This colorectal TME critically governs patient prognosis and response to immunotherapy[36]. Notably, the number of apoptotic cells increases when cells are treated with peptide-treated gliadin[22,37]. A decrease in cell viability of 20% to 80% was observed in LoVo cell lines with increasing concentrations of peptic tryptic digested peptide from bread wheat gliadin; cell damage, as shown by the presence of autophagic vacuoles and intracytoplasmic lipid-like droplets, also occurs[38].

Interestingly, the properties of gluten change in response to chemical and enzymatic activities. In the non-heat-treated state, acid undergoes deamidation with heat (90 °C) for 3 hours and renders more soluble and less immunoreactive in human colon LoVo cell lines than under the conditions of enzymatic changes in response to microbial transglutaminase, which leads to increased gluten immunoreactivity[39].

Treatment of experimental cell lines with gluten-specific immunodominant peptides (p56-88 and p57-68) results in reduced cell growth and inhibition of tissue transglutaminase (tTG). This effect was abolished by the addition of antibodies against tTG to CaCo2 cells. No inhibitory effect on cell growth or tTG activity was observed with the addition of the deamidated peptide p57-68 (E65). In contrast, inhibition persists with the other peptide, p69-82 (formerly nontoxic), which is produced through the substitution of glutamine 72 with glutamic acid[40,41].

Altered angiogenesis is a factor that is involved in tumorigenesis in CD, in which a regulatory single-nucleotide polymorphism in TNF-superfamily13 (rs11552708) is associated with CD. The expression of proangiogenic factors (G protein subunit alpha 13, TGF- α , v-erb-b2 receptor tyrosine kinase 2, and SGC2) is downregulated, while the expression of transglutaminase 2 and promyelocytic leukemia protein is upregulated, and the tTG antigen was shown to increase transglutaminase 2 expression[42,43]. Electron microscopy analysis of the sigmoid mucosa in CD patients revealed an abnormal microvillus that was irregular, short, and sparse, with fine granular material within its

borders and abundant round structures within the microvillus borders of the principal cells[23,44].

Tissue level

At the paracellular level, gliadin alters the expression of tight junction components (actin, zonula occludens-1, and occludin), as demonstrated in a 3-dimensional LoVo cell culture system, after treatment with enzymatically digested gliadin[45,46]. Notably, in areas of partial or total villous atrophy of the small intestine, several blisters within the subepithelium contain inflammatory COX-2 cells, indicating the presence of CD3+ and CD68+ T-cell subtypes[24,47].

Role of the microbiota in the intestine

The microbiota consists of bacteria, viruses, and fungi that interact in a state of symbiosis, maintain bowel barrier integrity, and serve as a defense mechanism. Several health disorders have recently been attributed to dysregulation of microbiota fingerprints in the gut that surprisingly affect gut health and several other organ systems[48]. The gut virome responds in a dynamic state and diversely to the type of dietary intake or restrictions, such as a GFD[21,49]. CrAssphage is a phage taxon among the human viromes that responds to dietary manipulation and is actively studied in response to different diets[50]. Metagenomic studies have shown that viral infections with enteroviruses early in life play a role in early/subclinical CD[51]. The microbiota, especially the virome, interact with intestinal immune cells in delicate balance. Disturbance in the interplay between mononuclear phagocytes and innate lymphoid cells (ILCs), as well as the adaptive immune system, results in intestinal inflammatory states and impaired immunity against enteric infections[52].

To understand the relationship between colon cancer, the microbiota and ILCs, which increase the release of inflammatory mediators from ILCs, constitute a unique family of innate immune cells, including natural killer cells, which differentiate from the bone marrow. IL-22 secreted by ILC-3 cells plays a role in controlling epithelial cell

proliferation and tumorigenesis. Intestinal dysbiosis leads to the release of IL-22 and IL-17 from ILC-3 cells, and the proportion of ILC-3s significantly decreases in colon cancer with increasing inflammatory activity of T helper 17 cells in the intestine. Notably, ILC-3s express the antigen-presenting factor MHC-II, which halts intestinal inflammation by limiting the activity of microbiota-specific T helper 17 cells in an MHC-II-dependent manner[53]. Direct microbial tumorigenesis effects are observed with *Escherichia coli*, *Bacteroides fragilis*, *Epsilonproteobacteria*, and *Proteobacteria*, with cancer-promoting effects via the production of colicin, *Bacteroides fragilis* toxin, and lethal cell-tumescence toxins[54,55]. These mechanisms are involved in the induction of ROS that lead to damage to host DNA[56,57].

Organ level

Gluten has been shown to exert several effects on various organs. Gluten challenge increases humoral and cellular responses, with increasing numbers of CD3+ and CD25+ cells, and the mRNA levels of the proinflammatory cytokines IL-8 and IL-1 β and the C-C chemokine monocyte chemoattractant protein-1 significantly increase as early as 2 hours following challenge; however, the levels of tumor necrosis factors (TNF- α and β 1) remain unchanged[58]. In the rectum of CD patients, most of the physiologically normal T-cell population is composed of α/β subtypes and contains a preponderance of γ/δ T cells. Furthermore, a rectal gluten challenge with Frazer fraction III (a mixture of gliadin and glutenin peptides that is used as a source of toxic gliadin peptides for experiments) markedly increased the number of CD3+ IELs but did not change γ/δ T lymphocyte receptor expression levels[59]. In the colon, examination of a sigmoid organ culture of CD patients on a gluten diet revealed the presence of endometrial (epithelial membrane antigen-immunoglobulin A and immunoglobulin G) and tTG antibodies. Therefore, on the basis of the trophic effect of a deleterious gluten diet, Catassi *et al*[75] proposed that a strict GFD could prevent this subset of aggressive lymphoma.

CD association with microscopic colitis

Chronic inflammation of the colon in patients with CD is traditionally associated with microscopic colitis (lymphocytic colitis (20%-27%) and microscopic gastritis)[60-63], and the incidence of lymphocytic colitis in refractory CD (RCD) has been reported to range widely from 0%-75% [64]. In clinical practice, CD is managed as a malabsorptive condition of the small bowel, and it is rare to perform lower endoscopy and biopsy for the investigation or surveillance of a pathology from that perspective, except for cases involving lower GIT bleeding[65], or to investigate new-onset diarrhea not explained by GFD adherence. Hence, the need to investigate or screen the colon for neoplasia, particularly among CD patients, has yet to be further explored in the context of its related neoplastic risk. Unusual associations between CD and related conditions should be considered a coexistent malignancy. A report of a lymphocytic colitis patient with monomorphic epitheliotropic intestinal T-cell lymphoma, formerly known as type 2 enteropathy-associated T-cell lymphoma (EATL), detected in a multifocal area of the GIT in a case series from East Asia; therefore, multiple biopsies from the GIT are needed[66].

Neoplasia and CD

CD is associated with an increased risk of various neoplastic conditions, including EATL and colorectal cancer[61,62,67]. In this section, the link between CD and the development of neoplasia is explored, particularly in terms of colonic inflammation mechanisms, carcinogenesis processes, and genetic factors.

Chronic inflammation and carcinogenesis

Chronic inflammation in patients with CD can induce carcinogenesis *via* several mechanisms. Increased expression of tumor promoters (inflammatory cytokines) through tumor-associated lymphocytes and macrophages, induction of COX-2, and loss of immune tolerance are caused by genetic and epigenetic shifts[65,68]. The explanation for this intolerance lies in the autoimmune nature of CD, with chronic activation of IELs and heightened cytokine expression (IL-15, interferon- γ). This chronic inflammatory state, a key component of the TME, drives DNA damage and induces epithelial stress,

epigenetic changes, and genomic instability, mimicking mechanisms implicated in CRC in other autoimmune conditions [e.g., systemic lupus erythematosus (SLE) and Sjogren's disease]. However, this robust immune surveillance may lead to effective clearance of emerging tumor cells, as evidenced by studies indicating a lower incidence of certain neoplasms in autoimmune conditions [i.e., SLE, rheumatoid arthritis (RA), and psoriasis] due to enhanced CD8+ T-cell-driven antitumor surveillance[69-72].

In contrast, other studies suggest that chronic antigen exposure and exhausted CD8+ IELs may lead to immune escape mechanisms, allowing tumor growth despite active immunity, and persistent IL-15 signaling has been linked with the downregulation of MHC1, leading to poor immune anticancer surveillance[73]. Recently, an umbrella review revealed that while many autoimmune conditions favor malignant transformation, RA is associated with a lower CRC risk[74]. Similarly, a review on female-specific cancer revealed detrimental breast and ovarian cancer risk in patients with known autoimmune conditions (i.e., RA, SLE), suggesting enhanced antitumor surveillance mechanisms[75,76]. Given the dual role of immune responses in both promoting and suppressing tumorigenesis, individualized risk stratification is essential. Further longitudinal studies are needed to clarify context-specific immune outcomes in CD-associated CRC. Moreover, NF- κ B acts as an intracellular transducer and tumor promoter with TNF and IL-1, which are involved in CD immunological reactions and act as potent activators[65].

EATL and genetic factors

EATL originates from α/β rather than γ/δ T cells, which express TCRs, as well as common neoplastic cells, which are CD3+, CD4, CD8-, and CD103-[77]. An analysis of a case series of gluten enteropathy patients revealed dense nonspecific infiltration of lymphocytes at the lamina propria of the colon[78]. The presence of aberrant IELs and a chronic inflammatory state in the gastric and colonic mucosa of RCD-II patients indicate an active lymphangiogenesis process[79,80]. A common signature observed for a monoclonal phenotypically abnormal IEL population exists in reticulum cell sarcoma

along the GIT in the stomach, duodenum, jejunum, and colon. This group of RCD patients has a greater number of IELs with CD3+CD8- cells than CD patients do, regardless of whether they are GFD adherent or nonadherent; these independent findings were attributed to infiltration by circulating T cells but supported by TCR- γ clonality and histological findings[64]. The pathogenesis of type 1 EATL is related to the activation of IELs and is associated with the downregulation of TCR CD3 expression, the loss of CD8 expression, and TCR gene rearrangement[81]. The characteristic TCR proteins associated with CD and EATL are CD45R0, CD3, CD8, and CD56[82,83]. Compared with solitary CRC, synchronous CRC has a different immune cell composition, with IELs more frequently on the surface epithelium than on the crypt epithelium, which is indicative of different functions of immune-related processes at the gene transcription level[84].

Risk and prognosis

Conflicting risk exists regarding the ⁹ risk of colorectal cancer and CD. Long-term follow-up studies have revealed an association between CD and Hodgkin lymphoma risk [risk ratio (RR) = 6.9] over 11.2 years of follow-up; for patients with colon cancer, the adjusted RR was 1.23 ($P = 0.6$), and for patients with rectal cancer, the adjusted RR was 1.04 ($P = 0.857$)[85]. Conversely, other reports have shown a decreased risk of CRC (RR = 0.7) after the diagnosis of CD[86]. A recent review by Pelizzaro *et al*[24] revealed variability in the risk of malignancy, with an increased risk of neoplasia associated with a long disease duration beyond ⁹ 10 years [standardized incidence ratio (SIR) = 1.3] and up to 15 years after diagnosis (SIR = 0.92). Interestingly, the diagnosis of colon cancer occurred soon after CD diagnosis (within the prediagnostic period), at less than 2 years (SIR = 2), and at more than 40 years (hazard ratio = 2.47)[87].

Individualized risk assessment

HLA-dq2/dq8 are essential for CD diagnosis when ambiguity exists in clinical and histopathological findings to support the diagnosis. Although they have insignificant predictive value for colon cancer risk alone, studies suggest that chronic immune

activation in genetically predisposed individuals may contribute to chronic inflammation (mucosal injury), adding to a tumor-promoting microenvironment[88]. More recent genome-wide association studies have indicated that many non-HLA variants (*e.g.*, IL-2 and IL-21) are associated with the severity of the inflammatory response and cancer progression[89]. Untreated CD, especially when the diagnosis is delayed (prolonged exposure to gluten), is associated with extensive periods of mucosal inflammation, which may trigger MMR and genomic instability[90]. Therefore, more neoplastic complications are observed in poorly compliant patients with a GFD[91].

Although not specifically linked to CD, genetic and environmental risk assessment in combination with genetic polymorphisms and biochemical markers (folate levels) enhances CRC risk in the general population, which mandates earlier colonoscopy, lifestyle interventions, and targeted surveillance[92]. More specifically, advanced Marsh classification suggests a greater neoplastic risk associated with persistent villous atrophy despite adherence to a GFD. Future biomarkers might include elevated IL-5, TGF- β , and MLH1 methylation for neoplastic transformation[93]. Incorporating these factors into individualized monitoring, potentially combining genetic profiling, serologic testing, and endoscopic surveillance, could help CRC prevention strategies in CD patients. Risk-based early colonoscopy screening intervals and immune profiling may emerge as future screening standards.

IMMUNOPHENOTYPING AND THE PREDICTION OF PROGNOSIS IN CD

It is used to study pathological masses of suspected neoplasms in CD patients and to characterize types of lymphoma with certain characteristic immunophenotypes that are associated with patient outcome. Considering RCD is a potential stage of disease where neoplastic complications may develop, understanding these types of lymphoma and their immunophenotypes would help to predict those patients with CD disease who develop neoplastic complications. Common types of lymphoma in CD with reported involvement of the colon are Burkitt lymphoma, which expresses CD19, CD2, and CD10 and is CL6

positive, and follicular lymphoma, which accounts for less than 7% of gastrointestinal-related lymphomas, with rare involvement of the colon and BCL-2 and CD20 positivity.

EATL or mature ²¹ T-cell lymphoma, natural killer/T-cell lymphoma with rare involvement of the colon, is characterized by CD3, CD7, and CD103 positivity, in addition to variable reactivity to CD8, CD30 and TCR- β . Specifically, EATL-II expresses CD8+, CD3+, and TCR- β , and the coexpression of CD56 positivity. However, obtaining information on the prognostic nature of these types of lesions from these types of lesions would require invasive biopsy. However, the combination of clinical parameters with biopsies could be a promising tool to predict the nature of prognosis in patients with RCD. The use of information from patients with RCD and symptoms of malabsorption and findings of anemia (low serum iron, B12 and folate), low electrolytes (Na, K, Cl, and zinc), elevated international normalized ratio and hypoalbuminemia applied in a structured malabsorption score (ranging from 0-8) and a cutoff of ≥ 3 is useful for identifying high-risk patients with RCD who would benefit from further evaluation to identify occult neoplasms, especially lymphoma. Colorectal cancer is a rare neoplasm in patients with RCD for which there is no available literature to investigate and link immunophenotyping to RCD patients.

Colonic lymphoma and CD

The development of lymphoma in CD patients is a significant complication of the disease secondary to the chronic immune-inflammatory response in the GIT. Ancient studies of malignancy and CD in 1974 described lymphoma as reticular cell sarcoma of the GIT, mostly in the stomach, small intestine, and lymph nodes[94]. The intestine is an extranodal site where the immune-inflammatory reaction occurs at the local lymphoreticular tissue of "gut-associated lymphoid tissue"[95]. Most lymphomas have a T-cell origin (96%), with BCL accounting for less than 5% of lymphomas[96], and BCL can present in multifocal areas such as the colon, stomach, and small bowel[97].

Notably, EATL and CD share similar IEL haplotypes, clinical presentations, and histological findings[98]. Predominantly, type 1 EATL accounts for 80%-90% of CD cases,

whereas type 2 EATL is a sporadic disease and accounts for the remaining 10%-20% of cases[99]. Risk factors for EATL include inflammatory bowel disease, CD, immunosuppressive states, and infectious etiologies such as Epstein-Barr virus and human T-lymphotropic virus type[100]. An alteration in chromosome 9, q33-34, is a hallmark of EATL that occurs in 70% of patients, and poor prognosis is associated with the presence of more than 3 chromosomal gains[101]. Advanced age at the time of diagnosis of CD (60 years) is more commonly associated with small bowel neoplasia than with colonic lesions such as colon adenoma[102]. EATL was the most frequently associated malignancy (RR = 35.8), followed by small intestine and duodenal adenocarcinoma (RR = 14.4 and RR = 10.2, respectively). The contributing risk factors are male sex, the classic form of CD, advanced age at diagnosis, delayed diagnosis, untreated CD, persistent villous atrophy, and HLA-DQ2 homozygosity[103]. The literature is immense, with case reports of EATL with the common presentation of abdominal pain and tumor perforation into the peritoneum with the development of peritonitis[104,105].

The described pathologies have different types of presentations of solitary or multiple lymphomas, such as non-B, non-T lymphoma[96], marginal cell lymphoma[106], and aggressive Burkitt-like lymphoma, which are histologically characterized as high-grade BCL[107]. Aggressive disease has been reported in patients as young as 29 years of age with metastatic colon type 1 EATL[99]. The disease survival and prognosis of EATL decrease with duration, with 1- and 5-year failure-free survival rates of 19.4% and 3.2%, respectively, and actuarial 1- and 5-year survival rates of 38.7% and 19.7%, respectively[108].

Colorectal adenocarcinoma and CD

The importance of colorectal adenoma and adenocarcinoma in patients with CD is of interest for further advancements in screening strategies for CD patients at risk of malignancy[61]. Although CD is commonly associated with small bowel lymphoma, risk and screening assessments for colorectal neoplasia remain a point of debate among researchers. The controversies surrounding the association between CD and colorectal

neoplasia are presented in Table 2 for colon adenomas and Table 3 for colon adenocarcinoma. Additionally, nonadenomatous dysplasia has been reported in CD, in which rectal neuroendocrine polyps (well-differentiated grade 1) have been described[109].

Suggested approach to the management of neoplasia in CD patients

There is no consensus or recommended approach for the surveillance, screening or early diagnosis of colorectal neoplasia in patients with CD. Our suggested approaches for the management of neoplasia in CD patients are as follows.

Initial clinical evaluation: Upon the diagnosis of CD, a ¹⁶ detailed clinical evaluation, including medical history and physical examination, should be performed. Changes in bowel habits in otherwise GFD-adherent patients should not be dismissed as coexistent irritable bowel syndrome. Abnormal physical findings, especially abdominal tenderness or masses, should prompt further evaluation *via* computed tomography or magnetic resonance imaging of the abdomen to investigate potentially growing masses, such as lymphoma or carcinoma, that might lead to abdominal adhesions and obstruction[120].

Diagnostic investigations: Biopsy and serology are necessary to confirm the diagnosis of CD. Biopsies are critical for detecting conditions that coexist with CD, such as lymphoma[121]. While general blood tests are of limited diagnostic utility for early lymphoma diagnosis, serum albumin level measurement might be helpful, and a low serum albumin level in elderly CD patients has been significantly associated with lymphoma[121].

Gastrointestinal evaluation: Colonoscopy is essential for ruling out microscopic colitis (including lymphocytic colitis) and for identifying dysplastic lesions in the colon, and it is particularly useful for investigating diarrhea that is not managed with a GFD. Iron deficiency anemia is a critical warning sign, especially in patients aged older than 45

years, and should prompt investigation[63,121-123]. No pathognomonic endoscopic findings for lymphoma exist, but findings of mucosal thickening, masses with circumferential ulcerations, and edematous mucosa might suggest underlying lymphoma[124].

Radiological findings: Radiological examinations are useful but not exclusive for the diagnosis of suspected intestinal and colonic lymphoma. Possible findings are polypoid masses, circumferential bowel thickening, and lymphadenopathy[125-127]. Positron emission tomography is performed to identify monomorphic epitheliotropic intestinal T-cell lymphoma, which typically manifests as endometriotic lesions[128-130].

Genetic testing and biomarkers: MMR gene testing and MSI analysis *via* the identification of MLH1, MutS homolog 2, MutS homolog 6, and PMS2 methylation or mutation can reveal the MSI-high status, guiding immune checkpoint inhibitor therapy, which is highly effective in colon adenocarcinomas with high neoantigen loads[131]. Additionally, elevated fecal calprotectin levels are a noninvasive marker of colonic inflammation and occult neoplasia. Meta-analysis revealed 5-fold greater odds of elevated fecal calprotectin levels than in controls[132]. Moreover, circulating tumor DNA and epigenetic markers [assays targeting methylated genes, *i.e.*, Septin9 (*SEPT9*) and vimentin (*VIM*)] are emerging tools as adjuncts for risk stratification in CD patients with borderline screening indications[133]. Emerging evidence supports the clinical utility of circulating tumor DNA methylation assays targeting *SEPT9*, *VIM* and related genes for early CRC detection[133]. Moreover, a large-scale panel including *SDC2*, *SEPT9*, and *VIM*, applied to fecal and tissue samples, achieved over 91% sensitivity and 100% specificity, underscoring its diagnostic accuracy in early-stage CRC[134].

Targeted and immune-based therapies: Immune-based and targeted therapies are transforming the management of CD-associated neoplasia. For MSI-high/deficient mismatch repair colorectal adenocarcinoma, pembrolizumab, as demonstrated in

KEYNOTE-177, results in ¹² significantly longer progression-free survival (16.5 vs 8.2 months; hazard ratio = 0.60) and improved 5-year overall survival compared with chemotherapy^[135]. In previously treated patients, KEYNOTE-164 showed a 33%-35% objective response rate and prolonged survival^[136]. Together, these developments underscore the benefit of genetic and molecular profiling to guide precision immunotherapy for high-risk individuals within the CD patient population.

Limitations

Current knowledge of the incidence and prevalence of colonic neoplasia is based on retrospective studies with limited longitudinal follow-up, mostly involving patients with a duration of follow-up of up to 10 years, and are prone to selection and reporting biases. Since CD is a life-long illness for which management depends on adherence to a GFD, several other key factors also need to be accounted for, including factors that may increase dysplasia in the intestine and demographic and genetic backgrounds that limit the generalization of these recommendations, as most data are derived from Western populations. The underdiagnosis of CD and inconsistent colorectal screening practices may result in underestimation of the incidence of neoplasms. Variations in diagnostic criteria and a lack of detailed molecular profiling in CD-associated colorectal tumors further limit the ability to draw definitive conclusions. Prospective studies with standardized protocols are needed to clarify the true nature of this association.

Future directions

Strategies are needed for the early diagnosis and detection of large bowel and small bowel lymphoma in CD patients. High-performance stool tests for detecting neoplasms, including lymphoma and adenocarcinoma, in CD patients also need to be developed. Notably, enrolling CD patients in a regular screening program for intestinal neoplasia *via* less invasive or invasive methods should be considered. These strategies should be feasible, less invasive, and appropriate for the management and follow-up of CD patients. Furthermore, biotechnology and artificial intelligence are needed to incorporate data

from biological samples to accurately detect abnormal lymphocytes and identify abnormal clones. Genetic testing for at-risk alleles in CD is considered among the possible targeted tests; hence, the identification of ²⁶ patients who may be at risk of developing EATL is a necessary future investigational target.

CONCLUSION

Accumulating evidence suggests that gluten exposure has a deleterious effect both locally and systemically. The mechanisms of gluten damage to the bowel, including small bowel changes with villous atrophy, have been proven to extend beyond the small bowel and involve genetic, cellular, and paracellular mechanisms. Although colonic lymphoma is rare, it has a poor prognosis because of its late and nonspecific clinical presentation. A GFD is a mandatory management strategy, and evidence shows that strict adherence is a therapeutic and preventative clinical outcome. A search for gastrointestinal lymphoma is warranted in patients with CD with symptoms of abdominal pain, weight loss, anemia, and hypoalbuminemia not otherwise explained.

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