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Celiac disease: a clinical review

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Abstract

Celiac disease (CD) is an immune-mediated inflammatory enteropathy triggered by gluten exposure in genetically susceptible individuals. It has a high prevalence approaching 1% of the US population. A high index of suspicion is warranted to diagnose CD as frequently patients present with extraintestinal or atypical manifestations. CD is diagnosed by a combination of serum serologies and duodenal biopsies. The majority of patients will respond to a lifelong gluten-free diet which is the cornerstone of therapy. Complications such as refractory CD, ulcerative jejunoileitis, enteropathy associated T-cell lymphoma and small bowel adenocarcinoma occur in a minority of patients.

Key words: Celiac disease—Enteropathy—Sprue—Gluten free—Refractory—imaging

Abbreviations

CD	Celiac disease
GFD	Gluten-free diet
EATL	Enteropathy-associated T-cell lymphoma

Celiac disease (CD) is a chronic immune inflammatory enteropathy triggered by gluten exposure in individuals with genetic susceptibility. Gluten is a protein found in wheat, barley, and rye. CD affects approximately 1% of the US population. Signs and symptoms of CD include diarrhea, abdominal pain, malabsorption, and weight loss. However, patients can present with extraintestinal symptoms or nonspecific signs such as iron deficiency anemia alone. Hence, a high index of suspicion is needed to diagnose CD. In the appropriate clinical setting, CD is diagnosed with serum serologies and duodenal biopsies. Tissue transglutaminase antibody is the most sensitive and specific serologic marker and has been recommended as the first-line testing in suspected CD. Duodenal biopsies showing villous atrophy and intraepithelial lymphocytosis confirm the diagnosis.

The mainstay of therapy for CD is a permanent gluten-free diet (GFD). The majority of CD patients respond to a GFD and have a favorable prognosis. Nonresponse to a GFD is more commonly due to gluten contamination or an alternate or additional diagnosis. Less commonly, persistent symptoms despite a GFD is due to complications such as refractory CD, enteropathy-associated T-cell lymphoma (EATL) or small bowel adenocarcinoma. Although GFD is the only currently available therapy, there are multiple promising therapeutic agents in the pipeline. This review will focus on the epidemiology, pathogenesis, clinical presentation, diagnosis, treatment and complications of CD.

Epidemiology

The prevalence of adult CD in the United States population is believed to be 0.95%, and the prevalence of child CD has been calculated at 0.31%, for an overall prevalence ranging from 0.69% to 0.75% [1–3]. This increases to 1.01% among non-Hispanic whites, with blacks and Hispanics in the United States having considerably lower rates of CD of 0.3% and 0.2%, respectively [2, 4]. These values mirror several epidemiological studies performed in Italy, which show similar ranges from 0.2% to 0.74% [5–8]. However, studies from other European nations, including the United Kingdom [9], Sweden [10, 11], Finland [12, 13], and the Netherlands [14], have found a slightly higher prevalence ranging from 1.0% to 2.0%. While it was traditionally believed that CD is an illness affecting primarily people of European descent, studies have shown rates of CD of up to 5.6% in specific North African populations [15]. A large review of CD in the Middle East and North Africa showed a wide range of CD prevalence by nation, ranging from 0.03% to 1.17%

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[16]. The disease is quite rare in East Asia and Pacific Islanders, and this has been attributed to the lack of the specific HLA haplotype in this population needed for CD to occur and/or a low consumption of gluten in the population [17–19].

The incidence of CD has steadily risen over the last 50 years, and this may be only in part attributed to heightened clinician awareness and the advent of serologic studies that can detect what used to be subclinical disease. Environmental factors, such as dose of gluten in the infant, infections, and socioeconomic status may also play a role [20]. During 1950–1989, an incidence of 0.9 per 100,000 was found in a US cohort, which increased to 17.4 per 100,000 in the 2010s [21, 22]. A study of active-duty US army personnel found a similar magnitude increase in detection from 1.3 per 100,000 in 1999 to 6.5 per 100,000 in 2008 [23]. Females make up 68–75% of diagnosed cases [21, 24, 25], but some screening studies have shown nearly equal prevalence of the disease in males and females [2]. Females are typically diagnosed at 40–45 years, whereas males have shown a bimodal peak of diagnosis, at 10–15 years as well as at 35–40 years of age [24].

Pathogenesis

The pathogenesis of CD revolves around complex interactions between genetic, environmental and immune factors. Genetics play a strong role in CD expression. Studies have shown that risk of developing CD in first degree relatives ranges between 5% and 20% [26–28]. The role of genetics is also highlighted by the high degree of concordance in monozygotic twins which approach 70% [29]. CD patients must carry HLA-DQ2 or HLA-DQ8 genotype with the rare exception of HLA negative CD [30]. Hence a negative test for HLA-DQ2 or HLA-DQ8 has a negative predictive value of $>99\%$ [31]. However, a positive test for HLA-DQ2 or HLA-DQ8 does not equate to having CD, as up to 30% of people of European ancestry will have the HLA genotypes, and only a minority of these patients will develop CD [32, 33]. Multiple other genes have also been identified via genome wide association studies to be linked to CD [34, 35].

There are multiple environmental factors that have been studied in CD. Recently, multiple randomized controlled trials have failed to show a link between age of gluten introduction and breast feeding practices and CD [36, 37]. However, there are some data to suggest that larger amount of gluten intake in the first 2 years of life is associated with a higher risk of developing CD [38]. In a large study of 11,000 patients, elective cesarean section was associated with a modestly higher risk of developing CD (OR = 1.15; 95% CI, 1.04–1.26) [39]. The use of antibiotics have also been linked to the risk of developing CD [40]. These are signals indicating that alterations in the microbiome likely play an important role in the pathogenesis of CD. In contrast to Crohn's disease, smoking does not seem to be associated with CD [41, 42].

The pathogenesis of CD encompasses both innate and adaptive immune responses. The gliadin (component of gluten) undergoes deamidation in the intestine which then triggers activation of lymphocytes and an inflammatory cascade that damages the intestines.

Signs and symptoms

CD may present clinically with a wide variety of manifestations involving one or multiple organ systems [43]. In children, the classical triad of CD includes abdominal distention, diarrhea and failure to thrive [44]. Expectedly, 90% of children will present with abdominal pain, and more than 50% will endorse weight loss, diarrhea, weakness, nausea, or vomiting [45]. Gastrointestinal symptoms predominate in children under the age of three, while extraintestinal manifestations, including iron deficiency anemia, short stature, mood disorders, and alopecia are typical presenting complaints of older children [46].

As in children, adults may present with a diverse symptomatology. While typical GI complaints such as postprandial abdominal pain and bloating, chronic diarrhea, and steatorrhea are common, the initial presentation of CD is often extraintestinal, with absent or subclinical GI findings [47]. These symptoms frequently arise as a result of chronic malabsorption of either one or more micronutrients. Fatigue is also a common symptom of CD, even in the absence of anemia [48]. In a large cross-sectional study, 3% of patients with chronic fatigue were noted to have CD [49]. The underlying pathogenesis of fatigue in this patient population is poorly understood and may not be directly related to malabsorption.

Anemia often precedes the diagnosis, and in many cases, is the finding that prompts further investigation for CD. Due to chronic malabsorption, patients may present with iron, folate, B12, or other nutrient deficiency anemias (or a combination of these) [50]. Rarely, radiographic and clinical features of hyposplenism may be seen [51]. Other possible presentations of CD include recurrent acute pancreatitis or intussusception [52, 53]. The classical dermatologic finding of CD is dermatitis herpetiformis, a pruritic, vesicular rash located mainly on extensor surfaces [54], and is prevalent in 24% of patients [55]. Other skin findings that are seen less frequently include psoriasis, alopecia areata, and chronic urticaria [56].

Neurologic manifestations can be quite dramatic and also may due to the chronic malabsorptive state that characterizes CD. Peripheral neuropathy (likely B12 deficiency related), cerebellar gluten ataxia, seizures in children, and cognitive impairment have been described in the literature [57]. Endocrine findings include short

Table 1. Manifestations of CD by organ system

Manifestations of CD by organ system	
Gastrointestinal [60, 123–126]	**Skin** [56]
Abdominal cramping	Dermatitis herpetiformis
Postprandial pain/bloating	Psoriasis
Diarrhea	Alopecia areata
Steatorrhea	Chronic urticaria
Constipation	Atopic dermatitis
Transaminitis	**Neurologic** [57]
Oral aphthous ulcers	Peripheral neuropathy
Dental enamel defects	Cerebellar (gluten) ataxia
Hematologic [50]	Seizure (children)
Anemia (Iron, B12, Folate, & other etiologies)	Dementia/cognitive impairment
Thrombocytosis	**Endocrine** [47]
Leukopenia	Short stature
Thromboembolism	Infertility
Musculoskeletal [47]	Osteoporosis/fractures
Arthritis/arthralgias	**Constitutional** [47]
Psychiatric [47]	Fatigue
Depression	Malaise
Anxiety	
Increased suicide risk	

stature, osteoporosis (mediated by poor vitamin D absorption), and infertility [58]. From a psychiatric standpoint, a moderately increased suicide risk in patients with CD has been described [59], as well as higher rates of depression, anxiety, and hallucinations [47]. Table 1 summarizes the manifestations of CD by organ system.

Diagnosis

Given the extraintestinal manifestations, a high degree of clinical suspicion is often needed in order to appropriately diagnose CD. A case finding approach, rather than only testing those with malabsorption or steatorrhea, will increase the rate of detection. However, even this strategy will fail to identify most affected patients. Nevertheless, general population screening is not yet advised due to insufficient supporting evidence [60]. Despite much recent debates on this topic, the USPSTF recommends serologic markers as the best screening test for CD with subsequent confirmation obtained through small bowel biopsy (with exceptions as described within this manuscript). HLA testing can aid in the diagnostic algorithm in certain clinical settings such as disagreement between serology and pathology findings or in patients being tested on a GFD.

For serologic markers in individuals older than 2 years of age, immunoglobulin A (IgA) antitissue transglutaminase (TTG) antibody is the favored test for screening for CD with sensitivities ranging from 93 to 95% and specificities approaching 96% [60, 61]. Patients must be on a normal gluten containing diet to maximize the sensitivity of the serological testing. Other serologic markers include antiendomysial-IgA, which is 90% sensitive and approaches 99% specificity [62]. Though it has a high specificity,—antiendomysial-IgA testing is expensive and time consuming, but is useful in the setting of an equivocal IgA-TTG [32]. The recent development of IgA antibodies to deamidated gliadin peptides (DGP) has been found to have sensitivities between 80% and 98% and specificities ranging from 86% to 96% [62]. DGP antibodies appear to have a particularly high sensitivity in infancy [63]. Table 2 summarizes the available serologic testing and associated sensitivities and specificities for the diagnosis of CD.

A caveat with serologic testing is that a null result can occur in patients with IgA deficiency, which is present in 2–3% of all CD patients [64]. In this situation, IgG antibodies may be used for appropriate screening. Our institutional protocol automatically assesses for IgA deficiency prior to running an IgA based serologic testing cascade. IgG based testing is added to those whose total IgA is low and supplants IgA based tests completely when IgA is absent.

Endoscopic findings of CD are not specific and normal appearing duodenal mucosa does not rule out the disease. Common endoscopic findings in uncomplicated CD include decreased to flattened duodenal folds, scalloping, mucosal fissures, and mosaic pattern (Fig. 1). Studies have demonstrated that these endoscopic findings have low sensitivity and lack specificity for CD [65]. Hence, duodenal biopsies are needed to confirm the diagnosis of CD in the appropriate clinical setting. The disease distribution in CD extends from the proximal to distal small bowel. Hence, proximal small bowel (duodenal) biopsies are recommended for diagnosis.

Positive serologic testing is followed up by duodenal biopsy, which classically demonstrates histopathologic

Table 2. Serologic tests in CD screening

Serologic marker	Sensitivity mean % (95% CI)	Specificity mean % (95% CI)
Anti-TTG IgA [61]	94.1 (92.5–95.5)	96.5 (95.2–97.5)
DGP-IgA [61]	87.8% (85.6–89.9)	93.0% (91.2–94.5)
Serologic marker	**Sensitivity range**	**Specificity range**
DGP-IgG [62]	80.1% and 98.6%	>95%
Antiendomysial-IgA [62]	>90%	>94.7%

TTG Tissue transglutaminase, *DGP* deamidated gliadin peptide

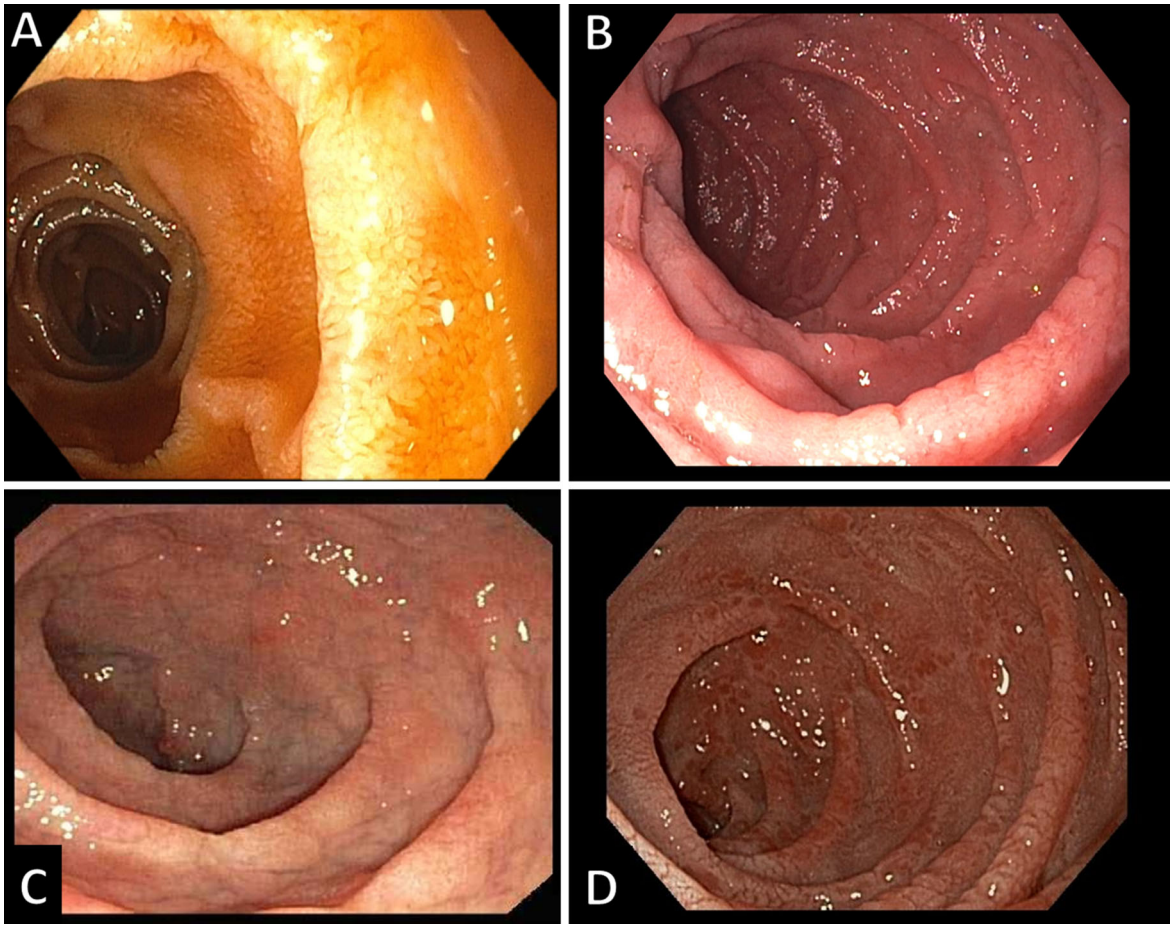

Fig. 1. **A** Endoscopic duodenal image demonstrating normal appearing mucosa with prominent villi. **B** Endoscopic duodenal image showing fissuring and scalloping of the mucosa in a 52-year-old woman with celiac disease. **C** Endoscopic duodenal image showing scalloping of mucosa along with nodularity and edema in a 39-year-old man with celiac disease. **D** Endoscopic duodenal image demonstrating scalloping, fissuring, and mosaic appearance of the mucosa in a 69-year-old woman with celiac disease.

changes of villous atrophy, crypt hyperplasia, and increased intraepithelial lymphocytes, which was a hallmark of the modified Marsh (Oberhuber) criteria [66, 67]. More recently devised simplified schema, such as the Corazza criteria, has been proposed [68]. A high degree of suspicion with negative serologies may also prompt small bowel biopsy. In general, adequate sampling includes one or two biopsies of the bulb and at least four biopsies of the distal duodenum [60].

It is now possible to diagnose CD in children without the need for small bowel biopsy if the following criteria are met: characteristic symptoms of CD, TTG-IgA levels >10 times the upper limit of normal (confirmed with a positive antiendomysial-IgA in a different blood sample), and positive HLA-DQ2 testing [60, 69–77]. For adults, the recommendation for biopsy stands, but non-biopsy diagnosis is an emerging area of research [78–80].

Serologic testing can be negative if the patient has been following a GFD for several weeks [60], although typically serologies normalize after 6–12 months of instituting a GFD [32]. If suspicion is high despite negative serologic testing, one can proceed to small bowel biopsy as the histologic changes on a GFD may persist for several months or years (median of 3.8 years) [81]. HLA-DQ2 and HLA-DQ8 testing is not recommended in the routine evaluation of CD [60]. However, it can be useful in certain clinical situations, especially those with equivocal serologic or histologic studies or in patients who are being tested on a GFD. These markers are found in virtually all patients with CD, but are also found in up to 30% of people of European ancestry [32, 33]. In essence, the absence of these markers effectively rules out the possibility of CD due to their high negative predictive value (>99%) [31, 82, 83]. Another option for patients being tested while on a GFD is a gluten challenge. This consists of reintroducing gluten in the diet and retesting with serologies and duodenal biopsies after 2–6 weeks.

Cross-sectional imaging with computed tomography enterography or magnetic resonance enterography tech-

Table 3. Conditions associated with CD

Specific conditions associated with CD	
Endocrine [58, 84--86, 90, 127, 128]	**Rheumatologic/connective tissue** [84, 129--135]
Type 1 diabetes mellitus	Sjögren's syndrome
Autoimmune thyroid disease	Systemic lupus erythematosus
Addison's disease	Juvenile idiopathic arthritis
Gastrointestinal [47, 52, 60, 84, 89, 92--94, 136--139]	Rheumatoid arthritis
Primary biliary cirrhosis	Sarcoidosis
Autoimmune hepatitis	**Hematologic** [84, 140--144]
Primary sclerosing cholangitis	Thromboembolic disease
Nonalcoholic fatty liver disease	Immune thrombocytopenic purpura
Budd Chiari syndrome	Enteropathy-associated T-cell lymphoma
Pancreatitis	**Cardiovascular** [144, 145]
Microscopic colitis	Atrial fibrillation
	Cardiovascular disease

nique has multiple potential roles in CD. This includes insinuation of underlying CD and workup of nonresponsive CD. We refer the reader to the role of cross-sectional imaging in CD review and original article on cross-sectional imaging in refractory CD in this same issue.

Associated conditions

A spectrum of disorders often coexists in patients with CD [84]. Type 1 diabetes mellitus is found in 1.6% to 16.4% of patients with CD [85, 86]. Clinical autoimmune thyroid disease may be found in up to 14% of adult CD patients [87, 88], and up to 8.1% of pediatric patients [89–91]. Primary biliary cirrhosis is prevalent in 3% of cases [92–94], and there is an association between CD and autoimmune hepatitis, primary sclerosing cholangitis, and fatty liver disease [94]. Furthermore, CD is associated with various disorders affecting the hematologic, cardiovascular, and rheumatologic realms of disease (Table 3).

Villous atrophy is not pathognomonic for CD, and there are other etiologies that clinicians must be aware of that may also present with villous atrophy on duodenal biopsy. These include certain medications (particularly olmesartan), tropical sprue, collagenous sprue, autoimmune enteropathy, and bacterial overgrowth for example [95, 96].

Treatment

The treatment of CD involves life-long dietary elimination of gluten. Gluten is found in wheat, barley, and rye. A strict GFD is often difficult to achieve due to inconspicuous sources of gluten, especially in processed foods. The absolute minimum amount of gluten needed to cause intestinal damage in CD is not completely understood but has been suggested to be 100 milligrams grams per day [97, 98]. A double blinded placebo controlled trial of microdose gluten challenge in CD patients demonstrated that 50 mg of gluten per day should be the threshold [99]. The definition of a gluten-free food item by the international Codex Alimentarius is one that contains <20 mg/kg of gluten [100]. A growing body of evidence suggests that CD patients can safely ingest pure oats in limited quantities which can replace nutritional components that are deficient in a GFD [101–103]. It is recommended to temporarily limit intake of lactose containing products after the initial diagnosis of CD in symptomatic patients if secondary lactase deficiency is suspected. Lactase deficiency usually resolves after intestinal healing.

A GFD can be deficient in certain vitamins and minerals including iron, calcium, and fiber all of which should be supplemented [104]. Hence, it is recommended that newly diagnosed CD patients visit with a registered dietician with expertise in a GFD to avoid gluten containing foods and for supplementation if needed. The success of a GFD is heavily dependent on patient education and motivation.

The majority of CD patients note symptomatic improvement in a matter of weeks after the institution of a GFD [105]. Monitoring is required to ensure adherence and improvement on a GFD. The components of monitoring include clinical visit with a physician/dietician and repeating serologic testing and duodenal biopsies. Serologic testing with TTG-IgA or DGP-IgA should be compared to baseline levels and are expected to normalize within 3–12 months. On the other hand, the median time to histologic healing is as high as 3 years after the initiation of a GFD [81].

There are currently no available or approved medical treatments for CD. Glucocorticoids can induce symptomatic improvement but are not recommended for use in uncomplicated CD due to long term side effects and relapse of symptoms upon discontinuation. Glucocorticoids may be used temporarily in severe or refractory CD. Multiple therapeutic agents are currently being investigated for CD, such as inhibition of tissue transglutaminase and HLA molecules, as well as immunosuppressants and immunomodulators [106].

Complications

Nonresponsive CD

Nonresponsive CD is defined as persistent symptoms or signs of CD in patients prescribed a GFD and can affect up to 10–30% of patients [107, 108]. The most common etiology of nonresponsive CD is inadvertent gluten contamination, present in up to 50% of such patients [109]. Therefore, the first step in evaluating nonresponsive CD, after confirming the initial diagnosis, is a careful review of dietary intake ideally with an expert CD dietician. Other etiologies of nonresponse include: lactose intolerance, fructose intolerance, small intestinal

bacterial overgrowth, microscopic colitis, pancreatic insufficiency or irritable bowel syndrome.

Refractory CD

Refractory CD is defined as persistent symptoms or signs of malabsorption together with small bowel villous atrophy despite at least 6–12 months of a strict GFD [110]. The above etiologies of nonresponsive CD should be excluded prior to making the diagnosis of refractory CD. True refractory CD is uncommon as it only affects 1% to 2% of all CD patients [111]. Refractory CD is subdivided into Type I and Type II. The two types are differentiated based on the presence of clonal/aberrant intraepithelial lymphocytes. Type II refractory CD is associated with the presence of aberrant intraepithelial lymphocytes lacking cell surface receptors and clonal T-cell receptor gene rearrangement [112].

It is important to distinguish Type I from Type II refractory CD as they differ in prognosis and management. Type II refractory CD has been associated with a poorer prognosis compared to Type I. For example, the 5-year survival in Type II refractory CD ranges between 44% and 58% compared to 96% in Type I refractory CD [113–115]. The increased mortality in Type II refractory CD is partially attributed to the increased risk of EATL in this patient population (see below). There are no controlled trials that have investigated medical treatment of refractory CD. Hence, the management of refractory CD includes the use of immunosuppressives such as glucocorticoids (budesonide), thiopurines, mesalamine, biologics including infliximab, and chemotherapy including cladribine and myeloablation with stem cell autotransplantation based on cases series and reports.

Ulcerative jejunoileitis

Ulcerative jejunoileitis clinically presents with abdominal pain, diarrhea, weight loss and malnutrition despite a GFD. It can result in gastrointestinal bleeding, bowel obstruction secondary to strictures and perforation in severe cases. It is a rare complication of CD and exact incidence and prevalence remains unknown. It can also occur de novo in the absence of CD. The diagnosis is made by deep enteroscopy, cross sectional enterography or video capsule endoscopy. Caution should be exercised in utilizing video capsule endoscopy in this setting to avoid capsule retention in strictured segments of the small bowel. Ulcerative jejunoileitis carries an increased risk of developing EATL and hence has a poor prognosis.

Enteropathy associated T-cell lymphoma

Enteropathy-associated T-cell lymphoma is a type of non-Hodgkin's lymphoma. It's a dreaded but rare complication of CD. It can present with small bowel ulcerations, obstruction, perforation, B symptoms, lymphadenopathy or gastrointestinal symptoms such as abdominal pain, diarrhea and weight loss. EATL is an aggressive malignancy with a dismal 5-year survival rate of 8% to 20% [115, 116]. The combination of chemotherapy and hematopoietic stem cell transplant, however, has shown to increase the 5-year survival up to 60% in a small series [117].

Small bowel adenocarcinoma

Small bowel adenocarcinoma is an uncommon malignancy in the general population accounting for only 3% of all gastrointestinal cancers [118]. The standardized incidence ratio of small bowel adenocarcinoma in CD has been shown to be as high as 10 [119]. In contrast to the general population, small bowel adenocarcinoma as a complication of CD is more likely to develop in the jejunum than in the duodenum [120]. Treatment involves surgical resection and adjuvant chemotherapy for positive lymph nodes. In the case of metastatic disease, chemotherapy is recommended. The prognosis of small bowel adenocarcinoma is poor as the 5-year survival ranges between 39% and 46% [121]. However, survival in CD-associated small bowel adenocarcinoma is significantly better than that in stage-matched patients without CD [122].

Conclusion

Celiac disease is the most common immune-mediated enteropathy. There is consistent evidence that the incidence of CD is increasing in the US and other parts of the world, despite stable genetics. Environmental factors and the microbiome likely play a significant role in the increased incidence of CD, but it remains poorly understood. CD is a multisystemic disease that may present with atypical manifestations requiring a high index of suspicion for diagnosis. Lifelong gluten avoidance remains the mainstay of therapy as multiple therapeutic modalities are currently in the investigative stages and not available for clinical use. Involvement of an expert dietician is key in ensuring adherence to a GFD. Complications of CD such as refractory CD, ulcerative jejunoileitis, EATL, and adenocarcinomas are rare but carry an unfavorable prognosis. Hence, a thorough investigation should be sought to identify patients who do not respond to GFD with these complications.

Compliance with ethical standards.

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Conflict of interest The authors declare that they have no conflict of interest.

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Informed consent Statement of informed consent was not applicable since the manuscript does not contain any patient data.

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