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MINI-REVIEW

A Review on the Clinicopathological Features and Management of the Celiac Disease

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Abstract: Celiac disease (CD) is a multifactorial and chronic autoimmune disease caused by the ingestion of gluten. Epidemiological studies have shown that the disease is currently becoming more common worldwide. Among the countries, North America, North Europe, and Australia have high prevalence of CD. CD is often confused with other chronic gastrointestinal tract-related diseases. Therefore, it is important to have a broad understanding of the clinicopathological features of CD. This review aims to illustrate the epidemiology, pathogenesis, clinical manifestation, and diagnosis and treatment of CD.

Keywords: Celiac disease, Gluten, Tissue transglutaminase, Small intestine biopsies

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1 Introduction

Celiac disease (CD) is a multifactorial and chronic autoimmune intestinal disease attributed to gluten consumption. Individuals carrying human leukocyte antigen (HLA) genes, notably the HLA-DQ2 and HLA-D8, are susceptible to the development of CD[1]. People who suffered from CD usually has malabsorption syndrome following a prolonged period of gluten ingestion. The clinical manifestations of CD include specific serum autoantibody reactions and damage to the small intestinal mucosa.

Gluten is a plant-based storage proteins widely found in wheat, barley, rye, and oats. The development of CD is the result of the pathological immune interactions caused by the alcohol-soluble part of gluten. Following the pepsin- and trypsin-mediated digestion, gluten causes toxicity in the susceptible individuals[2]. The ingestion of gluten triggers an immune response in which the immune system recognizes and attacks gluten as foreign particle, leading to the ultimate destruction of the small intestine's villi and inadequate food absorption. Among the four different gliadins, such as ω-, α-, β-, and γ-gliadins, the α-gliadin is the most bioactive peptide which can exert cytotoxicity and

stimulate an immune reaction. In addition, the intracellular accumulation of gliadin peptide p31-43 causes an increase in the reactive oxygen species level[3].

The genetic background of CD is quite complex and remains elusive. The genes located in the HLA region that codes for the HLA-II molecules (DQ2.5 and DQ8 heterodimers) are the genetic factors of CD. The HLA-DQ2.5 heterodimers of more than 90% of the Caucasian CD patients are produced by the combination of HLA-DQA1*0501 and DQB1*0201[2], whereas the remaining patients carry the heterodimer encoded by DQA1*03 (chain-chain) and DQB1*0302 (chain-chain). However, the individual presence of DQ2 heterodimer is inadequate for the development of CD. HLA-DQ2 haplotype exists in about 0–35% of the Caucasian population, where CD has a high prevalence rate[4], but only 2–5% of them are genetic carriers. Several additional loci had been identified as susceptible genes for CD through the genome-wide association study[5]. Therefore, genetic background plays a critical role in the development of CD. At present, more studies have begun to focus on the role of environmental factors on this disease.

The signs and symptoms of CD vary among individuals but some patients remain asymptomatic. Commonly, most of the CD cases are manifested by diarrhea, abdominal pain, abdominal distension, and other gastrointestinal (GI) disease features. Although traditionally being considered a rare disease, the recent epidemiological studies have shown an increase in the cases of CD. Furthermore, due to a lack of understanding, the clinical manifestations of CD can be easily confused with other chronic GI diseases. Therefore, an understanding of the clinicopathological features of CD is instrumental for successful management of the disease. In this review, we provide an overview of the clinicopathological features, diagnosis, and clinical management of CD.

2 Epidemiology and etiology

In the past 30 years, a large number of epidemiological studies had been conducted in Europe to determine the frequency of CD[2]. In 1950, one of the studies determined that the cumulative incidence of CD in England and Wales was 1 case per 8000 people, while in Scotland, it was 1 case per 4000 people[6]. This study was entirely based on the detection of typical symptoms, further confirmed by a combination of complex and non-specific tests. In the 1960s, more specific tests, including GI tract biopsy, were introduced to evaluate malabsorption problems in children, thereby increasing awareness about CD[7]. In the mid-1970s, studies in Ireland, Scotland, and Switzerland reported that the peak incidence of CD was 1 case per 450–500 people[6,8].

A serological screening study involving more than 17,000 school-going children in Italy found that the prevalence of CD was 1:48, and the ratio of known to undiagnosed CD cases was 1:7[8]. In Denmark, the estimated incidence of CD was 1:10 based on clinical findings[9]. At the same time, there was an increase in CD incidence in neighboring Nordic countries, such as Sweden and Finland, due to the decline in breastfeeding[9]. Subsequent serological screening studies showed that the incidence of CD in Denmark was 1 case per 50,072 people, which is quite comparable to that in Sweden. These results suggested that most of the CD cases in Denmark were not previously diagnosed, presumably due to a lack of typical GI symptoms. Furthermore, due to the increase in the diagnosis's surveillance and accuracy, the incidence of Scottish children with non-classical CD has increased dramatically over the past 20 years[4]. Thus, it is possible that the incidence of CD is underrated to varying levels in the areas that lack large-scale epidemiological research.

The clinical manifestations of CD may vary greatly. In some countries, CD is considered a rare disease but the prevalence and serological screening data pointed out that CD is a common disease with relatively rare GI manifestations[10]. The incidence of CD in the Netherlands became almost tripled when the disease was confirmed by a biopsy-based method between 1995 and 2012[11,12]. On the other hand, the incidence of CD has quadrupled in the past 22 years[12-16]. The incidence of CD is high among the Caucasian which is about 0.6–1%. According to the medical records of more than 2 million healthy Jewish blood donors from the youth conscription databases, the prevalence of diagnosed CD had increased from 0.5% in 1998 to 1.1% in 2015[16-18].

3 Pathology

The characteristics of small intestine biopsies from CD include partial or complete villous atrophy, crypt hyperplasia, and intraepithelial lymphocyte infiltration[2,7]. According to the modified Marsh classification, the intestinal damage is divided into four stages. Stage 0 intestinal damage is characterized by the lesion invasion in the mucous layer, the increased number of intraepithelial lymphocytes, and the presence of lymphocytes in the lamina propria, whereas Stage 1 damage features microscopic enteritis with an increase of intraepithelial lymphocytes. A feature of Stage 2 intestinal damage is crypt hyperplasia along with villous atrophy while Stage 3 is characterized by a complete atrophy of the intestinal villi[19,20]. According to the simplified classification systems, the intestinal damage can be categorized in three grades or types; the pathologic results of CD are more reproducible based on the simplified version. Grade A/type 1 damage features increased intraepithelial lymphocytes but no villous atrophy; Grade B1/type 2 damage is characterized by shortened villi; Grade B2/type 3 features complete villous atrophy[20,21].

4 Clinical manifestations

Patients with CD usually suffer from abdominal pain, diarrhea, constipation, nausea, vomiting, and anorexia[6]. Nevertheless, patients might exhibit symptoms

associated with the GI tract. Despite common genetic and environmental factors, the clinical manifestations of CD can be very diverse. After taking gluten-containing diet, the symptoms generally appear within weeks or years after the intake. Following this, weight gain declines quickly. Young children may suffer from watery diarrhea, accompanied by dehydration and electrolyte imbalances. A small number of these children may also develop severe hypoalbuminemia and edema. With these, they may experience a state of shock, known as "celiac crisis"[2]. In the atypical form, the onset of CD symptoms and clinical manifestations could be different[8]. According to Mancuso *et al.*, the reported diagnostic age had increased to 5-6 years of age and <50% of the new cases in Finland had experienced typical GI symptoms of CD. Reports from Scotland, Britain, Canada, and the United States also showed that almost 50% of newly diagnosed CD patients did not express GI symptoms[8].

The asymptomatic CD is characterized by pathological changes that may be limited to the proximal intestine[2]. Most of these cases are determined through screening programs involving relatively healthy subjects. The common clinical manifestations of asymptomatic CD include iron-deficiency anemia, behavioral abnormality, poor health status, and fatigue during exercise[8,11,22,23]. Non-GI symptoms experienced by asymptomatic CD patients include dermatitis herpetiformis, iron-deficiency anemia, short stature, enamel hypoplasia, osteoporosis, chronic hepatitis, elevated level of transaminases, delayed puberty, and recurrent abortions[2,3,24-26]. Besides, these asymptomatic CD patients have neurological manifestations such as idiopathic cerebellar ataxia, neuropsychosis, peripheral neuropathy, seizures, encephalopathy, and myopathy. Apart from that, patients with CD may suffer from autoimmune diseases, including type 1 diabetes mellitus, autoimmune thyroid disease, autoimmune hepatitis, rheumatoid arthritis, and Addison's disease[7].

5 Diagnosis

A few decades ago, the identification of CD had been entirely based on medical history and clinical symptoms of young patients with chronic diarrhea, abdominal symptoms, and weight loss[6]. Nowadays, however, the diagnosis of CD mainly depends on the identification of serum markers and the histopathology of intestinal mucosa following biopsy (Figure 1)[27]. The predicted positive and negative values of CD biomarkers, such as glutamine transaminase and anti-endomembrane bacteria antibody, were found to be more than 96% in the diagnosis of CD[28]. Therefore, the framework of CD diagnosis is based on three key components: Case identification, screening test, and confirmatory test[27].

The laboratory examination of CD includes the following[28-30]:

(i) The detection and determination of antibodies such as anti-tissue transglutaminase antibodies, endomysial antibodies, and deamidated gliadin peptide antibodies;
(ii) HLA gene detection (in patients with HLA allele DQ2 or DQ8, high-risk cases);
(iii) The pathological examination of small intestinal specimens, which is the gold standard technique for CD diagnosis;
(iv) Endoscopic examination for obtaining small intestinal mucosa by biopsy (Figure 1).

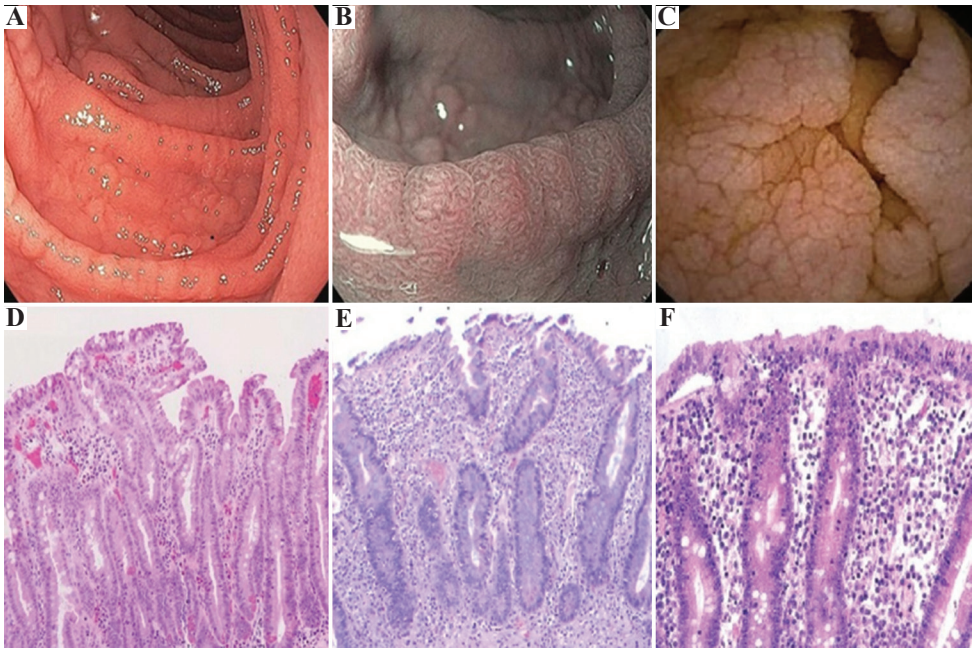

Figure 1. Endoscopic view of the duodenum and histologic findings in celiac disease. (A) The fissures are visible in the duodenal folds. (B) Narrow band imaging with near-focus mode shows the loss of duodenal villi. (C) Capsule endoscopy shows the fissure-like appearance and partial loss of small intestinal villi. (D) Partial villous atrophy. (E) Subtotal villous atrophy. (F) Complete villous atrophy.

6 Treatment

Treatment of CD includes lifelong abstinence from gluten[6]. So far, there is no test that can objectively detect the gluten intake in clinical practice. The ingestion of wheat might cause CD, thus severely affecting the quality of life. One of the main directions of CD control is to, with the use of breeding technology and food processing technology, devise the methods of producing wheat products that can decrease gluten sensitivity. In addition to gluten-targeted therapy, immunotherapy shows a promising result by modulating the mechanism of mucous membrane injury[30-32]. Although patients with CD must take a gluten-free diet, it has been reported that such a diet may increase the risk for metabolic syndrome[4,31-34].

Despite the improvement of lifestyle and medical technology, there is an increase in the cases of allergic diseases and autoimmune diseases. Several studies demonstrated that there is a strict association between CD and autoimmune endocrine diseases. For instance, transient endocrine growth axis dysfunction and growth hormone deficiency were associated with the high prevalence of CD. Thus, hormone-related therapies are gaining much attention[35,36]. Although the potential association between CD and vaccinations has not been widely investigated, studies on the potential immunotherapy for treating CD have been carried out[37].

7 Conclusion

At present, multidisciplinary research is being carried out worldwide to understand the pathogenesis of CD. More extensive studies are required for a better understanding of the clinicopathological features of CD. Given the higher-than-expected records of CD prevalence and the fact that CD shares some similar symptoms with some chronic GI disorders, it is important for clinicians and researchers to have a deep understanding of CD for better diagnosis, treatment, and clinical management.

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Conflicts of interest

None to declare.

Author contributions

F.W., Y.L., S.L., X.L., L.W., and F.J. conceived the idea of this review. F.W., Y.L., S.L., X.L., L.W., F.J., and ATMMC gathered data and information for this review. ATMMC wrote and reviewed the manuscript. MRK reviewed and edited the manuscript.

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