



## REVIEW ARTICLE

# Pathology of celiac disease: An insight about etiopathogenesis, pathophysiology and histologic diagnosis

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OPEN ACCESS

## PUBLISHED

30 September 2024

## CITATION

Tinguria, M., 2024. Pathology of celiac disease: An insight about etiopathogenesis, pathophysiology and histologic diagnosis. Medical Research Archives, [online] 12(9).

<https://doi.org/10.18103/mra.v12i9.5696>

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## DOI

<https://doi.org/10.18103/mra.v12i9.5696>

## ISSN

2375-1924

## ABSTRACT

Celiac disease (CD) is an immune mediated disorder characterized by intolerance to gluteins in certain grains like wheat, barley, and rye. The gliadin exposure in susceptible individuals leads to an inflammatory reaction with damage to the small intestinal mucosa with villous blunting, atrophy and ultimate disappearance of intestinal villi. The damaged intestinal villi lead to malabsorption.

The development of celiac disease (CD) is determined by both environmental and genetic factors. The gluten in the grains represents an environmental factor. In addition to this environmental factor, CD development involves genetic predisposition as most CD patients possess human leucocyte antigen (HLA) DQ2 and/or HLA-DQ8. The complex interplay of multiple genetic and environmental factors determines the development of CD.

Small bowel mucosal biopsies remain gold standard for the diagnosis of CD because of variation in the clinical findings and serologic testing. Histologic examination of small intestine also helps to monitor the course of disease, response to treatment, and in detecting potential complications of celiac disease such as enteropathy associated T-cell lymphoma, adenocarcinoma, and concurrent intestinal diseases.

There has been significant development in understanding the pathophysiology, pathogenesis, and diagnosis of celiac disease. The present review summarizes the important development in CD in last few years with special emphasis on etiopathogenesis, pathophysiology, and pathologic features of CD. Better understanding of these features is not only important for correct diagnosis but also results in better patient management and would pave a way for future research of this overly complex disease characterized by complex interaction of environmental, genetic as well as immunologic mechanisms.

## Introduction

Celiac disease (CD) is an immune mediated disorder characterized by intolerance to glutens in certain grains like wheat, barley, and rye. The gliadin exposure in susceptible individuals leads to an inflammatory reaction with damage to the small intestinal mucosa with villous blunting, atrophy and ultimate disappearance of intestinal villi. The damaged intestinal villi lead to malabsorption with diarrhea, steatorrhea, weight loss, fatigue, and abdominal pain. The CD is unique amongst autoimmune disorders. The typical autoimmune features include a strong human leucocyte antigen (HLA) association, production of specific antibodies, and immune-mediated killing of a particular cell type (intestinal cells). The uniqueness lies in the fact that the disease only manifests upon exposure to an exogenous factor.

The duodenal biopsy for histologic assessment remains the gold standard in the diagnosis of CD. The histologic changes in the duodenum include villous atrophy associated with increased intraepithelial lymphocytes. As similar changes can be seen in various other pathological conditions, the accurate diagnosis of CD involves integration of clinical, serological and genetic characteristics in the histologic assessment of CD.

The clinical presentation of celiac disease can be variable. In the mild form, patients can be almost asymptomatic whereas in the most severe form of disease patients may present with many complications which may be life threatening<sup>1-3</sup>.

The present article describes in detail etiopathogenesis, pathophysiology, and pathologic features of CD. Better understanding of these features is not only important for correct diagnosis but also results in better patient management and would pave a way for future research of this overly complex disease characterized by complex interaction of environmental, genetic as well as immunologic mechanisms.

## Pathogenesis

The development of celiac disease (CD) is determined by both environmental and genetic factors. The

gluten in the grains represents an environmental factor. In addition to this environmental factor, CD development involves genetic predisposition as most CD patients possess human leucocyte antigen (HLA) DQ2 and/or HLA-DQ8. In CD, CD4 + T-cell response is raised against several distinct gluten peptides and these peptides are recognized in the context of CD-associated HLA DQ molecules. In addition, the patients make antibodies specific for gluten proteins. The complex interplay of multiple genetic and environmental factors determines the development of CD.

### ENVIRONMENTAL FACTORS:

#### Gluten

Gluten is the name applied to a set of proteins found in grains of wheat, barley, and rye<sup>4,5</sup>. Gluten proteins are rich in glutamine and proline residues. In wheat, gluten proteins are divided into gliadins and glutenins. Each wheat variety expresses multiple  $\alpha$   $\beta$  and  $\omega$  gliadins in addition to low and high molecular weight glutenins. While gliadins are soluble in alcohol, glutenins are not soluble in alcohol. Gluten has an extremely high content of amino acids glutamine (30%) and proline (15%). High proline content renders gluten highly resistant to degradation by gastrointestinal enzymes, making it possible for large immunogenic gluten peptides to reach the mucosal surface<sup>6,7</sup>. There may be up to hundred different gluten peptides in a single wheat variety and many of these are implicated in the pathogenesis of celiac disease. Gluten proteins of barley, and rye are termed hordeins and secalins, respectively. Gut lesions of most patients with CD completely resolve when gluten is excluded from the diet, and they reappear when the patients again consume gluten.

#### Non-gluten factors

Environmental factors other than glutens have been suspected in the development of CD as only minority of individuals who carry HLA DQ2 and HLA DQ8 haplotypes ever develop the disease. Infections early in life are suspected and there appears to be role of Rota virus infection based on epidemiological evidence. Some studies suggested that rotavirus vaccination may protect against

development of CD<sup>8,9</sup>. There is some evidence for association of CD with other infectious agents including *Helicobacter pylori*, adenovirus, and enterovirus<sup>10</sup>.

#### GENETIC FACTORS:

##### HLA – genes

CD is a highly heritable disease as indicated by strong familial clustering and a high concordance rate in monozygotic twins<sup>11,12</sup>. The genes leading to susceptibility for CD have been mapped with Genome-Wide association studies (GWAS). There is strong genetic influence in CD as the concordance between monozygotic twin is 80% but only 11% in dizygotic twins<sup>8</sup> which is the same as the risk for first degree relative<sup>13</sup>. There is a strong association between CD and the HLA complex. The strongest association is observed with HLA DQ 2.5; more than 90% celiac patients possess one or two copies of HLA DQ 2.5<sup>14</sup>. CD is associated to a lesser extent with HLA DQ8<sup>15</sup>. Individuals homozygous for HLA DQ 2.5 have a fivefold increased risk for development of CD compared to individuals heterozygous for HLA DQ 2.5<sup>16</sup>. Another HLA – DQ variant – HLA DQ 2.2 has a peptide binding motif almost identical to that of HLA DQ 2.5<sup>17</sup>. Whereas HLA – DQ 2.5 predisposes to CD, HLA – DQ 2.2 does not. This difference is related to the peptide – binding properties of these HLA – DQ variants. The estimated risk effect of HLA – DQ2 and HLA DQ8 on CD development is estimated to be about 35%<sup>18</sup>. Not all HLA and DQ 2.5<sup>+</sup> and HLA DQ 8<sup>+</sup> individuals develop CD indicating that these HLA genotypes are necessary but not sufficient for the development of CD. Recently many additional genetic loci for CD have been identified. Most of these genes encode proteins involved in immunity in supporting the notion that CD is an immune mediated disorder.

## Gut Immune System and adaptive immune response in celiac disease

### GUT IMMUNE SYSTEM

The gut immune system involves both innate and adaptive parts and can be divided into geographically

distinct inductive and effector sites. The inductive sites comprise gut-associated lymphoid tissue (GALT), specifically Peyer's patches and isolated lymphoid follicles. In addition, antigens taken up from the lumen can initiate immune response in gut – draining lymph nodes<sup>19</sup>. In these structures, priming of B and T cells, as well as memory recall responses take place. In the GALT, B cells diversify their BCRs through somatic hypermutation and differentiate into long-lived plasma cells and memory B cells. The gut plasma cells display more mutation in their BCRs than any other B cells or plasma cell population in the body<sup>20</sup>. After antigen stimulation, the prime cells travel via thoracic duct and reach blood circulation and then via blood populate the epithelium (T cells) and lamina propria (T cells and plasma cells) as effector cells protecting the tissue against microbial intruders. These effectors are tissue resident and extremely long lived<sup>21-23</sup>.

### INTRAEPITHELIAL LYMPHOCYTES

The intraepithelial lymphocyte (IEL) compartment is composed of T cells expressing either  $\alpha\beta$  or  $\pi\Delta$  T-cell receptors with either helper (CD 4<sup>+</sup>) or suppressor (CD 8<sup>+</sup>) phenotypes. In celiac disease, the number of IEL is increased from a normal number of < 25 IELs per hundred enterocytes and although not unique to CD, is considered a diagnostic sign of the disease. Many of these T cells also express natural killer (NK) cell receptor – both activating and inhibitory receptors. NK cell receptors are believed to be responsible for killing of enterocytes which is an essential component of celiac disease<sup>24-26</sup>.

### LAMINA PROPRIA T CELLS

In active CD, there is a marked infiltration of TCR  $\alpha\beta$ <sup>+</sup> T cells in the lamina propria. Unlike the IELs both CD 4<sup>+</sup> and the CD 8<sup>+</sup> T cells in the lamina propria lack the proliferation markers Ki67 in active CD<sup>27</sup>. In active CD, fraction of CD4<sup>+</sup> T cells express markers associated with a subset of regulatory T cells; however, it is not clear whether regulatory CD 4<sup>+</sup> T cells play a role in the pathogenesis of CD<sup>28</sup>.

### LAMINA PROPRIA PLASMA CELLS

The active CD is associated with lamina propria plasmacytosis with an increased density of

immunoglobulin A (IgA), IgM, and IgG plasma cells by factors of 2.4, 4.6, and 6.5<sup>29</sup>. In normal small intestine, IgA expressing plasma cells dominate with very few IgG cells. In contrast to IgG plasma cells, IgA and IgM plasma cells express surface immunoglobulins<sup>30,31</sup>. These molecules act as functional B cell receptors (BCR). In addition to BCR, gut plasma cells express HLA class II molecules, raising the possibility that they might have role as an antigen presenting cells<sup>32</sup>.

#### LAMINA PROPRIA MYELOID CELLS

The CD lesion has increased density of neutrophils and monocyte -derived cells. In active CD, infiltration of neutrophils in the lesion has been demonstrated<sup>33,34</sup>.

#### LAMINA PROPRIA STROMAL CELLS

Lamina propria stromal cells such as fibroblasts and myofibroblasts are important for building the extracellular matrix. In addition, they are also involved in creating niches for the intestinal stem cells, maturation of the epithelial cells along the crypt-villous axis and have various immune functions like bone marrow where they are important for creating survival niches for long lived plasma cells<sup>35</sup>. Stromal cells in the lamina propria may support long-lived plasma cells in the gut<sup>36</sup>. In relation to CD, knowledge how the composition and function of lamina propria stromal cells may be altered is limited.

#### LOCAL CYTOKINE/CHEMOKINE ENVIRONMENT

The understanding of local cytokine and chemokines in the context of CD is limited. Gluten specific CD<sup>4</sup> T cells produce IFN - $\gamma$ <sup>37</sup> and intraepithelial TCR  $\alpha\beta$  + CD 8 and TCR delta  $\gamma$  T cells also likely contribute with production of this cytokine<sup>24</sup>. The chemokine CXCL 10 and CXCL 11 are produced by enterocytes in response to IFN - $\gamma$  stimulation<sup>38</sup> and they play a role in migration of lymphocytes in the epithelium. Increased expression of IL-15 is observed in CD lesion in both the epithelium and lamina propria<sup>39</sup>. The cytokine stimulates proliferation and survival of T-cells and NK cells<sup>40</sup> and promotes tissue destruction<sup>41</sup>.

#### ADAPTIVE IMMUNE RESPONSE

CD develops almost exclusively in HLA – DQ 2.5 or HLA – DQ 8 positive individuals. Gluten – derived

peptides presented by HLA DQ 2.5 or HLA DQ 8 induce CD<sup>4</sup> T cells response. HLA – DQ 2.5 and HLA – DQ 8 prefer to bind peptides with negatively charged aminoacids at anchor residues; however, gluten peptides do not carry negative charge and therefore bind poorly to HLA – DQ 2.5 or HLA – DQ 8. Tissue transglutaminase 2 (TG2) can convert non-charged glutamine in gluten into negatively charged glutamic acid (deamidation). This increases binding capacity of gluten peptides to HLA – DQ 2.5 and DQ 8<sup>42,43</sup>. TG2 for most parts remains intracellularly in an inactive form and is activated upon its release during tissue damage<sup>44,45</sup>. Tjon et al proposed two possible mechanisms which could trigger tissue damage. CD<sup>4</sup> T cell response against native gluten peptide could represent the first breach in oral tolerance to gluten. The presentation of native gluten peptides by HLA – DQ 2 and HLA – DQ 8 to CD 4<sup>+</sup> T-cells leads to production of IFN –  $\gamma$ . IFN –  $\gamma$  in turn leads to higher expression of HLA – DQ molecules thereby increasing gluten peptide presentation. In presence of gluten this could become a self amplifying loop causing some tissue damage. The tissue damage would lead to release of TG2 which would modify gluten peptides into high affinity ligands for HLA – DQ 2 and/or HLA – DQ8, by process of deamidation. The gluten specific CD<sup>4</sup> + T – cell response is thus expanded leading to additional tissue damage with initiation of second self amplifying loop. The second possible mechanism for tissue damage might be gastrointestinal tract infections<sup>46</sup>.

#### DAMAGE TO INTESTINAL EPITHELIUM

Intraepithelial lymphocytes (IEL) are localized between intestinal epithelial cells and play an important role in immunosurveillance of the epithelium. IEL represent a mixed population of TCR  $\alpha\beta$  + T cells, TCR  $\gamma\delta$  + T cells and NK cells with vast majority of IELs being CD 8<sup>+</sup> TCR  $\alpha\beta$  + T cells<sup>47</sup>. The NK - cell receptors expressed on TCR<sup>+</sup> IELs are distinct from NK – cell receptors expressed on blood T cells<sup>47</sup>. The NK cell receptors are thought to act mainly as T cell costimulators lowering the threshold for T-cell activation in stressful times<sup>48</sup>.



In active CD, CD8<sup>+</sup> TCR αβ<sup>+</sup> and TCR γδ<sup>+</sup> IELs are markedly increased. Akin to normal controls, IELs from active celiac disease express NK cell receptors. However, as compared to normal controls, IELs from active CD acquire more activating NK-cell receptors<sup>47</sup>. In healthy small intestine, IELs predominantly express inhibitory receptors. Interaction of activating NK-cell receptors with their ligands will enhance IFN-γ production and cytotoxicity leading to tissue damage. An important factor in acquiring an activating NK cell receptor repertoire is interleukin 15 which has been shown to upregulate both NKG2D and CD94/NKG2C on IELs of active CD patients and boost their ability to lyse enterocytes<sup>25</sup>. IELs can also alter the NK-cell receptor function leading to NK-cell receptor mediated cytotoxic independent of TCR specificity. While gluten-specific CD4<sup>+</sup> T cells elicit an inflammatory response in the lamina propria, IELs in the epithelium acquire activating NK receptors and the ability to lyse stressed epithelial cells independent of T-cell receptor signalling which likely contributed to the tissue damage in CD.

In refractory celiac disease, the survival, expansion, and acquisition of NK cell like phenotype is even more pronounced than in CD, probably due to presence of larger amounts of IL-15. RCD II patients have an aberrant clonal IEL population that lacks surface TCR-CD3 expression. Studies on aberrant TCR-CD3 negative IEL lines from RCD II patients showed that upon stimulation with IL-15, these cell lines express granzyme β and lyse intestinal

epithelial cell line HT29. This study suggests a role of abnormal IEL in perpetuating epithelial damage in RCD II patients<sup>39</sup>. IL-15 dependent NK cell like transformation of IELs may be an essential step in the immunopathology of RCD.

### Possible sequence of events in the development of celiac disease

Tjon et al suggested possible sequence of events in the development of celiac disease<sup>46</sup>(Table 1). The healthy individuals may have antibodies against gluten peptide and CD4<sup>+</sup> T-cells specific for native gluten peptide; however, regulatory processes in the intestine keep gluten specific T cell response in check. This steady state can be breached by frequent episodes of enteroviral infections leading to secretion of inflammatory cytokines and differentiation of Th 1 cells with enhanced response to gluten<sup>49</sup>. The low level of gluten reactivity and pathogen induced inflammation together could lead to tissue damage and release of TG2. The TG2 would generate a large repertoire of deamidated gluten peptides with high affinity for HLA DQ with boosting of gluten-specific T cell response. Regulatory processes are no longer able to contain T cell response and exposure to gluten leads to inflammation. At this point return to the steady state is possible only with the elimination of gluten. HLA DQ phenotype always plays an important role in the development of CD<sup>46</sup>.

**Table 1:** Possible sequence of events in the development of celiac disease

Healthy individuals:	May have antibodies against gluten peptide and CD4 <sup>+</sup> T-cells specific for native gluten peptides. Regulatory processes in intestine keep gluten specific T cell response in check.
Breaching of steady: state	Frequent episodes of enteroviral infections → secretion of inflammatory cytokines and differentiation of Th 1 cells with enhanced response to gluten → Tissue damage and release of TG2 → Large repertoire of deamidated gluten peptides with high affinity for HLA DQ → Boosting of gluten specific T cell response. Regulatory processes are no longer able to contain T cell response and exposure to gluten leads to inflammation.
Return to the steady: state	Possible only with the elimination of gluten.

Note: At all stages, HLA DQ phenotype plays an important role in the development of celiac disease.

## Pathology

### ENDOSCOPIC APPEARANCE

The celiac disease may be associated with mucosal abnormalities suspicious of CD. This should lead to duodenal biopsies even in the absence of classic symptoms of CD. The endoscopic abnormalities include decreased or absent Kerckring's folds<sup>50</sup>, mosaic pattern, scalloped folds, and visible underlying blood vessels<sup>51</sup>. The endoscopic findings of ulceration, stricture usually indicate complicated CD, inflammatory bowel disease, or malignancy. The presence of normal duodenal mucosa does not rule out CD<sup>52</sup>.

### BIOPSY RECOMMENDATIONS

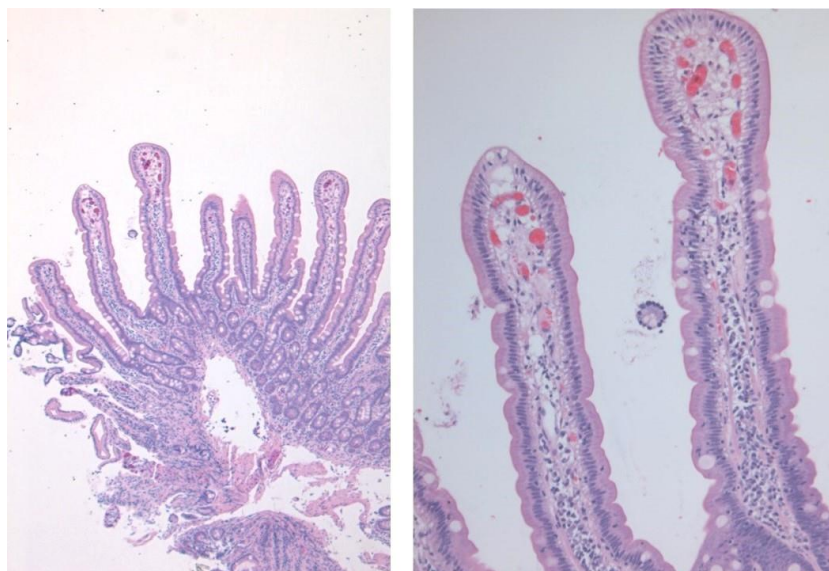
Small bowel mucosal biopsies remain gold standard for the diagnosis of CD because of variation in the clinical findings and serologic testing<sup>52-59</sup>. The optimum number of biopsies needed for the diagnosis of CD is not fully established. The pathological findings in CD can be patchy and can affect different areas of duodenum with varying degrees of severity. Therefore, multiple biopsies of the duodenum (at least four) should be performed if CD is suspected on clinical grounds. The American Gastroenterology Association recommends 6 biopsies from the distal duodenum for the diagnosis of CD<sup>55</sup> or 4 biopsies from the distal duodenum with 2 biopsies from the duodenal bulb

as an alternative approach<sup>60</sup>. The strict adherence to these guidelines in clinical practice is suboptimal ( about 35%), although strict adherence to these guidelines increases the detection of celiac disease<sup>61,62</sup>. An accurate diagnosis of celiac disease in suspected cases has 2 important prerequisites ; biopsies should be performed when the patient consumes gluten containing diet and biopsy tissue fragments are well-oriented.

### NORMAL HISTOLOGY OF DUODENUM AND JEJUNUM

In a well-oriented biopsy cut at right angle well formed, long, slender villi are seen projecting from a simple gland layer into the lumen. The glands are orderly arranged, regularly spaced, and rest on the muscularis mucosae (Figure 1). The normal crypt to villous ratio is about 1:3-4 in adults and about 1:2 in children. The villi are lined by columnar epithelium with brush border which can be appreciated in the hematoxylin and eosin (H and E) stained sections as a faint density. The villous epithelium is continuous with the crypt epithelium which represents the regenerative zone. The villous epithelium is composed of absorptive cells intermixed with variable number of goblet cells. Paneth cells and occasional enterochromaffin cells are scattered in the crypts. Mitoses are seen in the crypt epithelium but are normally not seen in the villous epithelium.

Figure 1: Normal duodenal mucosa showing long, slender, regularly spaced villi with orderly arrangement. The normal crypt to villous ratio of 1:3 - 4 is seen. The villi are lined by columnar epithelium with brush border which can be seen as a faint density on the luminal aspect.



Occasional IELs can be seen in normal small bowel epithelium which are part of gut-associated lymphoid system including gut associated lymphoid follicles, Peyer’s patches, and mesenteric lymph nodes. In normal small bowel mucosa, IELs demonstrate a “decrecendo” pattern i.e. the density of IELs in the tips of the villi is lower than that in the proximal third of villi<sup>63</sup>. In the jejunum, there are about 6 to 40 lymphocytes per 100 villous epithelial cells in adults<sup>64</sup> and 12 to 35 per 100 in children<sup>65</sup>. In the duodenum IEL count is lower than those in jejunum. The upper limit of normal IEL count in the duodenum is 20 to 25 IELs per 100 epithelial cells.

The lamina propria of the villous core and surrounding mucosa shows small number of lymphocytes with occasional plasma cells, eosinophils, mast cells and histiocytes. Brunner’s glands are seen in the duodenum but variably in the jejunum. These can be seen on either side of the of the muscularis mucosae. Prominence or hyperplasia of Brunner’s glands is usually associated with broad and short villous architecture.

#### MICROSCOPIC FEATURES OF CELIAC DISEASE

The key microscopic features of celiac disease include varying degree of villous atrophy, crypt hyperplasia, chronic inflammatory infiltrate, and increased IELs. The overall mucosal thickness is normal or only slightly decreased. The degree of

villous blunting can be variable ranging from minimal blunting to completely flat mucosa<sup>53,54</sup>. Accurate assessment of villous blunting needs proper orientation of the biopsies. The biopsies however are seldom well oriented; in such cases, attempt should be made to find 3 to 4 well oriented villi for architectural assessment. The lamina propria contains increased inflammatory infiltrate consisting of lymphocytes, plasma cells, with some eosinophils, histocytes, and basophils.

Various classification schemes have been developed for assessing the severity of CD. The original Marsh classification scheme recognises 4 types : an infiltrative lesion (Marsh Type 1), hyperplastic lesion (Marsh Type 2), and destructive lesion ( Marsh Type 3). The original Marsh classification does not mention cut off value for the number of IELs. The updated Marsh classification proposed 40 IELs /100 enterocytes as the upper cutoff point for normal and further subdivided group 3 into 3a, 3b, and 3c based on severity of villous shortening or blunting<sup>66</sup>. (Table 2). Marsh has strongly argued against the technical basis for this division<sup>67</sup>. The updated Marsh classification known as the Marsh – Oberhuber classification system describes 5 histologic lesions: preinfiltrative (type 0), infiltrative (type 1), infiltrative – hyperplastic (type 2), flat – destructive (type 3), and atrophic – hypoplastic (type 4).

**Table 2.** Marsh-Oberhuber classification of Celiac Disease by Oberhuber et al

Type	Intraepithelial lymphocytes per hundred enterocytes	Crypt	Villi
Preinfiltrative (Type 0)	Normal (< 40)	Normal	Normal
Infiltrative (Type 1)	> 40	Normal	Normal
Infiltrative hyperplastic (Type 2)	> 40	Hyperplastic	Normal
Destructive type 3a	> 40	Hyperplastic	Mild blunting
Destructive type 3b	> 40	Hyperplastic	Moderate blunting
Destructive type 3c	> 40	Hyperplastic	Severe blunting (Flat)
Hypoplastic type 4	> 40	Atrophic	Severe blunting (Flat)

Preinfiltrative lesions (type 0) are associated with normal mucosa seen mainly in patients with dermatitis herpetiformis with no evidence of malabsorption. Infiltrative lesions (type 1) show an

increased IELs with preserved villous architecture (Figure 2) while infiltrative – hyperplastic lesions (type 2) show in addition crypt hyperplasia. Both patterns can be seen in patients with CD with or



without symptoms, patients with dermatitis herpetiformis, and in first degree relatives of patients with CD. Destructive lesions (type 3), show villous blunting accompanied by crypt hyperplasia and IEL with variable degree increased chronic

inflammation in the lamina propria (Figure 3). The mucosal thickness is normal or near normal. Hypoplastic lesions (type 4), refer to an atrophic small bowel mucosa with complete villous blunting and crypt atrophy (Figure 4, 5).

Figure 2: Infiltrative lesion. Normal villous architecture with increased intraepithelial lymphocytes. CD 3 immunostain highlighting the intraepithelial T lymphocytes.

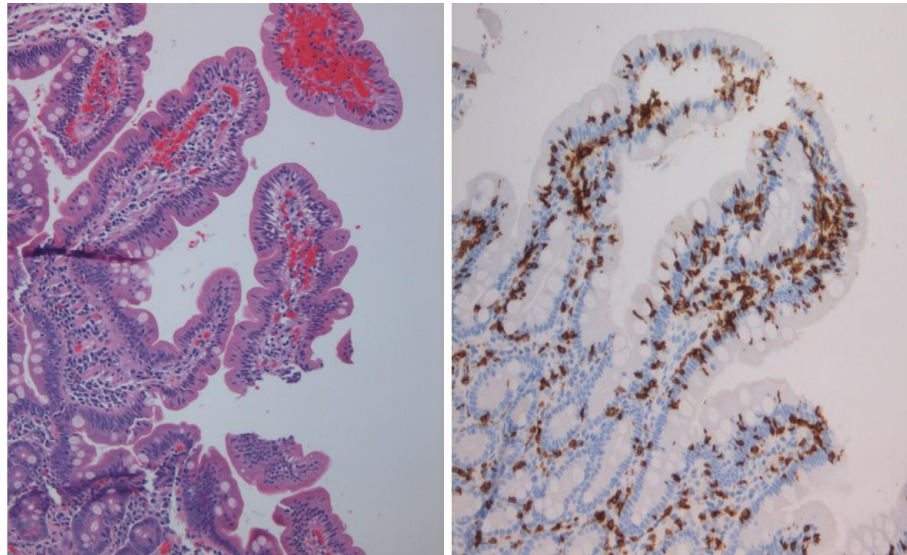


Figure 3: Subtotal villous atrophy. Atrophic small bowel mucosa with villous blunting and increased mucosal chronic inflammation with increased intraepithelial lymphocytes.

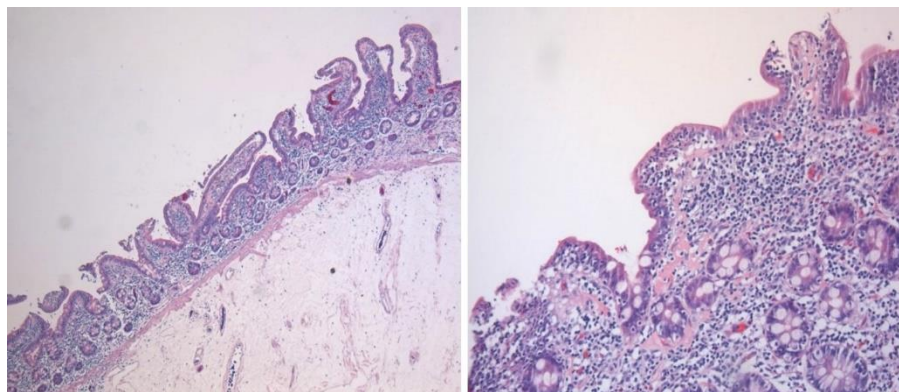
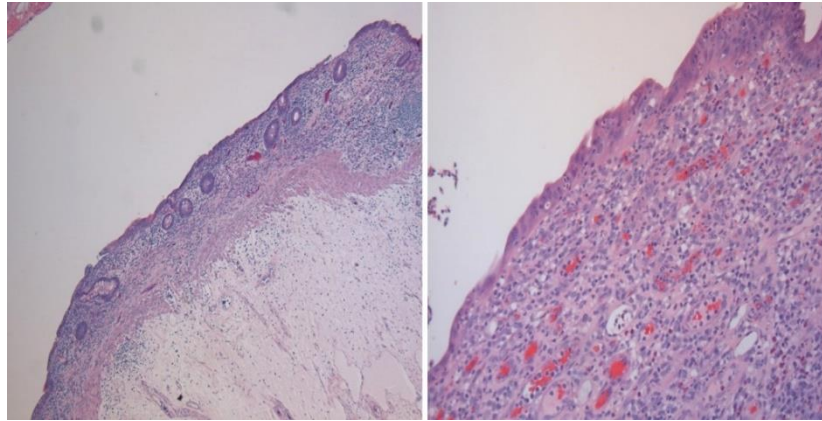


Figure 4: Celiac disease with complication. The patient presenting with intestinal obstruction. Resected segment of small intestine showing complete mucosal atrophy with flattened mucosa with loss of mucosal pattern.





Figure 5: Hypoplastic lesion with atrophic small bowel mucosa with complete loss of villous architecture and flattened mucosa and crypt atrophy.



Corazza – Vilanacci scoring system divided CD into 3 grades: grade A, grade B1, and grade B2<sup>68</sup> (Table 3). Grade A shows normal crypts and villous architecture but increased IELs (> 25 IELs/100 enterocytes). Grade B1 shows atrophic but

detectable villi and increased IELs, and grade B2 shows flat/undetectable villi and increased IELs. This scoring system has less variability and greater agreement between pathologists<sup>68</sup>.

**Table 3.** Corazza-Villanacci Score of Celiac Disease (Corazza et al)

Grade	Intraepithelial lymphocytes per 100 enterocytes	Villi
A	> 25	Normal
B1	> 25	Atrophic but detectable
B2	> 25	Flat/undetectable

#### ASSESSMENT OF RESPONSE TO GLUTEN FREE DIET (GFD)

The standard treatment of celiac disease with demonstrated villous atrophy is the institution of the GFD. This should result in rapid alleviation of symptoms and return of abnormal serology to normal range. The histological evidence of response with restoration of villous architecture and reduction of mucosal inflammation is important as negative celiac serology does not guarantee mucosal healing<sup>69</sup>. In a recent meta – analysis, the sensitivity of tTG for detection of persistent villous atrophy was only 50%.

Some patients fail to respond to GFD often because gluten is not adequately excluded from the diet. The second reason may be very severe initial lesion with completely flat mucosa. As IELs remain elevated for many years even in patients with GFD, assessment of the response to GFD relies on villous architecture. Unfortunately, studies detailing histological follow-up of celiac patients

on GFD are inconsistent with respect to the response<sup>70</sup>. One factor contributing to this variance could be inconsistency in the reporting of the response to a GFD. To address this issue, quantitative approaches such as Q-MARSH have been proposed. “Normalization” is defined as Vh/Cd ratio of >2.5:1<sup>71</sup>.

It is likely that 1 year is too short a follow-up for histology, and that a longer period of follow-up is required before labelling the patient as having refractory celiac disease. In one series, persistent villous blunting was present at 1 year; this reduced to 5% over 2 – 5 years of follow-up<sup>72</sup>.

#### Histopathological differential diagnoses of celiac disease

Depending upon the histologic pattern seen in CD i.e. increased IELs or villous blunting differential diagnoses may vary; nevertheless, it is important to rule out conditions with similar morphologic changes in the small intestine (Table 4).

**Table 4.** Differential Diagnoses of Celiac Disease

### Immunodeficiency

- Immunodeficiency
- Common variable immunodeficiency
- Infantile X-linked immunodeficiency
- Selected IgA deficiency
- T-cell deficiency or severe combined immunodeficiency

### Infection

- Helicobacter pylori gastritis
- Tropical sprue
- Bacterial overgrowth
- Viral gastroenteritis or postinfective malabsorption syndrome
- Parasitic infestation

### Diet, nutrition, and medication

- Food allergy
- Nutritional deficiency
- Morbid obesity
- Medication (including nonsteroidal anti-inflammatory drugs) and peptic injury

### Autoimmunity

- Refractory sprue
- Autoimmune enteropathy
- Crohn disease, ulcerative colitis
- Lymphocytic or collagenous colitis
- Autoimmune diseases

## Immunodeficiency

**INFANTILE X-LINKED IMMUNODEFICIENCY:** Small bowel biopsy usually shows sparsity or absence of mucosal plasma cells. The mucosa associated lymphoid tissue shows lack of germinal centres<sup>73,74</sup>. The small intestinal villous architecture is usually maintained.

**COMMON VARIABLE IMMUNODEFICIENCY (CVID):** CVID is a heterogenous condition with many common features such as recurrent infections, autoimmunity and lymphoproliferation and laboratory evidence of hypergammaglobulinemia<sup>70</sup>. The most common gastrointestinal symptom is diarrhea (92%), and evidence of malabsorption is seen in 54% patients of CVID in a large cohort

study<sup>75</sup>. Histological examination showed IELs in approximately 75.6 % cases, while villous atrophy was present in 51% cases<sup>75</sup>. These cases however showed marked depletion of plasma cells and follicular lymphoid hyperplasia<sup>75</sup>. Features which may be helpful in distinguishing CD from CVID associated enteropathy are profound depletion of plasma cells and follicular lymphoid hyperplasia as these 2 features are present in 96.3 % and 55 % cases of enteropathy associated CVID respectively. Celiac serology may also be helpful as only 11.5% of enteropathy associated CVID had celiac antibodies.

### SELECTIVE IGA DEFICIENCY

The most common intestinal symptoms include diarrhea, and steatorrhea. The gastrointestinal symptoms may be due to parasitic infestation – giardiasis, CD, or milk intolerance. In some patients CD like mucosal lesions such as villous blunting and IELs are seen<sup>76</sup>.

### IgG DEFICIENCY

Chronic diarrhea, villous blunting and crypt hyperplasia may be seen in patients with IgG deficiency. Perlmutter et al in their study these features in 50% of infants<sup>77</sup>.

### T CELL DEFICIENCY OR SEVERE COMBINED IMMUNODEFICIENCY

The jejunal biopsy may features akin to CD with villous blunting, crypt hyperplasia, IELs, mucosal edema. The mucosa however may show many foamy macrophages with material stainable with PAS, toluidine blue and Giemsa stain<sup>78</sup>.

## Infection

### HELICOBACTER PYLORI INFECTION

H. pylori infection may be associated with IELs but there is no or at the most only minimal villous blunting. The mucosa also shows considerable acute inflammation and there may be associated foveolar gastric metaplasia. The definite diagnosis requires assessment of gastric biopsies or demonstration of H. pylori by some other methods. Coexisting H. Pylori infection and CD have been reported.

### TROPICAL SPRUE

There is a considerable overlap between clinical presentation and endoscopic appearance of tropical sprue and CD. The tropical sprue is usually associated with milder villous abnormalities and IELs tend to concentrate in the basal one third of the villi or the mucosal crypts<sup>79</sup>. Tropical sprue tends to be patchy and shows more eosinophils<sup>79</sup>. Other helpful features to differentiate from celiac include history of travel to the endemic areas, negative celiac serology, and good response to antibiotics and folic acid.

### BLIND LOOP SYNDROME

In the blind loop syndrome bacteria colonise small intestine and with this mucosa may show changes akin to CD. The changes noted however are patchy in distribution and usually are of mild to moderate degree with slight to moderate villous atrophy. There may be history of intraabdominal surgery or bowel obstruction.

### VIRAL OR BACTERIAL INFECTION

Several viral infections including human immunodeficiency virus are known to produce villous blunting and intraepithelial lymphocytosis. The mucosal changes are usually mild to moderate; however very severe changes with marked villous abnormalities resembling CD can occasionally be seen. The inflammatory infiltrate is predominantly acute with numerous neutrophils associated with crypt abscesses. There may be history of acute onset gastroenteritis and mucosal abnormalities return to normal with resolution of symptoms. There is a direct evidence that celiac-like enteropathy can be initiated by norovirus infections and other viral infections<sup>80,81</sup>.

### PARASITIC DISEASE

Malabsorption associated with mucosal abnormalities with villous atrophy and crypt hyperplasia may be seen in parasitic diseases. The lamina propria inflammatory infiltrate is usually rich in eosinophils in parasitic infestations. The villous abnormality is seen at a very low rate. This means if villous abnormality comparable to that seen in CD is noted in association with parasitic organisms,

coexisting CD must be suspected. Giardiasis caused by *Giardia lamblia* is one of the most common intestinal parasitic diseases. *Giardia* can be easily identified in duodenal biopsy specimen as a pear-shaped organism with two paired nuclei, located in lumen adjacent to the epithelium. A celiac serology may not be helpful as transient elevation of IgA-TTG and IgA-EMA levels may be seen in *Giardia* infection<sup>82</sup>. Repeating celiac serology after *Giardia* eradication may clarify the situation.

## Diet and food allergy

Dietary proteins other than gluten can lead to malabsorption. The small intestinal histologic features may be like those seen in CD posing a diagnostic problem<sup>83-85</sup>. The condition is usually transient and clinical correlation with diet history is important.

### MALNUTRITION

Patients with severe protein calorie malnutrition can present with diarrhea and malabsorption. The small bowel histologic features may be like those seen in CD with villous blunting, increased mucosal inflammation and sometimes increased IELs<sup>86</sup>. However, these changes respond to oral or intravenous therapy<sup>86</sup>.

### MEDICATIONS

Certain medications can lead to malabsorption with small intestinal lesions akin to CD. Many types of NSAIDs show duodenal mucosal lesions including IELs<sup>87</sup>. Olmesartan, an angiotensin II receptor blocker used in the treatment of CD can cause severe diarrhea. The duodenal biopsy shows changes mimicking CD with partial or complete villous atrophy and increased IELs<sup>88</sup>. Other medications which can cause CD like intestinal changes include oxcarbazepine<sup>89</sup>, mycophenolate mofetil<sup>90</sup>, and azathioprine<sup>91</sup>. Immunotherapy used for cancer treatment can also lead to CD like enteropathy. History of medication usage, negative celiac serology and resolution of symptoms and intestinal pathologic features on discontinuation of medications are helpful features in arriving at a correct diagnosis

## Autoimmune enteropathy

In its pure form, autoimmune enteropathy is a disease of childhood, and it is likely that most pediatric cases have a genetic basis that remains to be uncovered. Approximately 20% of cases develop a celiac disease like pattern in the duodenum and is often associated with lymphocytosis throughout the remainder of the gastrointestinal tract<sup>92</sup>.

### INTRACTABLE DIARRHEA OF INFANCY

Intractable diarrhea of early infancy is characterized by severe protracted diarrhea in young infants younger than 3 months of age. There is no apparent cause on detailed examination and hence no definite treatment can be started. The condition at times may be fatal<sup>93</sup>. The condition is associated with small intestinal mucosal abnormalities such as total villous atrophy and crypt hyperplasia<sup>94</sup>. Some cases may show villous atrophy associated with crypt hypoplasia<sup>95-97</sup>. Some of these cases might be based on autoimmunity and circulating antibodies to intestinal goblet cells and enterocytes have been demonstrated<sup>89,90,96,97</sup>. A positive test for anti enterocyte antibody helps in establishing the diagnosis. A persistent high titre indicates a poor prognosis<sup>97,98</sup>.

### ADULT AUTOIMMUNE ENTEROPATHY

Adult form of autoimmune enteropathy associated with anti enterocyte antibodies may rarely present as refractory sprue<sup>99,100</sup>. In one study the jejunal biopsies demonstrated subtotal villous atrophy and increased IELs before steroid treatment<sup>100</sup>. Testing for anti enterocyte antibodies may be helpful in establishing diagnosis of autoimmune enteropathy.

### CROHN'S DISEASE

Crohn's disease can manifest as duodenitis, with villous atrophy and malabsorption. Diagnosis of Crohn's disease remains a diagnosis of exclusion after ruling out CD by negative celiac serology, absence of HLA DQ2/DQ8, and lack of response to gluten free diet.

### DIFFERENTIAL DIAGNOSIS OF LATENT CELIAC DISEASE

Intraepithelial lymphocytes with normal villous architecture (IELNVA) have been increasing

diagnosis in many patients with CD due to an increase in the utilization of serology testing and endoscopic examination of first degree relative of patients with CD. These findings although sensitive are not specific for CD and can be seen in a variety of other conditions. Several large studies have studied the prevalence of IELNVA. The prevalence of IELNVA varies from 1.3% to 2.2% when different cut off values are used<sup>87,101</sup>. Kakar et al. in their study, using 40 IELs as the cut off criteria for IEL, noted histologic pattern of IELNVA at a rate of 1.3% (43 out of 3190 patients undergoing upper GI endoscopy<sup>87</sup>. It is associated with CD (9.3%), immunologic disease (14.3%), NSAIDs use (14%), inflammatory bowel disease (11.6%), bacterial overgrowth (4.4%), tropical sprue (2.2%), microscopic colitis (6.9%), and other unspecified diagnosis (37.2%). Other diseases causing IELNVA include morbid obesity<sup>102</sup>, *Helicobacter pylori* gastritis<sup>63,103,104</sup>, partially treated tropical sprue<sup>87</sup>, cow's milk protein intolerance<sup>65</sup>. Immune disorders associated with IELNVA include Hashimoto's thyroiditis, Graves disease, rheumatoid arthritis, psoriasis, multiple sclerosis, systemic lupus erythematosus, ankylosing spondylitis, progressive systemic sclerosis, and glomerulonephritis<sup>87,105-108</sup>. For many patients, a specific diagnosis is never established. The absence of HLA DQ2/DQ8 in at least half of these idiopathic cases excludes potential celiac disease<sup>109</sup>. Goldstein et al. suggested that increased density of IELs at the distal sides and tips of villi is a relatively specific and reproducible feature of latent or potential CD<sup>63</sup>. Some other study, however, report no particular pattern of IEL distribution to be associated with latent or potential CD<sup>87</sup>.

Idiopathic inflammatory bowel disease such as ulcerative colitis or Crohn's disease and lymphocytic and collagenous colitis may be associated with IELNVA in the proximal small bowel<sup>87,110</sup>. HLA testing for relevant DQ3 alleles can be useful when diagnosis based on other tests is not useful.

## Conclusion

There has been significant development in understanding the pathophysiology, pathogenesis,



and diagnosis of celiac disease. The present review summarizes the important development in CD in last few years. The diagnostic criteria for the diagnosis have been developed in adult and pediatric population. There has also been refinement in celiac serology in the diagnosis of celiac disease. Despite these developments, histologic examination of small intestinal biopsies remains the gold standard for the diagnosis of celiac disease. Histologic examination of small intestine also helps to monitor the course of disease, response to treatment, and in detecting potential complications of celiac disease such as

enteropathy associated T-cell lymphoma, adenocarcinoma, and concurrent intestinal diseases.

### Conflict of Interest:

None

### Funding Statement:

None.

### Acknowledgements:

None.

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