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Review Article

Gluten Specific Autoimmunity and Susceptibility: Celiac Disease

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Abstract

Chronic, immune mediated gluten susceptibility of the small intestine is designated as celiac disease. Children elucidate a mal-absorptive syndrome with diarrhoea, poor thriving, loss of appetite, abdominal distension and inadequate growth whereas adults and young adults delineate diarrhoea, abdominal bloating, constipation, abdominal pain or weight loss. Microscopic quantification of intra-epithelial T lymphocytes with immune reactive anti CD3 antibodies is suitable for diagnosis. Intestinal mucosal pathology is currently categorized by the "Marsh classification". Intestinal lymphoma requires consideration with the influx of aberrant, monotonous lymphocytes. A gluten free dietary regimen for stipulated 12 - 24 months is a pre-requisite prior to initiating investigations of gluten intolerance.

Keywords: *Gluten; Celiac Disease*

Introduction

A pathological, chronic, immune mediated, small intestinal disorder with gluten susceptibility and activated by the gluten component of wheat, barley or rye is designated as celiac disease. The condition is encountered with a genetic predisposition in persons with specific auto antibodies against tissue transglutaminase 2 (anti t TG2), endomysium and/or deamidated gliadin peptide [1]. An estimated 40% of the population depicts genotype HLA DQ2 or HLA DQ8, mandatory for elucidation of celiac disease, although the disorder emerges clinically in only 2 - 3% of the carriers. The infrequent enteropathy is global, irrespective of the age or racial allocation of subjects. The considered disorder of young white children was initially scripted in 1887 and a concordance with wheat consumption was established in 1941 [1,2].

Physiological modification in celiac disease

The complex proteins of the gluten moiety are usually comprised by gliadins and glutenin's. An instantaneous and temporary elevation of the gastro intestinal permeability ensues due to gliadin. The particular gliadin moiety which resists degradation and coheres to the CXCR3 chemokine receptor engenders the permeability along with the dispensation of zonulin, the modulator of the interleukin tight junctions [3,4].

Subsequently, inflammatory reaction in susceptive individuals is a pre-requisite for the emergence of celiac disease. During the aggravated phase, gluten permeates the intestinal barrier in concordance with trans-cellular pathway aided by transferrin receptor CD71 [1,2].

Immune mediation in celiac disease

A crucial component of gluten sensitive celiac disease is the inherent immune response. Interleukin 5 (IL5) and interferon α (IF α) cytokines stimulate the innate immunity by polarizing dendritic cells along with activated intraepithelial lymphocytes [8,9]. The discontinuous mucosal barrier, epithelial function deficit and mucosal alteration primed by gliadin modulated zonulin dispersion mobilizes the undigested peptides from the intestinal lumen to the epithelial lamina propria. Following gliadin migration within the epithelial barrier, interleukin 8 (IL8) or an efficacious neutrophil chemo attraction mobilizes the neutrophils [7-9]. Intolerance to gluten moiety is evidenced within the genetically susceptible population.

Clinical attributes

Celiac disease is systematic autoimmune disorder which commences at any age.

Intestine of children below three years of age elucidates a mal-absorptive syndrome comprising of diarrhoea, poor thriving, loss of appetite, abdominal distension and inadequate growth. Adults and young adults delineate diarrhoea, abdominal bloating, constipation, abdominal pain or weight loss [1,2].

Extra-intestinal manifestations depict chronic inflammation and nutritional deficiencies along with immune adaptation. The features extend from the intestinal mucosa to neighbouring tissues and organs. Short stature, delayed puberty and inappropriate growth defines emergence of juvenile disease [1]. Celiac disease can manifest delayed puberty, the incidence of which is at an estimated 10% of freshly discerned instances. Delayed puberty is designated as an absence of physical or hormonal indications of pubertal development at the appropriate age. Evident secondary sexual characters appear at 11 years of bone age in young girls. Female subjects devoid of mammary augmentation at 13 years or an absent menarche within 3 years of breast enhancement or within 16 years is cogitated as delayed puberty. Mal-absorption and malnutrition associated with celiac disease inducing delayed puberty can revert with the institution of a gluten free diet which may prevent far reaching complications and restore unhindered sexual maturation.

A gluten free diet administered for 12 to 24 months if found incompetent in reversing the pubertal complications, concomitant deficiency of the reproductive system necessitate a consideration [5,6].

Dental enamel defects appear in the children below seven years. An estimated one third (32%) of the adults and 9% of the children demonstrate iron deficiency anaemia. Dermatitis herpetiformis, urticaria, psoriasis and dry skin are coexistent features. One fifth (22%) of the persons enunciate a combination of neurologic and/or psychiatric manifestations [1]. Nutritional deficiencies such as of vitamin B12, a chronic inflammation or an immune execution engender a frequent peripheral neuropathy.

Celiac disease displays an amplification of thyroid disorders with an estimated 2% to 5% incidence. Conditions associated incorporate Graves' disease inducing hyperthyroidism and Hashimoto's thyroiditis with concomitant hypothyroidism. The specific disorders are usually discerned prior to elucidation of Celiac disease, although the detection can be delayed. Genetic probability of thyroid involvement is manifested with HLA DQ2 and DQ8. The genomic aberration is frequent in Hashimoto's thyroiditis with a consequent elevated possibility of celiac disease in subjects of Hashimoto's thyroiditis, in contrast to Graves' disease. Additionally, a concurrence with a gene encoding cytotoxic T lymphocyte associated antigen can be elucidated.

An aberrant absorption ensues with celiac disease resulting in selenium deficiency. The aforementioned mechanisms of thyroid implication mandate a screening for thyroid disorders in celiac disease [6].

Breast feeding in celiac disease can either be efficacious in incurring a permanent disease prevention or may appropriately deter the emergence of celiac disease [5,6].

Attendant diagnostic attributes

With an absence of histological assessment in children, the European Society of Paediatric Gastroenterology and Hepatology (ESPGHAN) recommends specific evaluation for the disorder as an immune reactivity to the anti t TG antibodies (significant values ten times the upper normal), signs and symptoms of the celiac disease, immune reactivity to anti-endomysial antibody alternatively analyzed to the anti t TG antibody and a human leukocyte antigen(HLA) genotype consistent with celiac disease [1,4].

Distinct analytical methodologies such as a double balloon enteroscopy, video capsule endoscopy and magnetic resonance imaging (MRI) are infrequently employed. The procedures are indicated with complicated disease, with discordance of histology and serology or with a worsening of the symptoms subsequent to a gluten restricted intake [10,11].

Tissue morphology

The pre-requisite duodenal biopsy obtained following endoscopic examination along with adjunctive gastrointestinal biopsies, permits the duodenal evaluation. Crosby Watson capsule employed to retrieve duodenal samples through the per-oral route are considered redundant. Endoscopic tissue sampling can be recovered as four biopsies, two each from the second or third part of the duodenum. Evaluation of tissue from the duodenal bulb or proximal duodenum is inconsistent. Oriented biopsies on the cellulose acetate filters is a pre-requisite for adequate assessment as a 90^0 rotation assists the tissue embedding [2]. Mucosal and sub-mucosal analysis discerns the normal intestinal architecture. Cellulose acetate filters appropriately cohere the tissue, to avert the flotation of the biopsy within the fixative. Neutral cellulose acetate filters do not react chemically with the fixative and processing reagents. The technology is applicable to the entire gastro-intestinal tract. Haematoxylin and eosin, alcian blue along with periodic acid Schiff (PAS) stains and appropriate immune histochemistry are employed [2,3].

Microscopic analysis

The characteristic intestinal mucosa depicts digitiform villi with a crypt to villous ratio of 3:1 or more. The typical height of the enterocytes is 29 - 34 µm with a distinct brush border. The quantity of intra epithelial T lymphocytes may vary. The uninvolved intestine usually displays < 20 intra epithelial T lymphocytes per 100 intestinal epithelial cells. A quantification of > 25 T lymphocytes per 100 epithelial cells is considered pathological. Borderline cases with requisite clinical and laboratory correlation delineates approximately 25 - 30 T cells per 100 epithelial cells [2,3]. A count of 40 intraepithelial T lymphocytes per 100 epithelial cells is definitely pathological, though infrequent. Estimation of the intraepithelial lymphocytes is a pre-requisite in the preliminary lesions.

- Quantification of the T lymphocytes with the immune reactive anti CD3 antibodies is suitable.
- Evaluation of the properly oriented tissue with an accurate alignment of the intestinal epithelial cells is accomplished.
- Intraepithelial T lymphocytes are enumerated along the apical segments and the villous perimeter through precise, reliable microscopic fields.
- Regenerating glandular crypts exemplifies mitotic figures. Generally one mitosis per crypt is the norm. Endocrine cells, goblet cells and paneth cells are also discerned with a lack of connotation in celiac disease [2,3].
- Lamina propria delineates plasma cells, eosinophils, histiocytes, mast cells and lymphocytes. Neutrophils are absent except with progressive duodenitis or gastric metaplasia secondary to Helicobacter pylori infection. Plasma cells and lymphocytes are the predominant cellular constituents and configure lymphoid aggregates. Eosinophilic granulocytes are restricted to < 60 cells per 10 high power fields (40x) [2].

Concurrent classification

Intestinal mucosal pathology is categorized by the "Marsh classification".

- Normal villous with unremarkable morphology (villous/crypt ratio: 3:1).
- Type I or Infiltrative Lesions: An elevation of the intraepithelial lymphocytes (25 - 30 lymphocytes per 100 epithelial cells).
- Type II or Hyperplastic Lesions: The villi are classically configured. Intra epithelial T lymphocytes are enhanced up to > 25 - 30 lymphocytes per 100 epithelial cells. Glandular regeneration, glandular hyperplasia, diminished mucinous epithelial function with increased mitotic figures are evident [2,3].
- Type III or Destructive Lesions: Villous atrophy of varying magnitude accompanied by glandular crypt hyperplasia may appear. A decline in the surface enterocyte height with an inconsistent brush border, cytoplasmic vacuoles and amplified intraepithelial lymphocytes (as in Type I and II) are exhibited [2,3].

The histological manifestation of celiac disease signifies a perpetually evolving disorder concordant with quantity and duration of gluten ingestion.

Type I (Infiltration)	Type II (Hyperplasia)	Type III (Destruction)
Celiac disease families	Celiac patients with moderate gluten intake	Untreated celiac disease
Treated celiac disease with minimal gluten ingestion	Dermatitis herpetiformis without clinical enteropathy	Treated celiac disease with maximal gluten exposure
Dermatitis herpetiformis without clinical enteropathy		Dermatitis herpetiformis with clinical enteropathy
Tropical enteropathy		Tropical sprue

Table 1: *Marsh Classification (Adaptation) [2,3].*

Mild, moderate, and severe villous atrophy (complete villous flattening) is collated with a singular categorization (type 3 Marsh). The modified classification by Oberhuber., et al. delineates three sub categories for type 3 lesions [2,3].

1. Type 3(a): Mild villous atrophy with a pathological augmentation of the intra-epithelial T lymphocytes.
2. Type 3(b): Moderate (partial or subtotal) villous atrophy with a pathological elevation of the intra epithelial T lymphocytes.
3. Type 3(c) complete villous atrophy with a pathological amplification of the intra epithelial T lymphocytes [2,3].

Celiac disease in individuals on normal or gluten free diet is adequately assessed with the modifications.

A further adaptation as "Corazza classification" exemplifies:

- Grade A: Non atrophic lesions which typically depicts a pathological elevation of the intra T epithelial lymphocytes, as delineated by the immune histochemical evaluation. Type 1 and Type 2 of the Marsh- Oberhuber classification is equivalent to this grade.
- Grade B: Atrophic lesions subcategorized into Grade B1 with well demarcated villi though the villous/crypt ratio may be < 3:1. Type 3(a) and Type 3(b) of the Marsh Oberhuber classification is comparable to grade B1 [2,3].
- Grade B2: The villi are not detectable. Type 3(c) of the Marsh Oberhuber classification is analogous to grade B2.

Disease characterization

The morphological criterion such as villous tropism, quantity of intraepithelial lymphocytes or glandular structures within the lamina propria is employed for evaluation. The histological features with concordant clinical or laboratory evidence appropriately categorizes a patient of celiac disease. The draft conclusively delineates tissue analysis with histological interpretation. Villous sub-atrophy as a term is misleading and essentially describes the normal or atrophic villi, with mild, moderate or severe villous atrophy. Conferring numerical scores to various lesions elicits inadequate morphological information thus may be inconclusive [11,12].

Immune histochemistry

CD3+ and CD8+ immune reactive intraepithelial T lymphocytes are quantified. Normal values below 25 T lymphocytes per 100 epithelial cells can be accepted. An appearance of 25 - 30 T lymphocytes per 100 epithelial cells is consistent with borderline lesions. An accurate assessment of the pathological T lymphocytes is mandated with the detection of the preliminary or sub clinical celiac disease [12,13]. A well prepared formalin fixed paraffin embedded section stained with haematoxylin and eosin (H&E) with monoclonal CD3+ and CD8+ antibodies delineates the immune reactive T lymphocytes. CD8+ lymphocyte assessment benefits the elderly patients or the refractory celiac disease, unresponsive to the dietary restrictions. The lesions is designated as a pre-lymphoma, with a non-reactive CD8- [2,3].

Frozen section assay depicts an immune reactive gamma-delta T cell receptor. Approximately 2 - 3% of the normal T lymphocytes manifest the receptor, whereas with celiac disease, roughly 20 - 30% of the T lymphocytes demonstrates the receptor. It is advantageous in evaluating the preliminary lesions. Frozen material is not preferred for routine clinical assays [2,3].

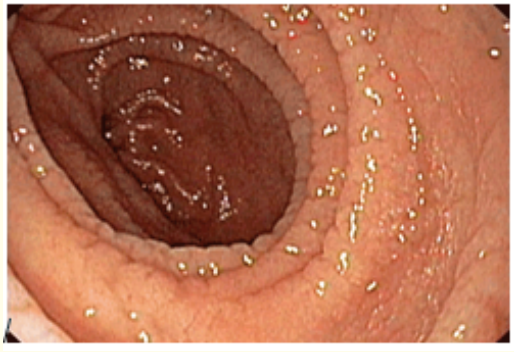

Figure 1: *Mucosal alterations of celiac disease with crypt hyperplasia [20].*

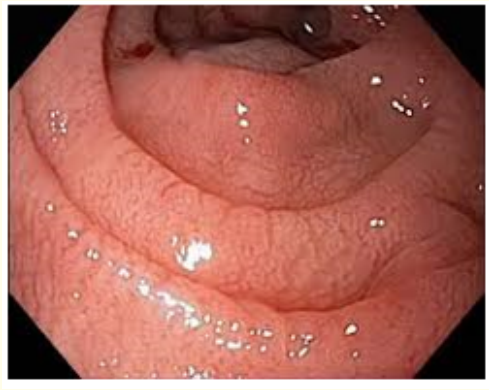

Figure 2: *Intestinal mucosa in celiac disease with mucosal atrophy [21].*

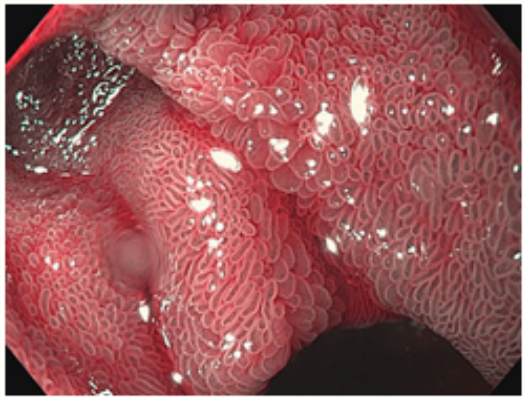

Figure 3: *Celiac disease-duodenal folds and villous projections [22].*

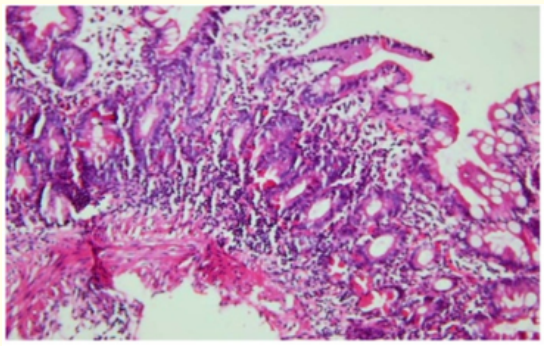

Figure 4: *Celiac disease: Partial villous atrophy with focal lymphocytes [23].*

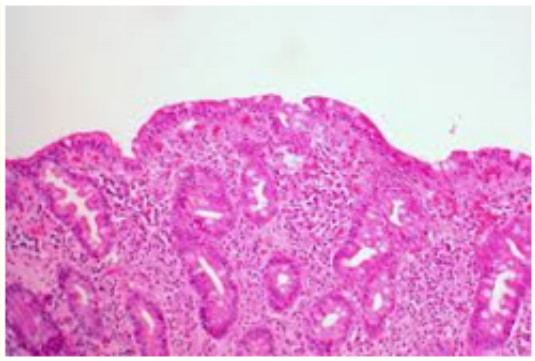

Figure 5: *Celiac disease: Flattened surface epithelium with crypt prominence [24].*

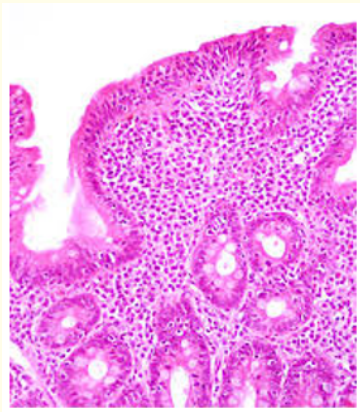

Figure 6: *Celiac disease: Atrophic villous architecture with intraepithelial lymphocytes [25].*

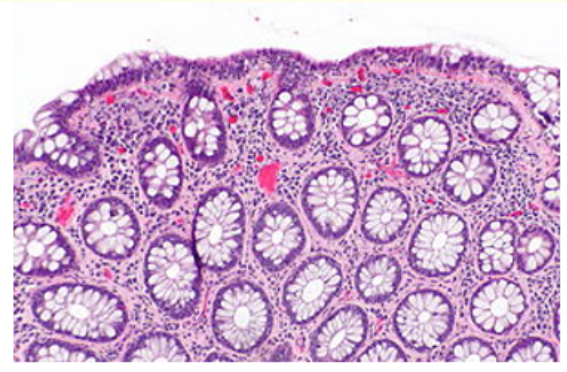

Figure 7: *Celiac disease: with surface flattening and preponderant crypts [26].*

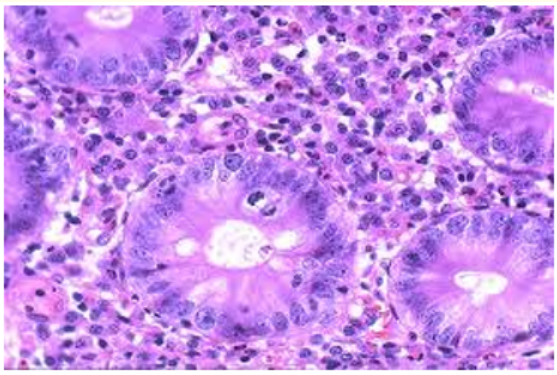

Figure 8: *Celiac disease: Elevated intraepithelial lymphocytes [27].*

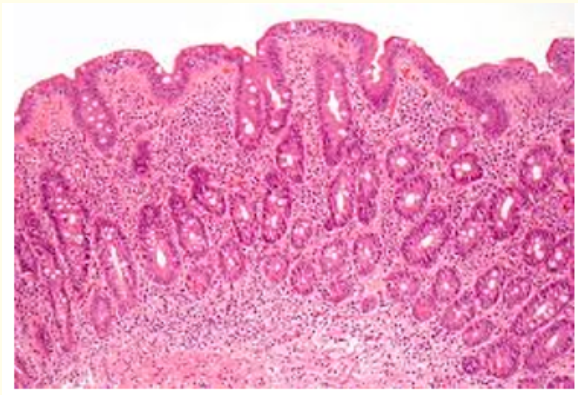

Figure 9: *Celiac disease: Partial villous atrophy with lymphocytic predominance [28].*

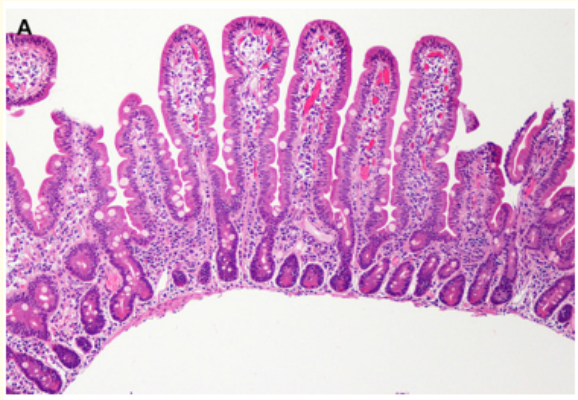

Figure 10: *Celiac disease: Partly shortened villous configuration with clustered crypts [29].*

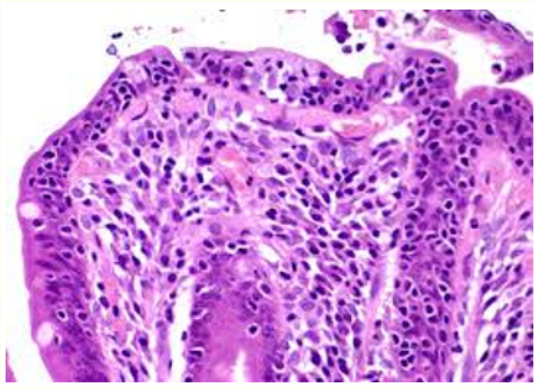

Figure 11: *Celiac disease: Villous flattening with intra-epithelial T lymphocytes [30].*

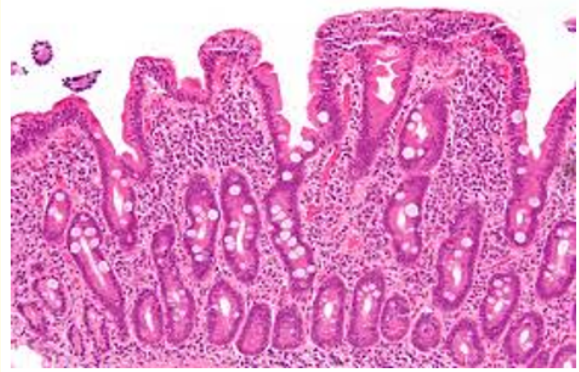

Figure 12: *Celiac disease: Mucosal flattening with lymphocyte aggregates and prominent crypts [31].*

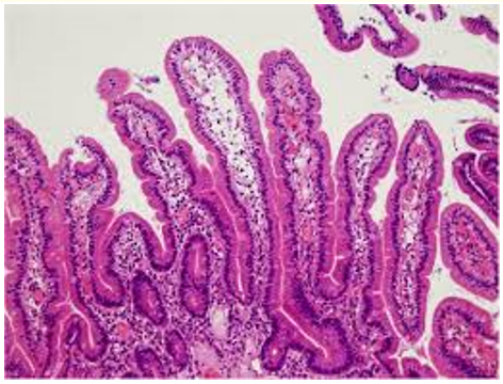

Figure 13: *Celiac disease Prominent villous architecture with mild lymphocytic infiltrate [32].*

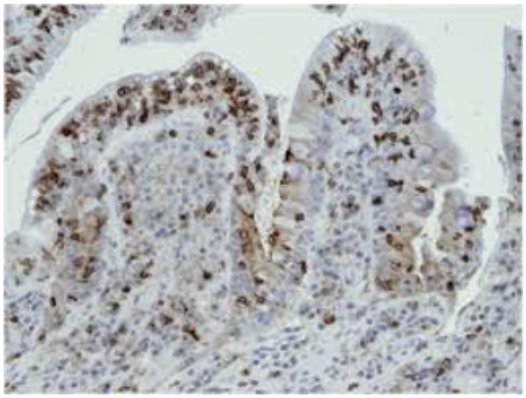

Figure 14: *Celiac disease Immune reaction for CD3+ lymphocytes [32].*

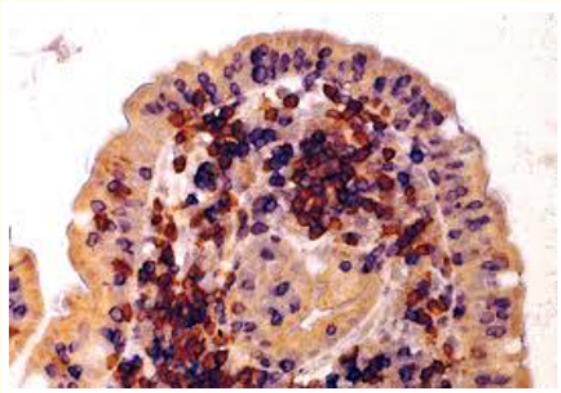

Figure 15: *Celiac disease: Immune positive CD3+ molecules [33].*

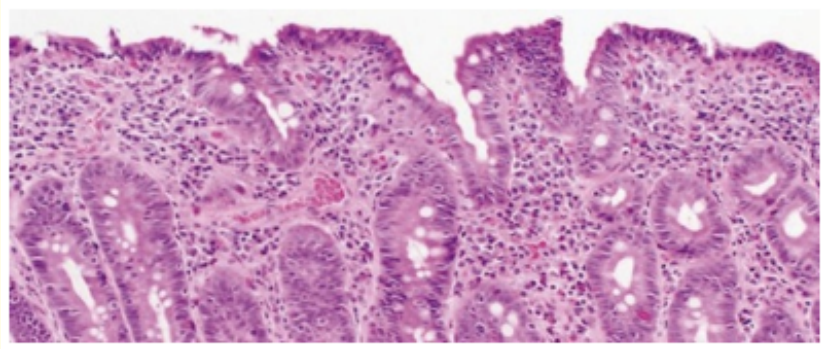

Figure 16: *Celiac disease: Prone mucosa with amplified intraepithelial lymphocytes [34].*

Discordant diagnosis

Mal-absorptive conditions of the proximal small intestine are [1,2]:

- Parasitic infestations (Giardia lamblia, Cryptosporidium, Micro-sporidium).
- Infectious conditions (Whipple disease).
- Viral infections (Cytomegalovirus, Herpes).
- Idiopathic conditions (Crohns' disease).
- Neoplasm of the small intestine.

A preliminary lesion is signified by a normal villous architecture with elevated intra epithelial T lymphocytes.

Numerous pathological conditions delineates an identical morphology as the preliminary celiac disease The villous architecture is unremarkable with a pathological elevation of the intra epithelial T lymphocytes (25 - 30 T lymphocytes per 100 epithelial cells, type 1 Marsh and grade A Corazza) as described below.

Gluten sensitivity- Celiac disease
Infections (Giardia, Helicobacter pylori, Cryptosporidium, Viral enteritis, Tropical sprue)
Bacterial overgrowth
Drugs (non-steroidal anti-inflammatory drugs, angiotensin II receptor antagonists “Sartans”)
Immune deregulation (Hashimotos’ thyroiditis, rheumatoid arthritis , systemic lupus erythromatosus, autoimmune enteropathy, graves disease, psoriasis, ankylosing spondylitis, scleroderma, type I diabetes)
Chronic idiopathic inflammatory bowel disease

Table 2: *Intraepithelial lymphocytes with normal villous pattern [5].*

Non-gluten food protein hypersensitivity (cereals, cow’s milk, soy products, fish, chicken, rice etc)
Infections (Cryptosporidium, Viral enteritis, Tropical sprue)
Bacterial overgrowth
Autoimmune enteropathy
Immune deficiency disorders (Immunoglobulin A deficiency, common variable immune deficiency, HIV enteropathy)
Drugs (angiotensin II receptor antagonists “Sartans”)
Lymphocytic and collagenous colitis

Table 3: *Intra-epithelial lymphocytes with villous atrophy (Marsh type 3) [5].*

Clinical investigations and laboratory data appear critical for an appropriate differential diagnosis. Therapeutic and behavioural modifications are permanent for subjects of celiac disease. An appropriate morphology is a pre-requisite for labelling a condition with the following:

- Infection with Giardia lamblia or adjunctive parasites.
- The emergence of immune deficiencies with concomitant celiac disease.
- The appearance of Crohn’s disease or aetiology specific enteritis with concordant, unremitting diarrhoea as with autoimmune enteritis, tufting enteropathy, atrophy of the micro-villous and graft versus host disease [2,3].

Coexistent characteristic disorders are:

- Auto immune enteritis with immune compromise in young individuals (common variable immune deficiency, X linked agammaglobulinaemia) where the intestinal biopsy demonstrates morphology consistent with celiac disease [2,3].
- Drug induced villous deterioration: Agents such as the non-steroidal anti-inflammatory drugs (NSAIDs) or angiotensin II receptor antagonists “Sartans” induces a configuration simulating celiac disease. It appears in the elderly with the absence of positive serological markers [2,5].
- Concomitant gastric infection with Helicobacter pylori resembles the histology elucidated by the preliminary celiac disease.

Aggravated celiac disease

Celiac disease in adults displays a higher mortality with a lack of meticulously restricted dietary gluten, a deferred diagnosis or an incompetent therapeutic management. The restricted dietary gluten prevents the complications with amelioration of the histological and clinical features [13,14].

Disease complexities are on account of:

- Collagenous sprue: Subjects may not respond to the lack of dietary gluten as elucidated by a suitable histology. The superficial, intestinal sub epithelium demonstrates fibrous tissue. A collagenous colitis with a dense connective tissue band of > 15 mμ can be detailed by the Masson's trichrome stain [2].
- Refractory sprue: The condition is clinically identical to the collagenous sprue as elucidated by the appearance of CD3+ reactive T lymphocytes and a lack CD8+ immune reactivity. Intra epithelial T lymphocytes are normally reactive for CD3+ and CD8+ immune markers [2,3].
- Ulcerative jejuno ileitis delineates prominent ulcerations of the intestinal mucosa in conjunction with refractory sprue [15,16].
- Lymphoma as a complication of celiac disease necessitates consideration with the histological influx of aberrant, monotonous lymphocytes. A predominant immune phenotype of the T lymphoid population is discerned. Persistent celiac disease with constitutional symptoms of fever, weight loss, finger clubbing, bowel ulcerations and abdominal pain or a continual rise in serum Ig A values are elucidated [2,3]. The complication appears within a median of 28 years. Expansive intestinal lymphomas depict extensive, random lesions with ulceration, stricture formation and perforation of the gastrointestinal tract. The disease is insidious with a mixed cell infiltrate permeating the lamina propria and accumulated atypical, large lymphoid cells, terminating in a large cell lymphoma. Aberrant bi-nucleate or multinucleate cells misrepresent an emergence of Hodgkin's lymphoma. Eosinophils and histiocytes are frequently admixed. A cytotoxic T cell lymphoma is elucidated on account of miniature population of intraepithelial T cells, designated as an enteropathy associated T cell lymphoma, immune reactive for CD3+ and CD103+ (markers of intraepithelial lymphocytes) with a non-reactivity for CD5- [16,17].

Enteropathy associated T cell lymphoma is of two subcategories: Type I (classical) variant is typical and non-reactive for CD4-, CD8-, CD56-. Type II (monomorphic) subclass lack a clinical corroboration of celiac disease and display a monotonous infiltrate of small to medium sized T lymphocytes with infrequent, admixed inflammatory cells. The immune phenotype is CD4-, CD8+ and CD 56+. Majority of the enteropathy associated T cell lymphomas demonstrate reorganized lymphocytic clones with the T cell receptor genes [2,3].

The typical genetic modifications incorporate +9q31-q33 (70% cases) and -16q12 (23%). Type I enteropathy associated T cell lymphoma characteristically depicts +1q32-q41, +5q43-q35 genotype. Celiac disease with associated HLA phenotype exhibit HLADQB1*02(3). Type II variant depicts a genotype of +8q24 with the MYC locus [17,18]. Co-infection with the Epstein Barr virus is absent.

Serologic investigations for celiac disease

The singular option for discerning celiac disease is the detection of immunoglobulin A (IgA) anti-tissue trans-glutaminase antibodies (t TG Ig A) with a sensitivity of 93% and a specificity of 95% [4]. The IgA anti-endomyosial antibodies (EMA) are frequently evaluated as it is an accurate methodology necessitating an immune fluorescence (quantitative assay). Solitary serological values are not confirmatory in celiac disease. False positive antibody cross reactions arise in enteric infection, chronic liver disease, congestive heart failure or hypergammaglobulinaemia [4].

False negative reactions are elicited if the patient lacks a gluten restriction prior to investigation. Concomitant Ig A deficiency is frequent as 2 - 3% of the celiac disease patients are implicated. The Ig A deficient individuals are examined by an Ig G based assay (anti-deamidated gliadin peptide [DPG]) or with t TG Ig G antibodies. A synergistic immune assay of t TG IgA and DPG Ig G is efficacious [18,19]. The antibody titres are concordant with the extent of villous atrophy. An intestinal biopsy is necessitated despite a non-reactive serology to determine celiac disease.

Celiac disease with non-reactive serology

A sero-negative celiac disease is designated as the absence of t TG antibodies coexistent with a diagnostic histopathology along with human leukocyte antigen (HLA) haplotype DQ2 and/or DQ8 [16,17]. An intense antigen antibody affinity engenders a mucosal accumulation of tissue transglutaminase (t TG/anti t TG immune complexes) besides an absence of circulating antibodies. The appearance of the immune complexes in the proximal small intestine conjectures the appearance of insufficiently mature plasma cells with a deficit of antibody formulation or a celiac disease. Approximately 6 - 28% of the sero-negative villous atrophy originates from the sero-negative celiac disease [4].

Latent celiac disease

A sero-positive disease in the absence of villous atrophy is designated as the "latent or prospective celiac disease". Minimal diagnostic histology such as augmented intraepithelial lymphocytes are enunciated. The disorder delineates asymmetrical lesions with villous atrophy confined to the duodenal bulb or distal part of the jejunum with a non-representative biopsy. If the disorder perseveres, a repetition of the tissue biopsy or a capsule endoscopy is required [4].

Refractory celiac disease

Primary refractory celiac disease is characterized when individuals fail to respond to preliminary restriction of dietary gluten [18,19]. A continual or relapsing mal- absorption or a villous atrophy in-spite of a meticulous gluten restriction for a period of six to twelve months is designated as "refractory celiac disease". Infrequent, severe complications such as the ulcerative jejunitis and enteropathy associated T cell lymphoma ensues following discernment of the refractory variant [4]. Approximately 10 - 18% of the instances are represented by the non-refractory celiac disease. The condition may appear beyond 50 years of age. The symptoms reappear after a long duration of remedial gluten free diet (secondary refractory celiac disease). The type II kind of refractory celiac disease depict a lack of immune reactive CD3+ or CD8+ surface markers with immune histochemistry, flow cytometry and by the molecular, clone specific T cell receptor rearrangements. The type II category of refractory celiac disease exhibits a worse outcome, in contrast to the type 1 variant on account of a greater proportion of transformation to enteropathy associated T cell lymphoma (EATL) [4].

Therapeutic intervention

A rigorous gluten free dietary regimen for a stipulated 12 - 24 months is a pre-requisite for the gluten sensitive disorders, prior to the investigations of gluten intolerance. It may comprise as the solitary, specific treatment for gluten associated conditions. A lifetime adherence to gluten restriction is the singular option for celiac disease [1,2,4]. Minimal quantities of gluten can be ingested along with the gluten free foods, despite the precautions. Regular consultations with a gastroenterologist and an experienced dietician are mandated in affected subjects [1,4].

Conclusion

The chronic, immune mediated, small intestinal gluten susceptibility with specific auto antibodies against tissue transglutaminase 2 (anti t TG2), endomysium and/or deamidated gliadin peptide may be designated as "Celiac Disease". A pre-requisite may be the genotype

HLA DQ2 or HLA DQ 8, though the disorder clinically manifests in 2 - 3% of the carriers. The paediatric intestine elucidates a mal-absorptive syndrome with diarrhoea, poor thriving, loss of appetite, abdominal distension and inadequate growth. Adults delineate diarrhoea, abdominal bloating, constipation, abdominal pain or weight loss. Extra-intestinal manifestations of chronic inflammation, dermatitis herpetiformis, urticaria, psoriasis, dry skin, nutritional deficiencies and immune modulation may be exemplified. On microscopy: a count of 40 intraepithelial T lymphocytes per 100 epithelial cells is definitely pathological. The contemporary "Marsh Classification" with modifications of "Oberhuber" and the "Corazza" adaptation may be employed to appropriately grade the lesions. The disorder may mandate a segregation from adjunctive mal-absorptive conditions such as parasitic infestations (giardia, cryptosporidium, microsporidium), infectious diseases (Whipple disease) viral infections (cytomegalovirus, herpes), idiopathic conditions (crohns' disease) and tumours of the small intestine. Lymphoma as a complication of celiac disease necessitates consideration with the histological influx of aberrant, monotonous lymphocytes. A sero-negative celiac disease may be characterized with the absence of t TG antibodies, a diagnostic histopathology and human leukocyte antigen (HLA) haplotype DQ2 and/or DQ8. Similarly, a sero-positive disease in the absence of villous atrophy may enunciate the "latent or prospective celiac disease. A perpetual or relapsing mal-absorption or a villous atrophy with a meticulous gluten restriction for six to twelve months may constitute a "refractory celiac disease". A rigorous, lifelong adherence to gluten restriction may be the singular, efficacious therapeutic option for celiac disease.

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20. Image 1 Courtesy: Endoscopy GP online.

21. Image 2 Courtesy: Gastro.cy.com.

22. Image 3 Courtesy: Endoscopic campus.

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24. Image 5 Courtesy: Patient celiac.com.

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