Clinical Features and Diagnosis of Celiac Disease

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Celiac disease is a chronic enteropathy caused by intolerance to gluten. The true prevalence of this condition is much greater than previously recognized, with increasing numbers of silent cases being diagnosed. Population-based studies, using serologic screening, have indicated that the prevalence of celiac disease in Caucasian populations is .5%–1%. The pattern of incidence is changing, with a greater proportion of cases diagnosed later in adulthood. The pathologic lesion is characterized by a flattened small intestinal mucosa with a lymphocytic infiltrate, crypt hyperplasia, and villous atrophy. Absorptive function may be impaired and patients can experience gastrointestinal symptoms and malabsorption leading to development of anemia, osteoporosis, or other complications. Untreated celiac disease is associated with significant morbidity and increased mortality, largely owing to the development of enteropathy-associated intestinal lymphoma. The pathologic changes and symptoms resolve when gluten is excluded from the diet for a sustained period.

Celiac disease was first described in a lecture by Samuel Gee[1] in 1887. He noted the classic symptoms of diarrhea, lassitude, and failure to thrive and commented from his observations that the cure might lie in the diet. The first accurate description of the celiac lesion was provided by Paulley et al[2] in 1954 who examined full-thickness biopsy specimens taken at laparotomy from a patient with celiac disease. They referred to broad flat villi and a dense chronic inflammatory cell infiltrate in the small intestinal mucosa. Following this, the use of unguided suction biopsy devices, such as the Crosby capsule, allowed the study of patients with malabsorption. The advent of fiberoptic endoscopy has led to the extensive study of the duodenal mucosa in less florid forms of celiac disease.

Clinical Presentations of Celiac Disease

In celiac disease there is an inflamed and flattened small intestinal mucosa with impaired function. This inflammation affects the proximal small bowel with variable sparing of the ileum distally. The small intestine has considerable functional reserve and this explains why many individuals have few or no symptoms and frequently no evidence of malabsorption. If the distal small bowel is involved then patients may be expected to develop diarrhea or nutrient malabsorption. Clinical presentation depends on age, sensitivity to gluten, and the amount of gluten ingested in the diet, as well as other unknown factors. Celiac disease has a highly variable clinical expression. There are some atypical clinical manifestations that are not understood because they do not appear to be related directly to the gastrointestinal pathology.[3]

There is a spectrum of gastrointestinal presentation that ranges from generalized malabsorption and protein-energy malnutrition to mild abdominal symptoms but no discernable abnormalities. Severe cases of malabsorption rarely are seen except in developing countries and in infants when gluten is introduced at weaning. The classic presentation associated with celiac disease is characterized by steatorrhea, abdominal distention, edema, and extreme lethargy. There has been a shift in the pattern of presentation with more cases diagnosed as a consequence of widespread serological testing and increased awareness. Some individuals may have no symptoms at all and can be termed as having *silent celiac disease*. It is clear from epidemiologic studies that there is a substantial number of undiagnosed cases in the general population, possibly 10 times as many as actually have been diagnosed.[4] Higher prevalence is found in certain risk groups, including those with anemia, osteoporosis, short stature, infertility, autoimmune disorders, and a family history of celiac disease.[5] Diarrhea occurs in less than 50% of patients at presentation compared with nearly 100% of patients who presented in the 1960s.[6] Weight loss is now an uncommon feature and tends to signify a dramatic presentation with more extensive disease. In contrast, at least 30% of patients are overweight at time of diagnosis.[7] Overall onset of symptoms is more gradual

Abbreviation used in this paper: IEL, intraepithelial lymphocyte.

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and there is often a considerable latency before the diagnosis of celiac disease. Sometimes patients describe a trigger event such as gastroenteritis, overseas travel, stress, or surgery. Constitutional symptoms such as lethargy, poor appetite, and depression frequently are reported but these may be insufficient enough to seek advice from a physician. Abdominal pain, bloating, and altered bowel habit may occur in the absence of malabsorption and this picture may be indistinguishable from irritable bowel syndrome. Patients satisfying the Rome II criteria have a 5% risk for having undiagnosed celiac disease as the cause of their symptoms[8] and therefore this group should be screened with serological testing. Iron and folate deficiency are commonly found, either in isolation or as a feature, and may occur with or without anemia. B_{12} deficiency may not be expected because absorption is cofactor dependent and occurs in the often unaffected terminal ileum. However, B_{12} levels are statistically decreased in celiac patients compared with controls and 12% of patients have actual deficiency.[9] This does not appear to be caused by an association with autoimmune gastritis.

Latent Celiac Disease

Certain detectable serum antibodies have a high specificity for a diagnosis of celiac disease, particularly immunoglobulin A (IgA) anti-endomysial antibody (>99%).[10] Those individuals who are antibody positive, but with normal or minimally abnormal small bowel biopsy examination, have been described as having *latent or potential celiac disease*.[11] The natural history of this condition is not understood but anecdotally some individuals have been reported to progress to develop unequivocal celiac disease with villous atrophy and clinical manifestations.

Small Intestinal Biopsy Examination

Diagnosis of celiac disease requires a small intestinal biopsy examination, and a specimen can be readily obtained during routine upper-gastrointestinal endoscopy. Duodenal biopsy examination should be performed in all patients suspected of having celiac disease and all those who merit exclusion of celiac disease. The diagnostic value of duodenal biopsy examination is extremely good with high positive and negative predictive values and the additional risk of performing a biopsy examination is negligible. Duodenal biopsy specimens should be taken in those with positive celiac antibodies, iron-deficiency anemia, folate deficiency, osteomalacia, malabsorption, abnormal duodenal appearances, and significant unexplained weight loss. Negative celiac serology should not preclude duodenal biopsy examination in those who have other indications.

Duodenal Appearances at Endoscopy

Visible abnormalities have been described at endoscopy such as mucosal pallor, scalloping, and a decrease in duodenal folds. These changes have been shown to correlate with degrees of villous atrophy but appearances often are normal and this cannot be relied on for diagnosis.[12] The use of magnifying endoscopes can identify marked villous atrophy readily but offers no advantage with a decreased sensitivity compared with the gold standard of a biopsy examination.

Pathologic Analysis and Potential Pitfalls in Diagnosing Celiac Disease

When attempting to interpret duodenal histology, it is important to note whether patients are consuming gluten currently and whether samples are taken for diagnosis, to check for mucosal recovery or as part of a gluten challenge. The histologic abnormalities in the small-bowel mucosa usually are more pronounced proximally and therefore samples taken from the second part of the duodenum or beyond should be representative. Certain patients in specialist centers occasionally require a more distal biopsy sample and this can be performed by suction capsule (in children) or push enteroscopy. At least 4 samples should be taken with large forceps to ensure that decent-sized specimens are obtained for analysis and that patchy changes are less likely to be missed. Despite this practice, false negatives can occur. If the clinical suspicion is high, repeat duodenal biopsy examination or sampling of more distal small bowel should be considered.

Specimens should be orientated correctly before mounting, preferably with low-powered magnification, and then cut to 3- or 4-μm thickness. In assessing villus height and crypt depth, it is necessary to identify at least 3 or 4 intact adjacent villi that are cut perpendicularly. Tangentially cut sections lead to an artificial appearance of villous atrophy and a potential overdiagnosis of celiac disease.[13] Additionally, villi adjacent to lymphoid follicles often are blunted in normal individuals so analysis of these areas should be avoided. If specimens show evidence of Brunner's glands, gastric metaplasia, and duodenitis then the sample should be disregarded and repeated more distally.

The characteristic histologic findings are blunted or flat villi, hyperplastic crypts, loss of surface enterocyte cell height, and a lymphocytic infiltration of the lamina propria. These changes occur in response to enterocyte injury, mucosal inflammation, and increased epithelial

proliferation. There is a specific increase in the number of intraepithelial lymphocytes (IELs) greater than normal, particularly in the villous tips. This is the earliest discernable abnormality using light microscopy.[14]

The Marsh Classification of Celiac Lesions

The Marsh classification[15] has been adopted to describe the progression of the abnormalities in the celiac mucosa. The initial categorization has been modified slightly to improve its application in clinical practice, although its use is not universal. A Marsh type I lesion (infiltrative) comprises normal mucosal architecture with a lymphocytic infiltration of the villous epithelial layer. The arbitrary threshold for a normal IEL count is debated but generally in excess of 30–40 per 100 surface enterocytes is taken to denote a significant increase.[15,16] Staining for CD3 can be used to facilitate identification and counting of IELs. A Marsh II lesion (hyperplastic) exists if, in addition to a lymphocytosis, there is crypt hyperplasia shown by crypt branching and elongation, and increased mitotic activity. The villus height/crypt depth ratio often will become decreased below a normal value of 3–5. The hallmark of Marsh III lesions (destructive) is villous atrophy. Marsh IIIA denotes partial villous atrophy, which is denoted as a villus height/crypt depth ratio of less than 1. Marsh IIIB describes subtotal villous atrophy where separate villi still are recognizable. Marsh IIIC is characterized by total villous atrophy with no discernable digitations, resembling colonic mucosa. A Marsh IV lesion (hypoplastic) describes a rare histologic finding of a flat atrophic mucosa thought to signify irreversible injury caused by chronic inflammation. It appears that these abnormalities are related to refractory celiac disease and the development of enteropathy-associated T-cell lymphoma. In these conditions, an abnormal monoclonal T-lymphocyte population with an aberrant phenotype has been shown. These cells are highly specific, such that their presence may represent a cryptic intestinal lymphoma.[17]

Minimal Change Lesions (Marsh I and II Lesions)

As with the clinical presentation of celiac disease, it is recognized that the pathologic lesion is part of a spectrum of severity, with more subtle abnormalities constituting a significant number of the cases. Traditionally, a diagnosis of celiac disease was made on finding mucosal abnormalities equivalent to a Marsh III lesion. It is now clear that many individuals have gluten-sensitive inflammation without villous atrophy. These borderline histologic abnormalities have been shown to improve on a gluten-free diet.[18] Marsh I lesions pose a particular problem because their interpretation often is controversial with poor interobserver correlation. Added to this the natural history has not been elucidated. It is not yet known whether these individuals have the same adverse health risks as the traditional celiac patient with villous atrophy. The morbidity data that currently is available largely is obtained from those who were symptomatic and were diagnosed with villous atrophy. This data cannot be extrapolated logically to apply to those with Marsh I–II lesions. Clearly, if an individual has symptoms or clinical manifestations attributable to celiac disease, a gluten-free diet should be advised. The decision is more difficult in the case of an apparently healthy person with positive celiac serology and a Marsh I lesion. It may be difficult to convince such a person to follow a gluten-free diet, although some asymptomatic individuals report unexpectedly feeling better on a gluten-free diet.[18] Further work is required to characterize the natural history and relative health risks for borderline lesions. However, it may be prudent at least to follow-up these patients in clinical practice to look for the development of potential complications such as anemia and osteoporosis. It should be remembered that an intraepithelial lymphocytosis is a nonspecific response to any adverse stimulus in the intestine and also can be found transiently in healthy individuals who do not have celiac disease. In one study, approximately 10% of individuals with an unexplained increased IEL count went on to be diagnosed with celiac disease, although suspected celiac patients already had been excluded.[19] An increased IEL count in itself is insufficient to diagnose celiac disease and requires correlation with clinical and serologic parameters. However, not all individuals with these minor abnormalities will be identified using celiac antibody testing. Many early studies reporting on the sensitivity of celiac antibody tests focused on Marsh III lesions and did not include many cases with lesser changes. The literature suggests that the sensitivity of antigliadin, antitissue transglutaminase, and antiendomysial antibodies may be much lower in Marsh I and II lesions,[20] which further adds to the diagnostic dilemma.

Repeat Small-Bowel Biopsy Examinations for Mucosal Recovery and Gluten Challenge

Central to the pathology of celiac disease is the demonstration that these abnormalities improve with a gluten-free diet and then recur with a further gluten challenge. Clearly, this series would require 3 separate

endoscopic procedures and the reintroduction of gluten with the potential to cause further illness. For this reason, many clinicians base the diagnosis on a single characteristic biopsy specimen supported by positive serology. There is no consensus between the guidelines produced by several advisory bodies.[21–23]

Repeat biopsy examination to check mucosal recovery on a gluten-free diet has some benefits. Demonstration of histologic improvement makes the diagnosis more secure and allows the physician to check adequate compliance with the gluten-free diet. This information also is reported as being reassuring to the patient. In a reassessment of a series of 110 celiac patients with ongoing symptoms, 12 (11%) were found not to have celiac disease.[24] None of these patients had undergone a repeat biopsy examination (although 4 patients had not had an initial biopsy examination either). A recovery biopsy examination also provides a comparison if patients should develop future problems because a further examination of small-bowel histology often is required as part of their assessment.

The argument against performing a second endoscopy procedure is that it is an unnecessary expense and a further invasive procedure. The information obtained will not necessarily influence management and is viewed as being superfluous by some physicians. Celiac serology can be used as an approximate marker of dietary compliance, although a decrease in titer does not correlate with histopathologic improvement.[25] Mucosal recovery has been shown to be protracted in some individuals and may take more than 18 months.[26] At 1 year, a percentage of biopsy specimens will be abnormal owing to noncompliance or despite a strict gluten-free diet. The treatment advice—to adhere to a gluten-free diet—is the same irrespective of the biopsy examination results. In straightforward cases, in which patients report symptomatic improvement and a decrease in celiac antibody titers on a gluten-free diet, there is no clear need for a repeat biopsy examination. In those whose antibody levels do not decrease within 12 months, dietary compliance should be checked and repeat biopsy examination should be performed as necessary by mutual consent. In cases in which there is diagnostic ambiguity a recovery biopsy examination is likely to be helpful. Particular examples are patients with initial negative serology, patients with continued symptoms, and those with minimal or ambiguous histologic changes.

Gluten challenge is not performed routinely now, unless there is diagnostic difficulty. The most likely scenario for using a gluten challenge is in a patient who is already on a gluten-free diet despite not having been diagnosed with celiac disease. With increasing public awareness of celiac disease, individuals may modify their diet before visiting their physician. Nearly half of patients with irritable bowel syndrome report improvement with restriction or total exclusion of wheat from the diet. The improvement usually is not sustained, particularly because a wheat-free diet tends to be low in fiber. A diet low in gluten may normalize small-bowel histology (and celiac serology) and thus gluten intake should be resumed before testing. Formal gluten challenge should comprise a daily intake of 10 g of gluten and this can be achieved by consuming 4 slices of white bread each day for a minimum of 4 weeks.[23] If patients are particularly symptomatic it may be helpful to shorten this period because 2 weeks may be satisfactory (personal observation). The development of symptoms on gluten challenge is not sufficient to make the diagnosis.

Differential Diagnosis

Celiac disease is the commonest cause of enteropathy by some margin. However, it should be appreciated that villous atrophy and an intraepithelial lymphocytosis are not exclusive to celiac disease. Other causes of enteropathy can be responsible such as infective gastroenteritis, bacterial overgrowth, lactose intolerance, giardiasis, anorexia nervosa, ischemic enteritis, tuberculosis, Crohn's disease, hypogammaglobulinemia, tropical sprue, Whipple's disease, collagenous sprue, autoimmune enteropathy, soya protein intolerance, Zollinger–Ellison syndrome, intestinal lymphoma, human immunodeficiency virus enteropathy, and other immunodeficiency states. With respect to self-limiting gastrointestinal infections, these changes will resolve spontaneously. The other more rare causes listed here should at least be remembered in cases that do not appear typical of celiac disease or do not respond as expected to a gluten-free diet.

Immune Response in the Celiac Mucosa

In active celiac disease, the lamina propria is expanded in volume, which is caused, in part, by recruitment of T lymphocytes, plasma cells, and dendritic macrophages expressing human leukocyte antigen (HLA) molecules, intercellular adhesion molecule-1, and CD25 (interleukin-2 receptor α-chain)—an infiltrate indicative of a T-cell–mediated immune response. There are several distinct populations of T lymphocytes in celiac disease. Within the lamina propria, a population of DQ2-restricted CD4+ T cells can be isolated, which become stimulated when cultured with gluten.[27] These gluten-sensitive T cells express a memory phenotype and the predominant cytokine secreted is interferon-γ.[28] Supernatant from isolated gluten-specific lymphocytes induces

damage to the normal intestine. The mucosa also contains an excess of fibroblasts with increased expression of matrix metalloproteinases, which activate degradation of extracellular matrix proteins.[29]

A separate population of IELs is present but their function remains unclear. The majority are CD8+ and express natural killer markers such as CD94, suggesting that they may be cytotoxic to enterocytes.[30] A smaller percentage of these lymphocytes are both CD4/CD8 negative and express the primitive γ/δ T-cell receptor. Unlike the CD8 IELs or lamina propria infiltrate, this population does not regress on gluten withdrawal. It has been proposed that these γ/δ lymphocytes form part of innate rather than acquired immunity. They do not appear to require human leukocyte antigen for antigen recognition and recognize stress proteins such as MICA and MICB (major histocompatibility complex class-I-related chains) expressed on epithelial cells, subsequently recruiting polymorphs and monocytes.

Pathogenesis of Celiac Disease: Innate Versus Acquired Immunity

The earliest changes in celiac disease after gluten challenge can be seen at 1 hour and this has led to the suggestion that the primary mechanism of injury is not related to a CD4+ T-cell response. Changes in intestinal morphology and membrane expression of human leukocyte antigen molecules and activation markers can be detected within 1 hour of gluten challenge, which precedes lymphocyte infiltration. CD4+ T-cell reactivity results in a delayed-type response, which would be expected to take days to effect significant cellular recruitment and an inflammatory response. Although much of the work has focused on these gluten-sensitive T cells, it is possible that they are a product of mucosal injury rather than the primary mechanism. It recently has been shown that interleukin-15 expression in the intestinal mucosa is up-regulated significantly in active celiac disease.[31] Interleukin-15 is expressed by cells from the innate immune system such as enterocytes and monocytes within the lamina propria. This indicates a role for the innate immune system at an early stage in disease pathogenesis, which might suggest an alternative toxic mechanism for gluten.

In this regard, the transport pathway for gliadin may be relevant. In rat intestine, gliadin administration results in increased permeability of tight junctions, mediated by zonulin, which is likely to facilitate the delivery of gliadin to the lamina propria via the paracellular route.[32] In human celiac mucosa, zonulin expression is increased. Further studies have examined the transcellular pathways in enterocytes using labeled monoclonal antibodies to a gliadin peptide.[33] In celiac patients, staining was found to be granular with gliadin located within apical vesicles and in larger vacuoles together with class II major histocompatibility complex antigens. In controls, the staining was uniform with no such localization. It is known that antigens within endosomal compartments have a tendency to be processed and presented to CD4+ T cells, which might explain the varied gluten epitopes that have been identified. Recent work has shown that several of the major epitopes remain largely undigested on delivery to the lamina propria.[34]

Summary

Celiac disease is far more common than previously considered and presents as a spectrum of clinical manifestations and histologic abnormalities. The health risks for untreated celiac disease appear to be greater compared with those who adhere to a gluten-free diet. There are many individuals with undiagnosed celiac disease in the general population and the health impact of this cannot yet be established. Duodenal biopsy examination remains the gold standard for diagnosis of celiac disease. Correlation of clinical, serologic, and histologic features is essential in the secure diagnosis of celiac disease.

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