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Review Article

Critical Definition of Celiac Disease and Sprue-Like Intestinal Disease in Adults

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Abstract

Adult celiac disease is an immune-mediated small intestinal mucosal disorder that may be clinically manifested by diarrhea, weight loss and nutrient malabsorption accompanied by characteristic histopathological changes in the small bowel. The disease occurs in genetically-predisposed persons and responds to a gluten-free diet. Serological screening studies have estimated that the disease occurs in about 1%. In recent years, however, similar clinical and pathologic features may result from an emerging array of infectious agents as well as newer pharmacological and biological medications. Thus, exclusion of these novel causes in this modern era may be critical in diagnosis of celiac disease. Indeed, and most important, only in celiac disease does a gluten-free diet lead to improved mucosal recovery and resolution.

Keywords: Adult Celiac Disease; Gluten-Sensitive Enteropathy; Sprue-Like Intestinal Disease; Medication-Induced Small Bowel Disease

Introduction

Celiac disease (also historically called celiac sprue or, more precisely, gluten-sensitive enteropathy) is a gluten-dependent small intestinal mucosal disorder present in persons that are genetically-predisposed. Diarrhea and/or unexplained weight loss are usually evident. The disease is immune-mediated, often with related systemic clinical features. Screening studies in different adult populations have estimated that about 1% of all sero-positive adults may have the disease [1-3].

Initial biopsies to define pathology

Assuming that endoscopic biopsies are properly processed (from the endoscopy suite through the laboratory), interpretation by an experienced gastrointestinal pathologist on serially sectioned biopsy material is optimal [3]. Some features include varying severity in architectural change with "flattened" villi and elongated crypts, increased crypt epithelial cell mitoses, increased lymphoid round cells (plasma cells, lymphocytes) in the lamina propria and increased intra-epithelial lymphocytes. Precise evaluation is also dependent on good communication by the endoscopist, including definition of the anatomical site of individual endoscopic biopsies. Biopsy interpretation may be variable between different pathologists, especially if classification systems are complex and even, in some instances, with the same pathologist re-examining the same biopsy (i.e., inter- and intra-observer error) [4]. In this initial assessment, the pathological conclusion is likely to be "characteristic or consistent (but not diagnostic) for untreated celiac disease".

Gluten-free diet response

The next phase, perhaps *most critical* for diagnosis, actually occurs *after* treatment with a gluten-free diet [5]. The patient may

have clinically responded to treatment with significant weight gain and complete resolution of diarrhea, if initially present. Indeed, even obese patients may demonstrate further weight gain. Further evidence for this diagnosis may result from quantitative serological studies showing improved or normalized anti-IgA antibody levels (e.g., transglutaminase antibodies). Here, however, a second set of biopsies in a patient with now normal or near normal antibody levels may show only limited (or possibly, unconvincing) histopathological improvement. Seroconversion (towards normal) usually occurs with gluten-free diet treatment, but underlying inflammatory changes in the mucosa may persist. The time required for a histopathological response to occur may also vary and appears to depend on the patient's age, sex and duration on the diet [5]. Elderly males with celiac disease may be most resistant to the effects of a gluten-free diet [5]. Other issues, including genetic factors, may play a role in a slow response to a gluten-free diet.

Biopsies should be obtained from similar sites for more precise comparison with earlier samples. Indeed, some have described a generalized "proximal-to-distal" gradient in the degree of severity of biopsy changes with most severe alterations in architecture occurring in the proximal small intestine, possibly reflecting greater luminal concentrations of the offending peptide. In contrast, the progression of mucosal healing with a gluten-free diet appears to occur initially in the most distal regions of the involved small intestine and only later in the more proximal small intestine, a so-called "distal-to-proximal gradient" [6]. In some with only limited clinical symptoms, biopsies taken at colonoscopy from the distal ileum, for example, may show only minimal changes, possibly only increased numbers of intra-epithelial lymphocytes. This finding alone may lead to suspicion for celiac disease and the need for biopsies from the more proximal small intestine where more characteristic changes may be present [7]. Stated differently, diagnosis of celiac disease or gluten-sensitive enteropathy depends on documentation of gluten dependence of the disease. This may include significant and documented weight gain or resolution of diarrhea. In others, however, repeated biopsies in the proximal small intestine over time may be required.

Added or high-gluten diets

Additional documentation of the effects of a high gluten diet may also be necessary. Normally, gluten does not cause histopathological changes in the normal small intestine. Studies in volunteers have shown that oral feeding up to 150 grams of gluten for at least 8 weeks produced no effects [8]. However, feeding high gluten containing diets to adults with occult celiac disease (so-called latent celiac disease with initially normal small intestinal biopsies) has been shown to precipitate the histopathological changes of overt celiac disease in both of 2 related or associated diseases: dermatitis herpetformis [9] and intestinal lymphoma [10]. Further biopsies in these patients with lymphoma and full-blown celiac disease treated with a gluten-free diet then led to improved biopsy architecture, further evidence of the gluten-dependent nature of celiac disease [10].

Iron absorption and anemia

Interestingly, iron deficiency commonly accompanies celiac disease [11]. Indeed, some celiacs present with anemia and iron deficiency without evidence of definite luminal blood loss to account for anemia. Although initial studies may lead some to explore the colon to define a source for blood loss and iron deficiency, no cause is found. However, impaired iron absorption (from the duodenum) may be responsible owing to significant proximal intestinal mucosal changes (due to celiac disease). Once identified, and treated *solely* with a gluten-free diet, normal mechanisms for duodenal absorption of iron from the proximal small intestinal lumen are thought to re-develop with eventual resolution of iron deficiency (and anemia), even without added dietary iron supplements [12]. Even here, however, anemia may have a second cause, including colon cancer [13]. Indeed, anemia due to iron deficiency is a special issue because of the possibility of a second, sometimes, ominous or complicating cause for iron loss, even if celiac disease is already well defined.

Adverse effects of gluten-free diet

Thus, it is important to define the presence of celiac disease so that the treatment, a gluten-free diet, can be instituted. This is a life-long diet, but some potential adverse health risks may occur [14]. These relate to the use of a diet deficient in recommended amounts of calcium, iron and fibre for both males and females [15]. Some gluten-free foods may be deficient in folic acid and other vitamins, including niacin, riboflavin and thiamine [16]. In family studies, use of a gluten-free diet apparently led to consumption of a more "obesogenic" diet with added junk food, snacks and candies, even in those without celiac disease [17]. Fish and rice, as part of a gluten-free diet may lead to increased mercury, lead and

cadmium blood levels as well as increased urinary arsenic levels, possibly due to high concentrations in the fish and accumulation of heavy metals [18]. These consequences will require further long-term studies to specifically define adverse effects as well as the frequency of this risk.

"Recurrence" in celiac disease

Even in well documented adult celiac disease, however, later recurrent symptoms may occur. In these patients, there is a need to consider several possibilities. Table 1 provides a list.

Poor or limited compliance to gluten-free diet [see text]
Pill capsules and communion wafers with gluten [19]
Other unrecognized sources of gluten [20]
Wrong initial diagnosis (e.g., "isolated" duodenal Crohn's disease) [21]
Related cause (e.g., collagenous colitis) [22]
Superimposed disease (e.g., collagenous sprue, lymphoma) [10]

Table 1: "Recurrence" in Celiac Disease.

Compliance or unrecognized gluten source

Most often, *poor or limited compliance* with a gluten-free diet may be responsible. Sometimes, poor compliance may be "intentional", particularly in teens and young adults. Besides psychosocial reasons, there may be added issues. A gluten-free diet is difficult to follow and represents a financial burden for some individuals, particularly elderly and retired subjects, now facing a "newly" diagnosed disorder and a changed lifestyle. In some progressive countries, costs of the gluten-free diet may be alleviated though government tax agencies. Access to gluten-free products may also pose difficulties by distance from shopping sites to home cooking facilities. Patient mobility may be a special issue. In others, compliance may relate to the source of gluten, sometimes not being recognized (e.g., pill capsules, communion wafers [19]. Even dental appliances have been associated with prevention of remission in celiac disease [20]. If requested by the patient, some restaurants and airlines may provide gluten-free meals. In summary, a gluten-free diet can lead to many issues that, in themselves, represent serious problems to navigate. Sometimes local educational groups may be helpful in providing a source for information for celiac patients.

Wrong initial diagnosis

A number of other diseases may superficially masquerade as celiac disease, especially in a patient with diarrhea and weight loss. *Crohn's disease* developing in the proximal duodenum may be mistaken for celiac disease. "Isolated" Crohn's disease in the duodenum is well described [21], but rare, and does not respond to a gluten-free diet. Granulomas, microgranulomata and other biopsy changes described in Crohn's disease may not be readily appreciated to permit differentiation from celiac disease with Crohn's disease only first diagnosed after clinical recognition of disease elsewhere in the intestinal tract, including the colorectum.

Superimposed disease or related cause

Recurrent symptoms may occur for other reasons, even in patients with celiac disease, including a *superimposed intestinal infection*, or a related disease like *collagenous sprue* or *intestinal lymphoma*. Finally, a related cause involving the colon, rather than the small intestine, may occur (e.g., *collagenous colitis*). In some, celiac disease may only be recognized after the diagnosis of collagenous colitis [22].

Sprue-like small intestinal diseases

A long list of different disorders may produce histopathological changes localized in the small intestine that may appear like the changes of celiac disease. These are often characterized by a failure to respond to a gluten-free diet and have been termed "sprue-like intestinal disease", recognizing the failure in a patient with a diagnosis of "celiac disease" to demonstrate the gluten-dependent nature in a specific case. Tables 2 and 3 provide a partial list of some of these entities.

Sprue-like syndromes
Collagenous sprue
Mesenteric lymph node cavitation syndrome
Oats-induced mucosal disease, soy protein injury
Infections
Protozoa (giardiasis, cryptosporidiosis)
Virus (COVID-19, HIV)
Bacteria (salmonella, shigella, tropheryma)
Parasite (strongyloides)
Stasis with bacterial overgrowth
Deficiency syndromes (zinc, folic acid, congenital or acquired immune)
Others (autoimmune enteropathy, genetic types (AIRE, IPEX), chronic granulomatous disease, mast cell disease, lymphoma, Zollinger Ellison with hypergastrinemia, post-gastrectomy and post-colectomy, transplant)

Table 2: Biopsy Changes with Similarities to Celiac Disease*.

*Adapted from prior reference [3]

Pharmacological agents
Triparanol
Alcohol
Neomycin
Stathmokinetic agents (vincristine, vinblastine, colchicine)
Non-steroidal anti-inflammatory agents (sulindac)
Immunosuppressive agents (azothioprine, mycophenolate)
Anti-hypertensive agents (olmesartan)
Biological agents
anti-CTLA-4 checkpoint inhibitors (ipilimumab)
anti-PD-1 checkpoint inhibitors (pembrolizumab)

Table 3: Drug-induced Small Bowel Disease*.

*Adapted from prior reference [3].

Usually, these are due to infectious agents or a nutrient deficiency. A long list of infectious agents may be recognized now to cause small bowel histopathological changes. These may actually dominate the clinical disorder, including protozoans (e.g., *Giardia lamblia*, *cryptosporidium*, *Isospora belli*). In giardiasis, for example, a wide array of histopathological changes may occur, sometimes mimicking severe changes of celiac disease. In some, a travel history to an endemic area may be appreciated. Treatment with an antibiotic agent, like metronidazole, usually results in resolution of symptoms, including diarrhea, not a gluten-free diet. Other bacterial agents may cause changes, including so-called tropical sprue as well as stasis with bacterial overgrowth. Parasitic disease may lead to small intestinal changes, including *Strongyloides stercoralis*. Other agents, such as DNA (deoxyribonucleic acid) viruses, like cytomegalovirus. Often there is an underlying immune deficiency state, including a prior hematopoietic or solid organ transplant. Most recently, RNA (ribonucleic acid) viruses, including some from the coronavirus family (COVID-19) [23], have been associated with small bowel histopathological changes that, if severe, could mimic celiac disease.

Nutrient deficiency (e.g., zinc, vitamin B12, folic acid) [24-27] have all been independently shown to cause similar small bowel mucosal mucosal changes. In some cases, initial treatment of this superimposed depleted nutrient is essential for changes of underlying celiac disease to be recognized (e.g., especially folic acid deficiency associated with use of medications or abuse of alcohol).

Immunodeficiency states have also be associated with pathological changes in the small intestine that may mimic celiac disease changes, but do not respond to a gluten-free diet. These have been poorly classified but include common variable or combined immunodeficiency [28] and acquired forms, including disease linked to the human immunodeficiency virus (HIV) [29].

Interestingly, immunoglobulin A deficiency [30] has been linked to biopsy changes of celiac disease. In some of these, a small bowel histopathological response to a gluten-free diet may occur suggesting that some of these patients may also, by definition, have concomitant celiac disease [30]. Even some HIV (human immunodeficiency virus) patients with so-called HIV enteropathy [31,32] may actually have underlying celiac disease as symptoms may resolve [33-35] and a small intestinal histopathological response may occur with a gluten-free diet [29].

Most intriguing in this modern era is the increased expansion of drug-induced small bowel mucosal disease [3].

Some are shown in Table 3. Initially, experimental animal studies with triparanol revealed small intestinal changes, similar to celiac disease. Later studies with alcohol-associated small intestinal mucosal injury were noted. Acid in Zollinger-Ellison syndrome (actually, hyperacidity) and non-steroidal inflammatory drugs may cause small bowel changes that could resolve with treatment, not with a gluten-free diet. Stathmokinetic agents, like vincristine, vinblastine and colchicine, may all cause small intestinal mucosal changes, including development of epithelial "spindles" from arrested metaphases. Chemotherapeutic agents, like methotrexate, and immunosuppressive drugs, like azathioprine and mycophenolate [36], used in treatment of a wide variety of chronic inflammatory diseases and advanced malignancies, may be associated with sprue-like small intestinal mucosal disease.

In recent years, recognition of powerful anti-hypertensive agents, specifically olmesartan [37-41], were recognized to cause small bowel changes typical of celiac disease. Some of the original cases appeared to be reported by different groups at the same institution [38,39]. Treatment with a gluten-free diet failed. In some, hospitalization with a clinically severe enteropathy and a fatal outcome resulted [38]. Subsequently, olmesartan was also associated with development of collagenous sprue [42]. And, in some cases, this disorder was preventable simply by cessation of olmesartan suggesting a spectrum of clinical outcomes [42,43].

In addition to pharmacological agents, the modern area has seen the development of a whole group of biological agents for treatment of chronic disease as well as advanced malignancies [44-49]. Ipilimumab, a monoclonal antibody versus CTLA-4 (**C**ytotoxic T-Lymphocyte Association) checkpoint inhibitors, and pembrolizumab, a monoclonal antibody versus PD-1 (Programmed cell Death) checkpoint inhibitors, have been used, especially in malignant melanoma and other advanced malignancies. Each has been documented in some to cause either a sprue-like intestinal lesion or an inflammatory small intestinal or colonic lesion or both (i.e., enterocolitis) [47].

Conclusion

In the majority of patients that present with clinical and/or histopathological changes typical of adult celiac disease, a diagnosis of celiac disease is eventually established as the patient responds to a gluten-free diet. Most respond quickly, within weeks to months, regain their weight and diarrhea resolves. This usually occurs within the first 2 years [5] but there are exceptions. Slow responses inevitably lead to added investigations. There may be an important role for more extended video exploration of the small intestine in some with possible celiac disease along with the long-term follow-up of established disease [50]. A role for artificial intelligence can be invisioned. It is critical, however, to conduct a detailed evaluation to exclude novel infectious agents along with an extensive exploration of current medication use including newer pharmacological agents and evolving biologicals.

Conflict of Interest

The author declares that there are no conflicts of interest.

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