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Adult Celiac Disease Diagnosis Critically Depends on Documentation of Gluten Dependence

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Abstract

Celiac disease (also called celiac sprue or gluten-sensitive enteropathy) is a gluten-dependent immune-mediated small intestinal mucosal disorder present in genetically-predisposed persons. Screening studies in different populations have estimated that about 1% of seropositive patients may have the disease.

However, there are other causes of small intestinal disease with similar symptoms and histopathological appearances to untreated celiac disease. These sprue-like small intestinal diseases may be due to non-gluten proteins (eg., soy), nutrient and immune deficiencies, infectious agents and an increasingly recognized array of pharmaceutical (eg., olmesartan) and biological agents (eg., checkpoint inhibitors). All may lead to a small intestinal mucosal disease that does not respond to a gluten-free diet emphasizing that demonstration of the gluten-dependent disorder in celiac disease is critical for diagnosis.

Keywords: Sprue-like Intestinal Disease; Adult Celiac Disease; Gluten-Free Diet; Medication-Induced Small Bowel Disease; Celiac Sprue; Gluten-Sensitive Enteropathy.

Introduction

A 1970 editorial [1] recognized that the histopathological changes of untreated celiac disease (celiac sprue, gluten-sensitive enteropathy) were characteristic, but not specific, for the disease. The key critical element has been evidence of responsiveness to a gluten-free diet since other disorders may have a similar appearance but are not responsive.

Importantly, it is worth noting that in normal volunteers the normal small intestinal mucosa has been previously documented to be unaffected by feeding of added dietary gluten, sometimes in large amounts for prolonged periods, specifically, up to 150 g gluten daily for at least 8 weeks [2]. In contrast, feeding gluten-containing diets to adults with occult celiac disease (so-called latent disease with initially normal small intestinal biopsies), has been shown to precipitate the classical histopathological changes of overt celiac disease [3,4]. In these studies, subsequent treatment with a gluten-free diet than resulted in normalization of biopsies [3,4], further confirming the gluten-dependent nature of the small intestinal biopsy lesion.

Endoscopic Biopsy Processing

Of course, changes ultimately reported by pathologists are based on proper technical handling of endoscopic biopsies. To obtain the most optimal results, much depends on cooperation of the clinician endoscopist and the pathologist based, not only on good communication, but on biopsy performance and presentation of this material to the laboratory for precise technical processing (embedding, sectioning, staining) of biopsies [5,6]. Even then, some degree of pathological variability in interpretation is likely. This may include observer variation between separate pathologists or, even, the same pathologist on different readings of the same biopsy. Studies have shown that the most complicated classification methods may lead to greater observer variation, even among experts [7]. Moreover, a number of artifacts (eg., tangential sectioning) may occur that are usually well appreciated by experienced and specialized pathologists, but not all. At best, the pathologist is dependent on clinical details for the most optimum result leading to an initial interpretation that biopsies appear to be consistent with, but not diagnostic, of untreated celiac disease.

The second phase of celiac disease diagnosis (and, perhaps, more critical) is evaluation after treatment with a gluten-free diet. After all, the disease has been defined as a gluten-dependent disorder. In the best of circumstances, the patient has clinically responded to a gluten-free diet by demonstrating documented weight gain, resolution of diarrhea, and perhaps, cessation of other symptoms (eg., skin rash in associated dermatitis herpetiformis) [8,9]. Added evidence for the clinical diagnosis may be obtained from serological normalization of elevated antibody levels (usually, IgA type in an IgA competent individual). In this setting, however, a second biopsy in a patient with now normal transglutaminase levels on a gluten-free diet may show only partial (and possibly, unconvincing) histopathological improvement. Seroconversion to normal may normally be expected to occur with a gluten-free diet, but, despite normal serological results, persistent inflammatory activity may still be present in biopsies from a gluten-free treated patient. In some, even more biopsies may be required at a later date to demonstrate a convincing definitive histopathological response. The amount of time for this response may differ depending on patient age, sex as well as duration on the diet [10]. Elderly men appear to be most resistant to histopathological improvement [10]. There may be other reasons, including inherited or genetically-based factors that result in an apparently slow response. Biopsies might best be compared from similar biopsy sites before and after gluten-free diet treatment since most severe changes appear to occur in the most proximal small intestine. Some have described this as a proximal-to-distal gradient in architectural change. Perhaps, this simply reflects a higher concentration of the offending peptide in the proximal small bowel. In contrast, pathological changes appear to initially normalize with a gluten-free diet in the most distally involved small intestine [11] in a distal-to-proximal gradient, so pre- and post-treatment biopsy comparisons are best done from similar sites in the duodenum and jejunum. Ideally, single pass biopsies from different sites should be individually fixed rather than mixed together with other biopsies in the same fixative container or embedded in the same paraffin block. Histolological improvement may require months, even years, to occur in the most endoscopically accessible portion, the proximal small intestine, especially since most severe changes develop in the most proximal duodenum. For this reason, gluten-free diet resistance to resolution of the pathological changes in the proximal small intestine may not be so readily explained by the label of so-called “refractory sprue”. Indeed, this process of mucosal healing with a gluten- free diet may not only be temporally-driv-

en and based on patient age and sex, but genetically-regulated. Further investigative efforts are needed to more precisely explore the effects of the gluten-free diet in celiac disease and its regulation of the healing process.

Recurrence in Celiac Disease

In well-defined celiac disease, symptoms may recur and several possibilities, in practice, should be explored and considered (Table 1). Poor dietary compliance is possibly the most common reason. Often, this is obvious and, in some patients may be intentional. Trace amounts of gluten may be present in the diet, even in commercially available products labeled as "gluten- free". Gluten is ubiquitous, being present in pill capsules and communion wafers [12], even in plastic devices used as orthodontic retainers [13]. In older children and young adults, freed from parenteral controls, diet compliance may be especially difficult, especially with evolving peer pressure. If symptoms do recur and persist, then other possible causes require exclusion. In some, an error in the original diagnosis may have resulted from the initial studies. In others, differentiation from another inflammatory process, particularly if initially thought to be "isolated" in the proximal small intestine, such as duodenal Crohn's disease [14]. An entirely novel syndrome has also been recognized as a post-colectomy enteropathy [15-17], both in the course of either Crohn's disease or ulcerative colitis. This rare post-colectomy disorder appears to be very uncommon, but may be seen more often than currently recognized and its immunopathogenesis may be completely unrelated to other forms of inflammatory bowel disease. This deserves added investigative study.

Occasionally, an associated disorder may develop in the course of well documented celiac disease. For example, a colonic inflammatory mucosal process may develop later (eg., lymphocytic colitis, collagenous colitis) while on a gluten-free diet suggesting a different pathogenesis and long-term natural history than a gluten-sensitive disorder, like celiac disease [18]. Moreover, other disorders may be superimposed on celiac disease, including collagenous sprue, intestinal lymphoma, or, rarely, both disorders [19-22].

Table 1: Considerations in "Recurrent" Celiac Disease**

Poor compliance with gluten-free diet
Unrecognized or ubiquitous gluten source (eg., pill capsules, communion wafers)
Initial wrong diagnosis (i.e., "isolated" duodenal Crohn's disease)
Superimposed or related cause (eg., collagenous colitis)
Superimposed disease (eg., collagenous sprue, lymphoma)

*Biopsy-defined adult disease with classical histopathological features and improvement after a gluten-free diet. Table modified from Freeman HJ. Sprue like intestinal diseases 2024. Inter J Celiac Dis 2024; 12: 12-15 [DOI: 10.12691/ ijcd-12-1-2].

Other Causes of Sprue-like Small Bowel Disease

Table 2 lists several entities that may have a similar appearance to adult celiac disease. Included among these is an ever--expanding list of infectious agents as well as deficiency states. These include deficiencies of specific nutrients that may be superimposed on an underlying small intestinal disorder, including deficiencies of zinc, vitamin B12 and folic acid. In addition, different immunodeficiencies may be associated with a sprue-like intestinal disease.

These include combined or common variable immunodeficiency diseases, usually congenital and affecting multiple immunoglobulins [23]. IgA-deficiency may be associated with celiac disease and, histopathological changes as well as immunoglobulin A levels may improve with a gluten-free diet [24]. In addition, immune deficiency states may result from infections (eg., HIV). HIV has been associated with an profound enteropathy [25, 26], however, in some, the HIV associated enteropathy may respond to a gluten-free diet [27]. Other causes of sprue-like intestinal disease, particularly, treatment-related causes, such as transplantation and drugs are noted.

Table 2: Biopsy Changes with similarities to Celiac Disease*

Sprue-type syndromes
Collagenous sprue
Mesenteric lymph node cavitation syndrome (often hyposplenism)
Oats-induced villous atrophy and other protein injury (soy, milk)
Infections
Infectious non-bacterial gastroenteritis (?viral agent, eg. COVID-19)
Protozoa (eg., Giardia lamblia, Isospora belli, Cryptosporidium sp.)
Bacteria (eg., Tropheryma whipplei, Mycobacterium), so-called "Tropical sprue"
Parasite (eg., Strongyloides stercoralis)
Stasis with bacterial overgrowth (contaminated small bowel syndrome)
Deficiency syndromes
Nutrient deficiency (eg., zinc, vitamin B12, folic acid) and kwashiorkor Immunodeficiency (congenital, combined or common variable, acquired, AIDS enteropathy)
Others
Autoimmune enteropathy (epithelial cell antibody positive enteropathy, including genetic types (eg., defect in regulator gene, AIRE, or defect in FOXP3 encoding gene, IPEX)
Chronic granulomatous diseases (including Crohn's disease of duodenum) Proliferative diseases (i.e., lymphoma, macroglobulinemia, mast cell disease) Zollinger-Ellison syndrome (i.e., gastrinoma with hypergastrinemia) Post-gastrectomy or post-colectomy enteropathy
Transplantation (including graft-versus-host disease) and drugs (see Table 3) Emerging in Infants and Children (CODEs)**

*Adapted from Freeman HJ. Sprue-like intestinal diseases 2024. Inter J Celiac Dis 2024; 12: 12-15 [DOI: 10.12691/i-jcd-12-1-2].

**Based on Gaibee Z, Warner N, Gwilt KB, Li W, Guan R, Yourshaw M, Hawkins RW, Zorbas C, St-Germain J, Tabatbaie M, Mao S, Pinsk V, Yerushalmi B, Wang L-K, Nelso SF, Wozniak L, Shouval DS, Jimenez L, Acra S, Walters T, Mouat S, Li M, Lafontaine DL, Tyska M, Raught B, Avitzur Y, Lencer WI, Goldenring JR, Martin MG, Thiagara JR, Muise AM. The genetic architecture of congenital diarrhea and enteropathy. N Engl J Med 2025; 392: 1297-1309.

Table 3 lists several pharmacological and biological agents that may induce sprue-like intestinal disease. Among pharmacological agents, a common anti-hypertensive agent, olmesartan, has been associated with both a reversible celiac-like disease after long-term use as well as a rare cause, collagenous sprue [28,29]. A number of monoclonal antibodies against checkpoint inhibitors for advanced malignancies have also been described, including ipilimumab and pembrolizumab [30-35]. Drug-induced small bowel disease is likely to increase with time, greater physician recognition and increasing development of new agents.

Finally, a number of newly recognized forms of congenital diarrhea with enteropathy (i.e., CODEs) are becoming better defined [36]. Although these have been described largely in infants and children [37-40], next generation sequencing methods to identify novel genes are being described that may impact normal nutrient absorption and malabsorption along with epithelial cell trafficking and polarity. Likely, this voyage of discovery will proceed into the adult realm.

Much research is needed to further define these disorders and this sprue-like intestinal disease paradigm.

Table 3: Drug-induced Small Intestinal Disease*

Pharmacological Agents
Triparanol
Alcohol
Neomycin
Stathmokinetic Agents (vincristine, vinblastine, colchicine)
Chemotherapeutic Agents (eg., methotrexate)
Non-steroidal Anti-inflammatory Agents (eg., sulindac)
Immunosuppressive Agents (eg., azothioprine, mycophenolate)
Anti-hypertensive Agents (eg., olmesartan)
Biological Agents (i.e., monoclonal antibodies)
Anti-CTLA-4 checkpoint inhibitors (eg., ipilimumab)
Anti-PD-1 checkpoint inhibitors (eg., pembrolizumab)

* Adapted from Freeman HJ. Sprue-like intestinal diseases 2024. Inter J Celiac Disease 2024; 12: 12-15 [DOI: 10.12691/i-jcd-12-1-2].

Conclusion

Accurate diagnosis of adult celiac disease depends on documentation of its gluten-dependent nature. Many sprue-like disorders have now been detected that have similar symptoms and histopathological appearances to untreated celiac disease. These include non-gluten proteins, nutrient and immune deficiencies, infectious agents and an increasing array of pharmaceutical (eg., olmesartan) as well as biological agents (eg., checkpoint inhibitors). All may result in a small intestinal mucosal disorder that fails to respond to a gluten-free diet emphasizing that demonstration of its gluten-dependent is a key element and crucial for diagnosis.

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