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Sprue-Like Small Intestinal Diseases 2024

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Abstract Celiac disease (also termed gluten-sensitive enteropathy) is a gluten-dependent immune-mediated disorder of the small intestinal mucosa. This disease occurs in genetically-predisposed individuals and serological studies in different populations estimate that about 1% of screen-positive individuals may eventually be diagnosed with celiac disease. However, a number of other disorders, labeled sprue-like intestinal disease, may also cause the pathological appearances of celiac disease, such as mucosal injury from oats or other proteins (eg., soy), along with a wide array of infections, including protozoans, viral, bacterial and parasitic agents. Some nutrient or vitamin deficiencies including zinc, folic acid and vitamin B12 along with an array of immune deficiency syndromes may cause a sprue-like enteropathy with the histopathological features of untreated celiac disease. None of these respond to a gluten-free diet. Instead, other forms of therapy may lead to resolution. Medications including pharmacological (eg., olmesartan) and biological agents (eg., checkpoint inhibitors) may cause sprue-like small intestinal disease. Ceasing use of the medication may lead to resolution of mucosal injury

Keywords: *sprue-like intestinal disease, celiac disease, collagenous sprue, gluten-free diet, medication-induced small bowel disease*

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1. Introduction

Celiac disease (gluten-sensitive enteropathy, celiac sprue) is an immune-mediated small intestinal mucosal disorder developing largely in genetically-predisposed persons. A complex reaction to the structural peptides in wheat and other grains, including barley and rye results [1,2]. Although the specific event that precipitates human clinical illness is unknown, diagnosis traditionally has relied on mucosal biopsies from the proximal small intestine followed by a response to gluten-free diet [3,4].

Clinical features (including diarrhea and weight loss) usually resolve in most with celiac disease after strict gluten-free diet treatment. In addition, serological abnormalities, including raised antibody levels (eg., anti-IgA) to tissue transglutaminase usually fall, often to within the normal laboratory range, and pathological changes in the small intestinal mucosa normalize, first in most distal involved small intestine. Histopathological improvement, however, may require months, even years, to occur in proximal small intestine [5]. In some, particularly the elderly diagnosed late in life, extended periods on a gluten-free diet (compared to younger patients) may be needed to show histological improvement [5].

2. Disease Recurrence

In well defined celiac disease, symptoms may recur and a number of possibilities should be considered (Table 1). Usually, recurrence is due to poor or limited dietary compliance. Even a so-called "gluten-free" diet may contain trace or measurable amounts of gluten, sufficient to cause recurrent symptoms and persistent inflammatory changes in biopsies [6,7,8]. In some, poor compliance to a gluten-free diet is obvious. Occasionally, gluten consumption may be intentional. Gluten, however, is ubiquitous (i.e., communion wafers, pill capsules) so that adherence to a strict gluten-free diet may be difficult. In others, particularly in older children and young adults increasingly freed from parental controls, and in the face with evolving peer-pressure, gluten may be consumed. However, if symptoms do recur, other possible causes (besides limited dietary compliance) should be considered.

Table 1. Recurrence In "Celiac Disease"*

Failure to comply with strict gluten-free diet
Ubiquitous gluten source (eg., pill capsules, communion wafers)
Error in initial diagnosis (eg., isolated Crohn's disease of the duodenum)
Related or additional cause (eg., microscopic, lymphocytic, collagenous colitis)
Superimposed disease (eg., collagenous sprue, lymphoma)

*Biopsy-defined adult disease classical histological changes with improvement after a gluten-free diet.

Indeed, the original diagnosis of celiac disease may be incorrect. Crohn's disease, in particular, may be difficult to differentiate pathologically from untreated celiac disease, especially if Crohn's disease only involves the proximal duodenum, especially early in its pathogenesis [9]. In addition, an entirely new syndrome associated with

inflammatory bowel disease has been recognized in patients that have undergone colectomy [10,11]. In both ulcerative colitis and Crohn's colitis, an extensive post-colectomy enteropathy has occasionally been recorded [12,13]. Information on this post-surgical entity is limited but it is likely more common than currently appreciated. A very different immune-mediated pathogenesis completely unrelated to the underlying inflammatory bowel disorder may exist.

Recurrent symptoms may also be due to an associated or complicating condition, including collagenous sprue or lymphoma. In some, it is conceivable that a "treatment-resistant" phenotype of celiac disease is present, or a treatment response may have occurred, but only in the distal small intestine. As noted above, however, response to a gluten-free diet also may be temporally-driven, particularly in males or the elderly since the biopsy response to a gluten-free diet may be sex- and age-dependent [5]. In addition, some may be exceedingly sensitive to minute amounts of dietary gluten and continue to show biopsy changes. In others, the small bowel never responds to a gluten-free diet; the disease cannot be defined as gluten-dependent and the term "refractory celiac disease" should not be used. As such, labels like "refractory sprue", "unclassified sprue" [14] or simply "sprue-like intestinal disease (enteropathy)" are more accurate. In the past, this entity was thought to represent a heterogeneous group, rather than a single homogeneous disease entity. The histopathological changes are often not distinguishable from untreated celiac disease and it has been suggested by others that this "sprue by any other name" may be simply a "wastebasket" diagnosis [14]. In some, abnormal biopsies may resistant to improvement with a gluten-free diet or even worsen.

Eventually, however, some prove to have a complicating "slow-to-develop" or "difficult-to-detect" lymphoma. Clonal expansion of an aberrant, but cryptic, intra-epithelial lymphocyte population has been described (so-called refractory "type II disease"). In these, a specific immune-based signature has been reported including intra-cytoplasmic CD3 without surface expression of CD3 and CD8 with clonally-restricted rearrangement of the T-cell receptor (based on immunohistochemical or flow cytometric methods) [15,16].

In rare individuals, an entirely new clinical presentation may occur. A primarily myopathic process, labeled inclusion body myositis, has been described with sprue-like intestinal disease, often with wasting [17]. In addition to small bowel changes, progressive muscle weakness may occur. Over the course of many years, a gluten-free diet, steroids and multiple nutritional supplements had no impact on either the progressive muscle weakness or the small intestinal mucosa. There may be other disease syndromes involving other systems, yet to be discovered or gene-based multi-system disorders (eg., AIRE and IPEX) [18], with small intestinal mucosal changes, similar to those of celiac disease.

3. Sprue-like Small Intestinal Disease

After recognition initially a half century ago [14], new entities have emerged that may mimic celiac disease. Some are noted in Table 2 and Table 3. None of these respond to a gluten-free diet. However, some, including infectious agents, may respond to specific treatment, such as antibiotics. Others, particularly those related to treatment medications, either pharmacologic and biologic, may cause sprue-like intestinal disease and often respond completely to simple removal of the offending medication. Although medications may affect the structure and function of either the small or large bowel, sometimes both, some drugs may induce small intestinal histopathological changes like untreated celiac disease. For others, underlying celiac disease may have been present, but not initially recognized (eg., isoretinoin) [19].

Table 2. Similar biopsy changes to Adult Celiac Disease

Sprue syndromes
Collagenous sprue
Mesenteric lymph node cavitation syndrome (often with hyposplenism)
Oats-induced villous atrophy and other protein injury (soy, milk)
Infectious causes
Infectious non-bacterial gastroenteritis (? viral agent, eg. COVID-19)
Protozoa (eg., Giardia lamblia, Isospora belli, Cryptosporidium sp.)
Bacteria (eg., Tropheryma whipplei, Mycobacterium), "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, HIV disease)
Others
Autoimmune enteropathy ("epithelial-antibody positive" enteropathy, incl. genetic types, (eg., defect in regulator gene, AIRE, and defect in gene encoding FOXP3, IPEX)
Crohn's disease of duodenum (without granulomas)
Proliferative diseases (i.e., lymphoma, macroglobulinemia, systemic mast cell disease)
Zollinger-Ellison syndrome (i.e., gastrinoma)
Post-gastrectomy or post-colectomy enteropathy
Transplant (incl. graft-vs-host disease) and drug-induced enteropathy (see Table 3)

Table 3. Drug-induced small bowel disease*

Pharmacological Agents
Triparanol
Alcohol
Neomycin and Antibiotics
Stathmokinetic Agents (eg., colchicine, vincristine)
Chemotherapeutic Agents (eg., methotrexate)
Non-steroidal anti-inflammatory Agents (eg., sulindac)
Immunosuppressive Agents (eg., azathioprine, 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 H.J. Sprue-like enteropathy. In: Duncan L.T., Advances in Health and Disease, Chapter 6. 2020; 25: 208-218.

4. Medication-induced Intestinal Disease

Pharmacologic Agents

Historically, a drug, triparanol, was used to experimentally induce a hypothetical animal (i.e., rat) model of celiac disease [20]. This agent was thought to increase lysosomal membrane lability leading to intracellular release of enzymes from epithelial cells. Subsequently, other agents were recognized to cause small

bowel injury, such as alcohol [21], by a direct focal or diffuse mucosal toxic effect. Ongoing chronic alcohol use may also indirectly result in mucosal injury due to folic acid deficiency. Folic acid is critical in the process of normal epithelial cell renewal and its depletion may result in "megaloblastic" epithelial cells, similar to classic bone marrow changes associated with either folic acid or vitamin B12 deficiencies. Eventually, in these disorders, the rate of epithelial cell renewal and mitotic figures are reduced, villi are shortened and the crypts appear hypoplastic (in contrast to hyperplastic crypts in untreated celiac disease). Similar effects may be induced by folate depleting agents, including chemotherapeutic agents, such as methotrexate [22]. Some antibiotics may affect the small bowel. Neomycin, for example, has been well documented to induce mucosal toxicities leading to light and electron microscopic changes and altered absorption of numerous nutrients [23,24]. Stathmokinetic drugs, like colchicine, may lead to marked mucosal changes including "colchicine spindles" (due to arrested metaphase) along with altered uptake of major nutrients like carbohydrate and fat as well as micronutrients, including vitamin B12 [25]. Vincristine and vinblastine may cause similar effects by disruption or assembly failure of the mitotic spindle [26]. Non-steroidal anti-inflammatory drugs (eg., sulindac) [27] and immunosuppressive agents (eg., azathioprine, mycophenolate mofetil) also may the small bowel mucosal architecture and these changes also fail to respond to a gluten-free diet [28].

Recently, olmesartan, an angiotensin II receptor antagonist, has been recognized as an anti-hypertensive agent that may cause sprue-like changes in the small bowel mucosa [29]. In some, a sprue-like small intestinal disorder has been documented often characterized by diarrhea, weight loss and small bowel biopsy changes of untreated celiac disease. In most, but not all patients treated with this drug and developing sprue-like biopsy findings, serological studies for tissue transglutaminase antibodies were negative. A gluten-free diet treatment was not effective in leading to resolution. A number of patients were only recognized after becoming severely ill, requiring hospital support and medication treatment, including immune suppressants or a biological agent. After cessation of the drug, reversal of clinical and pathological changes may happen. Similar reversal of biopsy changes have been documented with collagenous sprue induced by olmesartan in the absence of any other form of therapy [30].

Biological Agents

Another category of medication-related disease is only now becoming more frequently reported. Biological agents classified as immune checkpoint inhibitors, mainly monoclonal antibodies, have been infused in some with ongoing and severe inflammatory disorders as well as treatment-resistant malignancies, particularly melanoma. Ipilimumab is a humanized monoclonal antibody to limit the cytotoxic T-lymphocyte antigen 4, a critical negative feedback regulator of the T-cell anti-tumor response. The agent has been used for therapy of different malignancies, including metastatic melanoma, metastatic prostate cancer and other extensive malignancies. About 40% of those treated develop adverse effects, including an immune-mediated enteritis. If severe, the intestinal disease may be fatal. Endoscopic biopsies often show diffuse enteritis or sprue-like small bowel mucosal changes similar to untreated celiac disease [31]. Treatment has included fluid-replenishment, parenteral nutrition, corticosteroids and, in some, infliximab infusions. A sprue-like intestinal disorder with negative serological studies and no apparent response to a gluten-free diet has also been recorded [32]. Other checkpoint inhibitor agents used in treatment of metastatic malignancies, including pembrolizumab and nivolumab have also been noted [33,34,35,36].

5. Conclusion

In summary, diagnosis of celiac disease depends on: *first*, a small intestinal biopsy should demonstrate the features of untreated disease, even though these are not specific for the disease; and, *second*, improvement should be documented after treatment with a gluten-free diet. Antibody testing is a useful screening measure and offers support for a diagnosis of celiac disease. If the patient fails to respond to a gluten-free diet, then an exploration for other causes should be done. Infectious agents should be considered and, if present, specifically treated. Most important, medications may be a critical cause of symptoms and biopsy changes that may permit complete resolution of the celiac-like disorder with removal. Now, more than ever with emergence of novel drugs, anyone suspected to have celiac disease should have drug use documented.

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