

Sprue-like Intestinal Disease

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Abstract Recurrent symptoms in well-established celiac disease may result in further clinical evaluation. In most, poor diet compliance is present. Other considerations include an unidentified gluten source, an erroneous initial diagnosis, another or second and superimposed cause for symptoms, or a complication, including collagenous sprue or an intestinal lymphoma. Failure to define an initial gluten-free diet response, however, suggests that celiac disease may not be present. Instead, a distinctive enteropathic process, refractory to diet restrictions, including gluten, is evident. This “sprue-like” intestinal disorder or enteropathy remains unclassified, and probably, represents a heterogeneous entity. Molecular changes suggestive of early clonal expansion of an aberrant population of intra-epithelial lymphocytes may be detected in some (with or without a prior gluten-free diet response), and these changes may signify an early or “cryptic” lymphoma. Other newly recognized lymphoproliferative disorders occurring in the setting of celiac disease have been recorded, including hepatosplenic delta-gamma T-cell lymphoma, an indolent CD4+ T-cell lymphoma, particularly in younger males, and large granular lymphocytic leukemia, a possibly treatable disorder characterized by the clonal expansion of T-cells in blood and small intestinal mucosa. Studies using IL-15 blockade in a transgenic mouse model with pathologic features of a sprue-like intestinal disease has led to human clinical trials with encouraging positive results.

Keywords: *celiac disease, refractory celiac disease, sprue-like intestinal disease, sprue-like enteropathy, unclassified sprue, gluten-sensitive enteropathy, celiac sprue*

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1. Celiac Disease

Celiac disease (also termed gluten-sensitive enteropathy or celiac sprue) is a gluten-dependent disorder of the small intestine that occurs in genetically-predisposed individuals and results from a complex immune-mediated reaction to specific gluten-peptides in wheat and other grain products [1,2]. The precise precipitating event is not known. Key elements in the clinical diagnosis include demonstration of an enteropathic process, traditionally using mucosal biopsies from the proximal small intestine, followed by documentation of a treatment response to a gluten-free diet [3].

Usually, after initiation of a gluten-free diet, diarrhea resolves and weight gain occurs. Pathological changes in the small bowel normalize, initially in distal intestinal sites of involvement, and later, sometimes only after prolonged periods (even months to years), in the proximal duodenum [4]. Indeed, some investigators have reported that this may require extended periods, particularly the elderly [5].

Serological studies have estimated that up to 1% of screened individuals, perhaps more, are at risk for development of celiac disease. Greater detection has occurred in recent years due to more clinical awareness and increased use of screening methods [6,7].

Perhaps, other environmental factors play an important role. These include some newer bio-pharmaceutical agents

that can sometimes cause reversible sprue-like intestinal changes, including NSAIDs (eg., sulindac) [8] and, other drugs like olmesartan [9]. In addition, clinically occult celiac disease has appeared after use of novel biological monoclonal agents (eg., ipilimumab) [10]. Finally, in recent decades, a true increase in celiac disease *per se* may have occurred.

2. Recurrent Disease

Recurrence may develop in well-established celiac disease. Usually, this refers to recurrent symptoms, particularly weight loss. Most often, the re-appearance of symptoms is thought to be due to failed compliance with a strict gluten-free diet. However, even the term “gluten-free” may vary for different clinician investigators in different countries, and, sometimes, patient compliance may be difficult to define or fully ascertain. Poor compliance, however, is often clinically obvious, and may even be intentional. For some, limited awareness of foods that contain gluten may make recognition of an offending source difficult. Gluten is ubiquitous, present in pill capsules, communion wafers and a variety of processed food products. Indeed, many processed foods, and even new methods of food processing, are only now emerging. For these, quality control may be limited. Gluten-free foods are costly, often limited in palatability and, especially in developing countries, difficult to obtain.

Many professionals, including physicians and dietitians, along with support groups and the internet may provide inaccurate information. Some celiacs have limited motivation to follow a strict diet, especially if symptoms are absent or minimal after consumption of gluten-containing foods. Moreover, peer and social pressures, especially for adolescents and young adults, may also be problematic. Finally, trace dietary gluten contamination may well play an important role in both clinical and mucosal recovery process in some celiacs thought to be diet-adherent [11,12].

If symptoms recur, other causes may be responsible. Possibly, the original diagnosis of celiac disease was not correct, particularly if only limited attention was directed to documenting a convincing response to a gluten-free diet. Histological changes in the small intestine are typical, but not specific or diagnostic for celiac disease. Many other conditions may cause similar small bowel mucosal changes [3]. For example, changes in duodenal mucosal biopsies from some with Crohn's disease may be difficult to differentiate pathologically from untreated celiac disease [13]. In recent years, this list has expanded (see Table 1 and Table 2) as new disorders emerge. Of course, none of these other conditions are known to typically respond to a gluten-free diet.

Table 1. Disorders with Biopsy Changes similar to Celiac Disease

Sprue syndromes
Collagenous sprue
Mesenteric lymph node cavitation syndrome
Oats-induced villous atrophy
Other protein injury (soy, milk)
Sprue-like intestinal disease (unclassified sprue)
Infectious causes
Infectious gastroenteritis
Specific infections (eg., strongyloidiasis, giardiasis)
Tropical sprue
Stasis syndrome (contaminated small bowel syndrome)
Whipple's disease
Deficiency states
Nutrients (zinc, vitamin B12, folic acid)
Kwashiorkor
Immunodeficiency syndromes (congenital, combined, acquired (HIV))
Others
Intestinal lymphangiectasia
Crohn's disease (duodenum)
Transplant enteropathy (including graft-vs-host disease)
Lymphoproliferative disease (eg., lymphoma)
Macroglobulinemia
Zollinger-Ellison syndrome
Drug-induced small bowel injury*
* NSAIDs (sulindac), Olmesartan, Ipilimumab

Table 2. Causes of Symptoms in Established Celiac Disease

Compliance failure with gluten-free diet
Ubiquitous gluten source (eg., pill capsules, processed foods)
Wrong initial diagnosis
Associated or second cause (eg., collagenous colitis)
Superimposed complication (eg., collagenous sprue, lymphoma)

In others, recurrent symptoms may reflect a second or superimposed cause for symptoms. Commonly associated disorders, such as collagenous colitis [14], a poorly-defined "functional" disorder, or a superimposed infectious agent, may be present.

Of particular concern in those with recurrent symptoms is the possibility of a new and complicating disorder associated with celiac disease (eg., collagenous sprue, intestinal carcinoma, lymphoma) [3].

3. Sprue-like Intestinal Disease (Unclassified Sprue)

Although celiac disease may be suspected, changes may fail to improve despite strict compliance to a gluten-free diet. Symptoms, such as diarrhea and weight loss, may continue or actually worsen. Repeated small intestinal biopsies may show persistent, usually severe changes. In these, a "treatment-resistant" form of celiac disease could still be present, or a histopathological response may have actually occurred, but only limited to the most distal portion of the small intestine [4]. If a response to a gluten-free diet has never been documented, "refractory celiac disease" should not now be used. For these patients, other labels may be more appropriate, such as "sprue-like intestinal disease" or "unclassified sprue" [15].

These probably represent a heterogenous group, rather than a single entity. Mucosal biopsy changes are often not distinguishable based upon routine microscopic evaluation and staining methods from changes of untreated celiac disease. Others have previously opined that this condition represents a "wastebasket" diagnosis [15]. Some eventually prove to have lymphoma, some do not.

In recent decades, both children and adults have been recorded with persistent diarrhea, sprue-like small intestinal biopsy changes and positive epithelial cell antibodies, specifically anti-enterocyte and anti-goblet cell antibodies. No response to any form of diet exclusion occurs, including a strict gluten-free diet. Some, interestingly, however, also have antibodies to tissue transglutaminase. Possibly, this represents a truly distinctive and novel autoimmune intestinal disorder or group of disorders [16]. Moreover, T-cell lymphoma has also been recorded to complicate this clinical setting [17,18].

4. Lymphoma in Celiac Disease and Sprue-like Lymphoma

The relationship between celiac disease and intestinal lymphoma has been especially intriguing. Initially, long-term studies showed that malignant lymphoma may complicate the clinical course of celiac disease [19]. Conversely, in some patients initially presenting with malignant lymphoma, underlying celiac disease [20] with a biopsy-defined histopathological response to a gluten-free diet in non-neoplastic small intestinal mucosa were recorded [20,21].

In others, thought to have celiac disease, clonal expansion of an aberrant intra-epithelial lymphocyte population was described (so-called refractory celiac sprue, "type II disease") [22,23]. Some molecular markers used to define this entity were reported to reflect an already present, early "cryptic" T-cell lymphoma, as a high subsequent risk for overt histopathologically-defined T-cell lymphoma was recorded [23]. This high risk phenotypic "signature" included an aberrant intraepithelial

lymphocyte population containing intracytoplasmic CD3 without surface expression of CD3 and CD8 along with a clonally restricted rearrangement of the T-cell receptor (based on immunohistochemical or flow cytometric methods) [22,23]. In some, the gluten-dependent nature of celiac disease was not recorded, perhaps due to a rapidly progressive course. Indeed, in some with lymphoma, dramatic presentations may occur, with free perforation [24]. The histopathological changes in the mucosa, however, may be similar to untreated celiac disease. For these, the term “sprue-like intestinal T-cell lymphoma” was noted [25].

In celiac disease, multiple pathways in the pathogenesis of lymphoproliferative disorders likely exist. In large part, their recognition reflects further development and emergence of modern molecular biological methods that continue to refine classification of these complex disorders. In general, lymphomas of B-cell lineage affect the small intestine most commonly, while T-cell lymphomas are less common. Lymphomas are notoriously very heterogeneous [26,27,28]. Some may complicate well-defined celiac disease, but some may not [26,27]. For example, a natural killer cell form of T-cell lymphoma may occur in the intestine with a distinct immunophenotype. This entity is not known to be associated with celiac disease, progresses rapidly and has a poor prognosis [29,30]. In contrast, other rare peripheral T-cell types may occur with celiac disease, including a hepatosplenic form of gamma-delta T-cell lymphoma [31] or even T-cell type lymphomas in embryologically-related or gut-derived sites, including bronchopulmonary sites or the thyroid gland [32].

Recently, some novel lymphoproliferative disorders have been noted. For example, an indolent small intestinal form of CD4+ T-cell lymphoma was recently recognized, often in relatively young males with unique biological and clinical features, including histopathological changes mimicking or initially confused with celiac disease [33,34,35,36]. In a subsequent report, the apparently heterogeneous origin of this small intestinal CD4+ T-cell lymphoma was emphasized [18].

Another entity, large granular lymphocytic was also reported to complicate the clinical course of celiac disease [37,38]. Subsequently, 2 cases of celiac disease, reported to be initially responsive to gluten-free diets, were noted [39]. In both cases, sprue-like histopathological intestinal changes were present and clonal T-cell expansions, characteristic of large granular lymphocytic lymphoma, were shown in both small intestine and blood. Treatment for the leukemia with methotrexate and cyclosporine also resulted in a striking recovery of duodenal villous structure. The investigators suggested that IL-15 in the gut may be playing a role since IL-15 appears to play a critical role in the inflammatory process seen in celiac disease. Independent studies on the role of IL-15 in an animal model have been intriguing. Transgenic mice that overexpress IL-15 in enterocytes appear to develop a sprue-like small intestinal inflammatory process that can be reversed by antibody-mediated blockade of IL-15 [40]. Similar inhibition was noted in the same IL-15 transgenic mouse model with tofacitinib, a janus kinase inhibitor [41]. Although Phase 1 studies with a humanized monoclonal antibody agent in T-cell large granular lymphocytic leukemia failed to demonstrate a clinical hematologic

response [42], future studies are anticipated that will further explore the role of such biological agents in treating some intestinal lymphomas.

5. Conclusion and Future Issue

Recurrent symptoms in well-established celiac disease may result in further clinical evaluation. In most, poor diet compliance is common. Other considerations include an unidentified gluten source, an erroneous initial diagnosis, another or second and superimposed cause for symptoms, or a complication, including collagenous sprue or an intestinal lymphoma. Failure to define an initial gluten-free diet response, however, suggests that celiac disease may not be present. Instead, a distinctive enteropathic process, refractory to diet restrictions, including gluten, is evident. This disorder seems to be distinct, but remains unclassified, and probably, represents a heterogeneous entity. Molecular changes suggestive of early clonal expansion of an aberrant population of intra-epithelial lymphocytes may be detected in some (with or without a prior gluten-free diet response), probably a signature of an early or “cryptic” lymphoma.

Treatment in this setting has proven to be exceedingly difficult. Mortality has been estimated to be approximately 50%, especially in the first 2 to 5 years after first diagnosis. Most treatment studies are limited in numbers or reflect only anecdotal experience. Nutritional support, often with parenteral nutrition, is usually required. If the patient has confirmed celiac disease, then oral intake, if tolerated, should probably continue in the form of gluten-free food products. Steroids, including topical budesonide and immunosuppressants have been tried [43,44]. Some may show clinical improvement but histological changes are reported to be limited. Others have reported tioguanine (formerly, thioguanine) to be useful [45]. Use of monoclonal antibody agents, including infliximab and alemtuzumab have been noted in case reports [46,47,48]. Cladribine [49,50] has been tried in some, but progression to overt lymphoma was noted. Autologous hematopoietic stem-cell transplantation has been done in a few patients, but only with mixed results, especially if lymphoma is already present [51,52]. Further clinical study is needed, particularly to explore emerging molecular markers [53,54,55,56,57] that may identify risk of progression to an overt lymphoproliferative disorder. Recent studies in an animal model of sprue-like intestinal disease with IL-15 blockade are particularly intriguing and should lead to added clinical trials of novel treatment agents in this complex group of disorders.

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