

Drug-induced Sprue-like Intestinal Disease

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Abstract Celiac disease is a gluten-dependent small intestinal disorder with characteristic, but non-specific histopathological features. A number of disorders may cause similar changes in small intestinal biopsies, but fail to respond to a gluten-free diet. Traditionally, infectious agents, such as giardiasis, were often believed to be responsible, but in many patients with a sprue-like intestinal disorder, other causes were detected. The list continues to expand with the emergence of “new” diseases, including transplant enteropathy, distinct immune deficiency syndromes and postcolectomy enteritis, as well as new treatments. Many medications may cause a sprue-like small intestinal mucosal inflammatory process. Alcohol, antibiotics (eg., neomycin), non-steroidal anti-inflammatory drugs (eg., sulindac), stathmokinetic and chemotherapeutic agents (eg., colchicine, vincristine, methotrexate) and immunosuppressive medications (eg., azathioprine, mycophenolate mofetil) may all cause sprue-like small intestinal mucosal changes. A number of “new” drugs have also been recently recognized to cause a sprue-like intestinal disease. These include pharmaceuticals, such as olmesartan, an angiotensin II receptor antagonist used in treatment of hypertension, and biologicals, specifically ipilimumab, a humanized monoclonal antibody designed to overcome cytotoxic T-lymphocyte antigen-4, used in treatment of some advanced malignancies, including malignant melanoma. Increased physician awareness for medication-related sprue-like intestinal disease is critical as the list of emerging and novel medications expands.

Keywords: *celiac disease, sprue-like intestinal disease, sprue-like enteropathy, unclassified sprue, drug-induced small intestinal disease, post-colectomy enteritis*

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Celiac disease (also termed gluten-sensitive enteropathy or celiac sprue) is a gluten-dependent small intestinal disorder seen in genetically-predisposed individuals resulting 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. Critical in diagnosis is the initial 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]. Serological studies may also be useful to screen for individuals at risk for development of celiac disease, and sometimes, provide added or adjunctive evidence for a diagnosis of celiac disease.

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].

Unfortunately, diagnosis is not always easy and an extensive list of other disorders, particularly involving the proximal small intestine, should be considered, as noted previously in this journal [6]. The small intestinal mucosal histopathological features of untreated celiac disease, although characteristic, are not specific. A number of

other conditions may cause similar mucosal changes that mimic celiac disease [3,6].

Several infectious agents can provoke pathological features in the small intestine similar in appearance to untreated celiac disease. For example, giardiasis, sometimes epidemic, but usually sporadic, is caused by the protozoan parasitic agent, *Giardia lamblia*. The organism may be asymptomatic or can cause a severe and protracted diarrheal illness with weight loss, sometimes associated with profound malabsorption of multiple nutrients. Mucosal changes may be limited to the most proximal duodenum and only mild or minimal changes may be observed. However, in some, severe and much more extensive mucosal biopsy changes may develop with loss and “flattening” of villi and a hyperplastic crypt lesion typical of untreated celiac disease. Usually, organisms can be readily identified in biopsy specimens or fecal specimens, but in some, detection of this offending agent is very difficult and can be missed. If mucosal changes are due to giardiasis, a gluten-free diet response does not occur. Resolution of symptoms and biopsy changes in otherwise healthy adults results from administration of antibiotics. Other infectious agents may also cause similar “sprue-like” biopsy changes in both healthy and immune-compromised adults. In the latter, especially HIV-infected or transplant recipients, cryptosporidium has been recorded as the most common parasite encountered, followed by *Cyclospora* and

Isospora. Other agents, such as Microsporidia and Blastocystis have also emerged, in part, related to improved PCR-based molecular diagnostic assays [7].

In recent years, other “new” causes of “sprue-like” biopsy changes have been increasingly recognized. In part, novel diseases may be responsible including transplant enteropathy (i.e., graft-versus-host disease) and distinct immunodeficiency states, i.e., enteropathy associated with the human immunodeficiency virus (HIV) or associated with rare immunodeficiency types, including common variable immunodeficiency and X-linked agammaglobulinemia [8,9], as well as an increasingly recognized, but very unusual form of enteropathy following proctocolectomy for colitis, including patients treated with a prior pelvic pouch reconstruction procedure [10,11].

Even more frequently recognized now are the so-called “drug-induced” or “medication-related” forms of enteropathy that may, in some instances, alter small intestinal architecture and function causing “sprue-like” mucosal changes, diarrhea and nutrient malabsorption.

Drug-induced Sprue-like Enteropathy

From a historical perspective, drug-induced forms of small intestinal mucosal disease are not entirely novel. Triparanol was an injected agent used almost a half-century ago to, interestingly, induce a hypothetical experimental animal model of celiac disease [12]. This agent was believed to provoke labilization of lysosomal membranes within epithelial cells, liberating acid hydrolases leading to destruction of surface epithelial cells and creating a syndrome in animals initially believed to be identical to celiac disease. It was also believed that rats poisoned with triparanol could respond to a gluten-free diet suggesting a drug-induced experimental animal model of celiac disease [12]. Since then, a number of agents have been well documented to cause significant mucosal injury in the small intestine. Sometimes, these may cause “sprue-like” intestinal changes that necessitate differentiation from untreated celiac disease.

Alcohol

Alcohol is likely the most common cause of drug-induced nutrient malabsorption, especially with ongoing chronic ingestion. Several factors are responsible for impaired absorption, and, overall, may be much more important in leading to adverse clinical effects, including impaired pancreatic exocrine function and hepatobiliary disease. However, alcohol also has a direct “toxic” effect on the small intestinal mucosa. Usually, alcohol-associated injury produces a focal inflammatory process in the duodenal mucosa. However, more diffuse changes may also occur that make differentiation from changes of untreated celiac disease more difficult. Moreover, concomitant folic acid deficiency may also occur with chronic alcohol use and also cause direct changes to the small intestinal mucosa. Folic acid is critically essential for the normally rapid renewal and turnover of the small intestinal epithelial cells. Depletion of folic acid *per se* has been associated with a “sprue-like” form of enteropathy.

Like the effects of folic acid depletion on other rapidly renewing cells in bone marrow, distinct “megaloblastic” cellular changes occur with development of large macrocytic enterocytes in both villi and crypts that exhibit so-called “nuclear-cytoplasmic asynchrony”, particularly in the crypt region. As a result of reduced folic acid, the rate of epithelial cell renewal may be significantly reduced and diminished numbers of mitotic figures are evident in mucosal biopsies. Villi become blunted and crypts appear hypoplastic (distinct from the hyperplastic changes typical of untreated celiac disease).

Alcohol is rapidly and almost completely absorbed from the proximal small intestine (as well as gastric mucosa) though a limited amount may be metabolized by the intestinal mucosa. Both alcohol dehydrogenase and mixed function oxidase activities may be detected in intestinal epithelial cells and these enzyme activities may also be induced by chronic ethanol use. Light and electron microscopic changes occur in the small intestinal mucosa following acute and chronic ethanol administration and appear to be most significant in the most proximal small intestine. Changes have been shown to be alcohol concentration-dependent and associated with reduced enzyme activities in the proximal small intestine. In human volunteers ingesting ethanol for 3 to 6 days, there is a folic acid-reversible inhibition of glycolytic and gluconeogenic enzymes. Reduced intestinal disaccharidase activities and lactose intolerance occur following chronic alcohol ingestion. Abstinence from alcohol for 2 weeks, however, leads to a reversal with increased lactase and sucrase activities. Acute and chronic ethanol administration may impair transport of several substances, particularly those involved in carrier-mediated active transport. This may reflect the direct effect of alcohol on the intestinal epithelial cell membrane or a specific alteration to membrane-bound enzymes or transport carrier proteins. Passively absorbed substances, including most drugs, are either unaffected or their absorption is enhanced by alcohol administration. A single dose of ethanol, however, administered to healthy volunteers caused reduced absorption of L-methionine and D-xylose. In some, folic acid and thiamine absorption may become impaired and ferric iron absorption enhanced. Jejunal absorption of sodium and water may also be reduced by long-term ethanol administration and enhanced by a folate-deficient diet. Secretion of sodium and water into the small intestinal lumen also occurs. Vitamin B₁₂ absorption may be impaired, possibly related to altered ileal absorption [13].

Concomitant folate deficiency commonly occurs, possibly reflecting reduced intake (as for other macronutrients and micronutrients with chronic alcohol use), impaired absorption and direct effects of alcohol on folate metabolism. As noted above, significant morphologic effects on the small intestinal epithelia occur, and functional changes may predate detectable structural changes. In some, a synergism between alcohol and folic acid deficiency may be present, associated with superimposed changes in the small intestine seen in protein-energy malnutrition. Finally, some have suggested that chronic alcohol use *per se* may predispose the intestinal tract to other causes of drug-induced malabsorption [14].

Neomycin and Antibiotics

Neomycin, an aminoglycoside antibiotic, is a polybasic molecule containing six free amino groups. Oral neomycin binds and precipitates bile and fatty acid anions, impairs the absorption of monoglycerides, fatty acids, cholesterol and fat soluble vitamins and enhances the fecal elimination of sterols and bile acids. About 3 to 6% of the antibiotic is absorbed; the unabsorbed antibiotic suppresses the gram-negative bacterial flora. For this reason, neomycin was commonly used in the management of hepatic encephalopathy. In normal subjects, oral administration of 3g per day resulted in mild malabsorption while parenteral administration of up to 200 mg had no apparent effect. Impaired absorption of fat, nitrogen, protein, carotene, glucose, sodium, calcium and cholesterol was observed and appeared to be reversible. Some reversible defects were dose-related (eg., fat) whereas others were not (eg., D-xylose). Prothrombin times were prolonged, possibly as a result of vitamin K malabsorption.

Absorption of other drugs including digoxin and penicillin was impaired and mucosal toxicity occurred. Altered mucosal histology occurred associated with impaired absorption of D-xylose and sucrose, and inhibition of disaccharidase was detected 6 hours after a 2 gram oral dose. Histologic changes included "sprue-like" inflammatory changes with a reduction in height of villi and increased numbers of inflammatory cells [15]. Pigment-containing macrophages were also present. Overall, findings were not specific for a "neomycin-induced lesion", but if severe enough, could hypothetically, mimic changes of untreated celiac disease. Electron microscopic evaluation showed brush border fragmentation and ballooning of small intestinal epithelial cell microvilli [14].

Impaired absorption has also been historically recorded due to other antimicrobial agents, including oral kanamycin, paromomycin and chlortetracycline. However, studies for "sprue-like" morphologic alterations were not usually systematically done. Other agents, such as pyrimethamine and trimethoprim, may inhibit dihydrofolate reductase activity causing impaired folic acid absorption with, at least, indirect small intestinal histological changes. Chloramphenicol and tetracycline were also observed to inhibit disaccharidases and cause lactose intolerance. Sulphasalazine, used to treat inflammatory bowel and rheumatologic disorders, has been observed to inhibit folate transport, and conceivably, could be severe enough to cause some small intestinal mucosal changes. Probenecid, often administered in the past with penicillin, was reported to inhibit amino acid absorption.

Stathmokinetic Agents

Oral or intravenous colchicine often produces diarrhea, especially in higher doses. Steatorrhea and impaired absorption of carotene, D-xylose and vitamin B12 occur and appear to be dose-related and reversible. Colchicine may depress the activities of brush border hydrolytic enzymes, including disaccharidases. Hypocholesterolemia has been reported.

Morphologic changes in the small bowel have been observed with colchicine and range from minimal mucosal lesions with low doses to severe flattening of the villi at higher doses [16]. However, the morphologic changes are usually distinguishable from classical histopathologic changes of untreated adult celiac disease because of presence of metaphase arrest in many crypt epithelial cells. This occurs because of the colchicine interaction with the mitotic spindle or its subunits leading to assembly failure or actual disruption of the mitotic spindle. This "colchicine metaphase" is readily distinguishable from a normal metaphase in the epithelial cell and may also occur after other intravenous stathmokinetic agents including the periwinkle alkaloids---vincristine and vinblastine [17].

Chemotherapeutic Agents

Other chemotherapeutic agents may cause morphologic effects in the small intestine. Methotrexate, in particular, damages the small intestinal mucosa [18] by preventing crypt mitotic activity, inhibiting dihydrofolate reductase and subsequently impairing the absorption of folic acid as well as D-xylose. Effects usually occur for several days, but can last for a day or more after cessation of treatment. About 21 hours following a single dose of methotrexate, a maximal effect occurs, returning to normal in about a week after administration. Significant variation in the tolerance of individuals has been noted, and combination chemotherapy apparently induces more marked effects ranging from focal to more diffuse and severe changes. Similar morphologic changes in the small intestine have been noted with 5-fluorouracil treatment for malignant disorders in some patients [19].

Non-steroidal Anti-inflammatory Agents (NSAIDs)

Some non-steroidal anti-inflammatory agents have been well documented to cause mucosal toxicity, particularly in the stomach and small intestine. With sulindac, a variety of side effects have been recorded including abdominal pain and diarrhea, often associated with enteritis or overt ulceration. Biopsy studies done following oral sulindac administration over several months revealed changes in the proximal small intestine virtually indistinguishable from untreated celiac disease [20]. Symptoms and histopathological changes resolved with cessation of sulindac and then recurred again following re-introduction of the medication suggesting that the medication or a derivative of the medication caused the small intestinal lesion. Since the medication undergoes hepatic metabolism and its metabolites are excreted in bile, either the drug itself or a metabolite of the drug could have caused the observed small intestinal pathological effects. Further studies are needed to define the precise mechanism involved for the histopathologic mucosal changes following non-steroidal anti-inflammatory drug use.

Direct toxicity from the drug or a metabolite, a hypersensitivity form of pharmacological reaction, or alternatively, precipitation of an occult or sub-clinical form of celiac disease could have been responsible.

Immunosuppressive Agents

A number of immunosuppressive drugs have been implicated as a cause of severe villous atrophy associated with chronic malabsorption. Azathioprine, commonly used in the management of autoimmune liver disease and chronic inflammatory bowel disease, may provoke an acute gastroenteritis-like syndrome. More recently, however, chronic diarrhea was noted after azathioprine use for autoimmune hepatitis [21]. Chronic diarrhea on a low daily dose of 50 mg was associated with micronutrient depletion and severe protein-calorie malnutrition. Because of severe malabsorption, parenteral nutritional support was required for over a year. Once recognized, azathioprine use ceased, diarrhea resolved and parenteral nutrition support was no longer required. Prospective studies before and 4 months after azathioprine use showed complete reversal of severe duodenal villous atrophy and marked up-regulation of mucosal dipeptidyl-peptidase IV and PepT1 messenger RNA [21].

A number of reports have also described mycophenolate mofetil-induced villous atrophy after transplantation [22,23,24]. Usually, cessation of use of the drug resulted in resolution of the mucosal changes. In a detailed pathological evaluation [25], changes were quite variable, but seemed most reflective of graft-versus-host disease in both duodenal and ileal biopsies. Changes included crypt architectural disarray, lamina propria inflammatory changes and increased epithelial apoptosis. In these reports of mycophenolate mofetil-associated villous atrophy, treatment with a gluten-free diet, as anticipated, produced no clinical or histopathological benefit.

Olmesartan

Recently, a severe form of “sprue-like” enteropathy has been described after use of olmesartan, an angiotensin II receptor antagonist used for treatment of hypertension. Chronic diarrhea and weight loss were defined in 22 patients at a daily dose range of 10 to 40 mg. Mucosal changes were reported to include villous atrophy with variable degrees of inflammatory change. Others were observed to have marked sub-epithelial collagen deposition, a histopathological marker recorded in collagenous sprue, a disorder closely linked to celiac disease [26,27]. Several patients were severely ill requiring hospitalization. Serological studies with tissue transglutaminase IgA antibodies were negative and a gluten-free diet was not helpful. A clinical response occurred in all patients, usually with significant weight gain, after suspension of drug, and most re-biopsied showed duodenal mucosal improvement [28]. Olmesartan-induced enteropathy apparently may develop over prolonged periods, months to years following initiation of drug treatment [29]. Because of this lag time, the mechanism was believed unlikely to reflect a hypersensitivity response to the medication. Other angiotensin inhibitors appear not to have a similar effect [29]. In separate reports, olmesartan “sprue-like” enteropathy and olmesartan-induced collagenous sprue were reported with complete resolution after cessation of the medication [30,31]. In another study over a 10 year

period of villous atrophy and negative celiac serology, the most common cause of sero-negative “sprue-like” intestinal disease was medication-induced villous atrophy, usually from chronic olmesartan use [32].

Biological Agents

Another category of medications that may cause enteritis, potentially confused with the pathological features of a sprue-like small intestinal disorder, include an emerging array of biological agents. Usually, an immune-mediated colonic mucosal inflammatory process co-exists and is dominant [33].

One of these, ipilimumab, is a humanized monoclonal antibody developed to reduce and overcome cytotoxic T-lymphocyte antigen 4, a key negative feedback regulator of the T-cell anti-tumor response. The agent has been often used in the treatment of differing malignancies, particularly, advanced malignant melanoma and metastatic prostate cancer. Side effects occur in about 40% of patients treated with this agent, largely thought to be immune-related. In some, a severe form of enteritis or enterocolitis may occur, occasionally reported to be fatal. Endoscopic duodenal mucosal biopsies may show a diffuse, but non-specific, sprue-like small intestinal disorder. Infectious agents may not be detected and serological studies for celiac disease are negative. In some, the inflammatory process is focal or patchy in distribution and an abundant T-cell infiltrate has been recorded. For this disorder, the treatment has been largely supportive with intravenous fluids, parenteral nutrition, if required, and corticosteroids. In some, infliximab infusions have also been provided. Interestingly, in a single recent case report, ipilimumab use was also thought to be associated with celiac disease. The authors hypothesized that ipilimumab may have amplified the symptomatic presentation of previously unrecognized celiac disease, or alternatively actually triggered celiac disease [34].

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