Non–Gluten Sensitivity–Related Small Bowel Villous Flattening With Increased Intraepithelial Lymphocytes
Not All That Flattens Is Celiac Sprue

Neal S. Goldstein, MD
Non–Gluten Sensitivity–Related Small Bowel Villous Flattening With Increased Intraepithelial Lymphocytes

Not All That Flattens Is Celiac Sprue

Neal S. Goldstein, MD

Key Words: Duodenum; Pathology; Villi; Sprue; Gastroenteritis; Intraepithelial lymphocytes

DOI: 10.1309/10FCNCTC56N MN0YE

Abstract

Seven patients (mean age, 37.6 years; 5 women) had several weeks of gluten sensitivity (GS)-like symptoms; 2 had flu-like symptom prodromes. The 7 cases had morphologically similar biopsy specimens; all tissue fragments had uniform injury—increased lymphoplasmacytic lamina propria inflammation, moderate to complete villous flattening, numerous crypt mitoses, and markedly increased villous intraepithelial lymphocytes (IELs). All patients were diagnosed with GS and prescribed a gluten-free diet; all returned 9 to 38 weeks later questioning their diagnosis because symptoms had resolved substantially or completely. Clinical improvement was unrelated to gluten abstinence or ingestion. Repeated endoscopy and colonoscopy performed 4.1 to 16 months later showed normal mucosa in all 7 patients. Diseases other than GS can cause marked villous flattening and increased villous IELs in adults. The cause of small bowel mucosal injury is unknown. A similar non-GS–associated clinicopathologic complex, assumed to be due to a protracted viral enteritis or slow regression of a virus-induced immune reaction, occurs in children. The temporal aspects of symptom improvement and mucosal restitution in these 7 patients are similar to “acute self-limited colitis.” An overly exuberant immune response to an infectious agent is possible.

Increased villous intraepithelial lymphocytes (IELs) and villous flattening are the characteristic morphologic features of gluten sensitivity (GS) (celiac sprue). Diseases that can produce similar morphologic changes in nonimmunosuppressed adults are not well studied. I report the clinicopathologic findings of 7 such patients. All initially were thought to have GS; however, none responded to a gluten-free diet. Symptom resolution occurred in all patients, and repeated endoscopy showed normal small bowel mucosa while consuming a gluten-rich diet.

Materials and Methods

For 7 patients undergoing evaluation for possible GS, distal duodenal and jejunal biopsy specimens revealed morphologic changes characteristic of GS. Follow-up and outcome information from July 1994 to December 2003 was identified from my case files. All 7 initially were given a diagnosis of GS and prescribed a gluten-free diet. Each returned to the gastroenterologist questioning the diagnosis, and it was determined that the diagnosis of GS was incorrect. The cases were recorded retrospectively in my case files only after reevaluation determined that the initial diagnosis of gluten sensitivity was incorrect. None were identified prospectively.

The 7 patients underwent initial and follow-up upper endoscopy with distal duodenal and jejunal small bowel biopsies. The mean numbers of tissue fragments obtained from the initial and follow-up endoscopic small bowel biopsies for each patient were 3.1 (range, 2-6) and 5.7 (range, 3-10), respectively. The biopsy specimens were fixed in formalin and submitted in 1 tissue block.
Three-micrometer-thick sections from each case were stained with CD3 (clone A0452, dilution 1:200; DakoCytomation, Carpinteria, CA), CD4 (clone MT310, dilution 1:400; DakoCytomation), and CD8 (clone C8/144B, M703, dilution 1:400; DakoCytomation) using standard immunohistochemical procedures.1

Results

Clinical Findings

All 7 patients were white. Five were women. The mean patient age was 37.6 years (range, 21–51 years). All sought care from the gastroenterologist because of several weeks of altered bowel habits, including persistent, nonbloody, loose and frequent stools that occasionally were overly malodorous and steatorrheic; weight loss; postprandial abdominal cramps; bloating; and flatulence. Two patients had flu-like symptoms, including nausea, vomiting, abdominal cramps, fever, and nonbloody watery diarrhea for several days before the onset of altered bowel habits. All patients were previously healthy, 1 had Raynaud syndrome, and another had long-standing, medically controlled mild hypothyroidism. Although none of the patients were evaluated formally for immune deficiency, none had a history of an excessive number of viral infections; all had measurable, normal levels of serum IgA gliadin; and 5 previously were pregnant and had normal serum titers to the standard prenatal virus panel. None had a personal or family history of irritable bowel syndrome, gastroesophageal reflux disease, GS, or inflammatory bowel disease. Stool cultures and examinations were negative in all cases. None of the patients were taking antibiotics at the time of initial endoscopy, and all denied consistent use of nonsteroidal anti-inflammatory drugs.

Endoscopically, the distal duodenal and/or jejunal mucosal folds appeared scalloped in 6 patients (86%); there was no comment in the file of the other patient. The gastric antrum, fundus, cardia, and esophagus were normal endoscopically in all 7 cases. Four patients underwent simultaneous colonoscopy. Random colon and terminal ileum biopsy findings were normal in all 4 cases. One patient had a 0.3-cm sigmoid colon adenoma, and another had a 0.2-cm rectal hyperplastic polyp.

GS-associated serum antibody titers were evaluated at initial examination in all cases. Two patients had normal serum IgA gliadin and IgG gliadin levels and reticulin and transglutaminase antibody titers. Two patients had mildly elevated IgG and IgA gliadin levels and normal reticulin and transglutaminase antibody titers. Three patients had a mildly elevated IgG gliadin level and normal IgA gliadin level and reticulin antibody titer. In the latter 3 patients, the serum transglutaminase titer was normal in 1 and not evaluated in 2. These 2 patients had normal endomysium serum antibody titers.

Pathologic Findings

The initial endoscopic distal duodenal and jejunal mucosal biopsy specimens were morphologically similar in all 7 cases. The majority of tissue fragments had moderate or marked villous flattening, numerous crypt mitoses, and increased villous IELs Image 11 and Image 21. The amount of villous flattening and the density of villous IELs were homogeneous across the breadth of each biopsy fragment. The majority of villous IELs were CD3+CD4+ or CD3+CD8+ Image 31. Neither immunophenotype was consistently predominant. There was a variable admixture of the 2 cell populations in most biopsy specimens. The percentage of CD4–CD8– IELs was very small.

The gastric antrum, fundus, and esophagus were morphologically normal in all 7 cases.

Diagnosis and Follow-up

The small bowel biopsy specimens were diagnosed as marked or complete villous flattening, consistent with GS in all 7 cases. The patients were given a diagnosis of gluten sensitivity and prescribed a gluten-free diet. They returned to their gastroenterologists and questioned the accuracy of the GS diagnosis 9 to 38 weeks after the initial endoscopy, during which time all patients noted substantial or complete resolution of symptoms. All 7 patients had begun to ingest gluten-rich foods and found that their symptoms did not worsen after gluten ingestion and, furthermore, slowly resolved despite the gluten-rich diet.

Repeated endoscopy and colonoscopy were performed in all 7 cases 15 weeks to 16 months after the initial endoscopy. Microscopically, no residual morphologic abnormalities were seen. The distal duodenal and jejunal biopsy specimens were normal in all 7 cases Image 41. The villi were of normal length. IELs were sparse over villous tips and seemed to be of normal density. Approximately 1 mitosis was seen in each crypt base. Terminal ileum and random colon biopsy specimens also were normal. No patient had lymphocytic colitis or collagenous colitis, and repeated stool cultures were negative in all cases. Samples for serum GS-associated antibodies were redrawn in all 7 cases, and results were within normal ranges. Six patients underwent radiologic evaluation of the small and large bowels at that time, and results were normal. Serum gastrin levels were obtained and were normal in 5 cases. Four patients were evaluated for diabetes, and all had normal fasting serum glucose levels.

All 7 patients were free of similar gastrointestinal episodes and had not developed GS at the last follow-up, a mean of 4.9 years after initial diagnosis (range, 11 months to 9 years).

© American Society for Clinical Pathology

DOI: 10.1309/10FCNCTSG6MN9YE
Discussion

This report describes 7 nonimmunosuppressed adults with marked proximal small bowel mucosal villous flattening and increased villous IELs, features identical to the morphologic features of prototypic, Marsh stage 4, GS. However, none of these patients had GS on follow-up, as evidenced by a lack of worsening symptoms after gluten ingestion, slow symptom improvement while ingesting a gluten-rich diet, absence of elevated GS-associated serum...
antibody levels, and morphologic reconstitution of their small bowel mucosa to normal while ingesting a gluten-rich diet. Additional diseases were excluded confidently, including *Helicobacter pylori* infection, gastroesophageal reflux disease, parasitic infections, Crohn disease, diabetes, and Zollinger-Ellison syndrome.

There was a correlation between patients’ symptoms and small bowel morphologic features. Patients’ symptoms were greatest when the morphologic abnormalities were most abnormal, whereas the mucosa was normal following symptom resolution. This strongly suggests that symptoms were the direct result of small bowel mucosal injury.

The cause and underlying mechanism of mucosal injury in these cases are unknown. Several lines of evidence point to an aberrant immune reaction, possibly in response to a viral gastroenteritis. Much of the supporting evidence for this theory comes from pediatric patients and viral infection studies. Slowly resolving, idiopathic, protracted diarrhea of infancy is common. In infants who do not have GS, metabolic diseases, or inherited conditions, viruses are the most common underlying cause of protracted diarrhea.5 Transient steatorrhea and malabsorption occur occasionally in the acute and subacute phases of viral gastroenteritis or infection.6,7 Serial duodenal biopsy specimens from patients with viral gastroenteritis show changes similar to the initial biopsy specimens in the present study cases, including marked villous flattening, increased crypt mitoses, and increased villous IELs and lamina propria lymphocytes.6,8-12 In a related condition, children can develop temporary milk protein allergy sensitivity that manifests as late-onset protracted diarrhea and emerges after an episode of acute viral gastroenteritis.13 Biopsy specimens from these patients initially show villous flattening with increased lamina propria lymphocytes and villous IELs.5,14 The milk protein allergy sensitivity slowly resolves over months and is associated with restitution of the mucosa to normal in most cases. The similarities between this condition and that experienced by the present study patients are striking.

Additional support that an infectious agent initiated an abnormal immune reaction includes the temporal similarities of slowly resolving symptoms and restitution of normal mucosa in the study patients to the outcomes of patients with idiopathic, so-called acute self-limited colitis and lymphocytic colitis in which patients have nonbloody diarrhea that slowly resolves over months.15-22

Low-level elevations of gliadin antibodies in patients without GS are not uncommon. The gluten molecule contains deamidated and nondeamidated regions. Gliadin antibodies are produced to both regions; however, only the deamidated region is the immunogenic segment related to GS. Elevated serum gliadin antibody levels can occur from antibodies directed at the nondeamidated region of gluten.23,24 Antibodies to the nondeamidated region can fluctuate and normalize over time in patients without GS.25-31

The majority of IELs in the initial small bowel mucosal biopsy specimens in these 7 cases were CD3+CD4+ and CD3+CD8+ activated T cells.32-35 This is not a unique finding; other diseases cause increased activated villous intraepithelial T cells. As a clinicopathologic entity, GS-like disease, including architecturally abnormal villi and increased villous intraepithelial activated T cells, was described in association with methotrexate therapy in rheumatoid arthritis.36 A clinicopathologically similar syndrome was seen in patients with so-called tropical enteropathy who did not have malnutrition, enteric infections, or systemic illness and had undergone small bowel biopsy. These patients had architecturally flattened villi, crypt hyperplasia, and increased activated, villous, intraepithelial T cells, similar to the morphologic features of the initial small bowel biopsy specimens in the present cases. H pylori culture–positive, chronic, active gastritis can produce increased activated, villous, intraepithelial T cells in the adjacent duodenal bulb mucosa.38 Increased activated, villous, intraepithelial T cells have been suggested as a possible cause of villous flattening adjacent to enteric T-cell lymphomas.39 Mahadeva et al35 found that 57% of patients with GS-like symptoms and increased villous IELs had idiopathic disease. Although the subsets of T cells and specific antigenic interactions that lead to T cell activation are unique to GS and each of the aforementioned diseases, they might have common pathways of mucosal injury, which explains their morphologic similarity. In GS, activated T cells cause enterocyte injury and increased epithelial proliferation from increased apoptosis via the tumor necrosis factor α, FasL, and perforin mediator pathways, leading to villous architectural abnormalities.39-42 Activated mucosal T cells in non-GS diseases might function in a similar manner, activating similar cellular cascades that lead to enterocyte injury and epithelial proliferation.

This evidence in aggregate supports the existence of at least 1 non-GS disease that can produce temporary, prolonged small bowel injury with morphologic features similar to those of GS. It also supports the theory that small bowel injury was due to an aberrant or overly robust T cell–mediated immunologic reaction, such as viral gastroenteritis. Small bowel mucosal injury in these patients might have been as an “innocent bystander” rather than from direct enterocyte-targeted death. In this scenario, symptom resolution might have indicated sufficient down-regulation of the immune response, permitting enterocyte repopulation of the mucosal surface and reconstitution of villi.

From the Department of Anatomic Pathology, William Beaumont Hospital, Royal Oak, MI.

Address reprint requests to Dr Goldstein: Dept of Anatomic Pathology, William Beaumont Hospital, 3601 W 13 Mile Rd, Royal Oak, MI 48073.
References


