

Seymour Katz, M.D., Series Editor

Celiac Disease and the Colon

by William Dickey

Celiac disease, an autoimmune enteropathy of the proximal small intestine triggered by dietary exposure to gluten, affects 0.5%–1% of the general population. Serological testing for celiac related autoantibodies has facilitated diagnosis considerably, which still requires biopsy of the duodenum. There are now well described associations between celiac disease and both inflammatory bowel disease and microscopic colitis. Clinicians managing celiac disease should be aware of these associations and when to consider colon investigation.

INTRODUCTION

Celiac disease is an autoimmune enteropathy affecting primarily the proximal small bowel, triggered in genetically susceptible individuals by dietary exposure to the storage proteins of wheat, barley and rye collectively referred to as gluten. Virtually all patients carry the major histocompatibility class II human leukocyte antigen HLA DQ2 or HLA DQ8 haplotypes (1). Serological population screening indicates that celiac disease is common, affecting 0.5%–1% of individuals with European ancestry including those in North America (2,3). Currently, few cases of celiac disease meet the traditional perception of a childhood condition with malabsorption dominating the clinical picture. Despite gluten ingestion since infancy, most patients are diagnosed in adulthood with a significant minority presenting after the age of 65 years (4). Patients are often overweight (5) and many do not report diarrhea as a symptom; instead, non-specific gastrointestinal symptoms including dyspepsia and reflux, or non-gut manifestations such as iron deficiency anemia, chronic fatigue, peripheral neuropathy and ataxia, may dominate the clinical presentation (6,7).

Histologically, gluten enteropathy comprises a spectrum of abnormalities, first described by Marsh and later modified by Oberhuber, et al (8). Marsh I enteropathy is defined by an excess of intraepithelial lymphocytes (>30

per 100 enterocytes), Marsh II adds crypt hyperplasia, and Marsh III is the “classic” celiac lesion comprising the above plus villous atrophy. A majority of patients with celiac disease have specific serum autoantibodies to endomysium (EmA) and tissue transglutaminase (TTGA), but false negatives occur in 10% or more and biopsy of the duodenum during esophagogastroduodenoscopy remains mandatory for diagnosis (9).

The relative ease with which a diagnosis of celiac disease can be made, using serologic testing as a preliminary to duodenal biopsy, has facilitated early identification of the condition particularly in the primary care setting (6). As a result, many patients with anemia and diarrhea will have investigation focused on the upper small intestine. While this undoubtedly has improved the management of celiac disease, the downside is that associated or coincidental pathology in the colon may be overlooked at least initially. In this review, I will discuss the issues raised by colon pathology arising on a background of celiac disease.

MICROSCOPIC COLITIS AND CELIAC DISEASE

Microscopic colitis can be defined as a syndrome of chronic watery diarrhea associated with chronic inflammatory changes in the colonic mucosa but with absent or minimal mucosal abnormality seen at colonoscopy (10). While a variety of histologic changes has been recognized, most cases can be cate-

(continued on page 42)

William Dickey, Department of Gastroenterology, Altnagelvin Hospital, Londonderry, Northern Ireland.

(continued from page 40)

gorized as either collagenous or lymphocytic colitis. Collagenous colitis is characterized by thickening of the subepithelial collagen layer below the basement membrane to 10 μ m or more. In lymphocytic colitis there is an increase in intraepithelial lymphocytes in excess of 20 per 100 epithelial cells. There is histological overlap between the two diseases. Excess intraepithelial lymphocytes may be seen in collagenous colitis, and both feature epithelial damage and chronic mononuclear inflammation within the lamina propria. Unlike inflammatory bowel disease, crypt architecture remains intact. Although not described as distinct clinical entities until 1976 (collagenous colitis) (11) and 1989 (lymphocytic colitis) (12), they are now recognized as accounting for 10%–20% of cases of chronic non-bloody diarrhea, with an annual incidence comparable to those of Crohn's disease and ulcerative colitis. The onset of symptoms is typically after age 50 and there is a substantial female preponderance in collagenous colitis (13,14). There are now a number of papers documenting an association between celiac disease and microscopic colitis, though the prevalence varies substantially, reaching percentages as high as 20%–27% for lymphocytic colitis (15,16) and the mid-teens for collagenous colitis (13,16). Conversely, others have failed to demonstrate an association with collagenous colitis (15,17) and while Fernandez-Banares, et al obtained a prevalence for Marsh I duodenal pathology of 7% in DQ2 positive patients with microscopic colitis, none had villous atrophy (18). The variation may reflect in part the small size of many of these series. The prevalence of microscopic colitis in patients with a prior diagnosis of celiac disease is unclear, but it does feature prominently in several series of patients with celiac disease who have persisting symptoms despite gluten exclusion (19–21). When continuing gluten ingestion—inadvertent or covert—has been excluded, colon investigation should be considered as part of the investigation of these patients (Table 1).

The link may be genetic at least in part. Two studies have reported a high proportion of patients with microscopic colitis expressing the celiac disease-related HLA haplotypes (18,22) compared with controls.

Both types of microscopic colitis are known to resolve spontaneously in a majority of cases. Data are limited regarding pharmacological therapies, but budesonide

Table 1
Causes of persisting symptoms in celiac disease despite gluten exclusion (19–21)

- *Persisting gluten ingestion*
- *Wrong diagnosis*
- *Small intestine*
Refractory sprue
Ulcerative jejunitis
T-cell lymphoma
Bacterial overgrowth
Lactose or fructose malabsorption
- *Colon*
Irritable bowel syndrome
Microscopic colitis
Anal sphincter dysfunction
- *Pancreas*
Exocrine pancreatic insufficiency

appears best documented as showing efficacy in CC. Small studies have reported benefit from bismuth preparations, 5-aminosalicylates, and immunosuppressive agents, but there is to date a lack of controlled studies (10).

INFLAMMATORY BOWEL DISEASE IN CELIAC PATIENTS

While there have been a number of anecdotal reports describing the co-existence of CD and IBD, these are of limited value in CD where other conditions may well co-exist by chance. As celiac disease affects 1% of the general population, a similar percentage of patients with ulcerative colitis and Crohn's disease can be expected to have the condition coincidentally. However, several recent epidemiological studies indicate that ulcerative colitis and Crohn's disease do occur more often in celiac patients than expected by coincidence. The odds ratio for Crohn's disease in 458 US military veterans (23) over controls was 7.33. Yang, et al (24) reported that the prevalence of ulcerative colitis (prevalence rate ratio 3.6) and Crohn's disease (8.5) was significantly higher in a cohort of over 400 celiac patients than in the general population. The diagnosis of celiac disease preceded that of IBD by seven months to 12 years in five

(continued on page 44)

(continued from page 42)

Table 2
Significance of colon pathology in patients with celiac disease

<i>Colon Disease</i>	<i>Association</i>	<i>Relevance</i>
Microscopic colitis	Yes	<ul style="list-style-type: none"> • Consider as cause of persisting symptoms despite gluten exclusion • Test for celiac disease in patients with a diagnosis of microscopic colitis
Inflammatory bowel disease	Yes	<ul style="list-style-type: none"> • Consider if atypical features, e.g. hemochezia
Colon neoplasia	No	<ul style="list-style-type: none"> • Common coincidental finding in patients over 40. Consider in older patients presenting with diarrhea or iron deficiency even if initial workup suggests celiac

of the ten patients with both and had improved beforehand with dietary gluten exclusion in four, suggesting that gluten is not the trigger for IBD in celiac patients. Masachs, et al (25) found a relative risk for Crohn’s disease of 27.3, with three of 86 celiac patients affected compared with one of 809 healthy controls. However, no cases of UC were identified in either group. Of 264 patients with dermatitis herpetiformis, six (2%) had ulcerative colitis (26). It would seem reasonable to look for evidence of inflammatory bowel disease in patients with celiac disease whose bowel symptoms do not respond to gluten exclusion or who have atypical symptoms like rectal bleeding, although IBD was not identified in patients with celiac disease and persisting symptoms after gluten exclusion (19,20).

WHAT IS THE LIKELIHOOD OF COLON NEOPLASIA IN PATIENTS WITH CELIAC DISEASE?

The malignancies typically associated with celiac disease are T-cell lymphoma and adenocarcinoma of the small intestine. Epidemiological studies have shown no significantly increased risk of colorectal neoplasia in patients with celiac disease (27,28). However, both conditions are common and the likelihood of both conditions occurring by chance is therefore relatively high, particularly in older patients. Our unit’s policy is to perform colonoscopy in all patients over 40 presenting with altered bowel habit or iron deficiency anemia, even if initial investigations point to a diagnosis of celiac disease. Of 69 such patients (29), seven (10%) had colon neoplasia: five adenomas and two had carcinoma. Similarly, Hopper, et al (30) performed

colonoscopy on 98 new celiac patients, aged 40–92, presenting with IDA and identified neoplasia in 12 (12%): eight had adenomas and three had carcinomas. Neither study obtained prevalences of colon neoplasia different from non-celiac controls with IDA. A policy of routine colonoscopy on all patients over 40 with iron deficiency anemia or altered bowel habit should apply universally even if celiac disease is indicated by serologic testing or duodenal biopsy.

CAN CELIAC DISEASE BE DIAGNOSED DURING COLONOSCOPY?

Ileal intubation and biopsy is usually easily performed as part of colonoscopy in patients with diarrhea, raising the possibility of diagnosis of celiac disease particularly as wireless capsule endoscopy studies indicate that a significant minority of patients have changes of villous atrophy throughout the small intestine (31). Two studies have focused on histological changes within the terminal ileum of untreated celiac patients undergoing colonoscopy. Of thirty celiac patients (32) one had ileal villous atrophy, and the mean IEL count within the ileal mucosa was significantly higher than in controls (26 versus 10). An intraepithelial lymphocyte (IEL) count of >25 per 100 enterocytes had a sensitivity of 60% and specificity of 100%. Similarly, Hopper, et al (33) found that of twenty celiac patients, one (5%) had ileal villous atrophy and two others intraepithelial lymphocytosis consistent with a Marsh I lesion, and an IEL count ≥25 had sensitivity of 45% and specificity of 98% for celiac disease. Thus, while a finding of excess IELs on ileal histology should

prompt testing for celiac disease by duodenal biopsy, celiac disease can not be excluded by ileal biopsy. Generally, biopsies from the ileum are of limited value in the absence of endoscopic abnormalities (34).

CONCLUSIONS

Based on evidence cited in this article, Table 2 proposes an approach to possible colon pathology in patients with celiac disease. The possibility of additional pathology should be considered particularly in patients who fail to respond to, or who later relapse despite, dietary gluten exclusion. Recurrent diarrhea and anemia in particular should prompt colonoscopy. There is an increased prevalence of not only microscopic colitis but also ulcerative colitis and Crohn's disease in patients with celiac disease. Older patients with diarrhea or iron deficiency anemia should undergo colon investigation at initial presentation as coincidental colon neoplasia is common. ■

References

- Kaukinen K, Partanen J, Maki M, Collin P. HLA-DQ typing in the diagnosis of celiac disease. *Am J Gastroenterol*, 2002; 97:695-699.
- Fasano A, Berti I, Gararduzzi T, et al. Prevalence of celiac disease in at-risk and not-at-risk groups in the United States: a large multicenter study. *Arch Intern Med*, 2003; 163: 286-2923.
- Mearin ML, Ivarsson A, Dickey W. Coeliac disease: is it time for mass screening? *Best Pract Res Clin Gastroenterol*, 2005; 19:441-452.
- Gasbarrini G, Ciccocioppo R, DeVitus I, et al. Coeliac disease in the elderly. A multicentre Italian study. *Gerontology*, 2001; 47: 306-310.
- Dickey W, Kearney N. Overweight in celiac disease: prevalence, clinical characteristics and effect of a gluten-free diet. *Am J Gastroenterol*, 2006;101:2356-2359.
- Dickey W, McMillan SA. Increasing numbers at a specialist coeliac clinic: contribution of serological testing in primary care. *Dig Liver Dis*, 2005; 37:928-933.
- Zipser RD, Patel S, Yahya KZ, et al. Presentations of adult coeliac disease in a nationwide patient support group. *Dig Dis Sci*, 2003; 48:761-764.
- Oberhuber G, Granditsch G, Vogelsang H. The histopathology of coeliac disease: time for a standardized report scheme for pathologists. *Eur J Gastroenterol Hepatol*, 1999;11: 1185-1194.
- Dickey W, McMillan SA, Hughes DF. Sensitivity of serum tissue transglutaminase antibodies for endomysial antibody positive and negative coeliac disease. *Scand J Gastroenterol*, 2001; 36: 511-514.
- Nyhlin N, Bohr J, Eriksson S, Tysk C. Systematic review: microscopic colitis. *Aliment Pharm Ther*, 2006; 23:1525-1534.
- Lyndstrom CG. "Collagenous colitis" with watery diarrhoea- a new entity? *Pathol Eur*, 1976; 11: 87-89.
- Lazenby AJ, Yardley JH, Giardiello FM, Jessurun J, Balyless TM. Lymphocytic ("microscopic") colitis: a comparative study with particular reference to collagenous colitis. *Hum Pathol*, 1989; 20:18-28.
- Olesen M, Eriksson S, Bohr J, Jarnerot G, Tysk C. Microscopic colitis: a common diarrhoeal disease. An epidemiological study in Orebro, Sweden, 1993-1998. *Gut*, 2004; 53:346-350.
- Pardi DS, Loftus EV Jr, Smyrk TC, et al. The epidemiology of microscopic colitis: a population based study in Olmsted County, Minnesota. *Gut*, 2007;56(4):504-508.
- Gillet HR, Freeman HJ. Prevalence of celiac disease in collagenous and lymphocytic colitis. *Can J Gastroenterol*, 2000; 14: 919-921.
- Koskela RM, Niemelä SE, Karttunen TJ, Lehtola JK. Clinical characteristics of collagenous and lymphocytic colitis. *Scand J Gastroenterol*, 2004;39: 837-845.
- Matteoni CA, Goldblum JR, Ang N, et al. Celiac disease is highly prevalent in lymphocytic colitis. *J Clin Gastroenterol*, 2001; 32:225-227.
- Fernandez-Banares F, Esteve M, Rarre C, Salas A, Alsina M, et al. Predisposing HLA-DQ2 and HLA-DQ8 haplotypes of coeliac disease and associated enteropathy in microscopic colitis. *Eur J Gastroenterol Hepatol*, 2005;17:1333-1338.
- Fine KD, Meyer RL, Lee EL. The prevalence and causes of chronic diarrhea in patients with celiac sprue treated with a gluten-free diet. *Gastroenterology*, 1997;112:1830-1838.
- Abdulkarim AS, Burgart LJ, See J, Murray JA. Etiology of non-responsive celiac disease: results of a systematic approach. *Am J Gastroenterol*, 2002;97:2016-2021.
- Leffler DA, Dennis M, Hyett B, Kelly E, Schuppan D, Kelly CP. Etiologies and predictors of diagnosis in nonresponsive celiac disease. *Clin Gastroenterol Hepatol*, 2007; 5:445-450.
- Fine KD, Do K, Schulte K, et al. High prevalence of celiac sprue-like HLA-DQ genes and enteropathy in patients with the microscopic colitis syndrome. *Am J Gastroenterol*, 2000; 95:1974-1982.
- Delco F, El-Serag HB, Sonnenberg A. Celiac sprue among US military veterans: associated disorders and clinical manifestations. *Dig Dis Sci*, 1999;44:966-972.
- Yang A, Chen Y, Scherl E, Neugut AI, Bhagat G, Green PHR. Inflammatory bowel disease in patients with celiac disease. *Inflamm Bowel Dis*, 2005;11:528-532.
- Masachs M, Casellas F, Malagelada JR. Inflammatory bowel disease in celiac patients. *Rev Esp Enferm Dig*, 2007;99:446-450.
- Alonso-Llamazares J, Gibson LE, Rogers RS 3rd. Clinical, pathologic, and immunopathologic features of dermatitis herpetiformis: review of the Mayo Clinic experience. *Int J Dermatol*, 2007;46:910-919.
- Green PHR, Fleischauer AT, Bhagat G, et al. Risk of malignancy in patients with celiac disease. *Am J Med*, 2003;115:191-195.
- Viljamaa M, Kaukinen K, Pukkala E, et al. Malignancies and mortality in patients with coeliac disease and dermatitis herpetiformis: 20-year population study. *Dig Liver Dis*, 2006;38:374-380.
- Dickey W. Colon neoplasia co-existing with coeliac disease in older patients: coincidental, probably; important certainly. *Scand J Gastroenterol*, 2002;37:1054-1056.
- Hopper AD, Leeds JS, Hurlstone DP, et al. Are lower gastrointestinal investigations necessary in patients with coeliac disease? *Eur J Gastroenterol Hepatol*, 2005;17:617-621.
- Murray JA, Rubio-Tapia A, Van Dyke CT, et al. Mucosal atrophy in celiac disease: extent of involvement, correlation with clinical presentation, and response to treatment. *Clin Gastroenterol Hepatol*, 2008; 6:186-193.
- Dickey W, Hughes DF. Histology of the terminal ileum in coeliac disease. *Scand J Gastroenterol*, 2004;39:665-667.
- Hopper AD, Hurlstone DP, Leeds JS, et al. The occurrence of terminal ileal histological abnormalities in patients with coeliac disease. *Dig Liver Dis*, 2006;38:815-819.
- McHugh JB, Appelman HD, McKenna BJ. The diagnostic value of endoscopic terminal ileum biopsies. *Am J Gastroenterol*, 2007;102:1084-1089.