

## Celiac disease and microscopic colitis: A report of 4 cases

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### Abstract

Celiac disease (CD) is an autoimmune disorder of the small intestine that occurs in genetically predisposed people at all ages. However, it can be associated also to other immunopathological disorders, and may be associated with abnormal histology in segments of the gut other than the small bowel including colonic inflammation. While guidelines for endoscopic investigation of the jejunum are well defined, no indication is defined for colonic investigation. We describe four cases of concurrent CD and microscopic colitis (MC) diagnosed at our department over a 10-year period and analyzed the main features and outcomes of CD in this setting. The symptoms of these patients were improved initially by a gluten-free diet before the onset of MC symptoms. Two of the patients were siblings and had an atypical form of CD. The other two patients with CD and MC also presented with fibrosing alveolitis and were anti-Saccharomyces cerevisiae antibody positive. The co-existence of immune-mediated small bowel and colonic inflammatory and pulmonary diseases are not well-known, and no systematic approach has been used to identify the lifelong patterns of these immune-based diseases. Patients can develop, or present with CD at any stage in life, which can co-exist with other gastrointestinal diseases of (auto-) immune origin. In addition, the fa-

miliar co-existence and prevalence of MC in patients with a prior diagnosis of CD are unclear. Clinicians managing celiac disease should be aware of these associations and understand when to consider colon investigation.

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**Key words:** Collagen colitis; Lymphocytic colitis; Celiac disease; Fibrosing alveolitis; Anti-saccharomyces cerevisiae antibody

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### INTRODUCTION

Celiac disease (CD) is an immune-mediated disorder, an autoimmune enteropathy, triggered by the ingestion of gluten in genetically susceptible persons. The disease primarily affects the gastrointestinal tract and is characterized by chronic inflammation of the small bowel mucosa that may result in atrophy of intestinal villi, malabsorption, and a variety of clinical manifestations. Of genetic factors, the strongest recognized association is with HLA-DQ2 and/or -DQ8: 95%-100% of the patients carry these molecules. Dietary glutes interact with these HLA molecules to activate an abnormal mucosal immune response and induce tissue damage. Most affected individuals experience remission after gluten is excluded from their diet.

The diagnosis of CD is established by serologic testing, biopsy evidence of villous atrophy, and improvement of symptoms on a gluten-free diet. Avoidance of gluten

exposure is crucial for CD patients to reduce the risk of complications so the follow-up serological assessment of treatment effectiveness should be added to be sure of a good compliance.

There are atypical forms of CD. For example, silent CD is found in individuals who are asymptomatic but have a positive serologic test and villous atrophy on biopsy, and latent CD is defined by a positive serology but no villous atrophy on biopsy. These individuals are asymptomatic, but later may develop symptoms and/or histological changes<sup>[1]</sup>. The late concordance in the appearance of CD in monozygotic twins also suggests that the disorder may remain in the latent stage for a long time<sup>[2,3]</sup>. Small bowel villous atrophy with crypt hyperplasia and recovery of the lesion on a gluten-free diet suggest that villous atrophy comprises only the end stage of the clinical course of the disease and that CD clearly develops gradually from mucosal inflammation to crypt hyperplasia and finally to overt villous atrophy.

A typical feature of CD, in addition to mucosal changes, is gluten-dependent serum IgA class autoantibodies against transglutaminase 2 (TG2). These serum autoantibodies, endomysial and TG2, are powerful tools in disclosing CD with overt villous atrophy. Furthermore, positive serum celiac autoantibodies can predict impending CD in many patients evincing normal small bowel mucosal villous architecture. Hence, patients having “false-positive” celiac autoantibodies in serum are in fact at risk of developing overt CD. Some patients with positive serum endomysial or tissue TG2 antibodies may still seroconvert negatively during follow-up. However, it is well recognized that serum celiac autoantibodies in some cases fluctuate before a patient eventually develops overt CD after a longer follow-up period. The reason for this still remains obscure.

Transglutaminases are a family of 8 currently known calcium-dependent enzymes that catalyze the cross-linking or deamidation of proteins and are involved in important biological processes such as wound healing, tissue repair, fibrogenesis, apoptosis, inflammation, and cell-cycle control. Therefore, they play an important role in the pathomechanisms of autoimmune, inflammatory, and degenerative diseases, many of which affect the gastrointestinal system. Transglutaminase 2 is prominent, since it is central to the pathogenesis of CD, and modulates inflammation and fibrosis in inflammatory bowel and chronic liver diseases<sup>[4]</sup>. Respiratory disease and subclinical pulmonary abnormalities are the recognized complications of both CD and inflammatory bowel disease (IBD) but the mechanisms of lung disease in CD differ from that in IBD and support the hypothesis of a common mucosal defect in lung and small intestine in CD that allow increased permeability<sup>[5]</sup>.

Lymphocytic colitis (LC), together with collagenous colitis (CC), is included under the umbrella term “microscopic colitis” (MC), in which chronic gastrointestinal symptoms, including diarrhea, abdominal pain, fecal urgency, incontinence, and nausea, are not associated with endoscopic or radiological alterations. It is not known whether LC and CC are two different diseases or distinct manifestations of the same clinical condition. Data on pathophysiological conflict and different hypotheses refer to genetic pre-

disposition, immune dysregulation, autoimmunity, bile acid malabsorption, infection, and drug effect. Familial occurrence of MC has been identified in some families<sup>[6-13]</sup>. The central role of an altered immune system in MC pathogenesis is supported by the association with several conditions in which an immune dysregulation is involved, such as CD, rheumatoid arthritis, and hypo- and hyperthyroidism. Up to now, it has not been clear whether CC (or LC) is a distinct entity or only an epiphenomenon of another disease that leads to thickening of the collagen layer. However, whether MC (both CC and LC) is an autoimmune disease has not been conclusively established<sup>[14]</sup>. Diagnosis of MC can be established only by colonic biopsies and subsequent histopathological examination, when an increase in inflammatory infiltration and/or a thickening of the collagen layer are found. A number of papers have documented an association between CD and MC<sup>[15-18]</sup>. However, the prevalence of MC in patients with a prior diagnosis of CD is unclear, but it does feature prominently in several series of patients with CD who have persisting symptoms despite gluten exclusion. When continuing gluten ingestion, inadvertent or covert, has been excluded, colon investigation should be considered as part of the investigation of these patients. The link may be genetic, at least in part. Both types of MC are known to resolve spontaneously in a majority of cases. Data are limited regarding pharmacological therapies, but budesonide appears best documented as showing an efficacy against CC and MC<sup>[19]</sup>.

We report here 4 cases with sequential development of CD and MC and discuss the possible connection of these co-existences.

## CASE REPORT

### Case 1

A 42-year-old female with a previous history of both cognitive and neurovegetative symptoms of depression, including depressed mood, anhedonia, feelings of worthlessness, low energy, troubled sleep, and poor concentration, was evaluated in the local medical center for complaints of watery diarrhea. She had longstanding lactose intolerance for which she was taking a lactose-free diet. As her mother had manifestations of CD, enteroscopy was performed. However, the first endoscopic and histological evaluation showed no duodenal mucosal alterations (Marsh 0). Six months later, endoscopic findings were persistent and duodenal biopsies were taken which were not diagnostic for CD, and biochemical laboratory tests were within normal ranges. She was then referred to our clinic and additional laboratory tests showed increased antibody titers against gliadin, endomysium, and tTG. Her psychiatric disease was controlled after treatment and then remained stable. She was given a gluten-free diet, which resolved her diarrhea and allowed her to regain her lost body weight. Five years later, the patient presented with watery diarrhea occurring 8-10 times daily and mild body weight loss. At the beginning, this condition was associated with urgency, nocturnal stools, abdominal cramping, nausea, mild body weight loss, and fatigue, and persisted

despite strict adherence to the gluten- and lactose-free diet. With the loss of patience of the diet and of her symptoms she broke her diet and clinical signs remained. Small bowel biopsies at upper endoscopy demonstrated nothing (Marsh 0) but the gluten panel was unambiguously positive. Stool cultures and *Clostridium difficile* toxin assay were negative. After consultation with dietitians, the patient was maintained on a gluten- and lactose-free diet for six months but with mild improvement. Colonoscopy was performed later, and biopsies from her colon demonstrated LC. Her symptoms responded partially to mesalazine treatment over the subsequent two months, at which point her medical therapy was changed to budesonide (9 mg/d). After she was put on budesonide with a strict diet, both abdominal complaints and psychiatric problems resolved (Figure 1).

### Case 2

A 45-year-old woman with suspected irritable bowel syndrome was admitted to the hospital. Her bowel movements increased from one to six or eight a day with watery stools. She did not note any mucus or blood in the stool and could not identify any alleviating or aggravating factors. She consumed a normal diet, including meat, wheat, and dairy. Over-the-counter anti-diarrheal medications did not relieve her symptoms. She had no fevers, chills, or night sweats, but body weight loss. Her medical history included major depression for 10 years, which was controlled after treatment and remained stable at admission. Results of basic laboratory tests, including thyroid-stimulating hormone (TSH), complete blood count, blood chemistries, renal function, and liver function, were normal. Colonoscopy showed normal mucosa as far as the cecum. Colonic biopsy revealed a mildly expanded lamina propria and intraepithelial lymphocytosis with significantly thickening of the subepithelial collagen table. This set of features was consistent with CC, a variant of MC. Her symptoms were eventually controlled after a 6-mo course of oral budesonide (9 mg) and ongoing intermittent use of loperamide (Imodium). Six years later, similar problems with body weight loss caused her to be hospitalized at our clinic. A detailed previous history unraveled the familial connection with Case 1 and her mother with known CD. Psychiatric disease was controlled, so control and further GI investigations were organized. The histopathology report of colonic biopsy showed aspecific inflammation without MC. Further laboratory investigation revealed that the entire celiac antibody panel was positive. Results of duodenal biopsy did not reveal typical lymphocyte infiltration, crypt hyperplasia, and villous atrophy but normal mucosal architecture, without significant intraepithelial lymphocytic infiltration (Marsh 0). The diagnosis was latent CD, as the patient had abnormal antibody blood tests for CD but normal small intestines. After she was put on a strict gluten-free diet, both abdominal complaints and psychiatric problems resolved (Figure 1).

### Case 3

A 56-year-old woman with a previous history of chronic (non-specific) colitis and fibrosing alveolitis was referred

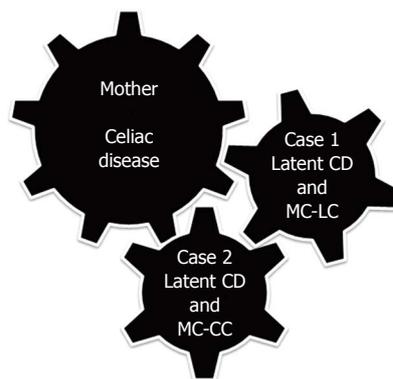


Figure 1 Family of cases 1 and 2.

to our hospital from an outside hospital because of continued signs and symptoms of CD that persisted despite self-reported adherence to a gluten-free diet. The patient reported abdominal pain, bowel distension, and body weight loss over the past few years. Diagnosis of CD was made 4 years ago, based on the small bowel biopsy results showing evidence of villous blunting with increased chronic inflammatory cells, positive laboratory tests, and typical gastrointestinal signs and symptoms with negative stool cultures and *Clostridium difficile* toxin assay. Repeated laboratory tests showed elevated antibodies against gliadin, endomysium, and tTG, and small bowel biopsy proved villous atrophy. The patient met with a nutritionist and implemented recommended dietary changes to eliminate gluten. Her symptoms temporarily improved with her bowel function returned to normal, but after a short time her symptoms recurred. Results of further tests excluded conditions known to complicate or coexist with CD, including bacterial overgrowth and lactose intolerance. Because of chronic watery stools, a colonoscopy was done with random biopsies from the colon for histological investigations. Based on the typical picture of prominent intraepithelial lymphocytes but no thickened collagenous layer, the pathologist diagnosed her with LC. She was started on strict gluten-free diet and budesonide with success. Five years later, she was free of complaints of CD and LC.

### Case 4

A man at age 31, with a previous history of bronchial asthma, was investigated for abdominal pain, chronic watery diarrhea, and body weight loss with negative stool samples (both the cultures and *Clostridium difficile* toxin assay). Findings from an upper gastrointestinal endoscopy were normal, but distal duodenal biopsies showed subtotal villous atrophy, inflammatory infiltration of the lamina propria, and an increase in intraepithelial lymphocytes. Based on the histology and positive laboratory tests, CD was diagnosed and the patient was started on a gluten-free diet. Abdominal pain ceased but he did not gain body weight and diarrhea remained a problem. Compliance with a gluten-free diet was confirmed by the assessment of dietitians. Repeated biopsies of the duodenal mucosa showed mild improvement in villous atrophy but serology

Table 1 Summary of the cases

	Case 1	Case 2	Case 3	Case 4
Sex/birth (yr)	Female/1956	Female/1955	Female/1945	Male/1964
Small bowel histology	Normal small-bowel mucosal structure	Normal small-bowel mucosal structure	Partial villous atrophy (Marsh 3A) according to the modified Marsh criteria	Total villous atrophy (Marsh 3C) according to the modified Marsh criteria
HLA-DQ2	Present	Present	Present	Present
IgA TTG	+	+	+	+
IgG/IgA EMA	+/+	-/+	-/+	+/+
IgG/IgA Gliadin	+/+	-/+	-/+	+/+
IgG/IgA ASCA	-/-	-/-	+/+	+/+
Celiac disease	Latent	Latent	Manifest	Manifest
Colon histology	Lymphocytic colitis	Collagenous colitis	Lymphocytic colitis	Collagenous colitis
Therapy	GFD and budesonide	GFD and budesonide	GFD and budesonide	GFD and budesonide
Other disease	-	-	Fibrosing alveolitis	Fibrosing alveolitis

Laboratory tests and histology of the small bowel before gluten-free diet, colon histology after gluten-free diet, therapy, and concomitant lung disease. TTG: Tissue transglutaminase; EMA: Endomysial antibody; ASCA: Anti-saccharomyces cerevisiae antibody; GFD: Gluten-free diet; HLA: Human leukocyte antigen.

was negative. Four years later, a dietitian again confirmed adherence to a strict gluten-free diet and colonic biopsies showed no alteration. A barium follow-through showed mild jejunal and rather featureless ileal mucosa but no obstructive lesion of the small bowel, nothing abnormal was seen on an ultrasound scan of the abdomen. Because of bloody stools and in view of his worsening symptoms despite the gluten-free diet, repeated colonoscopy with random biopsies was done for histological investigations from ileal and colonic samples. Both proved a submucosal thickened collagen layer, thus the diagnosis of collagenous enterocolitis (with CD) was made. He was started on mesalazine and budesonide but without effect. The next step was methylprednisolone, initially 32 mg/d, and then the dose was decreased to 4 mg/d. This therapy was continued with corticosteroids for three months. Over the next year, his clinical condition improved, with resolution of his diarrhea and a body weight gain of 3 kg. Three years later, his symptoms recurred. Results of further tests excluded conditions known to complicate or coexist with CD, including bacterial overgrowth and lactose intolerance. Repeated biopsies excluded collagenous enterocolitis, thus fibrosing alveolitis was diagnosed by the pulmonologist based on the lung function, laboratory and radio-imaging tests, chest X-ray, and high-resolution CT scanning (HRCT). Because the abdominal symptoms of the patient were refractory to treatment, he was treated again with budesonide and his clinical condition improved.

The diagnoses of CD, MC, and fibrosing alveolitis in all cases were made according to the formally accepted criteria. Two independent pathologists certified the diagnosis of MC by verifying the subsequent sections and completing the check with additional investigations (intraepithelial lymphocytes, tenascin labeling of the collagen layer, mast cells, and other lamina propria cell components). Fibrosing alveolitis was proved by HRCT and upon the ATS/ERS clinical criteria. The laboratory tests were performed. In brief, the HLA-DQ alleles were determined from whole blood samples by PCR with sequence-specific primers, traditional IgG and IgA AGA were detected by ELISA ( $\alpha$ -gliatest IgG and IgA; Eurospital, Trieste, Italy), anti-tTG was measured

by ELISA using recombinant human tissue transglutaminase as an antigen (EutTG, Eurospital), IgG and IgA EMA were investigated by indirect immunofluorescence using human umbilical cord cryostat sections prepared in our laboratory as a substrate, and both serum IgG and IgA levels in anti-Saccharomyces cerevisiae antibody (ASCA) were evaluated (separately) according to the manufacturer's protocol (ASCA IgG, ASCA IgA, QUANTA Lite, INOVA Diagnostics) (Table 1).

## DISCUSSION

Is CD much ado about nothing? This report presents four cases of CD with MC. The symptoms of these patients were improved initially by a gluten-free diet before the onset of MC symptoms. Their history indicates and underlines that patients can develop, or present with CD at any stage in life and that CD can co-exist with other gastrointestinal diseases of an (auto-) immune origin. Patients with CD can fail to respond to the initial introduction of a gluten-free diet or have a recurrence of symptoms after initial improvement, despite maintaining gluten exclusion. The most feared causes of either scenario are complicating malignancy, notably enteropathy-associated T-cell lymphoma, or refractory sprue. Other causes of persistent symptoms with increased prevalence in CD include lactose intolerance, exocrine pancreatic insufficiency, bacterial overgrowth, and microscopic (lymphocytic or collagenous) colitis. Thus, in patients whose symptoms fail to respond or who later relapse, despite the exclusion of gluten from their diet, the possibility of additional pathology should be considered and colonoscopy should, therefore, be part of the follow-up in patients who present with chronic watery diarrhea, even if initial tests indicate only CD.

Relations between CD and ulcerative ileojejunitis, polymyositis, and fibrosing alveolitis have been previously described<sup>[20,21]</sup>, and it is of interest that an auto-immune pathophysiology has been implicated in each of these conditions. An association has been suggested between CD and diffuse interstitial lung disease of the hypersensitivity pneumonitis type in several reports from Europe<sup>[22]</sup>. A case

of lymphocytic bronchoalveolitis and CD with improvement following a gluten free diet was also reported<sup>[23]</sup>.

Our patients with manifestations of CD and MC presented with fibrosing alveolitis and were ASCA (anti-yeast antibodies to yeast antigens that are found in bread and other cereal derived products) positive (both IgG and IgA types). Previously, ASCA positivity was shown to be evident in up to 40%-60% of CD patients and 13%-15% of MC patients, but its implication is disputed<sup>[24]</sup>. A possible connection between alveolitis and ASCA is also not known. Only one case of a Japanese patient was published: lung biopsy specimens showed alveolitis and serum-precipitating antibody gave a positive reaction for an extract from *S. cerevisiae*<sup>[25]</sup>.

In conclusion, the co-existence of immune-mediated small bowel and colonic inflammatory diseases (i.e. CD and IBD) and pulmonary diseases is not well-known and no systematic approach has been used to identify the life-long patterns of these immune-based diseases<sup>[26]</sup>. Such information may be useful for both disease prevention and treatment approaches. Clinicians managing CD should be aware of these associations and when to consider colon investigation.

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