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A case of refractory diarrhea

A 68-year-old white woman with irritable bowel syndrome has had worsening symptoms of right-sided abdominal pain, excessive bloating, and loose stools. Her bowel movements have increased from one a day to two or three a day. She has not noted any mucus or blood in the stool. She cannot identify any alleviating or aggravating factors, and the pain is not related to eating.

She consumes a normal diet, including meat and dairy. Over-the-counter antidiarrheal medications do not relieve the symptoms. She has had no fevers, chills, or night sweats, and she has not lost weight over the past year.

Her medical history includes breast cancer (in remission), alcohol abuse (in remission), and hypothyroidism, osteoporosis, and supraventricular tachycardia, all controlled with treatment as noted below. She has never undergone abdominal surgery.

A general review of systems is normal. Her current medications include oxybutynin (available as Ditropan, others), calcium polycarbophil (FiberCon, others), risedronate (Actonel), levothyroxine (Synthroid, others), simethicone (Maalox Anti-Gas, others), atenolol (Tenormin), trazodone (Desyrel), a calcium supplement, and aspirin. She began taking duloxetine (Cymbalta) 18 months ago, and the dose was increased from 60 mg to 90 mg 1 week before this visit.

She has never smoked, and she has abstained from alcohol for 10 years. She has no family history of colon cancer, celiac disease, or inflammatory bowel disease. She has not traveled outside the country in the past several years, and she notes no change in her source of drinking water.

On physical examination, she does not appear to be in acute distress. Her pulse is 64 and her blood pressure is 112/78 mm Hg. The cardiopulmonary examination is normal. Her abdomen is soft, symmetrical, nondistended, and nontender. Bowel sounds are normal. No abdominal masses, palpable organomegaly, or abdominal bruits are noted.

Results of basic laboratory tests, including thyroid-stimulating hormone (TSH), complete blood count, blood chemistries, renal function, and liver function, are normal. Colonoscopy shows normal mucosa as far as the cecum.

DIFFERENTIAL DIAGNOSIS

1 In addition to irritable bowel syndrome, which of these can explain her symptoms?

- ☐ Ulcerative colitis
- ☐ Celiac disease
- ☐ Microscopic colitis
- ☐ Hyperthyroidism
- ☐ Lactase deficiency

She has a history of irritable bowel syndrome, but could it be something more?

Ulcerative colitis typically presents with blood and mucus in the stool and gross abnormalities on colonoscopy, none of which is present in this patient.

Hyperthyroidism can be ruled out by the normal TSH level.

Lactase deficiency or lactose intolerance is unlikely because it is present in only 15% of people of northern European descent (compared with 80% of blacks and Hispanics and up to 100% of Native Americans and Asians).[1] Furthermore, her pain is apparently not related to consuming dairy products.

The hydrogen breath test can aid in the diagnosis of lactase deficiency. This test relies on the breakdown of malabsorbed lactose by colonic flora. This is the most widely used test for this deficiency, but its high false-negative rate

*Dr. Lashner has disclosed that he has received consulting fees from Prometheus corporation for membership on advisory committees or review panels.

of 25% means that a negative result does not exclude the diagnosis and should not be relied on in working up a patient with chronic diarrhea.[2] Simply noting whether symptoms develop after ingesting 50 g of lactose is clinically useful when lactase deficiency is suspected.

Based on the information so far, it is reasonable in this patient to evaluate for celiac disease and for microscopic colitis.

Celiac disease, also called gluten-sensitive enteropathy, has a varied presentation that includes nonspecific symptoms such as those in this patient. Classically, it causes diarrhea, but patients may present with a single nutrient deficiency and no diarrhea.

This patient lacks the elevated alkaline phosphatase or evidence of vitamin deficiencies characteristic of malabsorption in celiac disease (ie, vitamins A, B_{12}, D, K, and folate).[3] She also lacks evidence of malnutrition, such as iron deficiency anemia, weight loss, or low serum albumin. Finally, she does not have the dermatitis herpetiformis rash to suggest autoimmune gluten-sensitive enteropathy, nor does she have evidence of follicular hyperplasia or petechiae due to vitamin malabsorption.[3]

Symptoms of microscopic colitis range from an 'annoyance,' to 20 stools a day

Because no single serologic test is ideal for diagnosing gluten-sensitive enteropathy, several tests are typically used: immunoglobulin A (IgA) antigliadin antibody, IgG antigliadin antibody, IgA antitransglutaminase antibody, and IgA antiendomysial antibody. IgA antitransglutaminase antibody is 92% to 98% sensitive and 91% to 100% specific for celiac disease. IgG antigliadin antibody is 92% to 97% sensitive and 99% specific. The positive predictive value of the IgA and IgG antigliadin antibody tests is less than 2% in the general population, whereas the positive predictive value for antiendomysial antibody and antitransglutaminase antibody are 15.7% and 21.8%, respectively.[4] A positive serologic test for antiendomysial antibody is nearly 100% specific.

Our patient's entire celiac antibody panel is negative, and thus celiac disease is unlikely.

Case continued: Features of microscopic colitis

In our patient, colonic biopsy reveals a mildly expanded lamina propria, intraepithelial lymphocytes, and a patchy but prominent thickening of the subepithelial collagen table. This set of features is consistent with collagenous colitis, a variant of microscopic colitis. Histologic signs on biopsy specimens are fairly specific for the disease.[5]

Chronic, intermittent, secretory diarrhea without bleeding is the hallmark of microscopic colitis. Associated symptoms may include abdominal pain, weight loss, and fatigue. If biopsies are not taken at the time of the initial evaluation, and the colonic pathology is overlooked, patients with collagenous colitis may be diagnosed with irritable bowel syndrome with diarrhea.[6] The sedimentation rate is often elevated, and the antinuclear antibody test can be positive.[7] Steatorrhea or protein-losing enteropathy can occur, and fecal leukocytes are present in more than 50% of patients.[8]

This patient fits well the demographics of the typical collagenous colitis patient: ie, a middle-aged woman in her 6th decade in otherwise good general health. The female-to-male ratio is 15:1 overall, although the relative frequency of collagenous colitis in women is greater than that of lymphocytic colitis.[9] In a population-based study, the incidence of collagenous colitis was 5.1 per 100,000 per year, with a prevalence of 36 per 100,000; the incidence of lymphocytic colitis was 9.8 per 100,000 per year, with a prevalence of 64 per 100,000.[10]

Symptoms are typically vague and range from an annoyance to more than 20 nonbloody stools per day. The course of the disease also varies. Case series have reported a spontaneous remission rate of 15% to 20%,[11] though flare-ups are common. Microscopic colitis is largely a benign disease. It does not increase a person's risk of colon cancer.

CAUSES OF COLLAGENOUS COLITIS

2 What causes of collagenous colitis have been identified?

- ☐ Alcohol abuse
- ☐ Previous gastrointestinal surgery
- ☐ Drug-induced injury to colon

Neither alcohol use nor previous gastrointestinal surgery has been associated with the development of collagenous colitis.

Collagenous colitis has, however, been

linked to several causes. Abnormal collagen metabolism has been demonstrated in patients as a result of increased expression of procollagen I and metalloproteinase inhibitor TIMP-1.[12] Bacterial toxins and a bile-acid malabsorption defect in the terminal ileum and subsequent exposure of the colon to high concentrations of bile acids have also been linked to the development of collagenous colitis.

Many drugs have been linked to the development of collagenous colitis. Damage to the large intestine related to the use of nonsteroidal anti-inflammatory drugs has been attributed to the blockage of prostaglandin synthesis.[13] Simvastatin (Zocor), lansoprazole (Prilosec), and ticlopidine (Ticlid) have been linked to collagenous colitis; ticlopidine, flutamide (Eulexin), gold salts, lansoprazole, and sertraline (Zoloft) have been linked to the development of lymphocytic colitis.[14] In one small series, patients developed colitis after switching from omeprazole (Prevacid) to lansoprazole. All patients had their symptoms and biopsy findings resolve within 1 week of stopping the drug.[15]

WHICH DRUG IS BEST?

3 Which drug is best for microscopic colitis, based on the current evidence?

- ☐ Bismuth (eg, Kaopectate, Pepto-Bismol)
- ☐ Sulfasalazine (Sulfazine)
- ☐ Budesonide (Entocort)
- ☐ Prednisolone

Studies have evaluated bismuth subsalicylate, *Boswellia serrata* extract, probiotics, prednisolone, budesonide, and other drugs for treating collagenous colitis.[16]

Bismuth trials have been small. In an open-label study of bismuth,[17] symptoms improved in 11 of 12 patients.

Prednisolone recipients had a trend towards clinical response with treatment vs placebo, but it was not statistically significant, and there was incomplete remission of disease.[18]

***Boswellia serrata* extract**[19] and **probiotics**[20] showed no clinical improvement.

Cholestyramine has been shown to be helpful when used in conjunction with an anti-inflammatory agent,[21] and it may be helpful when used alone.

Aminosalicylate compounds have not been tested in prospective randomized trials, even though they are the cornerstone of treatment for ulcerative colitis. Retrospective trials have been equivocal.[22]

Budesonide currently has the best evidence of efficacy in collagenous colitis,[23,24] and some evidence suggests it is also effective for other variants of microscopic colitis.

A total of 94 patients were enrolled in three placebo-controlled trials of budesonide at 9 mg daily or on a tapering schedule for 6 to 8 weeks. The pooled odds ratio for clinical response to treatment with budesonide was 12.32 (95% confidence interval 5.53–27.46), with a number needed to treat of 1.58. Significant histologic improvement with treatment was noted in all three trials.[23]

Quality of life has also been studied in patients with microscopic colitis who take budesonide. Symptoms, emotional functioning, and physical functioning are improved. Budesonide also improved stool consistency and significantly reduced the mean stool frequency compared with placebo.[24]

Compared with cortisol, budesonide has a 200 times greater affinity for the glucocorticoid receptor, and a 1,000 times greater topical anti-inflammatory potency. It is also well absorbed in the gastrointestinal tract but is substantially modified into very weak metabolites as a result of first-pass metabolism in the liver.[25] This localized effect further supports the use of budesonide in patients with any form of microscopic colitis.

Microscopic colitis affects 15 times as many women as men

Although studies have shown budesonide to be effective, not every patient with a histologic diagnosis of microscopic colitis needs it. It is reasonable to try antidiarrheal agents, bismuth, or both as a first step because they are inexpensive and have few side effects. If budesonide is used, it should be given for 6 to 8 weeks, then stopped, and the patient should then be monitored for symptom recurrence. If a flare does occur, budesonide can be restarted and continued as maintenance therapy.

KEY CONSIDERATIONS

Microscopic colitis is diagnosed histologically, while irritable bowel syndrome is a clinical

diagnosis. In population-based cohorts of histologically confirmed microscopic colitis, 50% to 70% met symptom-based Rome criteria for the diagnosis of irritable bowel syndrome. The clinical symptom-based criteria for irritable bowel syndrome are not specific enough to rule out the diagnosis of microscopic colitis. Therefore, patients with suspected diarrhea-predominant irritable bowel syndrome should undergo colonoscopy with biopsy to investigate microscopic colitis if symptoms are not well controlled by antidiarrheal therapy.[26] The patient's management may be very different depending on whether colonoscopy is done.

Management of microscopic colitis should include stopping any drugs associated with it. Simple antidiarrheal agents should be tried first to manage symptoms. If symptoms persist, patients can be treated with budesonide (Entocort EC) 9 mg by mouth daily for 8 weeks to induce remission, or 6 mg by mouth daily for 3 months as maintenance therapy.

OUR PATIENT'S COURSE

Our patient's medication list includes duloxetine, a serotonin-norepinephrine reuptake inhibitor related to drugs that have been associated with the development of microscopic colitis. We tapered the duloxetine, and her symptoms improved by 50%. Her symptoms were eventually controlled after an 8-week course of oral budesonide 9 mg and ongoing intermittent use of loperamide (Imodium).

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