A 74-year-old woman presented with new-onset diarrhea for 3 months. Her medical history was pertinent for osteoporosis, poorly controlled type 2 diabetes mellitus, essential tremor, and depression but not cholecystectomy. She described her diarrhea as 4 to 5 watery, nonbloody bowel movements per day with nocturnal stools and endorsed an associated 15-lb (6.8 kg) weight loss. She denied abdominal pain, nausea, vomiting, difficulty flushing stools, fevers, or chills. Current medications included omeprazole for dyspepsia, amitriptyline for depression, and vitamin D supplementation. There was no recent travel or antibiotic exposure. Workup including antitissue transglutaminase immunoglobulin A (tTG-IgA) antibody testing, Giardia antigen testing, stool culture and stool Clostridioides difficile polymerase chain reaction (PCR), ova, and parasites was unremarkable. Stool osmolality and electrolyte measurements were consistent with secretory diarrhea. Her last colonoscopy done 14 years ago for colon cancer screening was normal. Loperamide 4 mg up to 4 times daily led to no improvement in diarrhea. No dietary restrictions or eliminations were attempted.

Vital signs were obtained in the clinic, which revealed a blood pressure of 119/76 mm Hg, a heart rate of 74 beats/min, and an oxygen saturation of 96% on room air. On physical examination, the patient appeared frail and her abdomen was soft and nontender with normal bowel sounds. Rectal examination revealed a strong sphincter tone with loose stool in the rectal vault without blood or anorectal tenderness. The remainder of the physical examination was unremarkable.

1. Which one of the following tests should be performed first for evaluation of this patient’s diarrhea?
   a. Fecal calprotectin
   b. Colonoscopy with biopsies
   c. Computed tomography imaging of the pancreas
   d. Stool pathogen panel
   e. Thyroid radioiodine uptake scan

Fecal calprotectin, a protein mainly found within neutrophils, is helpful in differentiating inflammatory bowel disease (IBD) from irritable bowel syndrome (IBS). It is a sensitive marker for gastrointestinal tract inflammation, but is not a good screening test for IBD as it can also be elevated in infectious and neoplastic etiologies of diarrhea.1

Colonoscopy allows the colon to be visually inspected for evidence of IBD, and random colonic biopsies are performed to evaluate the patient for microscopic colitis, a common cause of chronic diarrhea in elderly women. A change in bowel pattern with associated weight loss in an elderly patient without recent colonoscopy warrants further investigation for colorectal neoplasm.

Computed tomography imaging of the pancreas is indicated for the work-up of acute or chronic pancreatitis. Multiple pancreatic calcifications on computed tomography imaging would support the diagnosis of chronic pancreatitis. However, our patient does not have risk factors for chronic pancreatitis and lacks a history of recurrent abdominal pain and recurrent acute pancreatitis associated with this entity.

Infectious diarrhea typically presents as acute diarrhea, which is classically defined as diarrhea lasting less than 2 weeks. Certain pathogens including C. difficile or Giardia can
cause chronic diarrhea. Although *C difficile* is typically thought to be mainly associated with antibiotic intake and health care exposure, more recent reports have implicated the pathogen in patients without a history of either antibiotic or health care exposure. Her recent negative *C difficile* test results and lack of recent antibiotic exposure make *C difficile* a less likely cause of her diarrhea. Repeat testing for *C difficile* after PCR is not recommended because of the high sensitivity and specificity of the *C difficile* PCR assay.

Hyperthyroidism can present with diarrhea alongside more typical symptoms such as tremors and weight loss. Regardless, the possibility of hyperthyroidism should first be evaluated using laboratory testing (ie, thyroid-stimulating hormone and triiodothyronine/thyroxine levels) before further diagnostic work-up (such as a thyroid radiiodine uptake scan) is indicated.

Laboratory work-up revealed normal thyroid-stimulating hormone and thyroxine levels. Colonoscopy was performed, and preparation was deemed adequate by the endoscopist. The terminal ileum appeared normal, and no ulcers, erosions, polyps, or other masses were seen. Random biopsies were performed throughout the colon, which revealed a thickened colonic subepithelial collagen band.

2. On the basis of the finding of a thickened subepithelial collagen band, which one of the following is a risk factor for the most likely diagnosis?
   a. Smoking
   b. Plasma cell dyscrasia
   c. Hypertriglyceridemia
   d. Motility disorder
   e. Gastric hypochlorhydria

The presence of thickened colonic subepithelial collagen bands is consistent with a diagnosis of microscopic colitis (*P*< .001), collagenous subtype. Case-control studies have reported a significant association between cigarette smoking and microscopic colitis. In addition, smokers will on average develop microscopic colitis 10 years earlier than nonsmokers.

Plasma cell dyscrasias may lead to amyloidosis, a systemic disorder characterized by deposition of amyloid fibrils into tissue. Gastrointestinal amyloidosis is a rare condition that has various possible presentations including gastrointestinal bleeding, malabsorption, protein-losing enteropathy, and chronic gastrointestinal dysmotility. However, histology will reveal amyloid fibrils on Congo red staining, not thickening of the subepithelial collagen band.

Hypertriglyceridemia is a well-recognized risk factor for the development of acute and (consequently) chronic pancreatitis, not microscopic colitis. Both motility disorders and gastric hypochlorhydria are risk factors for small intestinal bacterial overgrowth.

The patient was diagnosed with microscopic colitis, collagenous subtype.

3. Which one of the following would be the most appropriate first next step in this patient’s management?
   a. Initiate prednisone and taper over 3 months
   b. Discontinue omeprazole
   c. Discontinue amitriptyline
   d. Initiate therapy with dicyclomine
   e. Initiate a low-FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) diet

Corticosteroids have been found to be effective therapies for microscopic colitis in several observational studies. Budesonide is preferred over prednisone because of its higher response rate in microscopic colitis. Our patient with poorly controlled diabetes mellitus and osteoporosis was reluctant to initiate corticosteroids.

Once a diagnosis of microscopic colitis is established, discontinuation of medications that are associated with microscopic colitis is the most appropriate next step in management. Proton-pump inhibitors have consistently been found to be associated with microscopic colitis and therefore should be discontinued. Among the antidepressants, only selective serotonin reuptake inhibitors have been found to be associated with microscopic colitis. Amitriptyline is a tricyclic
antidepressant and is not associated with microscopic colitis.

Dicyclomine is an anticholinergic drug that acts as an antispasmodic. It is mainly used for symptom relief in patients with abdominal pain related to IBS and has no role in the treatment of microscopic colitis–induced diarrhea. A low-FODMAP diet consists of a diet low in fermentable oligo-, di-, and monosaccharides and polyols. It is primarily used in patients with IBS and abdominal bloating.

Omeprazole was discontinued while loperamide was being continued but failed to improve our patient’s diarrhea.

4. Given the reported lack of response to loperamide, which one of the following is the most appropriate next step in management?
   a. Budesonide
   b. Mesalamine
   c. Infliximab
   d. Bismuth subsalicylate
   e. Azathioprine

   As mentioned earlier, corticosteroids are effective therapies for microscopic colitis and a higher response rate has been found for budesonide than for prednisone. Although budesonide would be an appropriate first-line choice for this patient with severe microscopic colitis, bismuth subsalicylate would be an acceptable alternative treatment option in our patient with poorly controlled diabetes mellitus and osteoporosis who is reluctant about initiating steroids.

   Mesalamine is a 5-aminosalicylic acid derivative most often used in ulcerative colitis. Some older observational studies have reported a benefit to mesalamine in microscopic colitis, but randomized controlled trials have failed to find a benefit of using mesalamine in microscopic colitis. Infliximab is a tumor necrosis factor-α (TNFα) inhibitor indicated for the treatment of IBD and multiple rheumatic conditions. Recent case reports have suggested a role for anti-TNFα therapy in steroid refractory microscopic colitis. However, anti-TNFα agents are notorious for their increased risk of serious infections and these adverse events are even more pronounced in elderly patients. Therefore, infliximab and other anti-TNFα drugs should only be considered as a fourth-line treatment option for severe therapy refractory microscopic colitis.

   Bismuth subsalicylate is an appropriate second-line alternative treatment option for symptomatic microscopic colitis when budesonide treatment is not feasible. It is thought to be most effective for patients with moderate microscopic colitis–related diarrhea and in older patients and would be an appropriate treatment option for our patient. Treatment duration is usually limited to 8 weeks as there is a theoretical risk of neurotoxicity with prolonged courses of high doses of bismuth subsalicylate.

   Immunomodulatory drugs such as azathioprine have found to provide benefit in patients with steroid-resistant microscopic colitis. However, azathioprine’s adverse effect profile (including pancreatitis, bone marrow suppression, and increased risk of infection) warrants usage of other therapies such as bismuth subsalicylate first.

   The patient was initiated on bismuth subsalicylate at a dose of 3 tablets (262 mg each) 3 times daily, resulting in resolution of her diarrhea after 1 week.

5. Which one of the following conditions is most associated with microscopic colitis?
   a. Colorectal adenocarcinoma
   b. Primary sclerosing cholangitis
   c. Celiac disease
   d. Erythema nodosum
   e. Anterior uveitis

   Patients with microscopic colitis have not been found to have an increased incidence of colorectal cancer, and some reports have even noted a decreased risk of colorectal cancer in this patient population. This is in contrast to ulcerative colitis, a condition for which screening colonoscopy is indicated 8 years after the diagnosis because of its associated risk of colorectal adenocarcinoma. Similarly, primary sclerosing cholangitis is a chronic progressive stricturing disease of the biliary tree that is
associated with ulcerative colitis but not microscopic colitis.

Up to 10% of patients with microscopic colitis have changes consistent with celiac disease in the small bowel. This is particularly relevant for patients with microscopic colitis that do not respond to standard therapy with bismuth subsalicylate or budesonide (or become therapy resistant), at which point duodenal biopsy is indicated to exclude celiac disease.

Erythema nodosum, a delayed hypersensitivity reaction that typically presents as tender and erythematous nodules on the shins, is not associated with microscopic colitis. It does exhibit an association with IBD, in which it typically parallels disease activity. Similarly to erythema nodosum, anterior uveitis is associated with IBD but not microscopic colitis.

After repeat anti tTG-IgA antibody test results were negative, our patient underwent upper endoscopy during the initial evaluation but duodenal biopsies did not reveal villous atrophy, the typical histological finding of celiac disease. She was treated with bismuth subsalicylate, weaned off over 2 months, and remained symptom-free since.

DISCUSSION

Microscopic colitis is a common cause of chronic watery diarrhea that typically presents in patients between the fifth and seventh decades. Microscopic colitis has a higher incidence in women than in men, and population studies have estimated the incidence of microscopic colitis to range from 1 to 12 per 100,000 persons per year.

Histologically, microscopic colitis can be distinguished into 2 distinct entities of colitis: collagenous colitis and lymphocytic colitis. Collagenous colitis is characterized by the presence of a thickened subepithelial collagen band, whereas the main finding in lymphocytic colitis is infiltration of more than 10% of intraepithelial lymphocytes. This distinction does not have much clinical significance as it does not affect the presentation, diagnosis, or management of microscopic colitis.

The pathogenesis of microscopic colitis is not completely known, although both autoimmunity and luminal factors are thought to play a role. The presence of a component of autoimmunity has been suggested in particular because of the association between microscopic colitis and celiac disease. Large cohort studies of patients with celiac disease have reported that as many as 30% of patients with celiac disease have colonic changes consistent with microscopic colitis. An important clinical implication resulting from this finding is that microscopic colitis should be considered in patients with celiac disease who have persistent diarrhea despite a strict gluten-free diet. Furthermore, as high as 9% of patients with microscopic colitis have small bowel changes consistent with celiac disease. However, anti tTG-IgA antibodies were not found in any patients with microscopic colitis, rendering celiac serologies a poor diagnostic test for celiac disease in patients with microscopic colitis.

Clinically, microscopic disease is characterized by chronic, watery, nonbloody diarrhea that ranges from mild (≤3 bowel movements per day, often self-limiting) to moderate (>3 bowel movements per day) and severe (resulting in dehydration and other metabolic abnormalities). Additional symptoms can include abdominal pain, nausea, weight loss, and fatigue. Because these symptoms are nonspecific, histological evaluation is often necessary to distinguish microscopic colitis from diarrhea-predominant IBS. Endoscopic evaluation will typically be grossly normal, although some macroscopic findings (such as erythema and petechiae) can be seen. A large cohort study found that 99% of patients diagnosed with microscopic colitis had positive biopsies in the left side of the colon, suggesting that flexible sigmoidoscopy alone is sufficient to confirm a diagnosis of microscopic colitis.

Once the diagnosis of microscopic colitis has been confirmed, the first step in management is to assess and remove exacerbating factors. Several drugs have been implicated in the pathogenesis of microscopic colitis. Nonsteroidal anti-inflammatory drugs, proton-pump inhibitors, and selective serotonin reuptake inhibitors are the main drugs that have been associated with microscopic colitis. Smoking has also been identified as a risk factor for
Microscopic colitis. Cigarette smoking increases the incidence of microscopic colitis, and the onset of microscopic colitis occurs earlier in smokers than in nonsmokers. Similar to other inflammatory conditions, the treatment goals for microscopic colitis consist of induction of remission followed by maintenance of remission. In 2016, the American Gastroenterological Association published an institutional guideline on the medical management of microscopic colitis and recommended bismuth subsalicylate as a first-line treatment for the induction of clinical remission. A dose of 3 tablets (262 mg each) 3 times daily is typically used, although robust data on the benefit of this regimen compared with lower doses are lacking. Long-term use of bismuth subsalicylate is not recommended because of the concern of adverse effects (mainly neurotoxicity), limiting its use as a drug to maintain remission. In patients with mild diarrhea, nonspecific antidiarrheal drugs such as loperamide or diphenoxylate may be sufficient in achieving symptom control.

For patients refractory to antidiarrheal drugs and bismuth subsalicylate or those who present with severe symptoms, steroids have been found to be among the most successful therapies. Budesonide is an oral steroid with a high first-pass metabolism, indicating that most of the drug is metabolized when it first passes through the liver. Because only about 10% to 20% of budesonide reaches systemic circulation, it has fewer systemic adverse effects. It has been found to have a higher response rate and a lower risk of recurrence than prednisone in microscopic colitis (complete therapy response in 82.5% vs 52.9% of patients for budesonide and prednisone, respectively) and is therefore the preferred steroidal agent. Patients who have a recurrence after stopping budesonide are typically placed on induction and maintenance budesonide to induce and sustain remission.

Mesalamine has previously been used as a treatment of microscopic colitis but was found to be no better than placebo in a prospective double-blinded randomized controlled trial. In patients with steroid refractory microscopic colitis, other therapeutic considerations include azathioprine and methotrexate, although recent studies have questioned the efficacy of these drugs in the management of microscopic colitis. Anti-TNFα agents have shown some promise for therapy-resistant microscopic colitis in a small case series but should be reserved as a last-resort medical therapy for microscopic colitis, given the possibility of life-threatening infections in this patient population.

Microscopic colitis is a common cause of chronic diarrhea, especially in elderly patients. Diagnosis is made through histopathological evaluation of endoscopically normal-appearing colonic mucosa. Drugs are a common cause of microscopic colitis, and inciting medications should be discontinued, if possible. Antidiarrheal drugs, bismuth subsalicylate, and budesonide are the most common therapeutic agents used for microscopic colitis and usually lead to satisfactory symptom control, although maintenance therapies are often required.

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CORRECT ANSWERS: 1. b. 2. a. 3. b. 4. d. 5. c