CASE STUDY

The Microscopic Colitides

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Collagenous and lymphocytic colitis are two diseases that present with watery diarrhea and abdominal cramping. Both require colon biopsy for diagnosis, as the traditional gastrointestinal (GI) workup is negative. Most cases follow a benign course and should not exhibit excess mortality.

CASE PRESENTATION

A 40-year-old woman applied for $100,000 of EWL life insurance coverage with waiver of premium option in January 1999. Her height on the application was 5 ft 7 in, and her weight was 145 lb. The only significant past medical history on the application was an overnight hospital admission for colitis in May 1998. She indicated that she was treated with mesalamine and had resolution of the colitis with no recurrence. There was no significant alcohol or caffeine intake listed on her application. She smokes a half a pack of cigarettes per day. Family history was negative for GI illnesses. For the amount of insurance requested, a medical or paramedical examination was not required.

Due to her history of colitis, an attending physician’s statement was obtained. Prior to April 1998, she was seen for routine pelvic exams and Papanicolaou test. History forms filled out by the patient at those visits listed no GI complaints. She also had hemoccult slides done with each of those appointments. These tests were negative for occult blood.

On April 21, 1998, the proposed insured called her doctor with complaints of diarrhea, abdominal cramping, and 1 episode of bright red blood in the stool. During the preceding 6–8 weeks, she had 4–5 episodes per day of severe abdominal cramps followed by watery diarrhea. Between episodes, she felt well and remained afebrile. There was no history of travel, recent antibiotic use, or exposure to individuals with acute gastrointestinal (GI) illnesses. She was evaluated by her doctor and found to be acutely ill with orthostatic hypotension. She was admitted to the hospital, where she was told to take nothing by mouth and placed on intravenous fluids. A workup included a complete blood cell count, meta-
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bolic profile, erythrocyte sedimentation rate, stool cultures, stool for ova and parasites, stool for *C. difficile* toxin, stool for occult blood and leukocytes, computed tomographic scan of the abdomen and pelvis and lower GI x-ray. All of these tests were negative or normal. Within 24 hours, she was much improved. The diarrhea had greatly diminished, and there was no more abdominal cramping. A gastroenterology consultation was obtained and she was scheduled for an outpatient colonoscopy. After 24 hours, she was discharged in improved condition without a specific diagnosis. She was discharged on loperamide and a bland diet.

An outpatient colonoscopy was carried out on May 6, 1998. The entire colon and terminal ileum were adequately visualized. Except for some petechiae in the ascending colon and cecum, the entire colon appeared to be normal. No mucosal abnormalities were seen and there were no colonic ulcerations. Random biopsies were taken throughout the colon. These biopsies showed a diffuse lymphocytic infiltration without any basement membrane thickening. There was no dysplasia or malignancy noted.

Review of the colon biopsies revealed features consistent with lymphocytic colitis; thus, mesalamine 400 mg TID was begun. She had fairly rapid improvement in her symptoms of diarrhea and abdominal cramping. A follow-up visit to her doctor on September 30, 1998, indicated she had complete resolution of her symptoms. Her annual gynecologic examination in February 1999 listed no GI complaints.

**DISCUSSION**

As clinicians and insurance medical directors, we are frequently presented with patients or applicants who have a significant history of GI complaints including diarrhea, abdominal cramping, and hematochezia. The symptoms can be very suggestive of infectious colitis, ischemic colitis, or inflammatory bowel disease. The traditional GI workup (as in the presented case) is, however, completely negative. With the recent description of 2 relatively new GI diseases, no workup can be considered complete without random colon biopsies. Collagenous colitis (CC) and lymphocytic colitis (LC) can be diagnosed only with colon biopsies. There is controversy over whether CC and LC are different diseases or opposite ends of the spectrum of the same disease. Most authors, however, feel they are distinct but similar diseases.

**COLLAGENOUS COLITIS**

CC was first described in 1976. It usually presents with watery, nonbloody diarrhea. There is a mean of 8 stools per day, although some patients may have as many as 30. There may be associated complaints of abdominal cramping, weight loss, fecal urgency, incontinence, and nausea. CC affects primarily women. In most studies, 80–90% of the patients are female. Patients are usually in their late 50s or 60s, with a mean age of 59 years. The disease typically follows a remitting and relapsing course. There may be long-term remissions; however, the symptoms may persist for years. Laboratory, x-ray and endoscopy workup tends to be negative. At endoscopy, the mucosa appears normal. Fecal leukocytes have been found in the majority of patients. Stool electrolyte studies confirm a secretory process.

CC can be diagnosed only with colon biopsies. The hallmark of CC is a subepithelial thickened eosinophilic collagen layer, which can be continuous or patchy. The thickness of this layer ranges from 12–100 μm (mean thickness is 2–7 μm in the normal colon). It is composed of type I and III collagen, which is generally seen in a reparative response to injury (type IV collagen is characteristic of the normal colon). In addition, an inflammatory infiltrate made up of plasma cells, lymphocytes, eosinophils, and mast cells is found in the lamina propria within the epithelium.

The etiology of CC is unknown. There seems to be an association between CC and nonsteroidal anti-inflammatory drug use;
however, this seems to be a weak association. The most popular theory on the etiology is that CC is an inflammatory disorder mediated through autoimmune mechanisms. A genetically predisposed individual is exposed to a noxious agent (infections, food, medication, environmental factors, etc) that prompts the inflammatory response. Patients with CC exhibit several autoimmune markers including antinuclear antibodies (up to 50% of patients in some studies), rheumatoid factor, elevated C3 and C4.

Treatment of CC is usually started with nonspecific therapy. Some patients may benefit from simple bulking agents or antidiarrheal medications. Caffeine should be removed from the diet. If there is no response to symptomatic therapy, anti-inflammatory agents such as sulfasalazine or 5-aminosalicylic acid can be tried. In patients still refractory to therapy, prednisone may be required.

Goff studied 31 patients with CC. In his study, 85% were women. The mean age was 66 years with a mean duration of illness of 5.4 years. Fifty-six percent of patients had some form of arthritic complaints, and 71% used nonsteroidal anti-inflammatory drugs regularly at the time of diagnosis. Four patients had hypothyroidism, 2 had diabetes, 1 had myasthenia gravis, and 1 had Sjogren's syndrome. The mean duration of symptoms after diagnosis was 1.5 years. Symptomatic patients were treated with antidiarrheals, sulfasalazine, discontinuation of nonsteroidal anti-inflammatory drugs, reversal of jejunoileal bypass, or nothing. Sixty-three percent of patients attained a long-lasting resolution of symptoms, either spontaneously or after treatment, while 37% continued to have symptoms that required constant or intermittent therapy (half of this 37% required steroids or immunosuppressives for control of diarrhea).

LYMPHOCYTIC COLITIS

The clinical presentation of LC can be very similar to that of CC. Typically, it also presents with watery, nonbloody diarrhea and abdominal cramping. Symptoms may be present for weeks to years at time of presentation. It usually occurs in the sixth decade with a mean age of 51. Unlike CC, males and females are roughly equally affected. As with CC, colon biopsy is required for diagnosis, as x-rays and endoscopic evaluation are negative.

The main difference in pathology between LC and CC is the absence of the subepithelial collagen band in LC. Otherwise, pathologic features are similar. A chronic inflammatory infiltrate made up of lymphocytes, neutrophils, and eosinophils is seen in the lamina propria.

The etiology of LC is unknown. An association with medication or dietary antigens has not been observed, as is seen with CC. It has been speculated that LC is an autoimmune disease. The pathophysiology of the diarrhea in LC is poorly understood. In one study, patients with LC had a significantly decreased colonic fluid absorption as compared to controls. Intestinal perfusion studies show a reduced active and passive absorption of sodium and chloride, as well as reduced chloride-bicarbonate exchange. In any event, the diarrhea in LC does not seem to be secretory, as it is in CC.

LC has been reported in some studies to have a higher incidence of autoantibodies, as compared to CC. Antinuclear antibodies, antiparietal cell antibodies, antithyroglobulin antibodies, and antimicrosomal antibodies have been detected with an overall frequency of 50%. Other studies have found a higher incidence of autoantibodies in CC. This suggests that there may be no difference between the incidence of autoantibodies in the two diseases and further study on larger numbers of patients is needed to clarify this issue.

Treatment of LC is similar to that of CC. Many patients may need only bulking agents and antidiarrheals. When symptomatic treatment fails, anti-inflammatory agents such as sulfasalazine, 5-ASA, or steroids could be required.

The clinical course seen in LC can be quite varied. Most patients have a self-limited dis-
ease with long-term remission. At the other end of the spectrum, there have been rare cases with a fulminant course requiring colectomy. In a study done by Mullhaupt et al, however, LC was found to be a fairly benign disease. They found resolution of symptoms and normalization of histology in over 80% of patients within 38 months.\(^7\)

**UNDERWRITING IMPLICATIONS**

There is still considerable controversy over whether CC and LC are different presentations of the same disease or whether they are different disease entities. The authors of articles reviewed for this paper seem to favor the position that they are indeed similar but different diseases.\(^{8-10}\) There were only a few instances where LC may have progressed to CC. Neither CC nor LC progresses to other inflammatory bowel diseases, and they do not seem to be premalignant conditions.

It is difficult to determine specific underwriting guidelines for the 2 microscopic colitides, since there are no long-term studies with large numbers of patients in the medical literature. We must, however, remember that probably more than 50% of individuals with CC, and possibly as high as 80% of LC cases, have a benign course with long-term remissions.

Cases of CC and LC need to be looked at individually. In cases where there is complete resolution of symptoms with only symptomatic therapy or short courses of sulfasalazine or 5-ASA (as in the presented case), there is probably no excess mortality. At the other end of the spectrum, cases that have frequent relapses and that require repeated treatment with steroids or other immunosuppressants could have a small excess mortality, with the most severe cases having a similar mortality to the other inflammatory bowel diseases. We must also look for autoantibodies and other autoimmune disorders that can be associated with microscopic colitis. If other autoimmune diseases are present, we must also consider their excess mortality in our final case assessment.

**CONCLUSIONS**

CC and LC are two fairly recently described diseases that fall under the umbrella term *microscopic colitis*. Both diseases present with a watery diarrhea syndrome and cramping abdominal pain. Traditional GI workups are generally negative and random colon biopsies are required for the diagnosis.

Cases of microscopic colitis are treated symptomatically or with anti-inflammatory agents such as sulfasalazine or 5-ASA. Severe cases may require treatment with steroids or other immunosuppressants. The majority of cases are benign in nature with resolution of symptoms and normalization of histology followed by long-term remission. These cases with long-term remission do not exhibit excess mortality.

**REFERENCES**