A Middle-Aged Woman with Diarrhea

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A 44-year-old white woman with a history of gastrointestinal problems presented with abdominal pain and diarrhea for 6 days. The patient stated that the abdominal pain had progressively worsened. The pain had come on suddenly and was described as "crampy." The pain was most intense in the right lower quadrant, worsened with eating, and was alleviated by defecation. The diarrhea was described as "watery," yellow in color, and occasionally contained mucus. The patient also reported intermittent bright red blood per rectum and tenesmus. Fatigue, malaise, and a subjective sense of weight loss were also noted. She denied melena, floating or oily stools, fecal incontinence, laxative use, nausea or vomiting, history of hepatitis, jaundice, fever, chills, hematuria, flank pain, or urinary incontinence. She also denied chest pain, shortness of breath, rash, mouth ulcers, back pain, pruritus, arthralgias, or skin abnormalities.

Her past medical history was significant for episodic bouts of alternating constipation and diarrhea during the past twenty years. A work-up performed one year earlier for diarrhea was remarkable for gastritis, a hiatal hernia, and hemorrhoids. A barium swallow with small bowel follow-through and a barium-enema study demonstrated no abnormalities. A colonoscopy with an "inadequate prep" was only remarkable for internal and external hemorrhoids. A history of anemia ascribed to heavy bleeding from menses and osteopenia with multiple wrist fractures was also reported. The patient was not taking any prescribed medications and denied recent antibiotic use. Her past surgical history was significant for a right hemicolectomy secondary to "intussusception" when she was 24 years of age. A veterinary technician, she smokes one-half pack of cigarettes daily, occasionally drinks alcohol, and denies intravenous drug use. She had not recently traveled.

At presentation, the patient's vital signs were: temperature of 100° Fahrenheit, pulse rate of 81 beats per minute, respiratory rate of 21 breaths per minute, and blood pressure of 135/66 mm Hg. The patient appeared to be in mild distress yet was oriented in all spheres. The abdomen was not distended and normal, active bowel sounds were appreciated. Tenderness of the abdomen was elicited with palpation of both lower quadrants, right greater than left. There was no evidence of a palpable mass, rebound tenderness, guarding, or hepatosplenom-

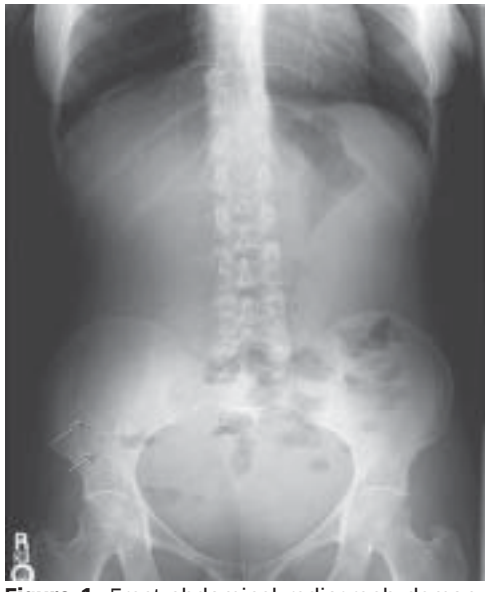

Figure 1. Erect abdominal radiograph demonstrates air fluid levels within multiple small bowel loops. Note surgical clips (arrows) from prior partial bowel resection.

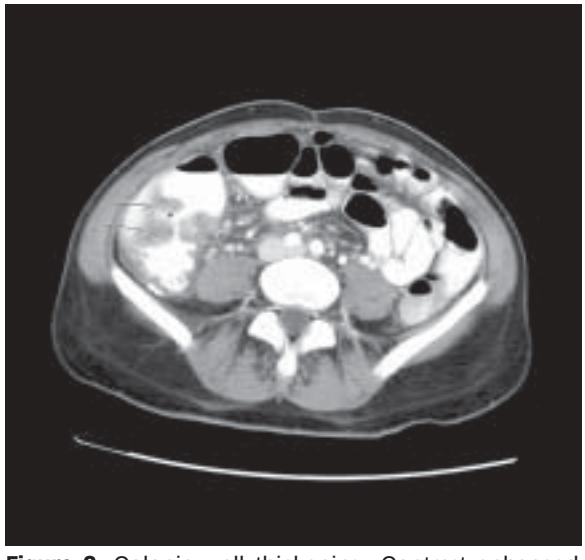

Figure 2. Colonic wall thickening. Contrast enhanced computed tomographic image demonstrates abnormal thickening of the ascending colon with characteristic "thumbprinting" (arrows).

egaly. Other pertinent findings included external hemorrhoids and heme-negative stool.

Laboratory data upon admission demonstrated: a white count of 3,400/μL (normal range, 4,500-11,000/μL), hematocrit of 27.0% (normal range, 40-51%), platelets of 153,000/μL (normal range, 130,000-400,000/μL), sodium of 140 mmol/L (normal range, 135-146 mmol/L), potassium of 3.1 mmol/L (normal range, 3.6-5.2 mmol/L), chloride of 105 mmol/L (normal range, 96-107 mmol/L), bicarbonate of 25 mmol/L (normal range, 24-32 mmol/L), blood urea nitrogen of 1 mg/dL (normal range, 7-25 mg/dL), creatinine of 0.6 mg/dL (normal range, 0.6-1.2 mg/dL), glucose of 82 mg/dL (normal range, 70-115 mg/dL), calcium of 8.8 mg/dL (normal range 8.4-10.3 mg/dL), total protein of 5.6 g/dL (normal range, 6-8 g/dL), albumin of 3.0 g/dL (normal range 3.4-5.0 g/dL), and normal liver transaminase values.

A flat and erect (Figure 1) abdominal radiograph revealed air-fluid levels within the small bowel and evidence of prior right lower quadrant surgery. An abdominal computed tomographic study demonstrated multiple areas of focal abnormal bowel wall thickening (Figure 2). Diffuse osteopenia was also noted. It was suspected that these findings could signify inflammatory bowel disease, an infectious process, or an intestinal neoplasm.

An iron profile study was suggestive of iron deficiency anemia. Symptoms of fatigue resolved with transfusion of packed red blood cells. Microscopic studies of stool revealed many white blood cells with no ova or parasites. Cultures for gastrointestinal pathogens and *Clostridium difficile* toxin analysis were negative.

Esophagogastroduodenoscopy illustrated gastritis, hiatal hernia, and an irregular squamocolumnar junction, with biopsies revealing gastric-type mucosa in the esophagus and mild chronic active gastritis in the antrum. Work-up for *Helicobacter pylori* was negative. Colonoscopy demonstrated multiple discrete areas of ulceration interspersed amongst areas of normal mucosa throughout the colon and cecum, with a narrowing of the anastomosis between the terminal ileum and cecum. Biopsies revealed focal, chronic inflammatory changes in the colonic mucosa as well as acute and chronic inflammation in the terminal ileum (Figure 3). A diagnosis of Crohn's disease was made, and the patient was started on mesalamine and azathioprine.

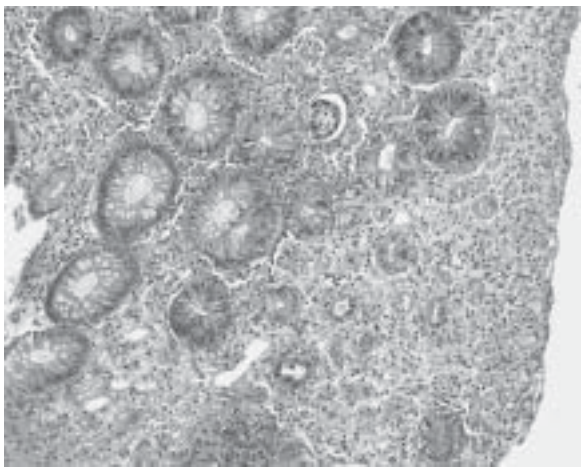

Figure 3. Photomicrograph of biopsy specimen of colonic mucosa showing reparative changes, granulation tissue formation, and acute and chronic inflammation. Dysplastic changes are not evident in this biopsy. The stain is H&E (Hematoxylin and Eosin), magnification is 100X.

DISCUSSION

Crohn's disease has a bimodal incidence curve with the first peak at age 20 years and a lesser peak at age 50 years. This disease affects both men and women at a respective ratio of 1.2:1.[1] It has an insidious onset, and similar to ulcerative colitis, exacerbations are recurring. Unlike ulcerative colitis, Crohn's disease can affect any portion of the alimentary tract from mouth to anus. Approximately 80% of patients have small bowel involvement, one-third of whom have exclusive involvement of the ileum. While 50% have involvement of the ileum and colon, approximately 20% have colonic involvement only.[2]

CLINICAL PRESENTATION

Patients may complain of fever, diarrhea, right lower quadrant abdominal pain, weight loss, or fatigue. In one case series that included 66 patients, 45 patients with Crohn's disease had symptoms for an average of 7.7 years prior to diagnosis.[3] "Crampy" abdominal pain, often in the right lower quadrant or periumbilical area, is a common symptom of Crohn's disease. On physical examination, focal tenderness is often elicited. A tender mass, which frequently represents matted loops of inflamed bowel, may be palpated. Fibrotic strictures caused by this inflammatory disease may cause repeated bouts of small bowel obstruction and, less often, colonic obstruction. Intermittent bouts of diarrhea are usually not bloody and as many as 10% of patients may not present with diarrhea. Hemoccult-positive stools, however, are common.[4,5]

A number of patients develop fistulas. Fistulas through the mesentery can cause retroperitoneal abscesses resulting in fevers, chills, and a tender abdominal mass. Fistulas through the bladder wall can lead to recurrent urinary tract infections with multiple enteric organisms. Patients may also develop pneumaturia. Enterovaginal fistulas may present with passage of feces through the vagina. Other associated manifestations include oral aphthous ulcers, pyoderma gangrenosum, erythema nodosum, iritis, sclerosing cholangitis, arthritis, ankylosing spondylitis, anal fissures, perianal abscesses, finger clubbing, nephrotic syndrome, and amyloidosis.

DIAGNOSIS

The diagnosis of Crohn's disease is not established with just one test or patient symptom. The diagnosis is made after a complete history is taken, thorough physical examination is performed, and confirmatory evidence from radiographic and endoscopic studies is obtained. Endoscopy is performed in the patient with a compatible history and particularly when there is a family history of inflammatory bowel disease. Often, the earliest lesion appreciated in Crohn's disease is the aphthous ulcer. These ulcers typically arise in the midst of normal mucosa, giving the appearance of "skip" lesions. It is believed that later in the course of disease these ulcers enlarge and develop a stellate appearance. Linear ulcers form when multiple ulcers come together in a longitudinal fashion. The classic "cobblestone" appearance develops when multiple ulcers converge in a transverse fashion representing the areas of ulceration interspersed with normal mucosa. Biopsies of the inflamed areas demonstrate non-caseating granulomas in 30% of patients.[6]

Radiologic studies can be used to document the extent of involvement. An upper gastrointestinal series with small bowel follow-through is warranted when small bowel disease is suspected. Barium studies may delineate the early findings of aphthous ulcers, thickened folds, and coarse villous patterns. An upper gastrointestinal series with small bowel follow-through may reveal narrowing of the lumen with ulcerations. A "string" sign is present when the luminal narrowing is more pronounced or there is severe spasm. A "cobblestone" appearance is noted when there is separation of bowel loops secondary to wall inflammation and wall thickening. Air-contrast barium enema may detect aphthous lesions and reveal fistulous tracts in the colonic region. These fistulous tracts represent a late finding in the chronic disease process.

While computed tomographic (CT) studies appear normal early in the course of the disease, CT scans should be used for addressing extraluminal features of disease and for identifying intra-abdominal and retroperitoneal abscesses. Air in the bowel wall can be detected on CT scan and is highly suggestive of intestinal perforation. Additionally, full-thickness wall involvement can be visualized as "thumbprinting."

Additional assistance for diagnosing Crohn's disease may now come from immunologic markers. Anti-*Saccharomyces cerevisiae* antibody (ASCA) in the serum is found 65% of the time in the serum of patients with Crohn's disease and in only 15% of patients with ulcerative colitis. Overall, the specificity is approximately 85% and the sensitivity approximately 50%. In contrast, the presence of perinuclear anti-neutrophil cytoplasmic antibody (P-ANCA) in the serum is associated with the diagnosis of ulcerative colitis. It is found in 70% of patients with ulcerative colitis and 20% of patients with Crohn's disease.[7]

It is important to distinguish between Crohn's disease and ulcerative colitis. The main diagnostic distinction between these two diseases is that ulcerative colitis is confined to the colon. When inflammatory bowel disease is considered and the disease is limited to the colon, it is imperative to examine the clinical picture. Features indicative of Crohn's disease include small bowel disease, predominately right-sided colonic disease, rectal sparing, the presence of fistulous tracts, granulomas, and perianal complications.

MEDICAL MANAGEMENT

The medical management of Crohn's disease is based on the location and severity of disease and the presence of extraintestinal complications. Therapy is directed at treating acute exacerbations and maintaining remission.

Mild-to-moderate Crohn's disease is diagnosed in patients who are ambulatory and able to take oral alimentation. There is no dehydration, high fever, abdominal tenderness, painful mass, obstruction, or weight loss of greater than 10%. These patients can be treated initially with a salicylate preparation, and when unresponsive, an antibiotic may be helpful.[8] Response to therapy should be assessed after several weeks. Patients who do not respond should be treated for moderate-to-severe disease. The salicylates include mesalamine (Rowasa®), olsalazine (Dipentum®) and sulfasalazine (Azulfidine®). In various preparations, mesalamine can be released in the stomach, duodenum, and colon (Pentasa®), or primarily in the terminal ileum and colon (Asacol®).[9]

The National Cooperative Crohn's Disease Study (NCCDS) and the European Cooperative Crohn's Disease Study (ECCDS) were the earliest large, placebo-controlled, randomized trials evaluating the use of sulfasalazine in Crohn's disease. These two studies demonstrated the efficacy of sulfasalazine at 3g to 5g/day in treating patients with active ileocolonic or colonic disease. However, sulfasalazine was not superior to placebo in patients with isolated small bowel disease and proved less effective than corticosteroids overall. In addition, sulfasalazine did not have significant benefit in maintaining remission.[10, 11] Mesalamine may maintain remission at higher doses.[12]

Side-effects of sulfasalazine include nausea, vomiting, abdominal pain, anorexia, malaise, and headache. These symptoms are dose-dependent and are primarily attributed to the sulfapyridine carrier.[13] Because of sulfasalazine's ability to impair intestinal folic acid absorption, folate supplementation is recommended.[14] The 5-ASA compounds, such as mesalamine and olsalazine, are devoid of the sulfapyridine carrier, thus allowing physicians to deliver a larger dose of active drug to the area of intestinal inflammation. As many as 80% of sulfasalazine-intolerant patients can take mesalamine without experiencing side effects.[15]

In the treatment of mild-to-moderate active Crohn's

disease, antibiotic therapy may be an acceptable alternative. Metronidazole is the best studied of the available antibiotics. This drug has demonstrated benefit in the treatment of ileocolitis and colitis, with most patients reporting clinical improvement and more than one-half achieving remission. These findings were reported in two major controlled trials by Ursing et al in 1982 and Sutherland et al in 1991.[16,17] Major side effects include metallic taste, disulfiram-like effects, and peripheral neuropathy with long-term usage. Ciprofloxacin has also been studied in the treatment of Crohn's disease. In one trial by Colombel et al, ciprofloxacin 1g per day was as effective as mesalazine (Mesasal®) 4g per day at inducing remission in patients with mild-to-moderate disease.[18]

Patients with moderate-to-severe disease have either failed treatment for mild-to-moderate disease or have more pronounced symptoms including fever, significant weight loss, abdominal pain/tenderness, intermittent nausea, vomiting, or significant anemia. Patients in this category should be treated with steroids until symptoms resolve and weight loss is reversed. Oral corticosteroids have been the mainstay for treating moderate-to-severe active Crohn's disease. This was first validated by the National Cooperative Crohn's Disease study, where 60% of patients receiving prednisone, 0.25-0.75mg/kg/day, achieved remission within 17 weeks compared with 30% receiving placebo ($p<0.001$). Later, in 1984, the European Cooperative Crohn's Disease Study proved an overall benefit with corticosteroids at all disease locations. In this latter study, patients initially received 48mg/day of methylprednisolone tapered to a 12mg/day over the ensuing 6 weeks.[10] The immunomodulators azathioprine (Imuran®) and mercaptopurine (Purinethol®) may also be used, but full response may not be achieved for several months. Infliximab (Remicade®) is another alternative if corticosteroids are ineffective or contraindicated.[19]

As evidenced in the NCCDS, steroids are not recommended in maintaining remission. In addition, corticosteroids produce numerous side effects that limit their chronic use. These side effects include diabetes mellitus, osteoporosis, myopathy, fat redistribution, and adrenal suppression.[10] Budesonide, a relatively new type of steroid, is highly potent and achieves poor systemic absorption. After its ingestion, 90% is metabolized in the liver and converted to metabolites with low systemic glucocorticoid activity. Campieri et al compared its activity to prednisolone and found them to be equally efficacious for the induction of remission.[20]

The role of immunomodulators in the treatment of Crohn's disease continues to be a topic of study. Azathioprine (AZA) and 6-mercaptopurine (6-MP) are thiopurine analogues that have become gradually more prominent in the management of both active and quiescent Crohn's disease. These medications should be considered in patients who are steroid-dependent or resistant to other forms of treatment.[21] AZA and 6-MP have allowed reduction in steroid dosages and maintenance of remission after induction therapy. Treatment can be initiated with either drug at a dose of 50 mg/day and can be increased to a maximum of 2 mg/kg per day for 6-MP and 2.5 mg/kg per day for AZA as indicated by clinical response and lack of bone marrow suppression. A response to these medications will usually be seen within three to six months.[22] During this period, patients often require concomitant steroid therapy with a gradual reduction in the steroid dose after one-to-two months of treatment with AZA or 6-MP. In one study by Candy et al, the percentage of patients remaining in remission was much higher with AZA than with placebo at 15 months (42 versus 7 percent).[23] Optimal duration of therapy with these agents has not been determined. Bouhnik et al did not find significant benefit of continued treatment in patients with quiescent disease for four years.[24] In contrast, Kim et al published data in 1999 suggesting that benefit continues beyond 4 years. Recommendations determining length of treatment require further study.

Methotrexate is an alternative for patients who are unresponsive to or intolerant of AZA or 6-MP. Methotrexate inhibits folate production, has anti-inflammatory effects, and is immunomodulating.[7] Controlled studies support weekly parenteral methotrexate at 25mg/wk for treatment and maintenance therapy.[25] Common side effects of methotrexate therapy include nausea, vomiting, headache, and hepatic fibrosis. Concomitant therapy with folic acid 1 mg/day may diminish adverse effects.

Infliximab, an antibody to human tumor necrosis factor-alpha, has been approved to treat patients with active enteric and fistula-producing Crohn's disease. In persons unresponsive to salicylates, antibiotics, corticosteroids, or immunosuppressants, infliximab has proven to be successful in the closure of fistulas, steroid refractory disease, and the improvement of moderate-to-severe disease.[19] In one trial,[26] response to infliximab was studied at three different doses, 5mg/kg, 10 mg/kg, and 20mg/kg, each given as a single two-hour intravenous infusion. The 5-mg/kg dose provided the best results, with 81% of patients achieving a clinical response after 4 weeks, compared with 17% of patients treated with placebo. Also, 48% of patients went into remission within 4 weeks compared with 4% of patients receiving placebo ($p=0.005$). Infliximab also appears to be useful in maintaining remission.[27, 28] Side effects such as mild serum sickness have been reported.

Severe Crohn's disease is characterized by persistent symptoms despite outpatient steroid therapy or by high fever, persistent vomiting, intestinal obstruction, rebound tenderness, cachexia, or abscess formation. These patients often require hospitalization and administration of parenteral steroids. Any clinical suspicion of an abdominal mass requires radiographic imaging for evaluation. Surgical consultation is recommended if there is evidence of intestinal obstruction, abscess formation, perforation, fistula formation, hemorrhage, or perianal disease.[19]

Other considerations in the management of Crohn's disease include mineral and vitamin supplementation. Potential deficits in vitamin B12, folic acid, fat-soluble vitamins, and calcium due to malabsorption should be considered, and periodic checks may be necessary. With severe degree of bile acid malabsorption, the concentration of bile acids required for fat absorption is impaired and steatorrhea ensues, leading to severe malnutrition, osteomalacia, and hypocalcemia. Bone loss is mainly related to steroid use and impaired vitamin D and calcium absorption. Osteopenia and osteoporosis are other potential complications of Crohn's disease, possibly secondary to increased levels of proinflammatory mediators, particularly interleukin-6, which inhibit bone mineralization. These complications are often worsened by chronic steroid use and thus should be closely monitored.[19, 29]

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