HPI: LC, a 23-year-old woman, presents with 9 months of low abdominal pain and intermittent diarrhea. The pain has intensified over the past few months greater on the right side. She characterizes it as crampy and constant; nothing worsens or relieves the pain. LC's bowel movements have become looser but do not contain any mucus or blood. She also notes weight loss, malaise, fatigue, and intermittent fevers.

PE: LC is 5'8" tall and weighs 115 pounds. She has normal vital signs and is afebrile. She is thin and appears ill. Her abdomen has positive bowel sounds, is soft, nontender, and slightly distended, with no rebound, no guard, a slight right lower quadrant fullness. Her rectum has normal tone, guaiac (+).

Labs: WBC 15 (4.5–11 $\times$ 10^3 per μL); hemoglobin 11 (12–16 g/dL); hematocrit 32 (35% to 45%); platelet 243 (159–450 $\times$ 10^3 per μL); bilirubin (tot) 0.2 (0.2–1.0 mg/dL); bilirubin (dir) 0.1 (0.0–0.2 mg/dL); AST/SGOT 12 (7–40 U/L); ALT/SGPT 23 (7–40 U/L); alk phos 100 (70–230 U/L); amylase 34 (25–125 U/L); lipase 5 (10–140 U/L); albumin 2.7 (3.5–5.5g/dL); ESR 60 ($<$ 20mm/hour)

LC undergoes several diagnostic examinations to better elucidate the source of her symptoms. An abdominal radiograph reveals dilated loops of small bowel with air-fluid levels and moderate air in the colon. Next, she undergoes a barium enema, which is significant for a normal colon and a stricture is noted in the distal ileum with proximal dilation. Finally, endoscopy is performed that is diagnostic. The findings include a granular mucosal surface with nodules and areas of friability as well as erosions and aphthous ulcers. A serpiginous linear ulceration is observed with sharply demarcated areas of normal mucosa. Mucosal biopsy of the affected areas reveals transmural involvement with non-caseating granulomas and significant inflammatory infiltrate.

Thought Questions

- What is the *most likely* diagnosis for this patient?
- Which key components of the history, physical exam, lab and study results lead to and confirm this diagnosis?
- How do you differentiate between the two main causes of this disorder?
- What are the common and rare sequelae of this disorder?
- What are the proposed etiologies of these disorders?

Basic Science Review and Discussion

LC has a chronic relapsing disorder broadly termed **inflammatory bowel disease** (IBD) and specifically, **Crohn's** disease. There are two types of IBD: Crohn's and **ulcerative colitis.** Each possesses a unique presentation, sequelae, and gross and histologic findings; however, they share in common an elusive etiologic process that results in a final common pathway of inflammatory damage. IBD runs in families as there is a tenfold increase in first-degree relatives as well as concordance in twin studies. Normally, the physiologic state of the intestine is one of balance between immune activation and down-regulation. It is unclear what tips the scales in favor of activation in cases of Crohn's disease and ulcerative colitis (UC); many theories exist but none adequately explains the pathogenesis. Proposed infectious etiologies are ambiguous at best with culprits including viruses, bacteria, atypical bacteria, and even food antigens, but the data are unclear; another theory stems from the observation of increased mucosal permeability and abnormal mucosal glycoproteins in patients with IBD; other theories point to psychological associations. The most plausible theory stems from altered immune system functioning. Possible causes include abnormal proliferation of cytokines, abnormal antigen-presenting cells or lymphocytes, or antiepithelial antibodies. Regardless of the exact mechanism, the immune system is activated and mucosal injury occurs.

Pathophysiology of Crohn's Disease LC suffers from **Crohn's disease**—a chronic inflammatory condition affecting mostly young women in their late teens and twenties (a second peak incidence occurs among women in their 50s and 60s). Crohn's affects all layers of the tract wall (i.e., **transmural**) most commonly in the small bowel and colon (40%), the terminal ileum alone (30%), or the colon alone (20%), but may affect any place in the alimentary tract. Patients present with chronic colicky pain often in the area where the disease is first active. LC's pain is the right lower quadrant, which is the area where the stricture was discovered. Another hallmark of Crohn's disease is the discontinuous nature of the lesions or "skip" areas (**skip lesions**) that are sharply contrasted with areas of normal mucosa. There are several hallmarks that help differentiate Crohn's disease from UC. Initially, the shallow ulcerations resemble canker

sores. As these lesions grow, the ulcerations coalesce into linear lesions, contrasted with nearby normal mucosa; the classic description is a "**cobblestone**" appearance. These linear lesions are at danger of becoming fistulae into any nearby structures (e.g., bowel, skin, bladder, vagina etc.). On gross inspection, the mucosal wall is noted to be rubbery, thick, and erythematous secondary to edema, inflammatory infiltration, fibrosis, and hypertrophy of the muscularis propria. This results in a narrowed lumen seen as a "**string sign**" on barium enema. Histologically, there is mucosal ulceration and inflammation characterized by neutrophils that invade the crypts and result in crypt abscesses. The destructive process continues with crypt atrophy. As in our patient, the inflammation and ulcerative destruction occurs through all layers; hence, the pathognomonic, **transmural** involvement. Finally, Crohn's disease is commonly accompanied by noncaseating granulomas.

The course of Crohn's is of relapsing and remitting symptoms, occasionally worsened by physical or psychological stress. **Microcytic anemia** is common with nearly perpetual loss of red blood cells. Other associations and sequelae help describe the disease, direct treatment, and differentiate Chron's disease from UC. As discussed earlier, strictures can complicate affected regions often in the small intestine as can fistulas to the bowel or other organs. If the small bowel has significant disease, the patient can suffer from malabsorption, protein loss, and various vitamin deficiencies (e.g., B_{12}). Additionally, sufferers of Crohn's can have a multitude of extra-intestinal manifestations including arthritis, ankylosing spondylitis, erythema nodosum, clubbing of the nails, perihepatic cholangitis, or uveitis. There is a five- to six-fold increased risk of GI cancers in patients with long-standing Crohn's disease.

Pathophysiology of Ulcerative Colitis UC is also a chronic ulcero-inflammatory condition of unknown etiology affecting only the colon. UC is rare but has a slightly higher incidence than Crohn's disease. In the United States, whites and females are more often affected than their counterparts and the onset of disease often occurs in the 20s. Patients complain of crampy pain, rectal bleeding, tenesmus and chronic diarrhea with blood and mucus. UC only affects the colon and the diseased tissues extend only into the submucosa; the anus is not involved. The disease begins at the rectum and extends proximally leaving behind a friable red mucosa. Characteristically, the diseased mucosa progresses to ulcerations with pseudopolyps that progress histologically into **crypt abscesses** with eventual atrophy. In only the most severe cases does the illness progress past the submucosa into the muscularis propria; in these severe cases there is a higher risk of toxic megacolon (complete cessation of bowel function). Histologically, there is mucosal damage and ulceration in affected areas with a mononuclear infiltrate in the propria with neutrophils and mast cells. Like Crohn's disease, there is an increased incidence in adenocarcinoma of the colon, which is proportional to the duration of the illness. Dysplasia can arise in different sites increasing a patient's risk of adenocarcinoma by almost 30 times. Clearly, surveillance is important. Common associations include sclerosing pericholangitis and ankylosing spondylitis (with HLA B-27).

Case Conclusion LC was treated with immunosuppressive medications and her symptoms improved greatly. She also noted the importance of limiting her psychological stressors because her number of exacerbations appeared to be related to the stress level of her job and personal life. LC's anemia and hypoalbuminemia also improved with immunosuppressive therapy. She has not had any extra-intestinal manifestations of her illness.

Thumbnail: Inflammatory Bowel Disease—Ulcerative Colitis versus Crohn's Disease

	Ulcerative Colitis	Crohn's Disease
Location	Begins at rectum, extends to colon commonly; rarely affects the anus	Small intestine, colon commonly, but any part of alimentary tract
Depth	Mucosa, submucosa	Transmural
Gross	Diffuse ulceration, pseudopolyps, no strictures, thin wall, dilated lumen	Skip lesions with strictures, thick or thin wall (thick in small bowel), cobblestone appearance
Histology	Crypt atrophy and abscess, many pseudopolyps, mild lymphocytes and PMNs	Deep linear ulcers, noncaseating granulomas, marked inflammatory infiltrate (lympho, polymorphonuclear [PMN]), fistulas
Sequelae	Increased risk for adenocarcinoma (30 to 35 years after diagnosis), sclerosing pericholangitis, toxic megacolon	Increased risk for GI malignancy (not as high as UC) extra-intestinal manifestations (polyarthritis, uveitis clubbing of the nails, ankylosing spondylitis), strictures, fistulas, malabsorption, protein-losing enteropathy, fat-soluble vitamin deficiency

Key Points

Ulcerative Colitis

- Presents with relapsing attack of bloody diarrhea, tenesmus, mucus in stool, pain
- Labs: may have no abnormalities, rarely microcytic anemia
- Etiology: ultimately idiopathic, several theories exist: infections, genetics, intestinal mucosal structural abnormalities, abnormal immunoreactivity
- Treatment: immunosuppression, surgery

Crohn's Disease

- Presents with intermittent colickly abdominal pain, diarrhea, fever
- Labs: Fat and vitamin malabsorption (low albumin, deficiency of fat soluble vitamins A, D, E, and K) abnormal liver function tests (cholangitis), elevated creatinine (strictures obstructing the ureters) electrolytes
- Etiology: ultimately idiopathic, several theories exist: infections, genetics, intestinal mucosal structural abnormalities, abnormal immunoreactivity
- Treatment: immunosuppression

Questions

1. A 28-year-old female presents with an 8-month history of bloody diarrhea, intermittent crampy abdominal pain, persistent spasms of the bowel, and stringy mucus in her stools. You suspect IBD, with the likely diagnosis of UC. Which of the following will allow you to differentiate it from Crohn's disease?
   - **A.** areas of affected and unaffected mucosa, "skip" lesions
   - **B.** Transmural involvement on biopsy
   - **C.** Involvement of the small bowel
   - **D.** Pseudopolyps
   - **E.** Fistula formation
2. A 33-year-old white female presents with colicky right lower quadrant abdominal pain, diarrhea, and rectal bleeding for over 10 years. You perform the appropriate work-up. Her biopsy reveals colon and small bowel involvement with characteristic transmural skip lesions, a cobblestone appearance, and a narrow lumen in the distal small bowel. She presents 3 months later with electrolyte abnormalities and complains of tingling and numbness in her hands and feet. Which of the following laboratory abnormalities would you expect to receive?
   - **A.** Decreased hemoglobin and hematocrit, macrocytosis
   - **B.** Low albumin
   - **C.** Decreased hemoglobin and hematocrit and microcytosis
   - **D.** Abnormal clotting profile
   - **E.** Decreased bone mineral density
3. A 55-year-old white female with a 30-year history of UC returns for a follow-up visit. She recently recovered from an acute exacerbation for which she was hospitalized and given immunosuppressive therapy, to which she responded. She knows about her increased risk for adenocarcinoma of the colon. Which of the following is *more common* in patients who suffer from UC than Crohn's disease?
   - **A.** Fistula formation
   - **B.** Aphthous ulcers
   - **C.** Toxic megacolon
   - **D.** Granulomas
   - **E.** Malabsorption