第２０号

出典：メルクマニュアル

メトロニダゾール１～１.５ｇ／日の投与が、特にクローン病の大腸炎に有益である。

抗炎症作用

Crohn's Disease

(Regional Enteritis, Granulomatous Ileitis Or Ileocolitis)

A nonspecific chronic transmural inflammatory disease that most commonly affects the distal ileum and colon but may occur in any part of the GI tract.

Etiology and Epidemiology

The fundamental cause of Crohn's disease is unknown. Evidence suggests that a genetic predisposition leads to an unregulated intestinal immune response to an environmental, dietary, or infectious agent. However, no inciting antigen has been identified. Cigarette smoking seems to contribute to the development or exacerbation of Crohn's disease.

Over the past few decades, incidence of Crohn's disease has increased in Western populations of Northern European and Anglo-Saxon ethnic derivation, third-world populations, blacks, and Latin Americans. The disease occurs about equally in both sexes and is more common among Jews. Approximately one of six patients has at least one first-degree relative with the same disease or, less frequently, with ulcerative colitis. Most cases begin in patients < 30 yr, with the peak incidence in those aged 14 to 24 yr.

Pathology

The earliest mucosal lesion of Crohn's disease is crypt injury in the form of inflammation (cryptitis) and crypt abscesses, which progress to tiny focal aphthoid ulcers, usually located over nodules of lymphoid tissue. In some cases, these lesions regress; in others, the inflammatory process evolves with influx and proliferation of macrophages and other inflammatory cells, occasionally forming noncaseating granulomas with multinucleated giant cells.

Transmural spread of inflammation leads to lymphedema and bowel wall thickening, which may eventually result in extensive fibrosis. Development of patchy mucosal ulcers and longitudinal and transverse ulcers with intervening mucosal edema frequently creates a characteristic cobblestoned appearance. The attached mesentery is thickened and lymphedematous; mesenteric fat typically extends onto the serosal surface of the

bowel. Mesenteric lymph nodes often enlarge. Transmural inflammation, deep ulceration, edema, muscular proliferation, and fibrosis cause deep sinus tracts and fistulas, mesenteric abscesses, and obstruction, which are the major local complications.

Granulomas can occur in lymph nodes, peritoneum, the liver, and all layers of the bowel wall and are occasionally seen at laparotomy or laparoscopy as miliary nodules. Although pathognomonic, granulomas are absent in up to 50% of patients and are therefore not essential to diagnose Crohn's disease. They appear to have no definitive bearing on the clinical course.

Segments of diseased bowel are characteristically sharply demarcated from adjacent normal bowel ("skip areas")--thus the name regional enteritis. Of all cases of Crohn's disease, about 35% involve the ileum (ileitis); about 45% involve the ileum and colon (ileocolitis), with a predilection for the right side of the colon; and about 20% involve the colon alone (granulomatous colitis). Occasionally, the entire small bowel is involved (jejunoileitis), and rarely, the stomach, duodenum, or esophagus. The perianal region is also affected in 1/4 to 1/3 of cases.

Symptoms, Signs, and Complications

Chronic diarrhea with abdominal pain, fever, anorexia, weight loss, and a right lower quadrant mass or fullness are the most common presenting features. However, many patients are first seen with an acute abdomen that simulates acute appendicitis or intestinal obstruction. About 1/3 of patients have a history of perianal disease, especially fissures and fistulas, which are sometimes the most prominent or even initial complaint. In children, extraintestinal manifestations frequently predominate over GI symptoms. Arthritis, FUO, anemia, or growth retardation may be a presenting symptom, and abdominal pain or diarrhea may be absent.

The most common patterns of Crohn's disease pathology are (1) inflammation characterized by right lower quadrant abdominal pain and tenderness; (2) recurrent partial obstruction caused by intestinal stenosis and leading to severe colic, abdominal distention, constipation, and vomiting; (3) diffuse jejunoileitis, with inflammation and obstruction resulting in malnutrition and chronic debility; and (4) abdominal fistulas and abscesses, usually late developments, often causing fever, painful abdominal masses, and generalized wasting.

Obstruction; development of enteroenteric, enterovesical, retroperitoneal, or enterocutaneous fistulas; and abscess formation are common complications of inflammation. Intestinal bleeding, perforation, and small-bowel cancer develop rarely. When the colon alone is affected, the clinical picture may be indistinguishable from that of ulcerative colitis.

Extraintestinal manifestations are categorized as:

- Complications that usually parallel the activity of the intestinal disease and possibly represent acute immunologic or microbiologic concomitants of the bowel inflammation: peripheral arthritis,

episcleritis, aphthous stomatitis, erythema nodosum, and pyoderma gangrenosum. These manifestations may be reported by > 1/3 of patients hospitalized with inflammatory bowel disease. They are twice as common when colitis is present as when disease is confined to the small bowel. When extraintestinal manifestations occur, they are multiple in about 1/3 of patients.

- Disorders associated with inflammatory bowel disease but running an independent course: ankylosing spondylitis, sacroiliitis, uveitis, and primary sclerosing cholangitis. The genetic association of these syndromes and of Crohn's disease (and ulcerative colitis) with the HLA antigen B27 is discussed under the extracolonic complications of ulcerative colitis, below.
- Complications that relate directly to disrupted bowel physiology: kidney stones from disorders of uric acid metabolism, impaired urinary dilution and alkalinization, and excessive dietary oxalate absorption; UTIs, especially with fistulization into the urinary tract; and hydroureter and hydronephrosis from ureteral compression by retroperitoneal extension of the intestinal inflammatory process. Other bowel-related complications include malabsorption, especially in the face of extensive ileal resection or bacterial overgrowth from chronic small-bowel obstruction or fistulization; gallstones, related to impaired ileal reabsorption of bile salts; and amyloidosis, secondary to long-standing inflammatory and suppurative disease. Thromboembolic complications may occur, usually with severe disease activity, as a result of hypercoagulability associated with altered levels of clotting factors and platelet abnormalities.

Diagnosis

Crohn's disease should be suspected in a patient with the inflammatory or obstructive symptoms described above and in a patient without prominent GI symptoms but with perianal fistulas or abscesses or with otherwise unexplained arthritis, erythema nodosum, fever, anemia, or stunted growth (in a child).

Laboratory findings are nonspecific and may include anemia, leukocytosis, hypoalbuminemia, and increased levels of acute-phase reactants reflected in elevated ESR, C-reactive protein, or orosomucoids. Elevated alkaline phosphatase and γ-glutamyl transpeptidase accompanying colonic disease often reflect primary sclerosing cholangitis.

Definitive diagnosis is usually made by x-ray. Barium enema x-ray may show reflux of barium into the terminal ileum with irregularity, nodularity, stiffness, wall thickening, and a narrowed lumen. A small-bowel series with spot x-rays of the terminal ileum usually most clearly shows the nature and extent of the lesion. An upper GI series without small-bowel follow-through usually misses the diagnosis.

In advanced cases, the string sign may be seen with marked ileal strictures and separation of bowel loops. In earlier cases, x-ray diagnosis may sometimes be difficult, but air double-contrast barium enema and enteroclysis may show superficial aphthous and linear ulcers. In questionable cases, colonoscopy and biopsy may help confirm the diagnosis of Crohn's colitis and allow direct visualization and biopsy of the terminal ileum. Upper GI endoscopy may identify gastroduodenal involvement in Crohn's disease patients with upper GI symptoms. Although CT can detect extramural complications (eg, fistulas, abscesses, masses), it is not

routinely needed for initial diagnosis. Ultrasound may help delineate gynecologic pathology in women with lower abdominal and pelvic pain.

Differential Diagnosis

Differentiation from ulcerative colitis may be difficult in the 20% of cases in which Crohn's disease is confined to the colon (Crohn's colitis). The principal differential diagnoses are acute infectious (self-limited) colitis and ulcerative colitis. Acute infectious colitis is best established by stool culture, rectal biopsy, and watchful waiting. Differentiating ulcerative colitis is detailed in Table 31-1. Ischemic colitis is discussed in Ch. 25. Although perinuclear antineutrophil cytoplasmic antibodies are present in 60 to 70% of ulcerative colitis patients and in only 5 to 20% of Crohn's disease patients, and anti-*Saccharomyces cerevisiae* antibodies are relatively specific for Crohn's disease, these tests are not sufficiently refined in routine clinical application as to reliably separate the two diseases.

Crohn's disease of the small bowel (ileitis) requires differentiation from other inflammatory, infectious, and neoplastic disorders in the right lower quadrant. If in the acute presentation a prior history of chronic bowel symptoms has not been elicited, ileitis may be first diagnosed during surgical exploration for suspected acute appendicitis. Periappendiceal abscess may produce more chronic symptoms and thus be more difficult to diagnose clinically.

Pelvic inflammatory disease, ectopic pregnancy, and ovarian cysts and tumors also produce right lower quadrant inflammatory signs and must be ruled out when considering Crohn's disease in women. Cancer of the cecum, ileal carcinoid, lymphosarcoma, systemic vasculitis, radiation enteritis, ileocecal TB, and ameboma may mimic the x-ray findings of Crohn's disease. AIDS-related opportunistic infections (eg, *Mycobacterium avium-intracellulare*, cytomegalovirus) must also be considered as causes of localized ileitis.

Yersinia enterocolitica enteritis must be excluded if an inflamed, edematous terminal ileum and associated mesenteric adenitis are seen during surgery for acute right lower quadrant pain. Although *Yersinia* enteritis is self-limited without chronic intestinal sequelae, the initial clinical picture may be indistinguishable from Crohn's disease, so appropriate serologic and bacteriologic studies are necessary. In questionable cases, a 3-mo follow-up x-ray of the terminal ileum is valuable, because *Yersinia* enteritis will usually resolve completely by this time but Crohn's disease will not.

Nongranulomatous ulcerative jejunoileitis has features of both Crohn's disease and sprue, with malabsorption, small-bowel ulceration, and villous atrophy, but it lacks granulomatous pathology, fistulization, and extraintestinal manifestations of Crohn's disease. Eosinophilic gastroenteritis generally has prominent gastric involvement (rare in Crohn's disease) and is often associated with peripheral eosinophilia, which is the clue to diagnosis.

Prognosis

Although spontaneous remission or medical therapy may result in a prolonged asymptomatic interval, established Crohn's disease is rarely cured but instead is characterized by intermittent exacerbations. In the absence of surgical intervention, the disease never extends into new areas of small bowel beyond its initial distribution at first diagnosis. With judicious medical and, where appropriate, surgical therapy, most patients with Crohn's disease function well and adapt successfully. Disease-related mortality is very low and continues to decrease.

GI cancer, including cancer of the colon and small bowel, is the leading cause of Crohn's disease-related death. Patients with long-standing Crohn's disease of the small bowel are at increased risk of small-bowel cancer, with bowel in continuity as well as in bypassed loops. Furthermore, patients with Crohn's disease of the colon have a long-term risk of colorectal cancer equal to that of ulcerative colitis, given the same extent and duration of disease.

Approximately 70% of Crohn's disease patients ultimately require surgery. Furthermore, Crohn's disease is likely to recur even after resection of all clinically apparent disease.

Treatment

No cure is known. Cramps and diarrhea may be relieved by oral administration up to qid (ideally before meals) of anticholinergics, diphenoxylate 2.5 to 5 mg, loperamide 2 to 4 mg, deodorized opium tincture 0.5 to 0.75 mL (10 to 15 drops), or codeine 15 to 30 mg. Such symptomatic treatments are safe, except in cases of severe, acute Crohn's colitis, which may progress to toxic megacolon as in ulcerative colitis. Hydrophilic mucilloids (eg, methylcellulose or psyllium preparations) sometimes help prevent anal irritation by increasing stool firmness.

Sulfasalazine primarily benefits patients with mild to moderate colitis and ileocolitis but has some efficacy in ileitis as well. It may also maintain remission, although it has not been proven to prevent recurrence after surgery. (For details of sulfasalazine therapy, see Treatment under Ulcerative Colitis.)

Mesalamine (5-aminosalicylic acid), the active moiety of sulfasalazine, is available in several oral formulations designed to release in various segments of the small bowel and colon. It is especially useful in patients who are intolerant of sulfasalazine. In doses of up to 4 g/day, mesalamine is effective for inducing and maintaining remission and is showing considerable promise for inhibiting postoperative recurrence.

Corticosteroid therapy treats the acute stages of Crohn's disease by dramatically reducing fever and relieving abdominal pain and tenderness, and improving the appetite and sense of well-being. Large doses of oral prednisone, 40 to 60 mg/day, should be given initially. The equivalent dose of hydrocortisone (200 to 300 mg) may be given by continuous IV drip to hospitalized patients with severe disease. The daily dose of prednisone is gradually reduced after a satisfactory response so that, after 1 or 2 mo, it is <= 10 mg.

Although as little as 5 or 10 mg/day of prednisone may help control symptoms in some patients, long-term

corticosteroid therapy often does more harm than good. Corticosteroids should be avoided when obvious infections (eg, fistulas, abscesses) are present. In uncertain cases (eg, those presenting with a tender, inflammatory mass), antibiotics should be given concurrently.

The new topically active corticosteroid budesonide can be given orally or as an enema and has low systemic bioavailability and thus reduced adrenal suppression. Controlled-release budesonide given orally induces remissions in Crohn's disease with somewhat fewer side effects than prednisolone, but it is not as effective as the conventional corticosteroid and seems no better than placebo in preventing relapses beyond 6 mo.

Broad-spectrum antibiotics that are active against enteric gram-negative and anaerobic flora may help reduce disease activity in many patients but are most consistently effective for suppurative complications (eg, infected fistula, abscess). Metronidazole 1 to 1.5 g/day has been shown to be beneficial, especially in Crohn's colitis, and is particularly useful for treating perianal lesions. Neuropathy manifested chiefly by paresthesias is a common, potentially serious side effect of long-term use; it is usually reversible when the drug is stopped. There is a high incidence of relapse after discontinuing the drug. Among other broad-spectrum antibiotics, ciprofloxacin has shown particular promise, but the results of multidrug antituberculous regimens have been mixed.

Immunomodulating drugs, particularly the antimetabolites azathioprine and 6-mercaptopurine, are effective as long-term therapy for Crohn's disease. Azathioprine 2.0 to 3.5 mg/kg/day or 6-mercaptopurine 1.5 to 2.5 mg/kg/day po significantly improves overall clinical status, decreases corticosteroid requirements, heals fistulas, and maintains remission for many years. However, these drugs often do not produce clinical benefits for 3 to 6 mo, and side effects of allergy, pancreatitis, and leukopenia must be watched for.

Methotrexate 25 mg IM or sc once/wk benefits some patients with severe corticosteroid-refractory disease, even those who have failed to respond to azathioprine or 6-mercaptopurine. High-dose cyclosporine has demonstrated benefits in inflammatory and fistulous disease, but its long-term use is contraindicated by multiple toxicities. Infliximab, a monoclonal antibody that inhibits tumor necrosis factor, can be given IV for moderate to severe Crohn's disease (especially fistulous disease) refractory to other treatments; long-term efficacy and side effects remain to be determined. Other potential immunoregulatory treatments include interleukin-1 blockers, antibody to interleukin-12, anti-CD4 antibodies, adhesion molecule inhibitors, and down-regulatory cytokines. These many experimental treatment approaches attest to the inadequacy of current drug therapy for Crohn's disease.

Some patients with intestinal obstruction or fistulas have improved with **elemental diets** or **hyperalimentation,** at least over a short term, and children often achieve increased rates of growth. Thus, these measures may serve as preoperative or adjunctive therapy and may even be valuable as primary therapy.

Surgery is usually necessary for recurrent intestinal obstruction or intractable fistulas or abscesses. Resection of the grossly involved bowel may ameliorate symptoms indefinitely but does not cure the disease. Sulfasalazine has not been shown to prevent postoperative recurrence, but mesalamine >= 2.0 g/day may be

effective. The recurrence rate, defined by endoscopic lesions at the anastomotic site, is > 70% at 1 yr and > 85% at 3 yr; defined by clinical symptoms, it is about 25 to 30% at 3 yr and 40 to 50% at 5 yr. Ultimately, further surgery is required in nearly 50% of cases. However, recurrence rates appear to be reduced by early postoperative prophylaxis with mesalamine, metronidazole, or possibly 6-mercaptopurine. Moreover, when surgery has been performed for specific complications or failure of medical therapy, most patients experience an improved quality of life.