INTRODUCTION

Inflammatory disorders of the intestines can be divided into those with macroscopic mucosal changes (the traditional inflammatory bowel diseases: ulcerative colitis and Crohn’s disease) and those with primarily microscopic changes.

Microscopic colitis is a chronic diarrheal condition that is separated into two main subtypes: collagenous colitis and lymphocytic colitis. These two conditions have similar clinical and histologic features, but are distinguished by the presence or absence of a thickened subepithelial collagen band. Inflammatory bowel disease (IBD) is traditionally separated into two distinct clinical entities: Crohn’s disease and ulcerative colitis. Although there is considerable symptom overlap between these diseases, there are several features that help distinguish them.

The aim of this review is to provide a concise comparison of the epidemiology, clinical features and natural history, pathophysiology and risk factors, and management of microscopic colitis compared to IBD.

EPIDEMIOLOGY

Incidence and Prevalence

A recent study in North America showed that the incidence of microscopic colitis has increased significantly over time and now approximates that of IBD. The prevalence of IBD, on the other hand, is higher than microscopic colitis, reflecting the younger age of onset in patients with IBD.

In North America, the incidence of microscopic colitis was 0.8/100,000 person-years from 1985 to 1989, and this increased significantly to 19.1/100,000 from 1998 to 2001 (1). The incidence of collagenous colitis and lymphocytic colitis was 5.1 and 9.8/100,000 person-years, and the prevalence was 36 and 64/100,000 persons, respectively (1). In Europe, the incidence of collagenous and lymphocytic colitis ranges from 0.6 to 5.2/100,000 person-years with a prevalence between 10 to 16/100,000 persons (2). The reason for the significantly higher incidence and prevalence of MC in North America compared with Europe is not known, though increasing recognition may play a role.

The highest incidence and prevalence rates for IBD have been reported from northern Europe and North America. In North America, the incidence of ulcerative colitis ranges from 2.2 to 14.3/100,000 person-years (3) and for Crohn’s disease, 3.1 to 14.6/100,000 person-years (4). The prevalence ranges from 37 to 140/100,000 persons for ulcerative colitis and from 26 to 200/100,000 persons for Crohn’s disease (3,4).

Demographic Features

Microscopic colitis is often seen at a more advanced age (sixth–eighth decade) with female predominance, particularly for collagenous colitis. Data on racial differences are not available. IBD is associated with earlier age of diagnosis (second–fourth decade), although some studies suggest a bimodal age distrib-
Clinic Features and Natural History

Clinical Presentation

Microscopic colitis is typically characterized by chronic or intermittent watery diarrhea. In contrast to IBD, microscopic colitis is not characterized by fever, vomiting or hematochezia. Crohn’s disease may involve any part of the GI tract from mouth to the perianal area, often occurring in different locations in the GI tract (skip lesions). The majority of the patients have distal ileitis, with or without colonic or perianal involvement, while others have isolated colonic or perianal disease. Sparing of the rectum is a feature of Crohn’s disease. Ulcerative colitis is characterized by inflammation limited to the mucosa and involving the colon in a continuous fashion usually beginning in the rectum.

Microscopic colitis is characterized by chronic or intermittent watery diarrhea, often associated with abdominal cramping and mild weight loss. Fecal leukocytes may be present, but fever, vomiting, or hematochezia are not, in contrast to IBD. Microscopic colitis is usually considered a pancolonic disease, but there is very little data on disease distribution. It does appear that histologic abnormalities are less evident in rectal and possibly also sigmoid biopsies.

Crohn’s disease is often characterized by abdominal pain, weight loss, fatigue, diarrhea with or without gross bleeding, abdominal pain and sometimes fever. Gastrointestinal bleeding is not as common as in ulcerative colitis. Development of sinus tracts may result from transmural inflammation, which can lead to bowel wall perforation and abscess formation. Fistula formation between the bowel and adjacent organs may have different clinical presentations, including enteroenteric, enterovesical, enterovaginal, and entero-cutaneous fistulas.

The clinical presentation of patients with ulcerative colitis usually correlates with disease extent and severity. Distal colitis refers to colitis extending into the sigmoid colon. Left-sided colitis extends up to the splenic flexure. Pancolitis describes inflammation extending beyond the splenic flexure, even if the inflammation does not reach the cecum. Disease severity is classified as mild, moderate or severe. Mild disease usually manifests as mild diarrhea, tenesmus and intermittent bleeding; moderate disease is characterized by bloody diarrhea (<10 stools per day), abdominal pain and low grade fever; severe disease is characterized by more significant bloody diarrhea (>10 stools per day), severe abdominal cramping, and high grade fever.

Associated Medical Conditions

Microscopic colitis has been associated with several autoimmune disorders, including celiac sprue. IBD is associated with several extraintestinal manifestations, particularly involving the joints, skin, eyes, and biliary tract.

Several autoimmune conditions, such as thyroid dysfunction, rheumatoid arthritis and diabetes mellitus, can be seen in patients with microscopic colitis. Of particular interest and clinical significance, celiac sprue appears to be associated with microscopic colitis. The prevalence of small bowel sprue-like changes in patients with microscopic colitis ranges from 2% to 40% (2). Thus, celiac sprue should be considered in treatment-refractory microscopic colitis patients or in those with steatorrhea or significant weight loss.

IBD is associated with a number of extraintestinal disease manifestations, which can involve almost any organ system. The mechanisms of these extraintestinal...
manifestations are not completely understood, and may be related to immunologic or non-immunologic processes. Some extraintestinal manifestations tend to follow the course of bowel activity while others do not. The organs most commonly involved include the skin, joints, biliary tract, and eyes, as reviewed elsewhere (12).

Natural History

Microscopic colitis often has a waxing and waning course. Most patients will respond to therapy, and spontaneous remission has been reported. IBD is also associated with intermittent exacerbations and periods of symptom remission. Microscopic colitis is not associated with colorectal cancer, while in IBD, both ulcerative colitis and Crohn’s colitis are.

The reported natural history of microscopic colitis in several studies has been quite variable (2). In lymphocytic colitis, resolution of diarrhea and normalization of histology was observed in over 80% after 38 months of follow up in one study (13). In collagenous colitis, the response rates with different treatments ranged from 40% to 81% (14). Spontaneous remission was reported in 15% of patients and treatment-induced remission was reported in 48% of patients after 3.5 years of follow-up (15). Spontaneous remission may be more likely in patients with shorter duration of disease. Although microscopic colitis is often associated with a negative impact on quality of life, the disease does not seem to have a malignant potential (16).

The natural history of Crohn’s disease and ulcerative colitis are similar, in that they are typically associated with intermittent exacerbations and periods of remission (17,18). The association between extensive, long-standing colonic involvement in IBD (either ulcerative colitis or Crohn’s colitis) and risk of colorectal cancer is well documented. Cancer in these patients often develops from areas of flat dysplasia rather than polyps; thus screening with colonoscopy and multiple biopsies is recommended (19).

Endoscopic and Histopathologic Diagnosis

In microscopic colitis, endoscopy is often grossly normal. Ulcers, ranging from small aphthous ulcers to large, deep or stellate ulcers, and discontinuous or skip lesions are common endoscopic findings in Crohn’s disease. Mucosal granularity, friability and edema are seen in mild ulcerative colitis, with frank ulceration in moderate to severe cases.

Histologically, microscopic colitis demonstrates an intraepithelial lymphocytosis with mixed inflammation in the lamina propria. In collagenous colitis, in addition to these inflammatory changes, the subepithelial collagen band is abnormally thickened. Colonic biopsies in ulcerative colitis and Crohn’s disease may reveal acute or chronic inflammation, typically with chronic architectural changes.

At endoscopy, individuals with microscopic colitis have grossly normal mucosa, or mild nonspecific changes such as erythema or edema (16). The diagnosis is determined by intraepithelial lymphocytosis, with more than 20 lymphocytes per 100 epithelial cells (normal ≤5). Mixed inflammation in the lamina propria is also present, with mononuclear cells (lymphocytes and plasma cells) more prevalent than eosinophils and neutrophils (20). In collagenous colitis, in addition to these inflammatory changes, the subepithelial collagen band is abnormally thickened, often with an irregular inferior edge and entrapped blood cells (21). Flexible sigmoidoscopy is sufficient to diagnose microscopic colitis in most cases, with biopsies from the descending colon missing fewer than 5% of cases. If left-sided biopsies are normal, but clinical suspicion is high, a colonoscopy with proximal biopsies can be considered (21).

Aphthous ulcers, cobblestoning, and large, deep and/or irregular ulcers, often with discontinuous or skip lesions, are common in Crohn’s disease (22). Endoscopic findings in ulcerative colitis include granularity of the mucosa, friability, edema, erythema and loss of vascular pattern in mild cases, and frank ulceration in moderate to severe cases. The inflammation is contiguous and circumferential, typically beginning in the rectum and continuing proximally. If the entire colon is not involved, there is often an abrupt transition to normal mucosa. Histologically, colonic biopsies in IBD may reveal acute or chronic inflammation, including crypt abscesses, and chronic architectural changes including branching of crypts, atrophy of glands, and loss of mucin in goblet cells. In quiescent
IBD, the inflammatory component may be lacking, but the architectural changes often persist.

Serologic Markers

Presently, there are no definitive serologic tests for microscopic colitis. The combination of pANCA and ASCA tests may help in distinguishing Crohn’s disease from ulcerative colitis, although the sensitivity and specificity of these tests are currently not sufficient for them to be diagnostic on their own.

Elevated sedimentation rate and a positive antinuclear antibody or other autoimmune markers have been reported in some patients with microscopic colitis (2). However, there currently is no serologic marker that is pathognomonic for microscopic colitis.

The most commonly used antibody tests for diagnosing patients with IBD are antineutrophil cytoplasmic antibodies (pANCA) and anti-Saccharomyces cerevisiae antibodies (ASCA). The combination of these tests has been proposed as a means for diagnosing IBD and distinguishing Crohn’s disease (ASCA+, pANCA–) from ulcerative colitis (pANCA+, ASCA–) (23). However, the sensitivity and specificity of these markers is relatively low, and many patients have either or both tests positive or negative. Furthermore, the accuracy of these tests for categorizing patients with clinically indeterminate colitis is suboptimal (24). Many other serologic tests are being studied in IBD, and future diagnostic algorithms will likely include a panel of serologic tests and other biomarkers.

Pathophysiology and Risk Factors

The pathogenesis of microscopic colitis and IBD is unknown. Several lines of evidence are consistent with a genetic predisposition. On the other hand, there are only a few cases reported of familial microscopic colitis. Crohn’s disease is more common in smokers while ulcerative colitis is more common in non-smokers. Some cases of microscopic colitis seem to be related to acute gastroenteritis or certain medications.

Several potential pathophysiological mechanisms have been suggested in microscopic colitis. These include immune dysregulation, autoimmunity, hormonal influences, genetics/familial association, infection, bile acid malabsorption, a reaction to undefined luminal antigens (2), and in some cases, medication effect (25). However, the majority of these data come from small studies that often have discordant results, and thus, at present, the pathogenesis of microscopic colitis is largely unknown. Two clear risk factors for microscopic colitis are increasing age (in lymphocytic and collagenous colitis) and female gender (for collagenous colitis) (1).

A number of risk factors have been identified in IBD, including race, genetic susceptibility, and cigarette smoking. In addition to the increased incidence of ulcerative colitis and Crohn’s disease in patients of Jewish descent, IBD tends to run in families (26). Furthermore, monozygotic twins have a higher concordance for IBD than dizygotic twins (27), all consistent with a genetic predisposition. Linkage studies of members of multiply-affected kindreds have identified a number of genomic areas of linkage in IBD, suggesting that several genes may contribute to disease susceptibility. The best characterized of these putative IBD genes (“IBD1”) is the gene for NOD2 (28). Smoking has different effects on IBD. Crohn’s disease is more common in smokers, while ulcerative colitis is more common in non-smokers and ex-smokers (29,30).

TREATMENT

The evidence base for treatments in IBD is much larger than in microscopic colitis, and expanding at a much greater rate. Some therapies are effective for both microscopic colitis and IBD (e.g. prednisone and budesonide) while others seem to be more specific for microscopic colitis (e.g. bismuth subsalicylate) or IBD (e.g. infliximab). Surgery is rarely necessary for microscopic colitis. In IBD, surgery is often necessary for medically refractory disease or for complications.

In microscopic colitis, very few randomized controlled treatment trials have been reported. A treatment algorithm has been proposed (21) and will be reviewed briefly. NSAIDs and agents that might exacerbate diarrhea (e.g., excess caffeine, alcohol, dairy products) should be discontinued. Non-specific antidiarrheal therapy, such as loperamide or diphenoxylate/atropine can be effective and well tolerated, and is often the first therapy prescribed, particularly in mild cases. If these agents are unsuccessful, bismuth subsalicylate is benefi-
cial in many patients. Diarrhea that fails to respond to bismuth is sometimes treated with mesalamine, sulfasalazine or cholestyramine, but these are often not very effective. If diarrhea is refractory to these agents, corticosteroid therapy may be initiated. However, there is a high rate of recurrence after discontinuation of steroids, with many patients becoming steroid dependent. Thus, before starting steroids, the diagnosis should be re-evaluated and alternative diagnoses, such as coexistent celiac sprue or hyperthyroidism, should be excluded if not done already. Budesonide is a synthetic steroid with low systemic bioavailability and less risk of steroid side effects and has been proven effective in collagenous colitis in three randomized controlled trials (31), and also appears to be effective in lymphocytic colitis. For steroid refractory or steroid dependent patients, immune modifiers such as azathioprine or 6-mercaptopurine can be used, although side effects are frequent and may be treatment limiting in some patients. Some clinicians are gaining experience with the long-term use of low-dose budesonide for the treatment of steroid-dependent microscopic colitis. Surgery is rarely necessary for medically refractory disease.

Management of IBD has been reviewed recently and will not be discussed in detail here (12). The main goals of IBD treatment are relieving symptoms and controlling inflammation. Aminosalicylates have remained the main treatment for induction and maintenance of remission in patients with mild to moderately active ulcerative colitis, but their value in Crohn’s disease has recently come into question. Corticosteroids are commonly used when 5-ASA compounds fail. Topical corticosteroids or mesalamine, in the form of suppositories or enemas, can be used for ulcerative proctitis or distal ulcerative colitis. Oral steroids are used for moderately severe ulcerative colitis or Crohn’s disease. In patients with ileal or ileocolonic disease, enteric-coated budesonide is an attractive option due to its high potency but limited side effects.

Intravenous steroids are used for patients who do not respond to oral steroids and for severe disease requiring hospitalization. Immunosuppressive drugs such as azathioprine, 6-mercaptopurine and methotrexate, are used for steroid refractory or steroid dependent patients, and in most who require steroids for induction. Infliximab, an anti-TNF monoclonal antibody, is effective for induction and maintenance of remission in patients with inflammatory and fistulizing Crohn’s disease, and was recently shown to be effective in patients with ulcerative colitis. Although medical therapy is central to the management of IBD, many patients require a surgical procedure during the course of their disease, often for intestinal obstruction and failure to respond to medical therapy (32–35).

**SUMMARY**

Microscopic colitis is a disease characterized by chronic, watery diarrhea, while diarrhea is usually bloody in ulcerative colitis and bloody or watery in Crohn’s disease. Abdominal pain is common in microscopic colitis and IBD. Systemic manifestations, such as fever and aphthous mouth ulcers, are uncommon in microscopic colitis but common in IBD. Perianal and fistulizing conditions are seen almost exclusively in Crohn’s disease.

The clinical course and natural history of microscopic colitis is relatively benign and the disease is not associated with increased mortality or risk for colorectal cancer. On the other hand, IBD is characterized by recurrent episodes of inflammation, often associated with morbidity, and complications can lead to serious consequences. Crohn’s colitis and ulcerative colitis are both associated with increased risk for colorectal cancer. Some therapies are effective for both microscopic colitis and IBD, while others seem to be more specific for microscopic colitis or IBD, based on currently available data.

**References**


