

Microscopic Colitis

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Abstract

Microscopic colitis is an idiopathic chronic inflammatory bowel disease presenting with watery diarrhea. While colonoscopy and radiology findings are normal, the colon shows striking pathologic findings, including lymphocytic colitis and collagenous colitis. The clinical course is usually benign with sustained remission. Recent medical evidence shows that bismuth and budesonide are effective treatments.

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Microscopic colitis is a chronic inflammatory bowel disease of unknown origin with well-defined histologic criteria in association with a clinical picture of chronic non-bloody watery diarrhea and a normal colonoscopy [1–5]. Microscopic colitis includes two forms based on strict histopathology criteria: lymphocytic colitis, characterized by the presence of intraepithelial lymphocytes numbering more than 20 per 100 epithelial cells and a mononuclear inflammatory infiltrate of the lamina propria [6–8], and collagenous colitis that typically shows a subepithelial collagen band of at least 10 μ with a mononuclear infiltrate in the lamina propria [6–8].

Epidemiology

Microscopic colitis accounts for 4–13% of patients investigated for chronic diarrhea, with a female predominance, occurring typically in the sixth and seventh decades of life [9]. In Europe lymphocytic colitis has a yearly incidence of 3.1/100,000 and a prevalence of 14.4/100,000, while the incidence and prevalence of collagenous colitis are 0.6–2.3/100,000 and 10–15.7/100,000 respectively [10]. In Israel there are no epidemiologic data on microscopic colitis.

Pathophysiology

Lymphocytic colitis and collagenous colitis are disorders of unknown etiology. The mechanism of diarrhea in collagenous colitis was recently investigated using human colonic biopsy specimens in a miniaturized Ussing chamber. It was shown that reduced net sodium and chlorine absorption is the predominant cause of diarrhea. This is accompanied by a secretory component of electrogenic chloride secretion [11,12]. Thickening of the collagenous band has been reported secondary to the use of medications like non-steroidal anti-inflammatory drugs [13], lansoprazol [14], ticlopidine [15], simvastatin [16], carbamazepine [16] and paroxetine [16]. It was also found to be associated with colonic infections, celiac disease, autoimmune thyroid disease and diabetes mellitus [4,5,16–18]. With regard to lymphocytic colitis,

the mechanism of diarrhea is unclear although retrospective data might suggest an infectious cause [16].

Clinical presentation

Microscopic colitis is characterized by chronic or intermittent watery non-bloody diarrhea, usually accompanied by abdominal cramping, anorexia and mild weight loss, without fever, habitually in females in their late fifties to early sixties [16,19–22]. It presents acutely in 40% and is insidious in 60% of cases [20–22].

Blood count and chemistry analyses are usually normal. Fecal leukocytes are seen in half the cases and the anti-endomysial antibody test for celiac disease is positive in up to 17% of patients. Actually there is an association between microscopic colitis and celiac disease, with 2–10% of patients with microscopic colitis showing small bowel histology consistent with celiac disease [16,19–22].

Small and large bowel radiology studies are normal. At colonoscopy the colon typically appears normal, although non-specific abnormalities, like patchy erythema, edema and a few erosions, have been reported [21,22]. Biopsies should be taken especially from the right colon where the diagnostic yield is optimal due to a reported gradient in density of intraepithelial lymphocytes and collagen thickening from right to left colon [21,22]. However, distal sigmoid biopsies could be sufficient to support the diagnosis with less than 5% of misdiagnosis [21,22].

Microscopic colitis is a major cause of chronic diarrhea in older women

The natural history is similar in lymphocytic colitis and collagenous colitis, characterized by a benign course with spontaneous remission in 20% of cases and a long-term cessation of diarrhea in more than 70% of patients [19,20,22]. Prolonged clinical and histologic remission and no evidence of life-threatening diarrhea during a mean follow-up of 3 years have been demonstrated in prospective studies [23,24].

Histopathology

The *sine qua non* feature for the diagnosis of lymphocytic colitis is the increased density of intraepithelial lymphocytes in the surface compartment, greater than 20 per 100 surface epithelial cells, most of them CD8+ [1–6]. In addition, there is an epithelial injury with

localized areas of epithelial detachment and a mononuclear cell infiltrate of the lamina propria, predominantly CD4+. Neutrophil infiltration is rare. The key histologic feature for collagenous colitis is the presence of a thickened subepithelial collagen band 10–100 μ wide (normal collagen band thickness in the colon is less than 3 μ) [1–6]; additionally, there is the same lamina propria expanded mononuclear cell infiltrate.

Treatment

Patients should be reassured, since microscopic colitis has not been associated with increased mortality or severe deterioration. Furthermore, the diarrhea may resolve within weeks with or without treatment, although relapses can occur [16,22–24]. Large randomized controlled trials do not exist for the treatment of collagenous or lymphocytic colitis; as a result the management has been based on anecdotal evidence and common sense once the diagnosis has been established. Offending medications like non-steroidal anti-inflammatory drugs, lansoprazole, ticlopidine and others that might exacerbate the diarrhea should not be offered to the patient. Dietary modification, symptomatic therapy (i.e., loperamide), sulfasalazine, mesalamine, antibiotics, cholestyramine, and prednisone have been prescribed empirically [16,25,26]. Immunomodulators like azathioprine and 6-mercaptopurine have been used occasionally in refractory cases of microscopic colitis [27].

However, in the last few years consistent medical evidence has been accumulated based on controlled studies of bismuth

compared with 21% in the placebo control (3 of 14 patients) after 8 weeks of placebo-controlled trial with budesonide (9 mg/day) [31]. The last randomized double blind placebo-controlled trial, published last year, of 20 patients affected with collagenous colitis, showed that the group treated with budesonide for 8 weeks experienced a significant clinical and histologic response in comparison to the placebo group [32].

A meta-analysis of the 94 patients with collagenous colitis, enrolled in the foregoing three trials treated with budesonide (9 mg

Bismuth subsalicylate and budesonide could be a good therapeutic option

daily or in a tapering schedule for 6 or 8 weeks), showed a pooled odds ratio for clinical response to budesonide treatment of 12.32 (95% confidence interval 5.53–27.46). The number needed to treat in order to achieve a clinical response to budesonide was two patients [33]. The effectiveness of any therapy for maintenance of remission has not been studied.

Conclusions

A colonoscopy with random sampling biopsies is the most important tool in the diagnostic evaluation of patients with unexplained diarrhea in order to rule out microscopic colitis, and the physician should be aware that despite a colonoscopically normal mucosa, significant pathology may be revealed by biopsies.

We suggest that all offending drugs be withdrawn, and that antidiarrheal therapy be initiated (such as loperamide) as a first and simple line of treatment. If there is no clinical response, bismuth subsalicylate should be given for 8 weeks. Patients with no improvement should be treated with budesonide, 9 mg/day, as an effective option with rare side effects, for a short period of 6 to 8 weeks. In cases refractory to the above-mentioned drugs a trial with immunomodulating agents, such as azathioprine or 6-mercaptopurine, might be of benefit but this requires a controlled trial.

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The diagnosis is exclusively based on histology grounds and colonic biopsies are essential

subsalicylate [28,29] and budesonide [30–32]. Fine and Lee [28], in an open-label study with bismuth subsalicylate for 8 weeks in patients with lymphocytic colitis, reported a clinical remission in 85% of patients and a histologic response in 75% of cases with an outstanding safe profile. These results were confirmed in a subsequent trial in which 14 patients were randomly assigned to receive bismuth subsalicylate (three 262 mg chewable tablets three times daily) or placebo for 8 weeks [29]. Compared to placebo, treatment was associated with a significant decrease in stool frequency and weight, with improvement in consistency. In addition, colonic histology improved more often in treated patients (57% versus 17%) and returned to normal in two patients [29].

More recently, three randomized double-blind placebo-controlled trials on the efficacy of budesonide in collagenous colitis have been published [30–32]. One trial with a dose of 9 mg/day for 6 weeks showed a significant clinical response of 86.9% in the budesonide group versus 13.6% in the placebo group, intention-to-treat of 76.9% versus 12%, respectively, and histologic improvement in 60.9% of the patients who received budesonide vs. 4% in the placebo control, without serious adverse event [30]. The second trial showed a statistically significant clinical improvement, with an intention-to-treat of 57% in the budesonide group (8 of 14 patients)

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I hate flowers – I paint them because they're cheaper than models and they don't move

Georgia O'Keefe (1887-1986), U.S. artist and pioneer of American abstract art

Capsule

Fast-acting thyroid hormone

In vertebrates, thyroid hormone is needed for normal physiology and development. Although thyroid hormone is known to regulate transcription via thyroid hormone receptors, there is a puzzling temporal aspect of hormone effects. Signaling to the nucleus has been shown to operate on the order of days; however, with exposure to thyroid hormone, rapid effects have been seen *in vivo*. Scanlan et al. synthesized several thyroid hormone analogs and examined their potencies. One of the thyronamine derivatives, TIAM, occurs naturally in the brains of vertebrates. When injected intraperitoneally, it caused hypother-

mia and inactivity in mice. Cardiovascular performance was also affected: In an *ex vivo* heart model, injection of TIAM produced a rapid reduction in cardiac output. In contrast to prior understanding of thyroid hormone function through regulation of expression, these results support a model in which thyroid hormone response is mediated on a much shorter time scale by differential processing of thyroid hormone and by signal transduction via G protein-coupled receptors.

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