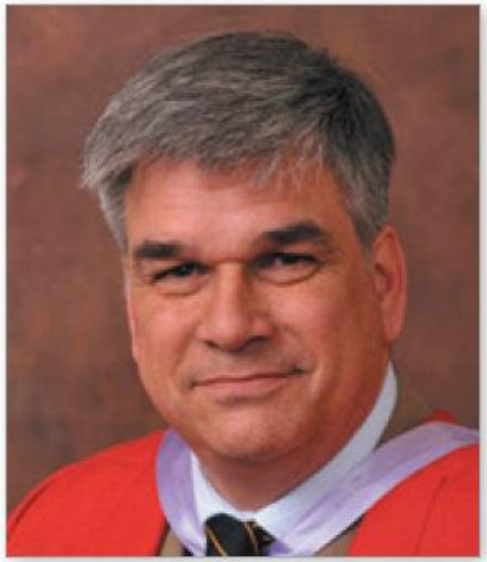

Professor Michael Schultz

Professor

Gastroenterologist and

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Sunday, August 11, 2019

(Room 10)

8:30 - 9:25 WS #154: Case Studies in Gastroenterology

9:35 - 10:30 WS #164: Case Studies in Gastroenterology (Repeated)

Microscopic colitis

Michael Schultz

Case

- 74 year old female patient, Mrs BC
- Seen in gastro clinic in February
- Noticed change in bowel habit since before Christmas
- 3 months history of abdominal pain with urgency to go to toilet and diarrhoea twice/day
- No blood in bowel motion
- Abdominal pain improved after passing bowel motions
- Background of SVT, HTN, Asthma
- Regular meds included Verapamil 120 mg daily, Inhibace plus daily, Aspirin 100 mg daily, Cholecalciferol 1.25 mg monthly, Symbicort inhaler

Investigations

- Stool PCR Negative including for *C. diff.*
- Normal Hb of 135g/L, Ferritin of 209, CRP of 1mg/L, normal LFT's
- Normal Thyroid function tests, negative Coeliac serology, normal B12/folate
- Faecal calprotectin < 16
- Differentials at this stage were microscopic colitis, IBD, diarrhoea predominant IBS
- Referred for flexible sigmoidoscopy with biopsies

Flexible sigmoidoscopy

- Flexible sigmoidoscopy done in March 2019. The entire examined colon appeared normal. Biopsies taken from left colon for histology
- Histology reported as showing large intestinal mucosa with normal crypt architecture and an increase in intraepithelial lymphocytes in the surface epithelium. There was no evidence of granulomata, dysplasia or malignancy. Diagnosis of lymphocytic colitis.

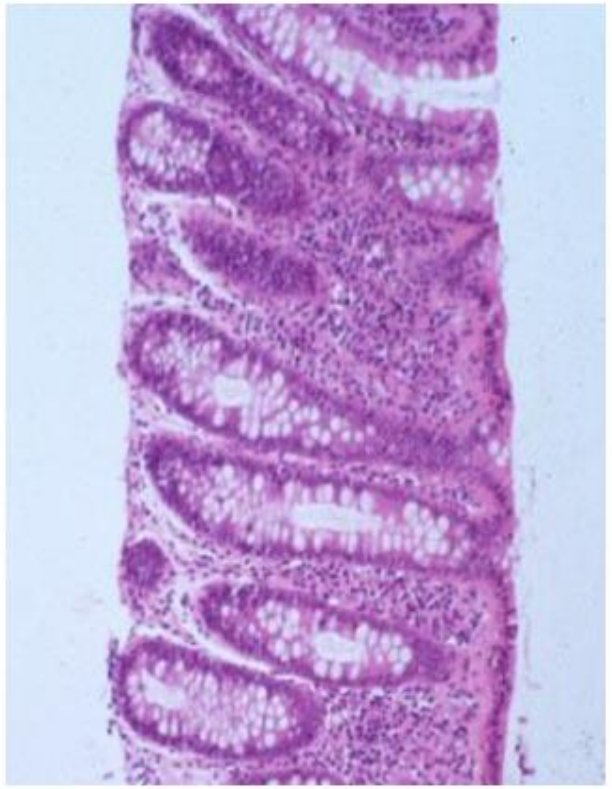
Treatment

- Budesonide 9mg od started in April 2019. Prior to starting treatment, patient was now down to 1 episode of watery diarrhoea per day
- She was on Budesonide 9mg od for 4 weeks but dose reduced to 6mg daily by GP as she had elevated BP and anxiety symptoms
- Patient seen in clinic again in June 2019
- Her bowel motions have normalized now to 1 formed bowel motion daily
- Already on budesonide for 14 weeks
- Plan made to reduce Budesonide to 3mg for 2 weeks then stop

Microscopic colitis

- Chronic inflammatory disease of the colon that is characterized by chronic, watery, non-bloody diarrhoea
- Typically occurs in middle-aged patients and has a female preponderance
- The colon appears typically normal or almost normal on colonoscopy
- Diagnosis is established by biopsy of the colonic mucosa demonstrating characteristic histologic changes.
- 2 main histologic subtypes, lymphocytic colitis and collagenous colitis

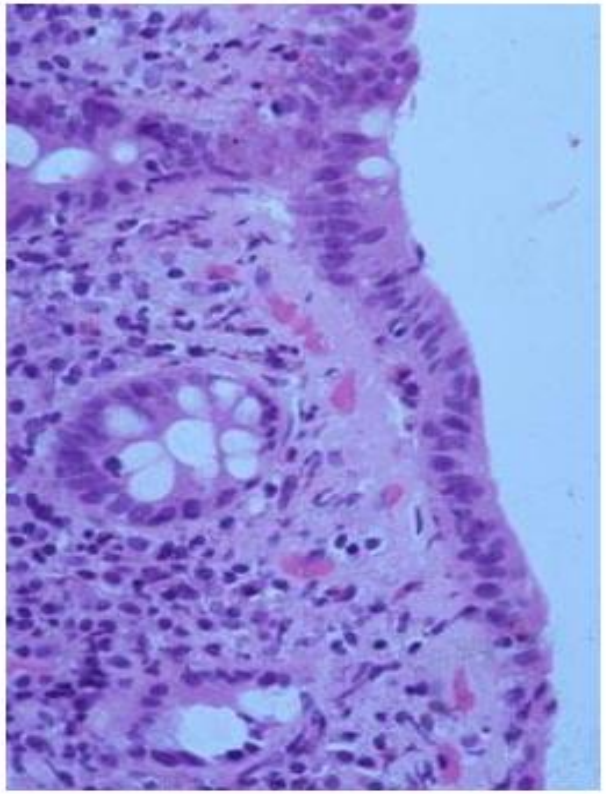
Lymphocytic colitis



Lymphocytic colitis (LC) showing marked chronic inflammatory cell infiltrate of the surface epithelium (on right) with preservation of crypt architecture. Subepithelial collagen layer is not thickened.

Lymphocytic colitis is characterized by ≥20 intraepithelial lymphocytes (IEL) per 100 surface epithelial cells. Crypt architecture is usually not distorted, but focal cryptitis may be present

Collagenous colitis



Collagenous colitis is characterized by a colonic subepithelial collagen band >10 micrometres in diameter. The band is most evident between the crypts.

Collagenous colitis (CC) showing similar inflammatory cell infiltration as in lymphocytic colitis (LC), with the characteristically thickened subepithelial collagen layer.

Microscopic colitis

- Estimated incidence of collagenous colitis and lymphocytic colitis are 2.0 to 10.8 and 2.3 to 16 per 100,000 per year respectively
- The median age at diagnosis is approximately 65 years
- Approximately 25 percent of patients are diagnosed before the age of 45 years.
- Rare in children
- Higher incidence in women
- Female preponderance appears to be more pronounced in collagenous as compared with lymphocytic colitis (female-to-male incidence rate ratios, 3.0 and 1.9, respectively)

Microscopic colitis

- Associated with several other diseases with autoimmune background (eg, autoimmune thyroiditis, type 1 diabetes mellitus, and non-erosive, oligoarticular arthritis)
- Concomitant autoimmune diseases were more common in patients with collagenous colitis as compared with lymphocytic colitis (53 versus 26 percent)
- Patients with coeliac disease have an increased risk of microscopic colitis, limited data suggests that the prevalence of celiac disease is relatively low among patients with microscopic colitis
- Prevalence of coeliac disease-like changes in the small bowel of patients with microscopic colitis ranges from 2 to 9 percent
- In rare cases, concurrent microscopic colitis has been reported in patients with inflammatory bowel disease, especially with ulcerative colitis, or vice versa

Natural history

- Microscopic colitis has a chronic, intermittent course in most patients
- Diarrhoea may resolve within weeks with or without treatment, but relapses are common (approximately 30 to 60 percent)
- The long-term course of patients with lymphocytic colitis may be more favorable than with collagenous colitis
- Microscopic colitis has not been associated with an increased risk of colorectal cancer

ETIOLOGY AND RISK FACTORS

- NSAIDs have been implicated as being causative or triggering flares of microscopic colitis
- Several other drugs have also been implicated as potential causes of microscopic colitis, including proton pump inhibitors (PPIs), specifically lansoprazole, statins, selective serotonin reuptake inhibitors (SSRI's) and other drugs, (eg, pembrolizumab)
- Concomitant use of PPIs and NSAIDs may increase the risk even further
- Cigarette smoking (past or present) was associated with a significantly increased risk of microscopic colitis

Assessment of the level of likelihood that a specific drug can trigger microscopic colitis

High likelihood	Intermediate likelihood	Low likelihood
Acarbose	Carbamazepine	Cimetidine
Aspirin and NSAIDs	Celecoxib	Gold salts
Clozapine	Duloxetine	Piascledine
Entocapone	Fluvastatin	
Flavonoid*	Flutamide	
Proton pump inhibitors	Oxetorone	
Ranitidine	Madopar	
Sertraline	Paroxetine	
Ticlopidine	Simvastatin	
	Stalevo¶	

Pathogenesis/ Mechanism of diarrhea

- The pathogenesis of microscopic colitis is unclear; however, it is likely to be multifactorial, involving mucosal immune responses to luminal factors in a genetically predisposed individual
- Diarrhoea in microscopic colitis is likely caused by mucosal inflammation
- However, concurrent bile acid malabsorption frequently coexists in patients with collagenous colitis.
- The severity of diarrhoea correlates with the inflammatory changes in the lamina propria and not with collagen band thickening.
- Element of secretory diarrhea and osmotic component

Clinical presentation

- Patients with microscopic colitis usually have between four and nine watery stools per day, but in rare cases, bowel movements can exceed 15 or up to 2 liters per day
- Onset of diarrhoea is often insidious, but sudden onset was reported in approximately 40 percent of patients
- Patients may have associated faecal urgency (70 percent), incontinence (40 percent), and nocturnal episodes (50 percent)
- Abdominal pain occurs in up to 50 percent of patients with active microscopic colitis (≥3 stools or ≥1 watery stool per day)

Diagnostic approach

- Colonoscopy with separate sampling of the right and left colon
- Rationale for performing colonoscopy rather than a more limited evaluation of the left colon with flexible sigmoidoscopy is that microscopic colitis can be patchy. The severity of histologic changes also declines from the proximal to the distal colon
- However, flexible sigmoidoscopy will diagnose more than 90 percent of microscopic colitis

Initial approach to management

- Patients should be advised to avoid NSAID drugs and if possible discontinue medications associated with microscopic colitis
- Smoking cessation if smoker
- Antidiarrheal agent loperamide in patients with mild disease (<3 stools daily and no watery stool daily) or in conjunction with other therapies based on the severity of symptoms

Management

- The primary goal of management in patients with microscopic colitis is to achieve clinical remission (<3 stools per day and no watery stool) and to improve the patient's quality of life
- Active disease is defined ≥3 stools daily or ≥1 watery stool daily
- It is unclear if histologic remission is necessary
- In patients with active disease (≥3 stools daily or ≥1 watery stool daily) or diarrhoea that persists despite the use of anti-diarrhoeal, we recommend the addition of budesonide (9 mg daily for six to eight weeks).
- Budesonide is a locally active corticosteroid with extensive first-pass metabolism in the liver and low systemic exposure

Budesonide

- Can continue budesonide for at least eight weeks and then gradually taper budesonide in patients in clinical remission (<3 stools daily and no watery stools).
- Can taper budesonide to 6mg for two weeks, followed by 3mg for another two weeks, and then discontinue therapy.
- Symptomatic improvement can be seen within a few days. However, complete resolution usually requires six to eight weeks or longer.
- In patients who are not in clinical remission at eight weeks, or if symptoms recur on tapering, the budesonide dose of 9 mg can be continued for 12 weeks or longer before tapering the dose.

Prednisone

- Reserve the use of prednisone for the treatment of microscopic colitis in patients in whom budesonide therapy is not feasible.
- Compared with budesonide, prednisone is associated with a lower response rate (53 versus 83 percent), more side effects, and a higher risk of relapse when therapy is withdrawn

Mild persistent symptoms despite glucocorticoids

- In patients with mild, persistent diarrhoea despite budesonide, could try use concomitant therapy with loperamide and cholestyramine (4g four times per day).
- In patients with an improvement in diarrhoea, to continue cholestyramine until the diarrhoea resolves
- Cholestyramine is a bile acid binding resin that is used to treat diarrhoea that is due to concurrent bile acid malabsorption in patients with microscopic colitis

Other treatment options

- In patients who fail to respond to a two-week trial of cholestyramine, another option is to use bismuth subsalicylate (three 262 mg tablets three times daily)
- Mesalamine previously used as treatment option but studies seem to indicate it is ineffective in the treatment of collagenous colitis and lymphocytic colitis
- Reserve the use of Anti-TNF agents for microscopic colitis that is refractory to a combination of budesonide, anti-diarrhoeal's, cholestyramine and/or bismuth salicylate once other causes of diarrhoea have been excluded.
- Reserve surgery for patients with microscopic colitis that is refractory to medical therapy
- Patients with recurrent symptoms after an initial response to budesonide can be retreated with budesonide as maintenance therapy at the lowest dose that maintains clinical remission.

Conclusion

- Microscopic colitis should be suspected in a patient with chronic non-bloody diarrhoea, particularly in middle-aged and older adults
- Microscopic colitis has a female preponderance, mean age 65
- Associated with NSAIDS's, SSRI's, PPI use
- 2 main subtypes-Collagenous and Lymphocytic colitis
- Active disease (≥3 stools daily or ≥1 watery stool daily) is indication to treat
- Budesonide is treatment of choice
- If no response, try concomitant therapy with cholestyramine

Conclusion

- If the combination of budesonide and cholestyramine not effective, could try trial of bismuth subsalicylate
- Anti-TNF agents for microscopic colitis that is refractory to a combination of budesonide, anti-diarrhoeals, cholestyramine and/or bismuth subsalicylate once other causes of diarrhea have been excluded.
- Surgery reserved for patients with disease refractory to medical therapy
- Relapses are common (approximately 30 to 60 percent)
- Patients with recurrent symptoms after an initial response to budesonide can be retreated with budesonide as maintenance therapy at the lowest dose that maintains clinical remission.

References

- UpToDate
- American Gastroenterological Association Institute guidelines on the management of microscopic colitis