ADVANCES IN ENDOSCOPY

Current Developments in Diagnostic and Therapeutic Endoscopy

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Endoscopic Evaluation of Microscopic Colitis

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G&H What is microscopic colitis?

SB Microscopic colitis generally refers to the finding of certain inflammatory changes in biopsy specimens of endoscopically normal-appearing colon. With the widespread use of colonoscopy, microscopic colitis was first recognized in the 1970s and is now an important consideration in evaluating patients with chronic diarrhea. There are 2 main types of microscopic colitis: lymphocytic colitis and collagenous colitis. The salient pathology findings are illustrated in the Figure. It is not clear whether microscopic colitis should be considered part of the spectrum of inflammatory bowel disease (IBD), but the fundamental concept of a perpetuated abnormal response to luminal antigens is shared.

G&H How should biopsy specimens be obtained when looking for microscopic pathology in a normal-appearing colon?

SB The data suggest that flexible sigmoidoscopy is often inadequate to diagnose microscopic colitis and that advancing to the more proximal colon is important. Ideally, a full examination, including intubation of the terminal ileum, should be performed.

There are several reasonable strategies for where to obtain specimens. The key take-home point is that the right and left colons are different. Their embryologic origin differs, and a normal finding in the right colon may be an abnormal finding in the left colon. The transition from right to left colon is in the distal third of the transverse colon, so my standard approach is to obtain 6 specimens in the ascending/proximal transverse colon and put them in a jar labeled "right colon" and 6 specimens from the distal transverse/descending/sigmoid colon and put them in a jar labeled "left colon." I use the hepatic and splenic flexures as landmarks for the proximal and distal transverse colons and generally avoid the mid–transverse colon.

There is debate as to whether specimens from the rectum require their own jar; I generally obtain 4 specimens and put them in a jar labeled "rectum." I do not generally take specimens from a normal-appearing cecum because cryptitis is common in this site in asymptomatic patients.

It is inadvisable to take random specimens throughout the colon and put them into a single jar. For example, Paneth cells are part of the innate immune system in intestinal crypts. These cells are considered to be a normal finding in the small bowel as well as in the right colon. However, when found in the left colon, these cells are considered to be a metaplastic change that demonstrates chronic inflammation.

Another example involves collagenous colitis, which is diagnosed by assessing the thickness of the collagen layer. In collagenous colitis, the subepithelial collagen band is at least 10 μm, as opposed to a normal band, which is less than 3 μm. There are also characteristic inflammatory changes in the lamina propria. The collagen band may be thickened throughout the colon, but analyses have shown that the collagen band may also be thickened only in the right colon, beyond the reach of the sigmoidoscope.

G&H What testing is required before proceeding to a colonoscopy with biopsy in patients who have unexplained diarrhea, including microscopic colitis?

SB Conventional testing for chronic diarrhea is addressed in guidelines from both gastroenterology and

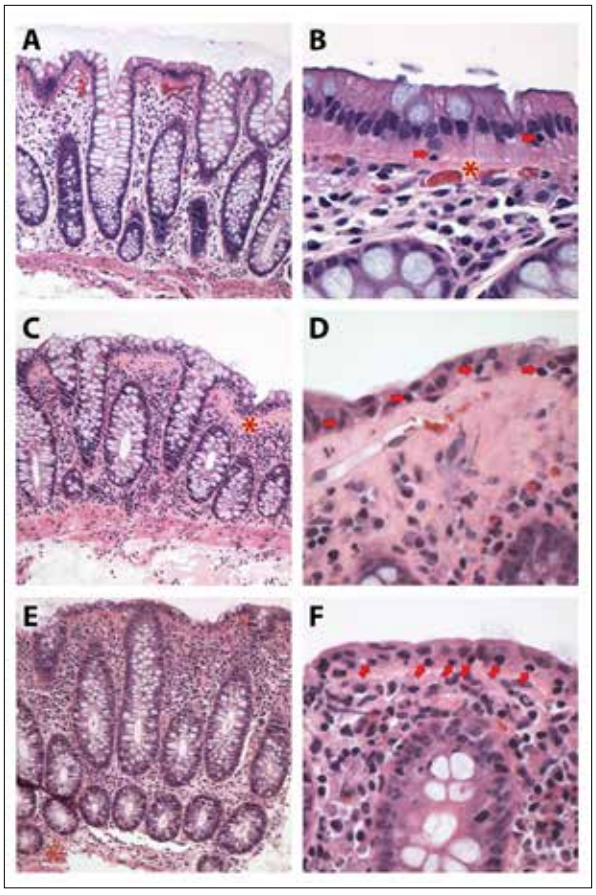

Figure. Panels **A** and **B** show a normal colon with typical numbers of mononuclear inflammatory cells in the lamina propria, most of which are concentrated in the superficial portion of the mucosa. The basement membrane (asterisk, panel **B**) is barely discernible as a smooth line of collagen below the surface epithelium, which does not encircle capillaries or inflammatory cells. There are only widely scattered intraepithelial lymphocytes (arrows, panel **B**). Panels **C** and **D** show an example of collagenous colitis. There are increased numbers of lymphocytes, plasma cells, and eosinophils in the lamina propria, including at the base of the mucosa. There is a band of collagen of increased thickness below the surface epithelium (asterisk, panel **C**). The collagen fibrils encircle surface capillaries and entrap inflammatory cells (best seen in panel **D**). The surface epithelium is injured, becoming flattened or cuboidal, and has increased numbers of intraepithelial lymphocytes (arrows, panel **D**). Panels **E** and **F** show an example of lymphocytic colitis. The lamina propria has an increased number of lymphocytes and plasma cells. There is no increase in subepithelial collagen, but the surface epithelium is injured, with flattened to cuboidal morphology, and there is a marked increase in intraepithelial lymphocytes (arrows, panel **F**). (Panels **A**, **C**, and **E**: hematoxylin and eosin, ×100 magnification. Panels **B**, **D**, and **F**: hematoxylin and eosin, ×400 magnification.)

Figure courtesy of Christopher Moskaluk, MD, PhD, University of Virginia, Charlottesville, Virginia.

primary care societies. A careful patient history is the first step. I have seen quite a few patients with diarrhea caused by sorbitol found in elixir medications, sugar-free gums, and candies, and many of these patients had gone through considerable workup before referral. Nocturnal symptoms support organic causes of diarrhea rather than irritable bowel syndrome. Therefore, it is important to note any over-the-counter and prescription medicines being taken by the patient, particularly laxative agents, such as magnesium supplements, and medications that commonly cause diarrhea, such as colchicine.

If microscopic colitis is found, a detailed medication history can help determine which drugs may need to be discontinued or replaced with other agents. The most common medications associated with microscopic colitis include nonsteroidal anti-inflammatory drugs, proton pump inhibitors, and selective serotonin reuptake inhibitors. It is also worth mentioning that olmesartan has been associated with spruelike enteritis, which can be associated with microscopic colitis.

Stool studies are noninvasive and should generally precede endoscopic tests. Few infections commonly cause chronic diarrhea, but the most notable are *Clostridium difficile* and *Giardia*. Clinicians usually use an ultrasensitive polymerase chain reaction for the former and a *Giardia* fluorescent antibody test for the latter. Ordinary testing for ova and parasites has unacceptably high false-negative rates for *Giardia.*

The patient's history should guide whether other tests are warranted. For example, serologic testing for celiac disease may be warranted in a patient with type 1 diabetes, and fecal elastase testing may be appropriate when pancreatic disease is suspected. This latter study should not be performed on overly watery stool because the enzyme level may be falsely low from dilution. It is also important to recognize that diarrhea is a frequent presenting symptom of HIV infection.

The fecal markers conventionally used for detecting intestinal inflammation in IBD (calprotectin and lactoferrin) do not appear to be useful in microscopic colitis, but fecal lactoferrin is more useful than stool leukocytes when one is looking for inflammatory diarrhea and is a routine part of the initial evaluation.

G&H Can microscopic colitis be patchy rather than diffuse? If so, how does this affect the biopsy strategy?

SB Absolutely. This is the underpinning of why samples are placed in separate jars and why a full colonoscopy should be performed rather than a sigmoidoscopy when diarrhea is being investigated. Some microscopic changes may be found only in the more proximal colon and, thus,

may not be detected when biopsy specimens are taken only from the sigmoid or descending colon.

G&H What is the connection between celiac disease (gluten enteropathy) and microscopic colitis? Does the finding of lymphocytic colitis in a patient with known celiac disease make a diagnosis that can and should be treated?

SB There is a significant prevalence of microscopic colitis in patients with celiac disease. Generally, the association comes up when the finding of lymphocytic colitis triggers clinical suspicion of celiac disease. Microscopic colitis has been suggested as a possible distinct entity in patients whose celiac disease does not respond to a gluten-free diet. In this setting, eliminating classic offending medications (ie, nonsteroidal anti-inflammatory drugs, selective serotonin reuptake inhibitors, and proton pump inhibitors) makes sense. That being said, diet or compliance issues are the most common reasons for refractory celiac disease.

G&H Are there any data to suggest that techniques other than standard "pinch" biopsy can increase the diagnostic yield of microscopic colitis?

SB There are limited data on the use of indigo carmine to identify endoscopic changes in microscopic colitis; vital staining may then allow targeted biopsies. There are also reports of real-time diagnosis using confocal microscopy. This modality holds promise, but the current costs of fixed and disposable components make it more of a research tool at this point. I do not think that cytologic brushing or large-particle biopsies with a snare are useful, and although there may be advantages to using jumbo forceps, their use is not considered mandatory.

G&H Will capsule endoscopy have a role in the detection of microscopic colitis in the future?

SB I believe that wireless capsule endoscopy will continue to advance in both its optics and ability to obtain specimens. Capsule endoscopy was developed around 1990 and went from being obscure to being commonplace nowadays. In 2014, the US Food and Drug Administration cleared a colon capsule, PillCam Colon (Given Imaging). The main issue seems to be how soon capsules will be equipped to offer confocal images and/or be able to acquire targeted biopsy specimens. I would speculate that these advances will occur in the next few years and will probably reach common use in 5 to 10 years.

G&H What are the next steps in research in this area?

SB As with IBD, a surge of attention is being given to the microbiome in patients with microscopic colitis. Alteration of the microbiome has been invoked as a possible intermediate reason why the drugs associated with this condition may not only act as direct antigens but also bring about other changes. I think that the concept of an exposome is useful because it means looking at more than just the flora to include environmental exposures, such as microparticles or nanoparticles, that are encountered.

Another area under investigation consists of biomarkers, specifically fecal eosinophil protein X, fecal eosinophil cationic protein, and secretoneurin.

Dr Bickston has no relevant conflicts of interest to disclose.

Suggested Reading

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