

Colitis nucleomigrans

Microscopic colitis (MC), encompassing collagenous colitis and lymphocytic colitis, is featured by chronic diarrhea, normal-looking endoscopic findings and unique microscopic appearance. Tachibana, et al proposed the third type of MC termed colitis nucleomigrans (CN). Histopathological criteria of CN include: (i) chained nuclear migration to the middle part of the surface-lining columnar epithelium; (ii) apoptotic nuclear debris scattered below the nuclei; and (iii) mild/moderate chronic inflammation in the lamina propria. Among 33 patients (M:F = 20:13; median age 63 years, range 17-88) fulfilled the criteria, seven cases demonstrated MC-like clinical/endoscopic features. Mucosal reddening with or without erosion/aphtha was endoscopically observed in the remaining 26 cases with inflammatory bowel disease (IBD)-like features: occult/gross hematochezia seen in 19, abdominal pain in two and mucin secretion in two. Cleaved caspase-3-immunoreactive apoptotic debris appeared more frequently in IBD-like CN than in MC-like CN, while CD8-positive intraepithelial lymphocytes comparably appeared in both. Proton pump inhibitors (PPIs) were administered in five (71%) cases with MC-like features, and in three diarrhea improved after drug cessation. In IBD-like CN cases, eight (31%) received PPIs. Four patients received chemotherapy against malignancies. Four patients associated immune-related disorders. Microscopic appearance of CN also appeared in a remission state of ulcerative colitis (12/20 lesions). In addition, a localized form of CN is common, and presents with small mucosal elevation, corresponding to so-called hyperplastic mucosal nodule of the colon.

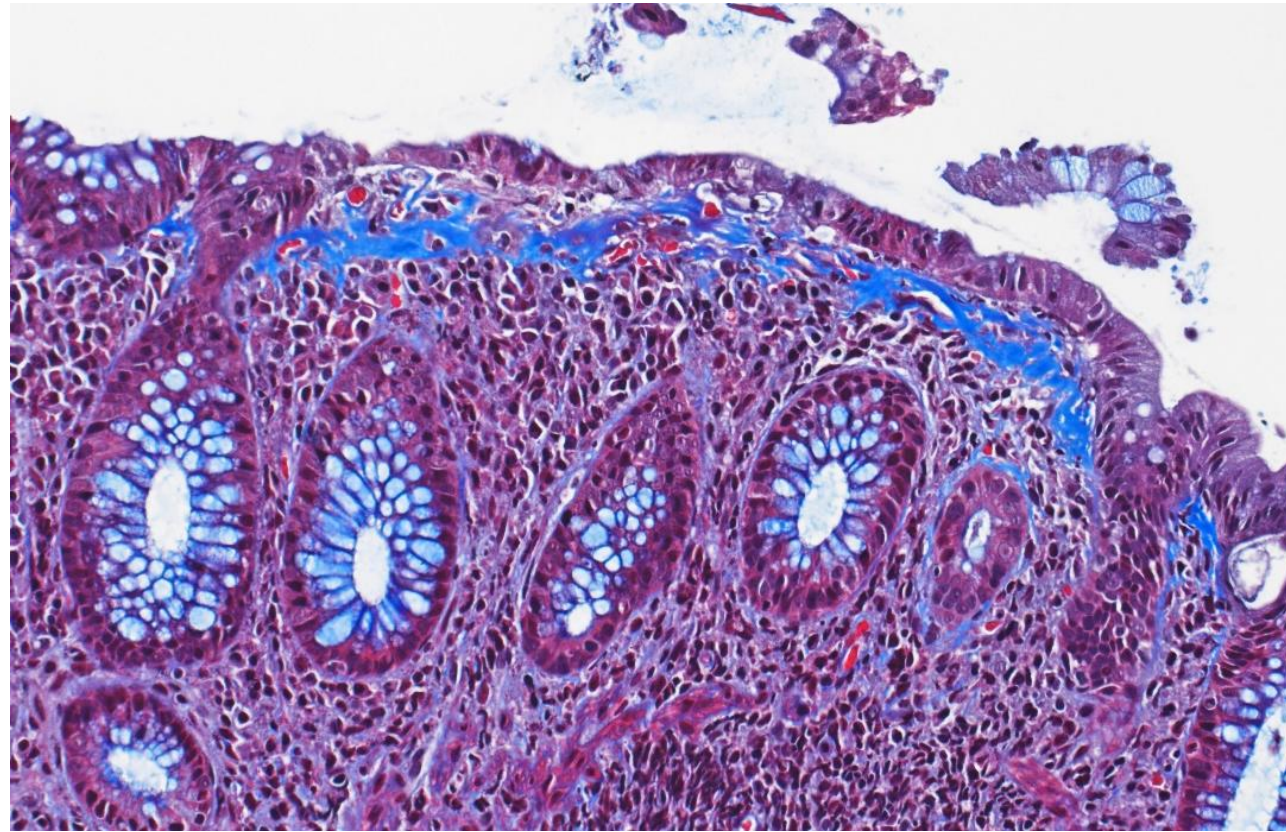
Ref.-1: Tachibana M, et al. Colitis nucleomigrans: The third type of microscopic colitis (part 1). *Pathol Int* 2020; 70(10): 752-760. doi: 10.1111/pin.12996

Ref.-2: Tachibana M, Tsutsumi Y. Colitis nucleomigrans: the third type of microscopic colitis (part 2). An ultrastructural study. *Pathol Int* 2020; 70(10): 761-766. doi: 10.1111/pin.12995

Ref.-3: Tachibana M, Tsutsumi Y. Colitis nucleomigrans: a proposal for the third type of microscopic colitis. *Arch Clin Med Case Rep* 2021; 5(2): 342-354. doi: 10.26502/acmcr.96550365

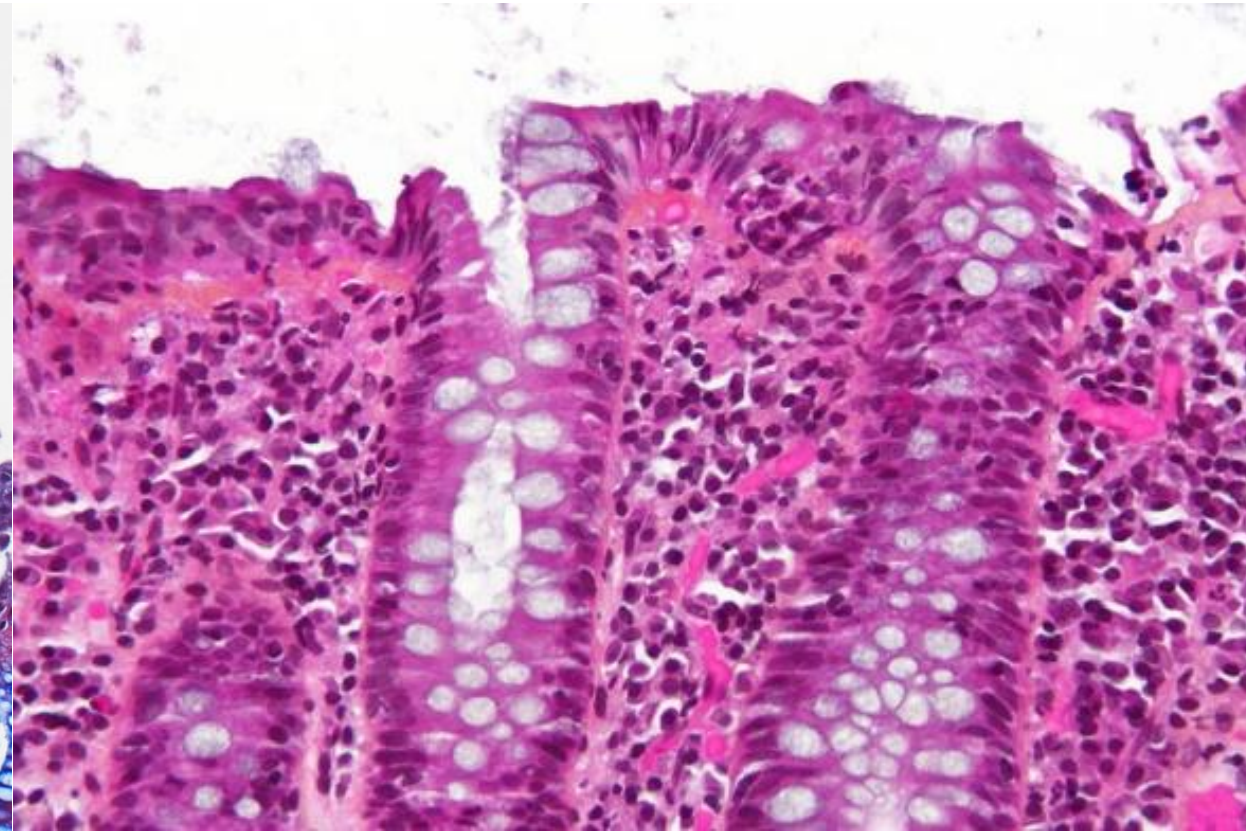
Microscopic colitis

accompanying chronic diarrhea with normal-looking endoscopic findings



Collagenous colitis

Collagen band (thickness $>10\text{ }\mu\text{m}$)
Masson trichrome staining

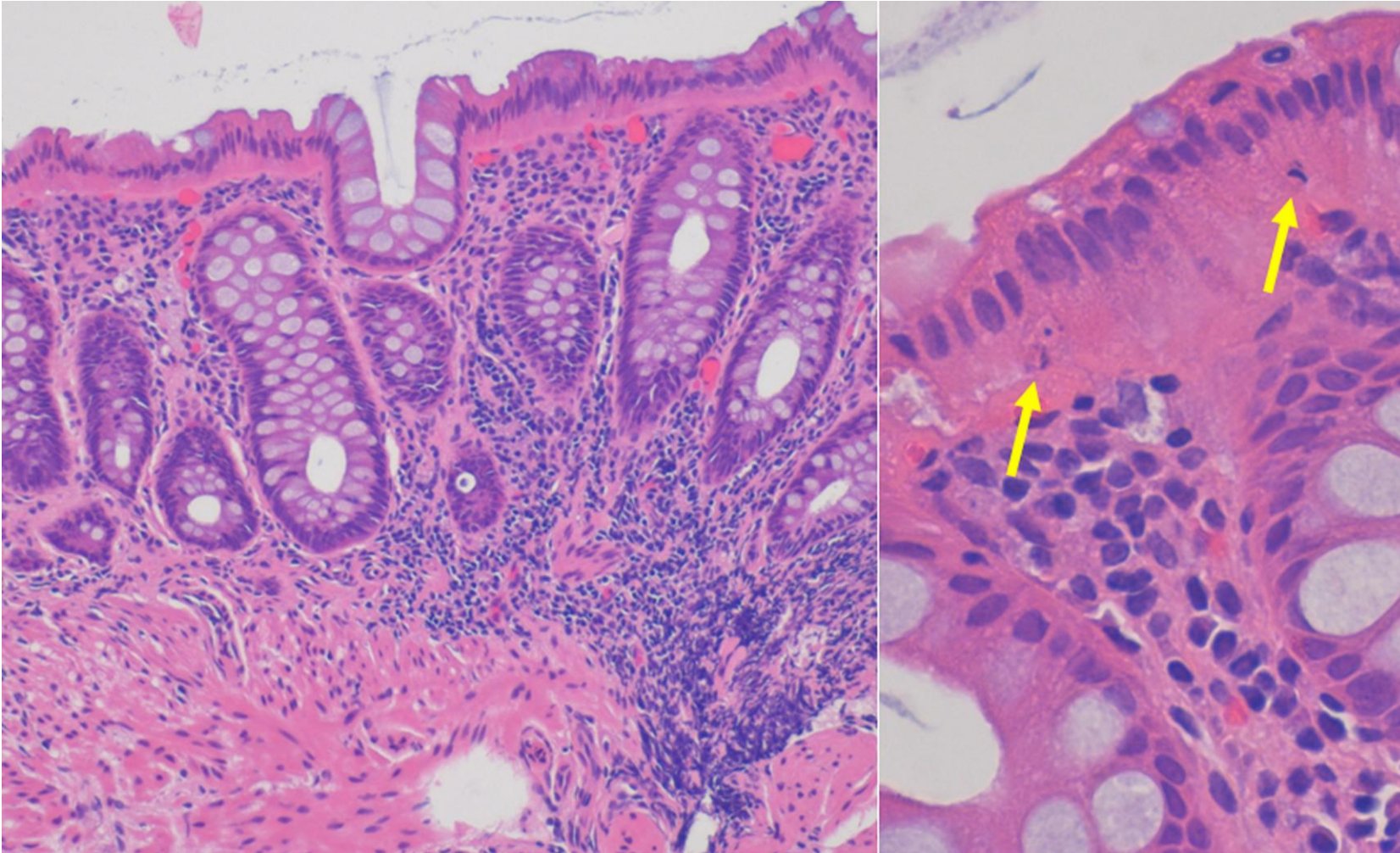


Lymphocytic colitis

Increased CD8-positive intraepithelial lymphocytes
 $>20\text{ CD8}^+\text{Tcells}/100\text{ epithelial cells}$

The third type of microscopic colitis (MC)

Yutaka Tsutsumi found unique features of chronic colitis clinically with chronic diarrhea: band-like nuclear migration into the middle part of the epithelial cells and increased apoptosis beneath the nuclei



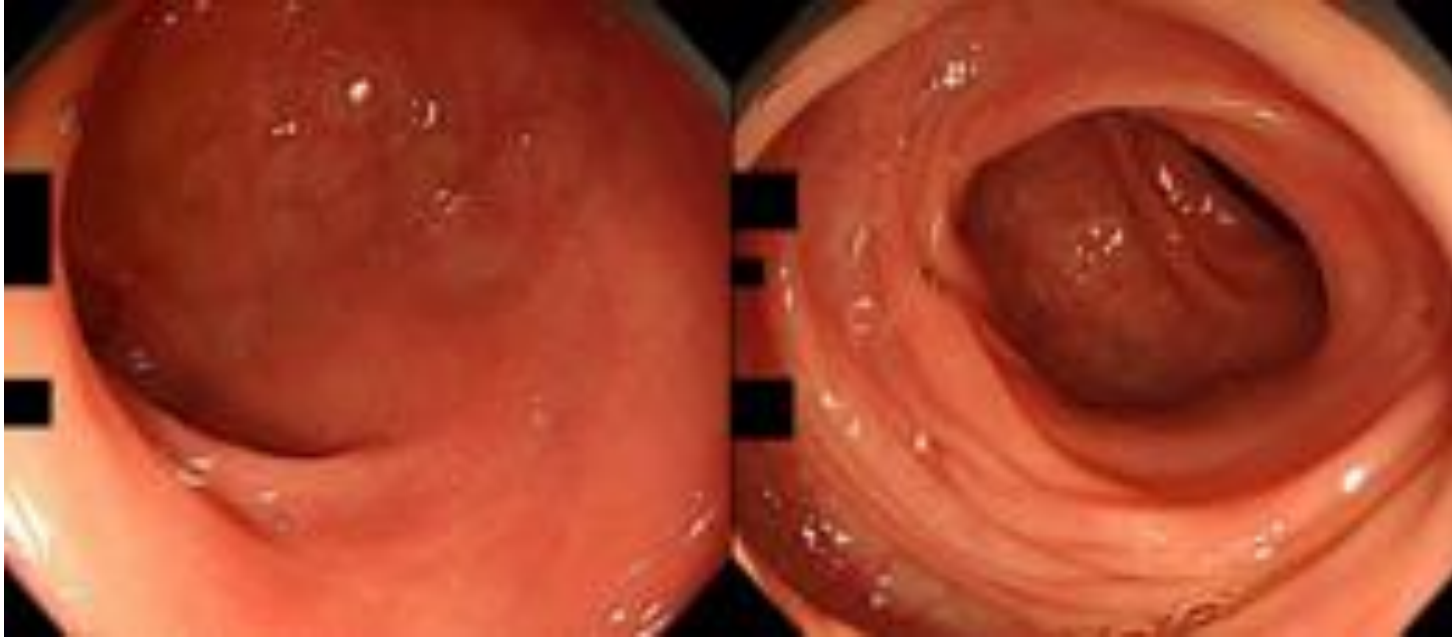
Tachibana et al. reviewed 1,287 colonic biopsy specimens diagnosed as nonspecific colitis during 2016-2019 at Shimada Municipal Hospital, Shimada, Shizuoka, Japan, and found 33 samples showing such microscopic features and termed “**colitis nucleomigrans (CN)**”. In the same period, collagenous colitis (n=5) and lymphocytic colitis (n=0), and ulcerative colitis in remission (n=20) can be detected.

CN (n=33): M:F 20:13, age: 17-88 (mean 58.4, median 63)

CN with MC-like symptoms (watery diarrhea and normal endoscopy) **n=7**

CN with IBD-like symptoms (hematochezia, abdominal pain or mucin secretion with mucosal reddening) **n=26**

Endoscopic findings of colitis nucleomigrans (CN)-1



CN with MC-like symptoms:

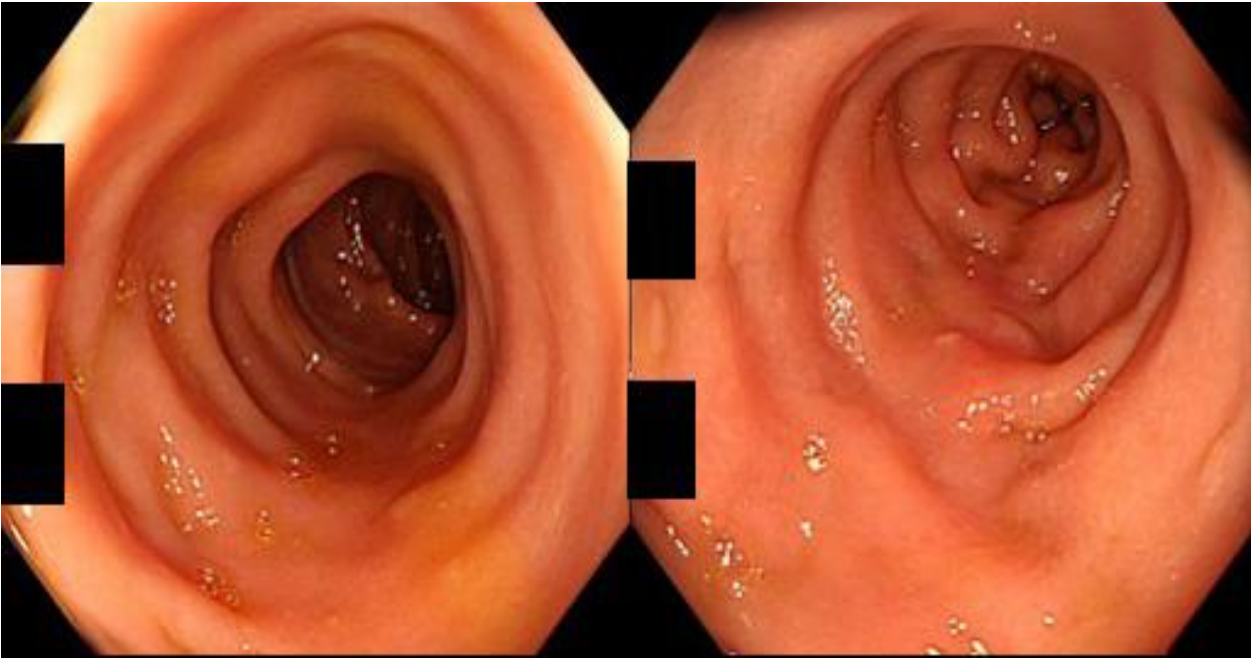
Patients manifesting chronic non-bloody watery diarrhea (MC-like symptoms) with normal endoscopic appearance (n=7)



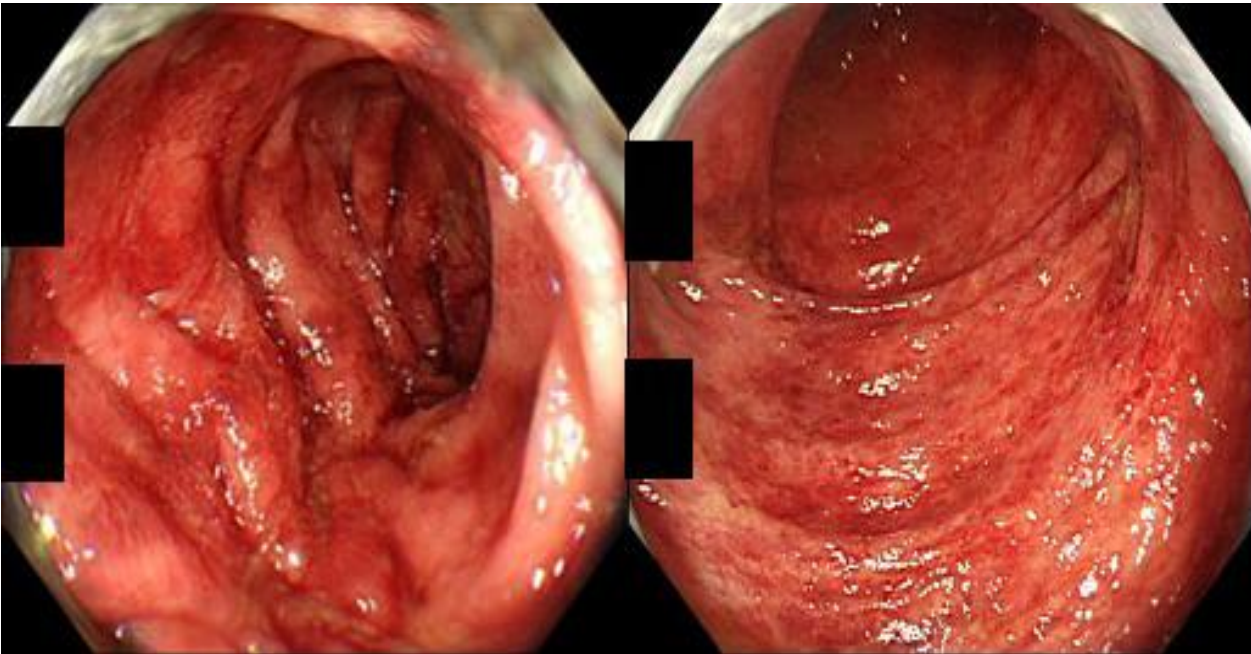
CN with IBD-like symptoms:

Patients manifesting occult (n=9)/gross (n=10) hematochezia, abdominal pain (n=2) or mucin secretion (n=2) (IBD-like symptoms), endoscopically showing mucosal reddening with or without focal erosion/aphtha (n=26)

Endoscopic findings of colitis nucleomigrans (CN)-2

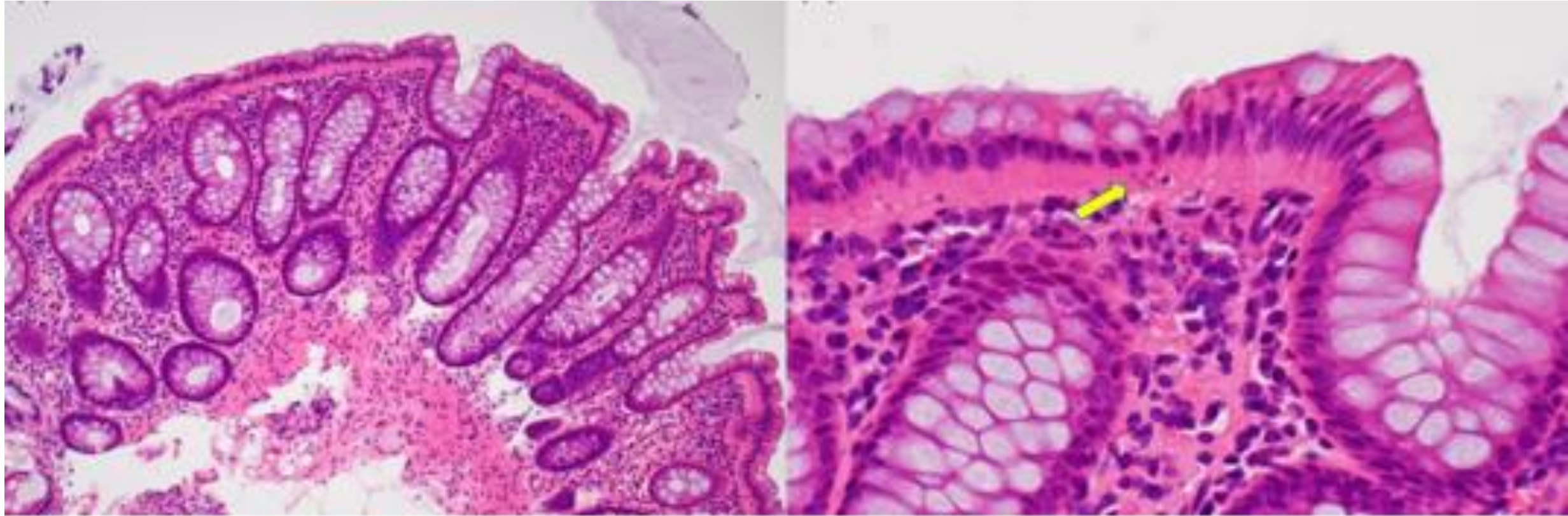


CN with MC-like symptoms



CN with IBD-like symptoms

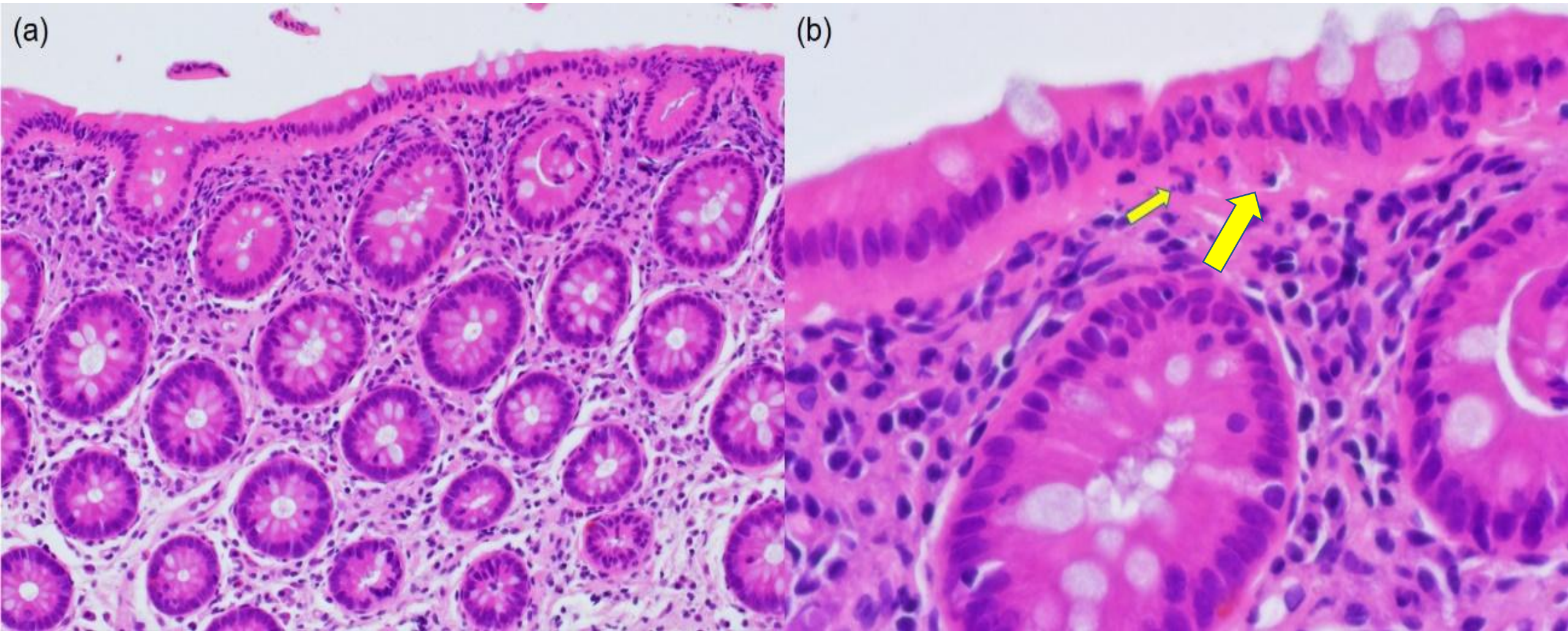
Microscopic findings of colitis nucleomigrans (CN)



Diagnostic criteria of CN

- 1) Nuclear migration in chain to the middle part of the surface-lining columnar epithelium (abundant eosinophilic cytoplasm seen below the nuclei)
- 2) Fragmented apoptotic figures (nuclear debris) scattered below the nuclei
- 3) Mild to moderate nonspecific chronic inflammation in the lamina propria

Microscopic findings of CN with MC-like symptoms



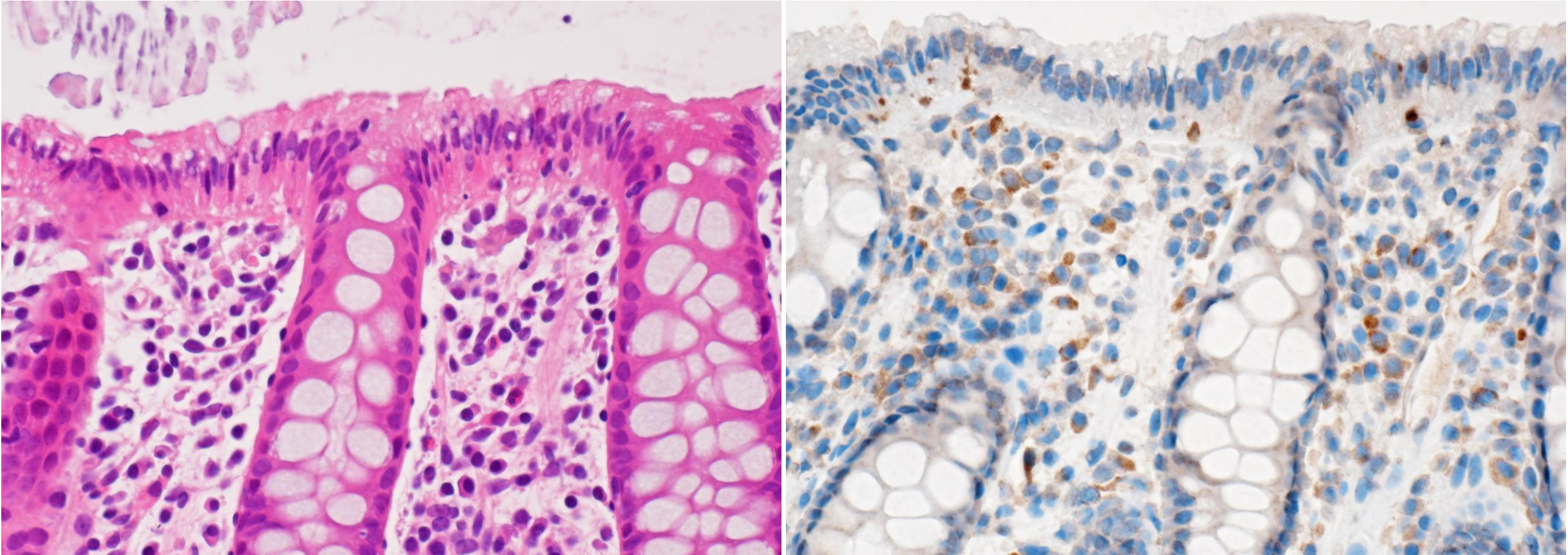
Apoptotic bodies are scattered beneath the band-like migrated nuclei of the surface epithelial cells (arrows).

Microscopic findings for CN with IBD-like symptoms



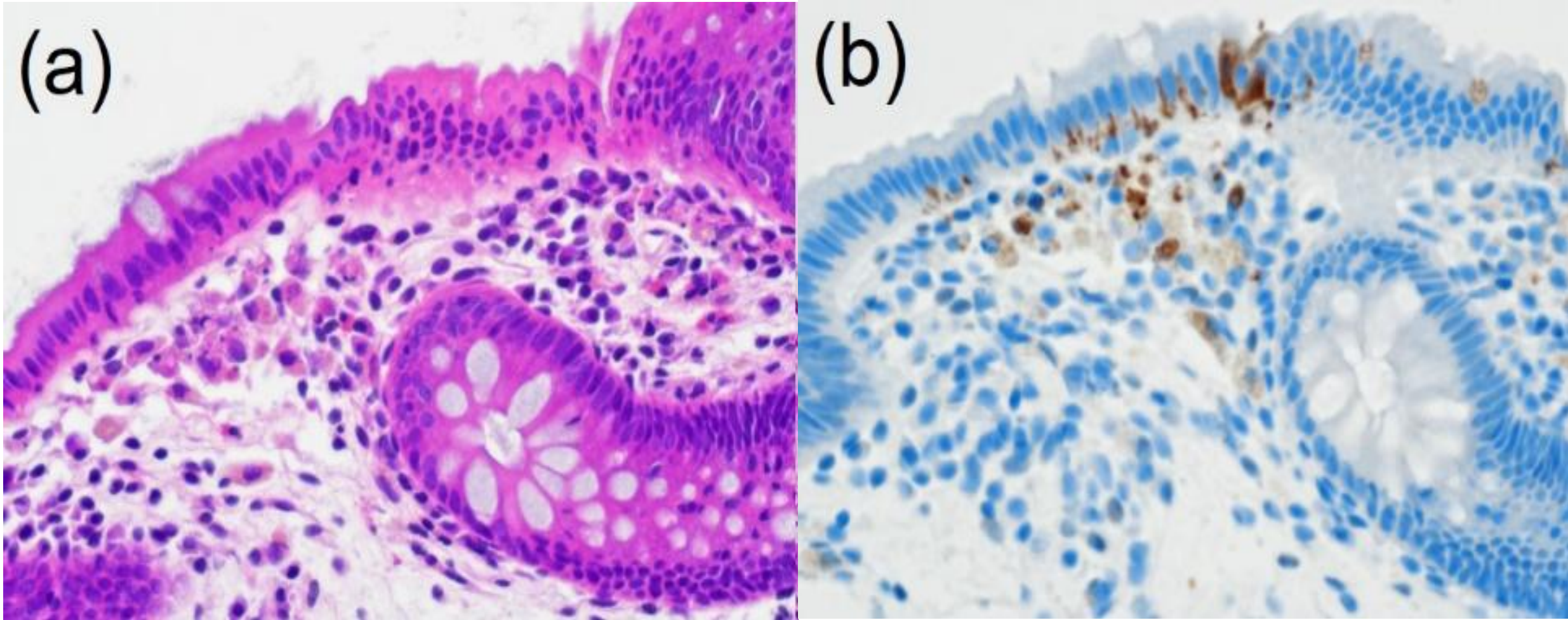
Apoptotic bodies beneath the band-like migrated nuclei are prominent (arrows).

cleaved caspase-3 immunoreactivity in colitis nucleomigrans (CN) with MC-like symptoms



Apoptotic bodies with a 'debris pattern' (clustered fragments of nuclear debris) beneath the chained migrated nuclei in colitis nucleomigrans (CN, left: H&E): Apoptotic bodies are immunoreactive for cleaved caspase-3 (right).

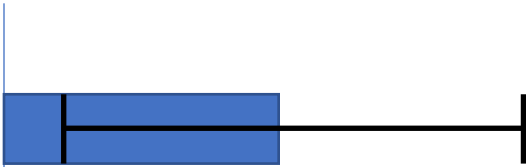
cleaved caspase-3 immunoreactivity in colitis nucleomigrans (CN) with IBD-like symptoms



Apoptotic bodies with a 'debris pattern' (clustered fragments of nuclear debris) beneath the chained migrated nuclei in colitis nucleomigrans (CN, left: H&E): Apoptotic bodies are immunoreactive for cleaved caspase-3 (right).

Cleaved caspase-3 immunoreactivity in CN with MC-like symptoms (n=7) and CN with IBD-like symptoms (n=26)

MC-like symptoms



10.3/100 epithelial cells
(Median: 9.9, range: 1.4-22.6)

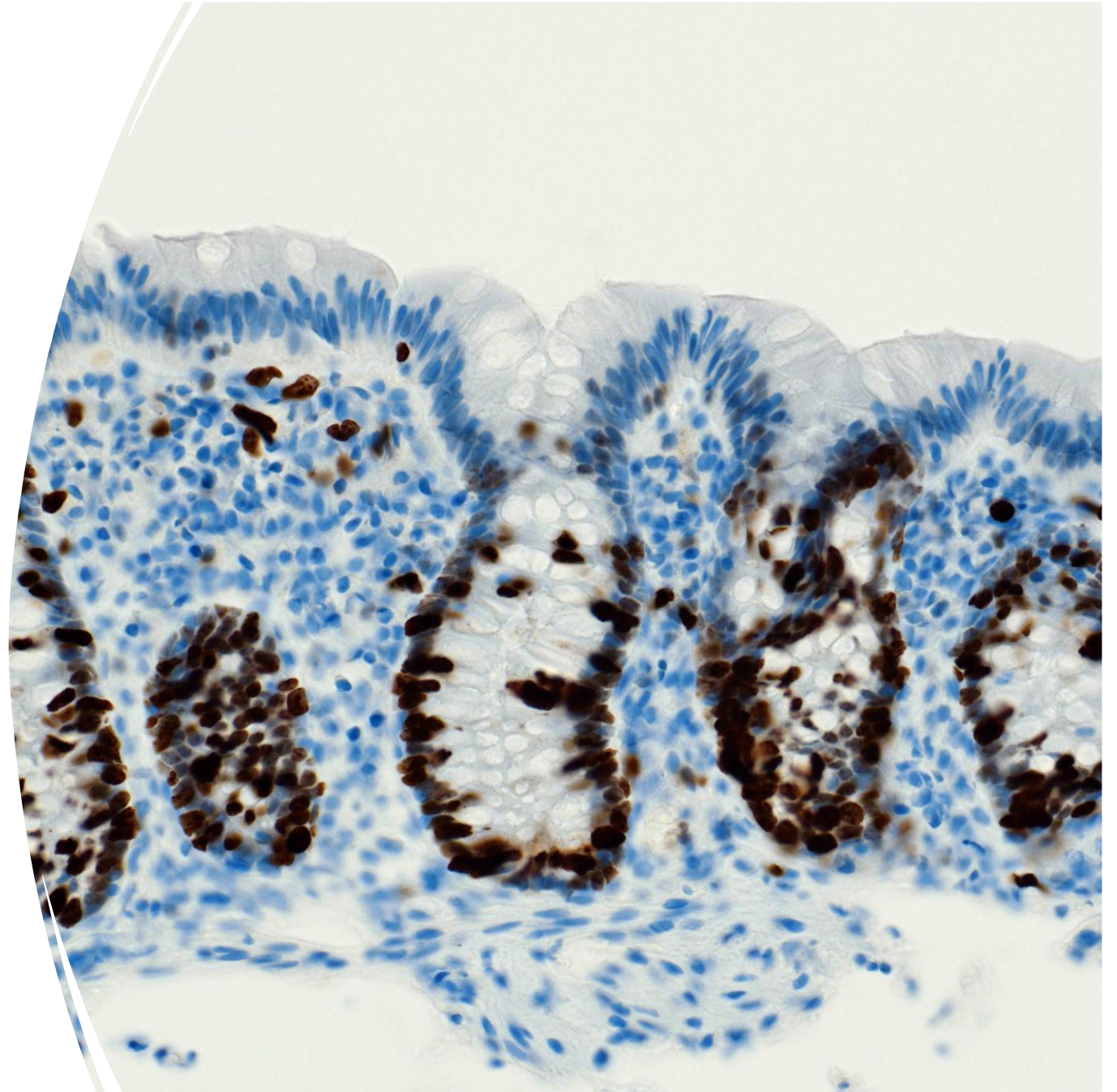
IBD-like symptoms



28.2/100 epithelial cells
(Median: 20.5, range: 1.8-64.8)

Increased Ki-67 labeling in colitis nucleomigrans

The turnover rate of colonic
crypts may be activated in
relation to increased
apoptotic activity.

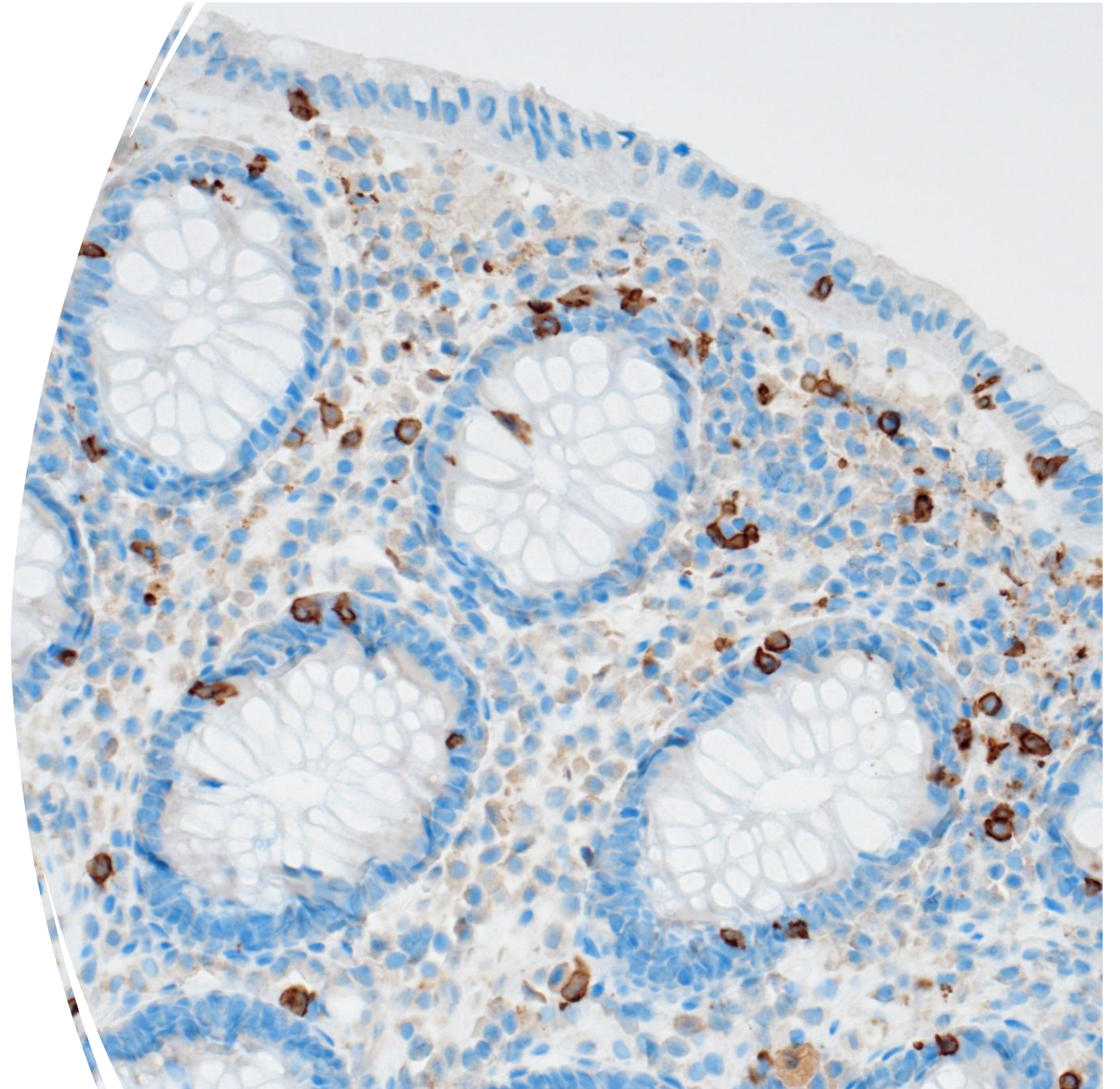


CD8-positive intraepithelial lymphocytes (IELs) in colitis nucleomigrans

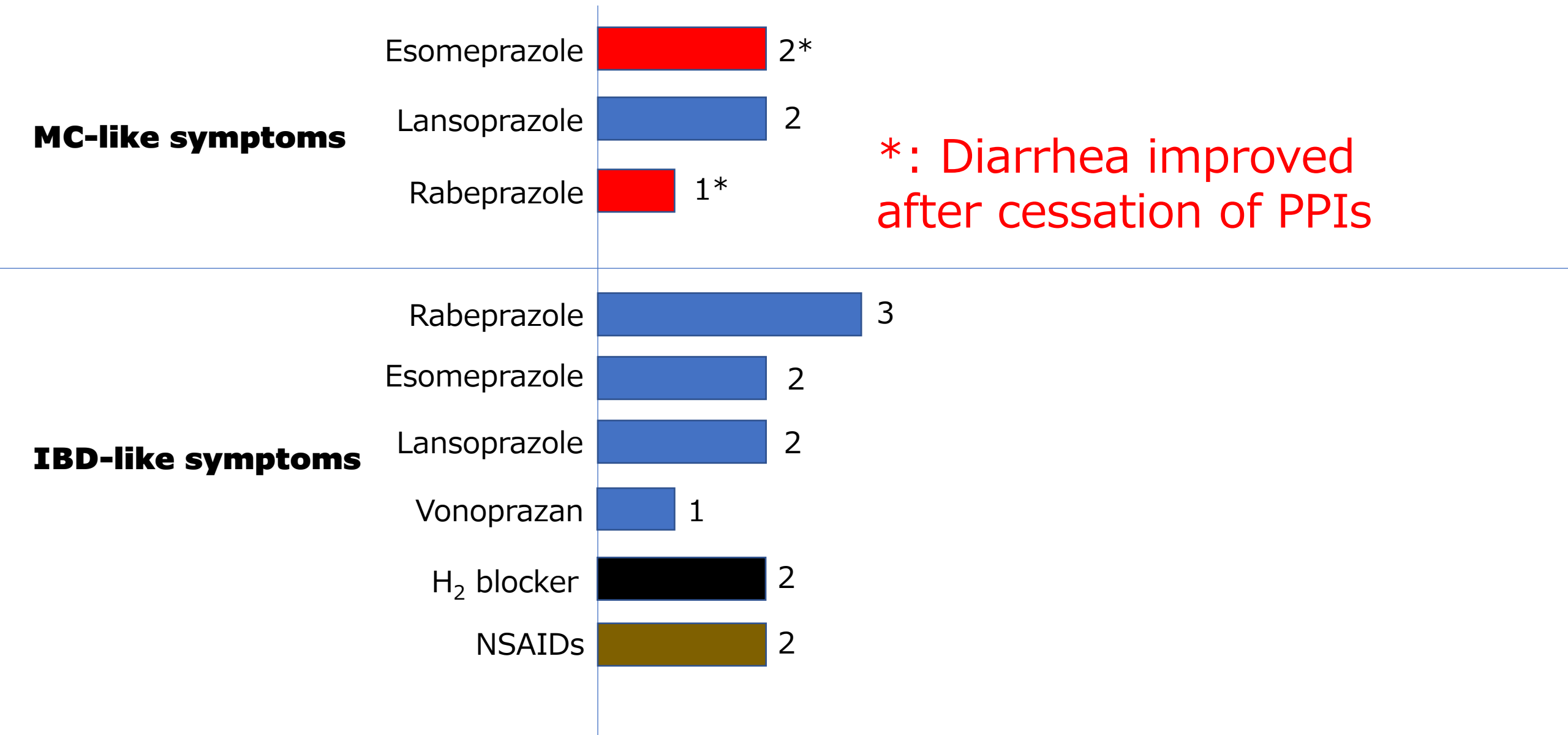
IELs are CD3+/CD8+T-lymphocytes located among the colonic epithelial cells. Lymphocytic colitis is featured by marked increase of IELs.

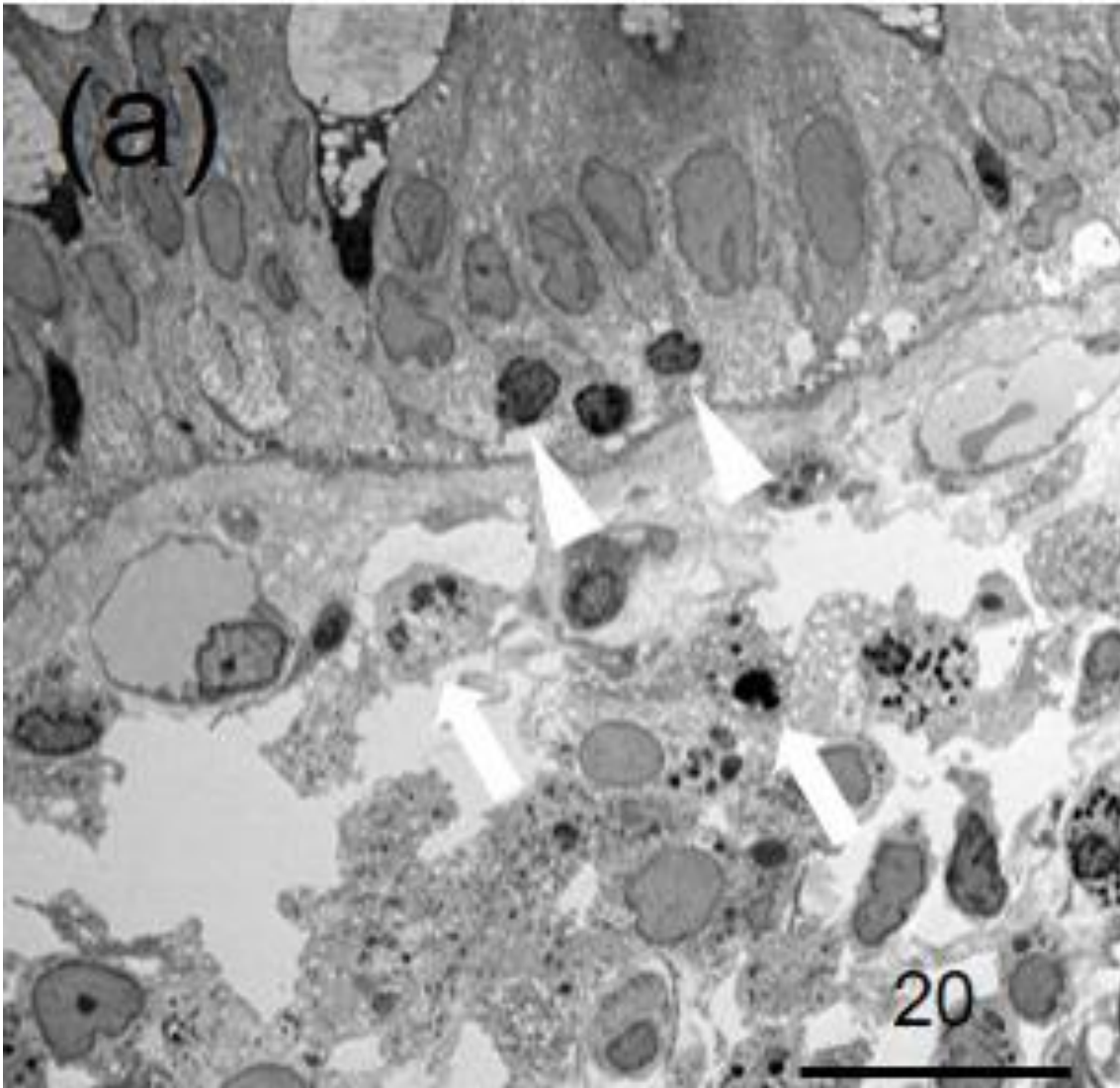
MC-like type: 7.0/100 epithelia

IBD-like type: 7.9/100 epithelia



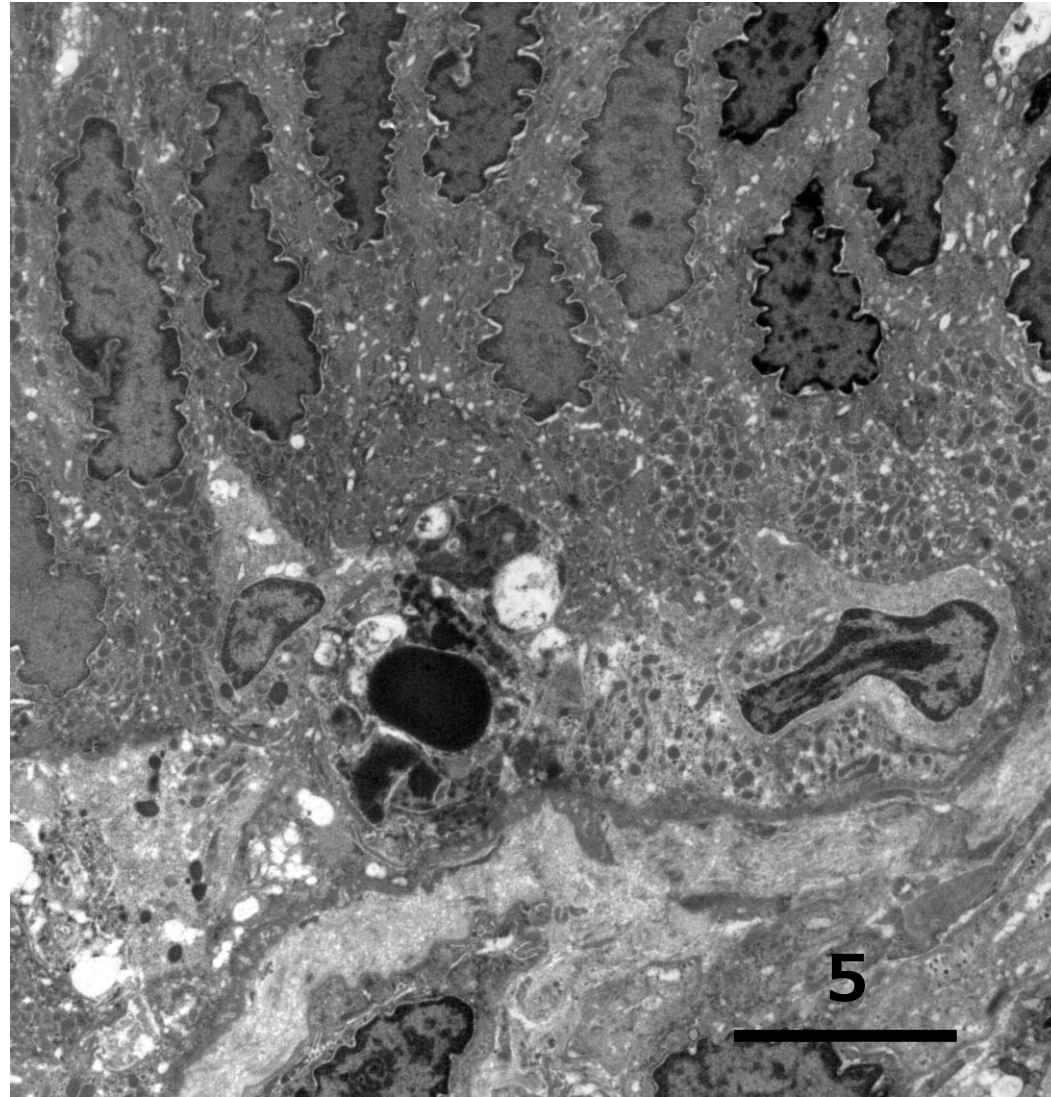
Medication of antacids/proton pump inhibitors (PPIs) for CN with MC-like symptoms(n=7) and CN with IBD-like symptoms (n=26)



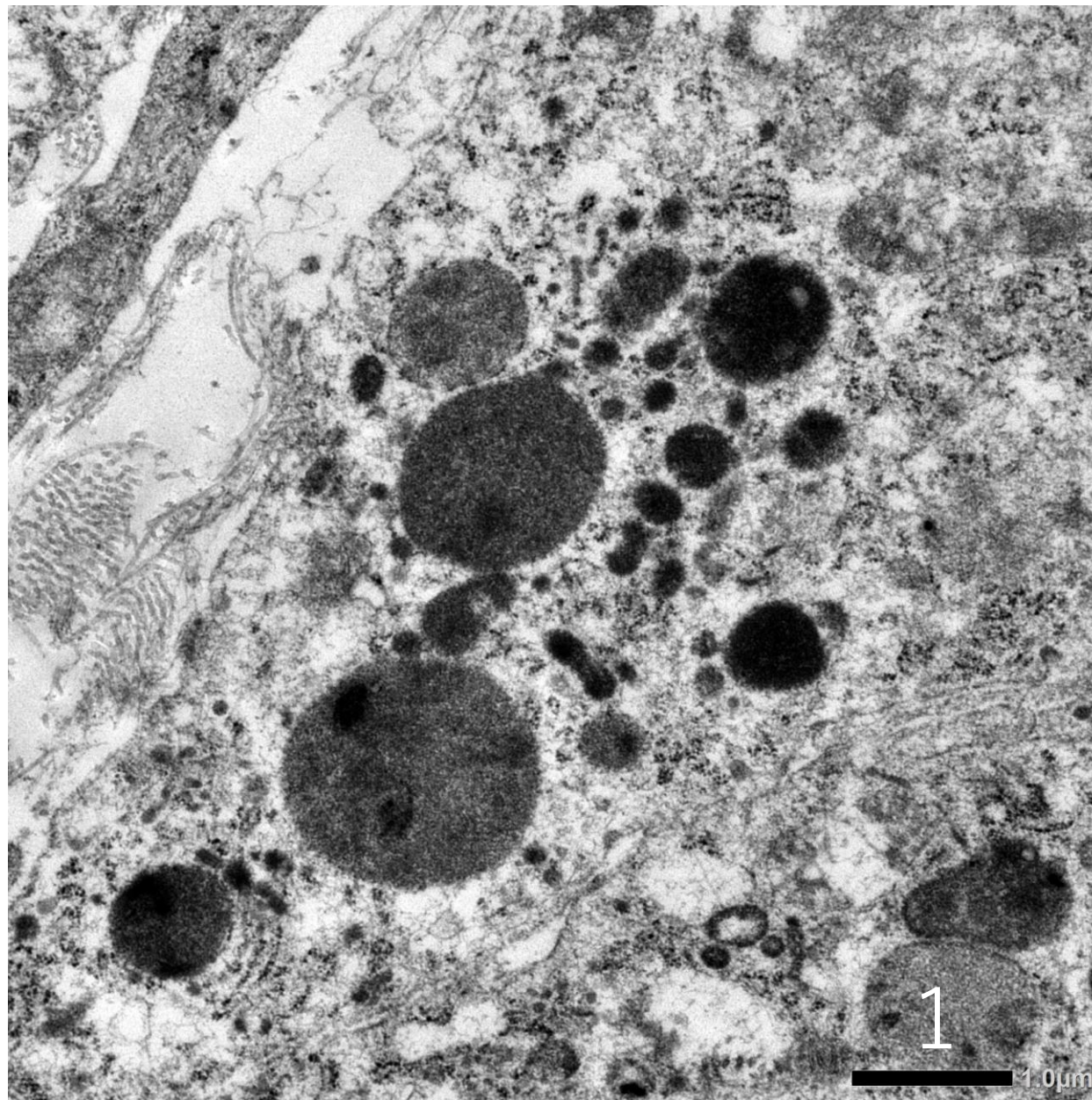


EM study was done using formalin-fixed, paraffin-embedded blocks. The paraffin block of the biopsy specimen was re-embedded into the Epon block to prepare ultrathin sections routinely. The fine morphological preservation is excellent, as shown here.

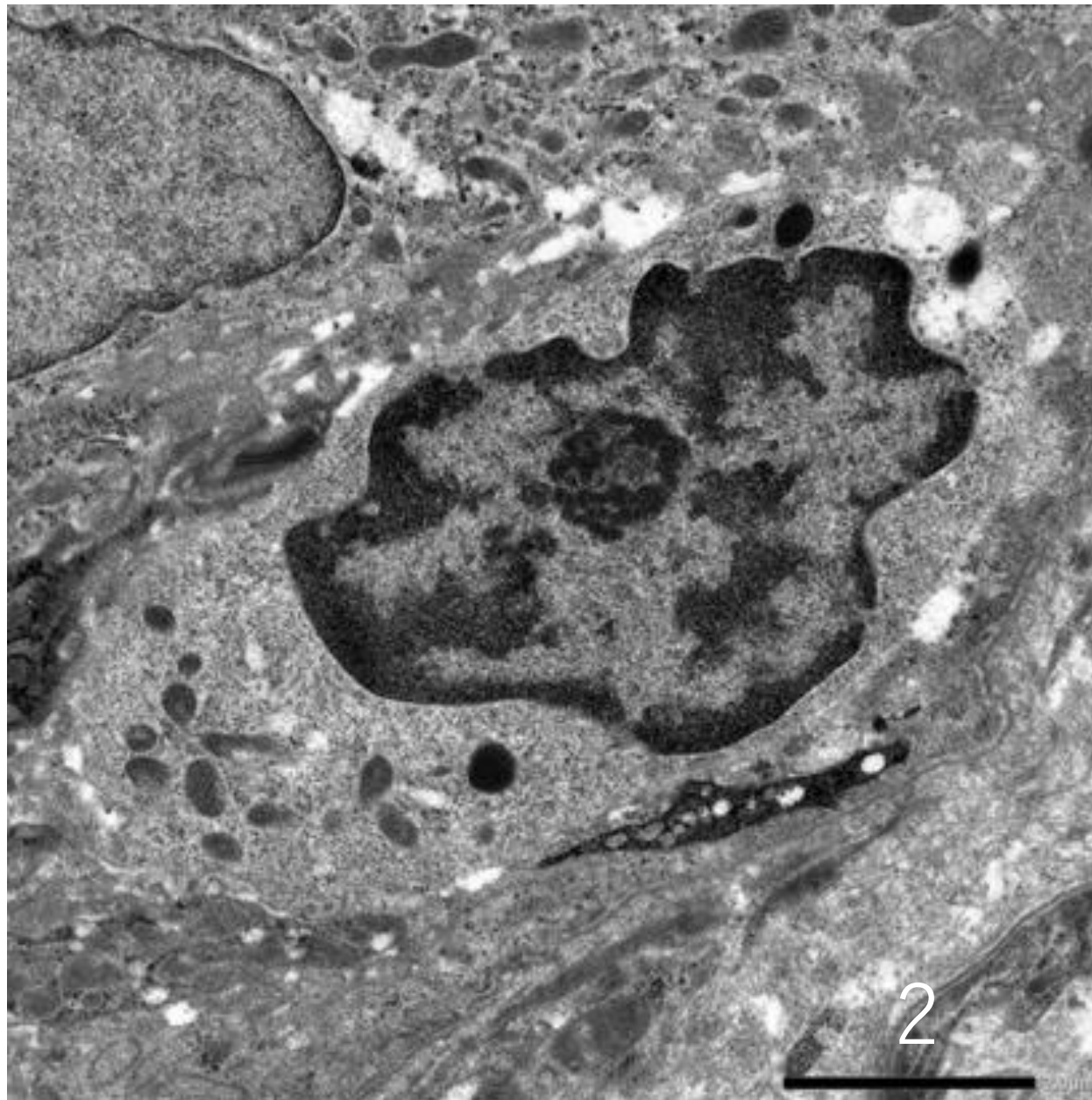
Ultrastructure of colitis nucleomigrans (1). Nuclear migration to the middle part of the cells is seen in the surface-lining cells (a). Arrowheads indicate IELs. Arrows indicate macrophages with apoptotic bodies.



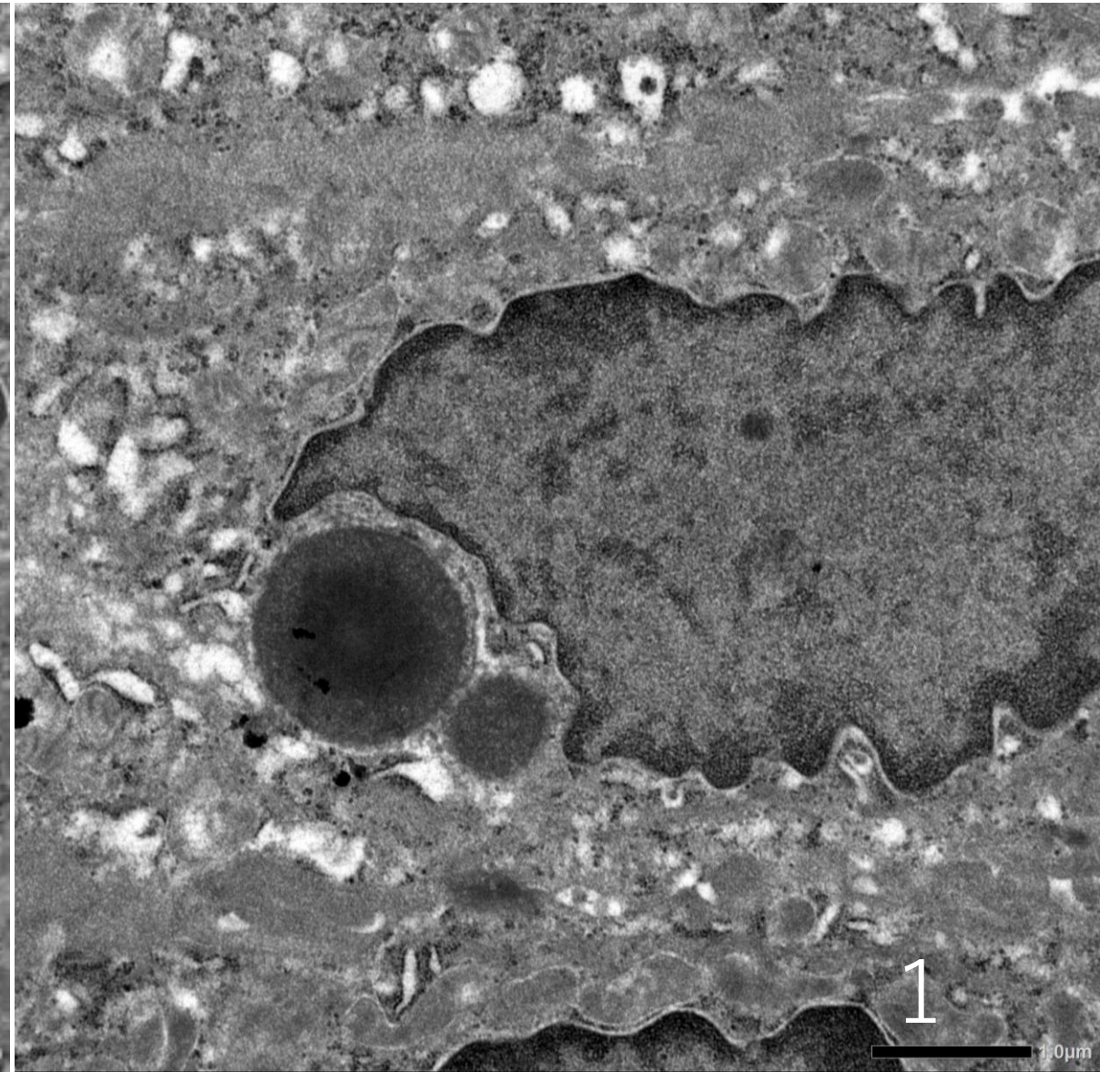
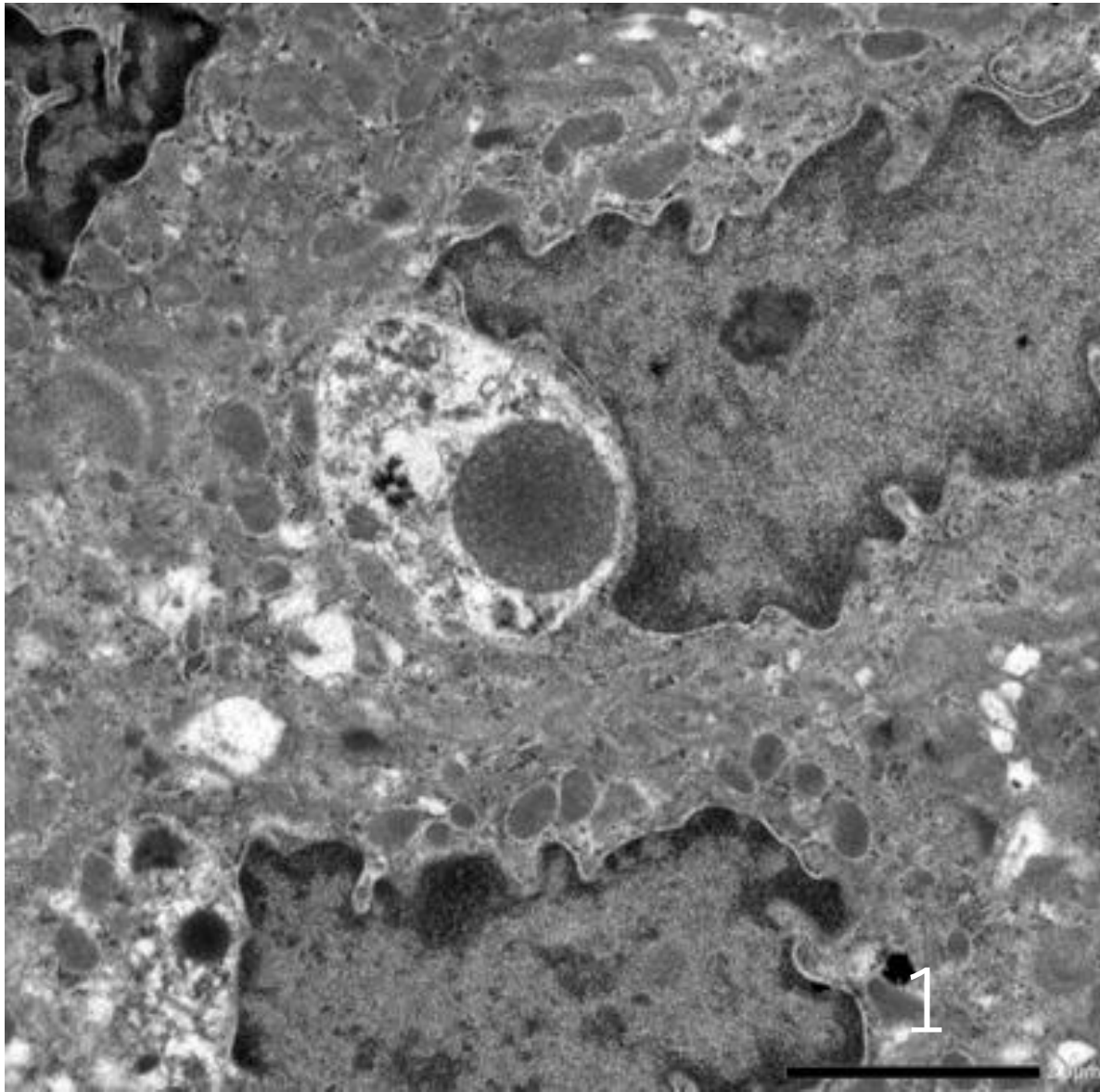
Ultrastructure of CN (2). Mechanisms of nuclear migration to the unusual position or impairment of nuclear anchoring to the basal situation remain unsettled. Little ultrastructural abnormality of cytoskeletal components can be recognized in the epithelial cells.



Ultrastructure of CN (3). Apoptotic bodies are seen in macrophages in the lamina propria mucosae.

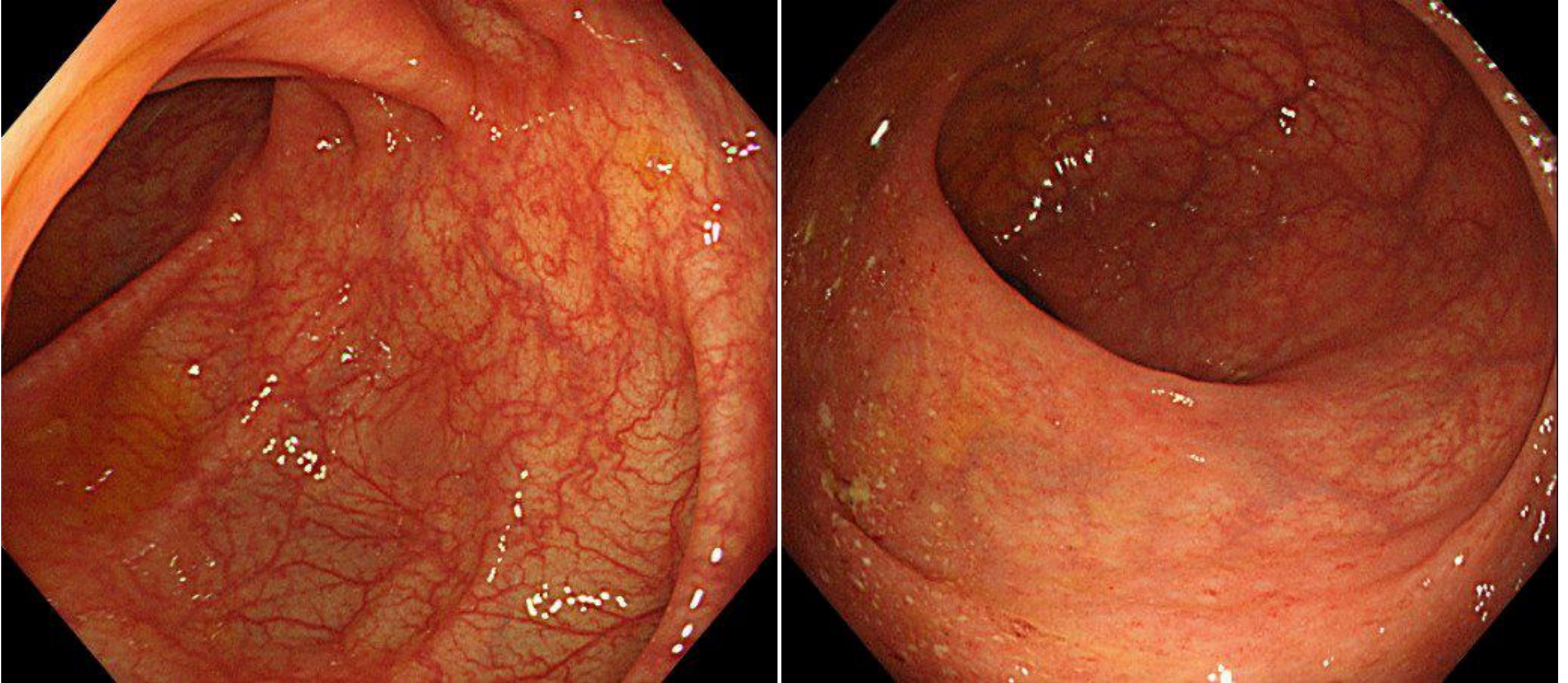


Ultrastructure of CN (4). Intraepithelial lymphocyte (IEL) among the surface epithelial cells of the colon. Clusters of dense bodies features a killer-type lymphocyte.



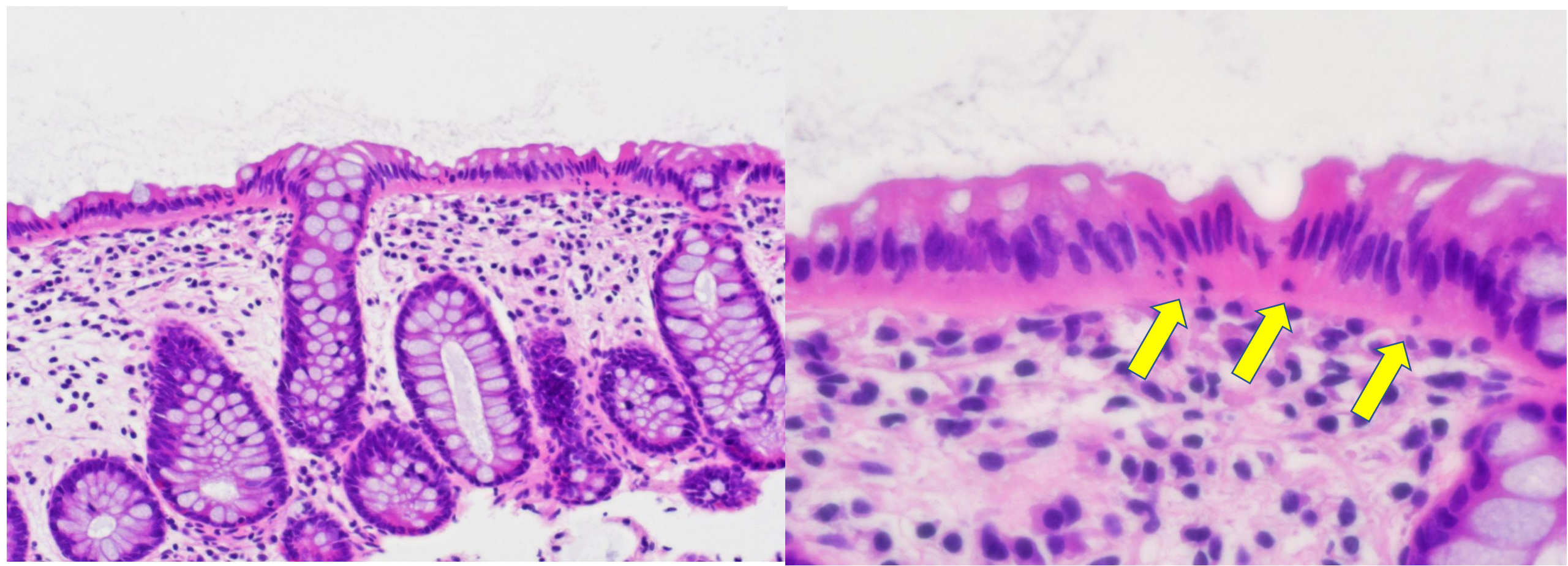
Ultrastructure of CN (5). Apoptotic bodies are seen in the surface epithelial cells of the colon.

UC remission state-related CN-1

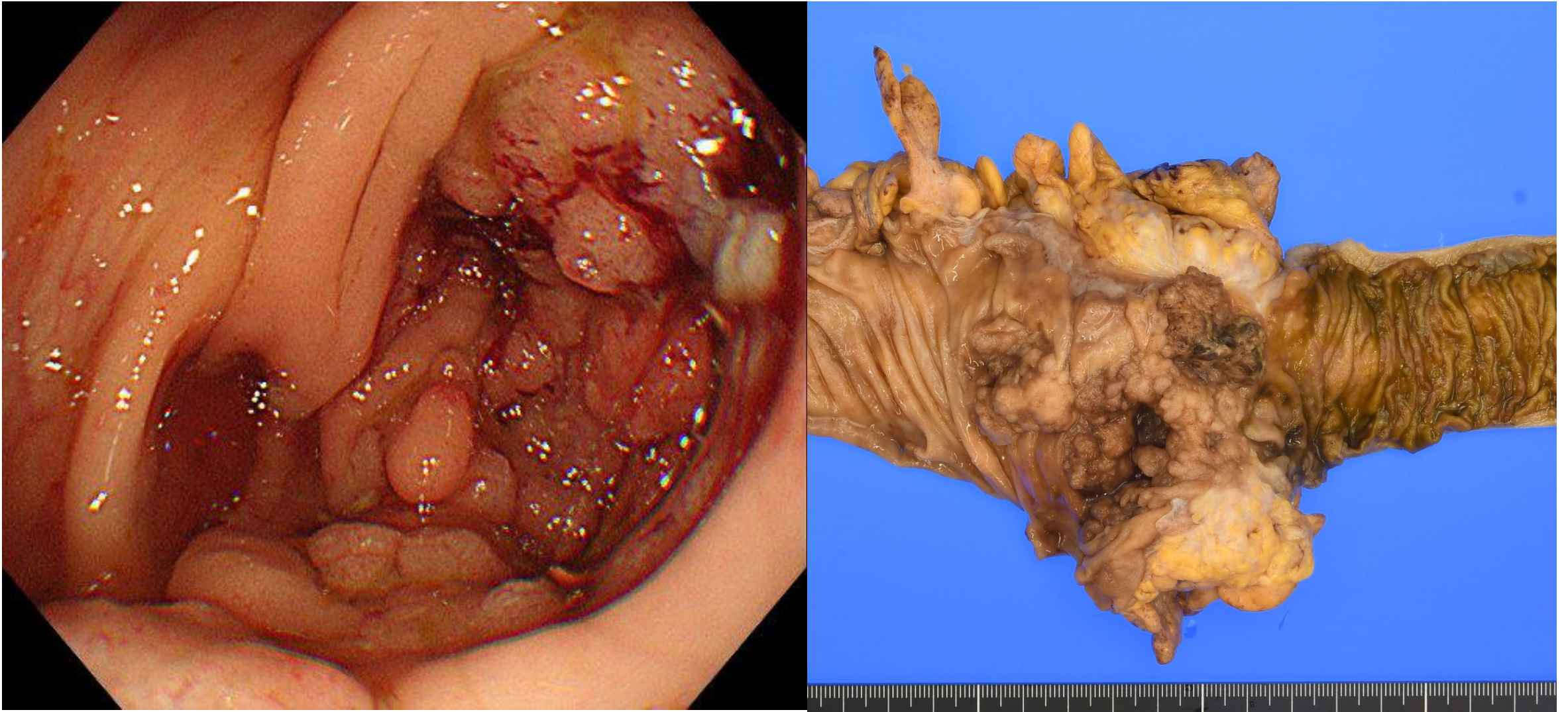


Endoscopically, a remission state of ulcerative colitis is indicated in a lady aged 30's. Diarrhea, bloody stool and abdominal pain has been relieved.

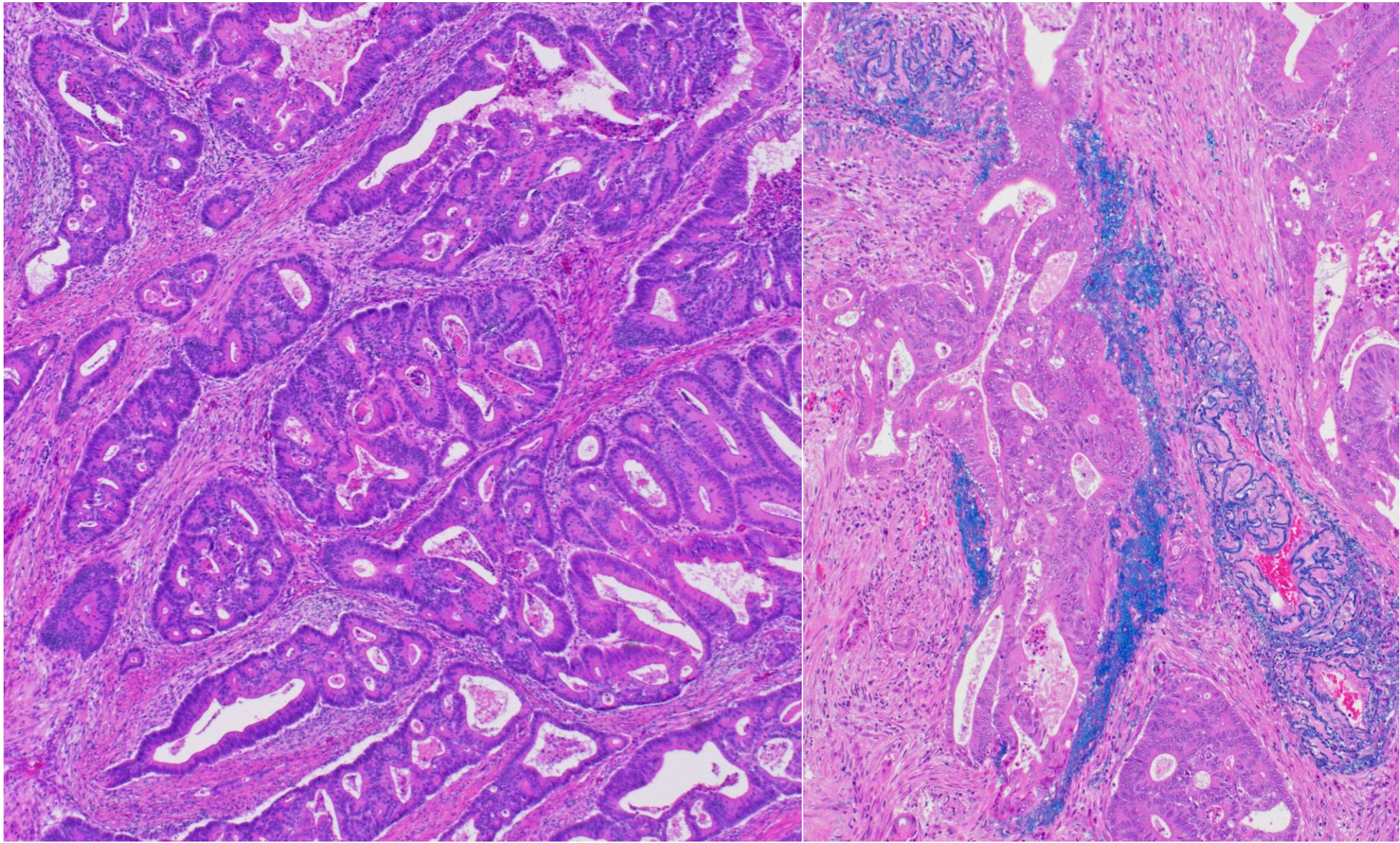
UC remission state-related CN-2



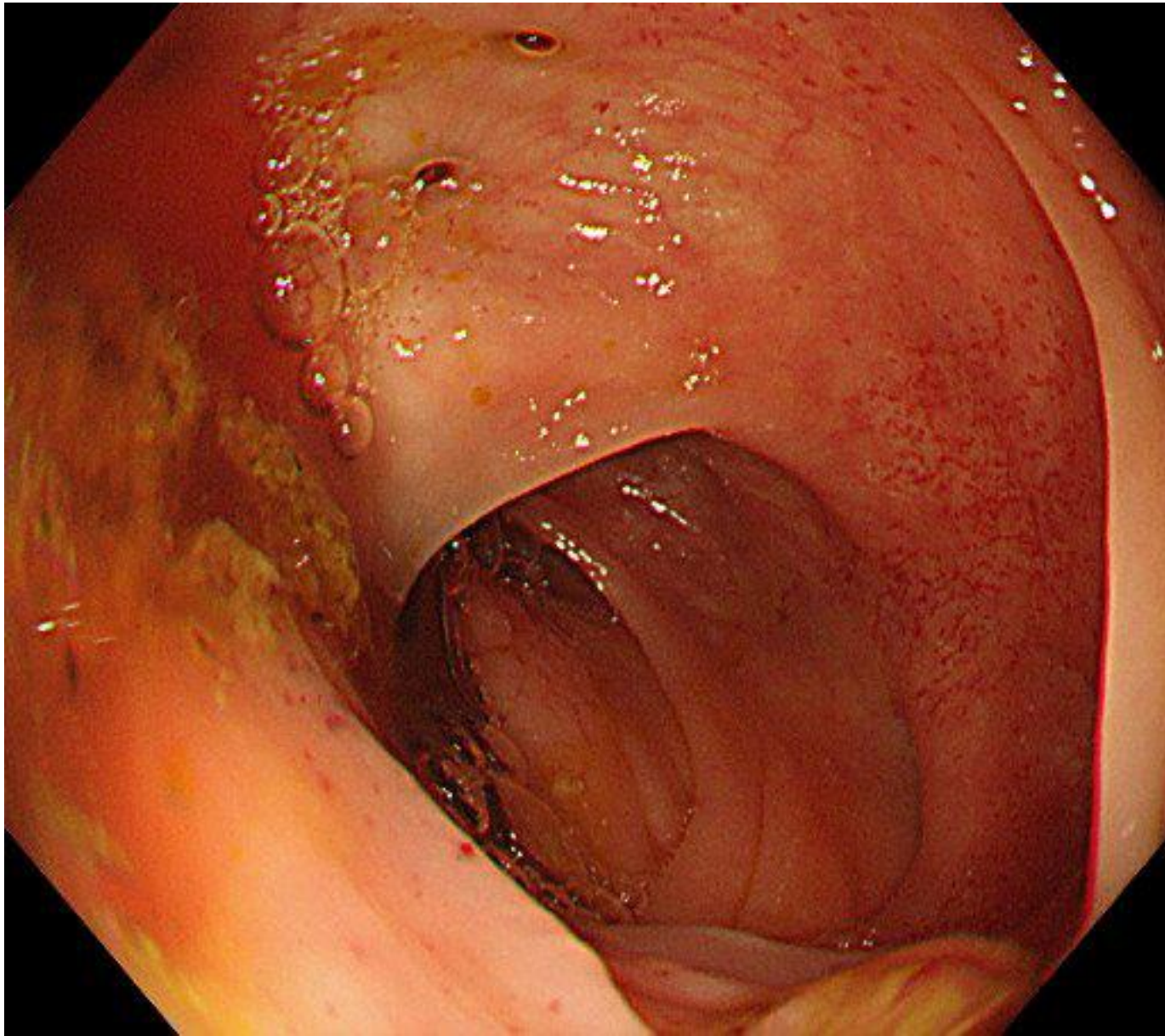
Microscopically, typical features of colitis nucleomigrans are seen in a remission state of ulcerative colitis in a lady aged 30's. Apoptotic bodies (arrows) are seen beneath the band-like migrated nuclei. H&E



Advanced colon cancer, type 1, of the ascending colon of a female patient aged 60's. Left: endoscopy, right: gross appearance of the surgical specimen after formalin fixation

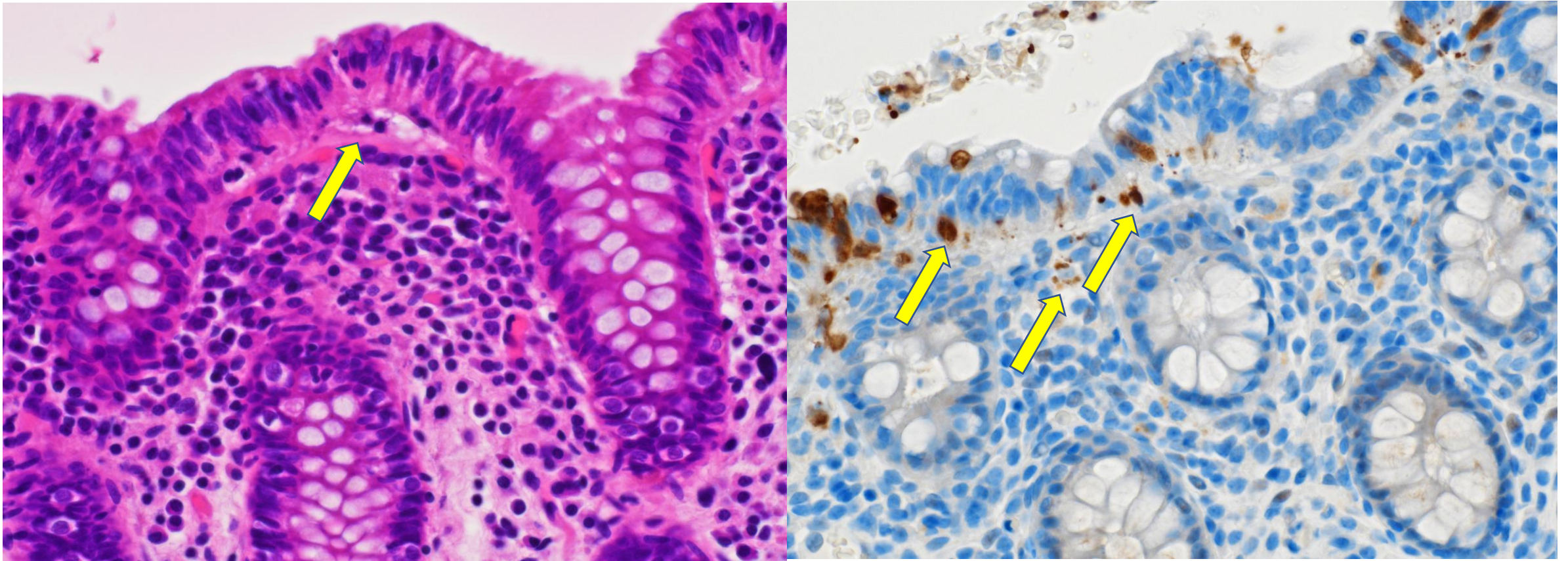


Advanced colon cancer microscopically show transmurial invasion of well-differentiated adenocarcinoma. VB-HE staining demonstrates venous involvement (right).



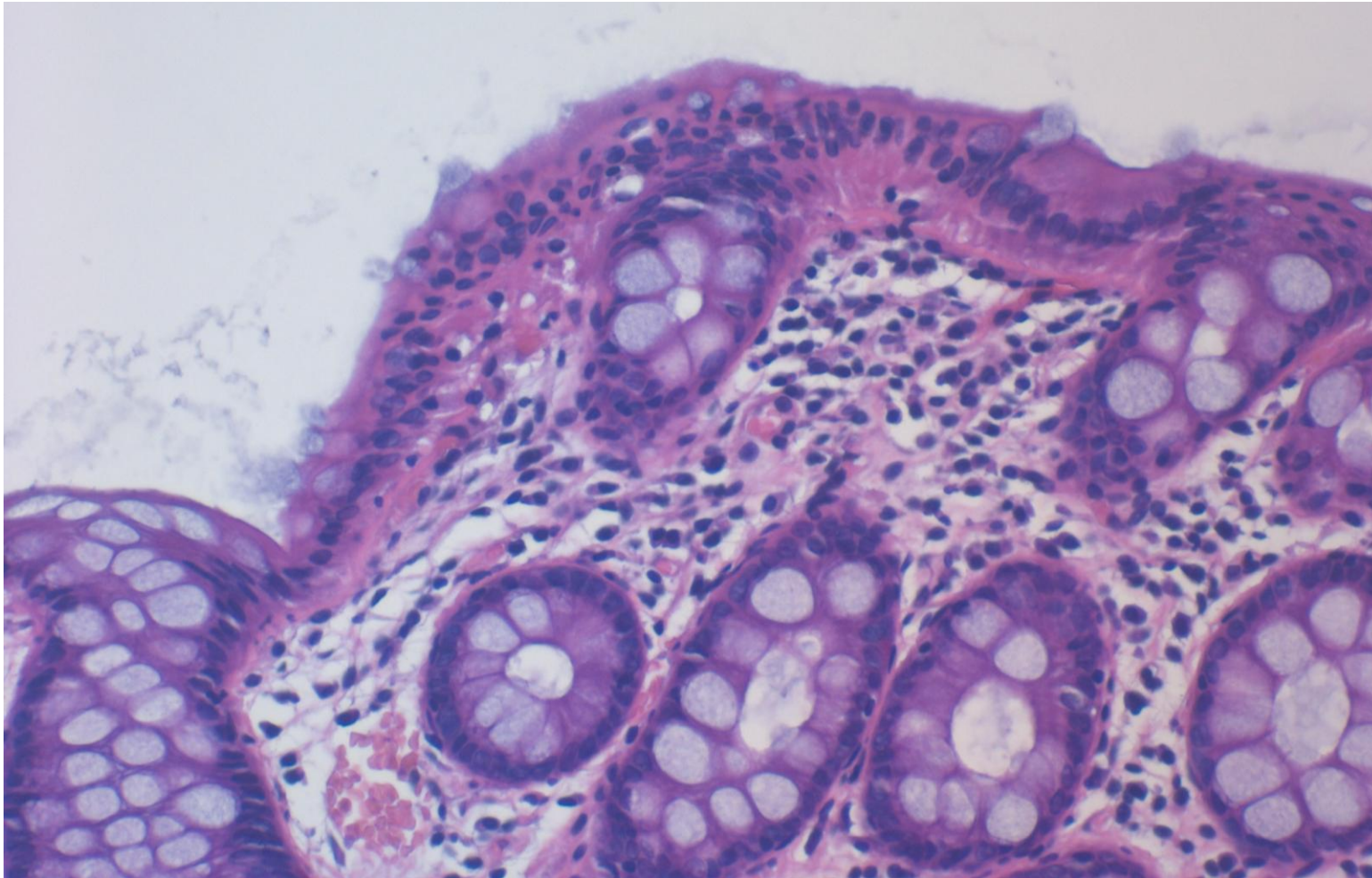
Endoscopic features of the non-neoplastic colonic mucosa in a case of advanced colonic adenocarcinoma.

Colitis nucleomigrans in colon cancer case

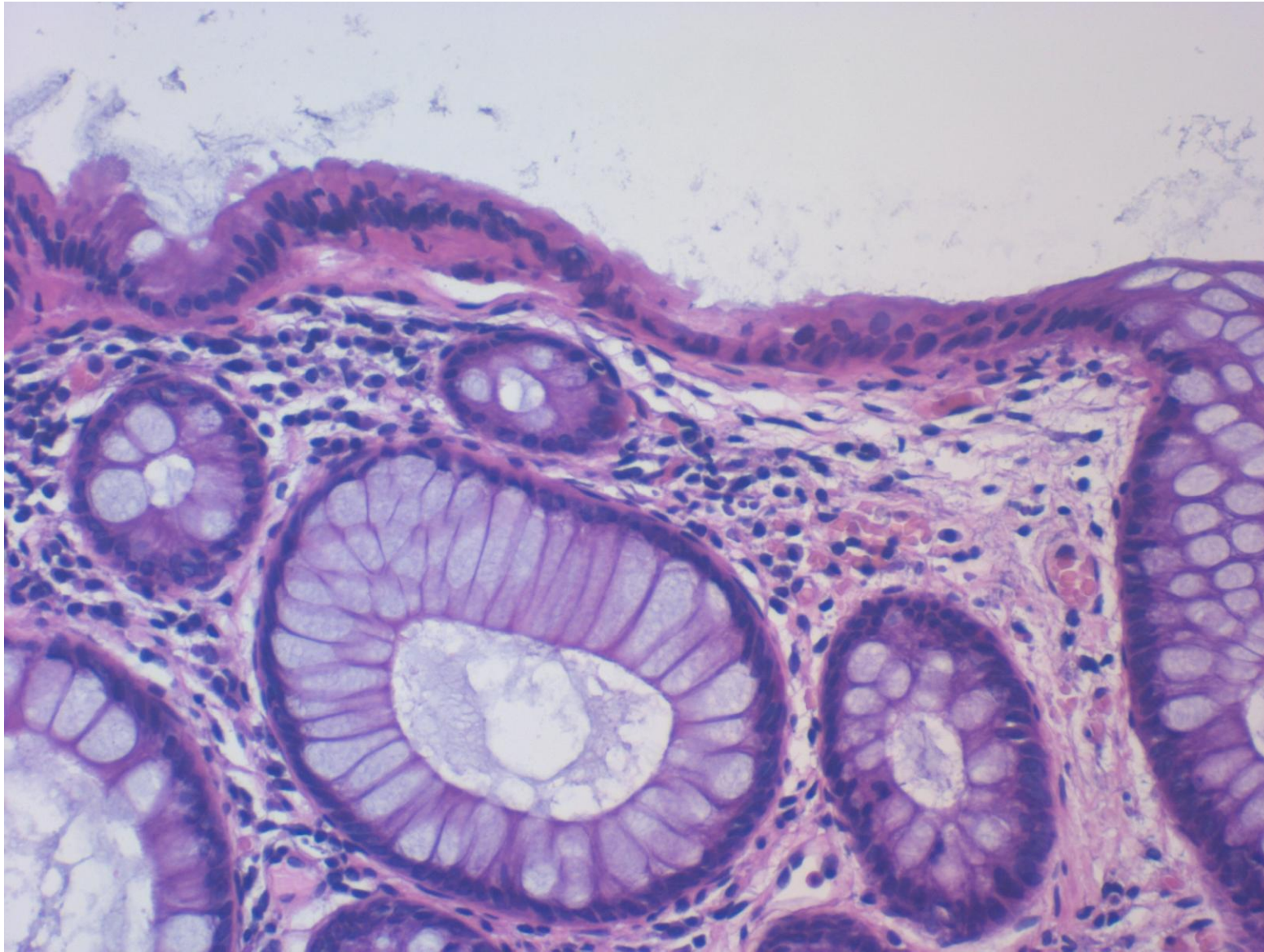


Microscopically, typical features of colitis nucleomigrans are seen in the non-neoplastic colonic mucosa near the anal-sided surgical margin of the ascending colon of advanced colon adenocarcinoma seen in a lady aged 60's. Apoptotic bodies (arrows) are seen beneath the band-like migrated nuclei. Left: H&E, right: immunostaining for cleaved caspase-3

Colitis nucleomigrans in hyperplastic mucosal nodule



In hyperplastic mucosal nodule of the colon, microscopic features of colitis nucleomigrans are observed. This may represent a localized form of CN: localized mucosal edema may provoke an elevated mucosal lesion. H&E-1



In hyperplastic mucosal nodule of the colon, microscopic features of colitis nucleomigrans are observed. This may represent a localized form of CN: localized mucosal edema may provoke an elevated mucosal lesion. H&E-2