Syndromic serrated lesions of the colon

Christophe Rosty

Brisbane, QLD, Australia

Outline

- Serrated polyposis: updated criteria, pathologist's role
- Serrated lesions/polyps of the colon: updated nomenclature and histological criteria
- Serrated lesions/polyps in genetic syndromes of the GI tract

What’s new in serrated polyposis

Why were the criteria updated?

- 2010 criterion 2 (Any number of serrated polyps proximal to the sigmoid colon in an individual who had a first-degree relative with SP) not used
- 50% of CRC in serrated polyposis patients from the rectosigmoid
- Include distal polyps in the definition with some restriction for size and number of rectal polyps

Updated 2019 WHO criteria

Criterion 1	≥ 5 serrated lesions/polyps proximal to the rectum, all being ≥ 5 mm in size, with ≥ 2 being ≥ 10 mm in size
Criterion 2	> 20 serrated lesions/polyps of any size but distributed throughout the large bowel, with ≥ 5 being proximal to the rectum

- Polyp count is cumulative over multiple colonoscopies
- Any histological subtype of serrated lesion/polyp is included in the final polyp count

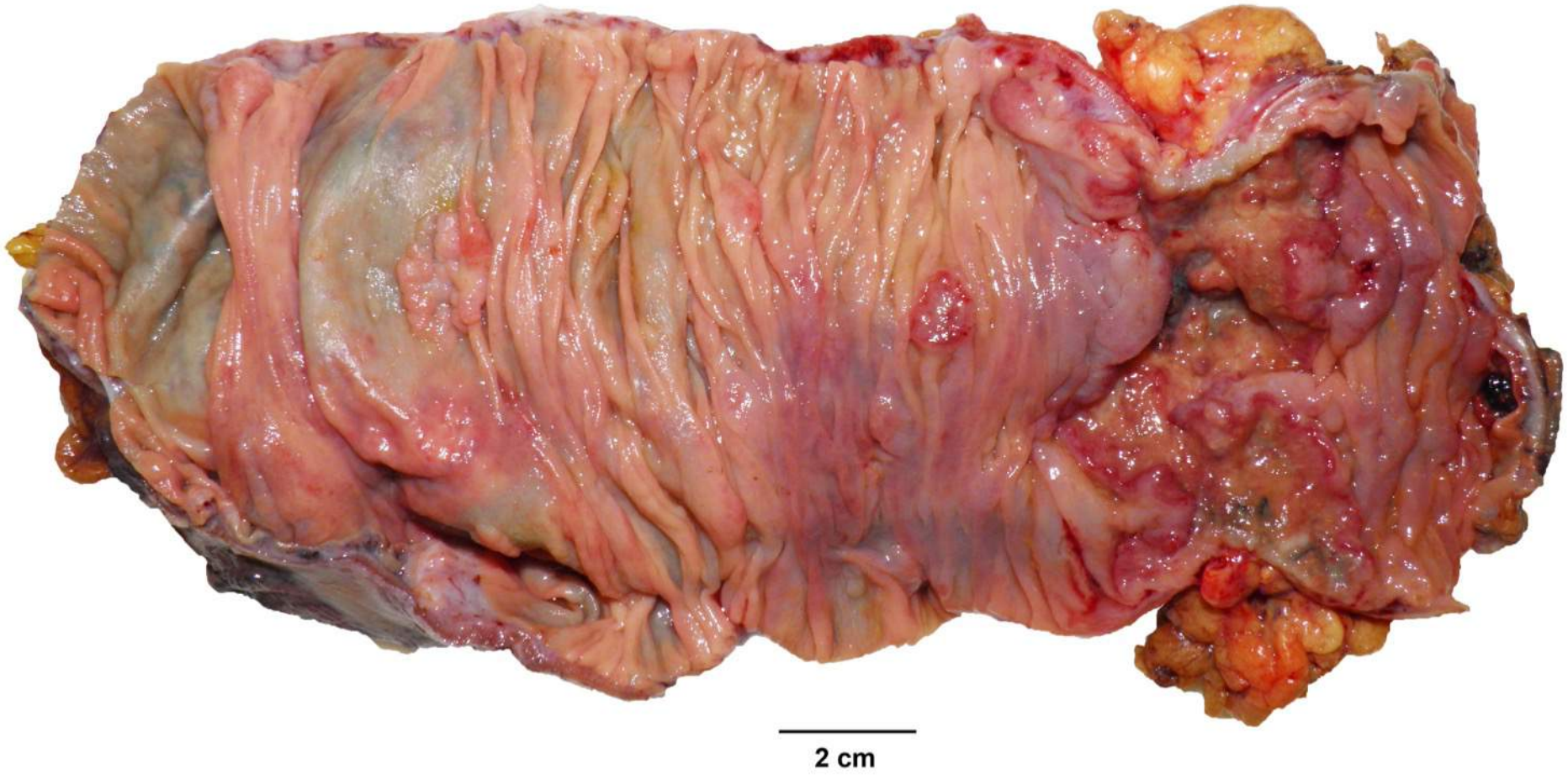
Clinical features of serrated polyposis

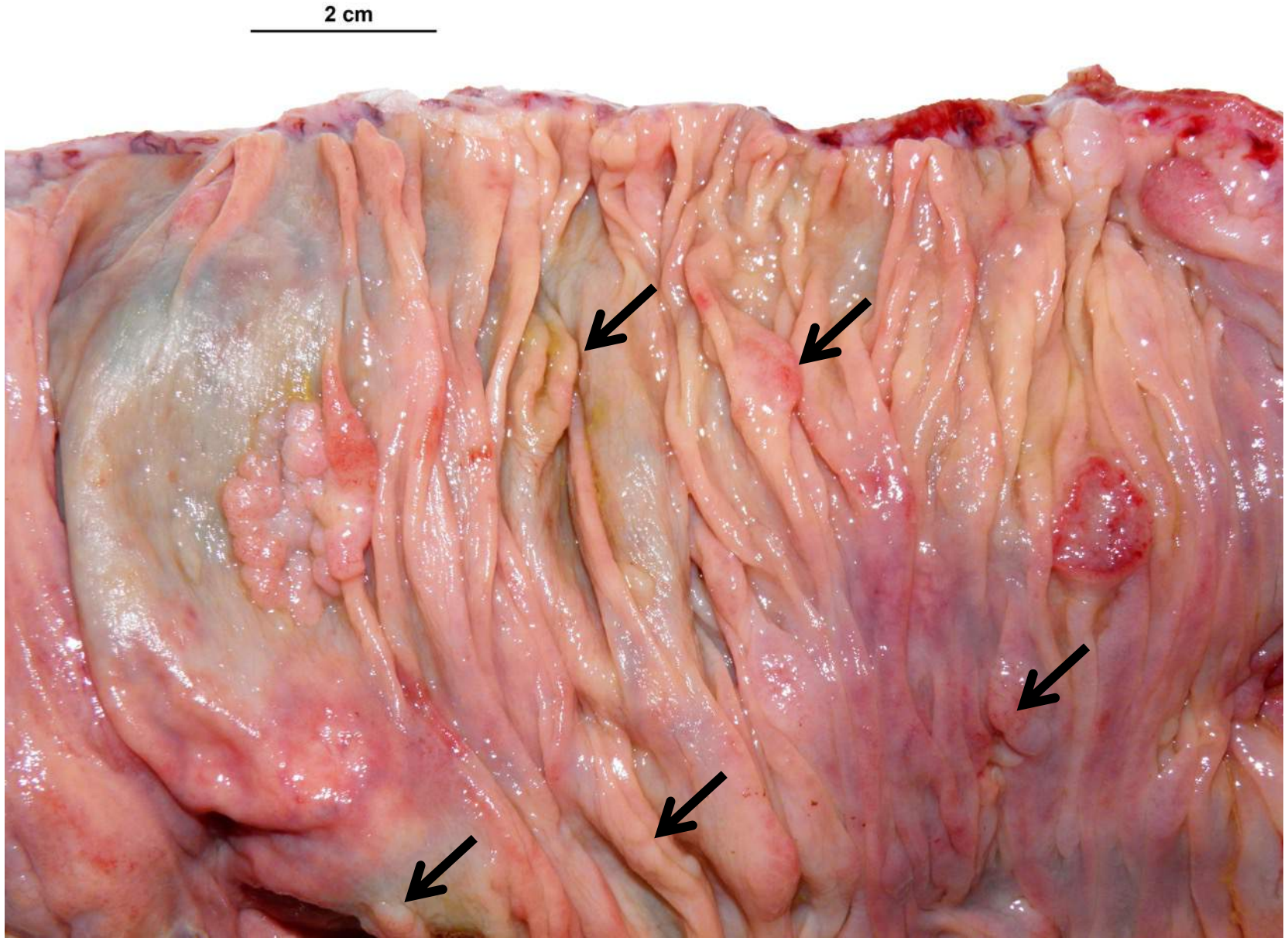
- Risk of CRC: 15-30%
- CRC risk increased if:
  - Fulfillment of both diagnostic criteria
  - > 2 serrated lesions/polyps proximal to splenic flexure
  - At least 1 SSLD
  - At least 1 advanced conventional adenoma
- Risk of serrated polyposis in first-degree relatives: 5%
- CRC risk in first-degree relatives: 5x
- Management:
  - Refer to specialised centres
  - Colonoscopic clearance
  - 1-2 yearly surveillance colonoscopy

Role of the pathologist in the diagnosis

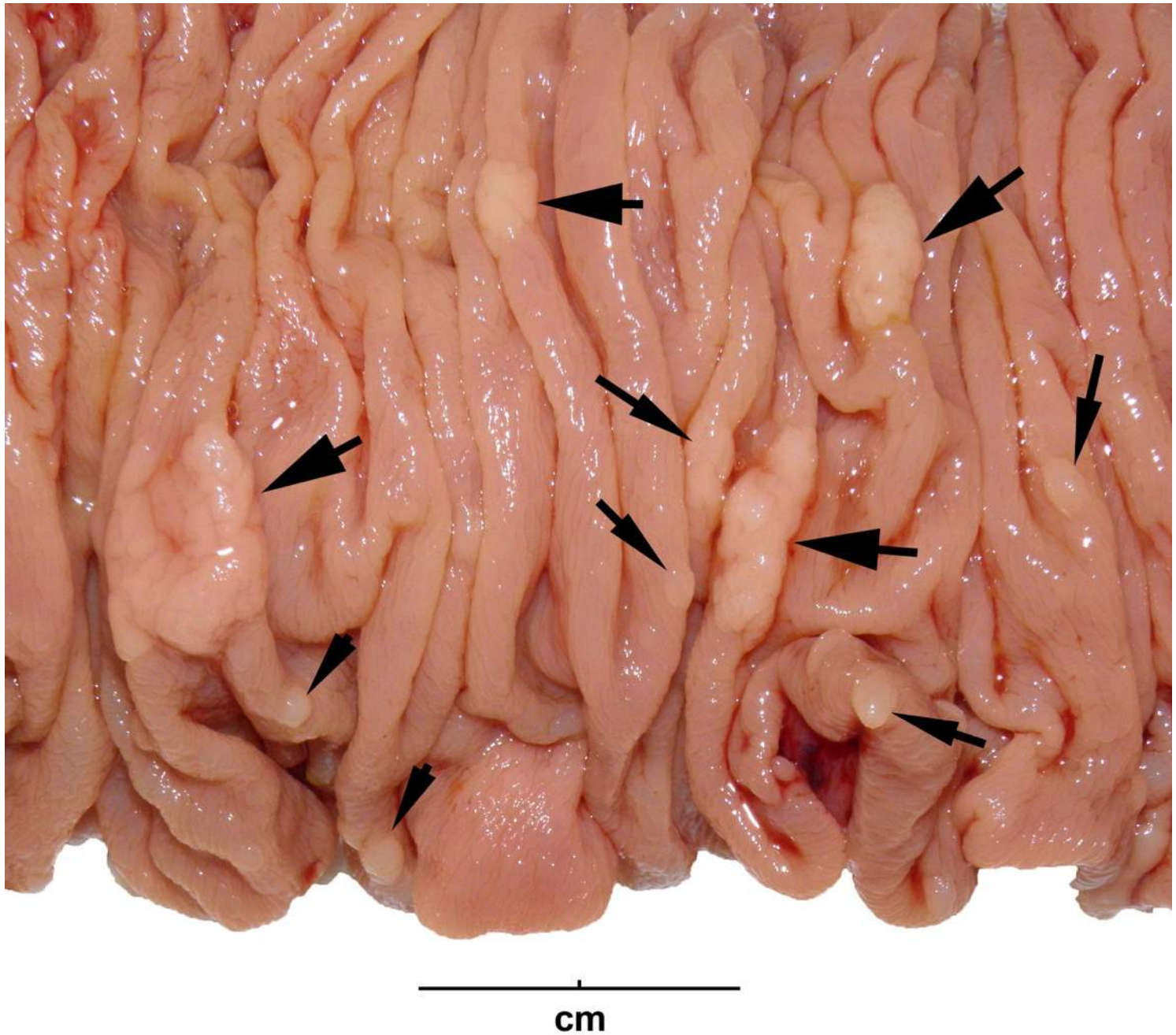
- Make the diagnosis if all information is available
- Suggest the diagnosis if criteria are likely to be fulfilled
  - Comment: “Depending of polyp location and size, the patient may fulfil one of the criteria for serrated polyposis. The revised 2019 WHO criteria are (1) at least 5 serrated polyps proximal to the rectum all ≥ 5 mm, with at least two ≥ 10 mm and (2) > 20 serrated polyps of any size but distributed throughout the large bowel, with at least 5 proximal to the rectum.”
- Look for and sample polyps in surgical resection specimens for CRC

Right hemicolectomy for synchronous CRCs




2 cm

Colectomy for high polyp burden


cm

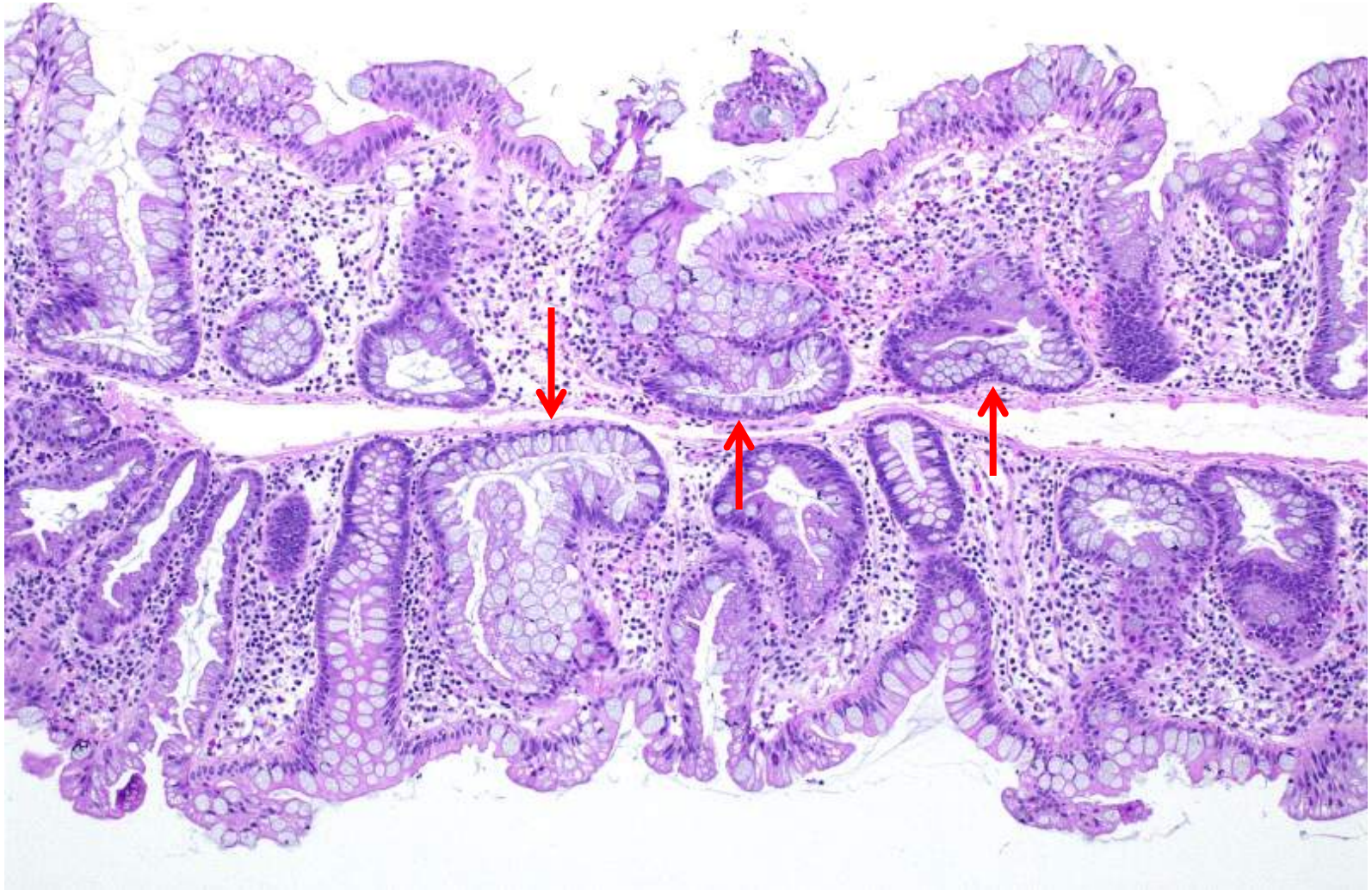
5th WHO classification of serrated lesions/polyps

- Hyperplastic polyp (HP)
  - Microvesicular type
  - Goblet cell type
  - ~~Mucin poor type~~
- Sessile serrated lesion (SSL)
- Sessile serrated lesion with dysplasia (SSLD)
- Traditional serrated adenoma (TSA)
- Serrated adenoma unclassified

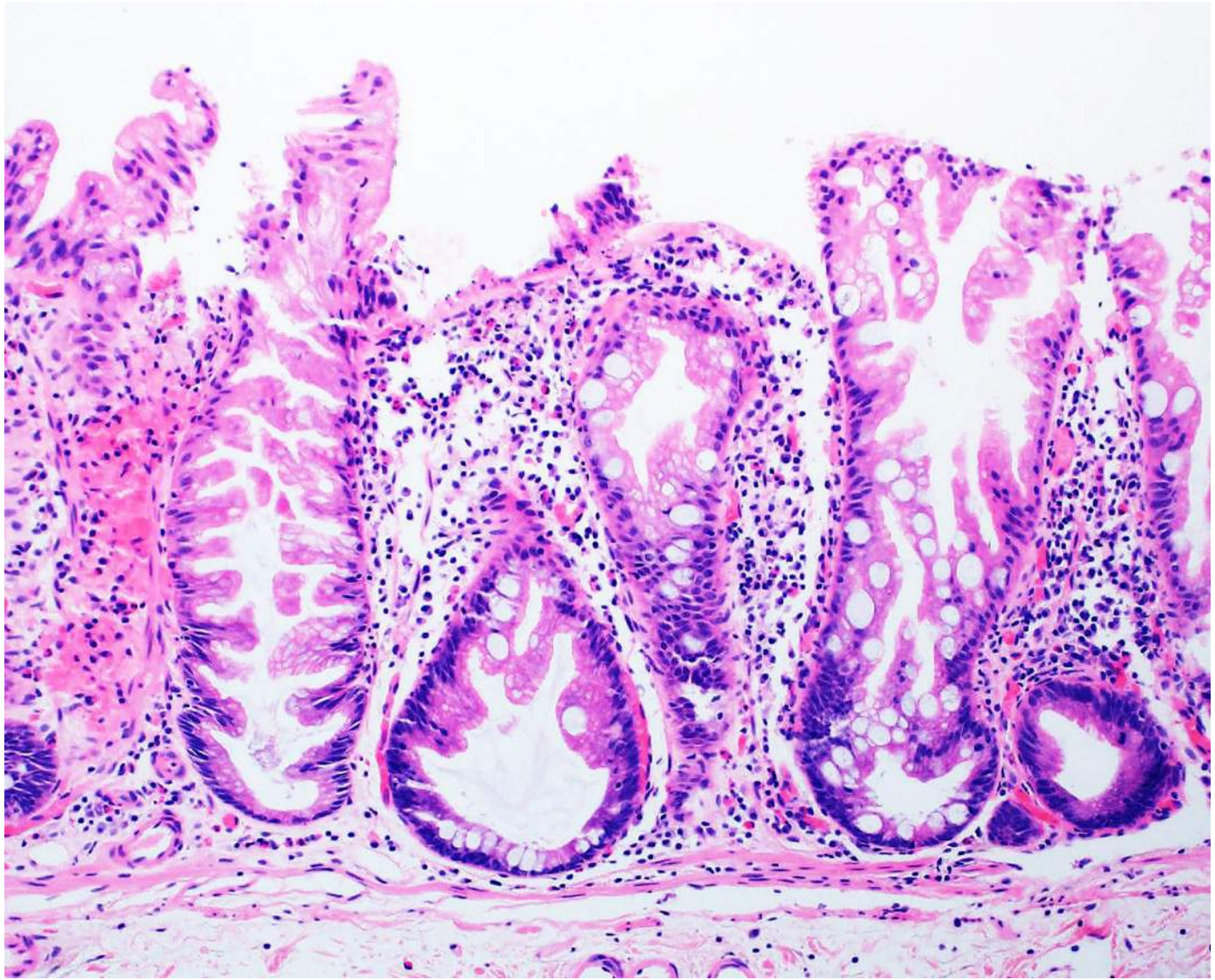
Sessile serrated lesion (SSL)

- SSA and SSP no longer recommended
- A single unequivocal architecturally distorted serrated crypt is sufficient:
  - Asymmetrical dilatation of basal third of the crypt
  - Horizontal growth along the muscularis mucosae
  - Serration extending into the crypt base
- Not enough for SSL diagnosis
  - Mild symmetrical crypt dilatation
  - Occasional branched crypts
  - Goblet cells in the crypt bases

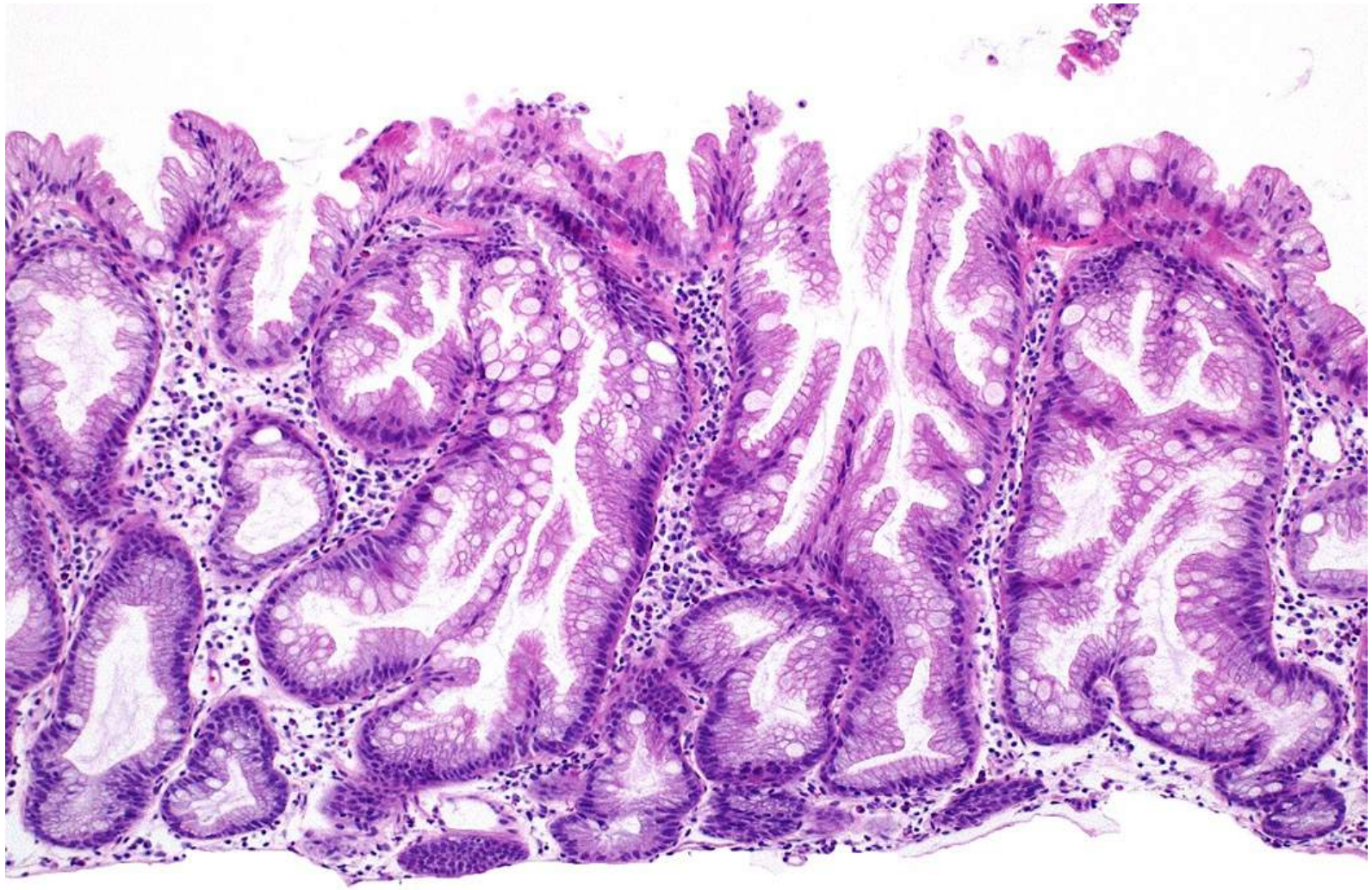
Asymmetrical dilatation of the crypt base



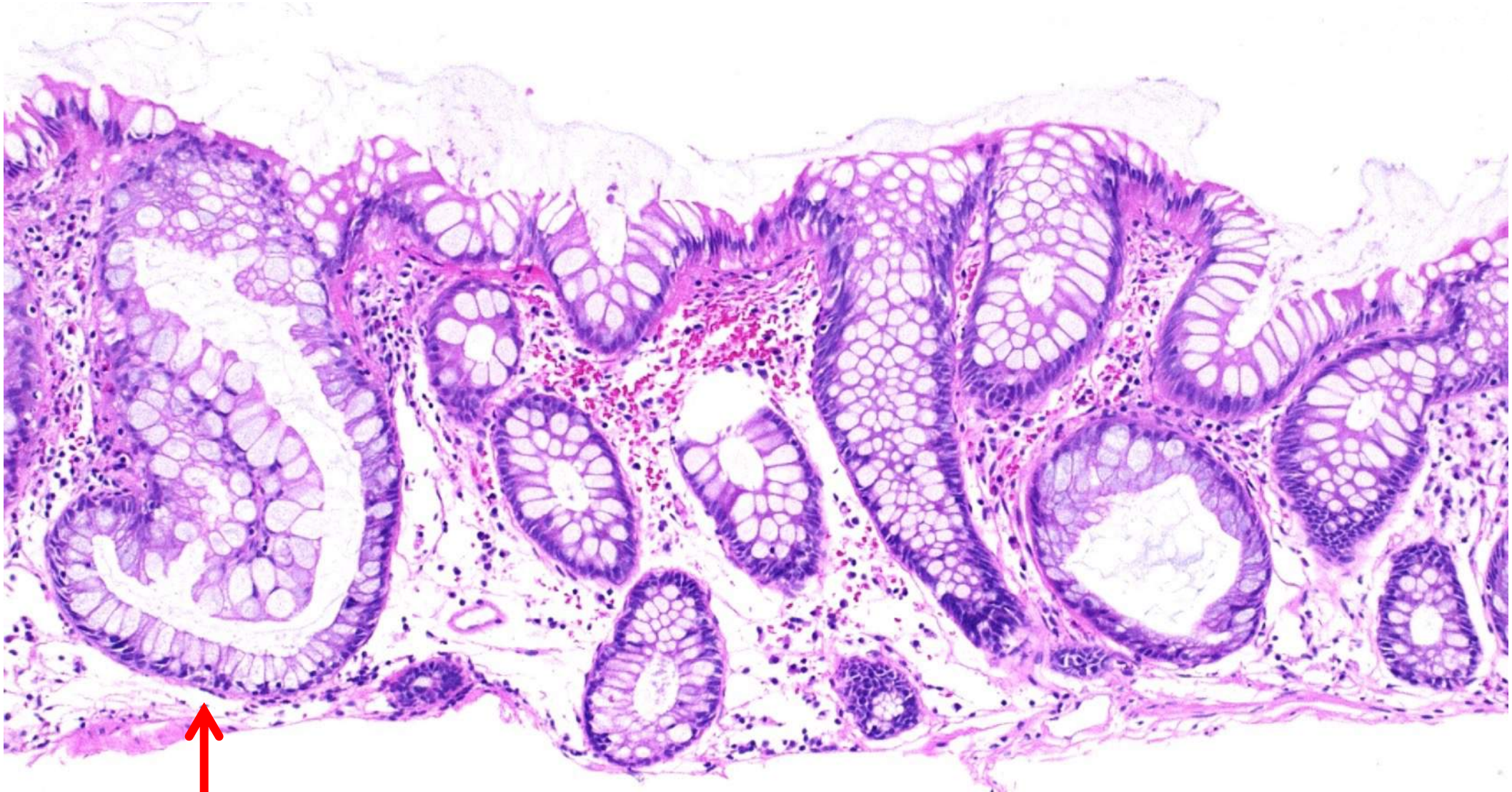
Serration extending into the crypt base



Asymmetrical proliferation

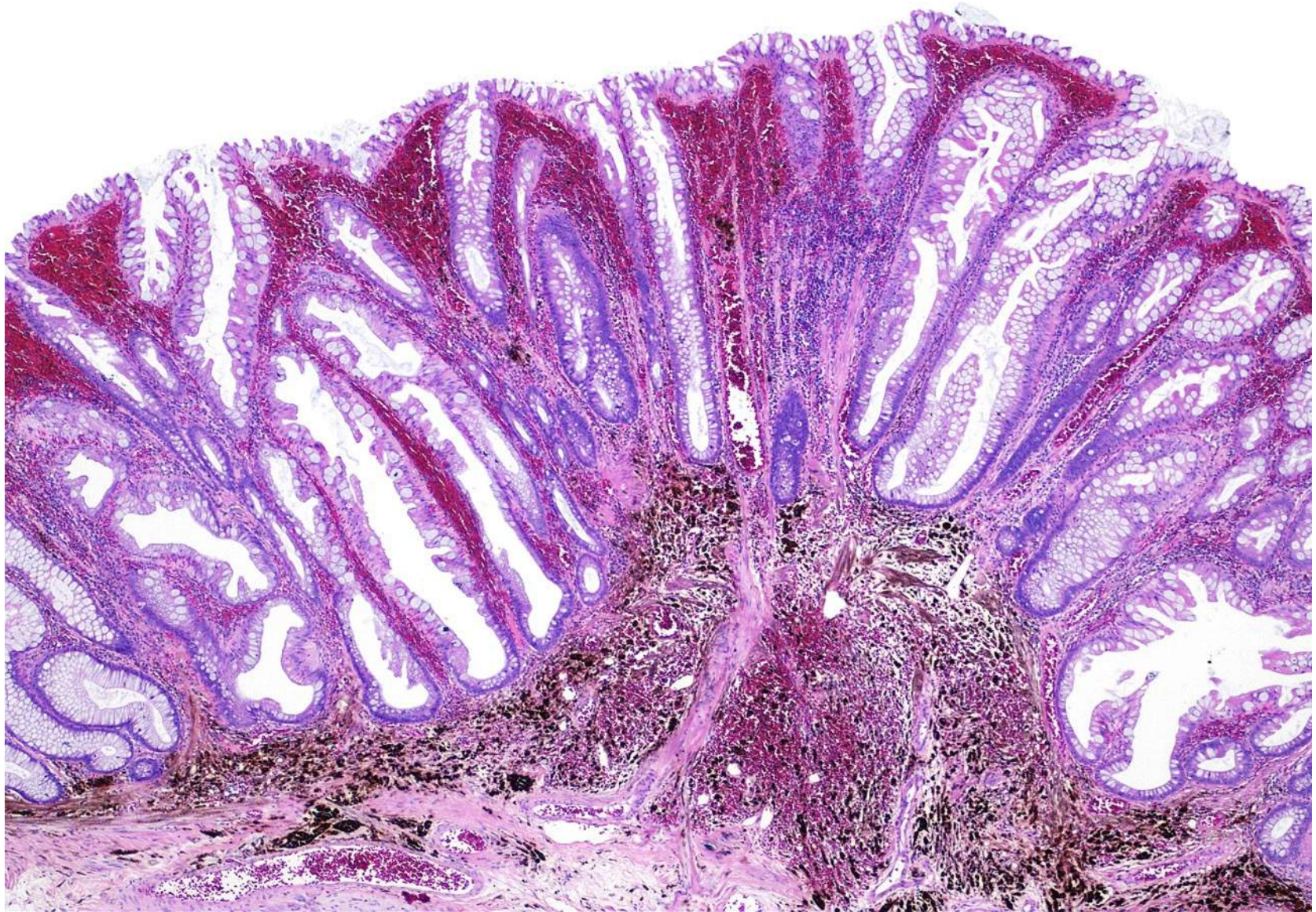


Unequivocal SSL crypt in a 2 mm lesion

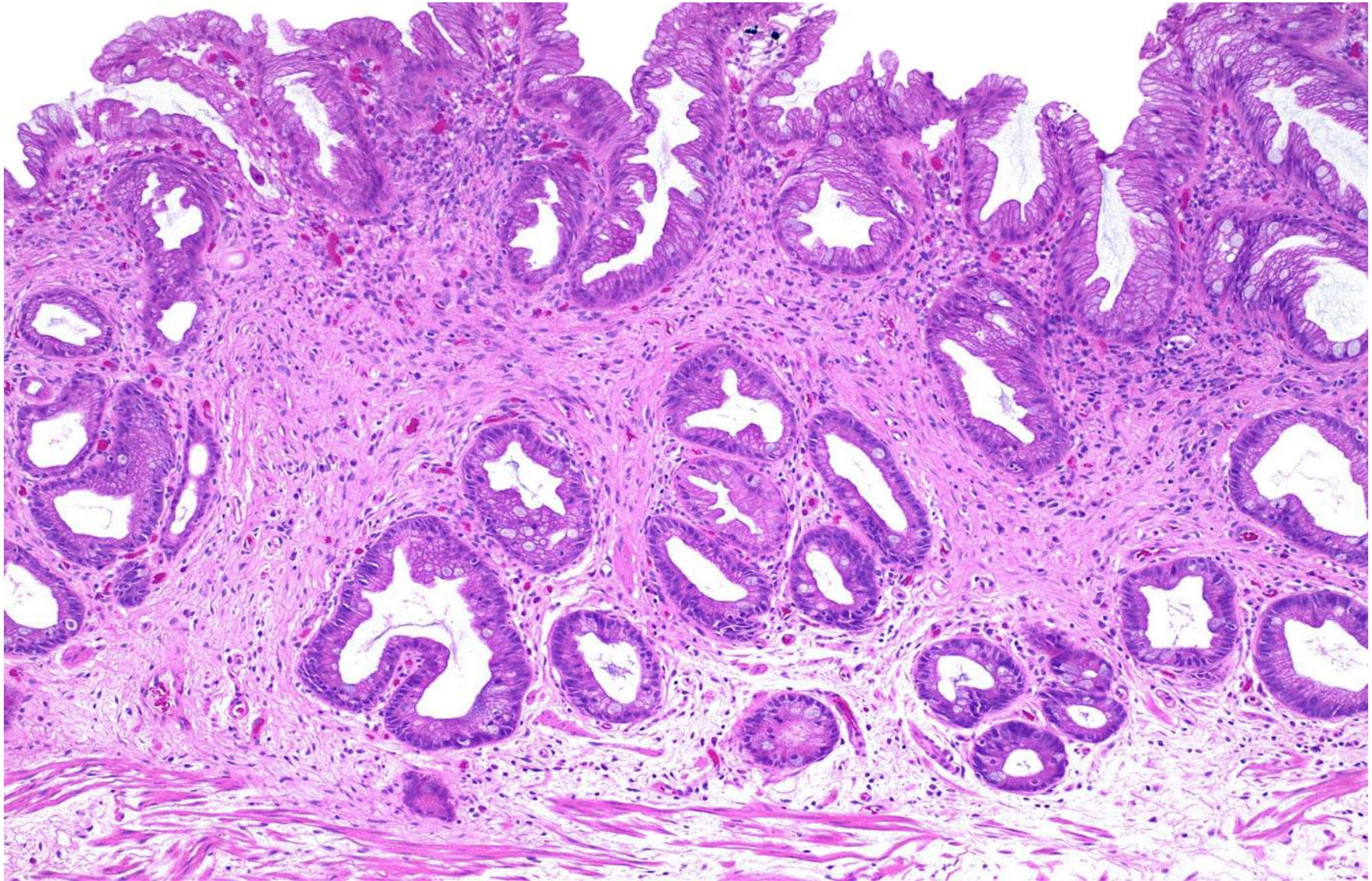


Not an SSL

Mucosal prolapse changes in HP



Perineurial-like stromal proliferation in HP

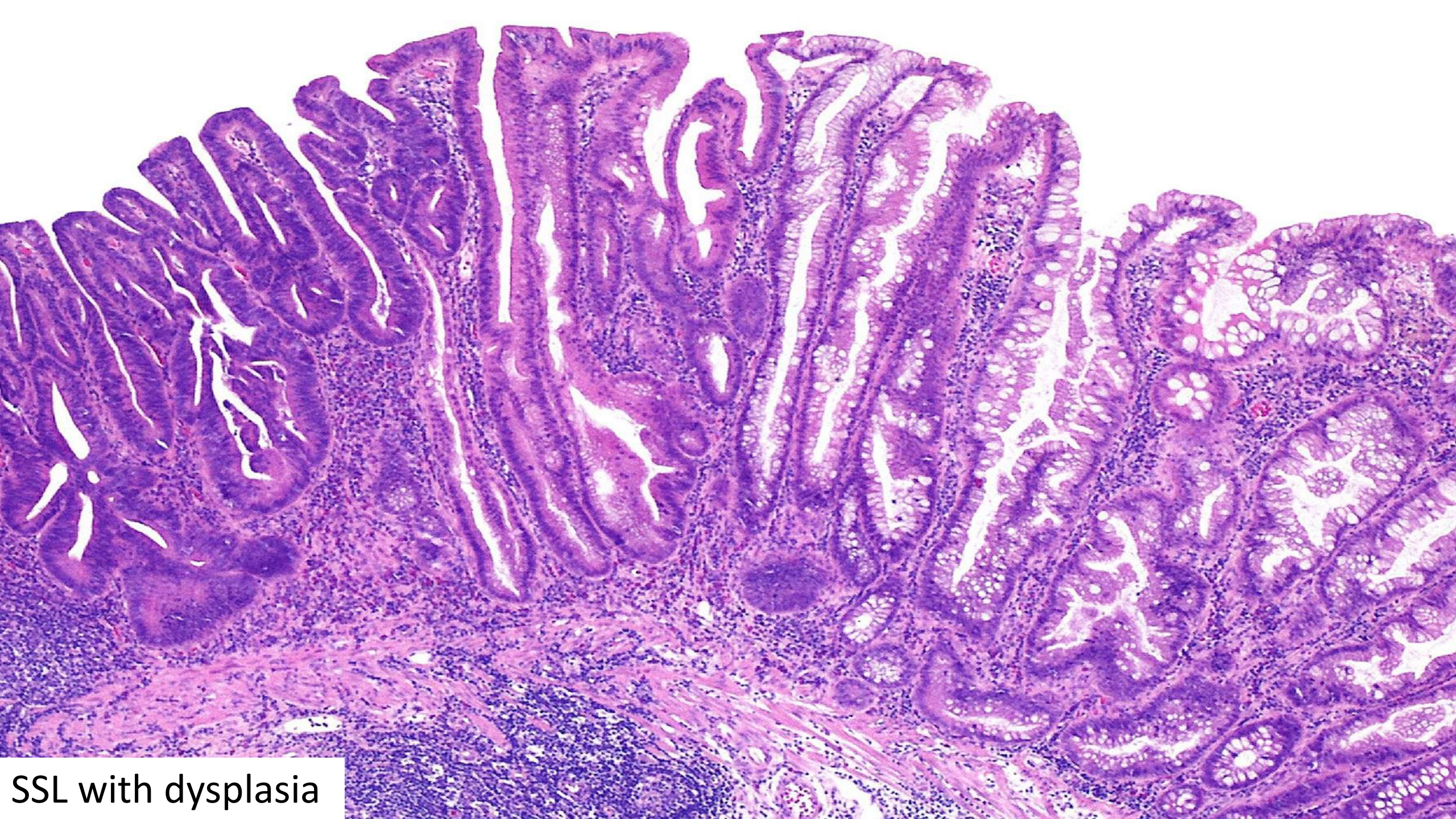


SSL versus HP

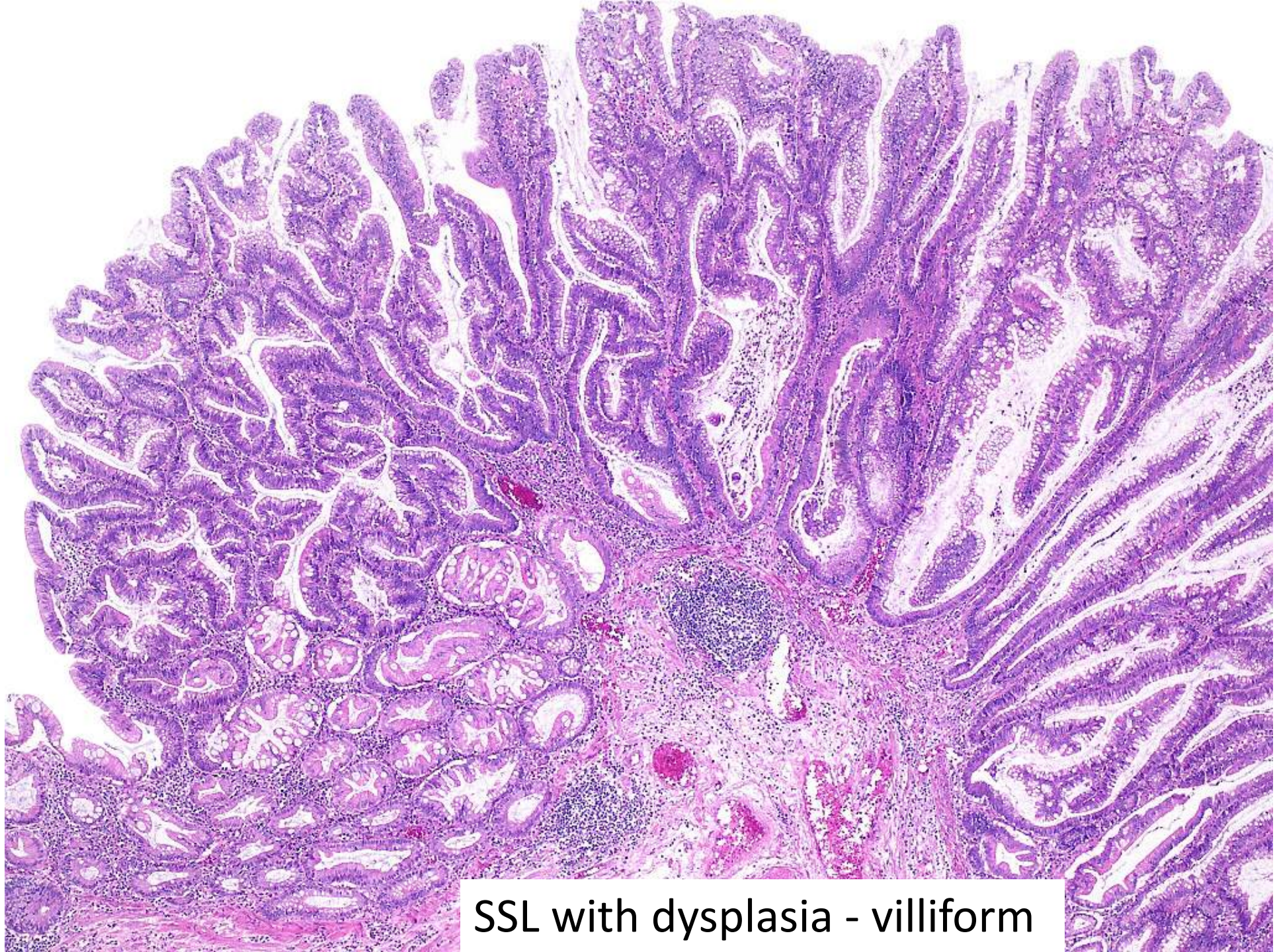
- Well-oriented tissue section is essential
- HP is a diagnosis by exclusion when no SSL crypt is present
- Proximal HPs do exist but are usually small (< 10 mm)
- SSLs can be diminutive polyps (< 5 mm)
- Distal colonic SSLs do exist; rectal SSLs are rare
- Superimposed mucosal prolapse changes in HP and SSL

Sessile serrated lesion with dysplasia

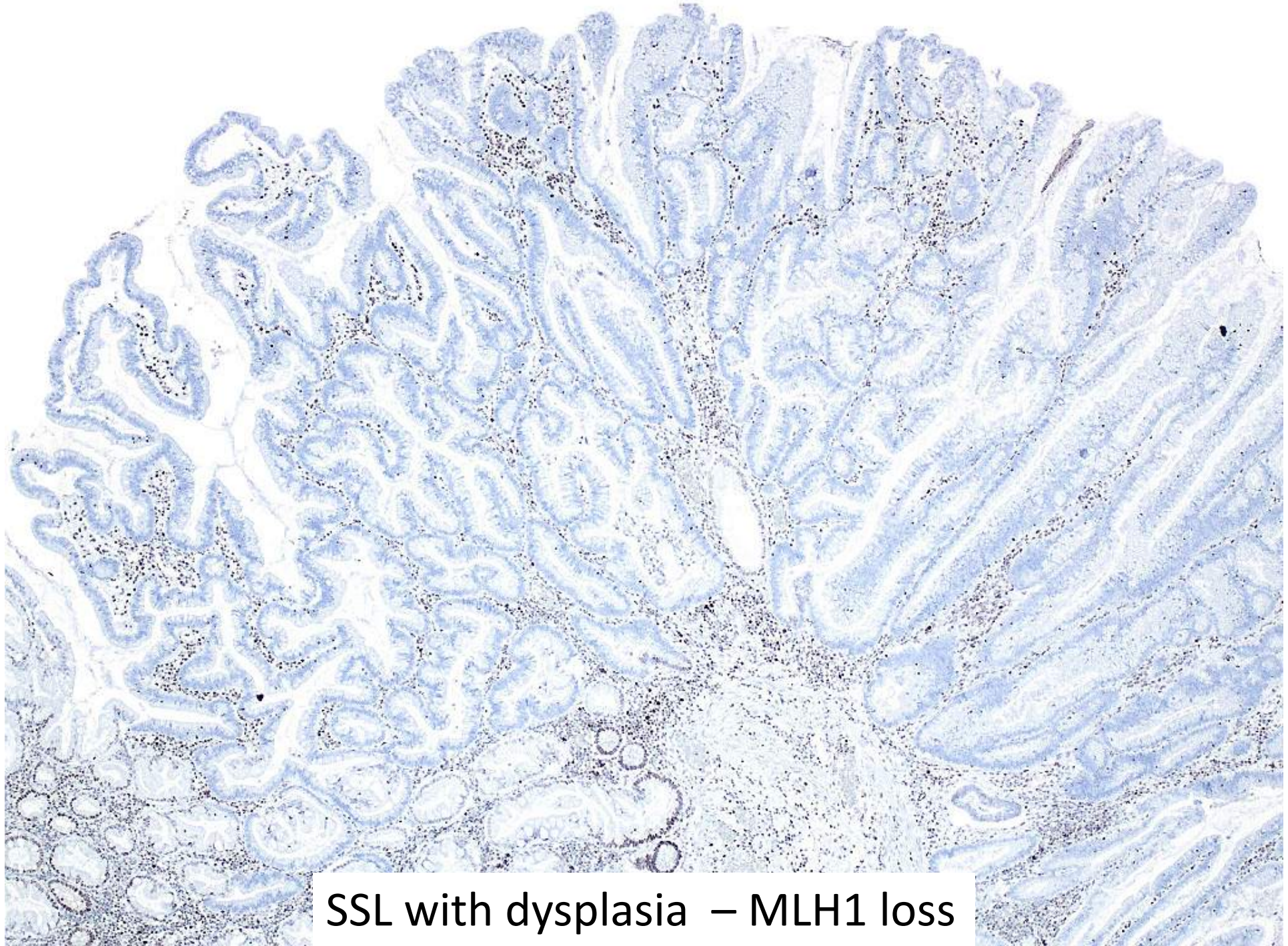
- Most advanced and clinically relevant type of serrated lesion
- Main precursor lesion of *BRAF*-mutated CRC
- Varied morphological patterns of dysplasia
- Abrupt transition from SSL
- Dysplasia in SSLD is not graded
- Loss of MLH1 expression in 75%



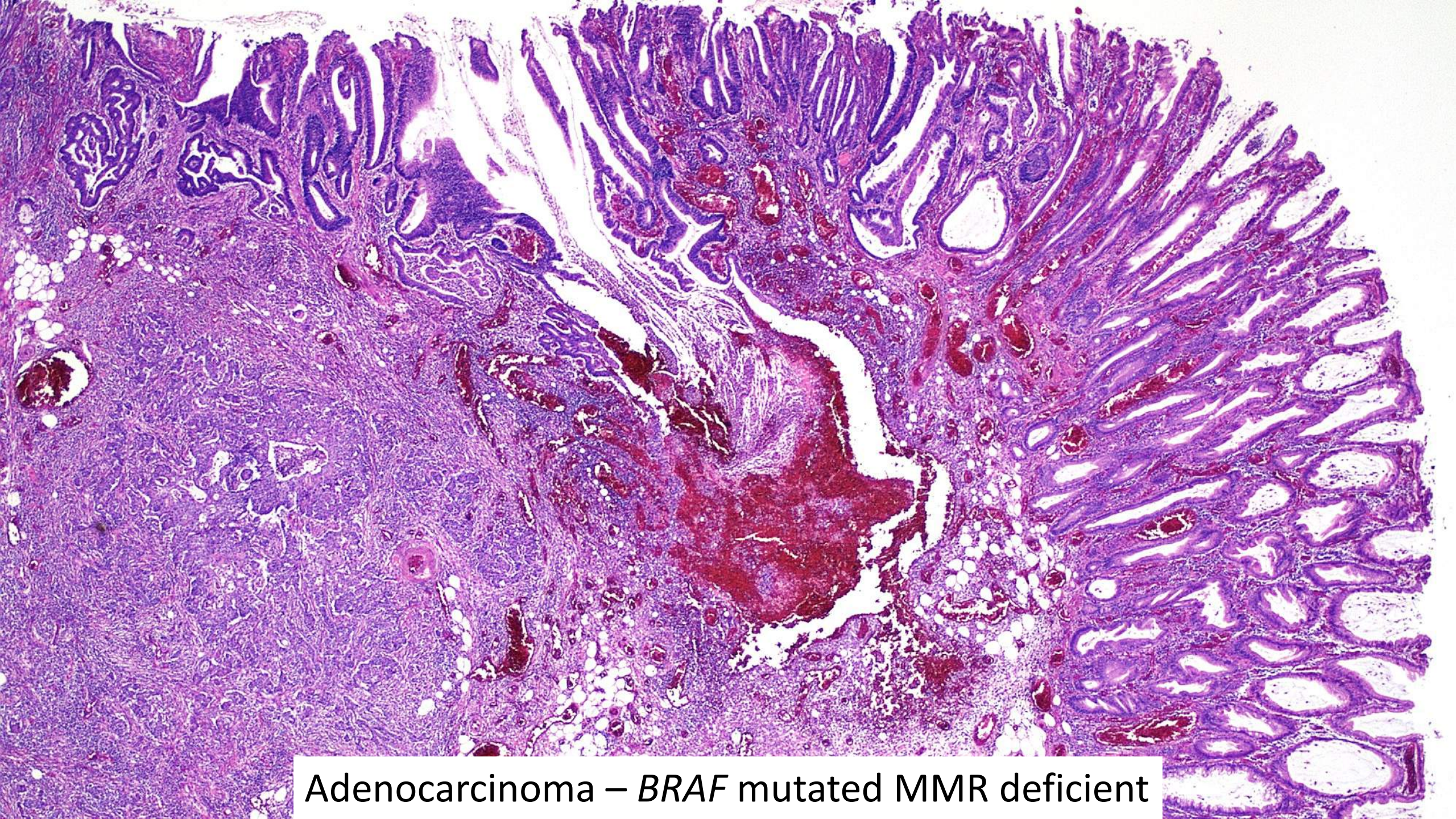
SSL with dysplasia



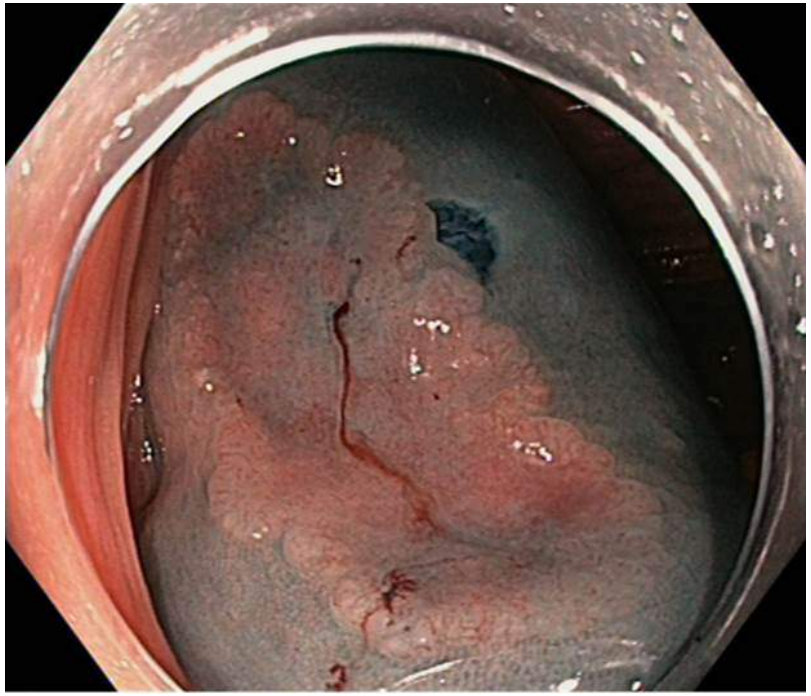
SSL with dysplasia - villiform

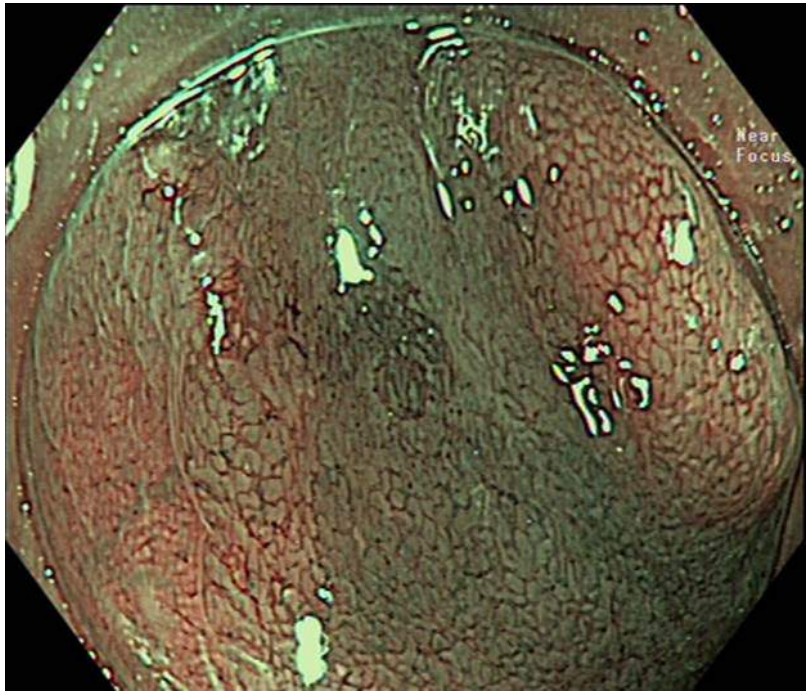


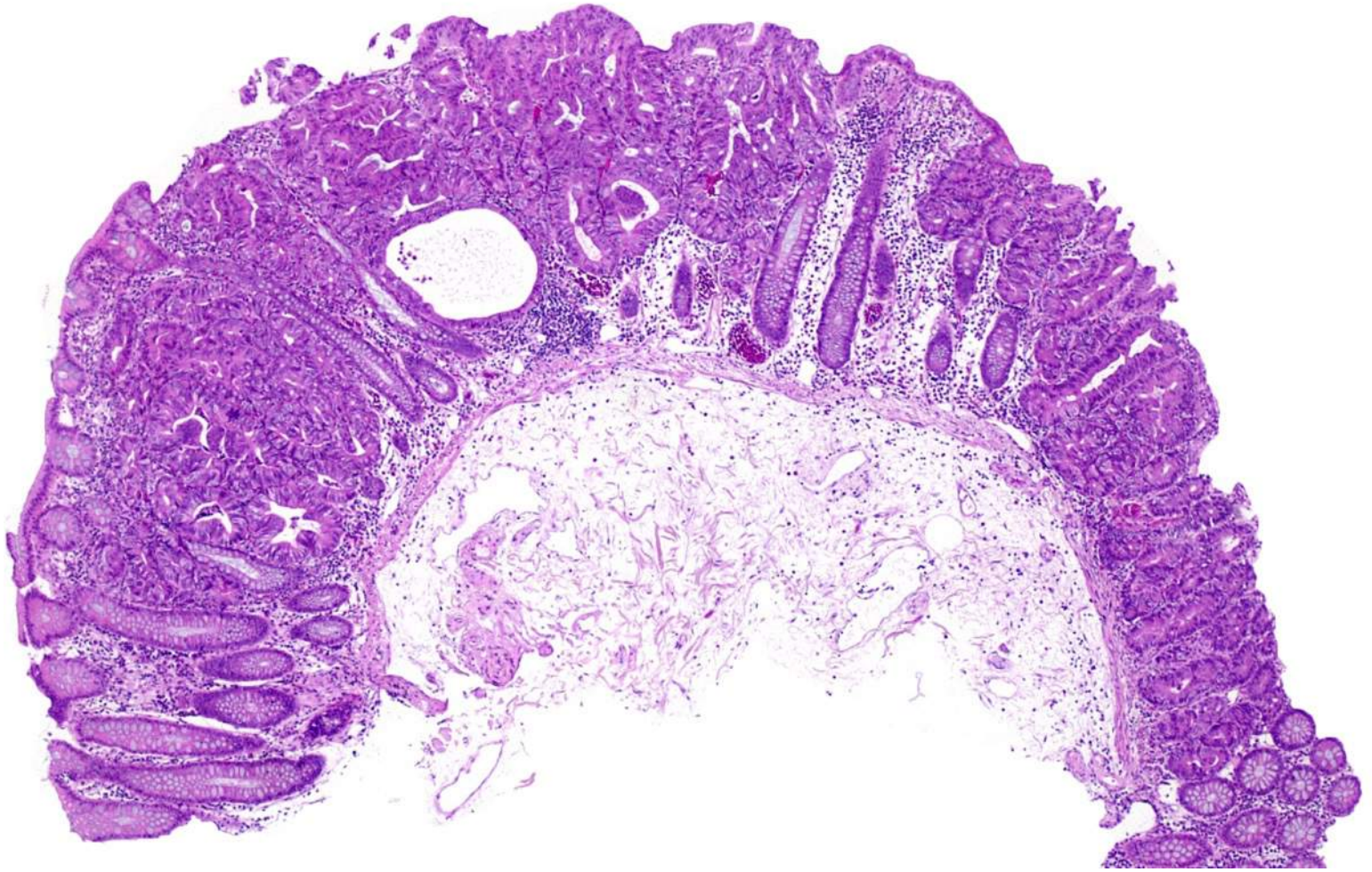
SSL with dysplasia – MLH1 loss



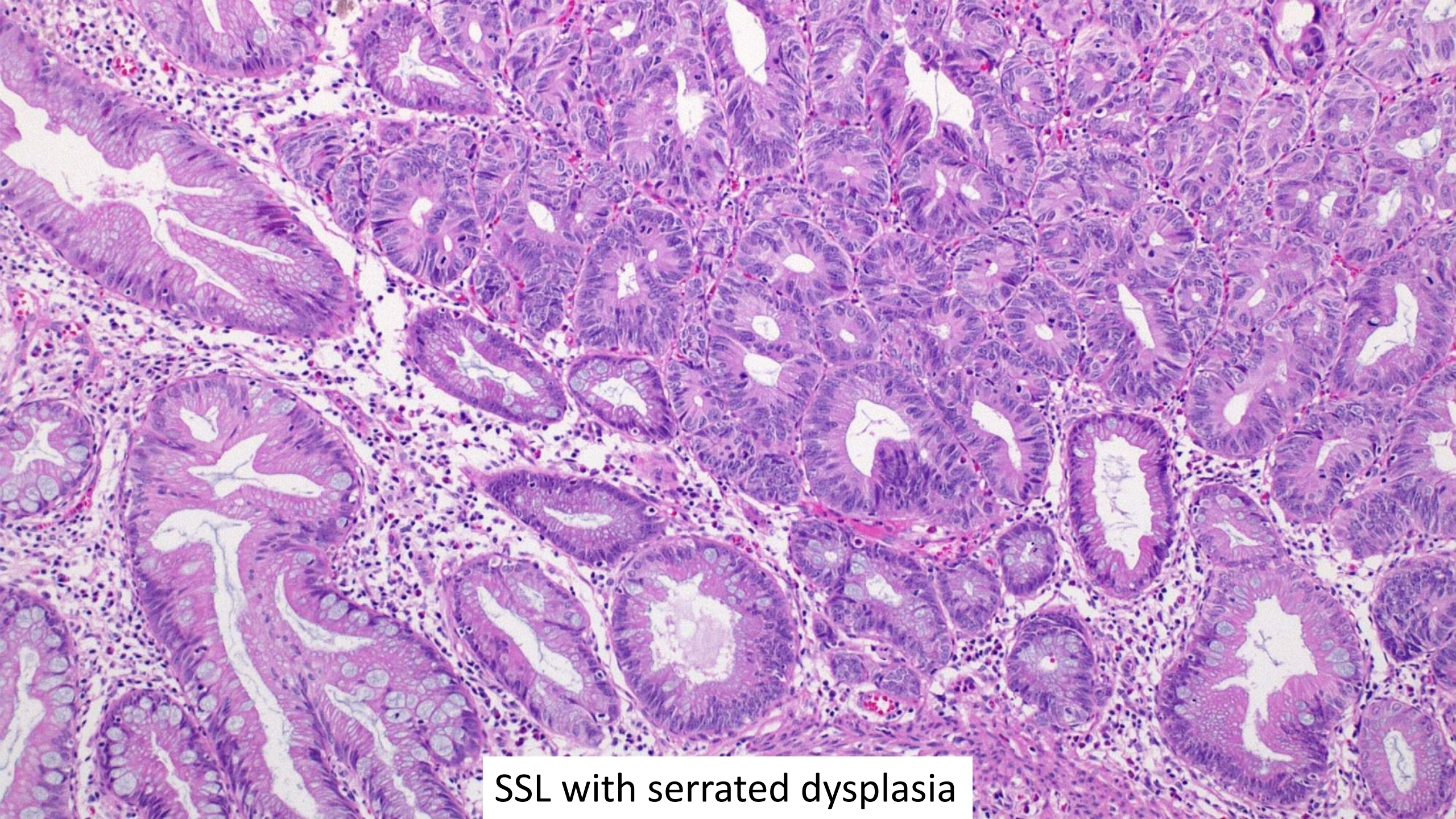
Adenocarcinoma – *BRAF* mutated MMR deficient

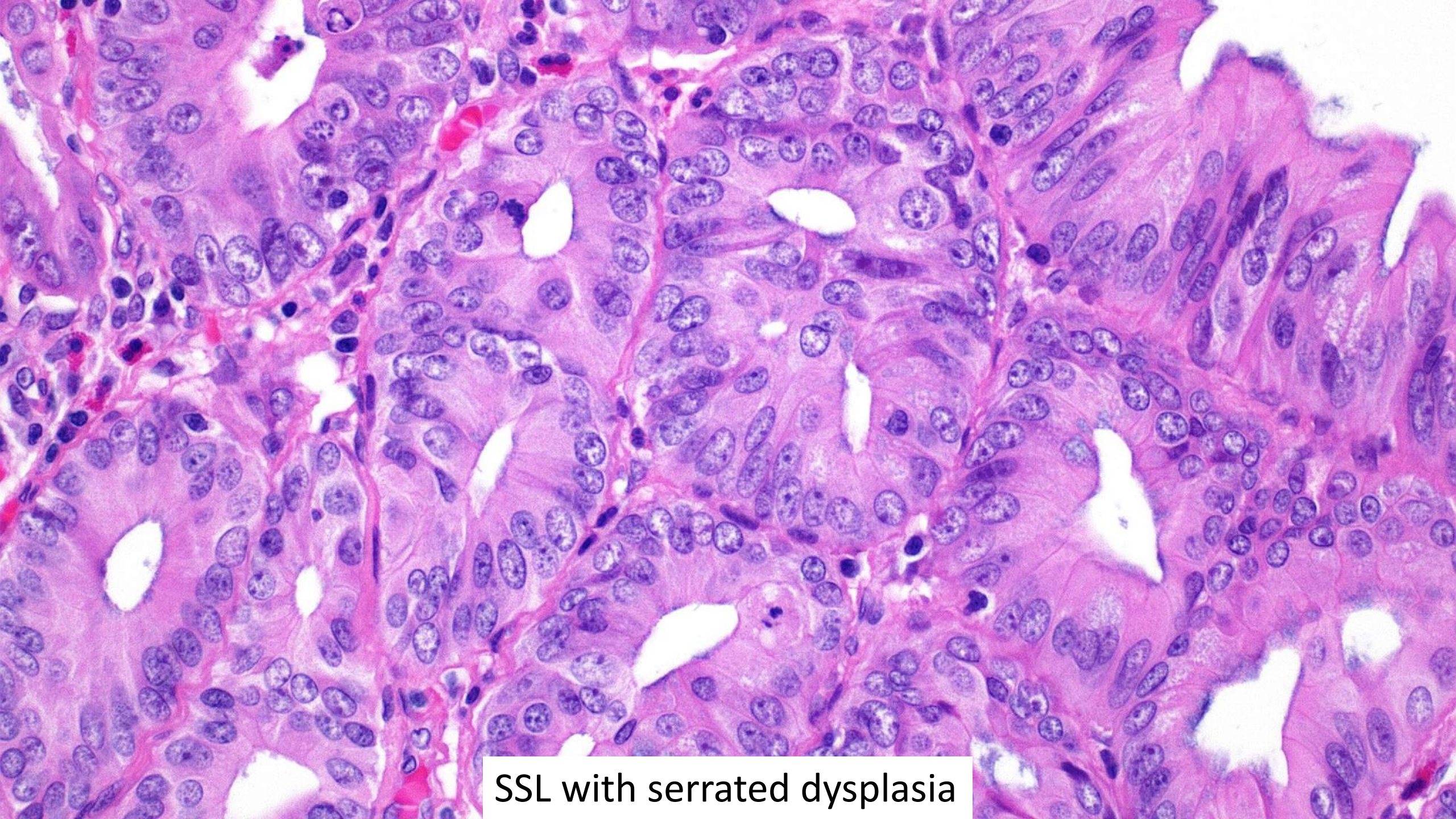


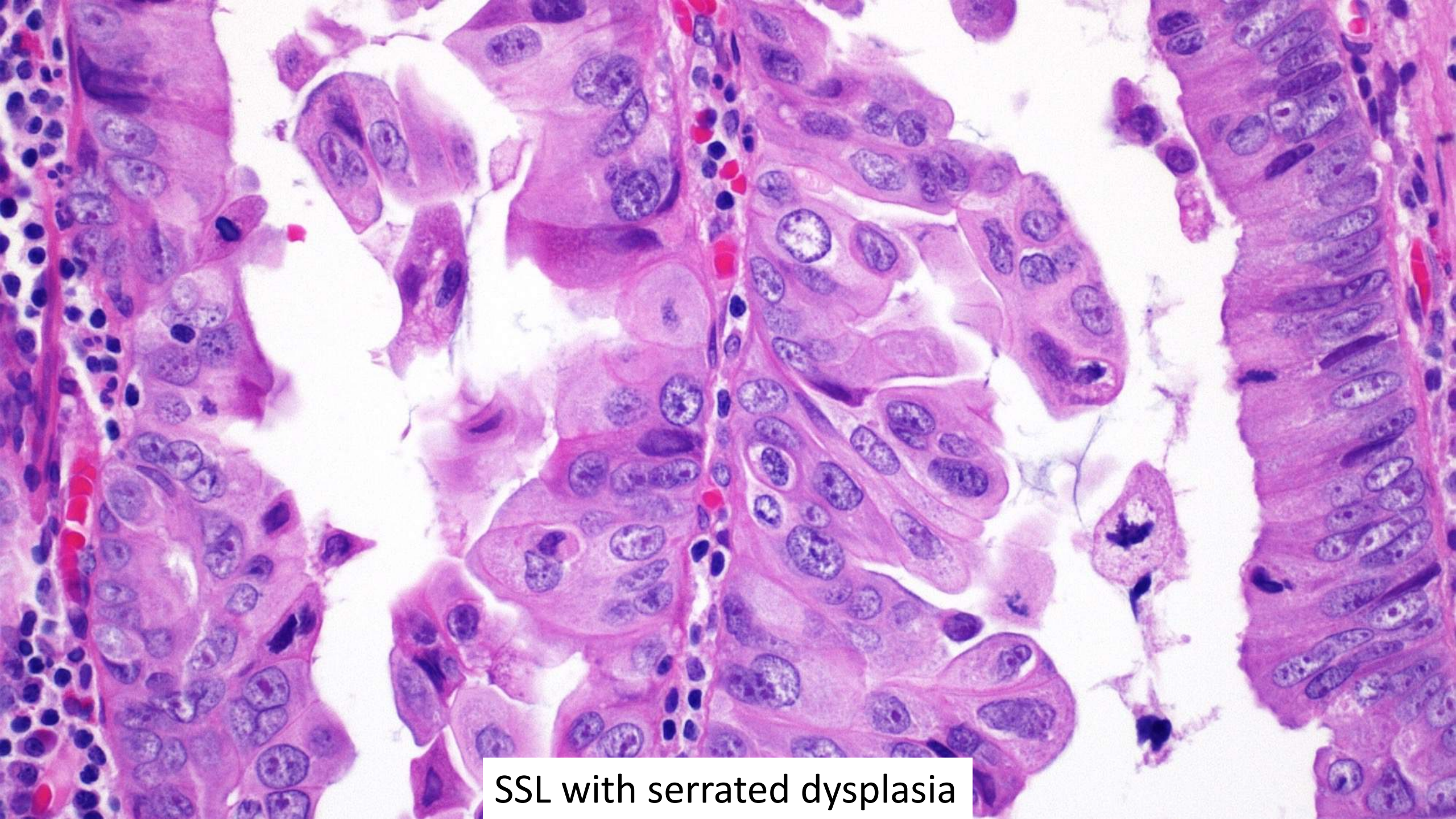




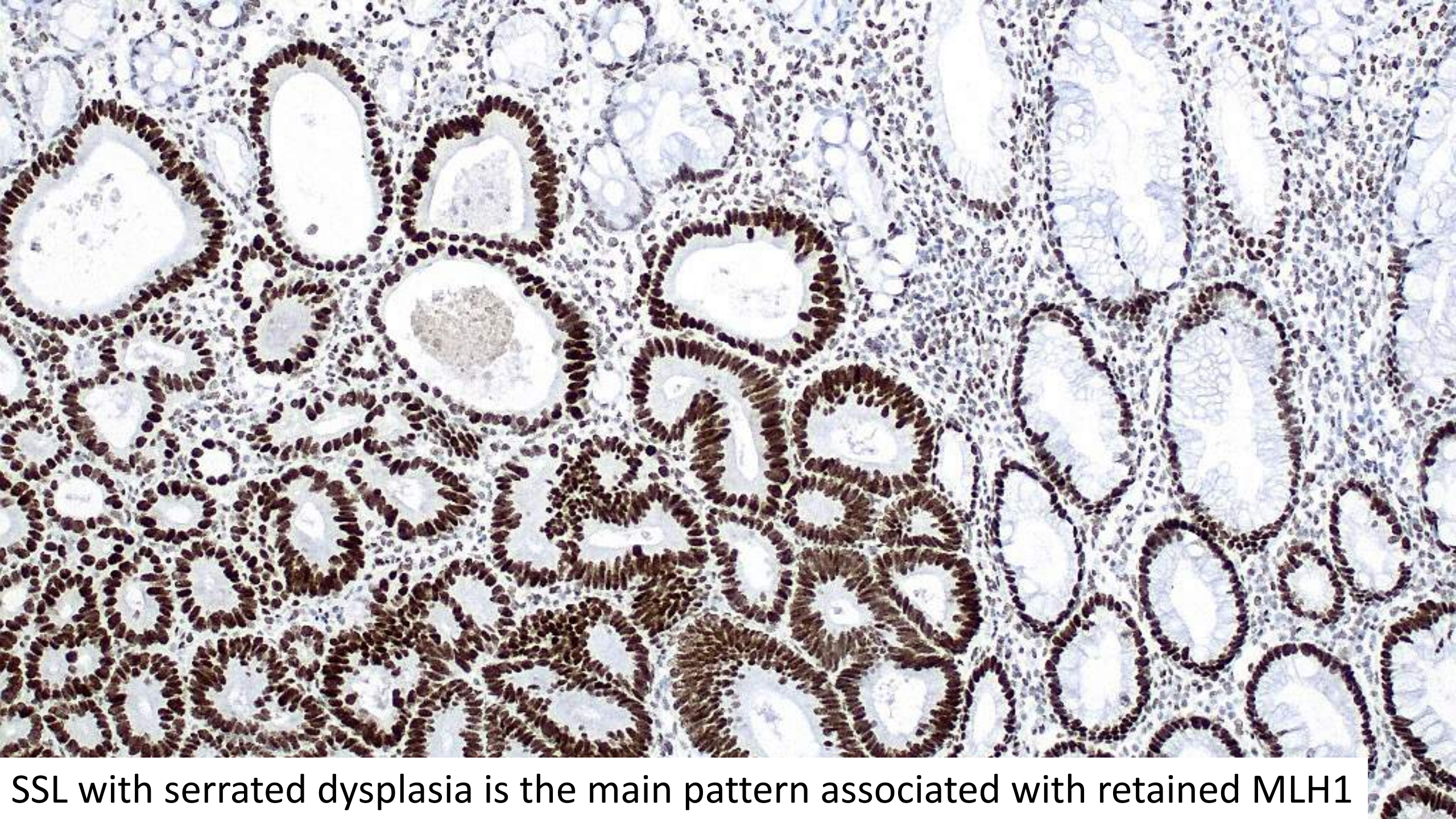
SSL with serrated dysplasia


SSL with serrated dysplasia

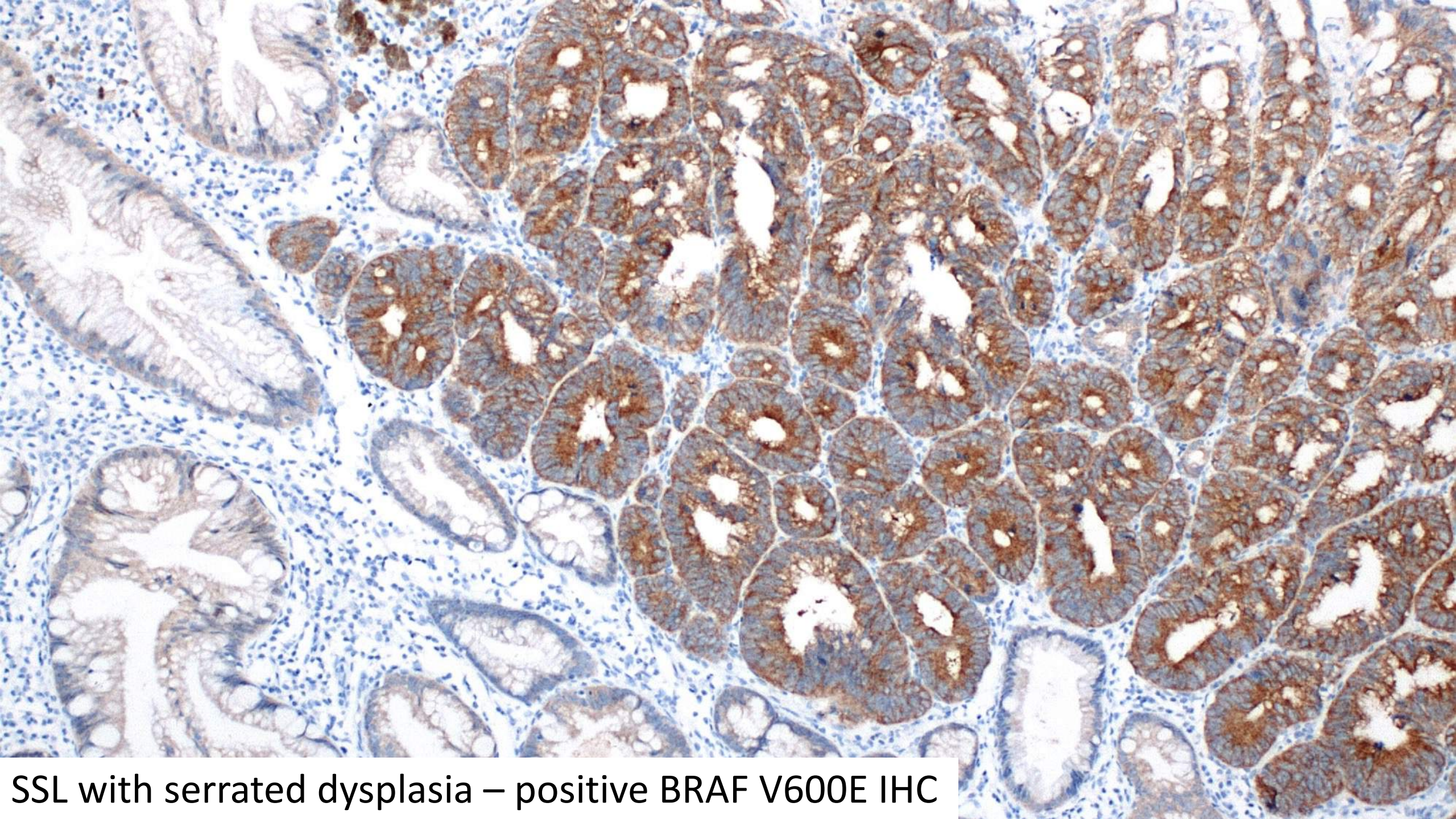

SSL with serrated dysplasia



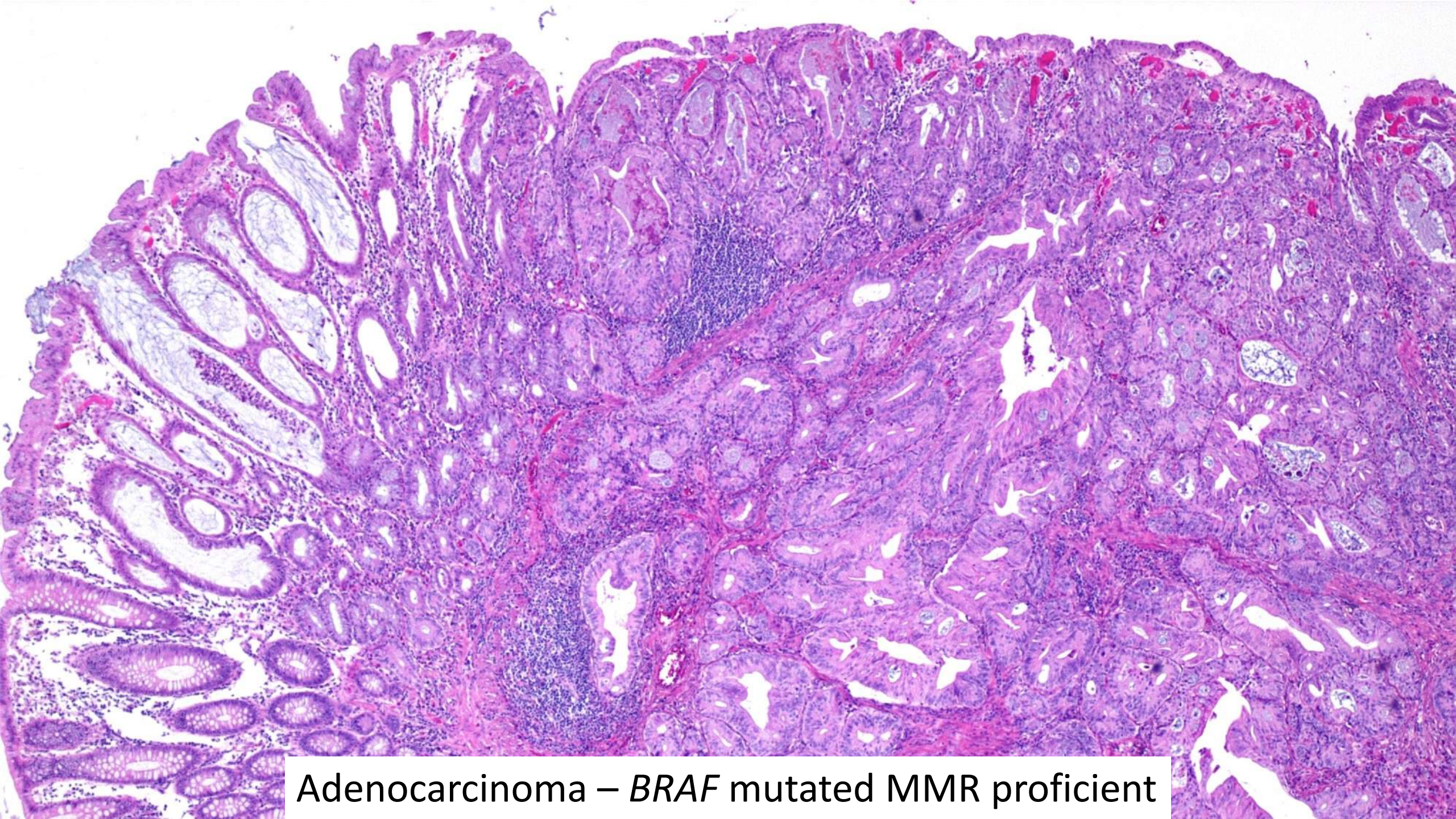
SSL with serrated dysplasia



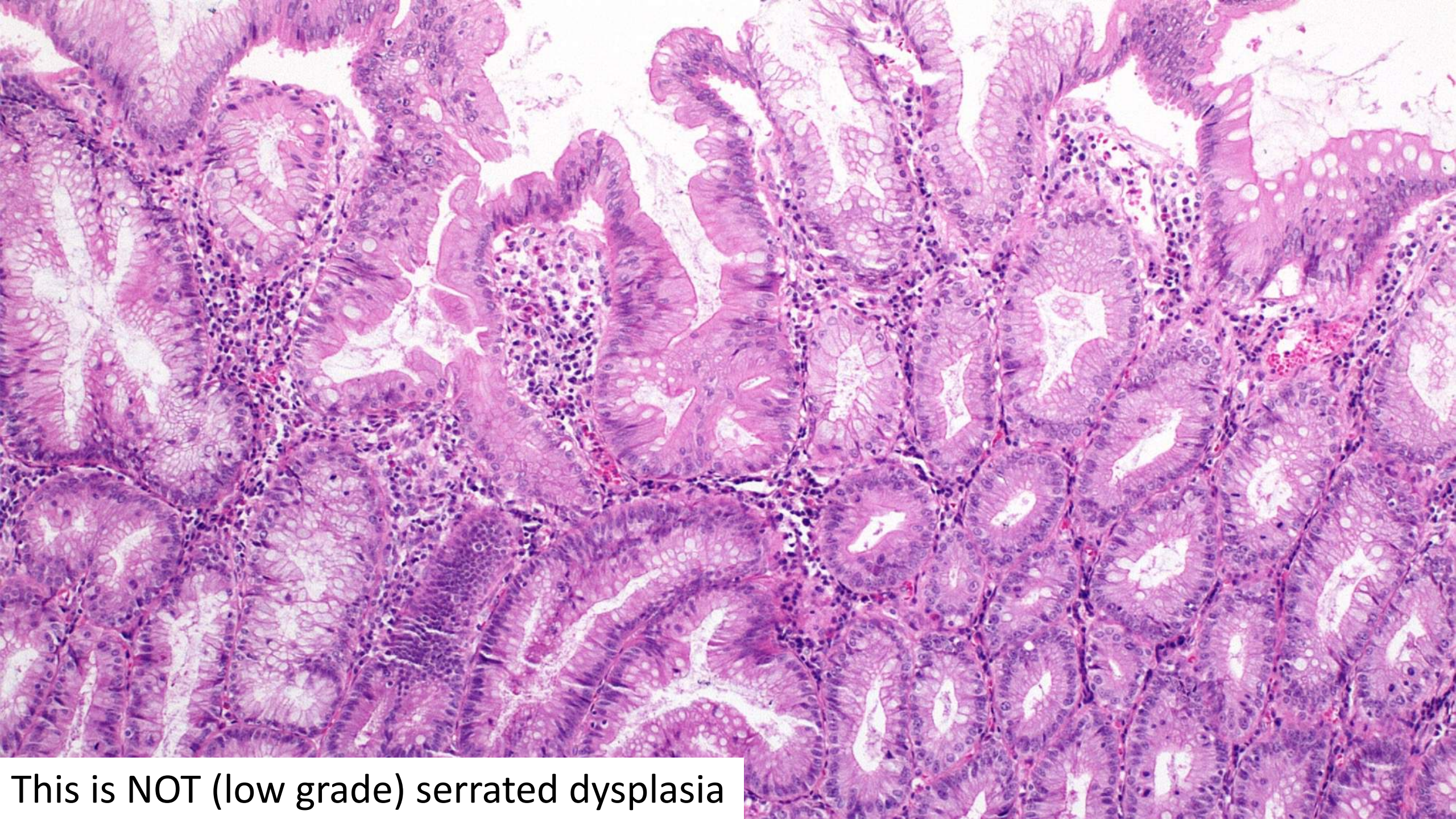
SSL with serrated dysplasia is the main pattern associated with retained MLH1

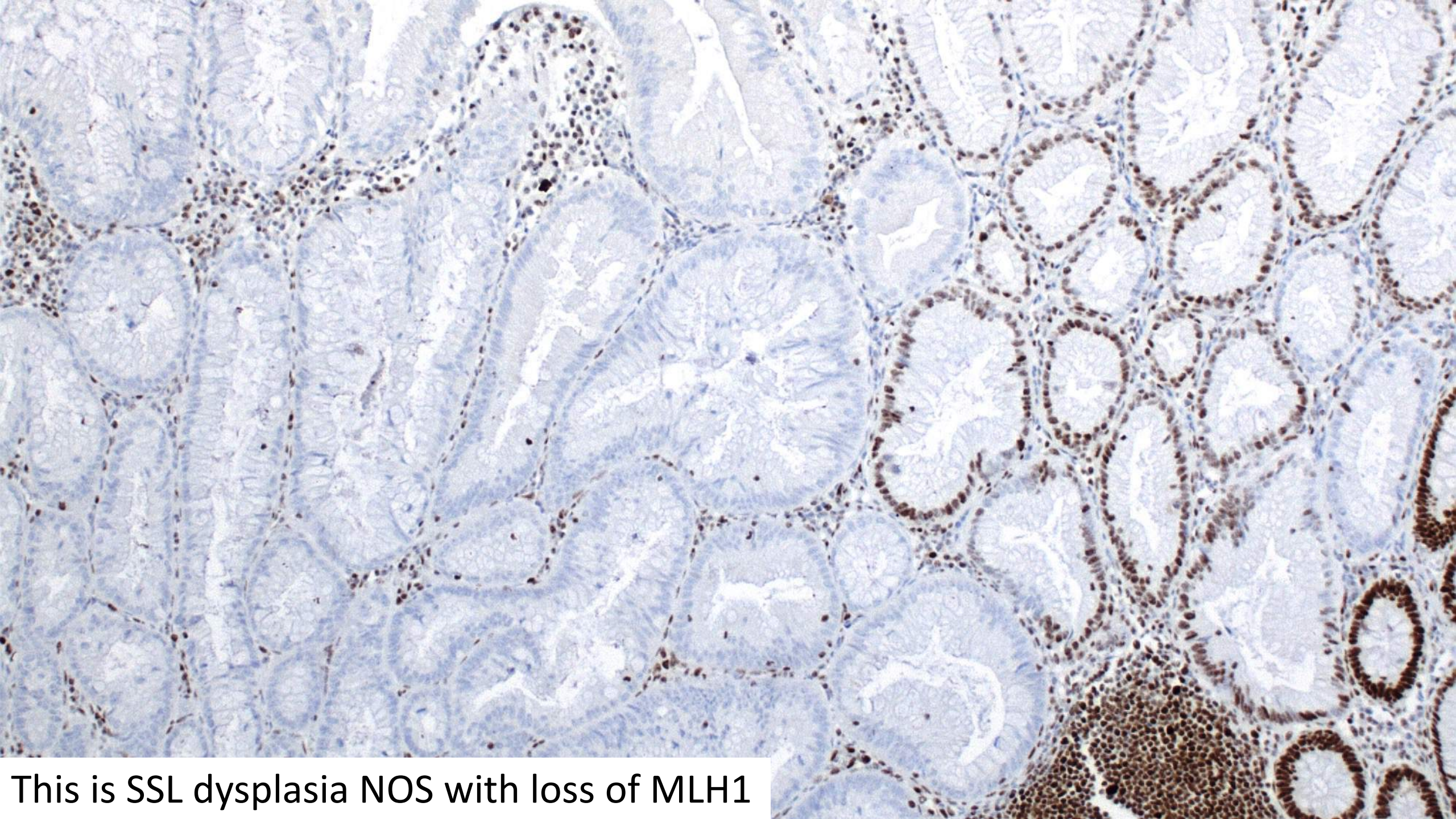


SSL with serrated dysplasia – positive BRAF V600E IHC

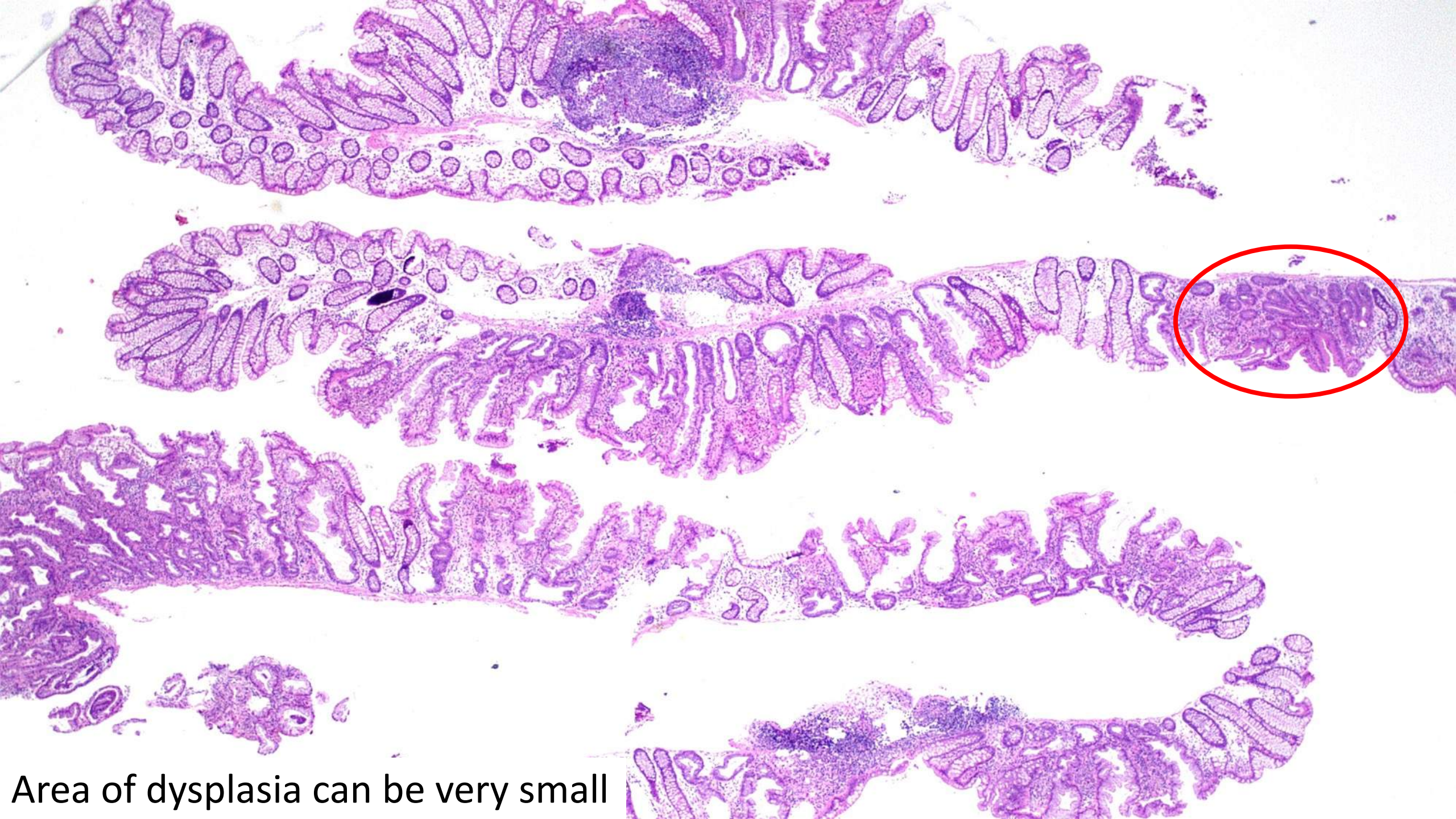


Adenocarcinoma – *BRAF* mutated MMR proficient

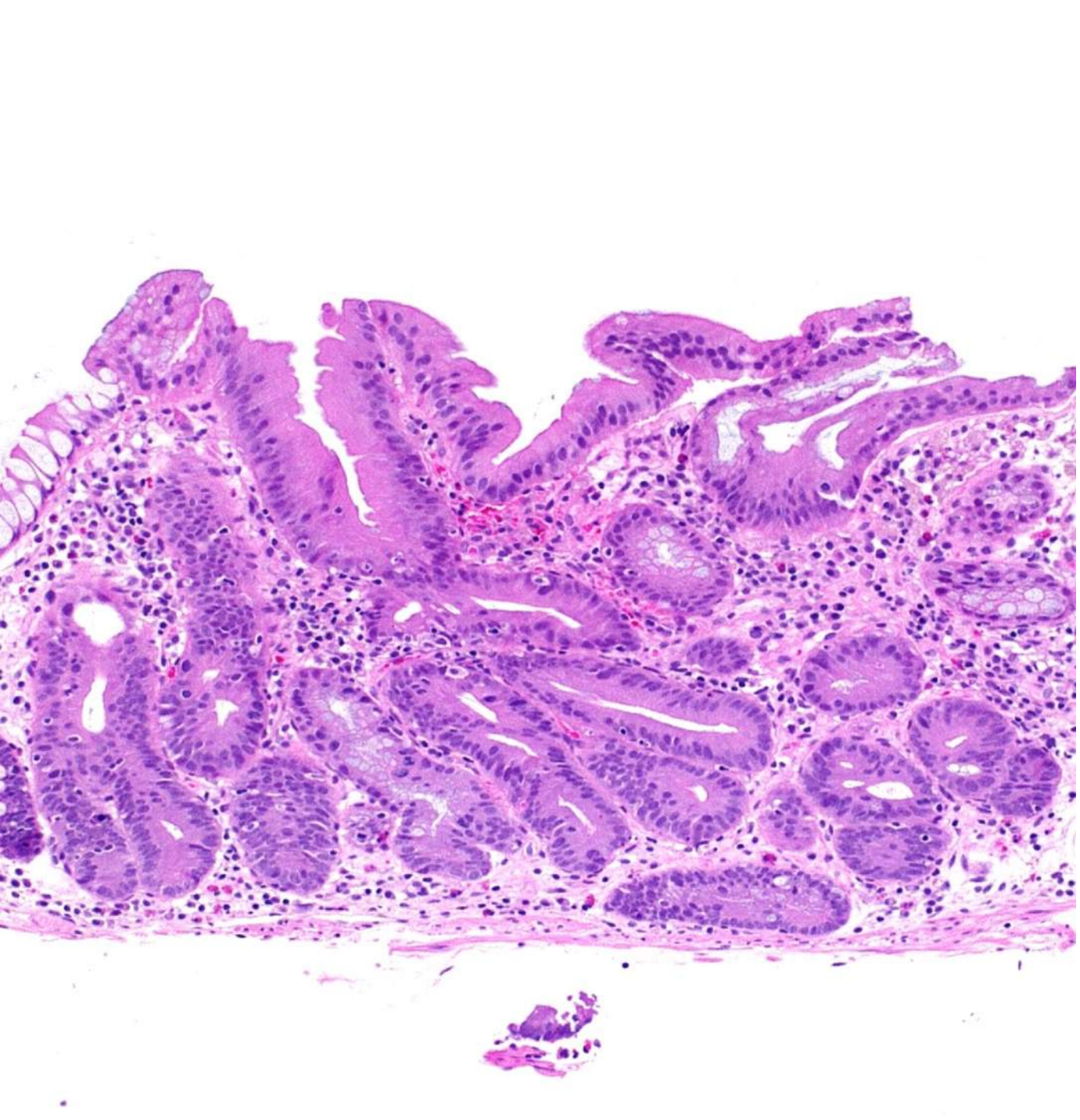

This is NOT (low grade) serrated dysplasia

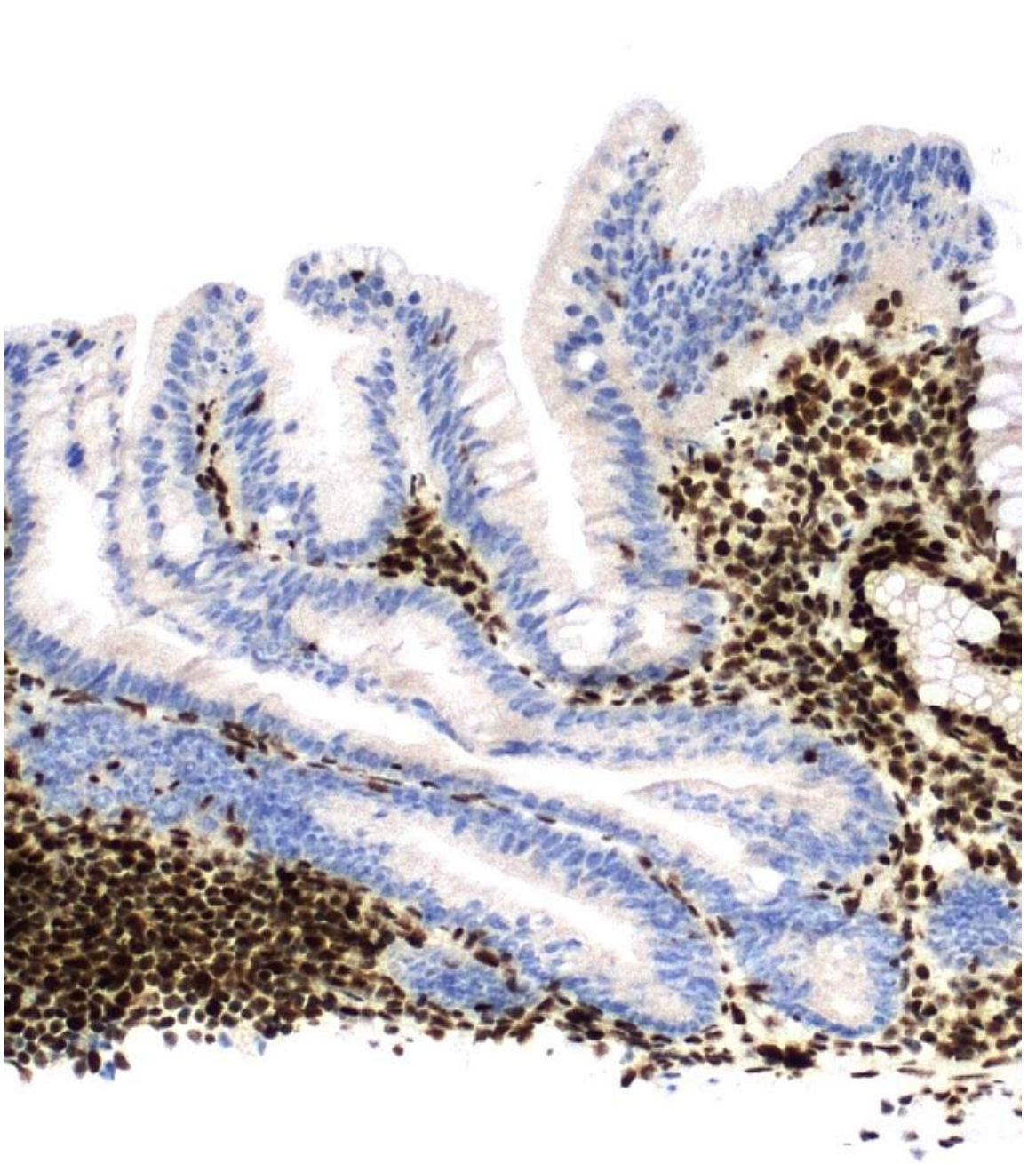


This is SSL dysplasia NOS with loss of MLH1



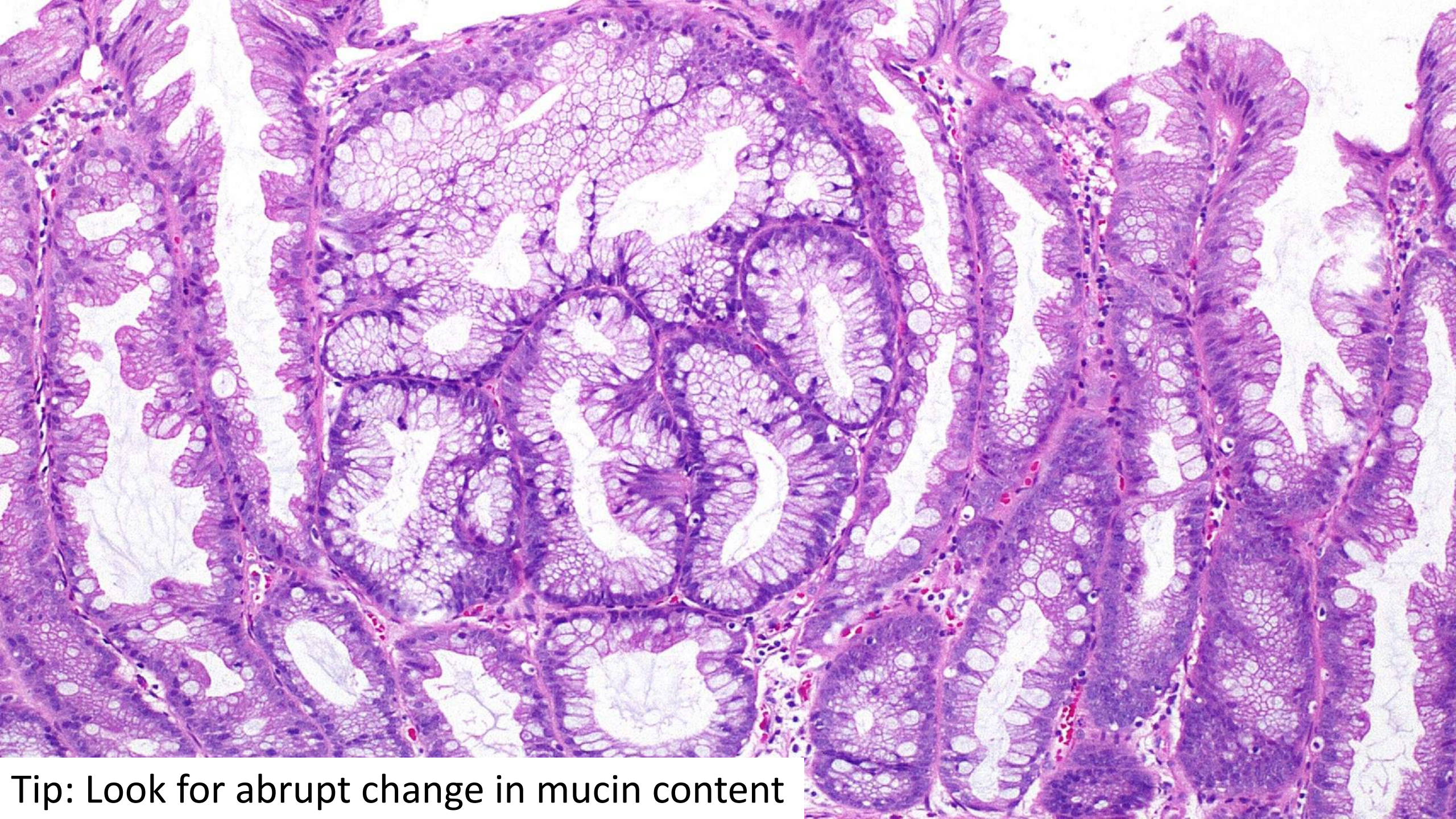
Area of dysplasia can be very small





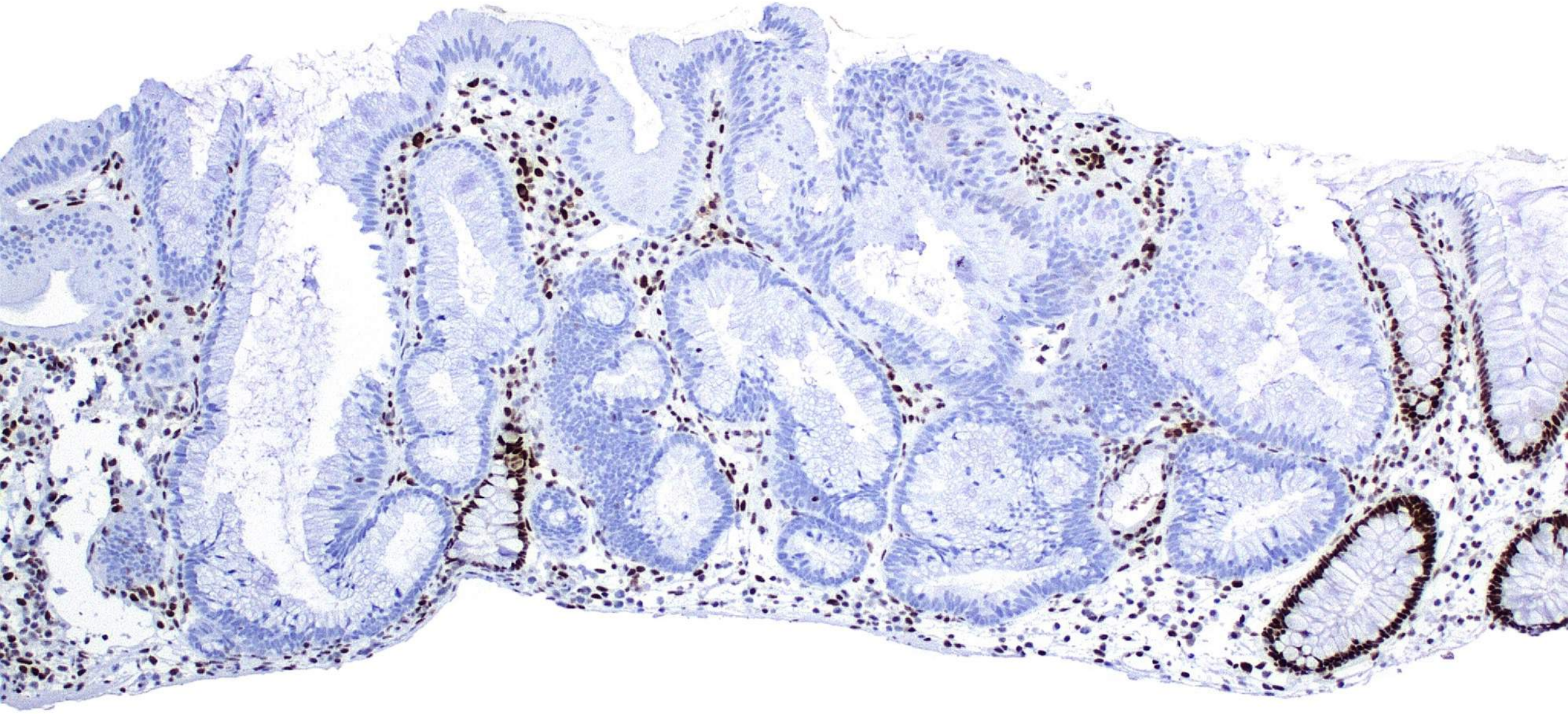
MLH1

Area of dysplasia can be difficult to identify

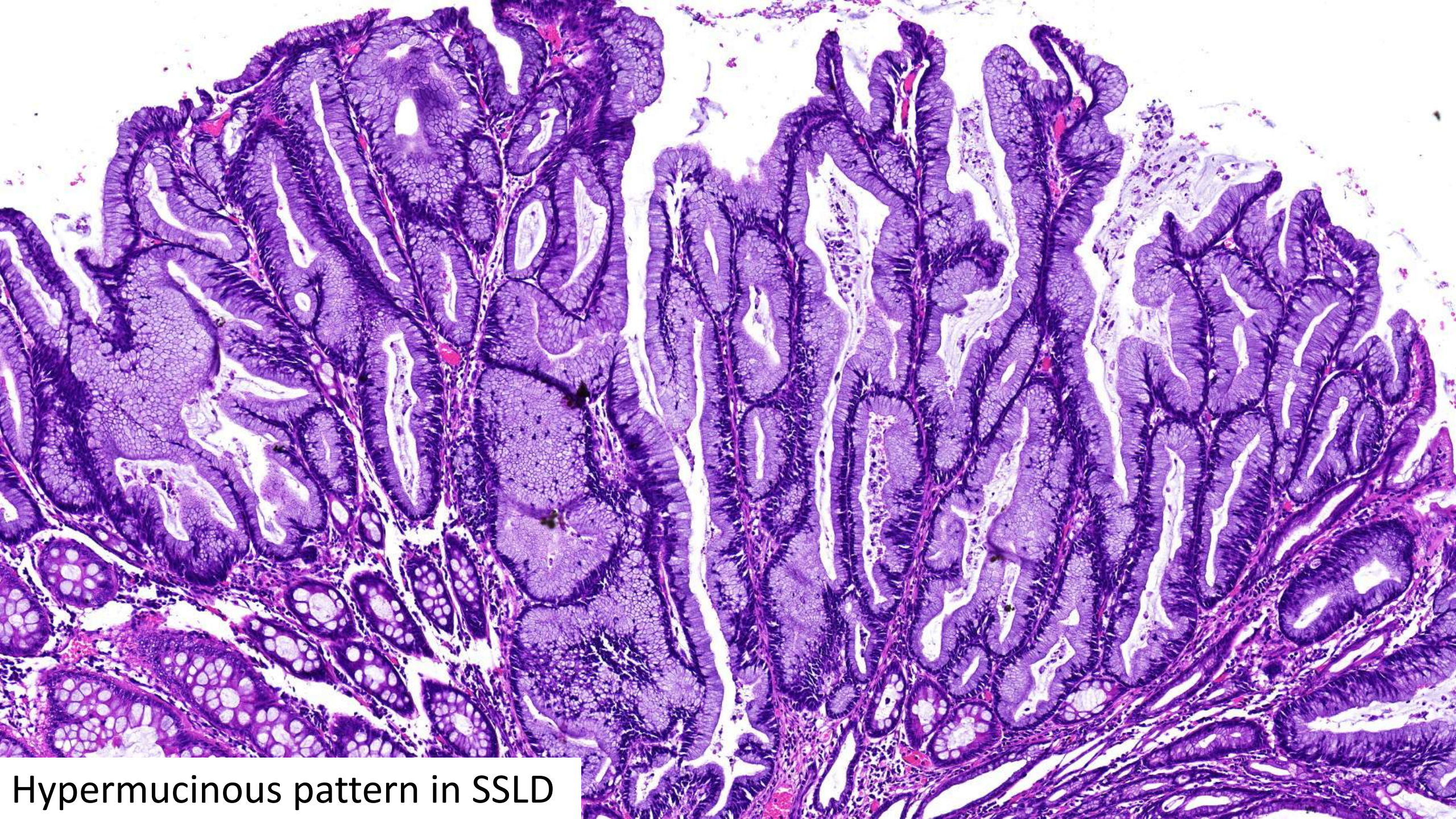


Tip: Look for abrupt change in mucin content

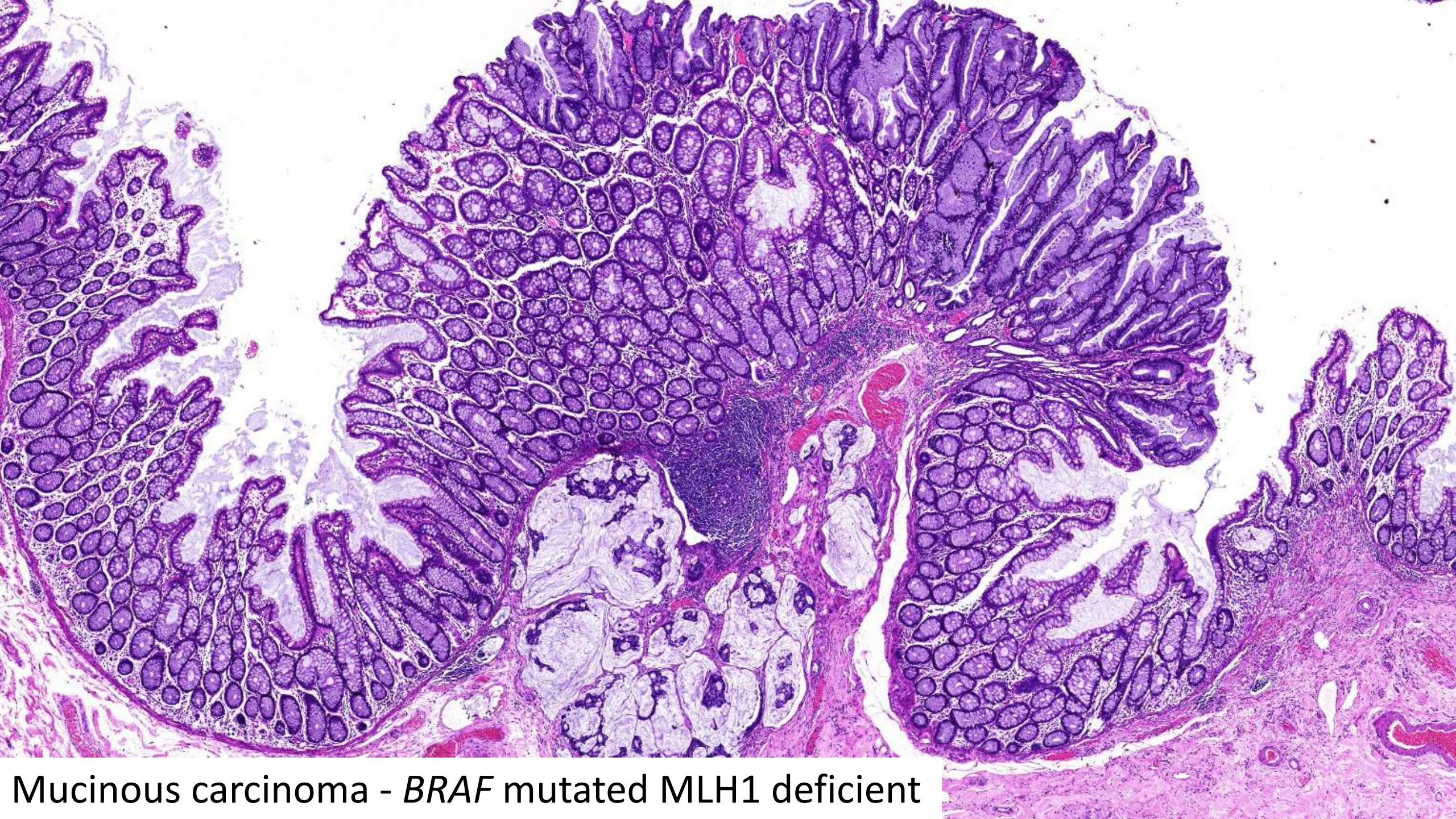
SSL with minimal deviation dysplasia



SSL with minimal deviation dysplasia – MLH1



Hypermucinous pattern in SSLD

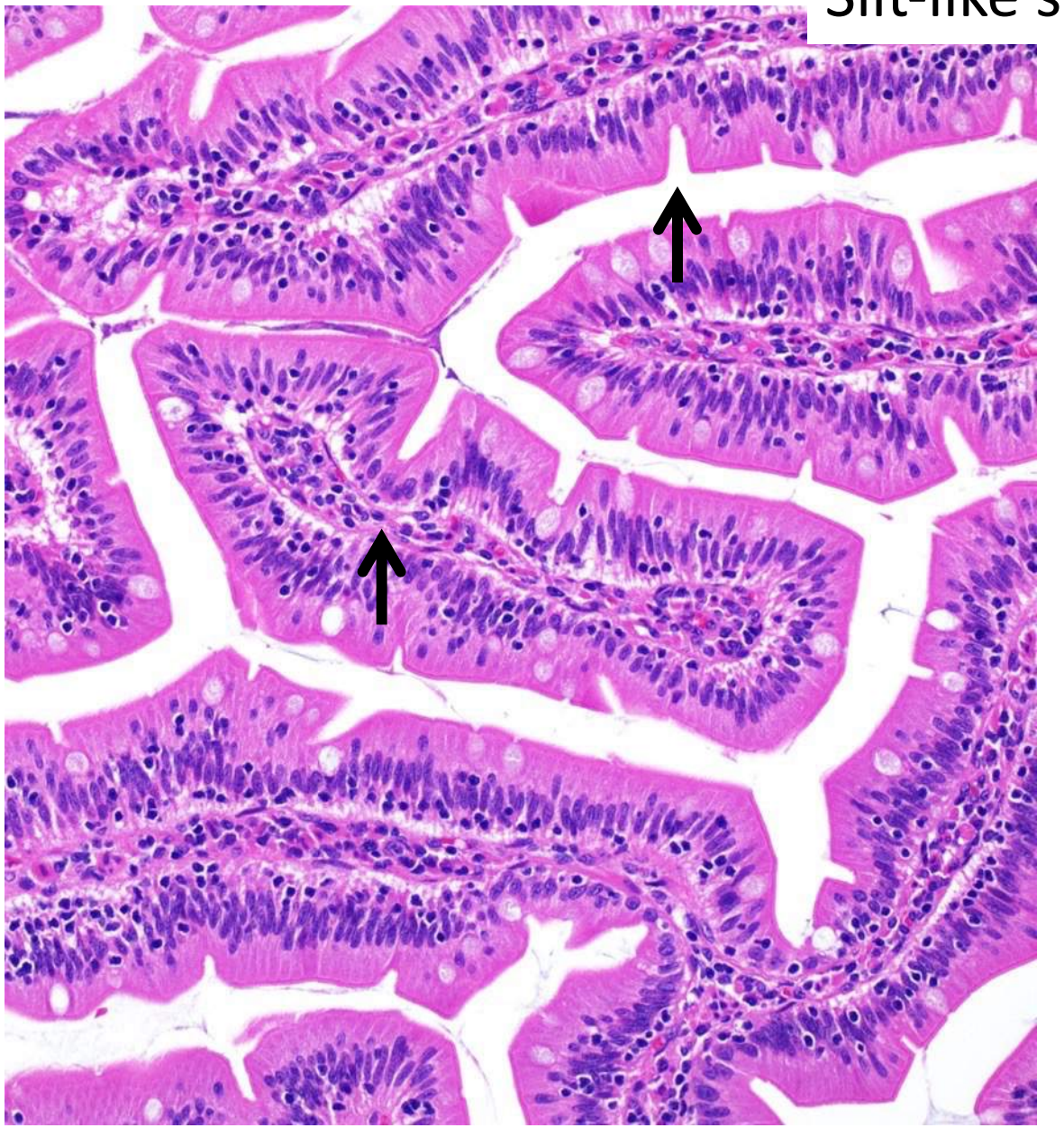


Mucinous carcinoma - *BRAF* mutated MLH1 deficient

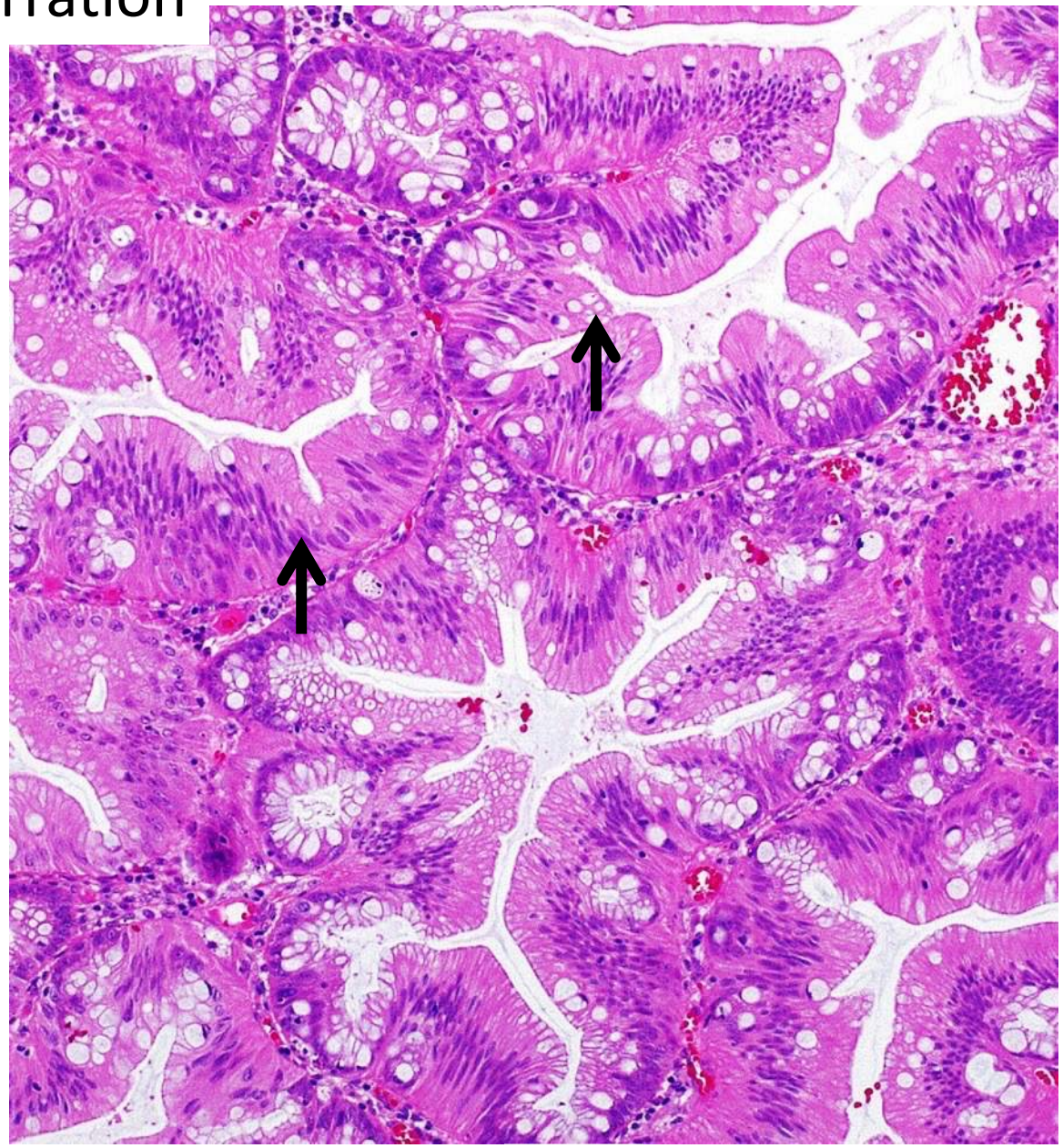
The diagnosis of traditional serrated adenoma

- Two of the following 3 features are required and sufficient:
  1. Slit-like serration
  2. Typical cytology
  3. Ectopic crypt formations
- Mucin-rich TSAs lack typical cytology
- Flat TSAs often lack ectopic crypt formations
- 50% of TSAs have a precursor polyp: HP or SSL
- TSA can be diminutive in size

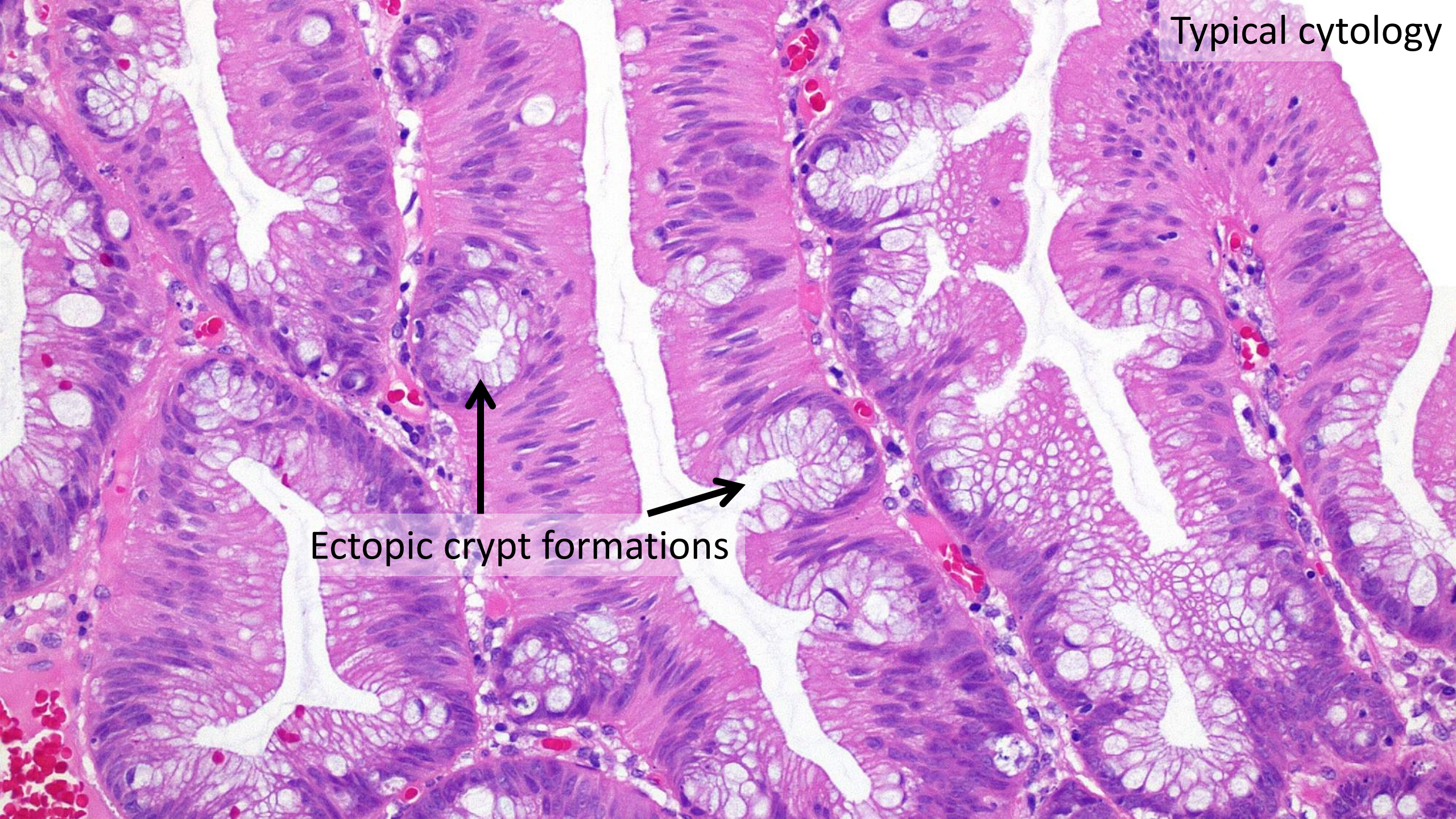
Slit-like serration

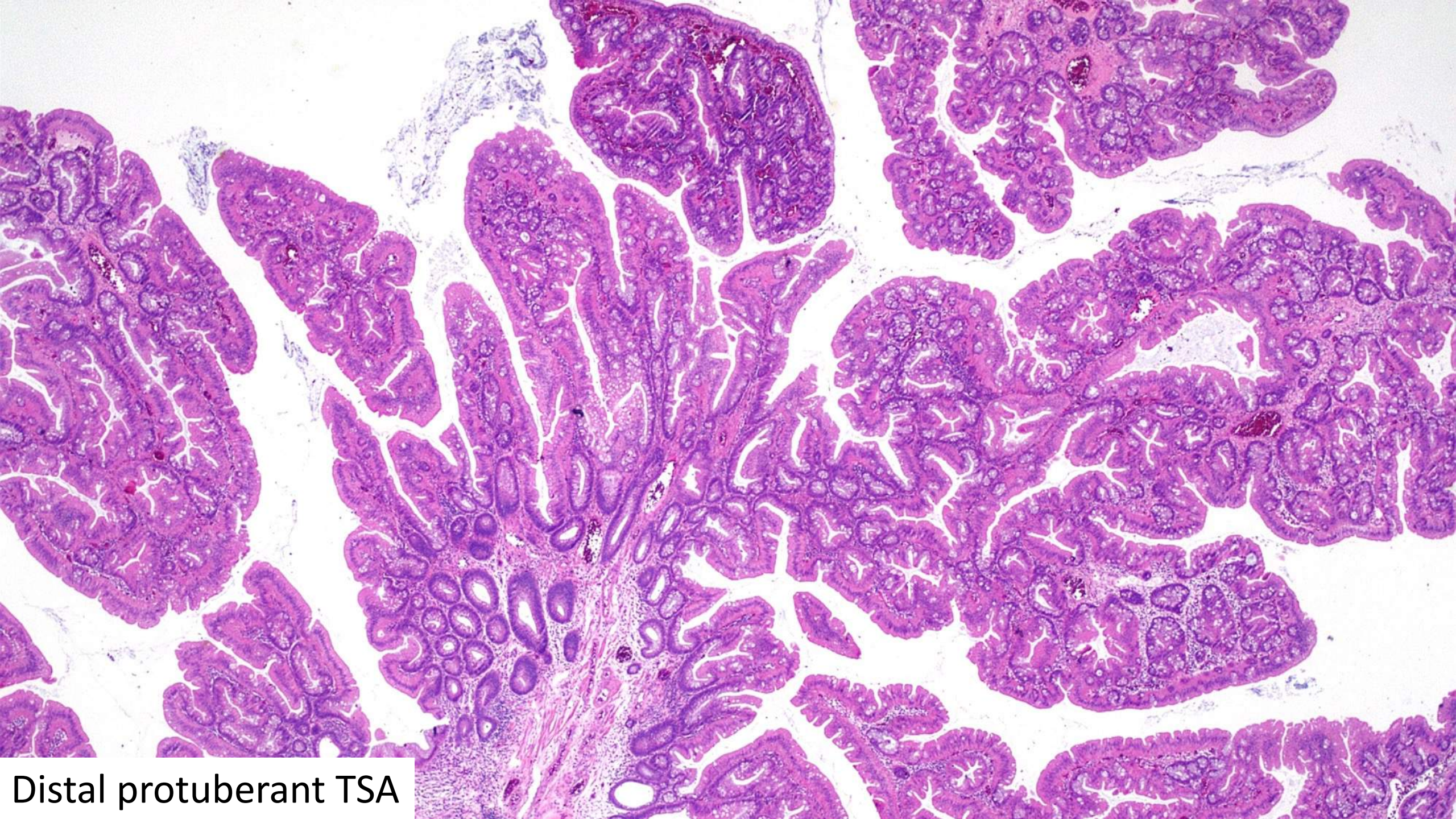


Normal small intestine

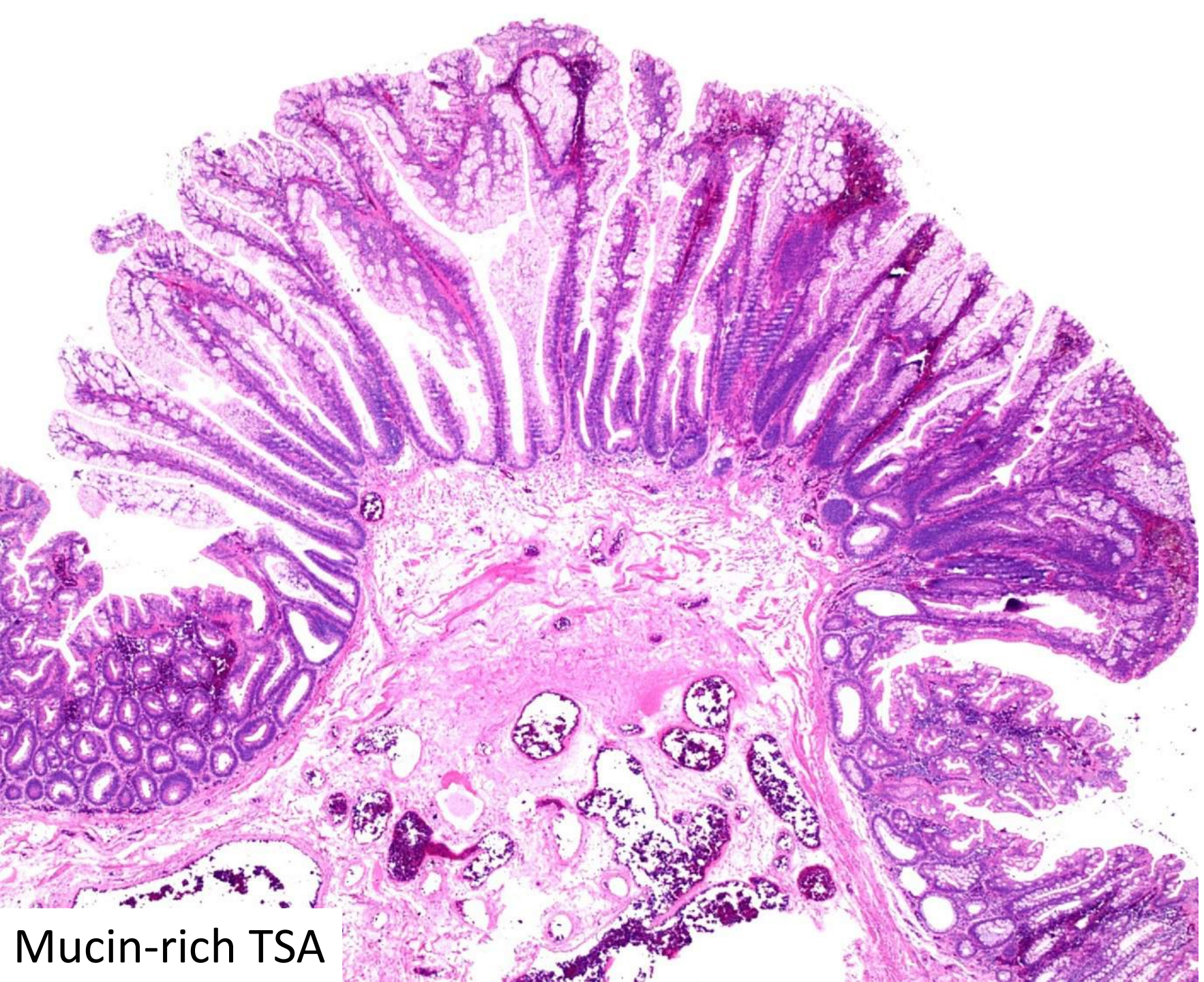


TSA

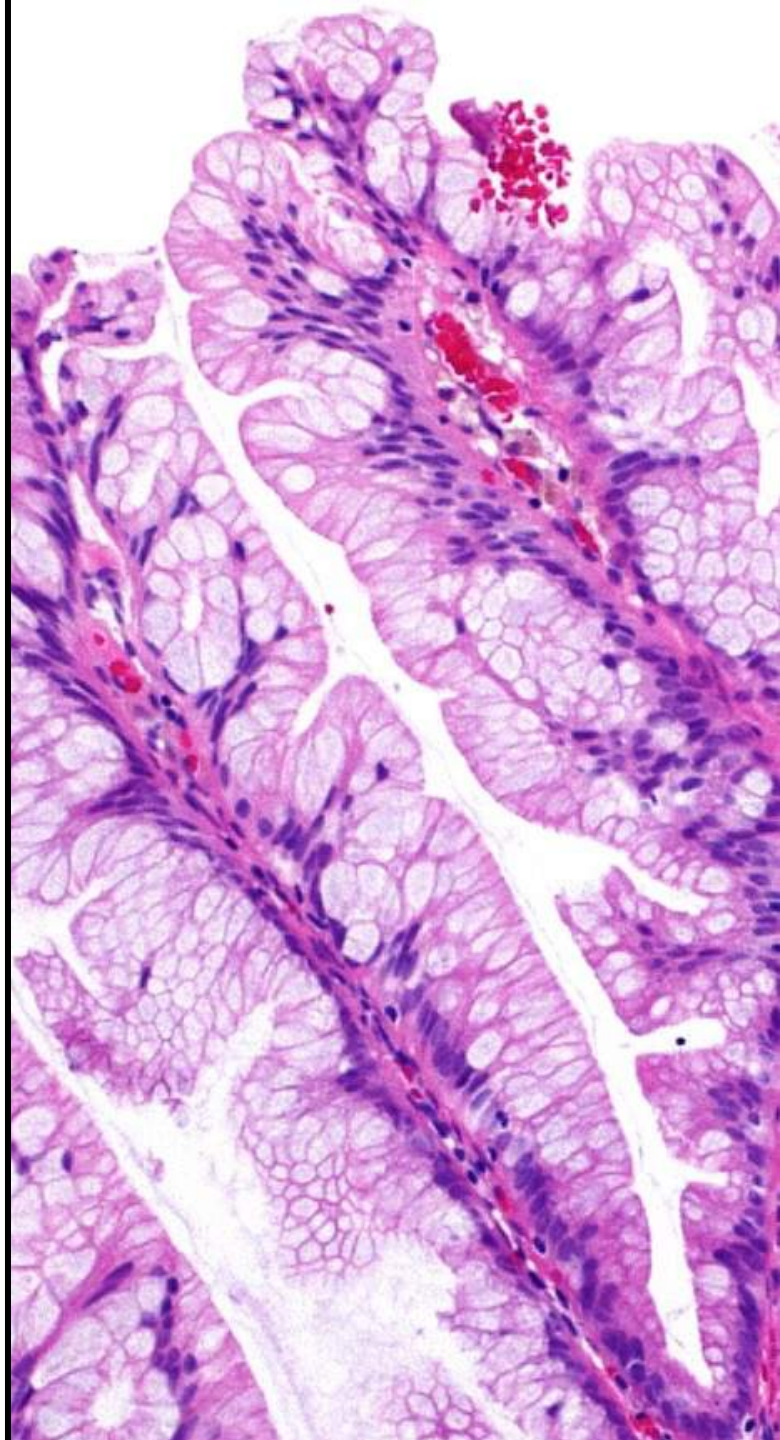

Typical cytology
Ectopic crypt formations

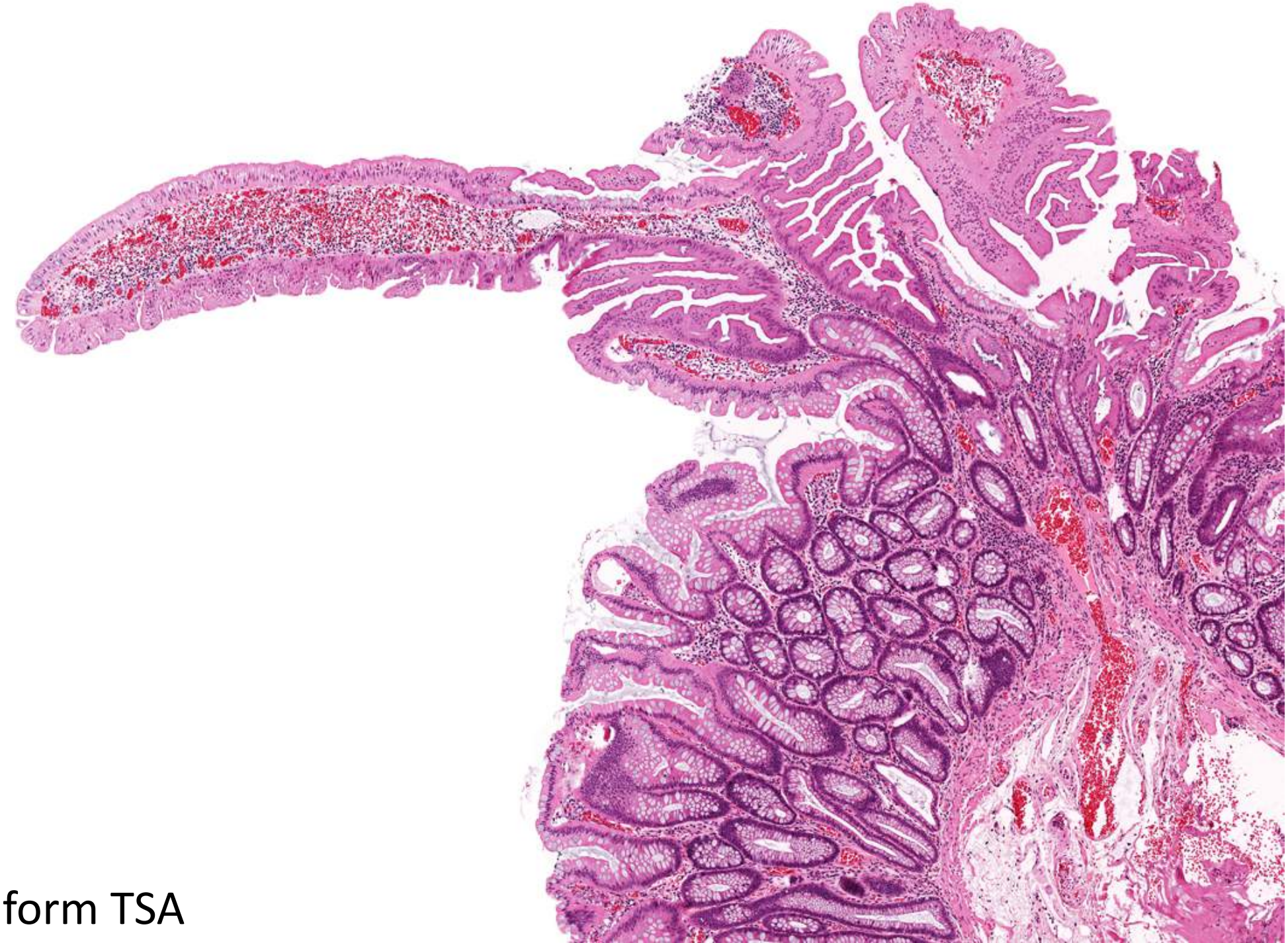


Distal protuberant TSA

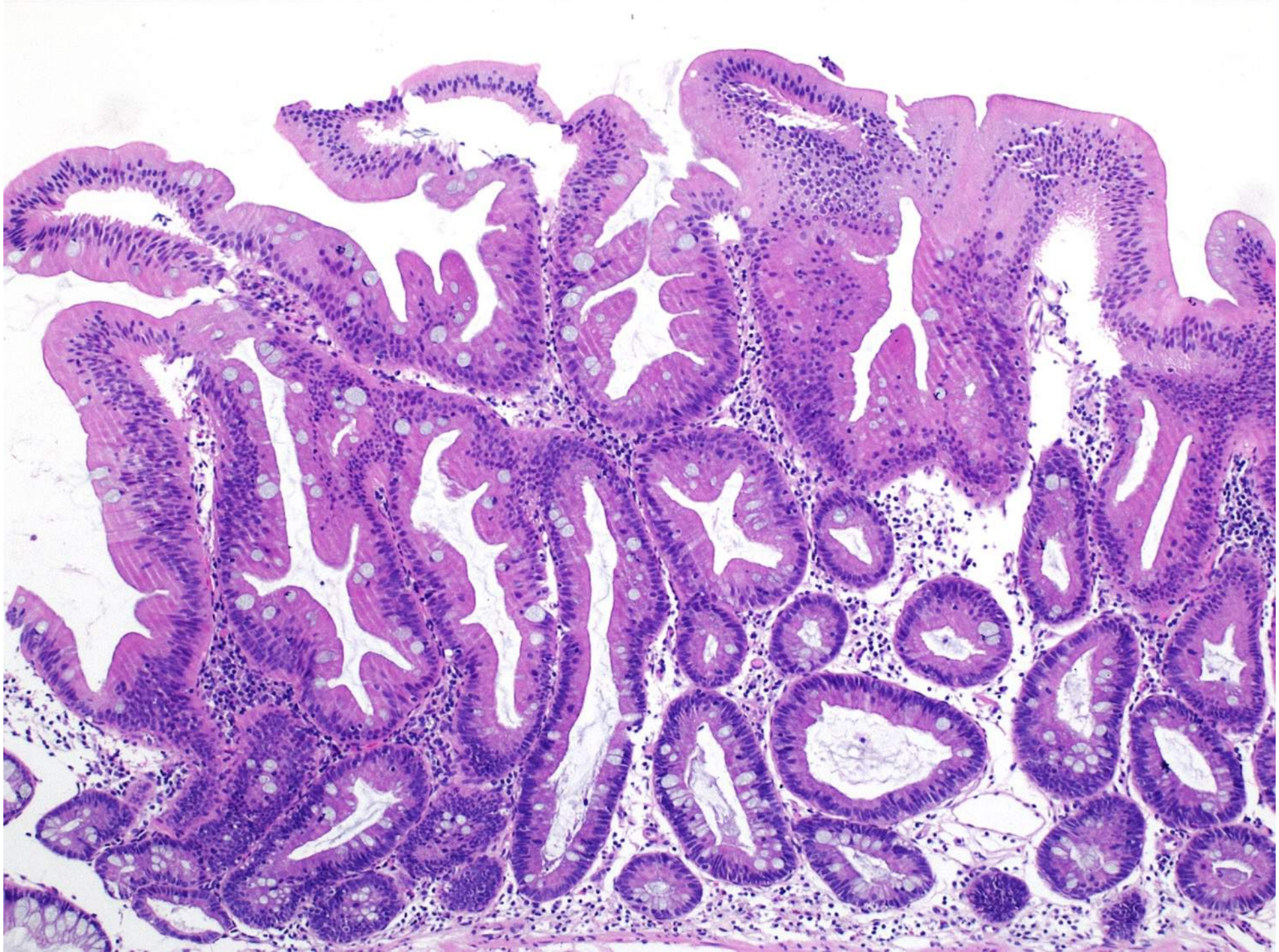


Mucin-rich TSA

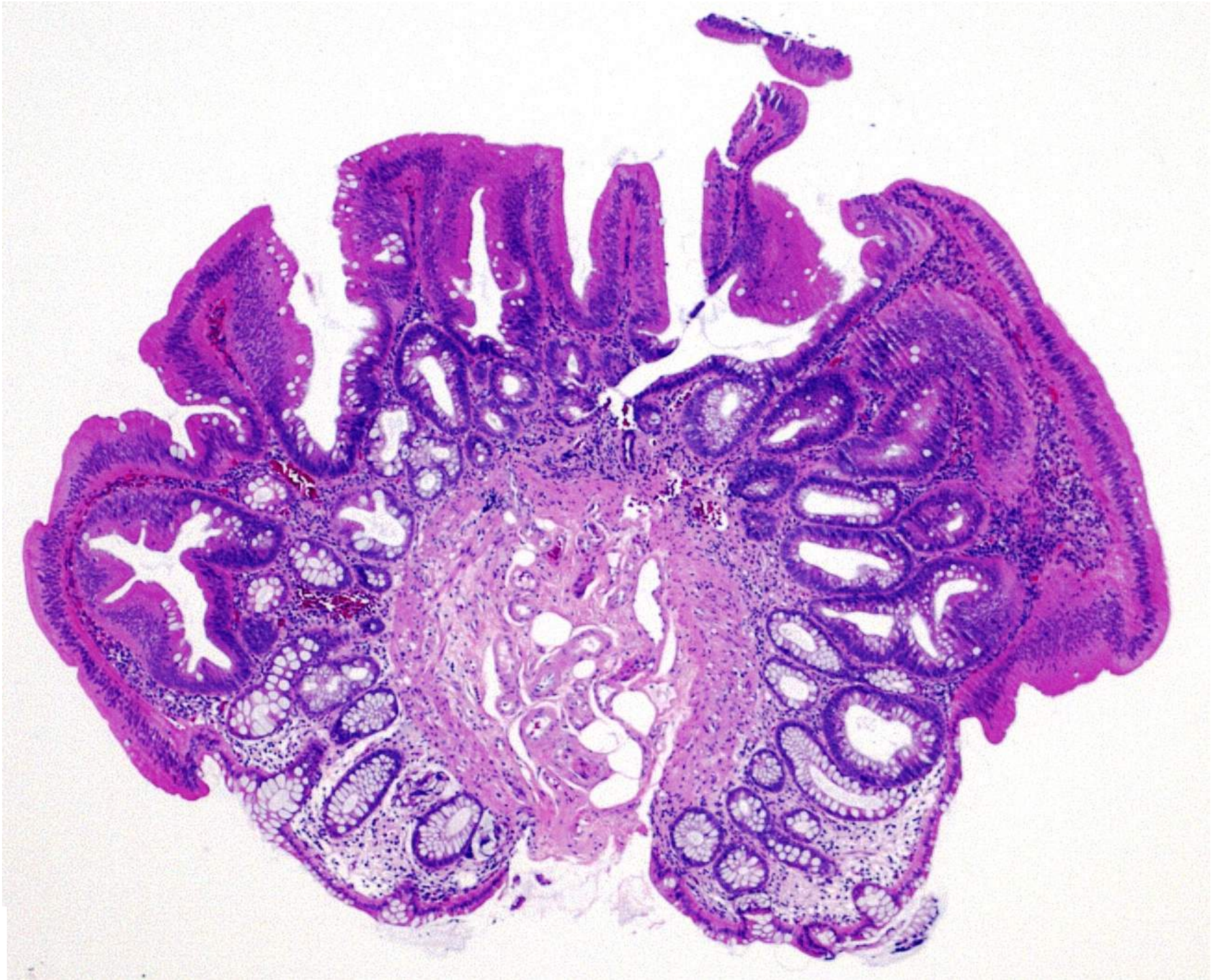




Small villiform TSA



Proximal flat TSA

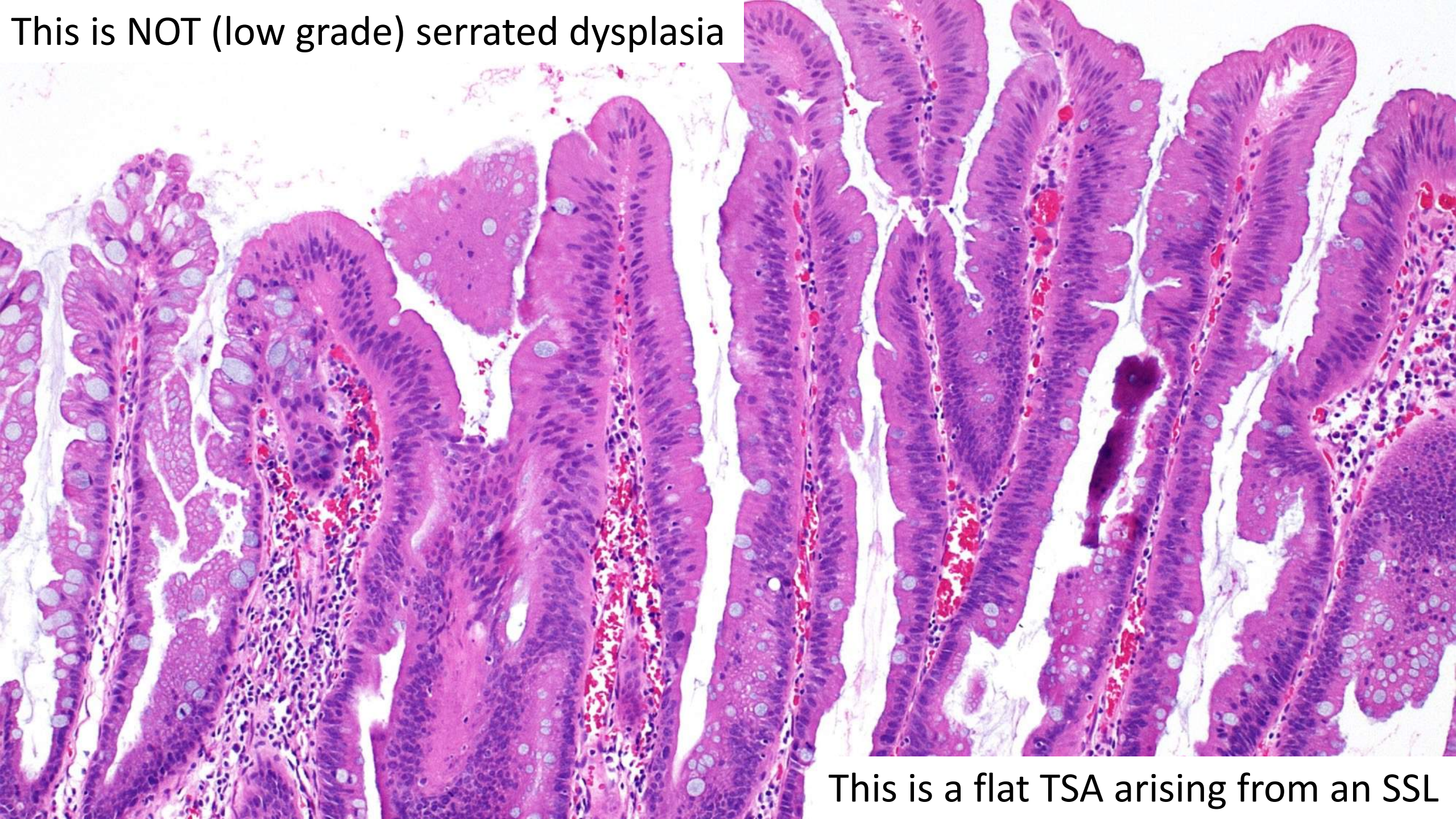


Small distal flat TSA

TSA versus SSL(D)

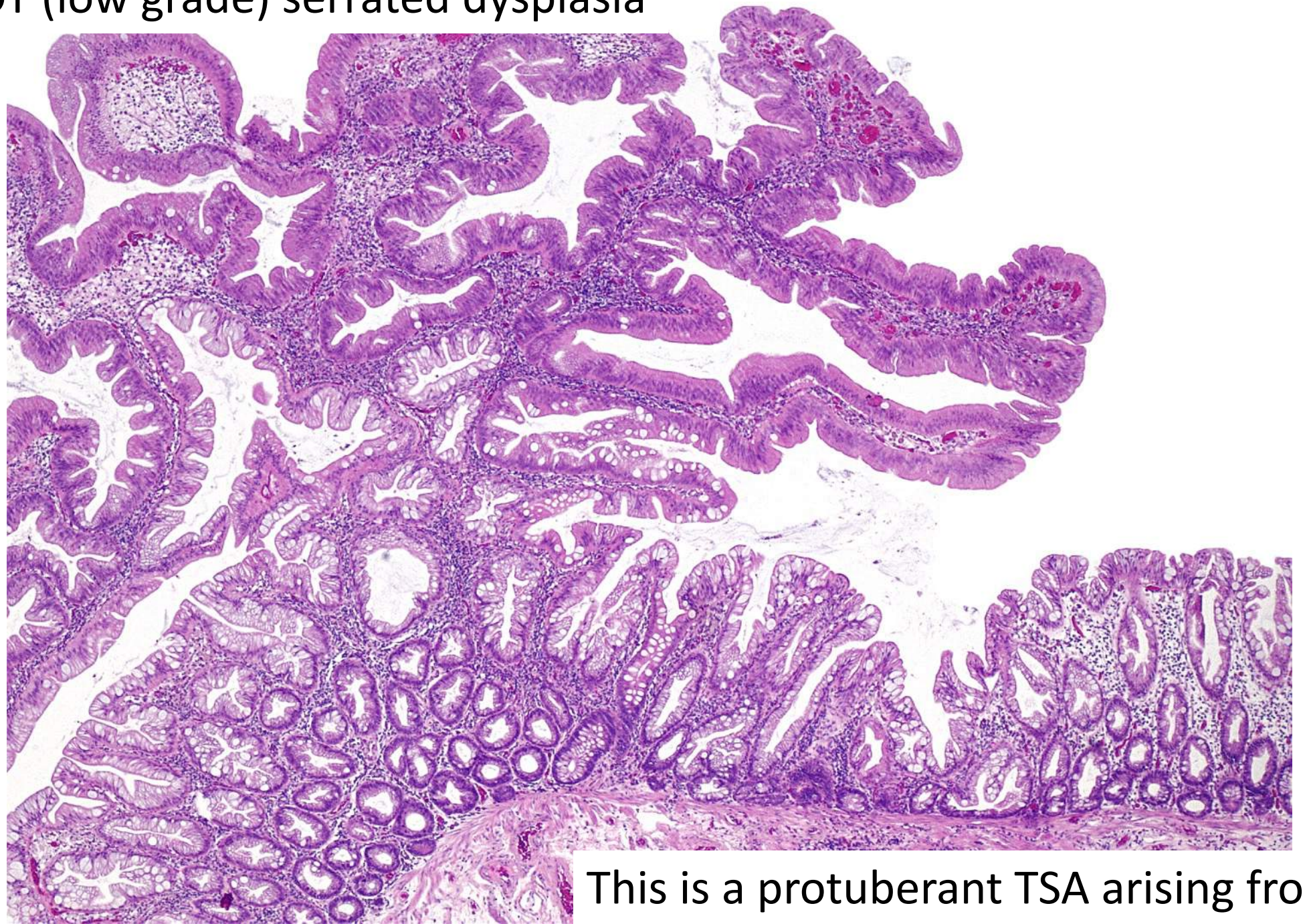
- TSA biologically less advanced than SSLD
- If TSA features present in an SSL, it is reported as TSA not SSLD
- TSA is not low grade serrated dysplasia
- Serrated adenoma unclassified
  - For lesions difficult to classify as SSL or flat TSA
  - Not for HP versus SSL
  - Sparingly used

This is NOT (low grade) serrated dysplasia



This is a flat TSA arising from an SSL

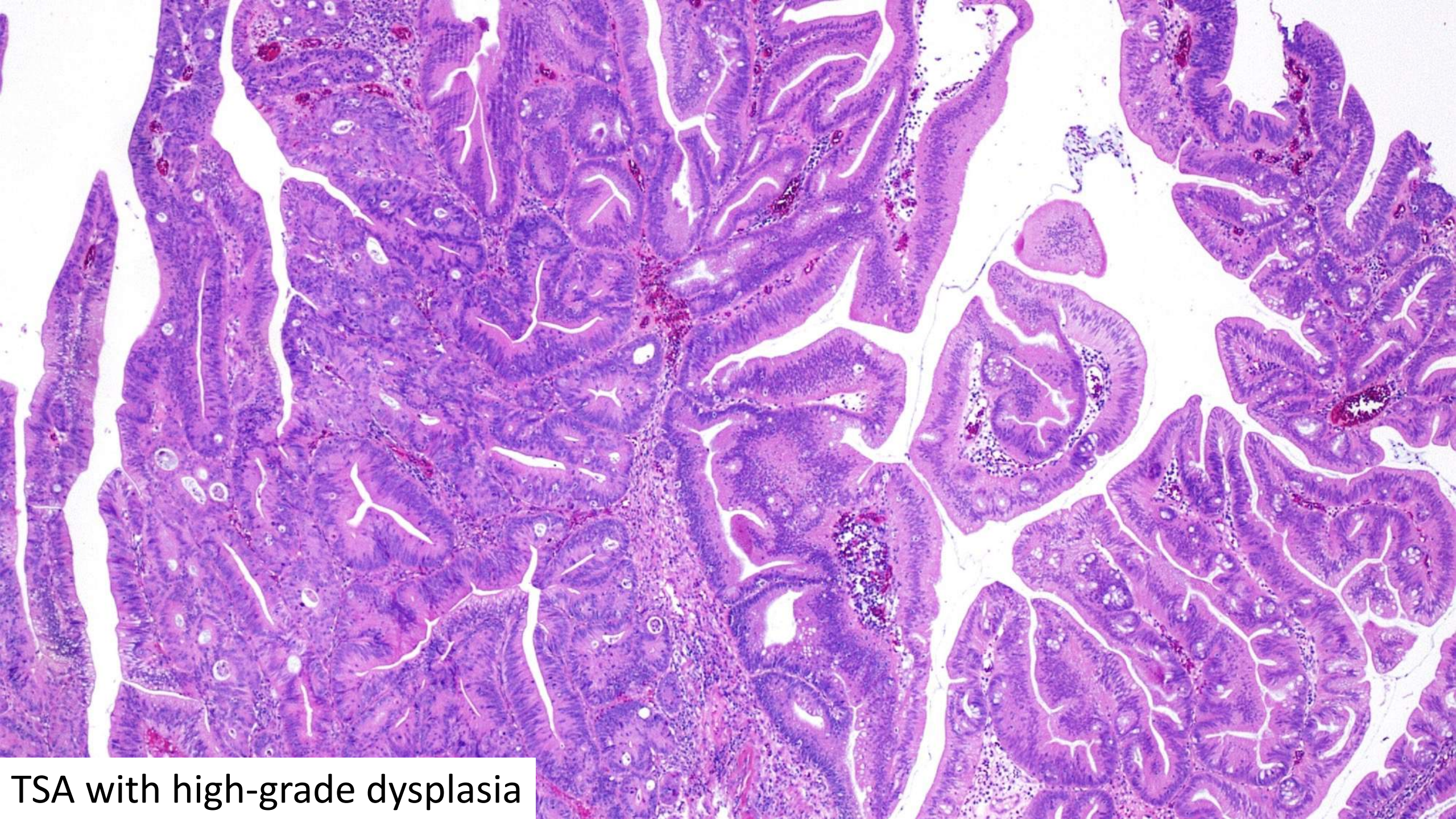
This is NOT (low grade) serrated dysplasia



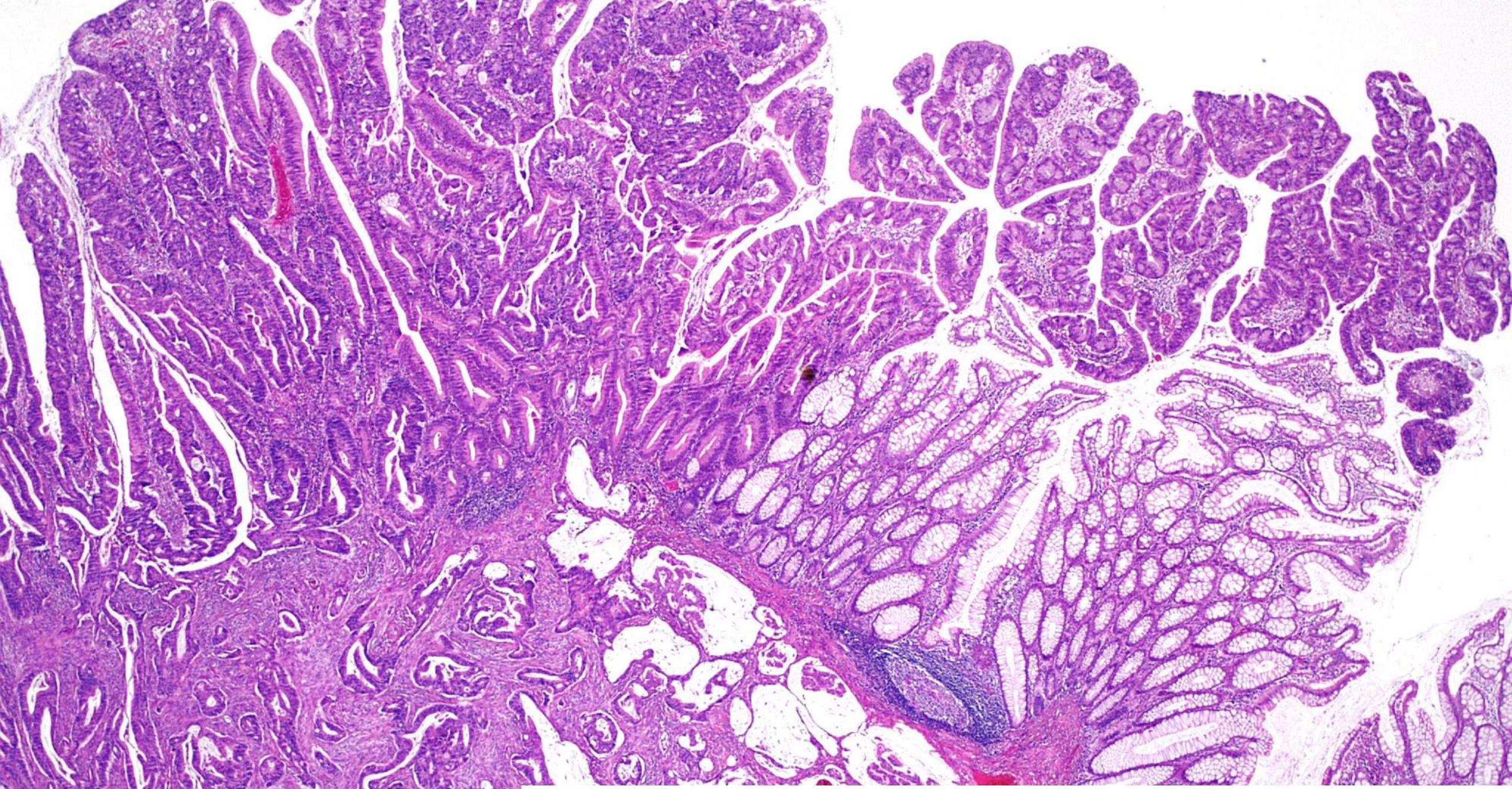
This is a protuberant TSA arising from an SSL

Advanced TSA

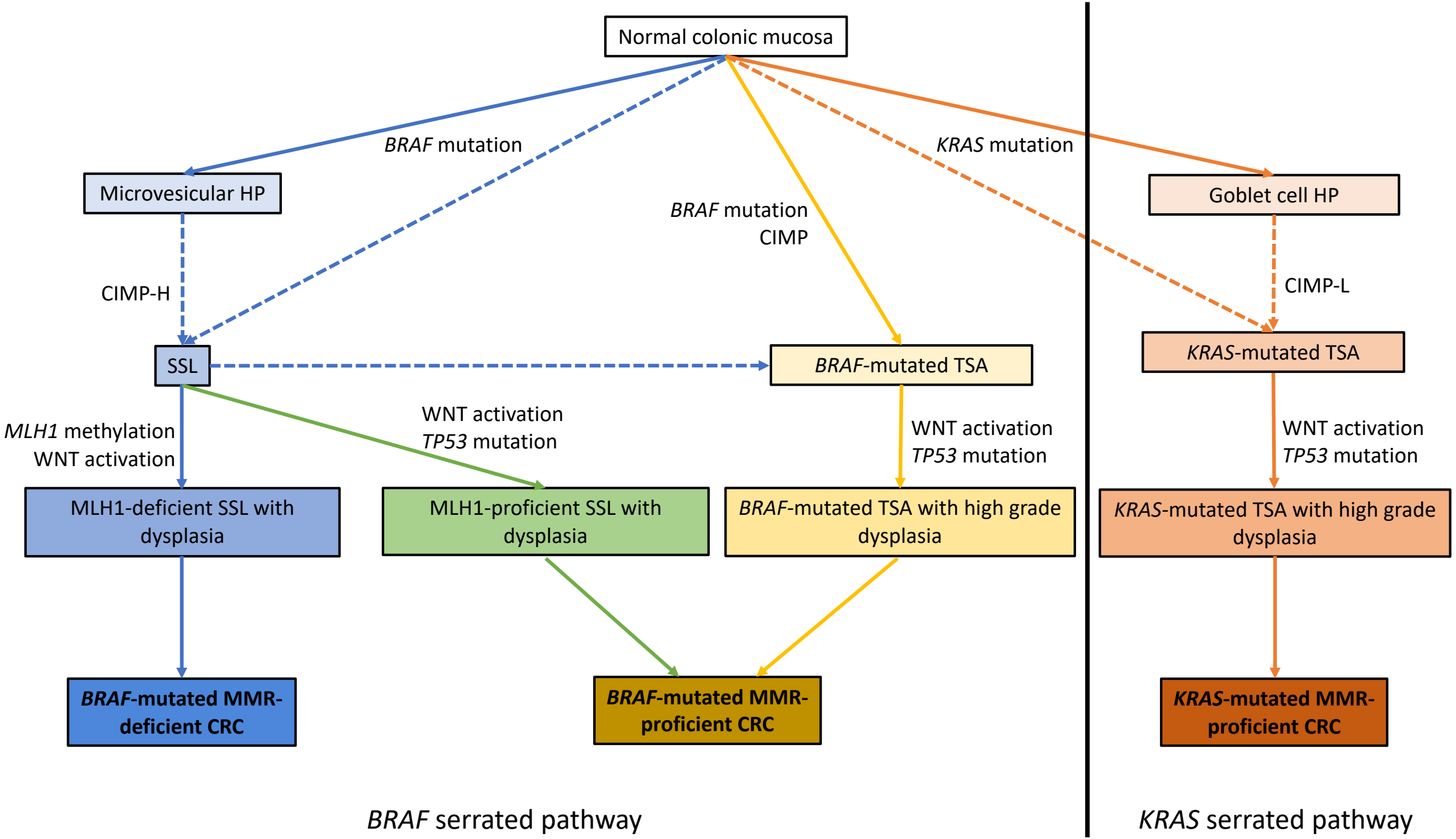
- Superimposed dysplasia can develop in TSA
- Usually resembles the dysplasia of conventional adenoma
- The significance of low-grade dysplasia is not clear
- High-grade dysplasia represents an advanced stage and should be summarised as “TSA with high-grade dysplasia”
- Nearly always retain MLH1 expression



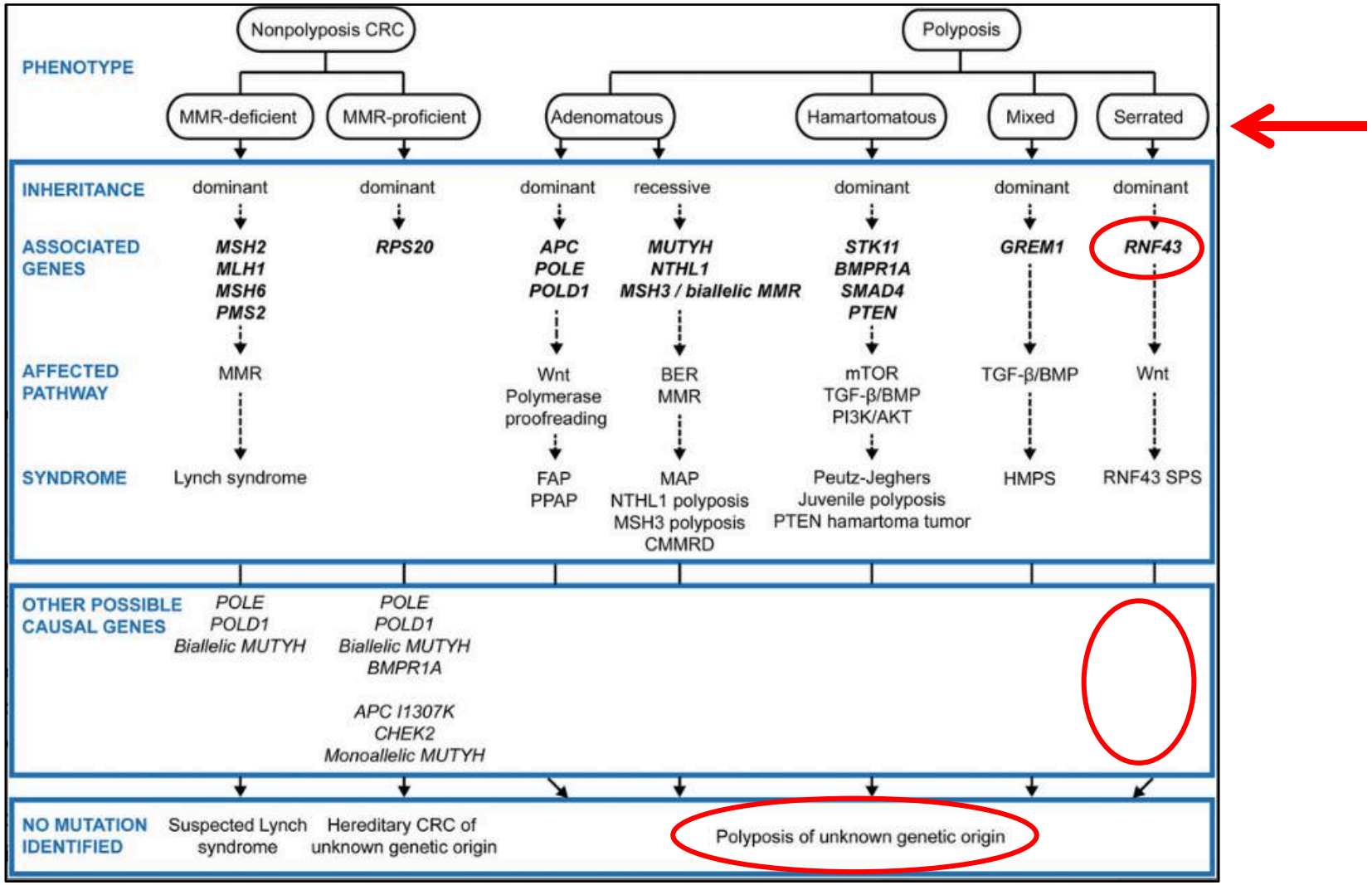
TSA with high-grade dysplasia



Serrated adenocarcinoma from TSA – MMR proficient


Normal colonic mucosa
BRAF mutation
KRAS mutation
Microvesicular HP
BRAF mutation
CIMP
Goblet cell HP
CIMP-H
CIMP-L
SSL
BRAF-mutated TSA
KRAS-mutated TSA
MLH1 methylation
WNT activation
WNT activation
TP53 mutation
WNT activation
TP53 mutation
WNT activation
TP53 mutation
MLH1-deficient SSL with dysplasia
MLH1-proficient SSL with dysplasia
BRAF-mutated TSA with high grade dysplasia
KRAS-mutated TSA with high grade dysplasia
***BRAF*-mutated MMR-deficient CRC**
***BRAF*-mutated MMR-proficient CRC**
***KRAS*-mutated MMR-proficient CRC**
BRAF serrated pathway
KRAS serrated pathway

Is serrated polyposis a genetic syndrome?



Valle L et al. J Pathol 2019; 247: 574-588

What is the role of *RNF43* in serrated polyposis?

- RNF43 is a negative regulator of the WNT signalling pathway
- Initial reports of germline variants in serrated polyposis families
- Mutation testing from large series of serrated polyposis patients found a <2% prevalence
- Currently no role for *RNF43* mutation testing in clinical practice

Serrated polyps/lesions in GIT genetic syndromes

- *MUTYH*-associated polyposis:
  - 18% *MUTYH* biallelic mutation carriers fulfilled serrated polyposis criteria (Boparai et al. Gut 2013)
  - But conventional adenomas are often predominant
- Cowden syndrome:
  - 24% *PTEN* mutation carriers fulfilled serrated polyposis criteria (Heald et al. Gastroenterology 2010)
  - But CS-type hamartomatous polyps are always present and often predominant
- Juvenile polyposis syndrome (*SMAD4*, *BMPR1A*)
  - But juvenile polyps are always present

The role of genetic testing for typical serrated polyposis patients is uncertain

Summary

- Improve consistency and reproducibility of serrated lesions/polyps
- More research necessary for evidence-based guidelines
- Serrated polyposis remains poorly understood
- Serrated lesions/polyps sometimes a secondary component in MAP, Cowden syndrome, juvenile polyposis