

Hyperplastische Polyps Innocent bystanders?

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Content

- **Historical Classification**
- **Relation Hyperplastic polyps – carcinoma**
- **The concept “sessile serrated adenoma”**
- **Classification of hyperplastic polyps**
- **Sessile serrated adenoma e.a. and carcinoma**
- **Conclusions**

Classification of colorectal polyps until 1996

– Epithelial

- Hyperplastic = benign
- Adenoma = neoplastic
 - Tubular
 - Tubulovillous
 - Villous

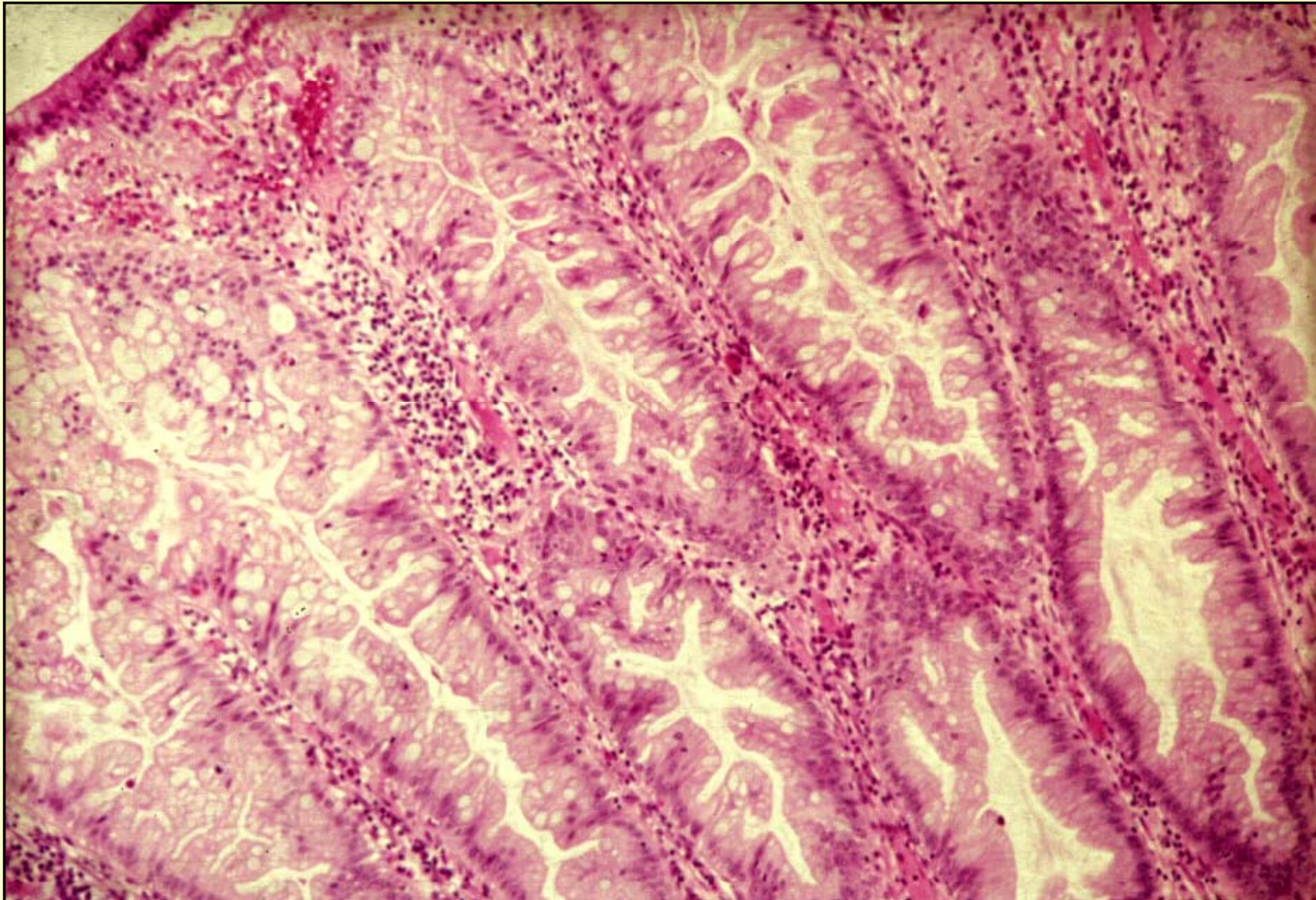
Non-epithelial

Juvenile
Hamartomas
Inflammatory
.....

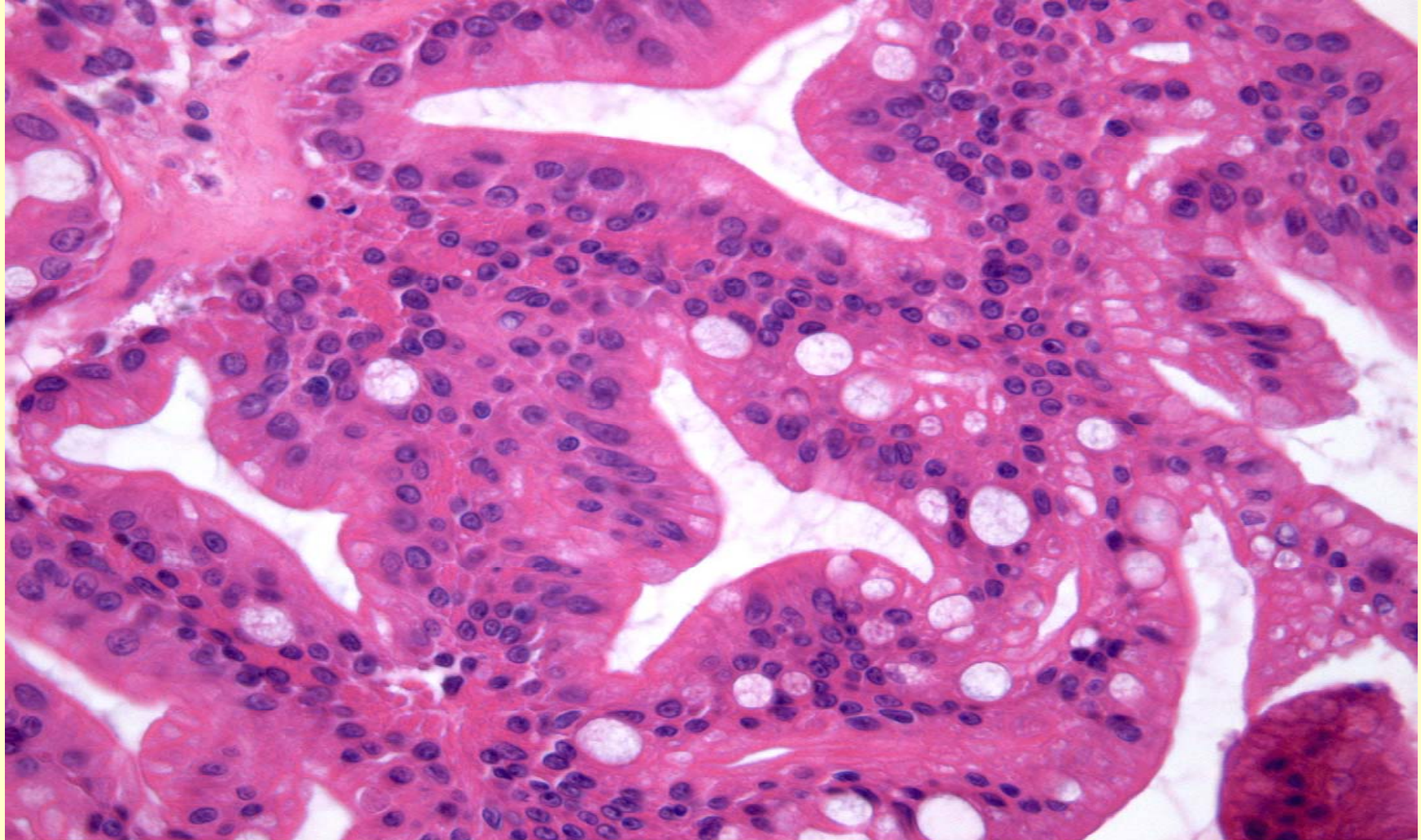
Adenomas and classical Hyperplastic polyps



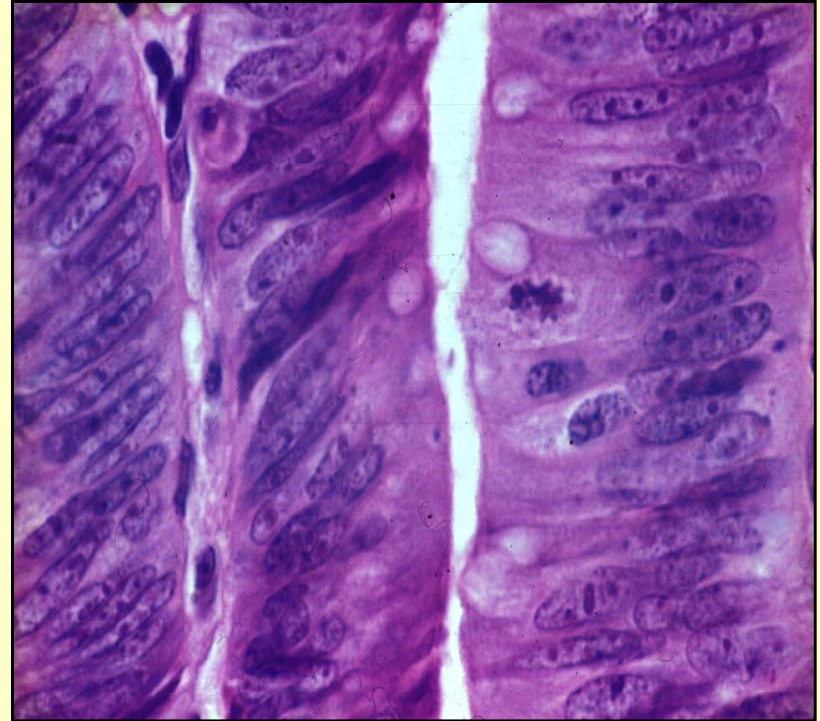
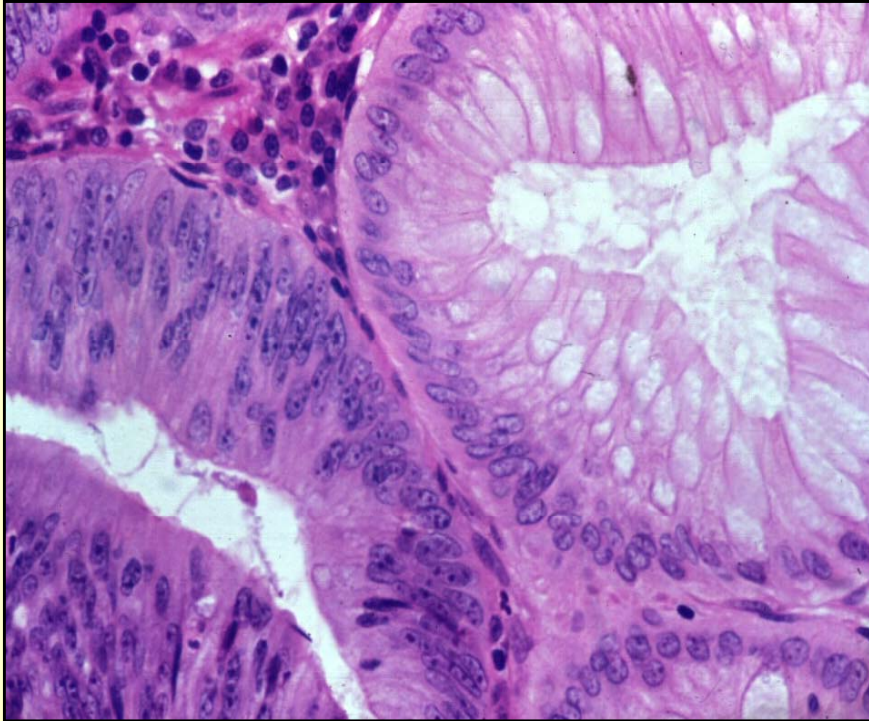
Hyperplastic polyp



Hyperplastic polyp - microvesicular



Adenoma – Normal



Hyperplastic polyps and colorectal cancer

- **Hyperplastic polyps are present at the margin of a significant percentage of adenomas (Goldman et al 1970) Sentinel lesions?**
- **Hyperplastic polyps can become very large, especially in the ascending colon**
- **Occasionally large hyperplastic polyps may contain adenocarcinoma (Urbanski et al 1984)**
- **Hyperplastic polyps are more frequent in populations at risk for colorectal cancer (Eide 1986)**

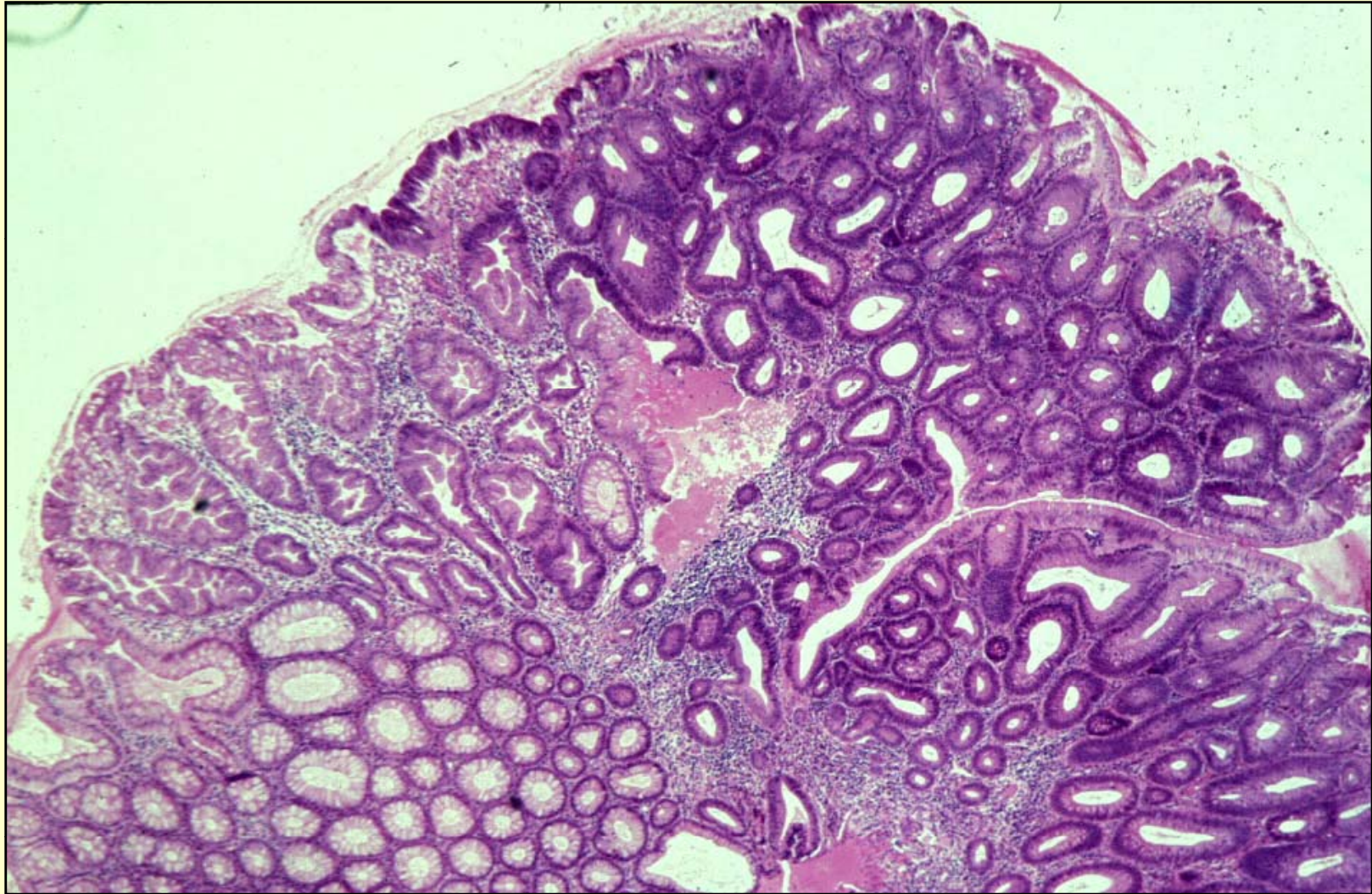
Hyperplastic polyps and colorectal cancer

- **Histologic serrated? polyps are present adjacent to adenocarcinoma, particularly of the ascending colon (Makinen et al 2001)**

Hyperplastic polyps and colorectal cancer

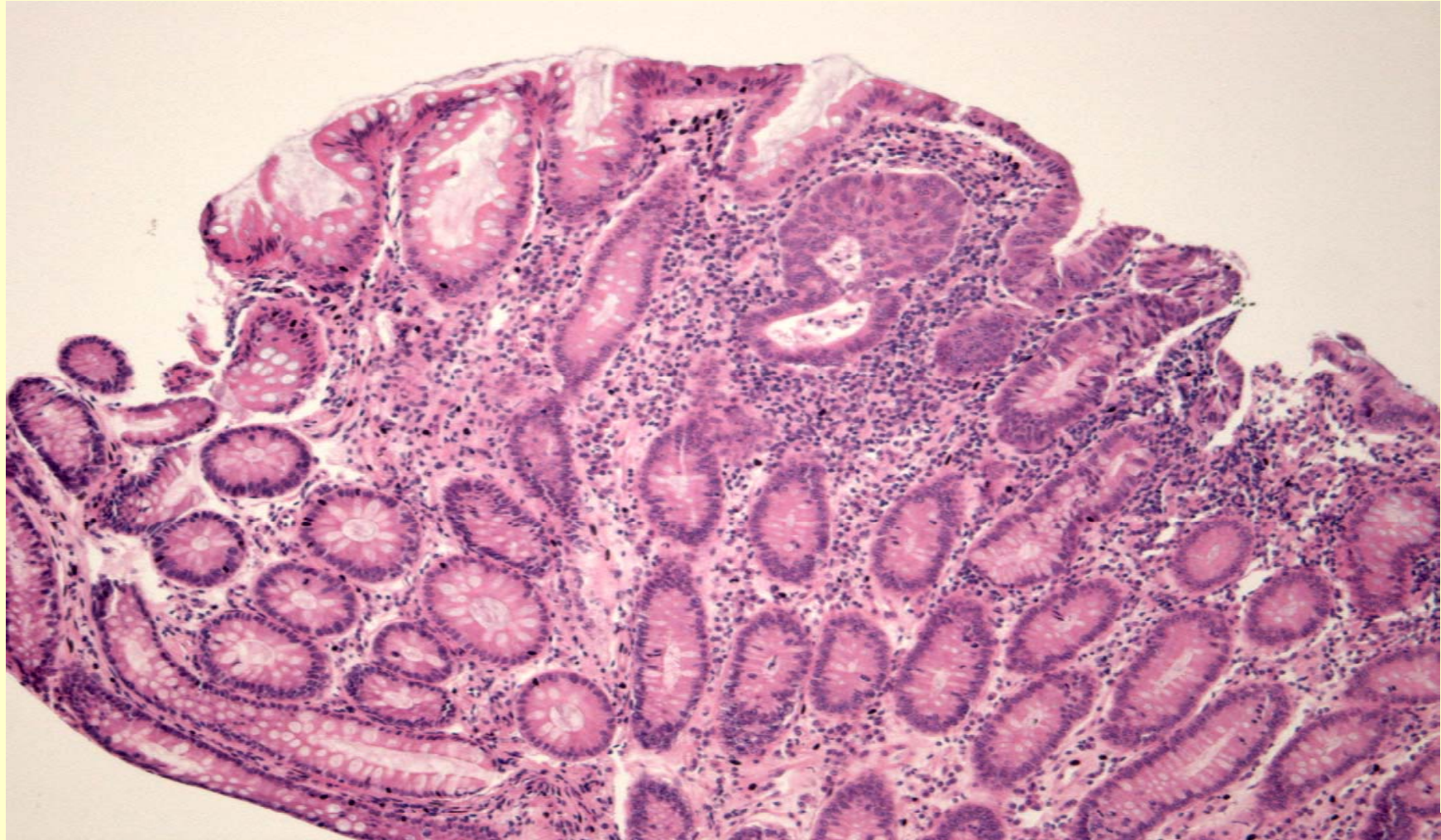
- **1990 : Longacre & Fenoglio Preiser describe a group of patients with mixed features of hyperplastic polyps and adenomas Am J Surg Pathol**

Mixed Hyperplastic - adenomatous



B-1352989

Mixed adenomatous – hyperplastic with squamous metaplasia



Hyperplastic polyps and colorectal cancer

- **1996 : Torlakovic and Snover : Review of cases with hyperplastic polyposis : risk of colorectal cancer is increased**
Gastroenterology
- Polyps in hyperplastic polyposis show significant morphologic differences when compared with small sporadic hyperplastic polyps

Hyperplastic polyposis

(sessile serrated adenomatous polyposis)

- Rare syndrome
- Two phenotypes
 - Multiple small, mainly distal polyps
 - Small numbers of large and proximal polyps
- Polyps : hyperplastic, serrated adenomas, adenomas, admixed hyperplastic / adenomatous
- Definite but poorly defined cancer risk
- Diagnostic criteria

Hyperplastic polyposis

- Diagnostic criteria
 - at least five histologically confirmed hyperplastic polyps proximal to the sigmoid colon, of which at least two are greater than 10 mm in diameter
 - any number of hyperplastic polyps proximal to the sigmoid in a patient with a first-degree relative with hyperplastic polyposis
 - more than 30 hyperplastic polyps of any size distributed evenly throughout the colon
- Pathogenesis
 - Family history (rare, 2/38 cases)
 - Hypermethylation of multiple gene promoters

Hyperplastic polyposis

- Polyps in hyperplastic polyposis show significant morphologic differences when compared with small sporadic hyperplastic polyps
- The features are similar to mixed lesions but most lesions have a sessile configuration > Sessile serrated adenoma (SSA)
- (to be distinguished from the traditional serrated adenoma (TSA) which is often pedunculated)

Sessile Serrated adenoma

A “polypoid” or “discretely elevated” lesion with morphologic features of “architectural dysplasia” rather than “cytologic dysplasia”

Diagnosis requires well-oriented sections because the most diagnostic features are present at the base of the crypts

Presents as “solitary lesion” or in a setting of a polyposis (Torlakovic & Snover 2006)

SSA & HP

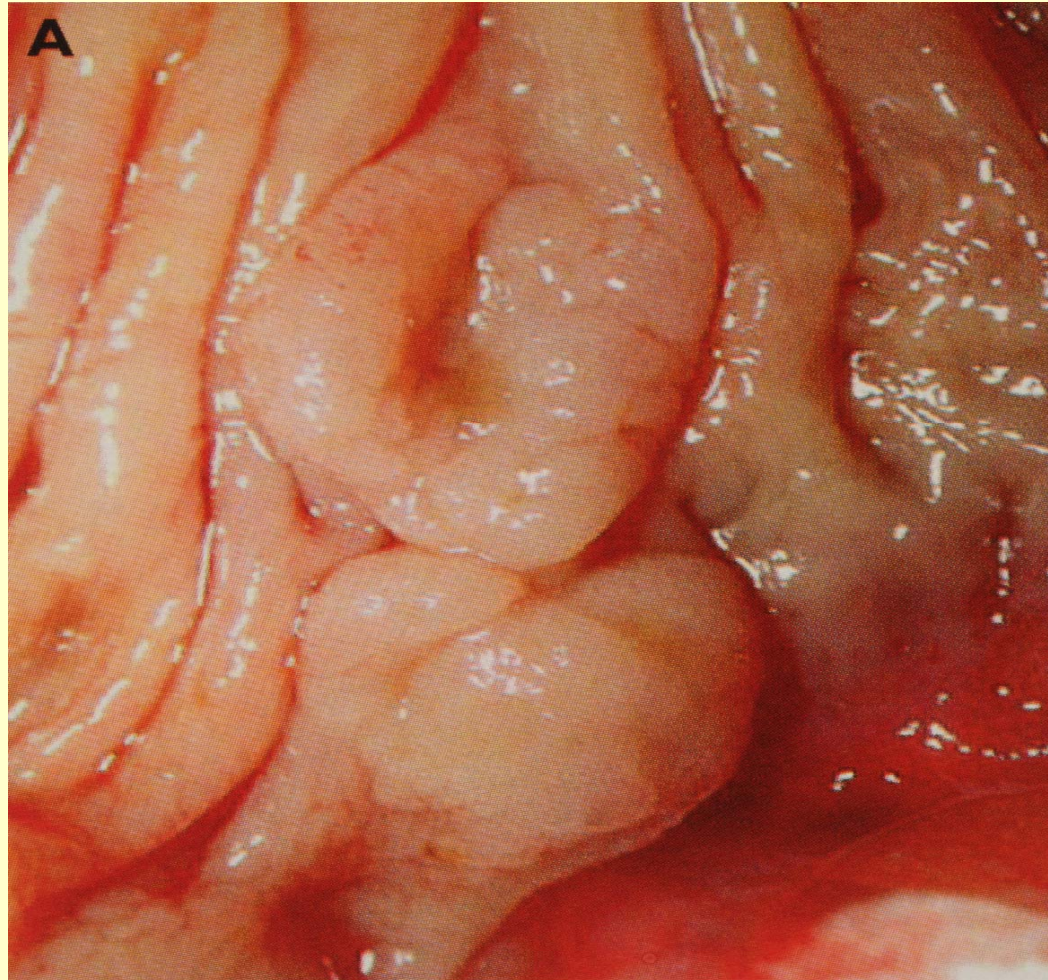
Sessile serrated adenoma

- Serrated feature along the crypt axis
- Rarity of undifferentiated cells in the lower third of the crypts

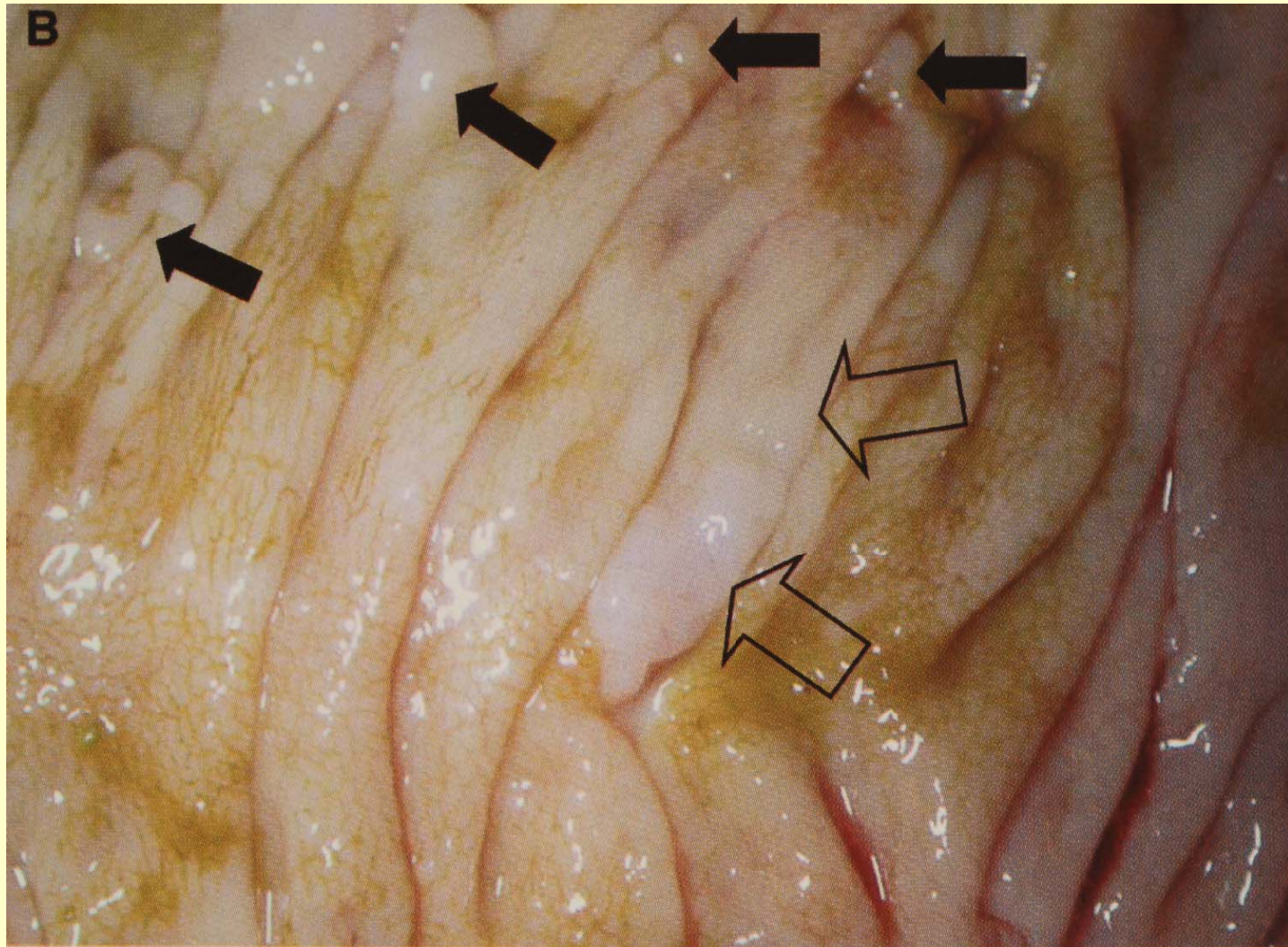
Hyperplastic polyp

- Crypts serrated at the surface
- Base of crypts narrow, lined predominantly with undifferentiated cells

(Raised sessile) serrated adenoma

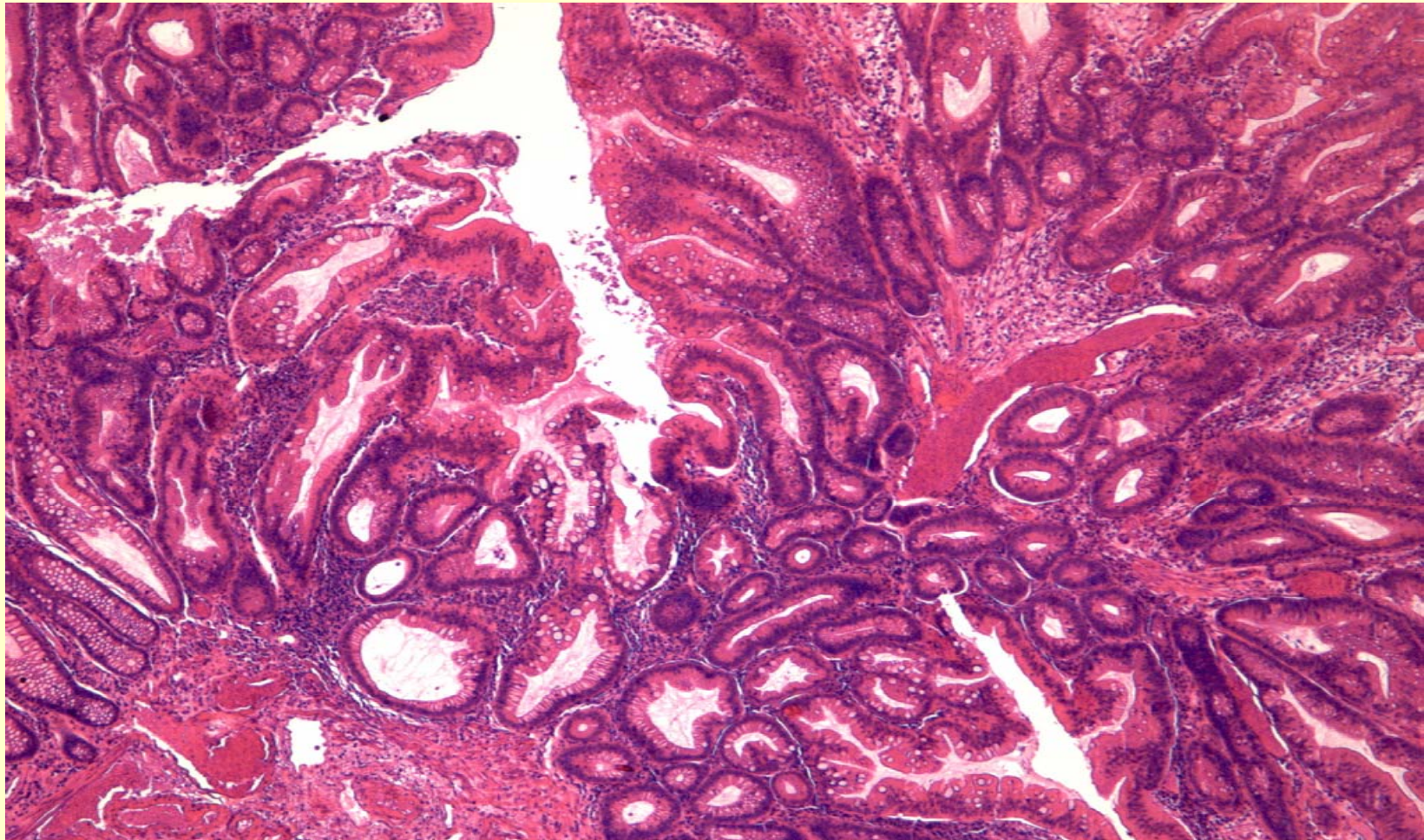


Hyperplastic polyps (closed arrows) and a sessile serrated adenoma (open arrows)



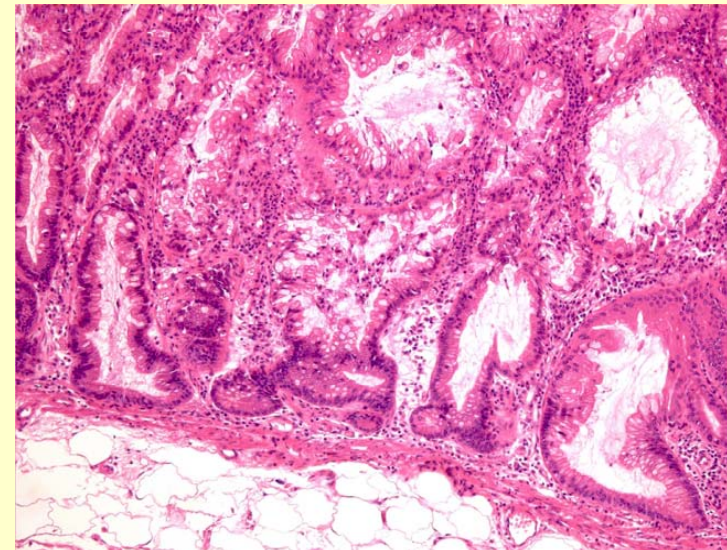
Sessile serrated adenoma 1458015

**Abnormal maturation – epithelial
hyperchromasia - dilated mucin-filled crypts**



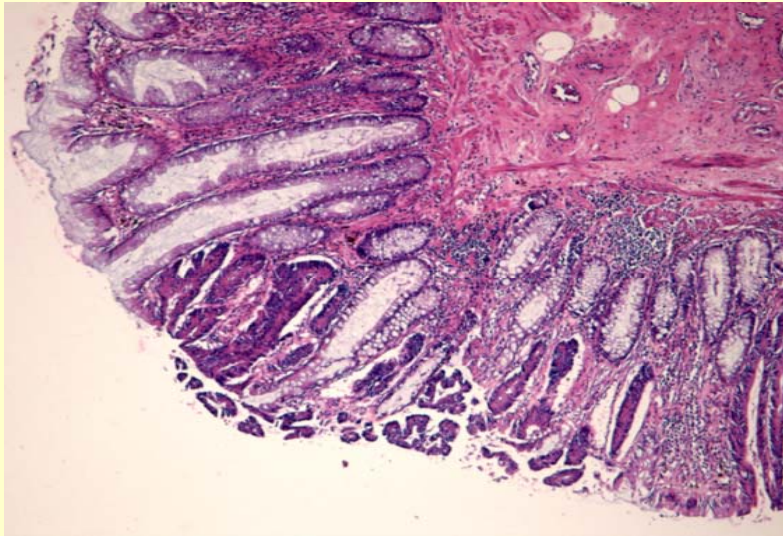
Sessile Serrated adenoma

Areas of mucin production in deep crypts - deep crypt branching (B-1467357)



Sessile serrated adenoma p12229

Crypt dilatation and (lateral spread)



Hyperplastic polyps

Heterogeneous lesion

Summary comparison of features of left-sided and right-sided serrated polyps p <0.001 for these variables; see text for details.† Observation, not recorded for all cases.*

From: Torlakovic: Am J Surg Pathol, Volume 27(1).January 2003.65-81

	Left side	Right side
Number of cases	243	46
Size in millimeters (mean)*	3.54	5.15
Abnormal proliferation*	+	+ /+++
Intraluminal mucin*	0/+	+++
Architecture		
Overall architectural distortion*	+	++ /+++
Serration of the crypts*	+ /++	+++
Overall crypt dilatation*	+	+++
Thickened surface basal membrane*	+++	+
Thickened muscularis mucosae/extension into lamina propria*	+++	+
Cellular composition and distribution		
Irregular distribution of goblet cell*	+ /++	++ /+++
Decreased goblet cells*	+ /++	-
Kulchitsky cells (eosinophilic neuroendocrine cells)*	+++	+
Neuroendocrine cells with clear cytoplasm*	++	+
Cytology		
Vesicular cells/mucin	+++	+++
Dystrophic goblet cells*	++	++ /+++
Goblet cell mitoses	++	++
Apoptosis	0/+	+ /++
Nuclear atypia*	0 /++	+ /+++
Atypia of neuroendocrine cell†	+	++

* p <0.001 for these variables; see text for details.

† Observation, not recorded for all cases.

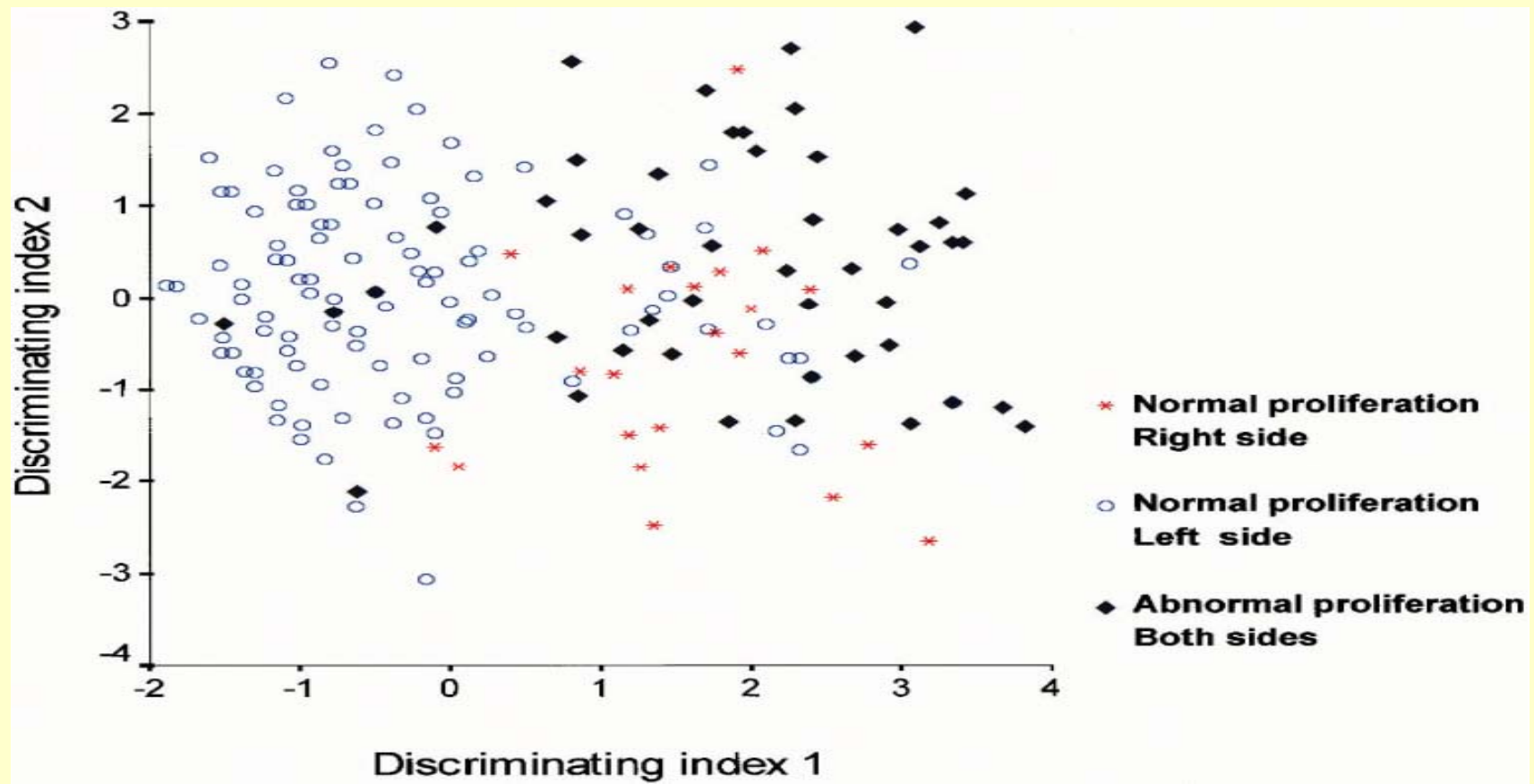
Hyperplastic polyps

Heterogeneous group

- Serrated polyps with normal proliferation (Torlakovic et al 2003)
- Serrated polyps with normal maturation (Batts et al)
- Serrated polyps without dysplasia (Jass et al)
- Serrated polyps with abnormal proliferation
- Serrated polyps with abnormal maturation (Torlakovic 2003); dysmaturation (Goldstein 2003)
- Serrated polyps with dysplasia

Grouping of cases based on the site of the polyp and the type of proliferation. Right-sided serrated polyps with normal proliferation separate from left-sided polyps with normal proliferation. **Polyps with abnormal proliferation group more with right than left side.**

From: Torlakovic: Am J Surg Pathol, Volume 27(1).January 2003.65-81



Classical – Traditional Hyperplastic polyps

TABLE 2. Putative Subtypes of Serrated Polyps with Normal Maturation²

Microvesicular Cell Type

Common, small, usually left colon

Microvesicular mucin with few goblet cells

Some dystrophic goblet cells, nuclear atypia

Probably equates to classical HPPs

Goblet-cell Type

Small, almost all left colon

Elongated crypts with prominent goblet cells, little serration

Mucin-poor Type

Small, rare; unclear niche—possibly regenerative or neoplastic

Small cells with little cytoplasm

No neuroendocrine cells

Some crypt dilatation

HPPs, hyperplastic colorectal polyps.

Hyperplastic polyps – Serrated polyps

Frequency distribution

- Hyperplastic polyps or serrated polyps with normal proliferation

80-

95%

- Serrated polyps with abnormal proliferation
(?)

5-

20%

- Traditional serrated adenoma < 1%
- Mixed polyps (mixed sessile serrate adenoma-tubular adenoma) < 1%
- Sessile serrated adenoma 4-19%

Classification

- **Serrated polyps with dysplasia (abnormal proliferation)**
 - **Mixed hyperplastic adenomatous (cytologic dysplasia) !!!**
 - **Serrated adenomas (TSA) (cytologic dysplasia) !!!**
- **Serrated polyps with no dysplasia**
 - **Classic hyperplastic polyps**
 - **Sessile serrated adenoma (SSA) (no or little cytologic dysplasia) !!!**

Sessile serrated adenoma

TABLE 1. Major Morphologic Features of 'Sessile Serrated Adenoma'²⁻⁴

Abnormal Proliferation/ Dysmaturation

- Nuclear atypia in mid/upper crypts
- Oval nuclei in middle crypts
- Prominent nucleoli in middle/superficial crypts
- Dystrophic goblet cells
- Irregular distribution of goblet cells
- Mitoses in mid/upper crypts
- Excessive crypt or luminal mucin

Architectural Features

- Basal crypt dilatation
- Horizontal orientation of deep crypts
- Prominent serrations
- Inverted crypts

Other Features

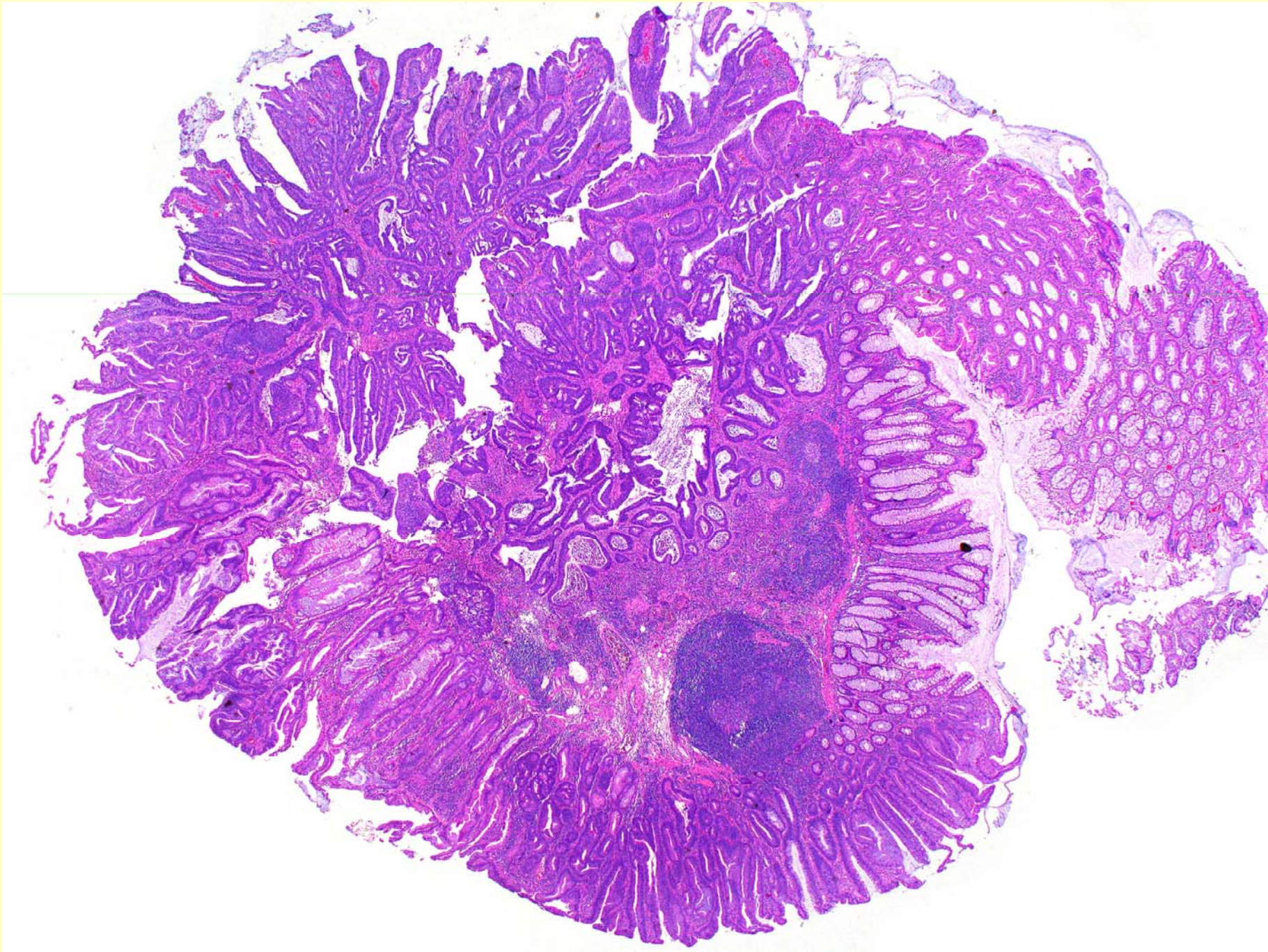
- Lack of thickened basement membrane
 - Focal loss of hMLH1 positivity
 - Decreased/absent neuroendocrine cells
-

Sessile Serrated adenomas as Cancer precursors

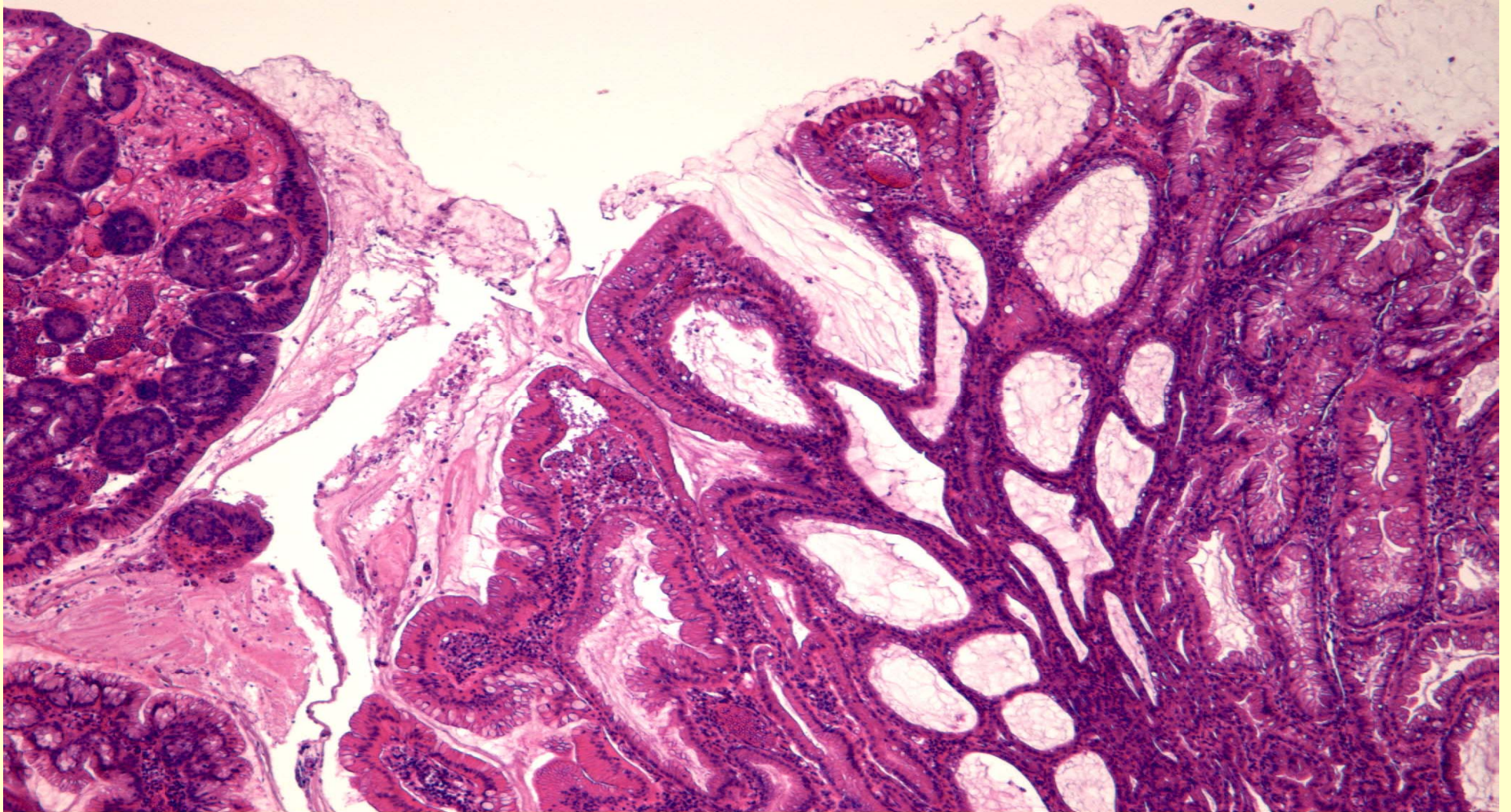
- Case reports of giant HPP associated with adenocarcinoma
- Hawkins et al J Natl Cancer Inst 2001
 - Microsatellite unstable colorectal cancers often arise from a background colon with increased hyperplastic polyps but not adenomas
- Goldstein et al AJCP 2003
 - 91 cases of microsatellite unstable AdCa's had hyperplastic polyps previously sampled at / near cancer site

Sessile Serrated adenomas as Cancer precursors

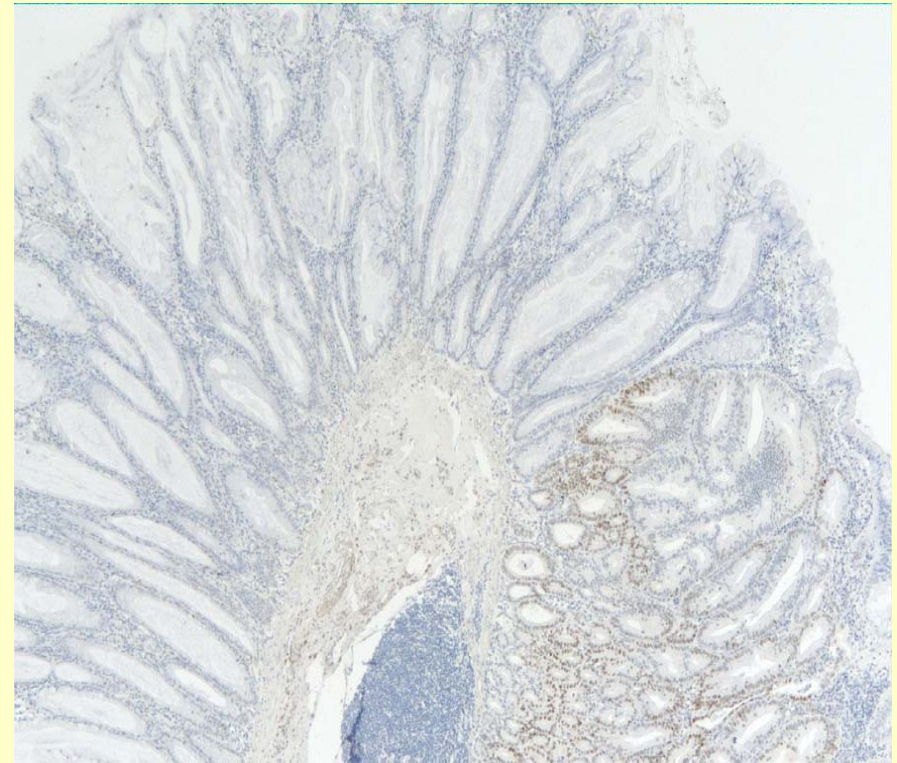
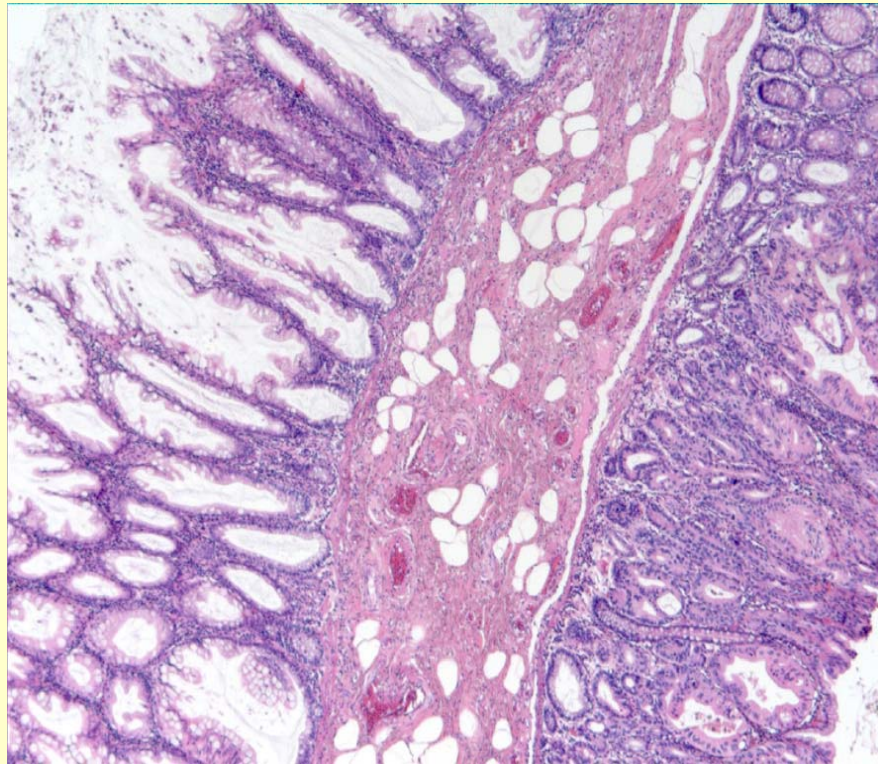
- Lazarus et al Am J Clin Pathol
 - Serrated adenomas grow faster than tubular adenomas (retrospective study, 239 colon polyps, mean of 94 months follow up)
- Goldstein et al
 - Small adenocarcinomas arising in SSA : 6 small right sided AdCa's, all MSI, all arising in SSA



Sessile serrated adenoma & carcinoma 1460862



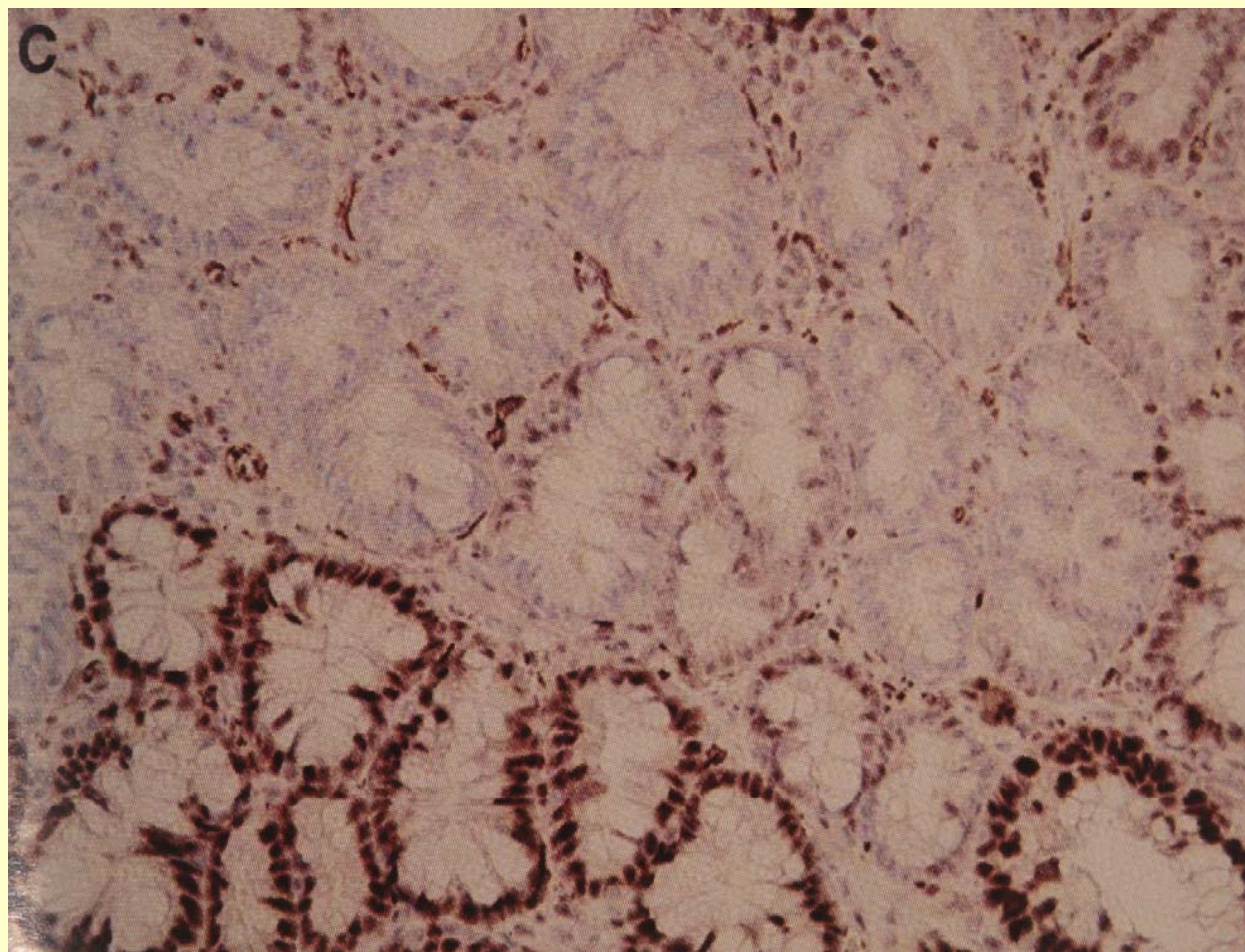
Sessile serrated adenoma + carcinoma (657634/9) H&E p53



Sessile Serrated adenomas as Cancer precursors

- **Molecular data**
 - **Large survey of a variety of serrated polyps : hypermethylation status of a large number of different genes in SSA (65%) and mixed polyps (82%) compared with HPP (25%) Wynter et al Gut 2004**
 - **Large number of MSI**

Focal loss of nuclear expression of hMLH1 in SSA



Sessile Serrated adenomas as Cancer precursors

- Molecular data
 - Data linking Serrated Polyps to MSI (lino et al J Clin Pathol)
 - % MSI
 - Traditional Adenoma +/- 14%
 - Hyperplastic polyp +/- 30%
 - Serrated adenoma > 50%
 - Mixed polyps > 80%

Sessile Serrated adenomas as Cancer precursors

- Molecular data
 - SSA frequently show mutation of BRAF, which is a step within the mitogen-activated protein kinase signaling pathway
 - Traditional hyperplastic polyps show K-ras mutation
 - Both are linked to inhibition of apoptosis

Sessile Serrated adenomas as Cancer precursors

- **Morphologic similarity between “Mucosal Hyperplasia” of the appendix, an established preneoplastic lesion and sessile serrated adenoma**

Sessile Serrated adenomas as Cancer precursors

- **Serrated neoplasia pathway**
 - **Stepwise?**
 - **Transition from no cytologic dysplasia through cytologic dysplasia (mixed type)**
- **Time of progression to cancer : unclear; probably slow (> 3 to 5 yrs)**
- **Recurrence rate : unclear**
(Snover et al Am J Clin Pathol 2005)

Recommendations for treatment

- **For right-sided sessile serrated adenomas without cytologic dysplasia (adenomatous change)**
 - Endoscopic removal
 - Repeat colonoscopy (begin at 1 yr interval)
 - Evidence of cytologic dysplasia : surgery
- **Left-sided lesions (?)**
 - Endoscopic removal
 - Resection : left-sided MSI related cancer is rare

Proposal for classification

- **Non-dysplastic serrated polyp**
 - Normal architecture
 - Abnormal architecture/abnormal proliferation (= sessile serrated polyp or sessile serrated adenoma)
- **Dysplastic serrated polyp**
- **Unclassifiable**

Conclusions

- Hyperplastic polyps = Heterogeneous
- Larger lesions + aberrant histology = evidence points towards preneoplastic potential through serrated pathway
- There is a terminology problem
- Sessile serrated adenoma, serrated adenoma and mixed hyperplastic/adenoma polyp were the first names
- Optimal treatment is complete endoscopic removal and probably adenoma-like follow up

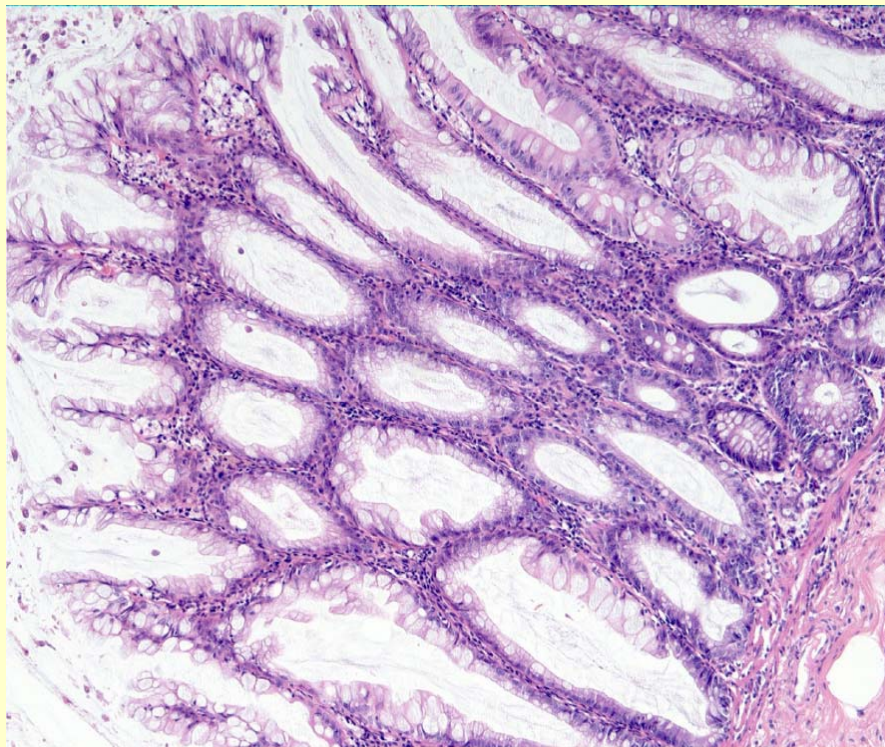
Conclusions

The majority of small, whitish sporadic polyps are still traditional “hyperplastic polyps” !

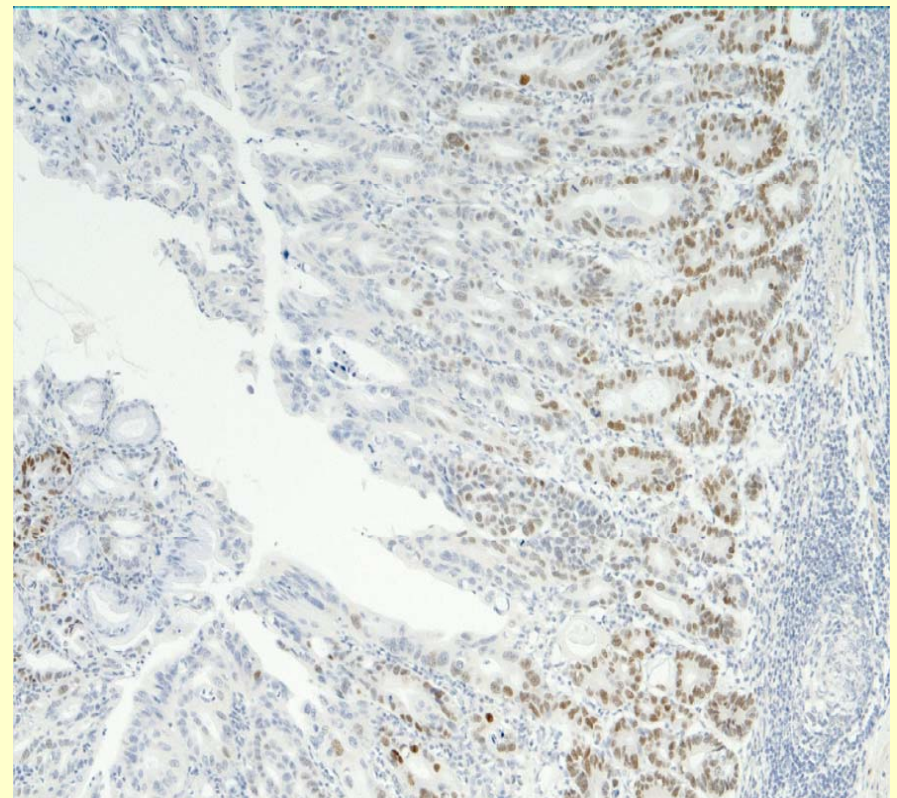
(Basal proliferative compartment with immature cells)

Sessile serrated adenoma + carcinoma (657634/9)

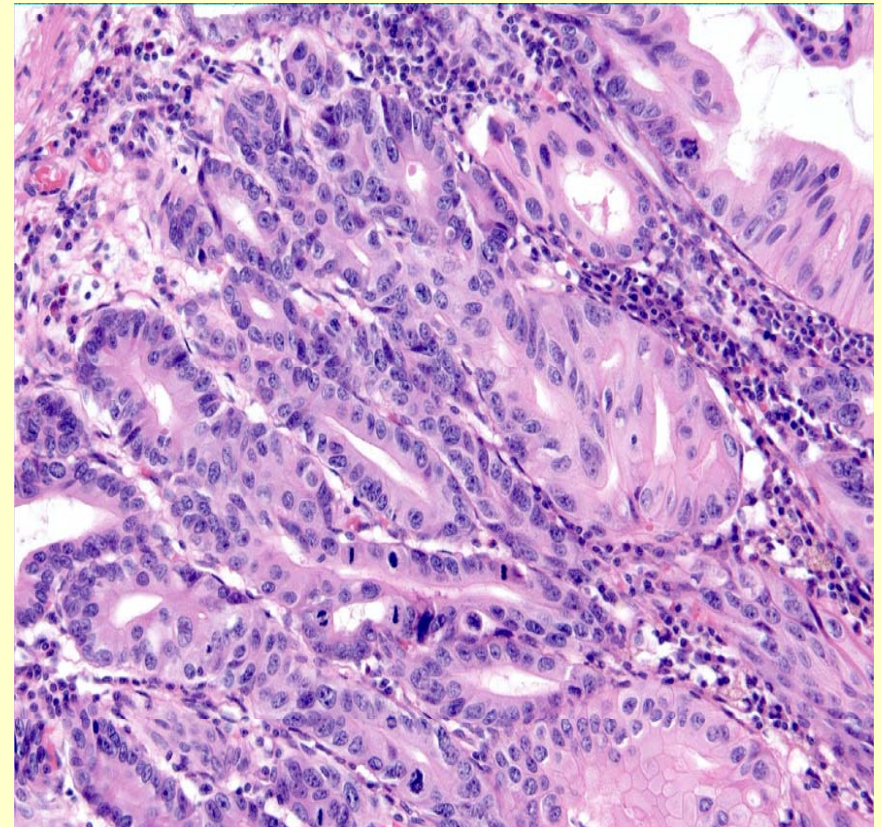
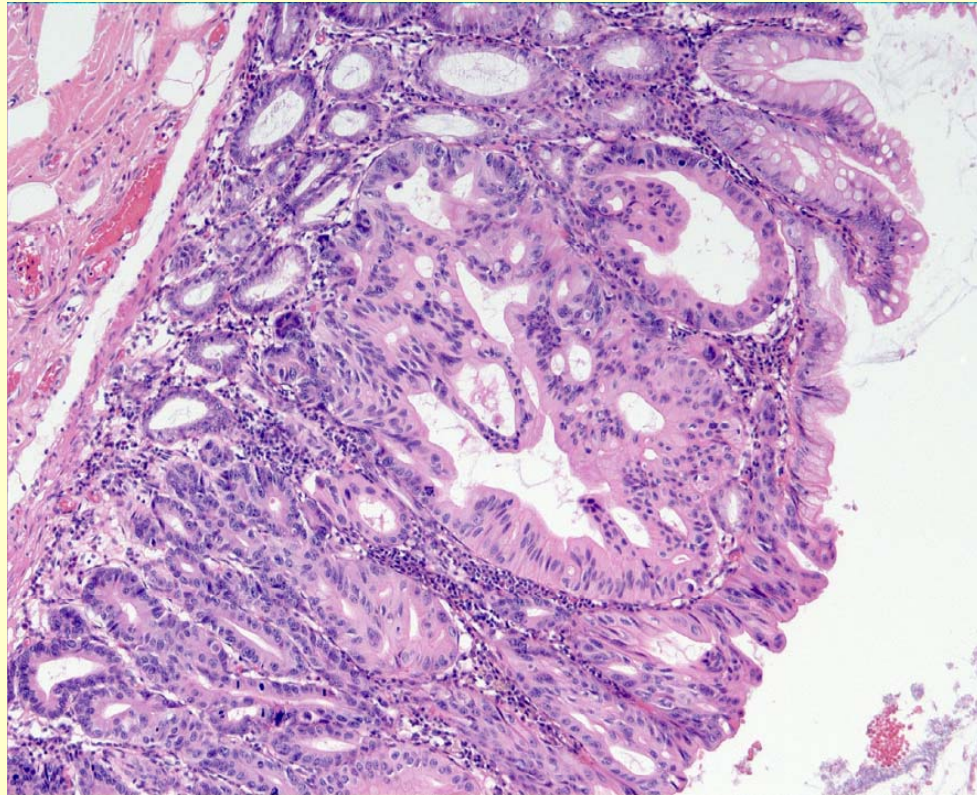
H&E



p53



Sessile serrated adenoma + carcinoma (657634/9) H&E



Inflammatory Cap Polyp

- **Solitary lesion**
- **Polyposis**

cap polyposis の組織診断

国際比較

渡辺 英伸 ¹⁾	橋立 英樹	味岡 洋一	西倉 健
向井 玄	五十嵐俊彦 ²⁾	櫻井 俊弘 ³⁾	中野 浩 ⁴⁾
赤松 泰次 ⁵⁾	山野 泰穂 ⁶⁾	岩下 明德 ⁷⁾	八尾 隆史 ⁸⁾
石黒 信吾 ⁹⁾	服部 隆則 ¹⁰⁾	小野 祐子 ¹¹⁾	藤盛 孝博
Jeremy Jass ¹²⁾	Karel Geboes ¹³⁾	Joel Greenson ¹⁴⁾	
Sarah M. Dry ¹⁵⁾	Klaus J. Lewin	Santiago de Elizalde ¹⁶⁾	
Carlos Rubio ¹⁷⁾	Axel von Herbay ¹⁸⁾	Robert Ibrahim ¹⁹⁾	

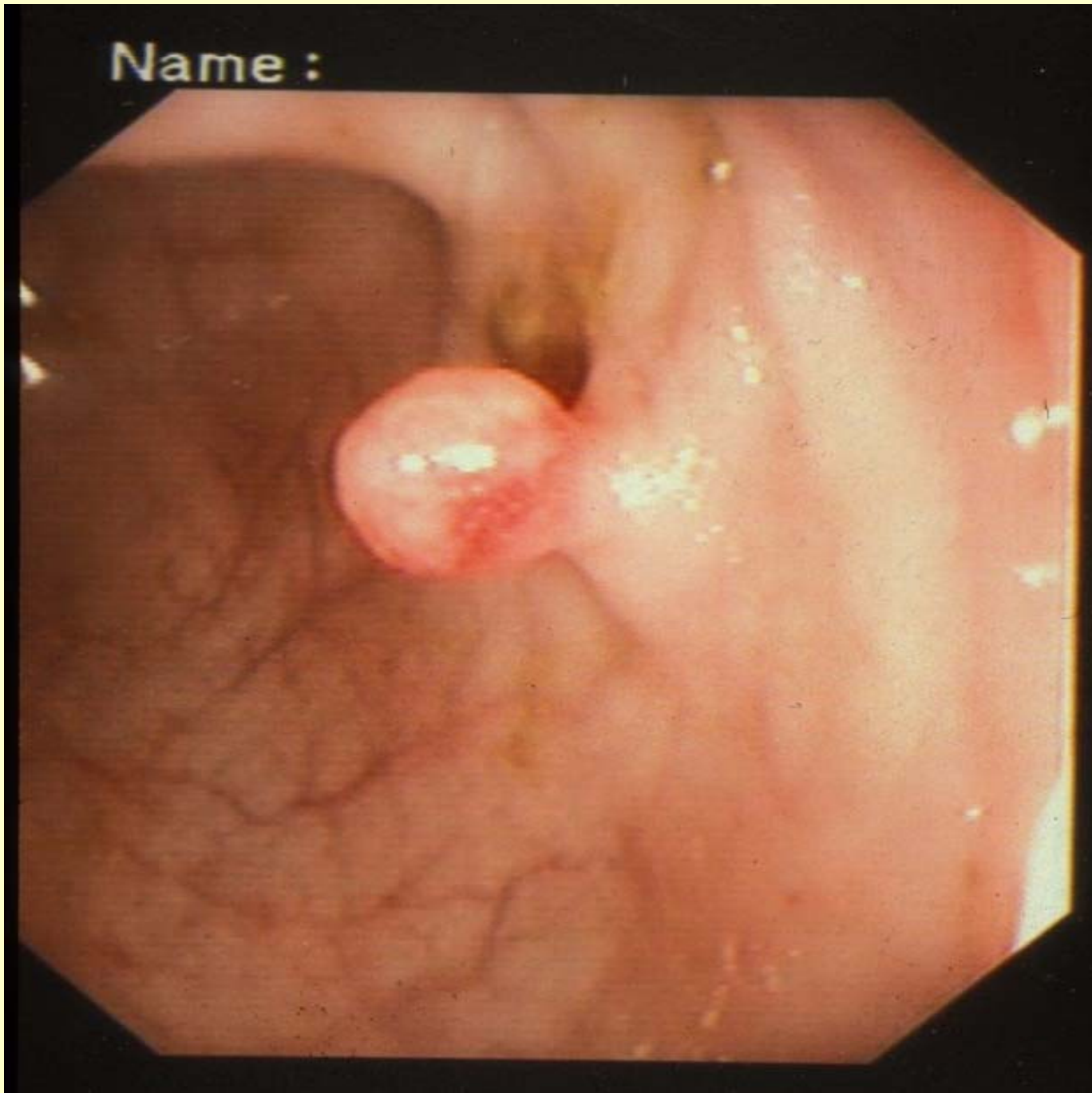
Cap polyposis

- **Rare, but distinct disorder**
- **No sex predilection**
- **Age range : 17-82 yrs**
- **Clinical presentation : mucoid or bloody diarrhea, abdominal pain**
- **Endoscopy : multiple sessile polyps; in rectum and sigmoid; rarely entire colon**
- **few mm to 2 cm**

Table 1 Brief macroscopic findings of cap polyposis

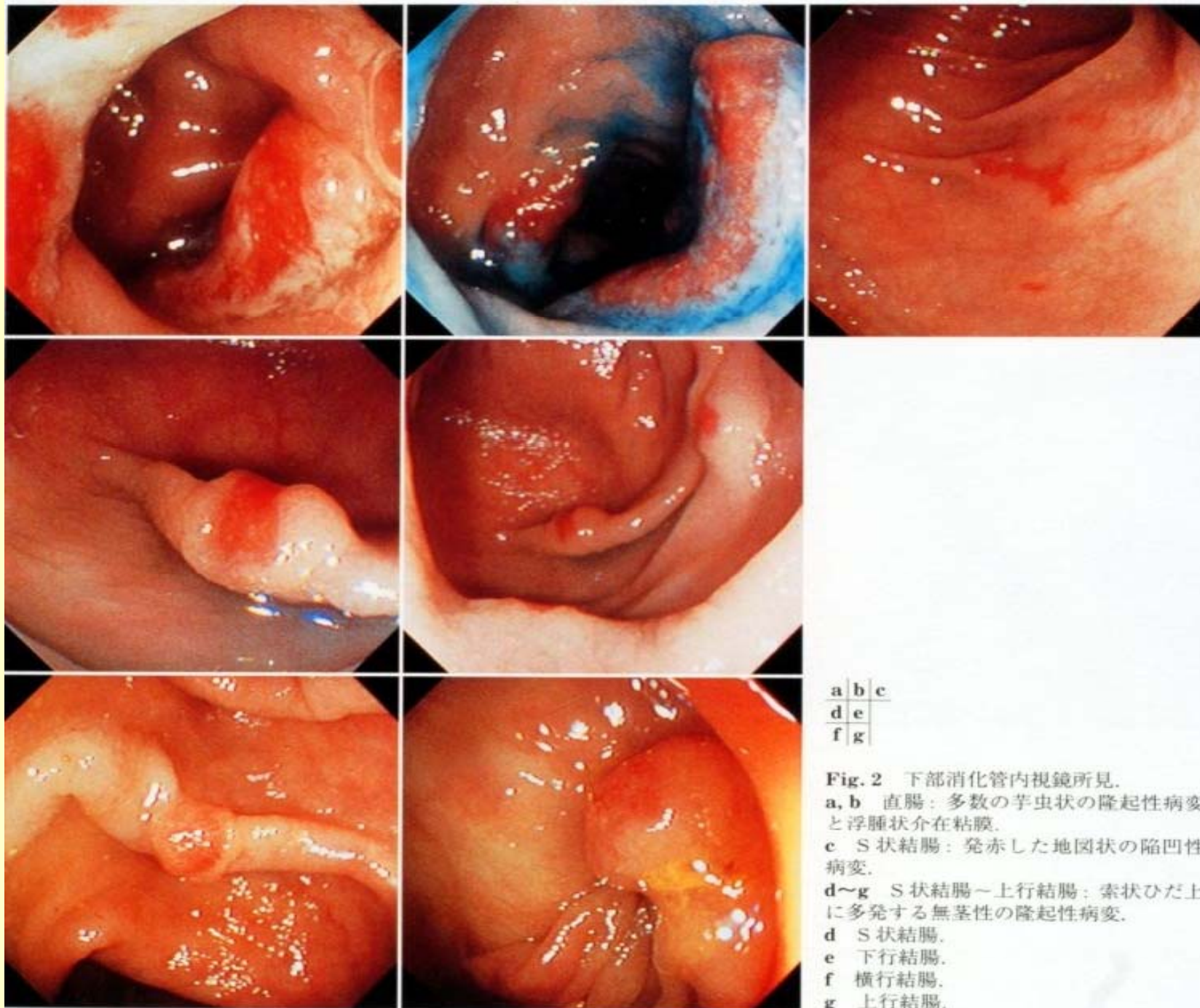
Case No.	Age	Sex	Macroscopic findings
1	75	M	Multiple slightly elevated lesions with red color and necrotic tissue on their surface are located from the sigmoid to the rectum. Biopsy was taken from one lesion with red color and one with necrotic tissue.
2	76	M	Slightly elevated multiple polypoid lesions with red color and covered necrotic tissue at the cener (0-IIa like type), sigmoid to rectum. Biopsy (1, 2, 3) from an 0-IIa like rectal lesion, 11×8 mm in size. EMR (endoscopic mucosal resection) from a rectal lesion.
7	61	M	Multiple slightly elevated lesions (distributed from the ascending colon to the sigmoid colon) surrounded by normal-appearing mucosa. Biopsy specimen.
11	33	F	Several broad-based elevated lesions with red color in the rectum. Biopsy specimen.
12	42	F	Several broad-based elevated lesions (0-Is, or 0-IIa like) with red color were found in the rectum to the rectosigmoid colon. Endoscopic mucosal resection.
16	76	F	Chief complaints ; muroid and bloody diarrhea, 5 times a day. Multiple polypoid lesions in the sigmoid colon. Surgical specimen (1) and endoscopically resected specimen (2).
26	62	M	Chief complaint : melena. Multiple 0-IIa and 0-IIa + IIc (size ; 49×48 mm) like lesions with red color in the rectum. The photos (1-7) from the 0-IIa + IIc like lesion. Surgical specimen.

Name :



Name :





a	b	c
d	e	
f	g	

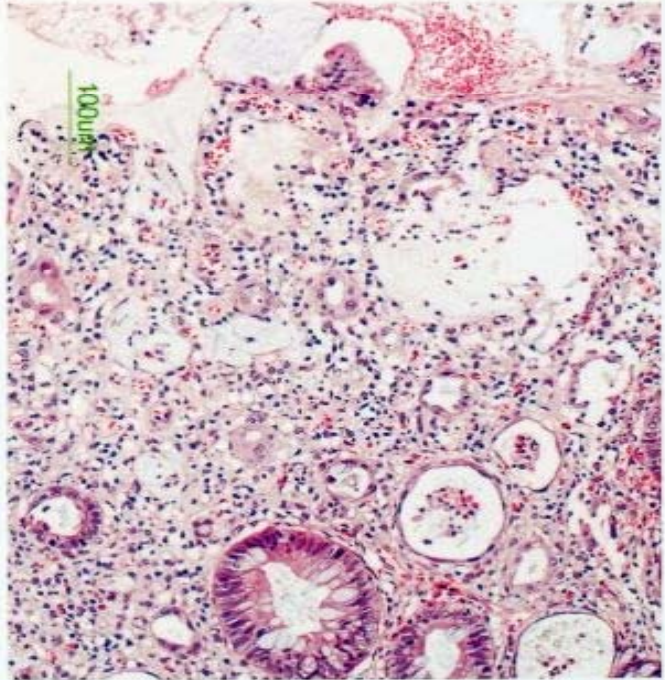
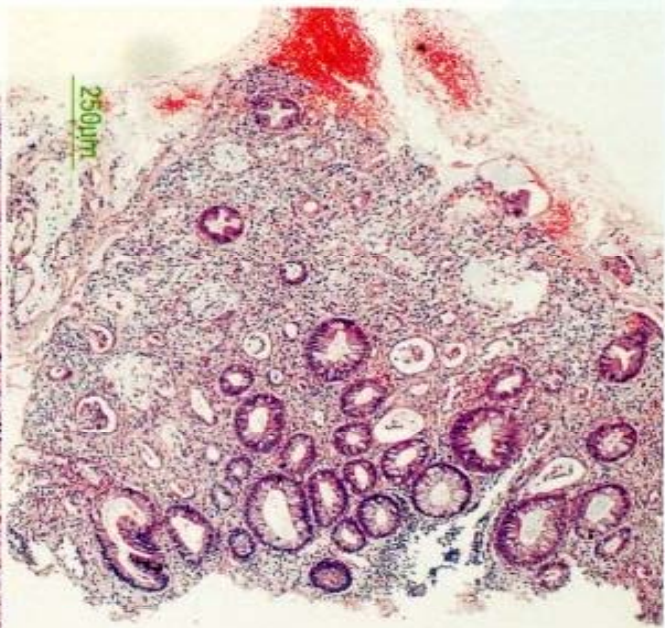
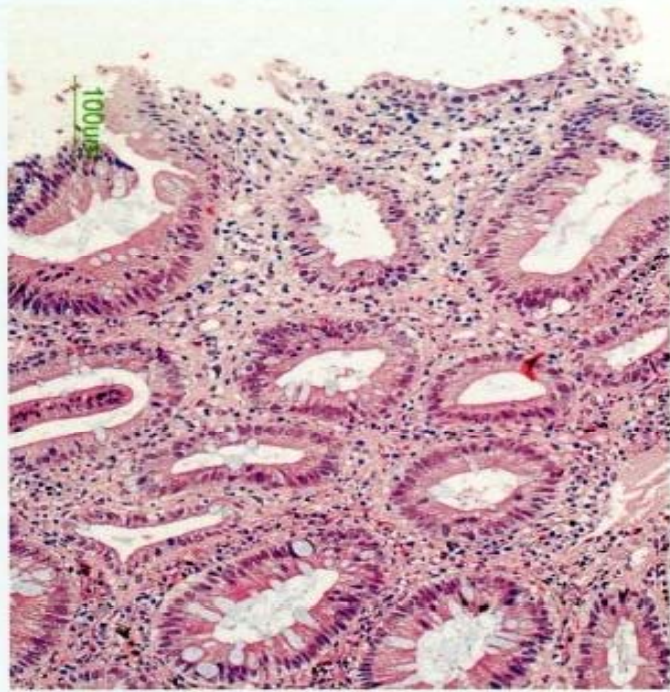
Fig. 2 下部消化管内視鏡所見.
 a, b 直腸: 多数の芋虫状の隆起性病変と浮腫状介在粘膜.
 c S状結腸: 発赤した地図状の陥凹性病変.
 d~g S状結腸~上行結腸: 索状ひだ上に多発する無茎性の隆起性病変.
 d S状結腸.
 e 下行結腸.
 f 横行結腸.
 g 上行結腸.

Cap polyposis

- **Histology**
 - **Elongated tortuous crypts**
 - **A cap of granulation tissue**
 - **Mixed inflammation**
 - **Splayed smooth muscle fibers may be present**

Table 2 Histologic features of cap polyposis

Histological items	Findings
Crypts	Straightly elongated, distended, and mildly tortuous or branching
Density of crypts	Normal
Cryptal cells	Containing much sialomucin (clear cytoplasm in H•E section) in goblet cells in the lower distended crypts of large polyps. No desquamated cells taking the form of signet-ring cells in the lumen of the lower distended crypts as seen in pseudomembranous colitis
Length and location of proliferative zone (PZ) in crypts	PZ is elongated, and located in the lower 2/3 ~ 4/5 of crypts in small non-erosive polyps, and the upper 2/3 of crypts in large erosive polyps. The lower distended crypts have fewer Ki-67-positive cells and more abundant sialomucin-positive cells
Vascular proliferation	Proliferation and dilatation of capillaries with swollen endothelial cells particularly in the superficial layer of the lamina propria mucosae
Spindle-shaped stromal cells	Proliferation of myofibroblasts and fibroblasts in the upper one third and smooth muscle cells in the lower two thirds of the lamina propria mucosae
Chronic inflammatory cells	Mild (non-erosive part) to moderate (erosive part) infiltration in the superficial part of the lamina propria mucosae
Neutrophil infiltration	Secondary to superficial erosion (summit erosion)
Fibrosis in the superficial layer	No or very mild
Erosion with pseudomembrane	Superficial erosion with so-called 'cap' (pseudomembrane and granulation tissue) (pseudomembrane: mucofibrinopurulent material)
Phase corresponding to that of mucosal prolapse ¹⁷⁾¹⁸⁾	Vascular phase or low-grade fibromuscular phase
Intervening mucosa	Normal, or mildly elongated, distended, vascular



a	b
	c

Fig. 1 Cap polyposis, biopsy (Case 1). The red polypoid lesion shows proliferation of capillaries with swollen endothelial cells, stromal spindle cells (myofibroblasts) in a background of a mild chronic inflammatory cells, and depletion of mucin (a). The polyp with necrotic tissue reveals superficial erosion, degeneration of epithelial cells in the upper half of the mucosa, proliferation of small capillaries in the upper half of the mucosa, mild chronic inflammatory cells, and dilated crypts in the deep mucosa (b, c).

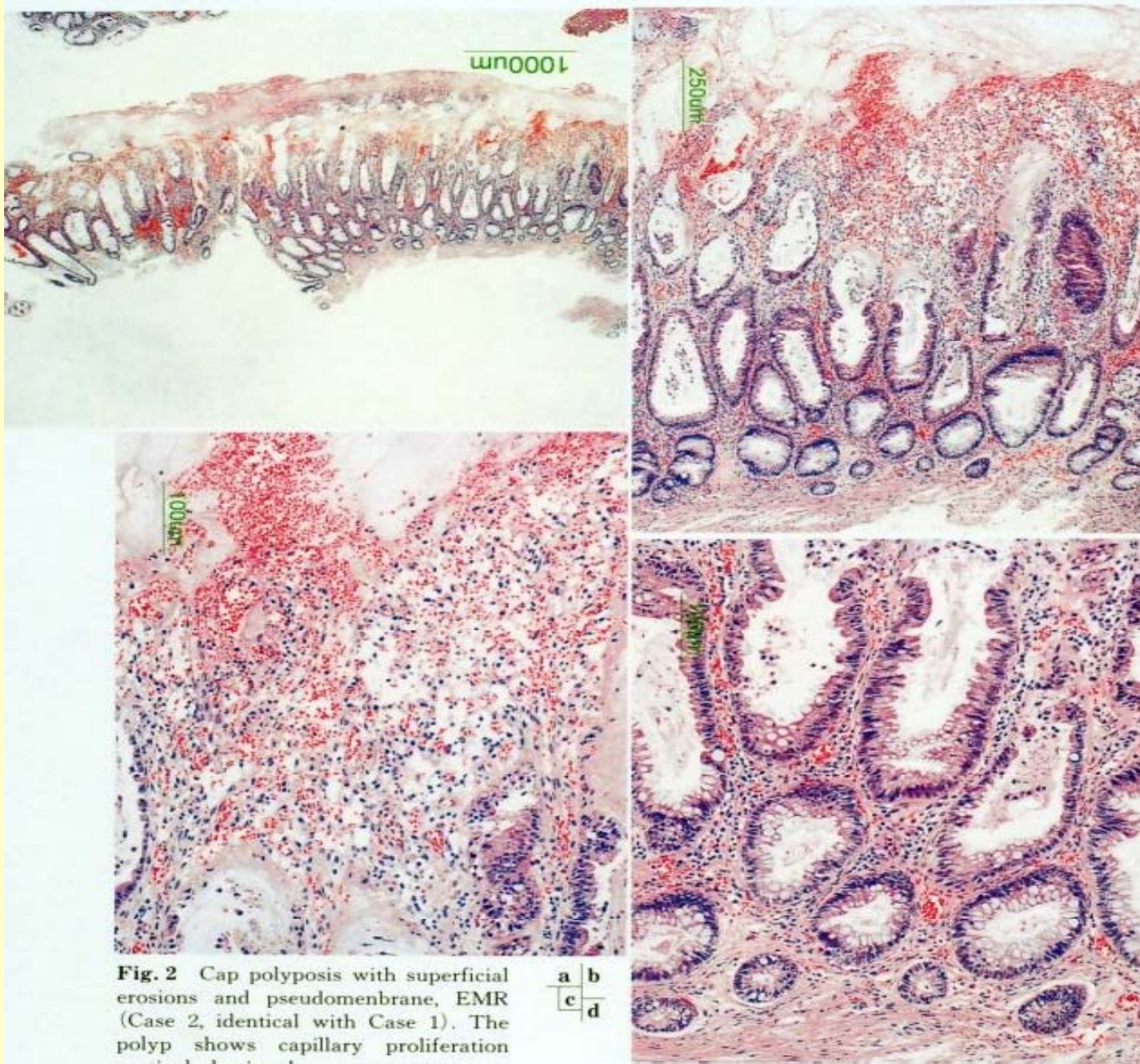
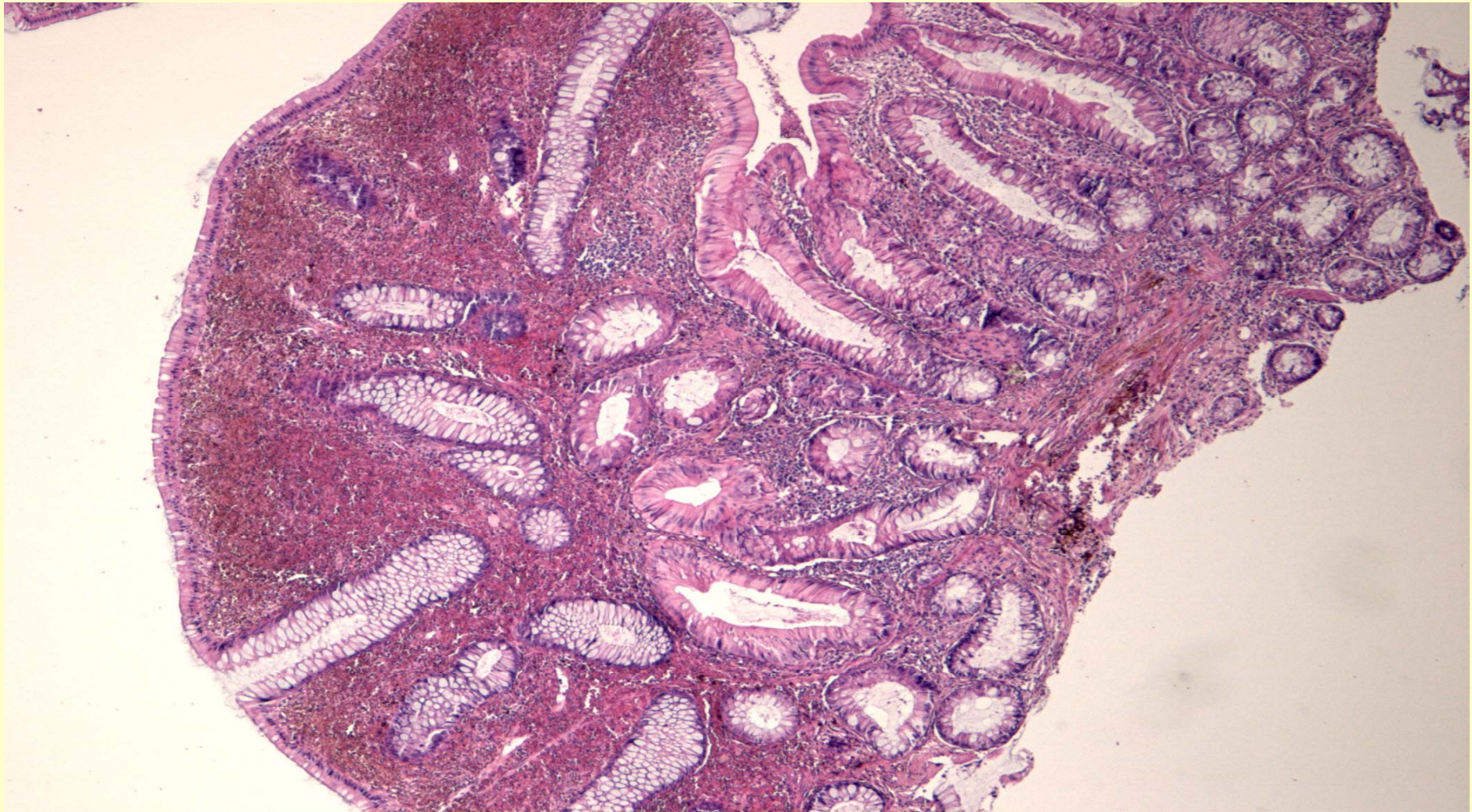


Fig. 2 Cap polyposis with superficial erosions and pseudomembrane, EMR (Case 2, identical with Case 1). The polyp shows capillary proliferation particularly in the upper mucosa, a mild chronic inflammatory infiltrates, a few polymorphs (not so many as in active pseudomembranous colitis), and proliferation of spindle-shaped cells in the deep mucosa (**a~d**).

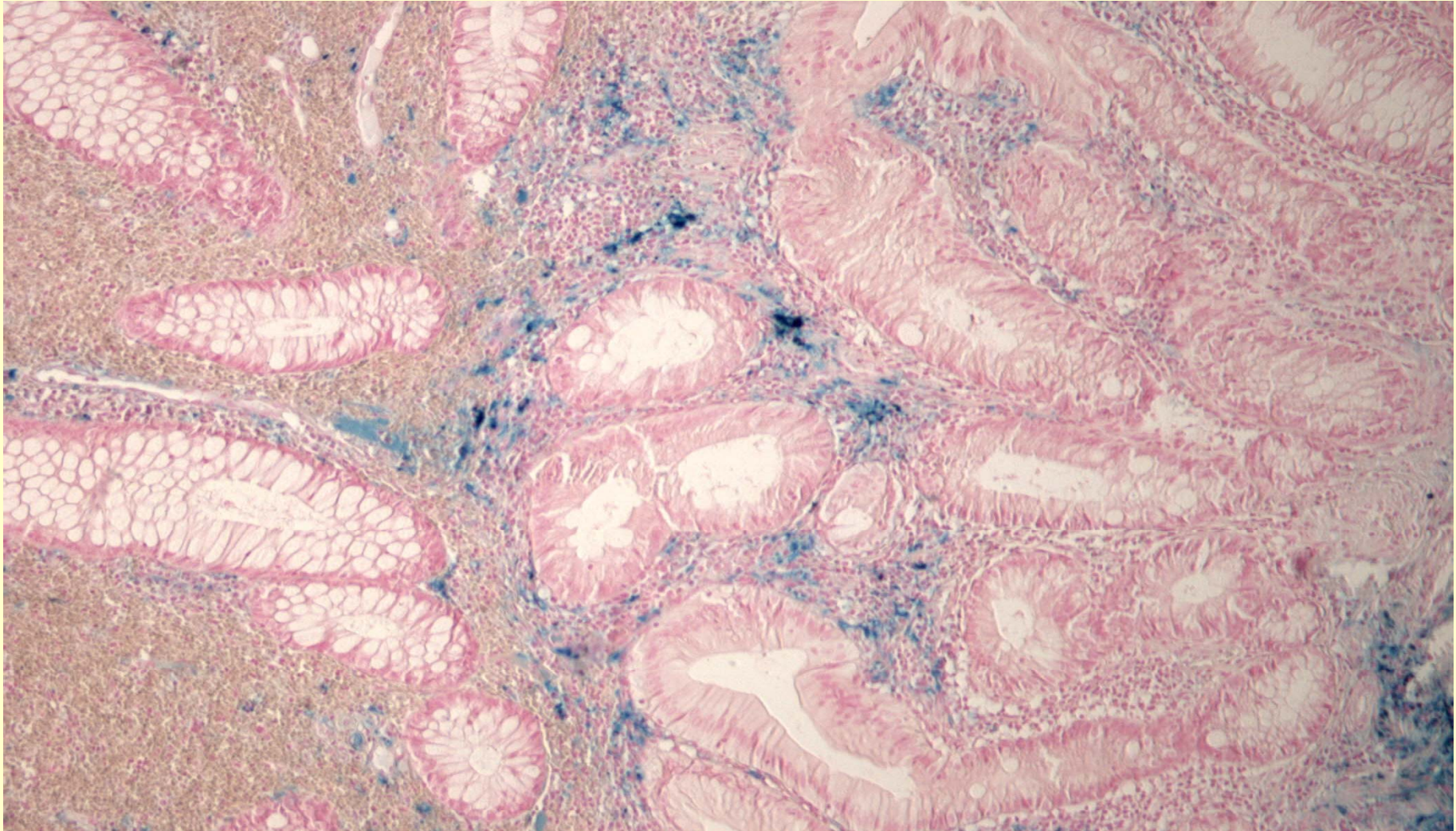


Fig. 4 Cap polyposis, EMR (Case 11, identical with Case 11). The crypts are elongated and some of them show budding. The widened lamina propria of the upper mucosa is vascular and moderately inflamed (**a, b**). a | **b**

1312779 Inflammatory cap polyp

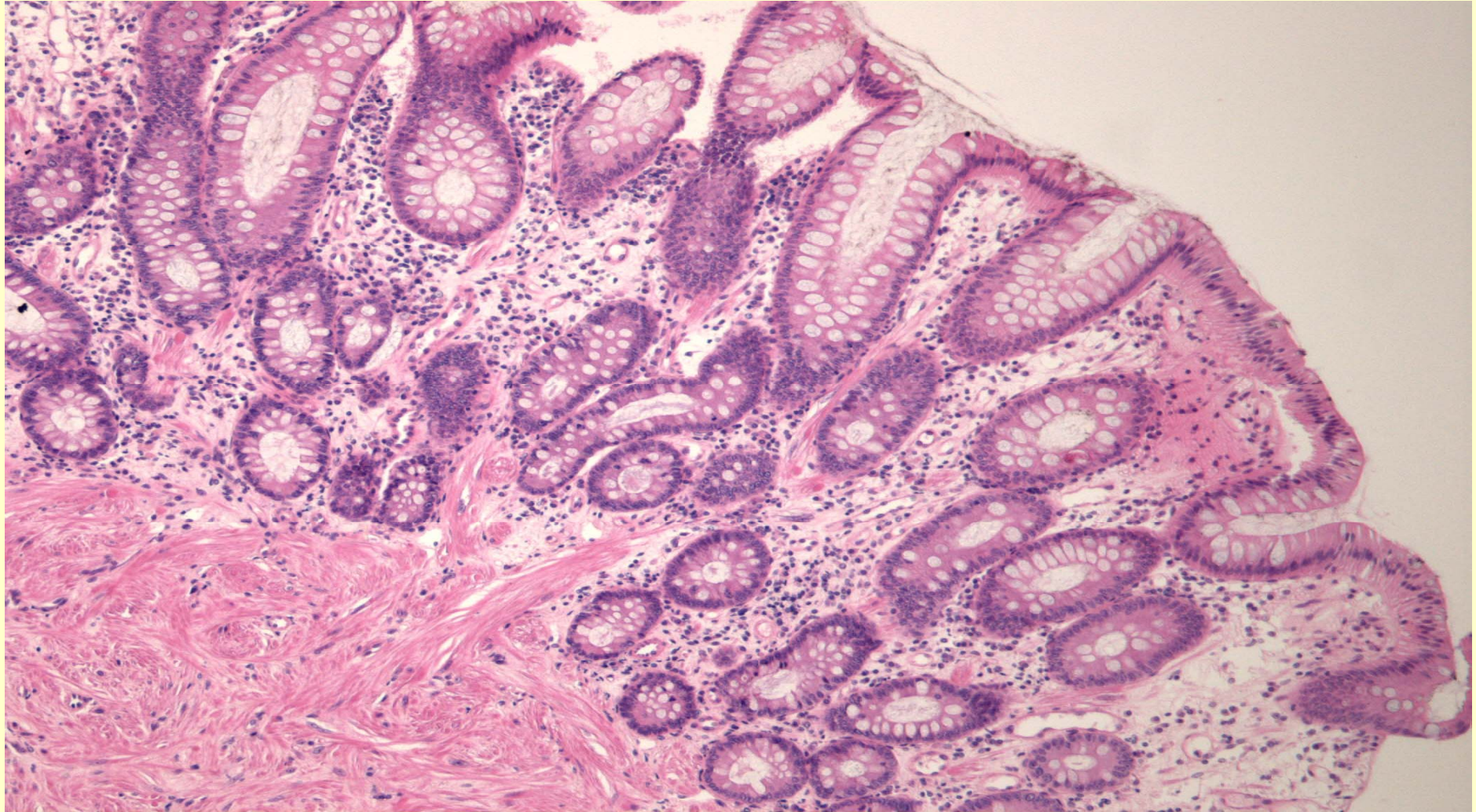


1312779 Inflamm cap polyp (Perls)



Inflammatory cap polyp

1317149



Cap Polyposis

- **Pathogenesis**
 - **Unknown**
 - **Spectrum of mucosal prolapse syndrome**
 - **Specific inflammation**
 - **Successful treatment with anti TNFa**

Other non-neoplastic colorectal polyps

- **Mucosal prolapse**
 - Cap polyp
 - solitary rectal ulcer syndrome
 - Inflammatory cloacogenic polyp
 - Diverticular disease-associated polyps
- **Hamartomatous polyps**
 - Juvenile
 - Peutz-Jeghers
 -

Other non-neoplastic colorectal polyps

- **Benign fibroblastic polyps**
- **Inflammatory fibroid polyp**
- **Vascular lesions**
- **Lymphoid polyps**
- **Endometriosis**
- **Amyloidosis**
- **Neurogenic polyps**