Fibroblastic Polyp or Intestinal Perineurioma or just …

A/Prof Andrew Ruszkiewicz, MD FRCPA
SA PATHOLOGY
ADELAIDE, SOUTH AUSTRALIA

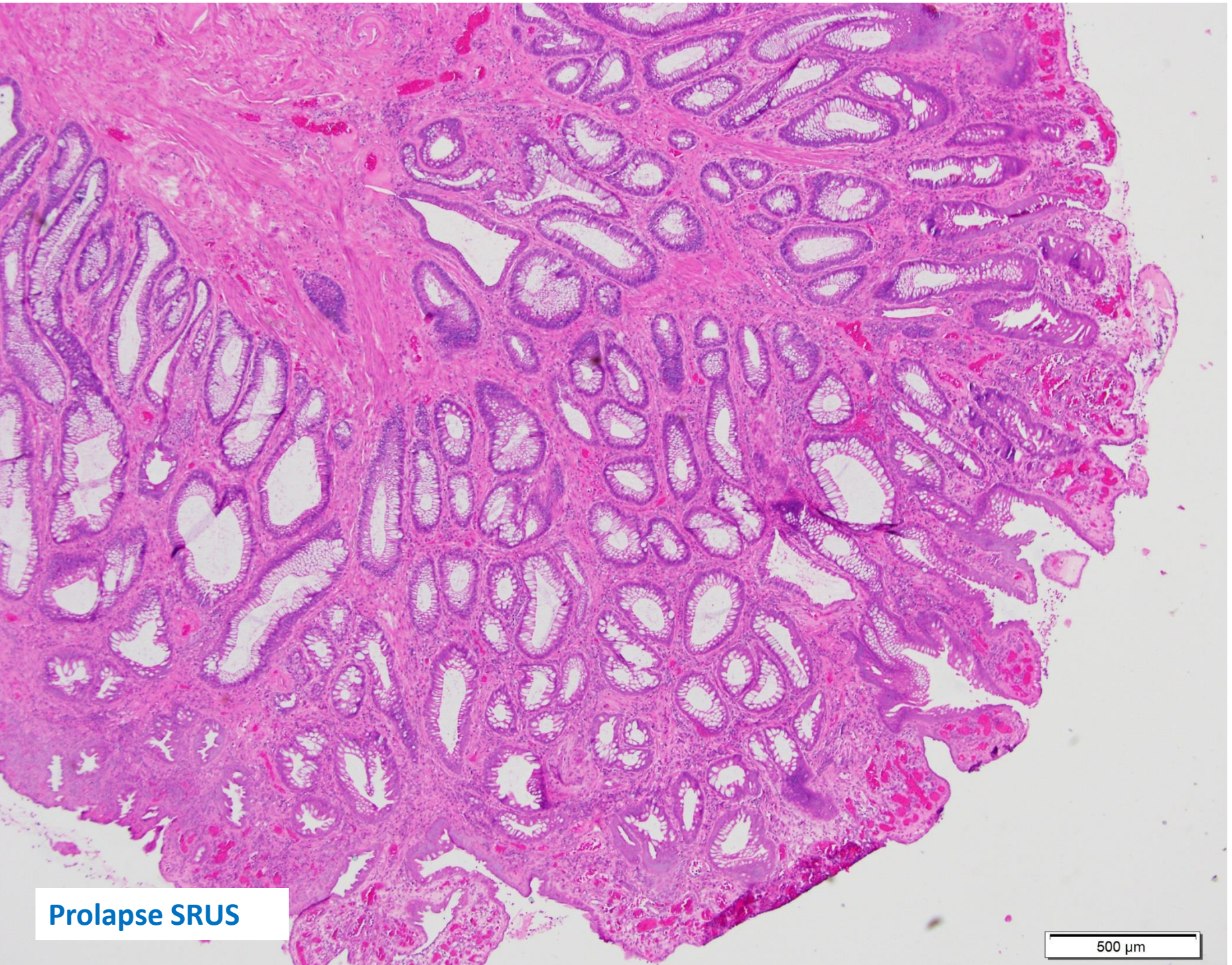
SA PATHOLOGY

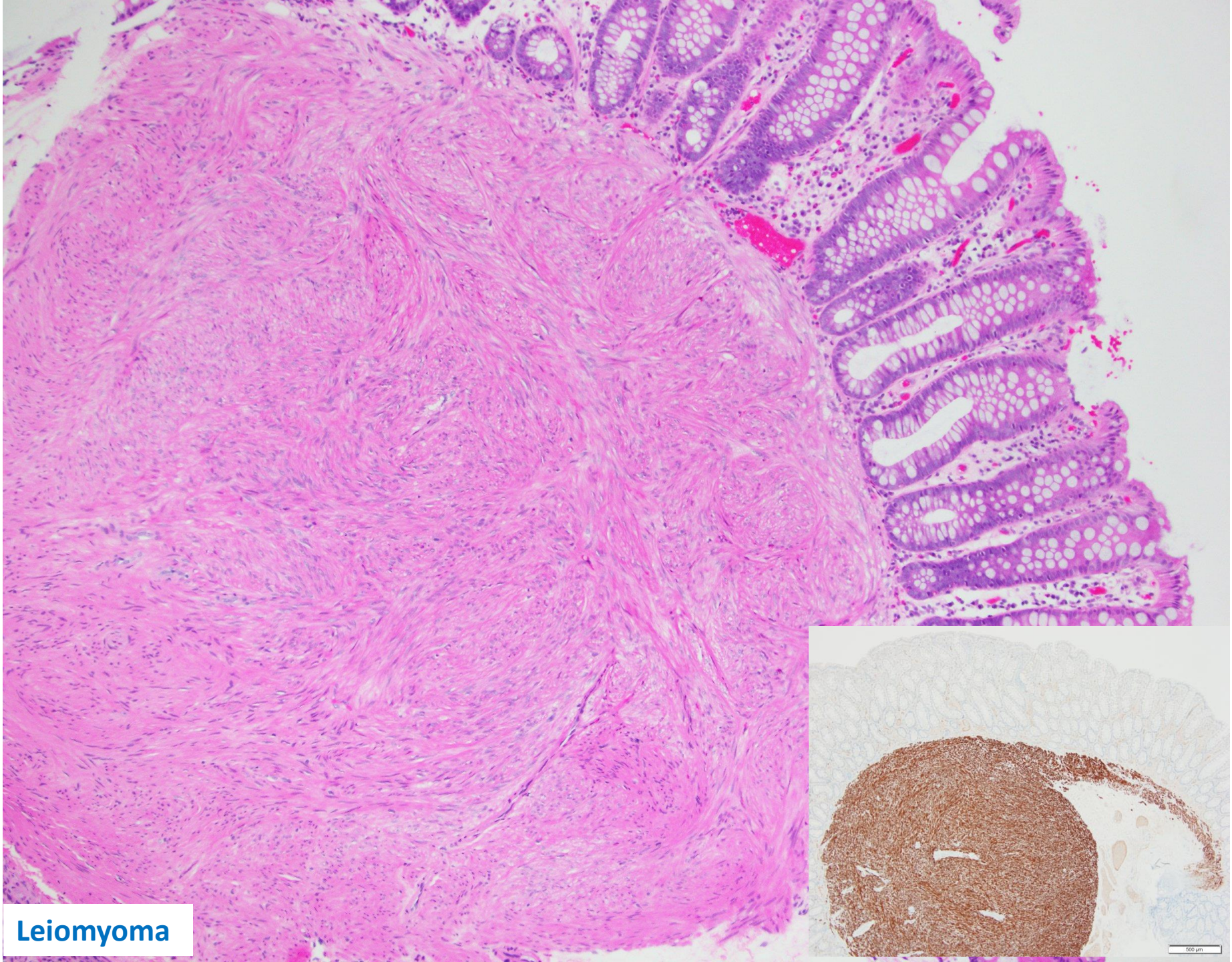
THE UNIVERSITY of ADELAIDE

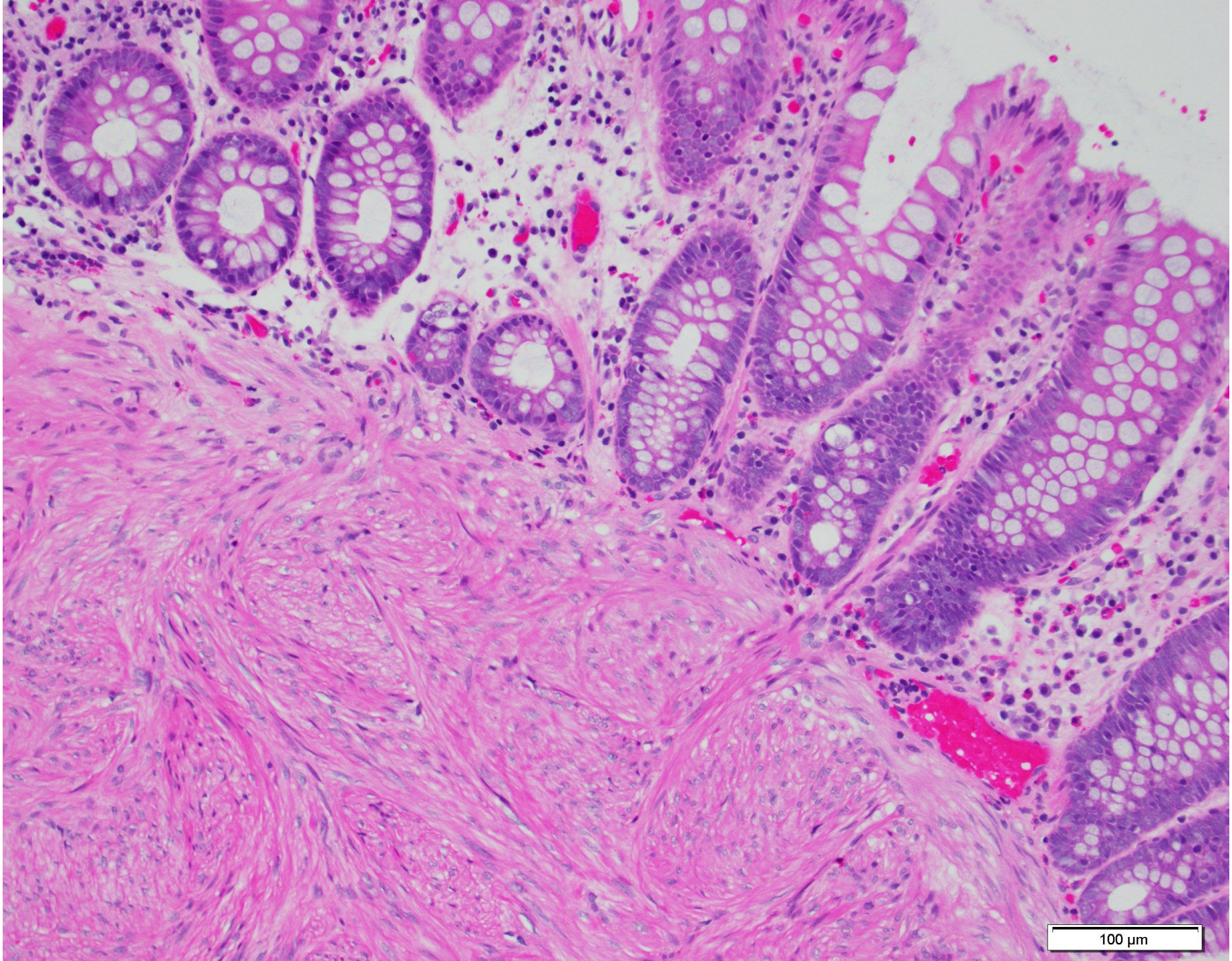
University of South Australia

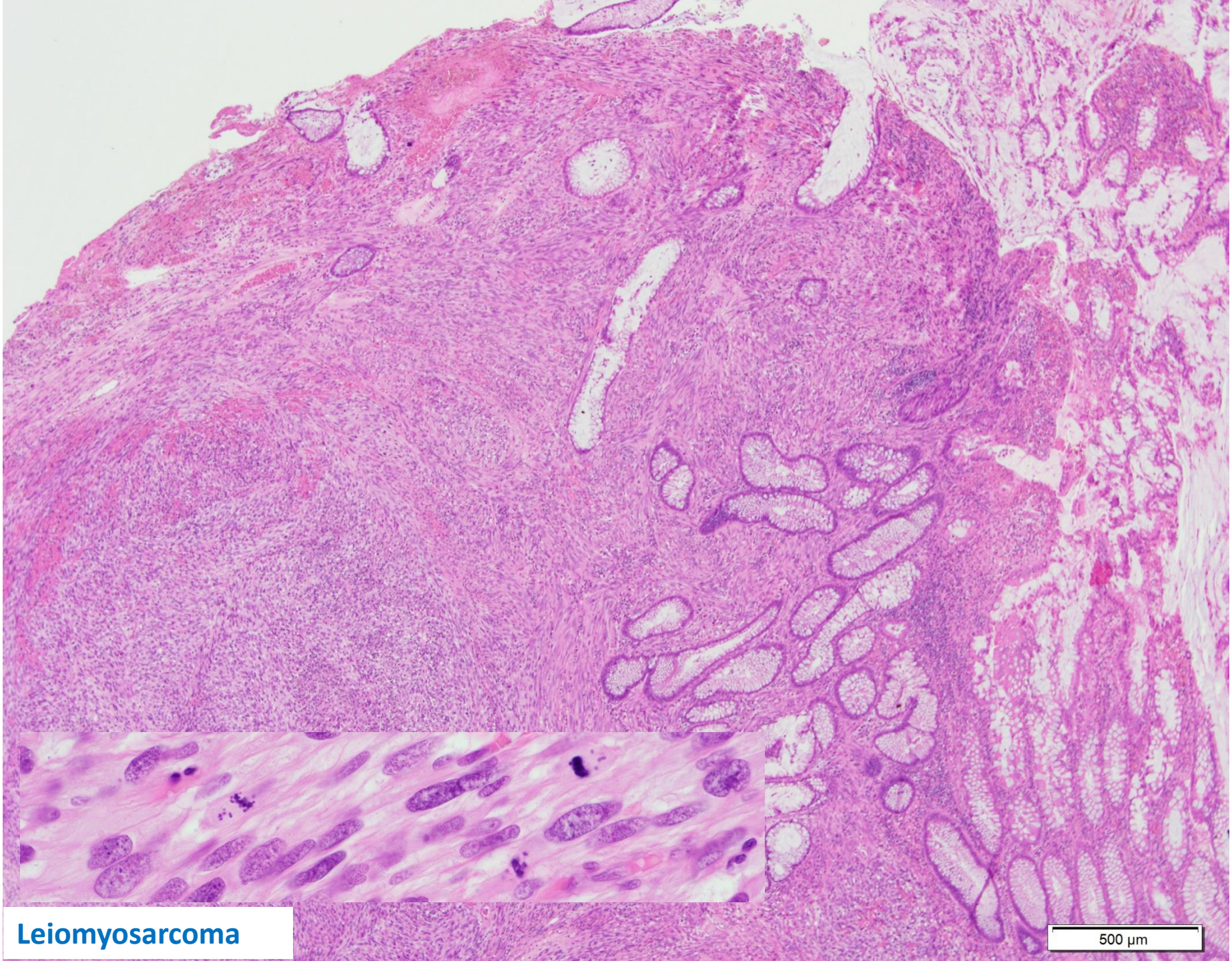
Centre for Cancer Biology

Colorectal polyps with spindle cells

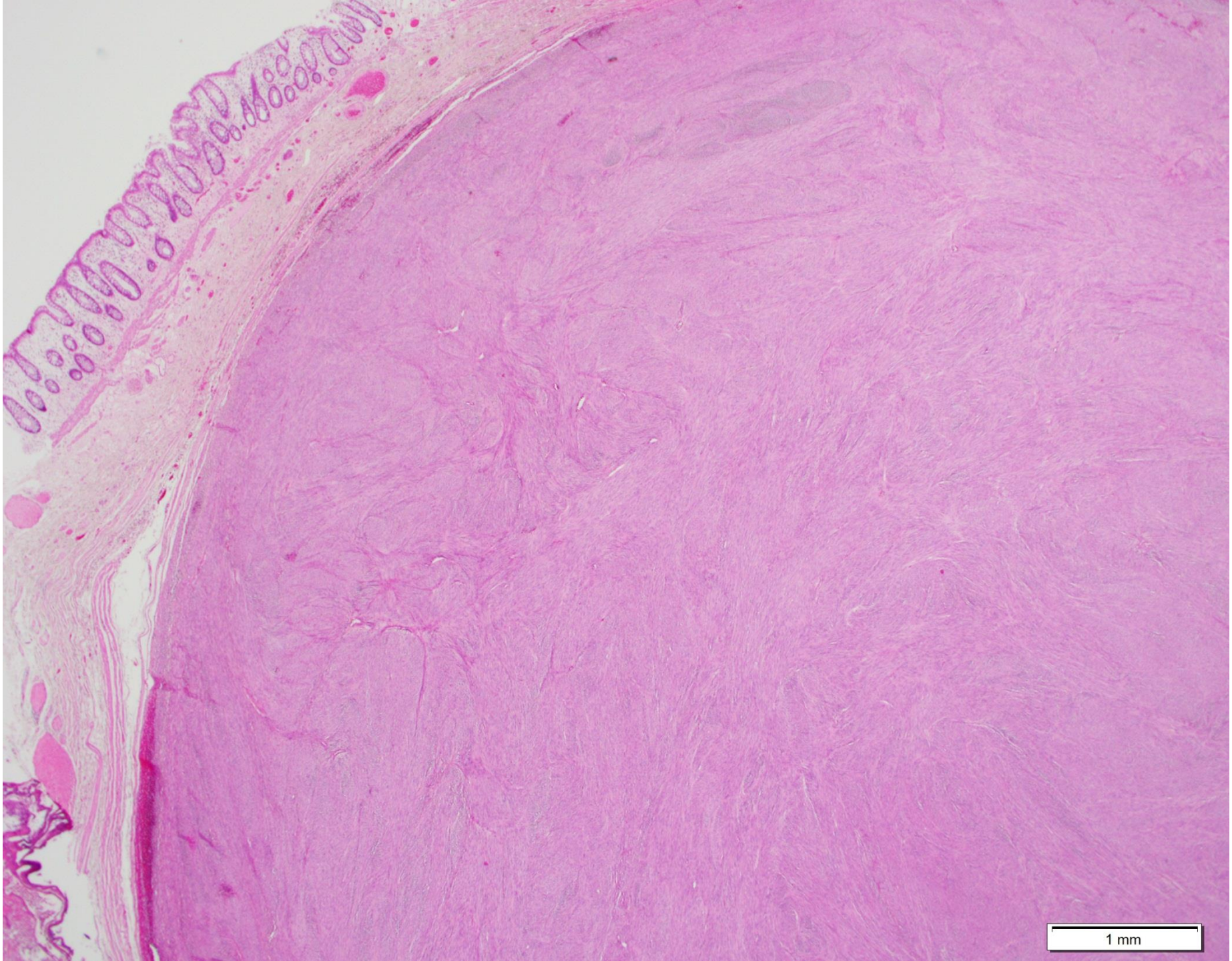

Prolapse SRUS
500 µm

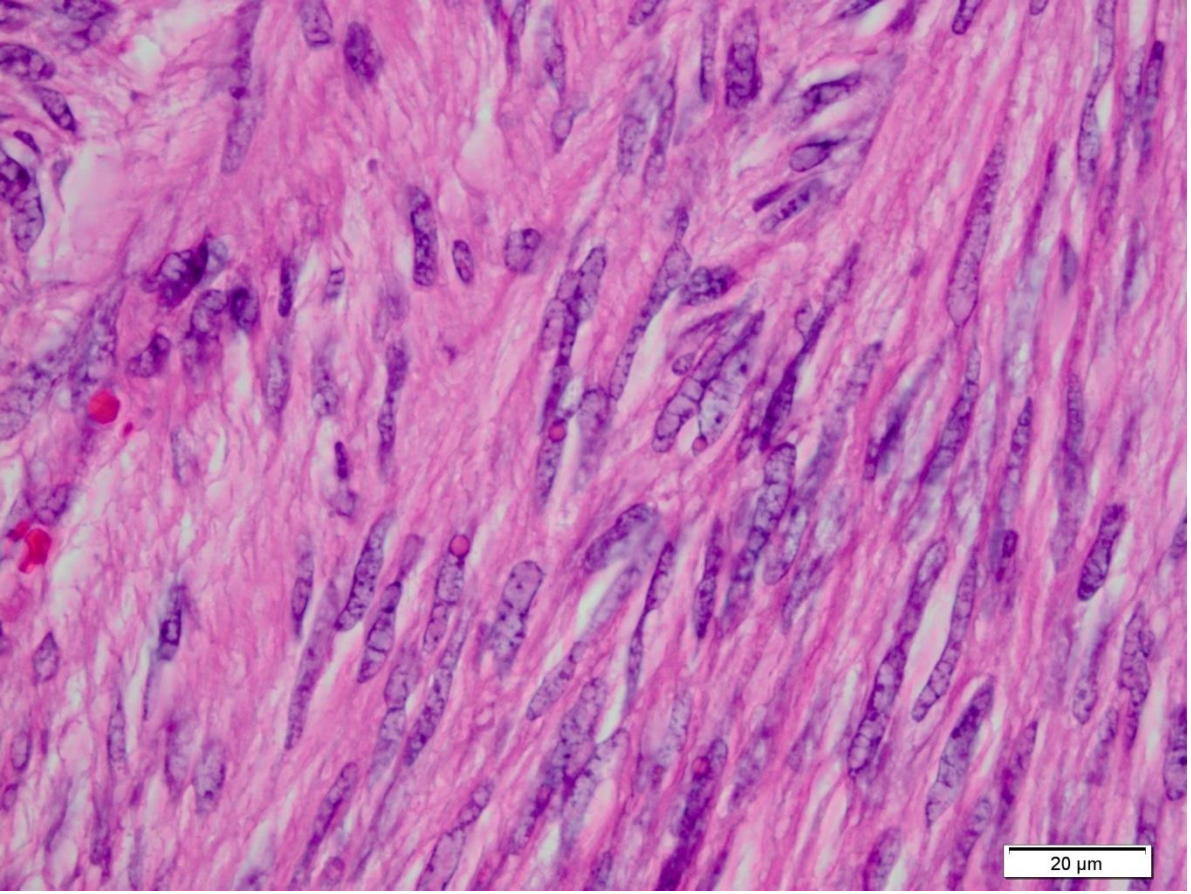

Leiomyoma


100 µm

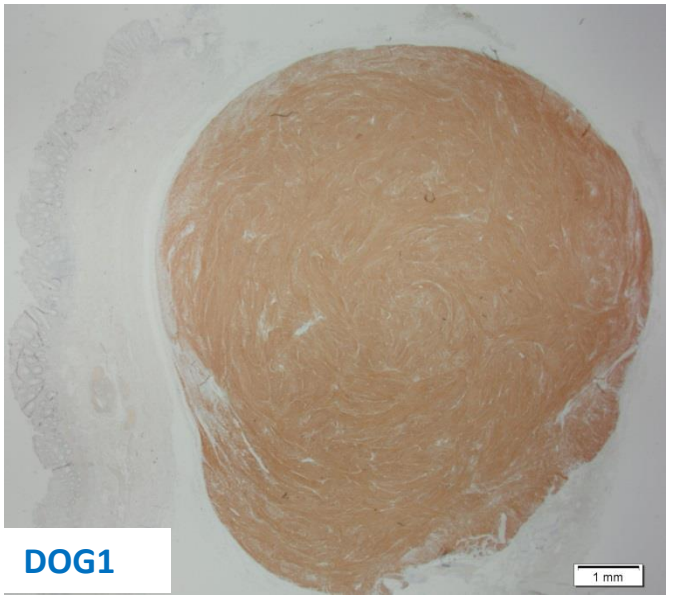


Leiomyosarcoma

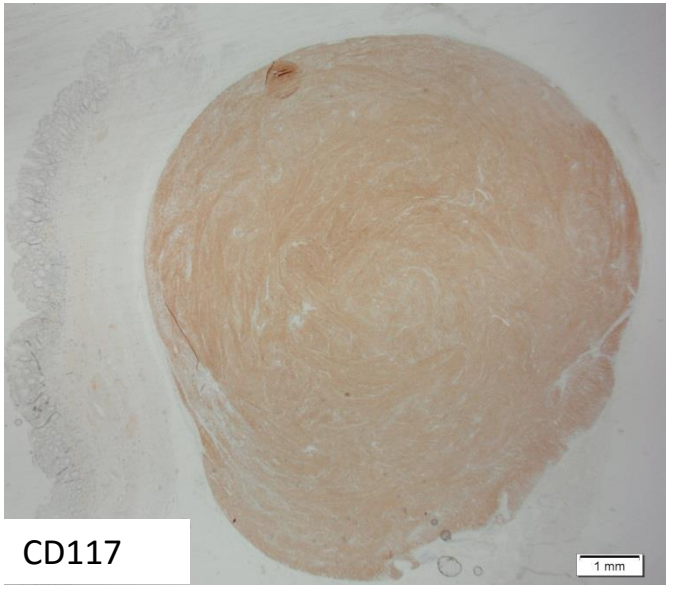

1 mm



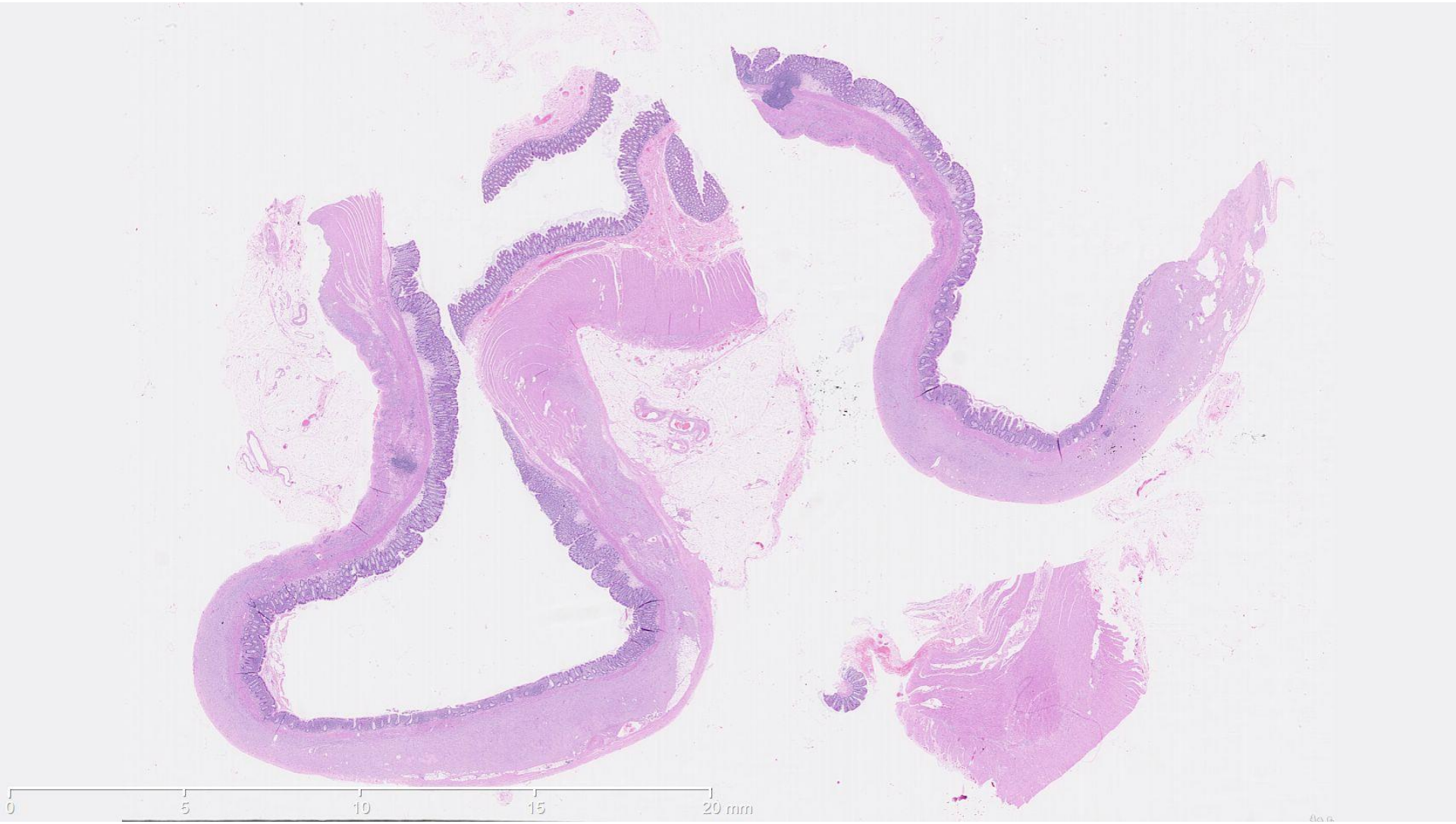
GIST



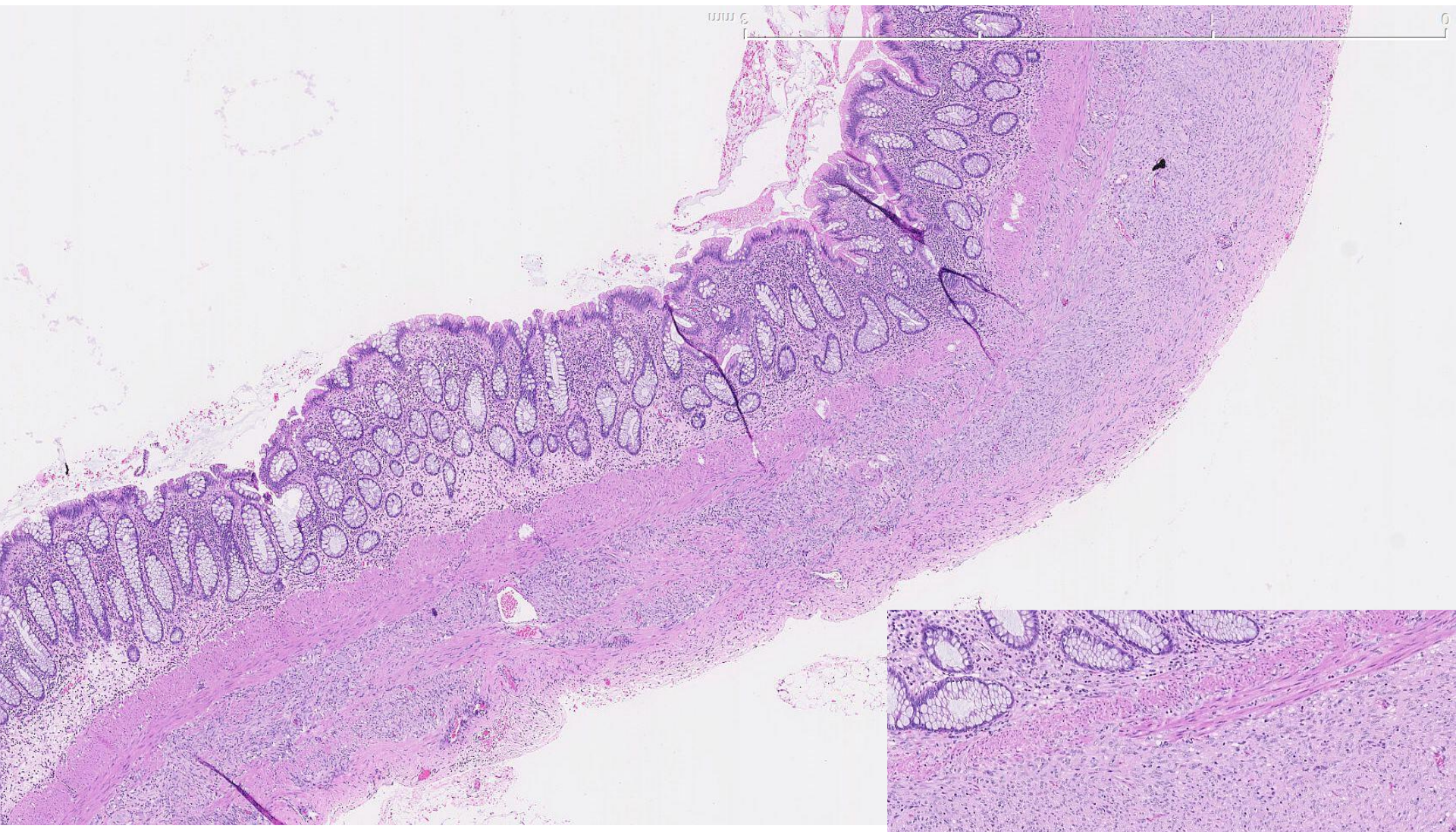
DOG1

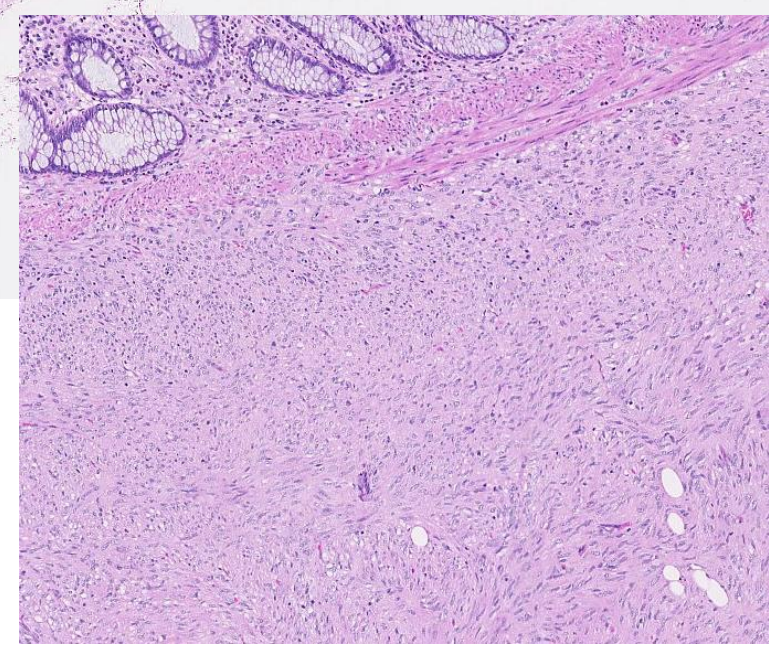


CD117



Long segmental hyperplasia of interstitial cells of Cajal with giant diverticulum formation



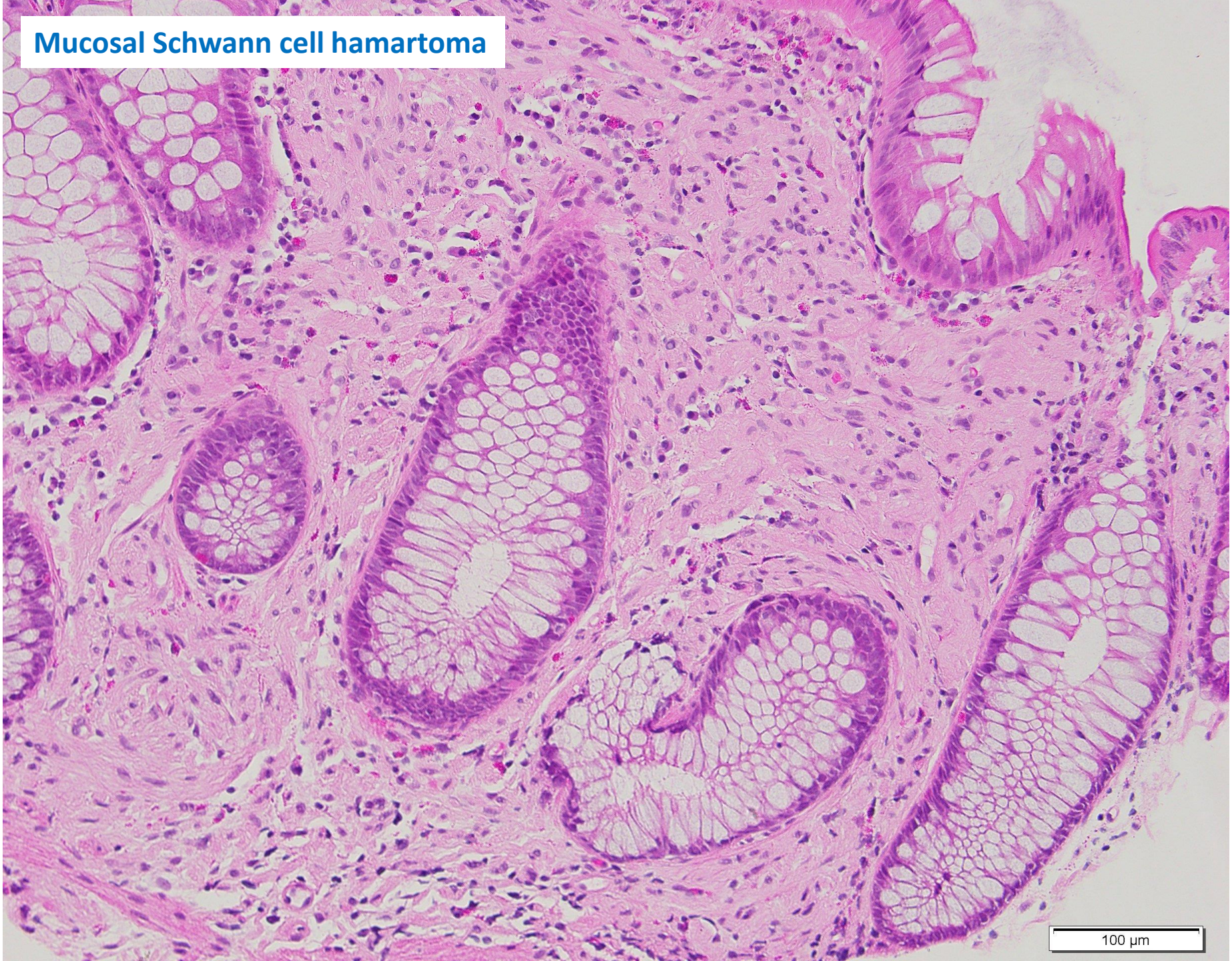


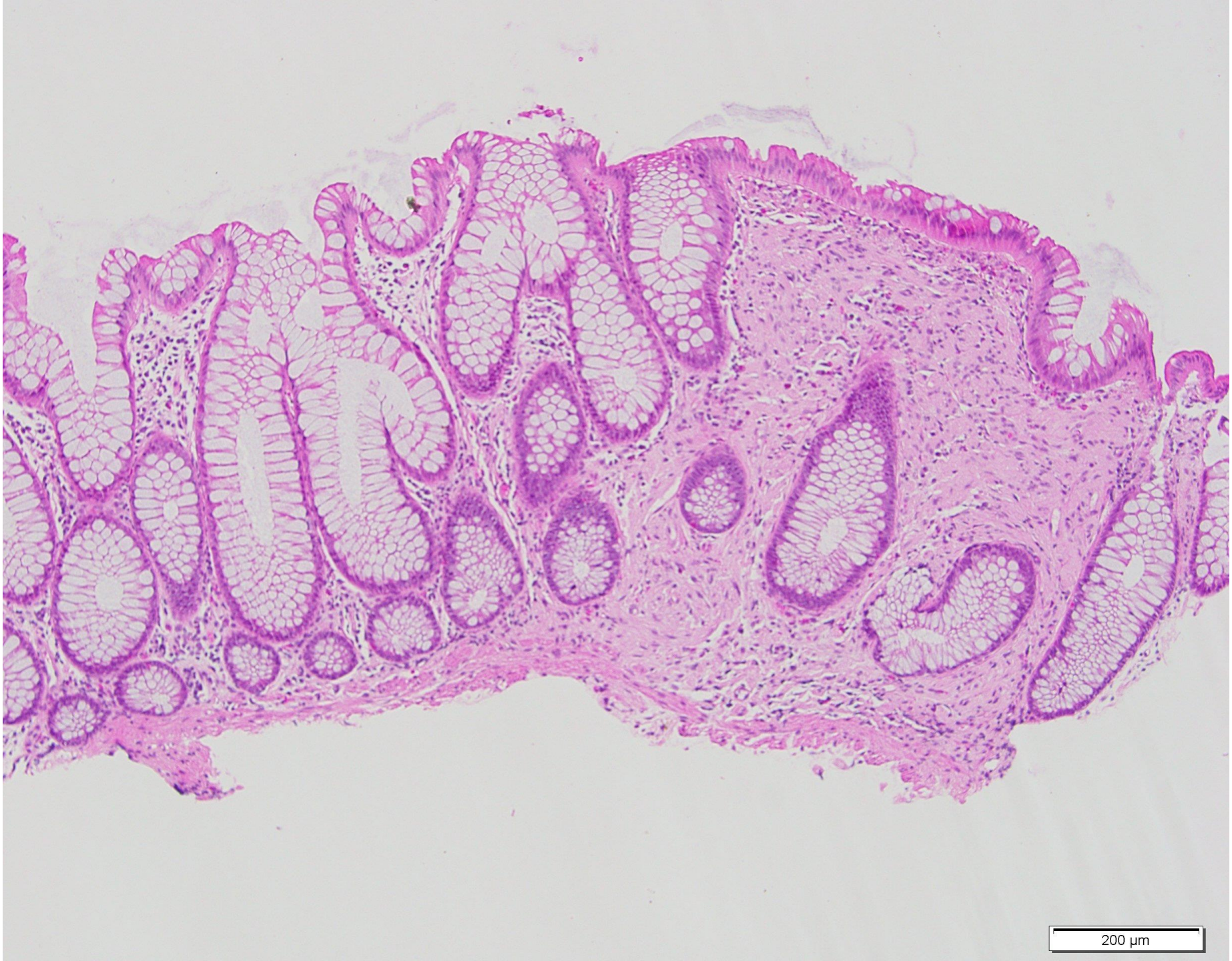
Int J Clin Exp Pathol. 2010 May 31;3(5):549-56.

Sporadic segmental Interstitial cell of Cajal hyperplasia with unusual diffuse longitudinal growth replacing the muscularis propria: differential diagnosis to hereditary GIST syndromes.

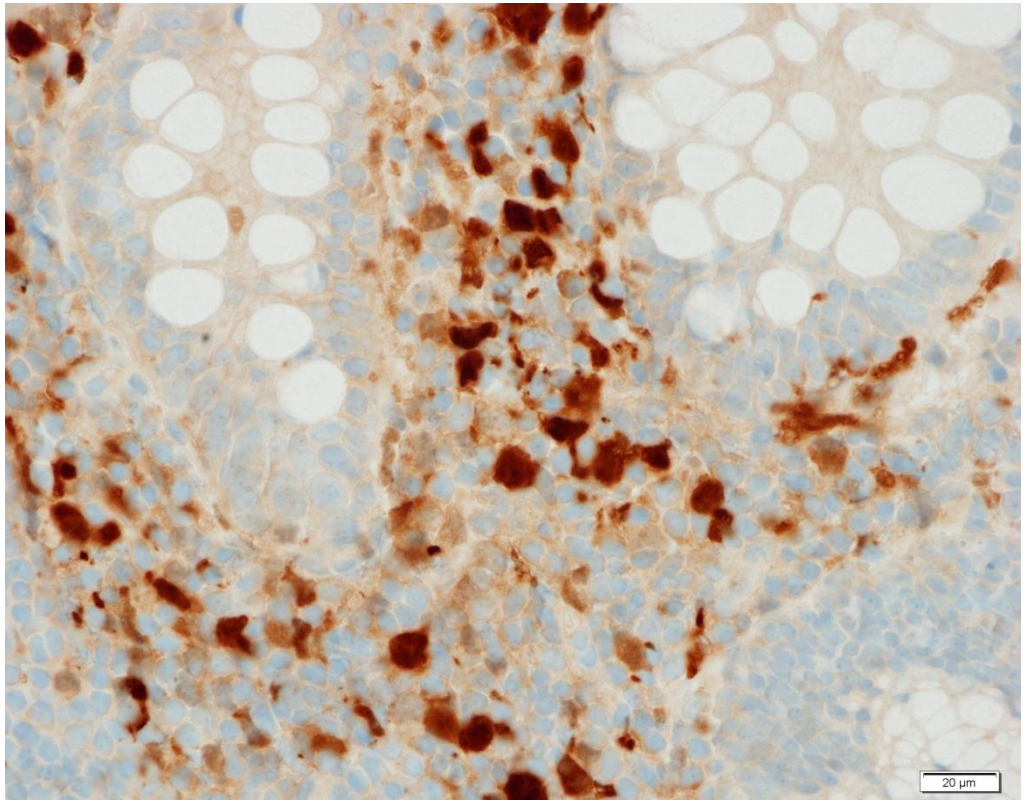
Agaimy A[1], Märkl B, Arnholdt H, Hartmann A, Schneider-Stock R, Chetty R.

Mucosal Schwann cell hamartoma

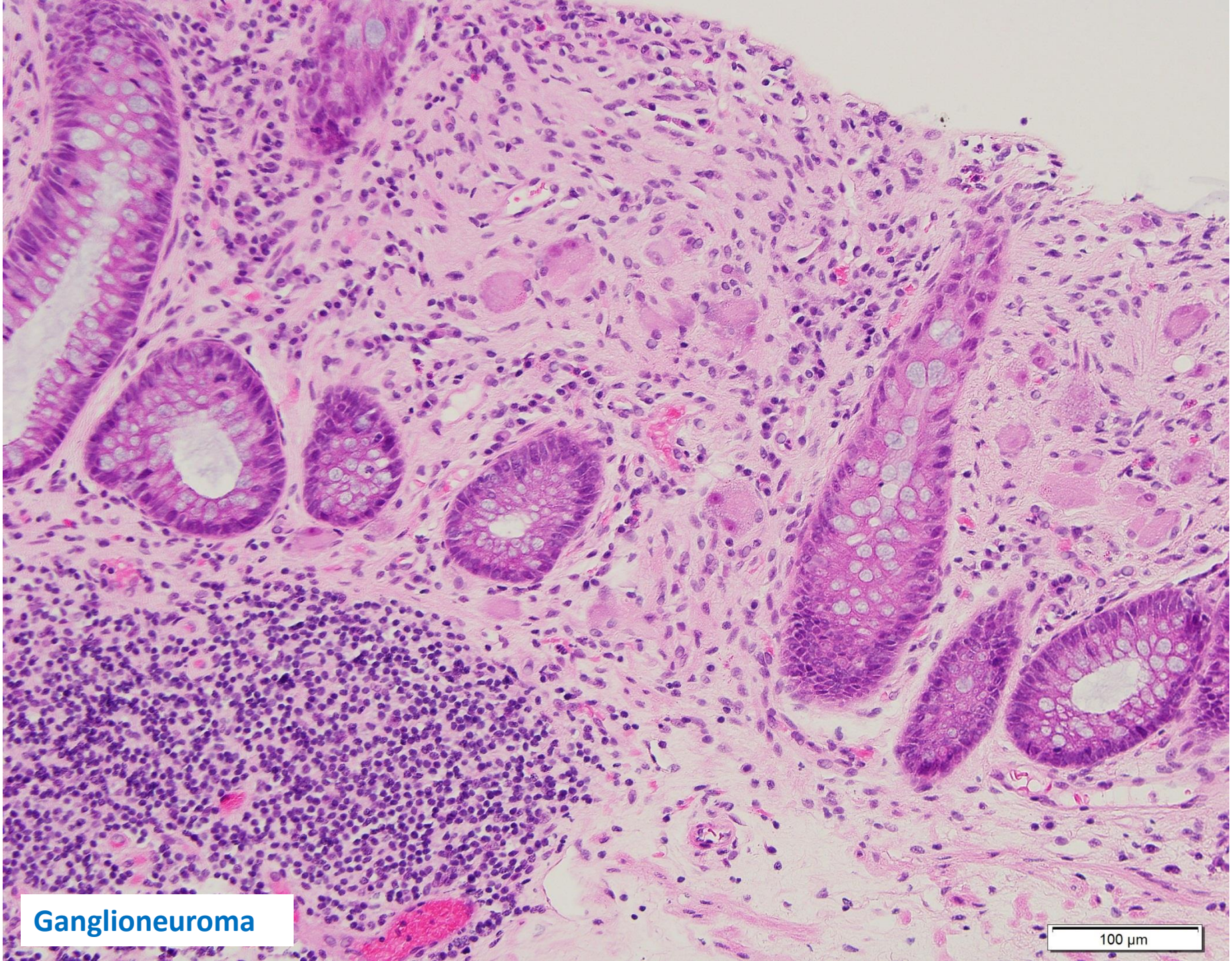


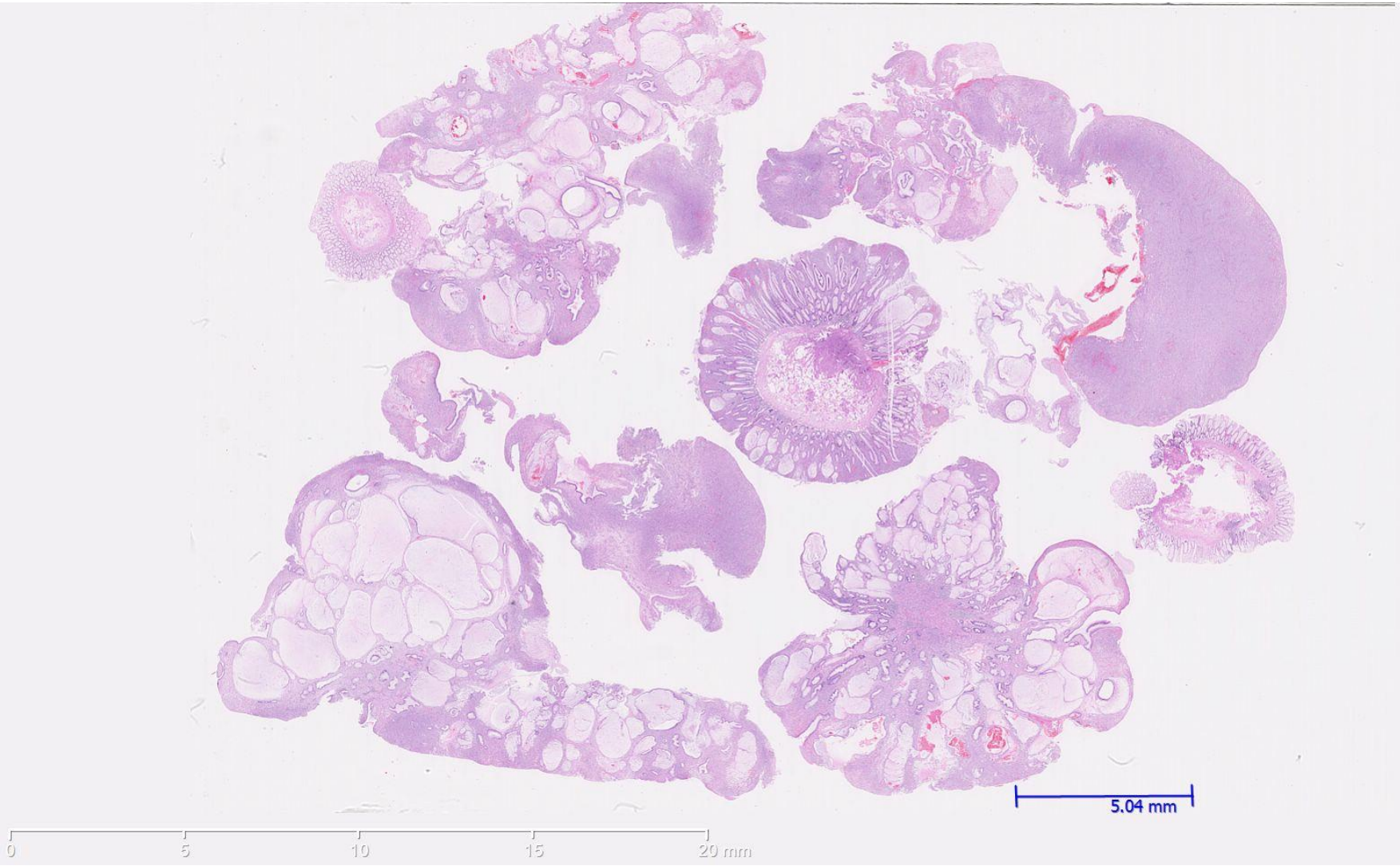

200 µm

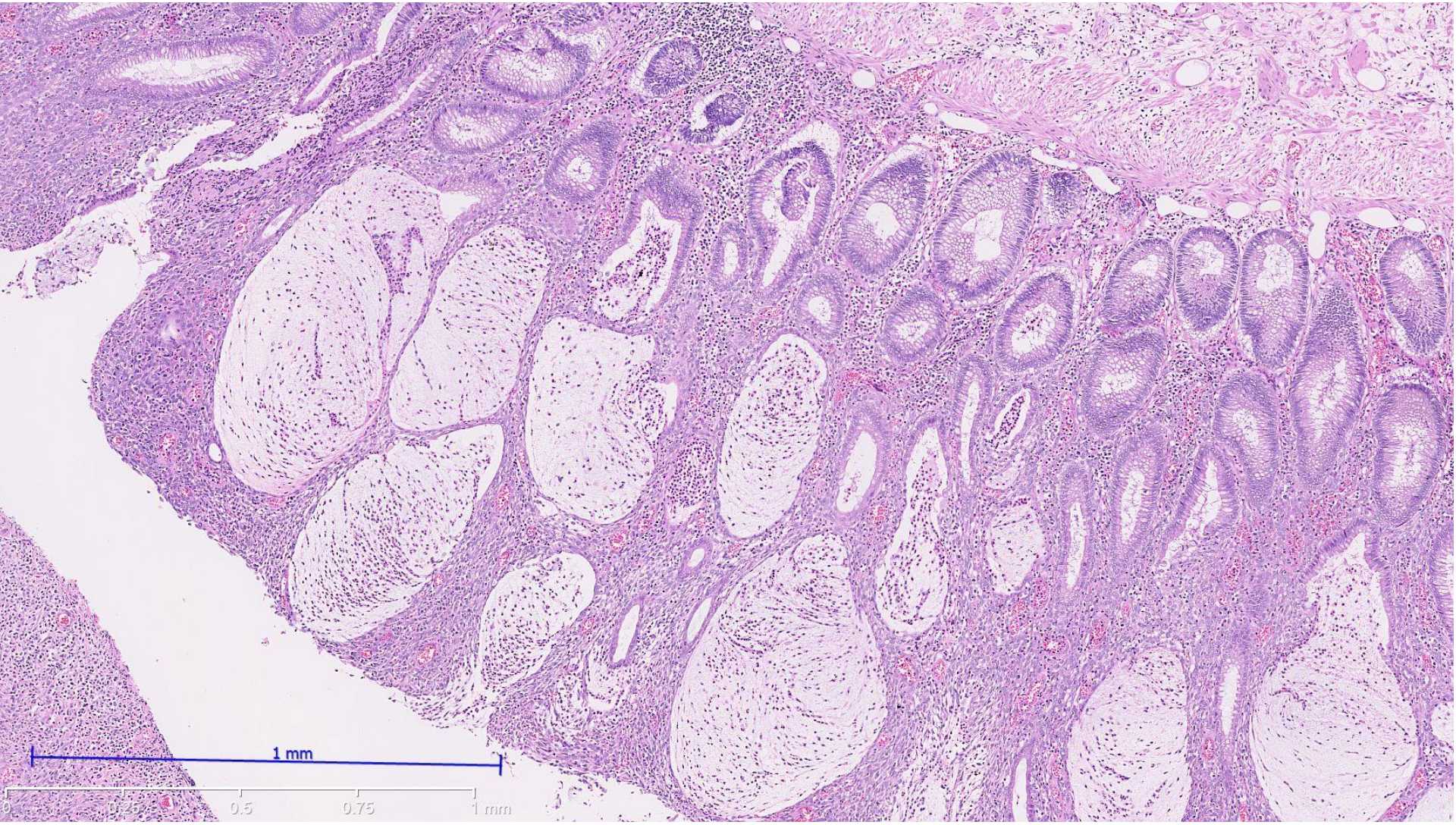
Mucosal Schwann Cell Hamartoma

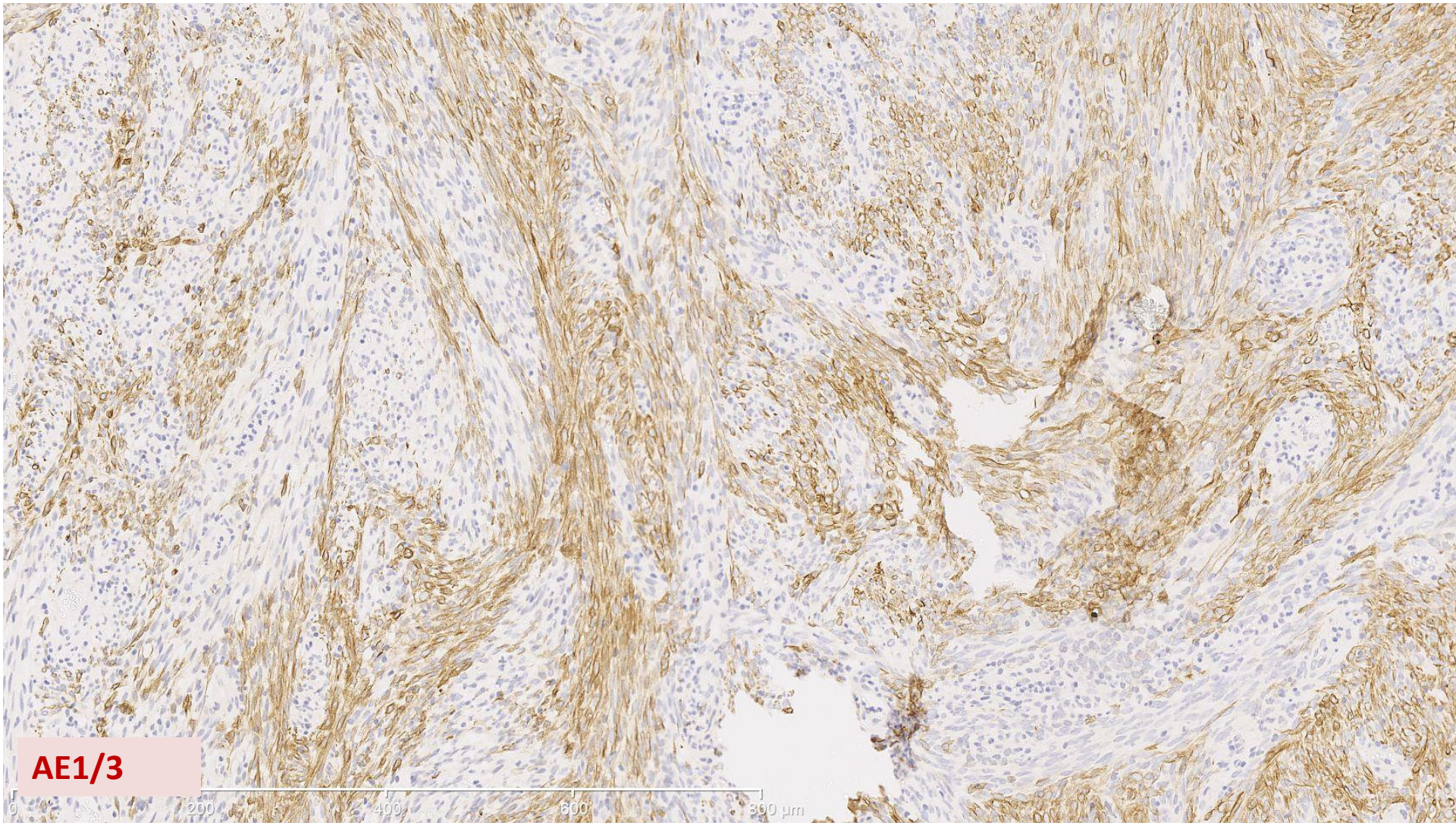


- S-100 neural proliferation
- Lack of Ganglion cells
- Previously referred as “neuromas” of “neurofibromas”
- Distal colon, small solitary lesions
- Mean age 62
- Distinguishing from neurofibromas is difficult based on histologic features and the presence of underlying submucosal nodule should be endoscopically excluded
- Sporadic, no NF1 or inherited syndromes


Ganglioneuroma
100 µm


5.04 mm
0
5
10
15
20 mm

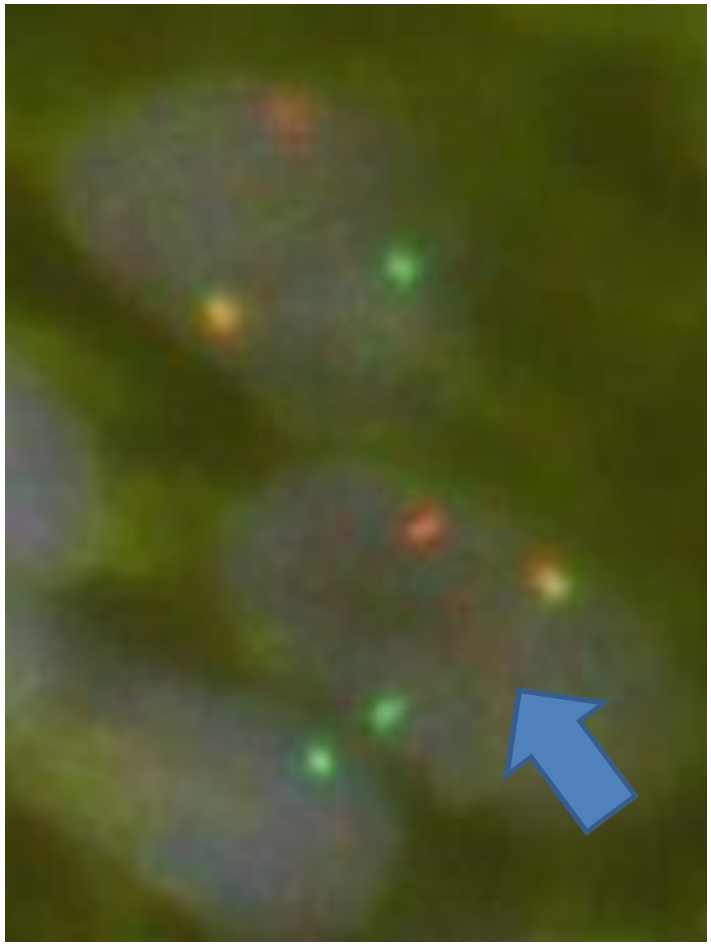

1 mm
0
0.25
0.5
0.75
1 mm



S-100 - ve
smooth muscle actin - ve
desmin - ve
C D117 - ve

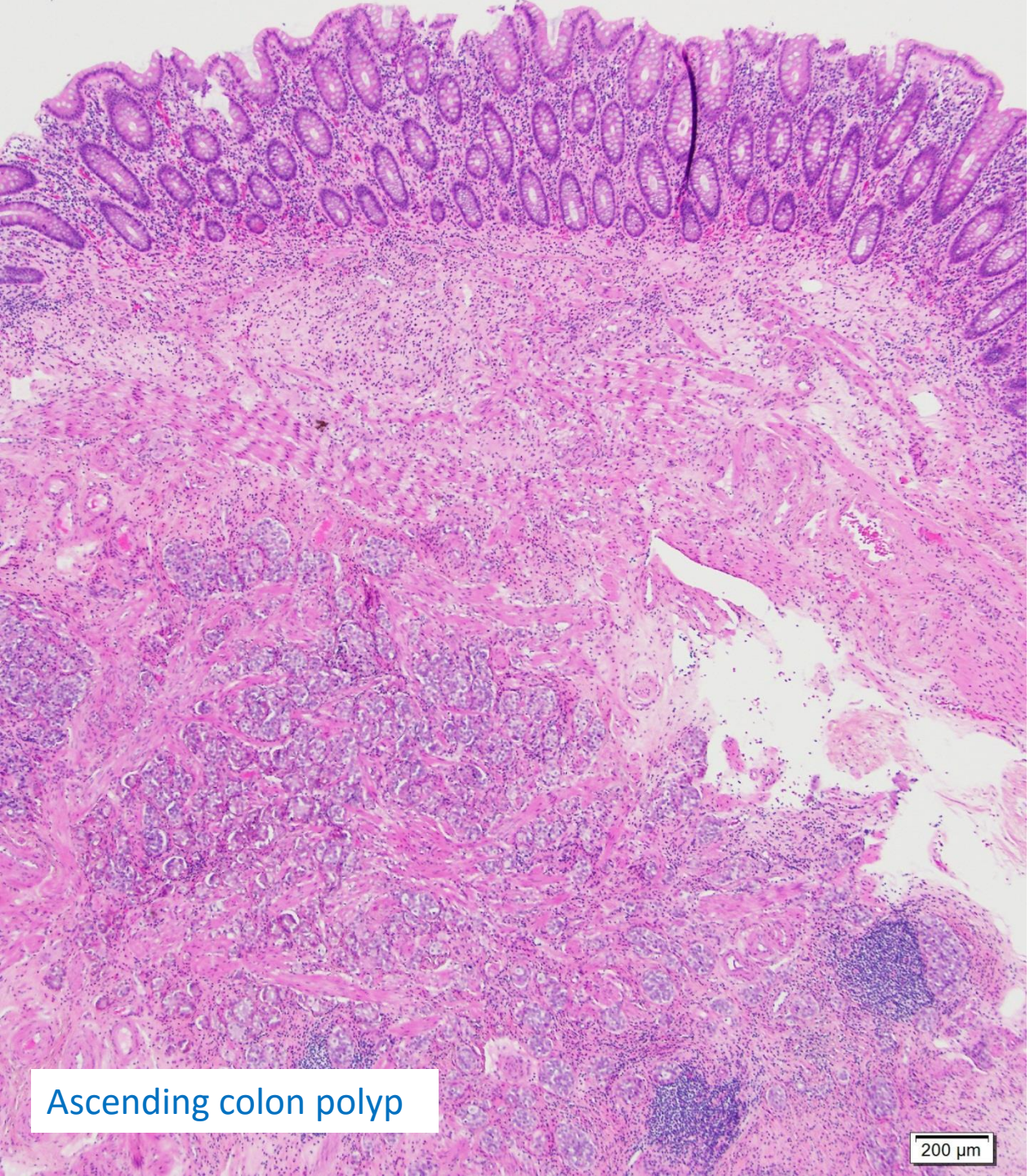
Primary Rectal Synovial Sarcoma (biphasic)

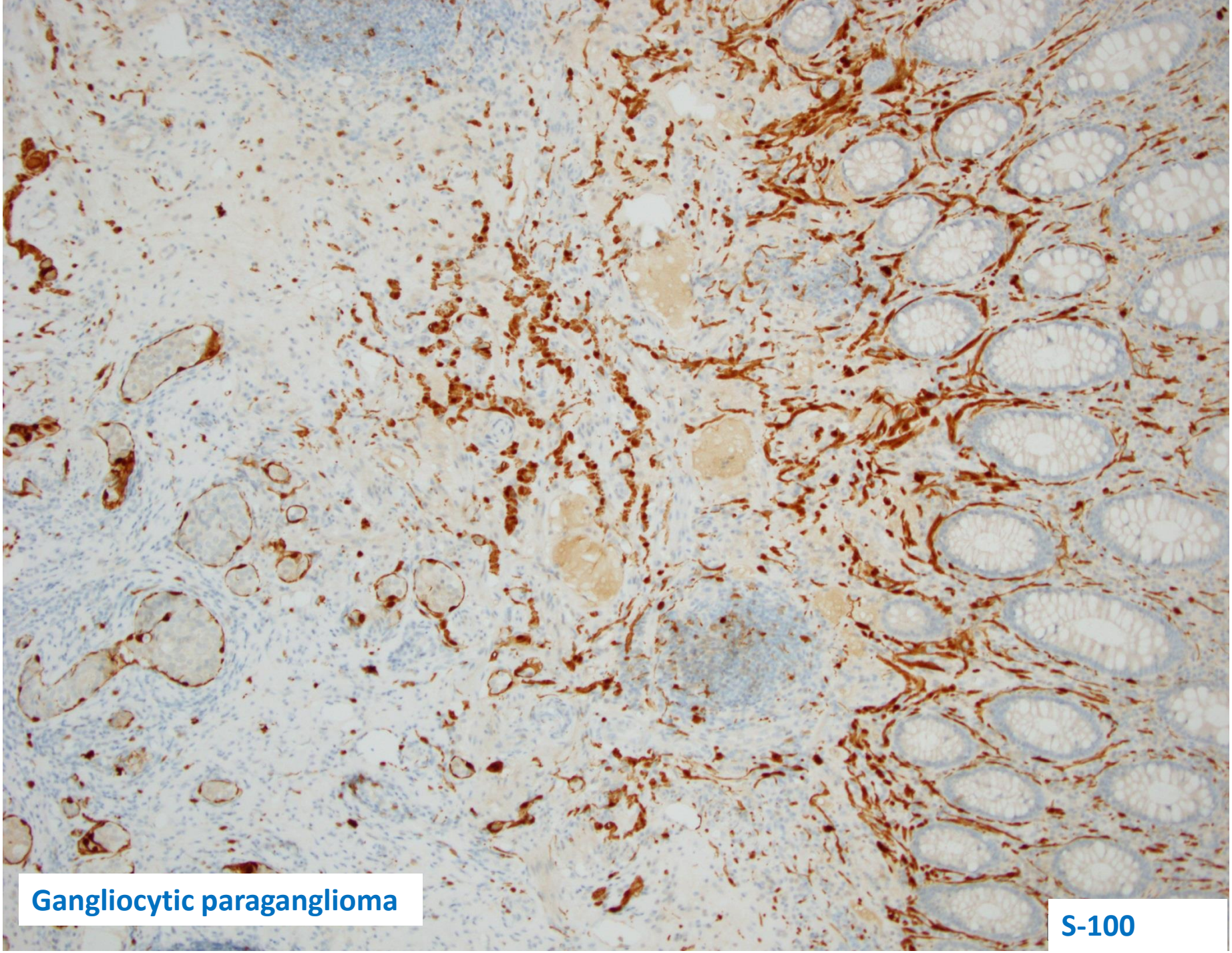
RT-PCR showed t(X;18)(p11.2;q11.2) translocation

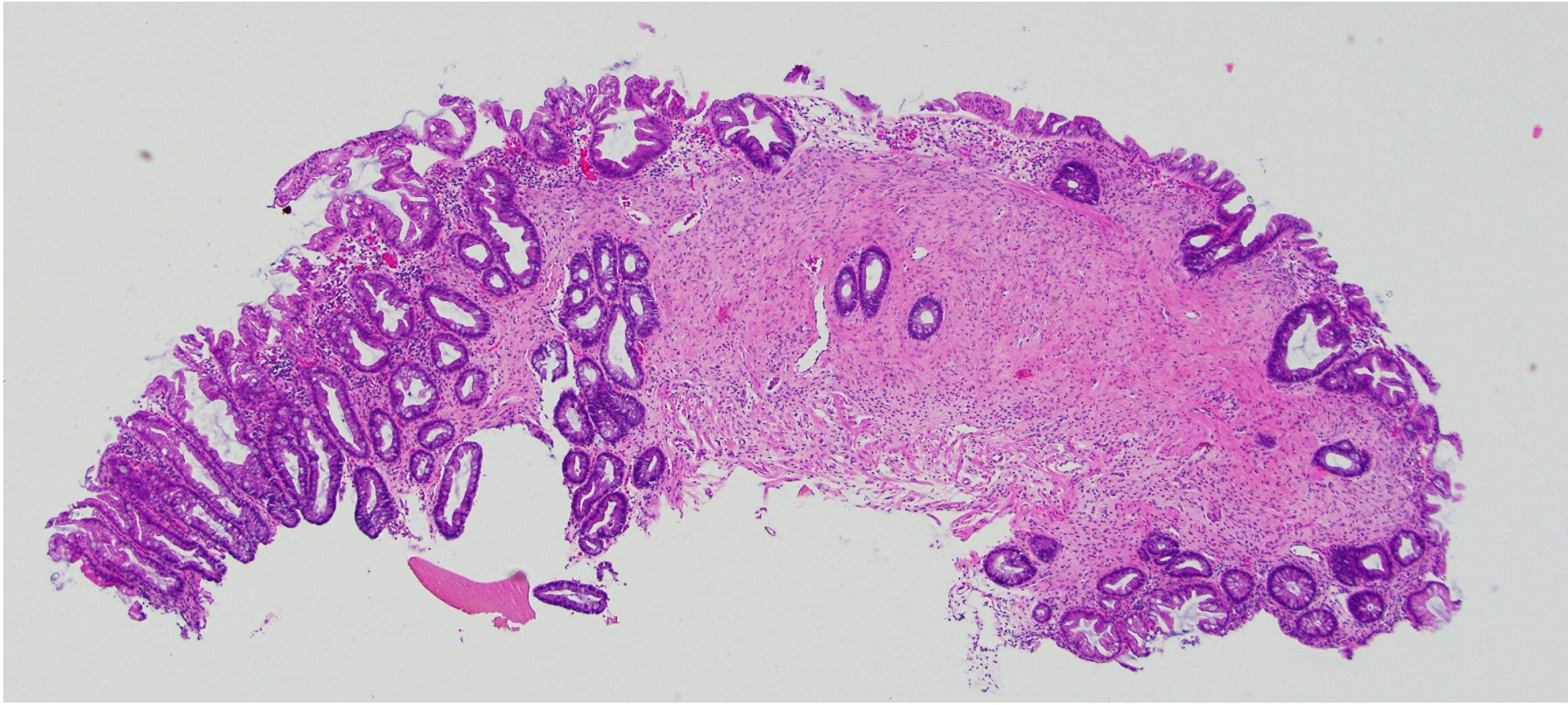


- No other lesions on CT
- Anterior resection – no residual tumour
- No recurrence after 6 years

FISH - SYT gene rearrangement in 36 of the 40 nuclei examined.
The arrow points to a cell showing SYT split signal)


Ascending colon polyp
200 µm


Gangliocytic paraganglioma
S-100



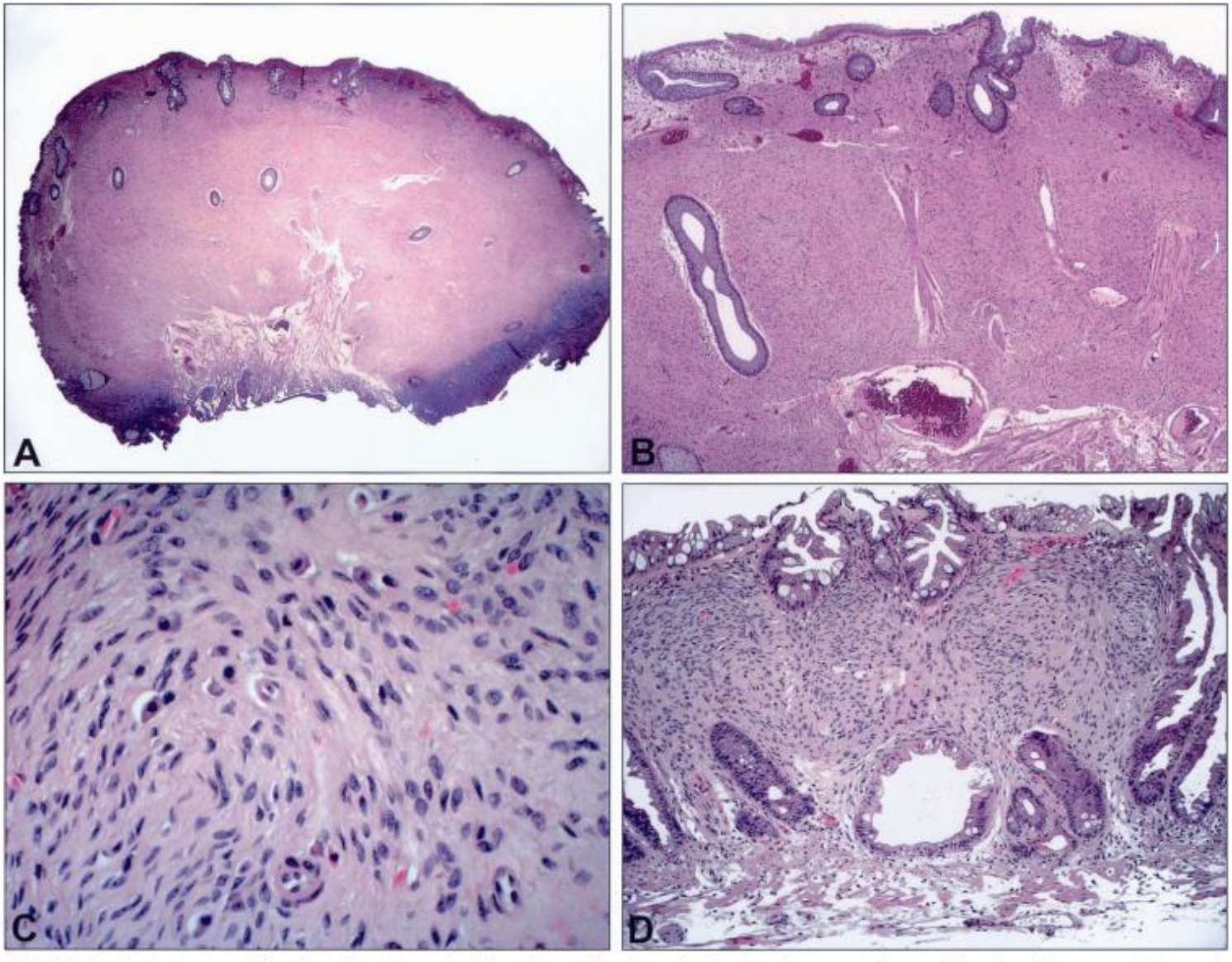


FIGURE 1. A: Low magnification showing spindle cell proliferation in the lamina propria resulting in wide separation and disorganization of colonic crypts (hematoxylin and eosin stain). **B:** Higher magnification showing the intimate relationship of the spindle cell proliferation with the muscularis mucosa seen at the bottom of the photograph. Longitudinal bands of smooth muscle emanating form the muscularis mucosa and extending between the crypts can also be noted (hematoxylin and eosin stain). **C:**

Benign Fibroblastic Polyps of the Colon

A Histologic, Immunohistochemical, and Ultrastructural Study

Fatima Eslami-Varzaneh, MD, Kay Washington, MD, PhD,† Marie E. Robert, MD,**
Michael Kashgarian, MD, John R. Goldblum, MD,‡ and Dhanpat Jain, MD**

Abstract: Mesenchymal proliferations presenting as mucosal polyps are relatively uncommon and are represented by gastrointestinal stromal tumors, smooth muscle and neural tumors, and inflammatory fibroid polyps. In this report, we describe the clinicopathologic features of a distinctive type of mucosal polyp composed of cytologically bland spindled cells with fibroblastic features. Fourteen cases with histologic features of "fibroblastic polyps" were identified from our case files from January 2000 to December 2003. The clinical and endoscopic findings were reviewed. Immunohistochemistry using a panel of antibodies (vimentin, smooth muscle actin, desmin, CD31, CD34, Bcl-2, c-Kit, S-100, and epithelial membrane antigen) was performed in all cases, and electron microscopy was performed in two cases. The lesions were solitary in all cases and not associated with an identifiable polyposis syndrome. Associated adenomata and/or hyperplastic polyps at different sites were present in 10 cases and hyperplastic polyps were seen in close association in 3 cases. These polyps were characterized by a monomorphic spindle cell proliferation in the lamina propria, without necrosis or mitotic activity. The lesions were intimately associated with the muscularis mucosae and resulted in wide separation and disorganization of the colonic crypts. Immunohistochemical analysis revealed strong and diffuse positivity for

Gastrointestinal polyps are common lesions encountered daily in any surgical pathology practice. Broadly speaking, mucosal polyps may represent epithelial proliferations, lymphocytic infiltrates (benign or neoplastic), inflammation, or various types of mesenchymal/spindle cell proliferations. The majority of gastrointestinal polyps are epithelial and are comprised of hyperplastic, adenomatous, or hamartomatous polyps.[3,8,17] The majority of polyps in children occur in the context of a genetic polyposis syndrome, while in adults they are largely sporadic.[3] Mesenchymal or spindle cell proliferations presenting as mucosal lesions are far less common and may represent gastrointestinal stromal tumors (GIST), smooth muscle and neural tumors, and inflammatory fibroid polyps (IFPs).[2,12–16,23]

In this study, we report a distinctive previously unreported type of mucosal polyp composed of benign-appearing spindle cells in the lamina propria. Immunohistochemical and ultrastructural features of these cells are most consistent with fibroblastic differentiation.

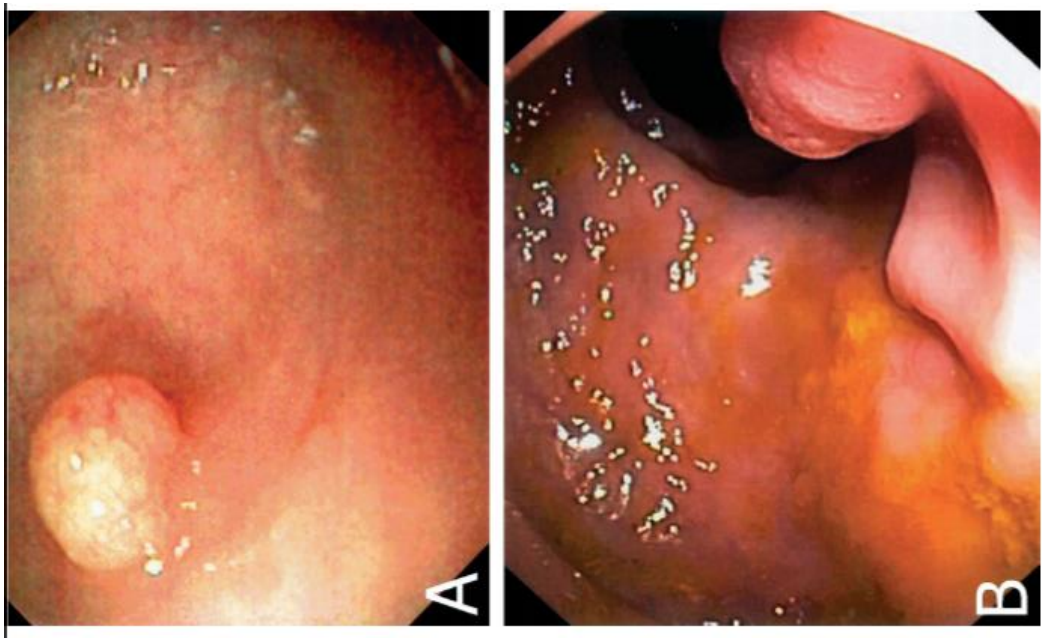
(Am J Surg Pathol 2004;28:374–378)

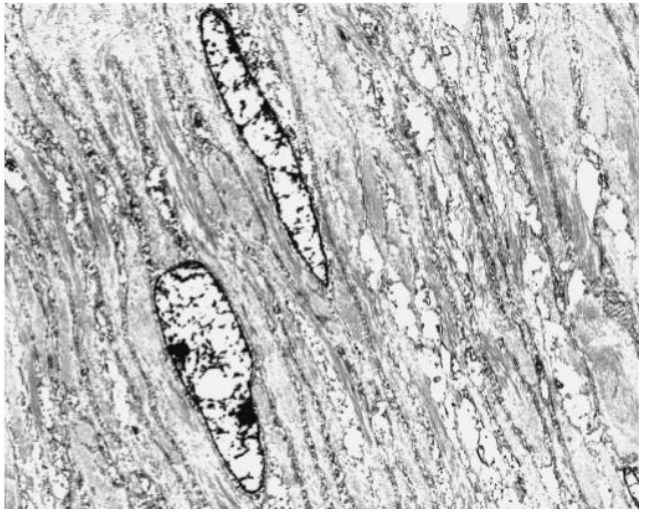
Benign Fibroblastic Polyp of the Colorectum

Alexandra N. Kalof, MD, Bobbi Pritt, MD,* Kumarasen Cooper, MD,*
Neil H. Hyman, MD,† and Hagen Blaszyk, MD**

Goals: We present the clinicopathologic features, endoscopic appearance, and ultrastructure of a newly described mesenchymal polyp of the colorectum, termed benign fibroblastic polyp.

mucosal polyp, termed "benign fibroblastic polyp,"[5] whic
morphologically and immunohistochemically distinct
inflammatory fibroid polyp. Immunohistochemical and u
structural analyses were performed and the electron m





(J Clin Gastroenterol 2005;39:778–781)

Intestinal Perineuriomas

Clinicopathologic Definition of a New Anatomic Subset in a Series of 10 Cases

Jason L. Hornick, MD, PhD and Christopher D. M. Fletcher, MD, FRCPath

Abstract: Benign peripheral nerve sheath tumors are uncommon in the gastrointestinal tract, and perineuriomas have not previously been reported to occur at this anatomic location. In this study, we analyzed the clinicopathologic and immunohistochemical features of 10 perineuriomas arising in the intestine. Eight patients were female and 2 male (median age, 51 years; range, 35–72 years). Eight of the lesions were intramucosal perineuriomas presenting as small sessile polyps detected during colonoscopy; 6 of these 8 patients were asymptomatic and undergoing colorectal cancer screening. The remaining 2 cases were submucosal masses, one each located in the colon and jejunum. Of the mucosal polyps, six were located in the rectosigmoid or sigmoid colon and one each was detected in the descending colon and transverse colon. The polyps ranged from 0.2 to 0.6 cm (median, most often as intramucosal lesions detected as colorectal polyps with distinctive histologic features including entrapment of colonic crypts. Distinguishing perineuriomas from other spindle cell neoplasms of the gastrointestinal tract can be facilitated by immunostaining for EMA and claudin-1.

Key Words: perineurioma, schwannoma, neurofibroma, nerve sheath, soft tissue, gastrointestinal tract, colon, polyp

(*Am J Surg Pathol* 2005;29:859–865)

Benign peripheral nerve sheath tumors uncommonly occur in the gastrointestinal (GI) tract and include ganglioneur-

(Am J Surg Pathol 2005;29:859–865)

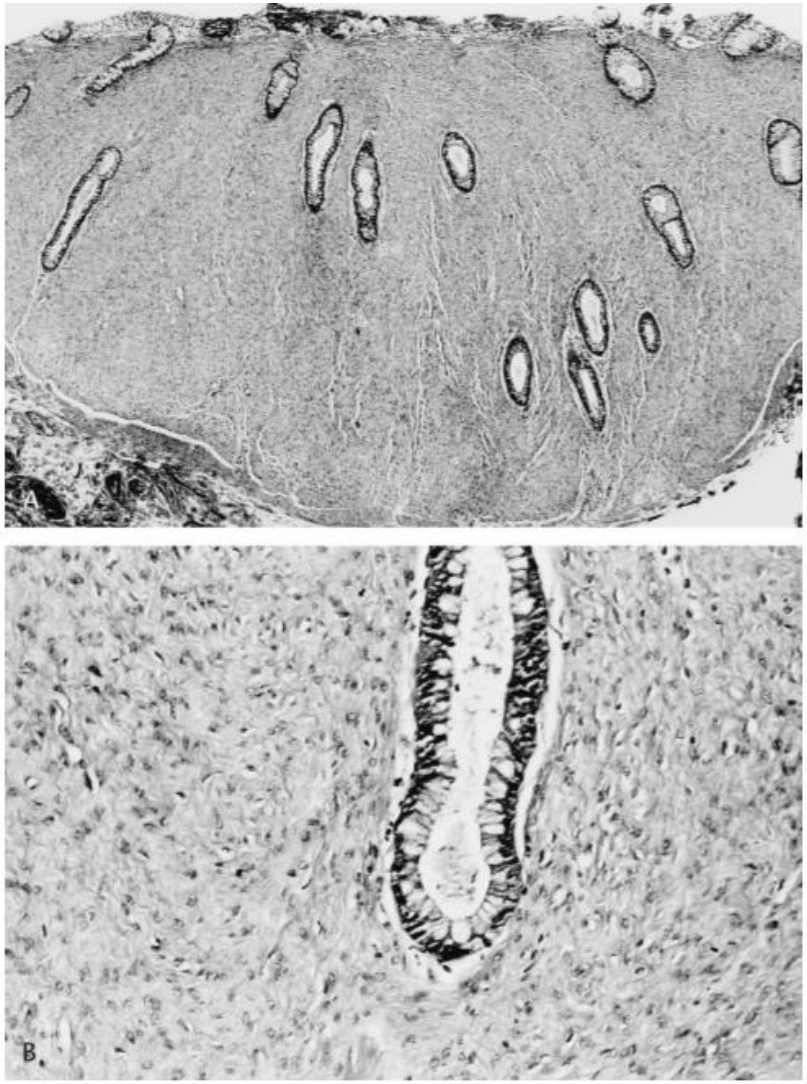


FIGURE 1. A, Colorectal intramucosal perineuriomas expand the lamina propria and entrap crypts (case no. 7). B, A high-power view showing a colonic crypt surrounded by

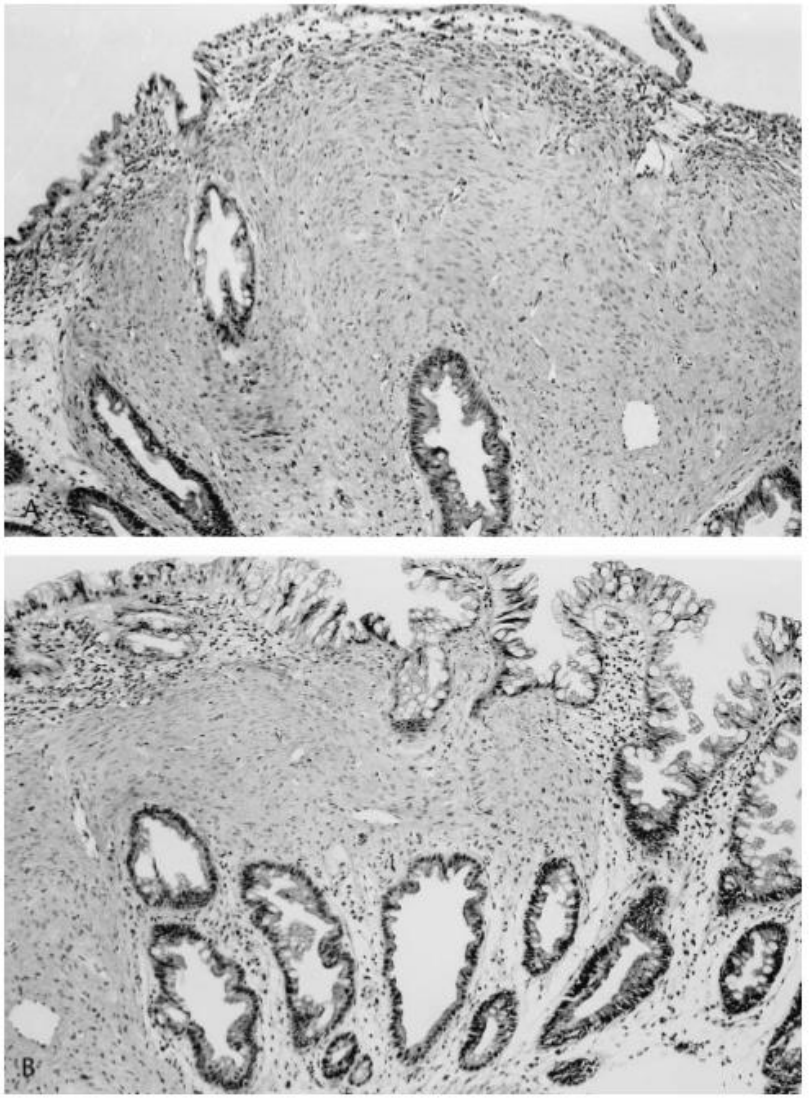


FIGURE 2. Hyperplastic changes are often seen in the entrapped (A) and adjacent (B) colonic epithelium (case no. 4).

(Am J Surg Pathol 2005;29:859–865)

Series of consult cases – in one was the diagnosis of “perineurioma” offered

In one case, the referring diagnosis was a spindle cell sarcoma

? heterogenous series (submucosal lesions, jejunal, not all Claudin 1 positive)

Not extremely rare but are probably under recognized and diagnosed as neurofibromas, “fibromas” *etc*

Similarity to soft tissue perineuriomas

9/10 positive for EMA
4/10 positive for Claudin 1

The first study to report perineuriomas arising in the GI tract

(Am J Surg Pathol 2005;29:859–865)

? Benign fibroblastic polyps of the colon

Morphologically very similar to Intestinal Perineuriomas

All polyps in the original report were EMA negative

Original report did not examine Claudin 1

Benign fibroblastic polyps of the colon **= Intestinal Perineuriomas**

(Am J Surg Pathol 2005;29:859–865)

Fibroblastic Polyp of the Colon and Colonic Perineurioma: 2 Names for a Single Entity?

Gabriel M. Groisman, MD and Sylvie Polak-Charcon, PhD†*

Abstract: Fibroblastic polyps of the colon and intestinal perineuriomas are unusual mucosal lesions with identical clinical and histologic features, and apparent different immunohistochemical and ultrastructural characteristics. However, immunohistochemical distinction was solely based on the results obtained with epithelial membrane antigen (EMA), an antibody whose reactivity on perineuriomas is difficult to demonstrate. Likewise, accurate ultrastructural diagnosis may be flawed by sampling error, preservation artifacts, or paucity of specific diagnostic features. In a recent short communication, it was suggested that both lesions may represent the same entity. To further evaluate this hypothesis, 28 colorectal polyps with clinical and histologic features of colonic fibroblastic polyps/perineuriomas (including 10 cases previously reported as fibroblastic polyps) were stained immunohistochemically for 4

Fibroblastic polyp was first described in 2004 by Eslami-Varzaneh et al[4] as a distinctive type of mesenchymal polyp of the colorectum characterized by a mucosal proliferation of monomorphic spindle cells leading to separation, entrapment, and disorganization of the colonic crypts. In their series of 14 cases, fibroblastic polyps occurred almost exclusively in the left and distal colon and all but one lesion measured < 10-mm in diameter. Following the original description, 42 additional cases were reported including 24 cases published in abstract form,[17] 2 small series of 4 cases each,[13,25] and a series of 10 cases reported by us in which the frequent presence of hyperplastic/serrated crypts within these lesions was emphasized.[9] On electron microscopy, fibroblastic polyps were reported to display changes compatible with fibroblastic differentiation whereas

Am J Surg Pathol Volume 32, Number 7, July 2008

Benign Serrated Colorectal Fibroblastic Polyps/Intramucosal Perineuriomas Are True Mixed Epithelial-stromal Polyps (Hybrid Hyperplastic Polyp/Mucosal Perineurioma) With Frequent BRAF Mutations

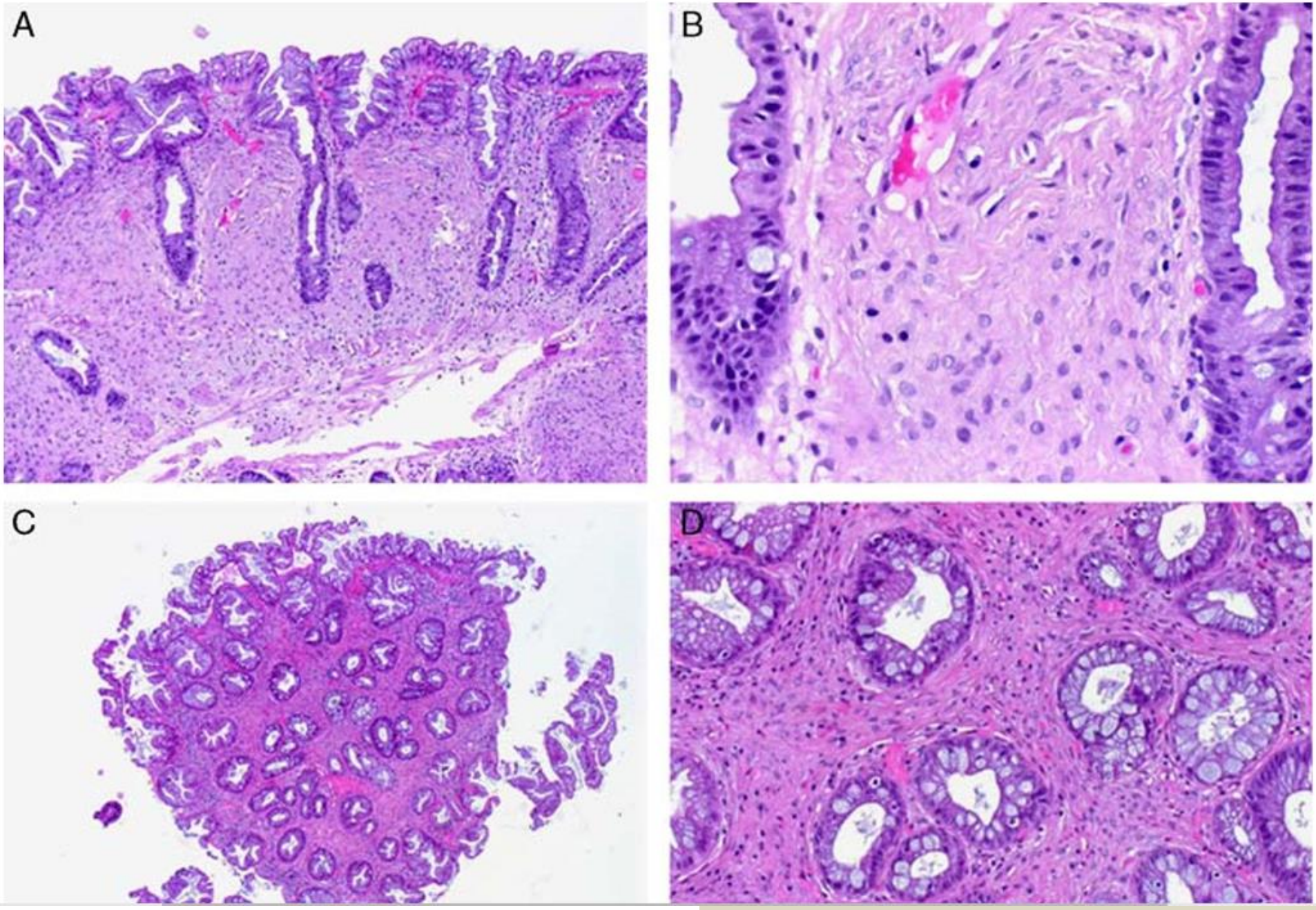
Abbas Agaimy, MD, Robert Stoehr, PhD,* Michael Vieth, MD,† and Arndt Hartmann, MD**

Abstract: Colorectal fibroblastic polyp and intramucosal perineurioma are 2 synonyms for a recently described benign mucosal lesion with a predilection for the rectosigmoid colon. These lesions are characterized by aggregates of bland spindled cells separating and distorting mucosal crypts. The latter frequently showed a serrated architecture. The pathogenesis of fibroblastic polyp/intramucosal perineurioma and the nature of serrated crypts observed in them are poorly understood. We derived from modified pericryptic fibroblasts as a consequence of a yet poorly understood epithelial-stromal interaction.

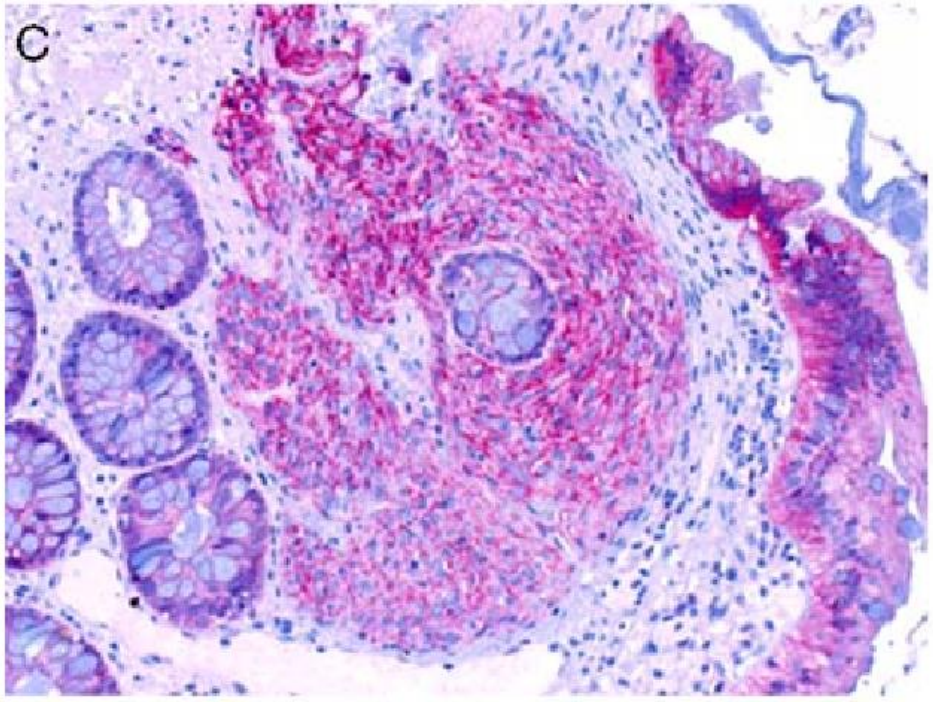
Key Words: BRAF mutations, fibroblastic polyp, hyperplastic polyp, mixed epithelial-stromal polyp, perineurioma

(*Am J Surg Pathol* 2010;34:1663–1671)

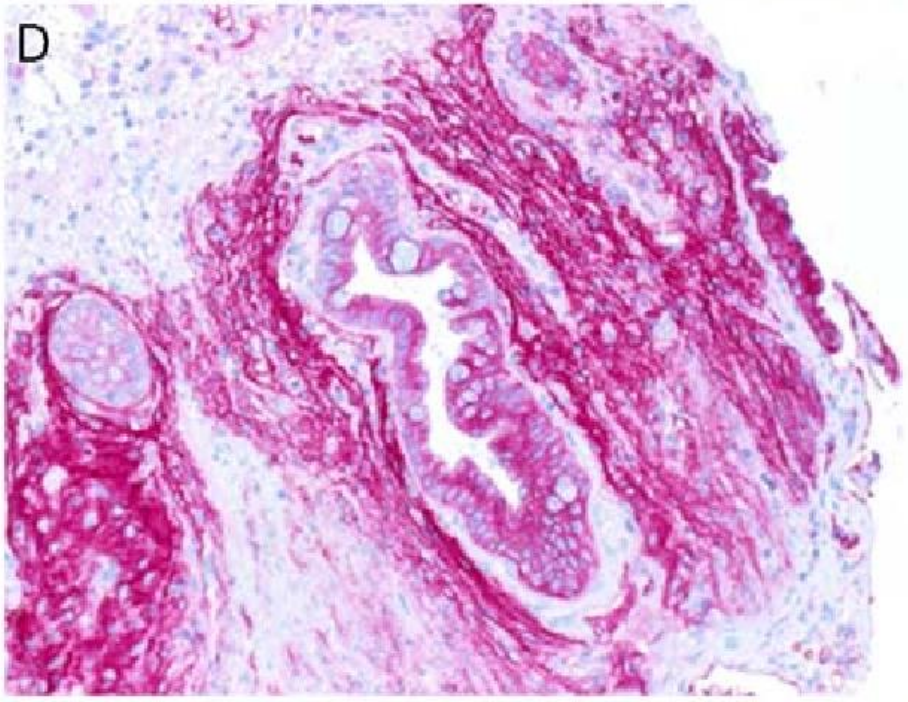
(Am J Surg Pathol 2010;34:1663–1671)



Am J Surg Pathol 2010;34:1663–1671



Claudin 1



GLUT-1

Frequent V600E BRAF somatic mutations

Presence of serrated crypts

Expression of perineurial cell markers (EMA, Claudin 1, Glucose transporter 1) in spindle cells

Spindle cells still mysterious

Am J Surg Pathol 2010;34:1663–1671

Early Colonic Perineurioma: A Report of 11 Cases

18(4) 292–297

DOI: 10.1177/1066896909350883
http://ijsp.sagepub.com
SAGE

Gabriel Groisman, MD,[1] Mary Amar, MD,[1] and Meir Alona, MD[1]

Abstract

Colonic perineurioma has been depicted as characterized by a mucosal proliferation of monomorphic spindle perineurial cells leading to an evident separation, distortion, and entrapment of colonic crypts. The authors, however, believe that a sizable subset of the cases differ in that they display only a limited perineurial proliferation leading to only mild crypt separation without crypt entrapment. This morphological variant (early perineurioma) has not yet been documented. The authors herein present the clinicopathological and immunohistochemical features of 11 cases. Polyp size ranged from 2 to 4 mm, and 8 (73%) were located in the sigmoid. Histologically, they revealed small, frequently noncontiguous nests or bundles of uniform round to oval cells, causing slight separation of parallel or mildly distorted crypts, which displayed a serrated/hyperplastic architecture in 8 (73%) cases. Immunostaining for perineurial markers showed strong expression for claudin-1, GLUT-1, and collagen type IV and weak reactivity for epithelial membrane antigen. In conclusion, early perineurioma is a morphological variant of colonic perineurioma in which the perineurial proliferation is limited and consequently more difficult to recognize. Using perineurial markers is helpful in reaching an accurate diagnosis.

International Journal of Surgical Pathology, 2010 , 18(4) 292 –297

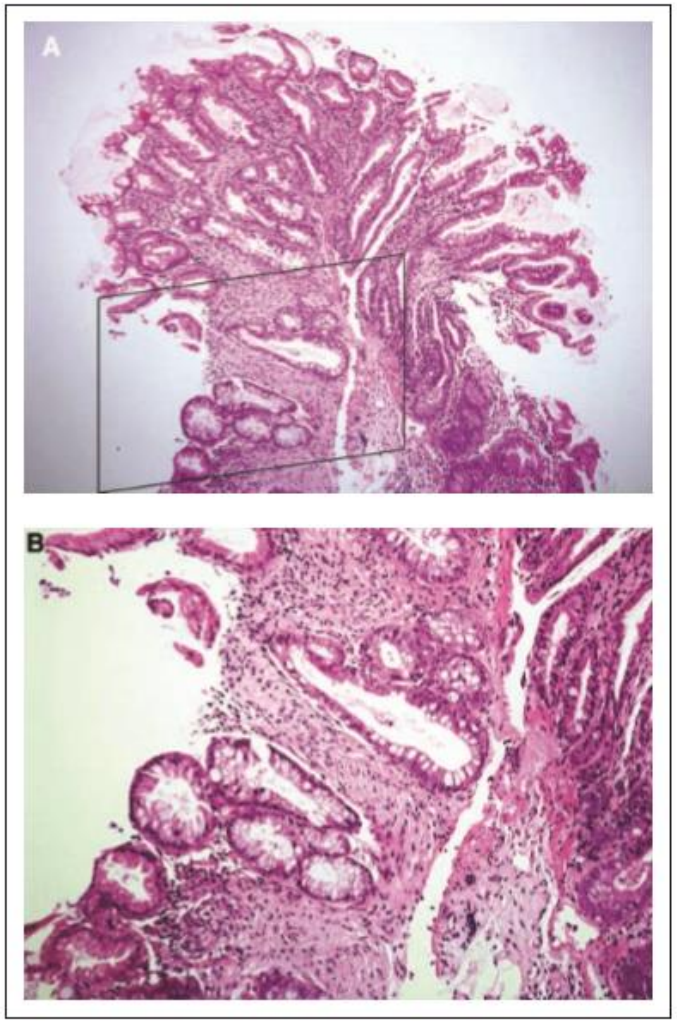


Figure 1. A. Early perineurioma showing serrated/hyperplastic crypts slightly separated by bundles of monomorphic, bland, plump, perineurioma cells; B. the enclosed area in higher power

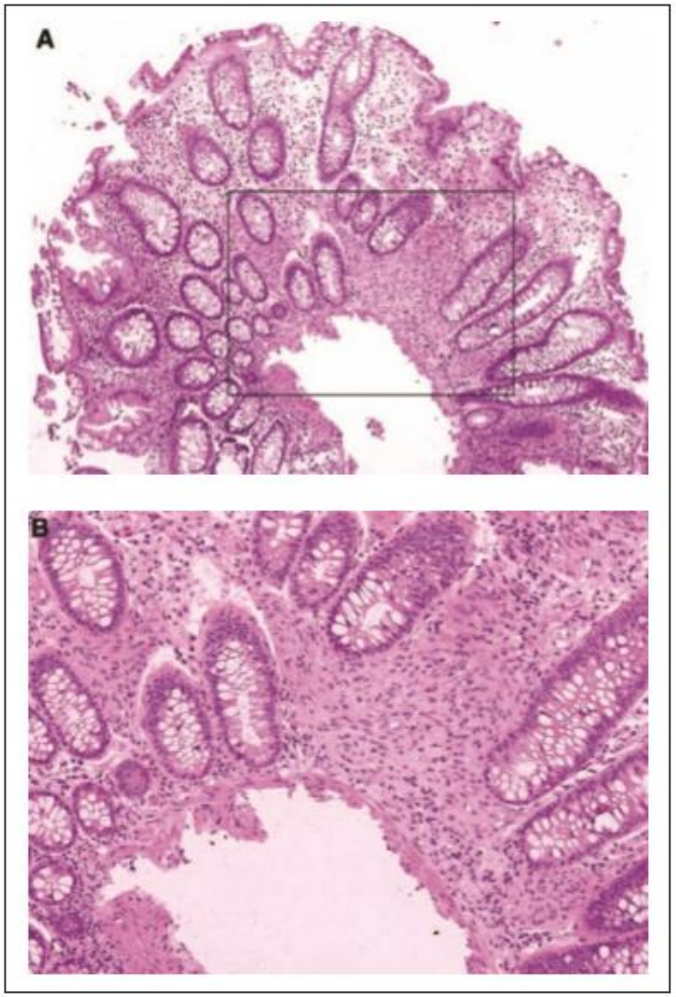
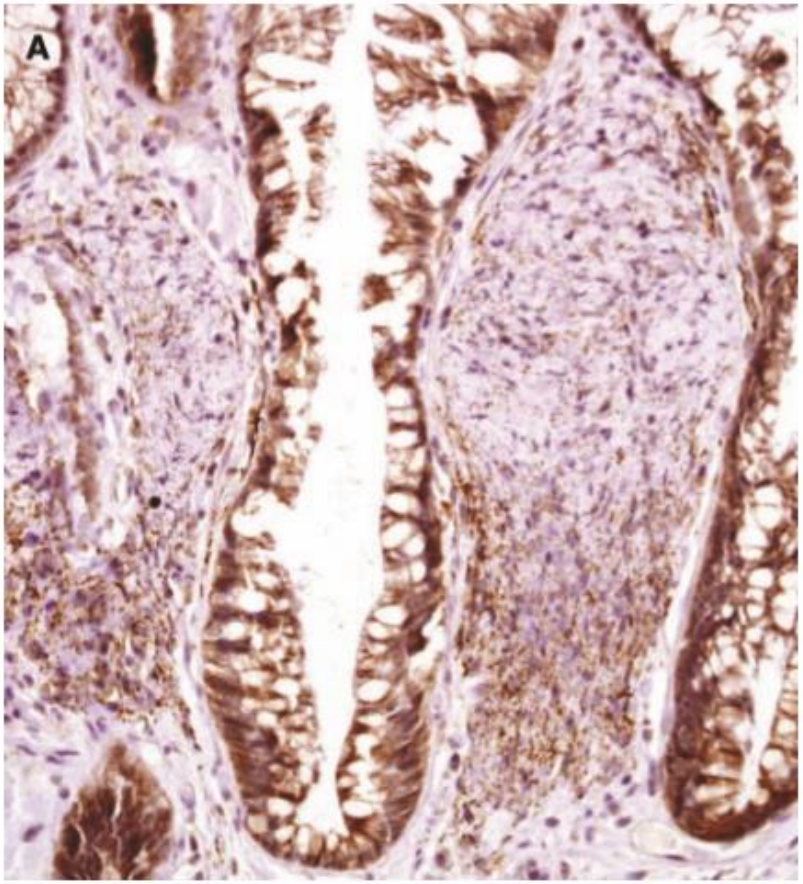


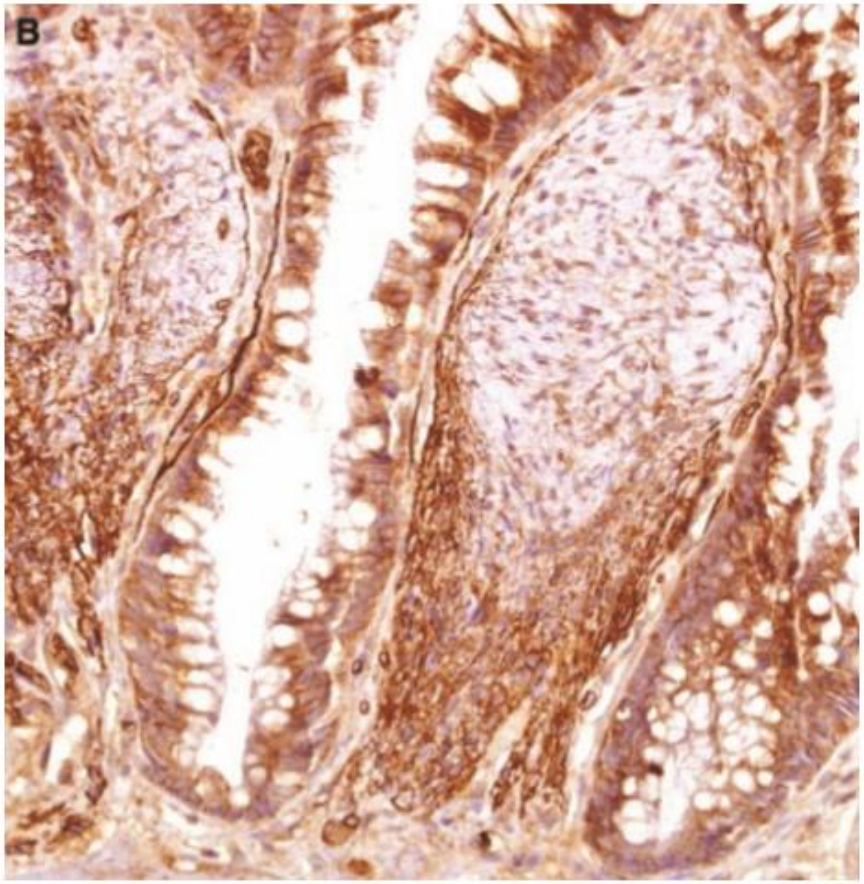
Figure 2. A. Early perineurioma displaying serrated and nonserrated crypts and bundles of monomorphic, bland, plump, stromal perineurioma cells in the base of the mucosa and 3 whorls of monomorphic, bland, eosinophilic perineurioma cells among serrated and nonserrated crypts; B. the enclosed area in higher power

Early Colonic Perineuriomas !

International Journal of Surgical Pathology, 2010 18(4) 292 –297



Claudin 1



GLUT 1

International Journal of Surgical Pathology, 2010 18(4) 292 –297

Histologic and Molecular Analyses of Colonic Perineurial-like Proliferations in Serrated Polyps: Perineurial-like Stromal Proliferations Are Seen in Sessile Serrated Adenomas

Reetesh K. Pai, MD, Amirkaveh Mojtahed, MD,* Robert V. Rouse, MD,* Roy M. Soetikno, MD, MS,† Tonya Kaltenbach, MD, MS,† Lisa Ma, MS,* Daniel A. Arber, MD,* Thomas P. Plesec, MD,‡ John R. Goldblum, MD,‡ and Rish K. Pai, MD, PhD‡*

Abstract: Colonic perineuriomas are recently described benign mucosal polyps that are composed of a bland spindle cell proliferation surrounding crypts that often demonstrate hyperplastic/serrated epithelial changes. However, the origin of this unique stromal proliferation is still unclear, and the association with serrated polyps, including sessile serrated adenomas, has not been fully described. We evaluated the pathologic and molecular features of colonic polyps associated with perineurial-like proliferations in 2 retrospective cohorts: (1) a series of 198 consecutive sessile serrated adenomas and (2) 20 colonic polyps diagnosed as a perineurioma irrespective of the presence of serrated colonic crypts. Thirteen of 198 (6.5%) sessile serrated adenomas demonstrated a perineurial-like stromal proliferation, with most (12 of 13, 92%) involving the right (9 cases) and transverse colon (3 cases). In all 13 cases, the perineurial-like

2 (11%) polyps in the right colon demonstrated histologic features diagnostic of sessile serrated adenoma. All 18 polyps with serrated crypts demonstrated a pV600E *BRAF* mutation. In contrast, the 2 polyps not associated with serrated crypts were negative for a *BRAF* mutation. Our results show for the first time that perineurial-like stromal proliferations frequently occur in sessile serrated adenomas. The presence of focal perineurial-like stromal proliferations in sessile serrated adenomas and the common finding of serrated crypts in colonic perineuriomas are likely indicative of an epithelial-stromal interaction, possibly related to some factor elaborated by the serrated epithelium.

Key Words: perineurioma, fibroblastic polyp, BRAF, hyperplastic polyp, sessile serrated adenoma

(*Am J Surg Pathol* 2011;35:1373–1380)

(Am J Surg Pathol 2011;35:1373–1380)

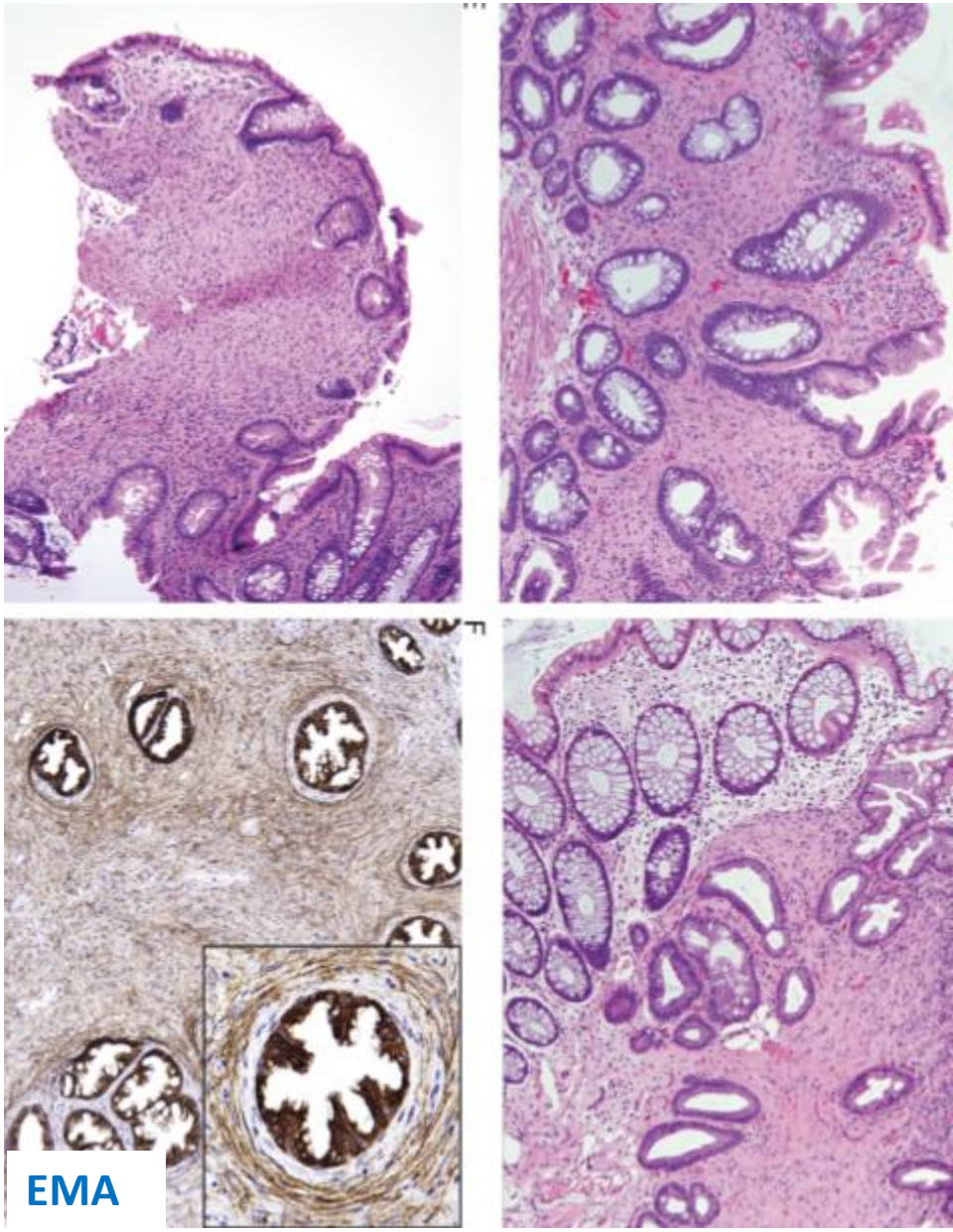
6.5% of all sessile serrated adenomas had perineurial-like stromal proliferation

Most polyps in right colon

92% of SSAs demonstrated V600E BRAF mutation

Present also in microvesicular hyperplastic polyps and “perineuriomas”

Nature and origin of perineurial-like proliferation unclear



(Am J Surg Pathol 2011;35:1373–1380)

Claudin-1 positive proliferations in serrated colorectal polyps

Melissa Thompson[1], Maria Caruso[2], James Moore[2], Andrew Ruszkiewicz[1,2]

[1]SA Pathology, Adelaide, South Australia.

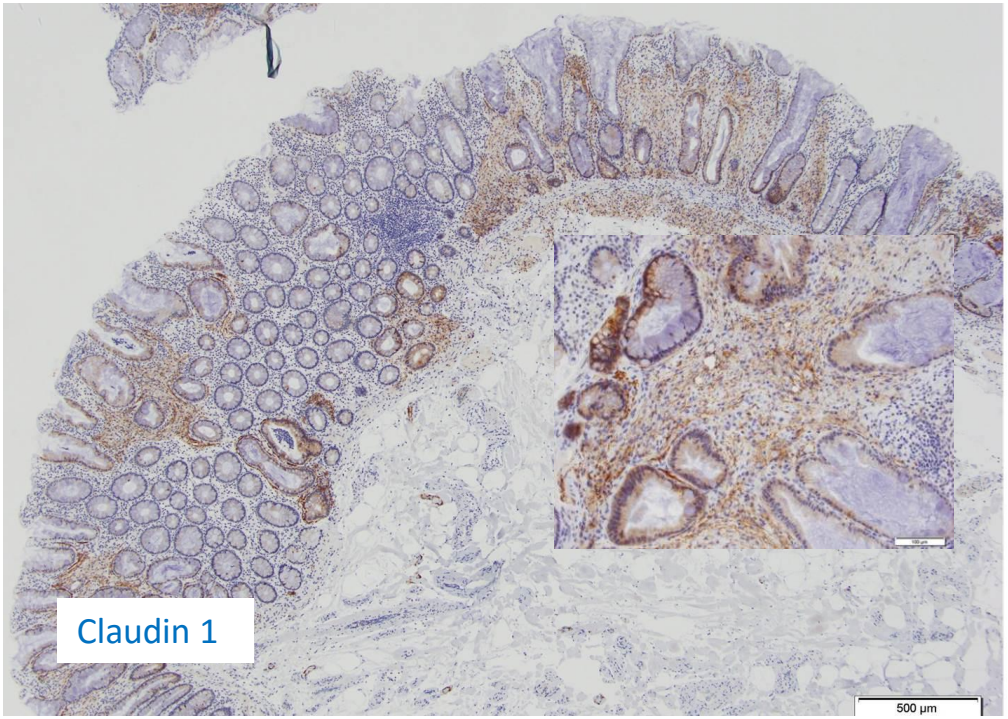
[2]Centre for Cancer Biology, University of South Australia, Royal Adelaide Hospital , Adelaide, South Australia.

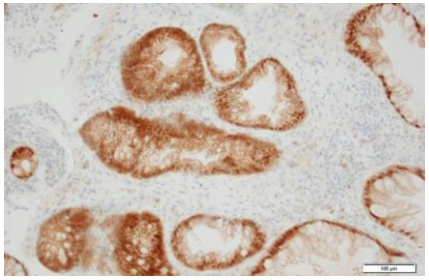
Aim: To analyse the frequency of Claudin-1 positive proliferations in serrated colorectal polyps.

Polyps:

- 377 polyps including:
- 174 consecutive SSA
- 203 MVHP and SP NOS

- Somatic KRAS and BRAF mutation in all cases
- Immunohistochemistry for Claudin1 in all cases
- BRAF immunohistochemistry in selected cases only



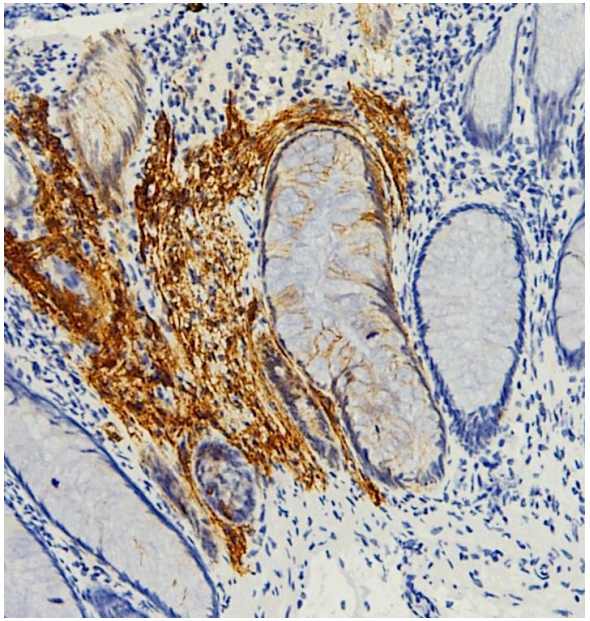


BRAF

Claudin-1 spindle cell proliferations in serrated colorectal polyps

- IHC Claudin 1 +ve spindle cells present in (35/377) 9.3% of all polyps
- Of these 82% (29 of 35 polyps) also harboured BRAF mutation

(23/24 SSA, 6/9 SP NOS, 0/2 MVHP)



Claudin 1

- **Claudin 1 IHC identified higher prevalence of spindle cells than in the original report (9.3% vs 6.5%)**
- **strong indication of epithelial-mesenchymal interactions in BRAF positive serrated polyps and raises the possibility of epithelial mesenchymal transformation occurring in proportion of serrated polyps**

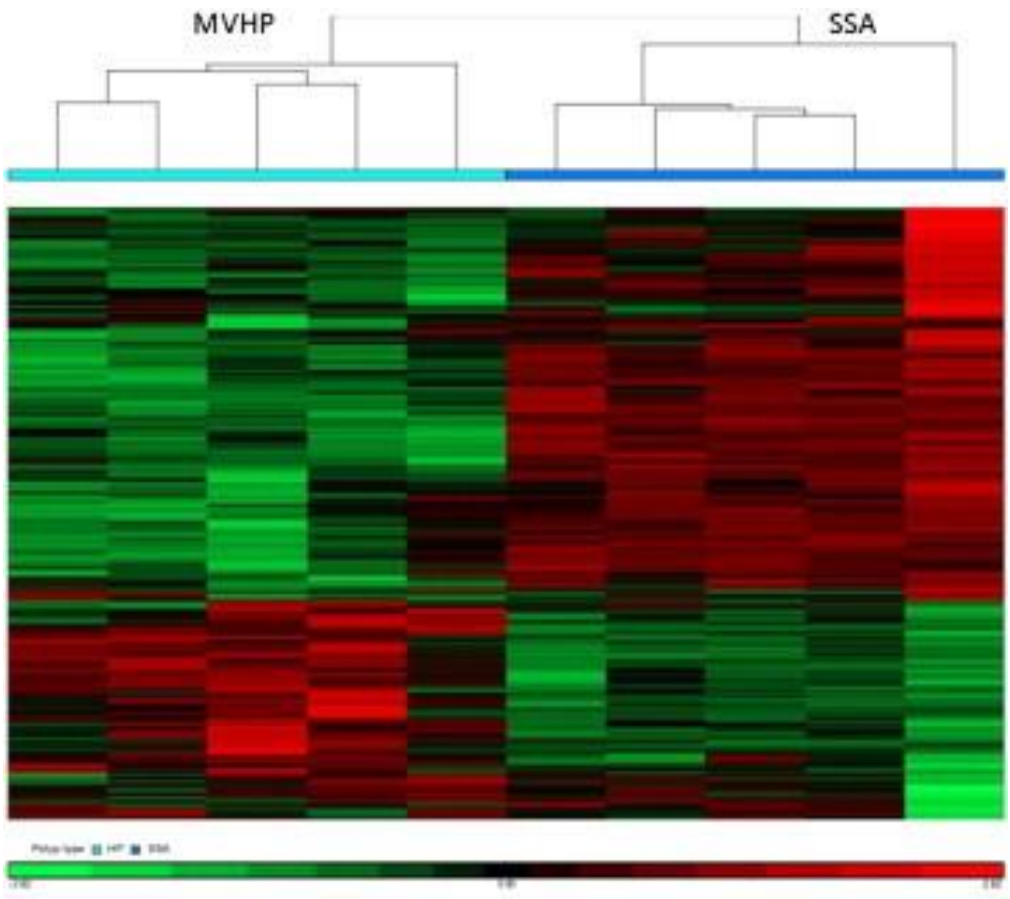
Gene expression profiling:

- **MVHP (n=5, all BRAF V600E wild-type)**
- **SSA/P (n=5, all BRAF V600E mutant)**

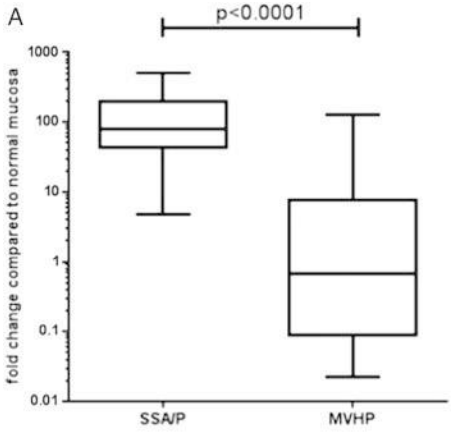
LCM dissected serrated crypts without stroma were analysed

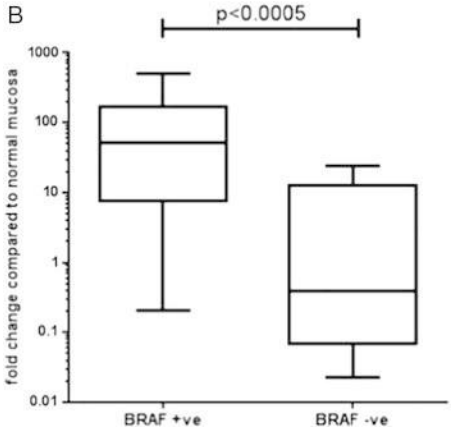
Validation:

- **qRT-PCR**
- **Immunohistochemistry**



CLAUDIN 1 - the most statistically significant differentially expressed gene (p <0.05)





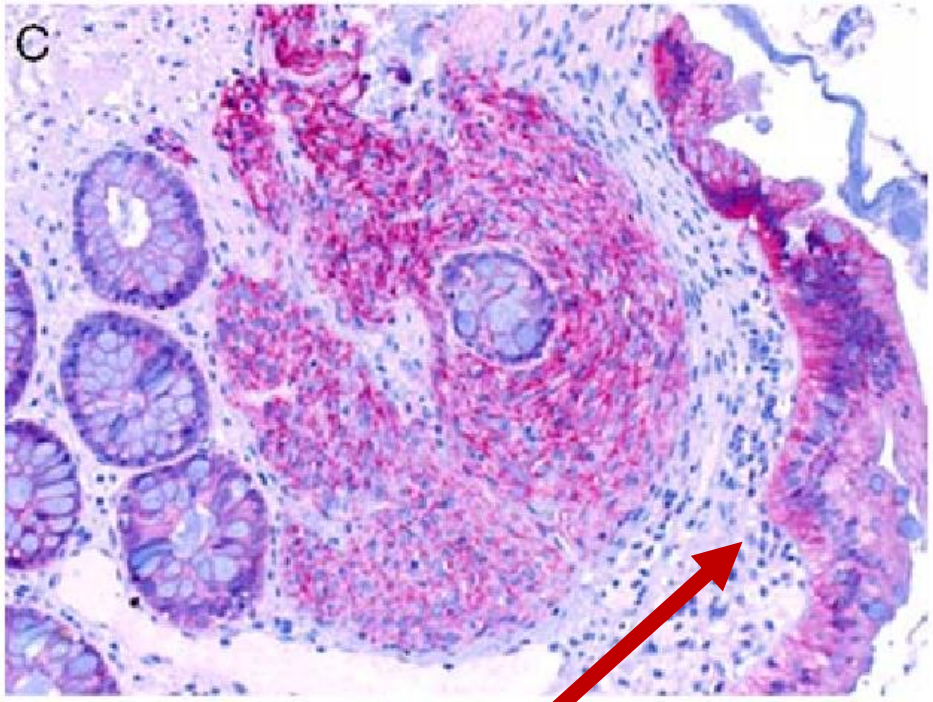
Translational Oncology
www.transonc.com

Volume 7 Number 4 August 2014 pp. 456–463 456

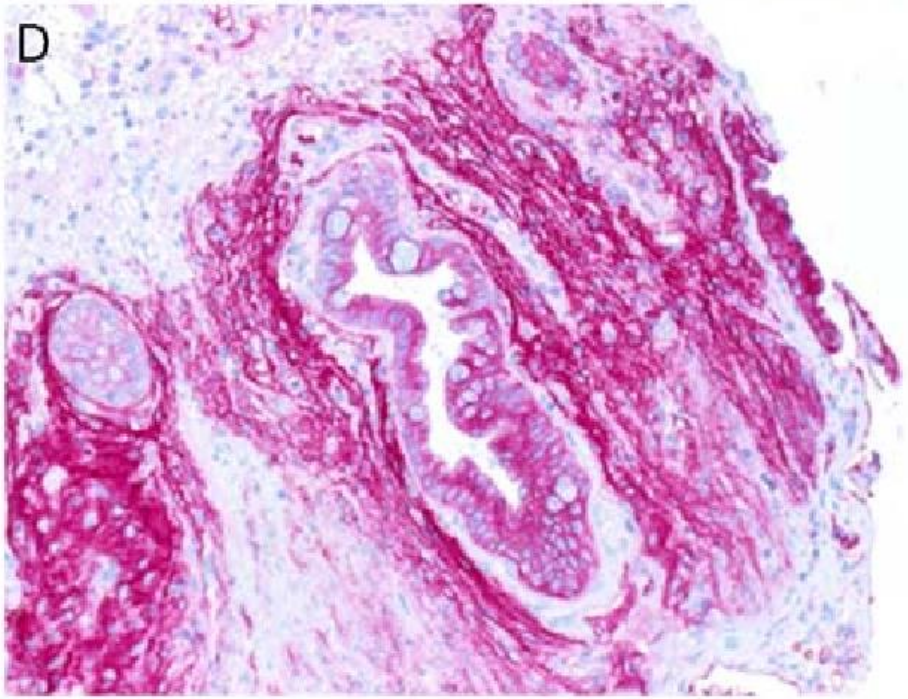
Claudin-1 Expression Is Elevated in Colorectal Cancer Precursor Lesions Harboring the BRAF V600E Mutation[1,2]

Maria Caruso*, Kim Y.C. Fung†, James Moore‡,¶, Gemma V. Brierley†, Leah J. Cosgrove†, Michelle Thomas‡,¶, Glenice Cheetham§, Emma Brook¶, Louise M. Fraser¶, Teresa Tin*, Ha Tran* and Andrew Ruszkiewicz*,¶,#

*Centre for Cancer Biology, Gastroenterology Research Laboratory, University of South Australia, Adelaide, Australia; †CSIRO Preventative Health National Research Flagship, Adelaide, Australia; ‡Royal Adelaide Hospital, Adelaide, Australia; §Molecular Pathology, SA Pathology, Adelaide, Australia; ¶University of Adelaide, Adelaide, Australia; #Genetic Pathology, SA Pathology, Adelaide, Australia



Claudin 1

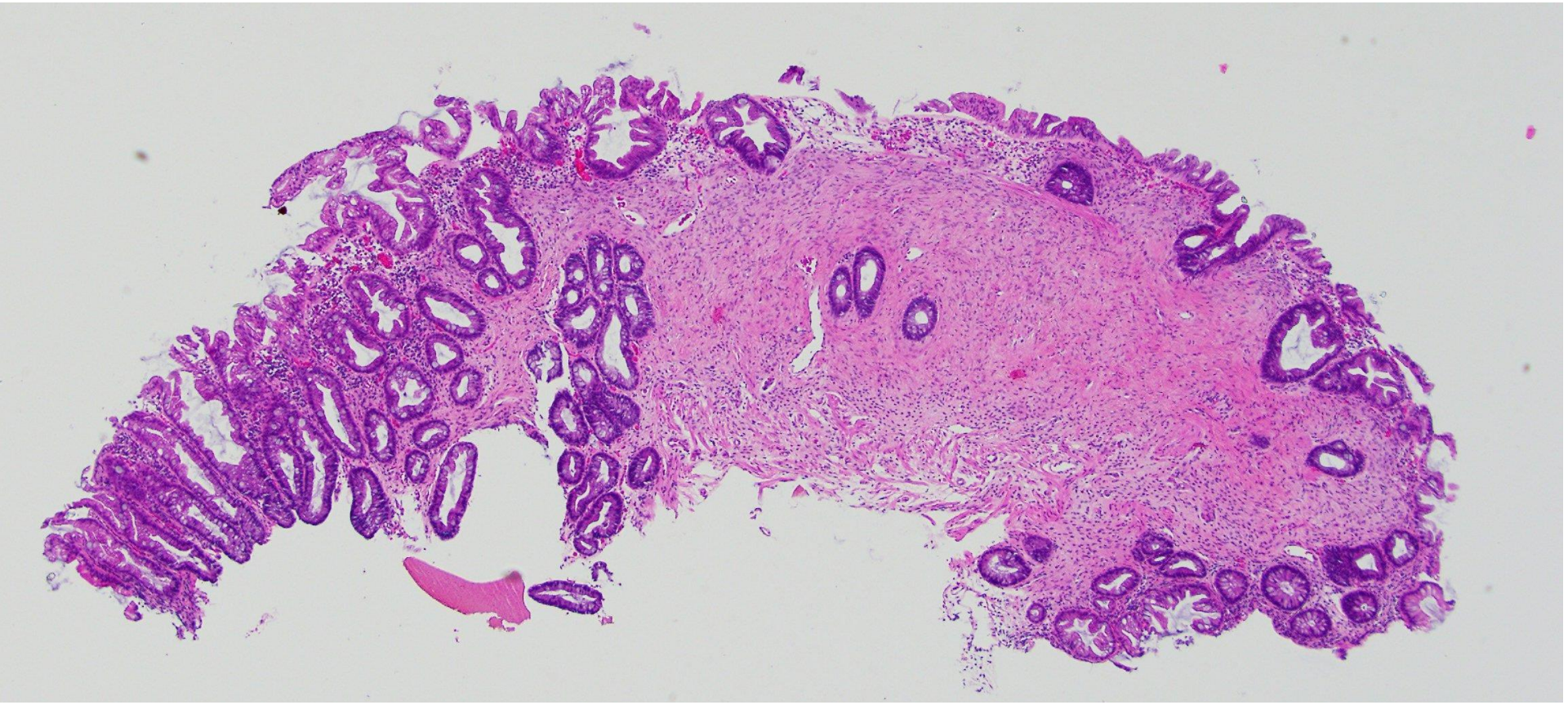


GLUT-1

"… also note the expression in serrated crypts on the right but not in normal crypts on the left"

Am J Surg Pathol 2010;34:1663–1671

Fibroblastic Polyp, Intestinal Perineurioma or **SSA variant**



- Serrated crypts,
- Focal pericryptal spindle cells in 10% of serrated polyps
- Frequent V600E BRAF mutation
- Claudin 1 in crypts and spindle cells

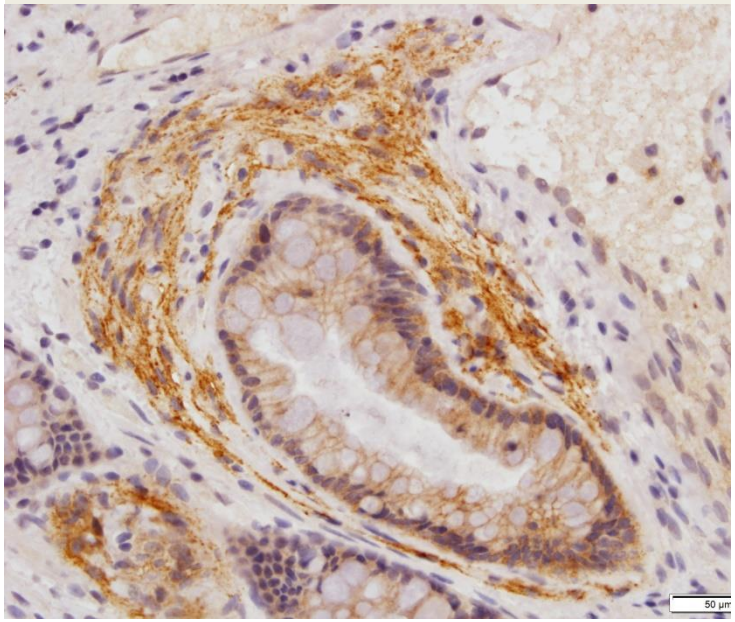
Nature and origin of perineurial-like proliferation unclear

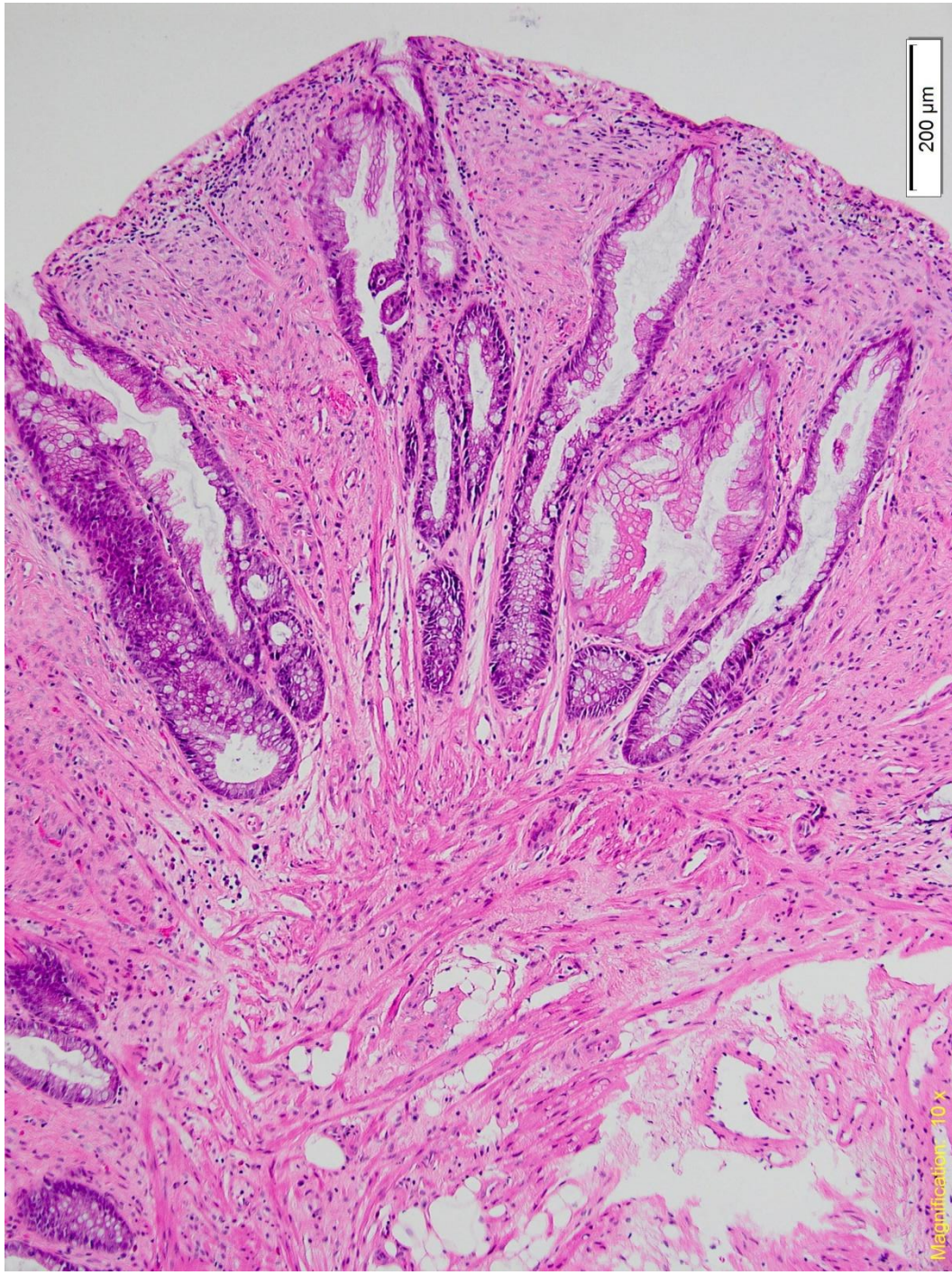
? Perineurial differentiation metaplastic process

? Trully perineurial origin

? reactive phenomenon induced by serrated colonic epithelium

? Epithelial stromal interaction
? EMT





Thank you

15 perineuriomas without and 45 with crypt serration

All lesions showed expression with at least 2 of 4 perineurial cell markers (epithelial membrane antigen, claudin-1, GLUT-1, and collagen type IV).

Our findings confirm that BRAF mutations originate in the serrated epithelium of SPs and demonstrate that SPs and NSPs have similar clinical and endoscopic characteristics and similar stroma, suggesting that they might represent 2 variants of a single lesion.

Am J Surg Pathol 2013;37:745–751

Benign Fibroblastic Polyps of the Colon

Aaron R. Huber, DO; James F. Shikle, MD

• **Benign fibroblastic polyps of the colon are a recently described entity among mucosal polyps found in the colorectum. These polyps are typically discovered on routine screening colonoscopy within the distal colon. Benign fibroblastic polyps occur most commonly in adult women in the sixth decade of life. Histologically, benign fibroblastic polyps are bland spindle cell lesions that fill the lamina propria and displace the surrounding crypts. The spindle cell proliferation lacks atypia and significant mitotic activity. Hyperplastic changes are frequently present both in the adjacent epithelium and within the lesions. Immunohistochemically, the cells of benign fibroblastic polyps are invariably positive for vimentin with rare focal positivity for CD34 and smooth muscle actin. They are negative for CD117 and S100 protein. Ultrastructurally, benign fibroblastic polyps have features of fibroblastic differentiation. These polyps are benign with no reports, to our knowledge, of recurrence or metastasis.**

(***Arch Pathol Lab Med.*** **2009;133:1872–1876)**

Benign fibroblastic polyps of the colon are mucosal spindle cell proliferations first described by Eslami-Varzaneh et al[1] in 2004. The pathogenesis of these lesions is unknown. Theories include an origin from dendritic interstitial cells, follicular dendritic cells, an early stage of

CLINICAL FEATURES

Benign fibroblastic polyps are rare lesions with an estimated incidence of 0.1% to 1.46% of all colonic polyps in different series.[1–3] Benign fibroblastic polyps most commonly present as solitary mucosal polyps in asymptomatic patients undergoing routine screening colonoscopy.[1–4] Rarely, they have been associated with rectal bleeding and clinical diagnoses of colitis and dyspepsia.[2,4] Associated findings have included adenomatous and hyperplastic polyps at different sites, diverticulosis, internal hemorrhoids, and a prolapsing mucosal polyp.[1–4] They have a predilection for the rectum and sigmoid colon but may occur anywhere in the colorectum.[1–4] The age of patients varies from 37 to 84 years, with a mean of 60 years, and occurs most commonly in women.[1–4] As the name implies, these polyps are entirely benign with no reported recurrences or metastases.[1,3–4]

Endoscopic and Gross Findings

Endoscopically, benign fibroblastic polyps appear as single, sessile, well-circumscribed submucosal masses with overlying surface mucosal hyperplasia.[3] Grossly, these polyps range in size from 0.2 to 1.5 cm with a mean, from 4 series,[1–4] of 0.45 cm.

Histopathology

(Arch Pathol Lab Med. 2009;133:1872–1876)

Benign Gastrointestinal Mesenchymal BUMPS

A Brief Review of Some Spindle Cell Polyps With Published Names

Ahren C. Rittershaus, MD; Henry D. Appelman, MD

• ***Context.***—**There are several benign, predominantly spindle cell, mesenchymal proliferations involving the mucosa and/or submucosa in the gut, which present as polyps and pathologists see as polypectomy specimens. These include perineuriomas, Schwann cell nodules, ganglioneuromas, leiomyomas of the muscularis mucosae, inflammatory fibroid polyps, and granular cell tumors.**

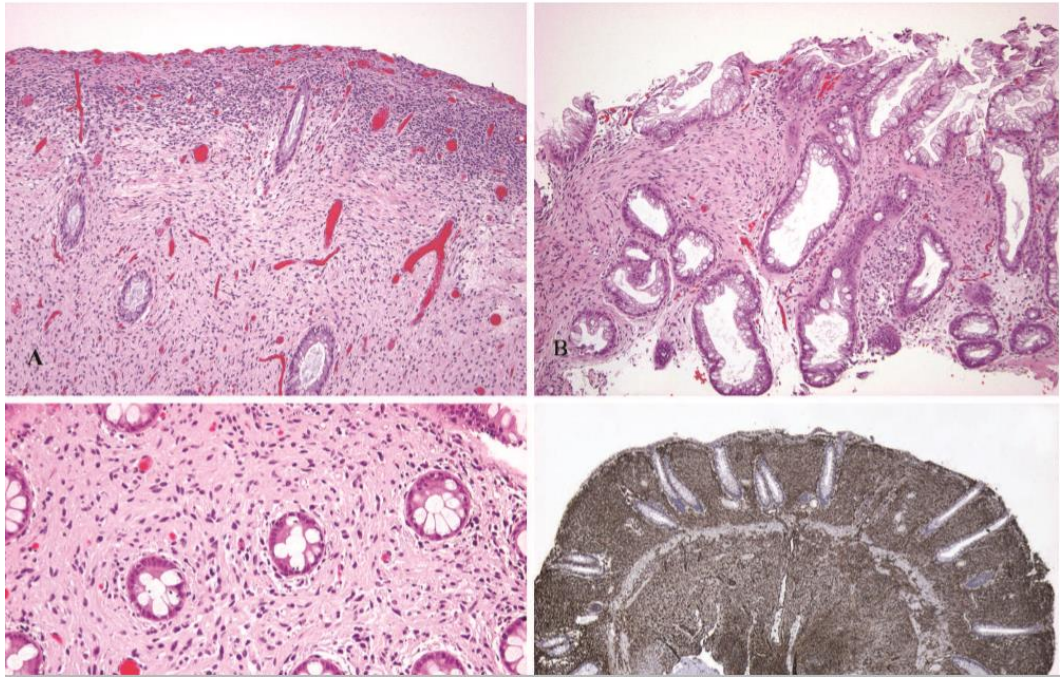
Objectives.—**To evaluate these mesenchymal polyps for their morphologic, immunohistochemical, ultrastructural, and molecular characteristics and to determine some of their associations.**

Data Sources.—**Personal observations based on years of analyzing endoscopic biopsies and a review of the world's literature.**

Conclusions.—**These polyps do surface every so often. There is significant literature covering inflammatory fibroid polyps and granular cell tumors, but there is little literature about the other entities.**

(*Arch Pathol Lab Med.* 2011;135:1311–1319; doi: 10.5858/arpa.2011-0038-RA)

Benign mesenchymal polyps of the gastrointestinal (GI) tract are a group of unusual and interesting lesions. There has been great progress recently in their categorization, including more detailed analysis of their light microscopic features as well as their immunohistochemical and molecular characteristics. The field has changed dramatically during the past 10 years, when, in 2001, new legislation modified Medicare, which then began reimbursement for screening colonoscopy in patients at an average risk for colorectal carcinoma.[1] This has led to more of all types of polyps being identified, including benign mesenchymal polyps, particularly in the colon. These benign mesenchymal polyps of the colon present as small, asymptomatic, and usually solitary polyps. However, [illegible] features that are specific for each polyp type. Similarly, all the polyps are the differential diagnosis for each other, so we will not belabor the differential diagnosis issue. Distinctive names have been given to several such polyps, but in practice, we still see many mesenchymal polyps that are, as yet, unnamed. In our institution, we diagnose these unnamed mesenchymal polyps simply as *benign unclassified mucosal polyps* or BUMPs. Almost all of these small polyps occur in the mucosa and submucosa of the gastrointestinal tract only, yet in many publications, gastrointestinal stromal tumors are included in the differential diagnosis. Gastrointestinal stromal tumors are mural tumors that only involve the mucosa when they are large and malignant and invade into the mucosa. They should not really be part of the [illegible]



No specific clinical features

The trapped crypts have serrated architecture, so they have an appearance identical to the crypts in a hyperplastic polyp

They referred to: Agaimy A, Stoehr R, Vieth M, Hartmann A. Benign serrated colorectal fibroblastic polyps/intramucosal perineuriomas are true mixed epithelial-stromal polyps (hybrid hyperplastic polyp/mucosal perineurioma) with frequent BRAF mutations. Am J Surg Pathol. 2010;34(11):1663–1671

3. Murphy WM, Grignon DJ, Perlman EJ. In: Silverberg SG, Sobin LH, eds. *AFIP Atlas of Tumor Pathology, Fourth Series Fascicle 1, Tumors of the Kidney, Bladder, and Related Urinary Structures.* Washington, DC: American Registry of Pathology; 2004:173.
4. Skinnider BF, Folpe AL, Hennigar RA, et al. Distribution of cytokeratins and vimentin in adult renal neoplasms and normal renal tissue: potential utility of a cytokeratin antibody panel in the differential diagnosis of renal tumors. *Am J Surg Pathol.* 2005;29:747–754.

Perineurioma Versus Fibroblastic Polyp of the Colon

To the Editor:

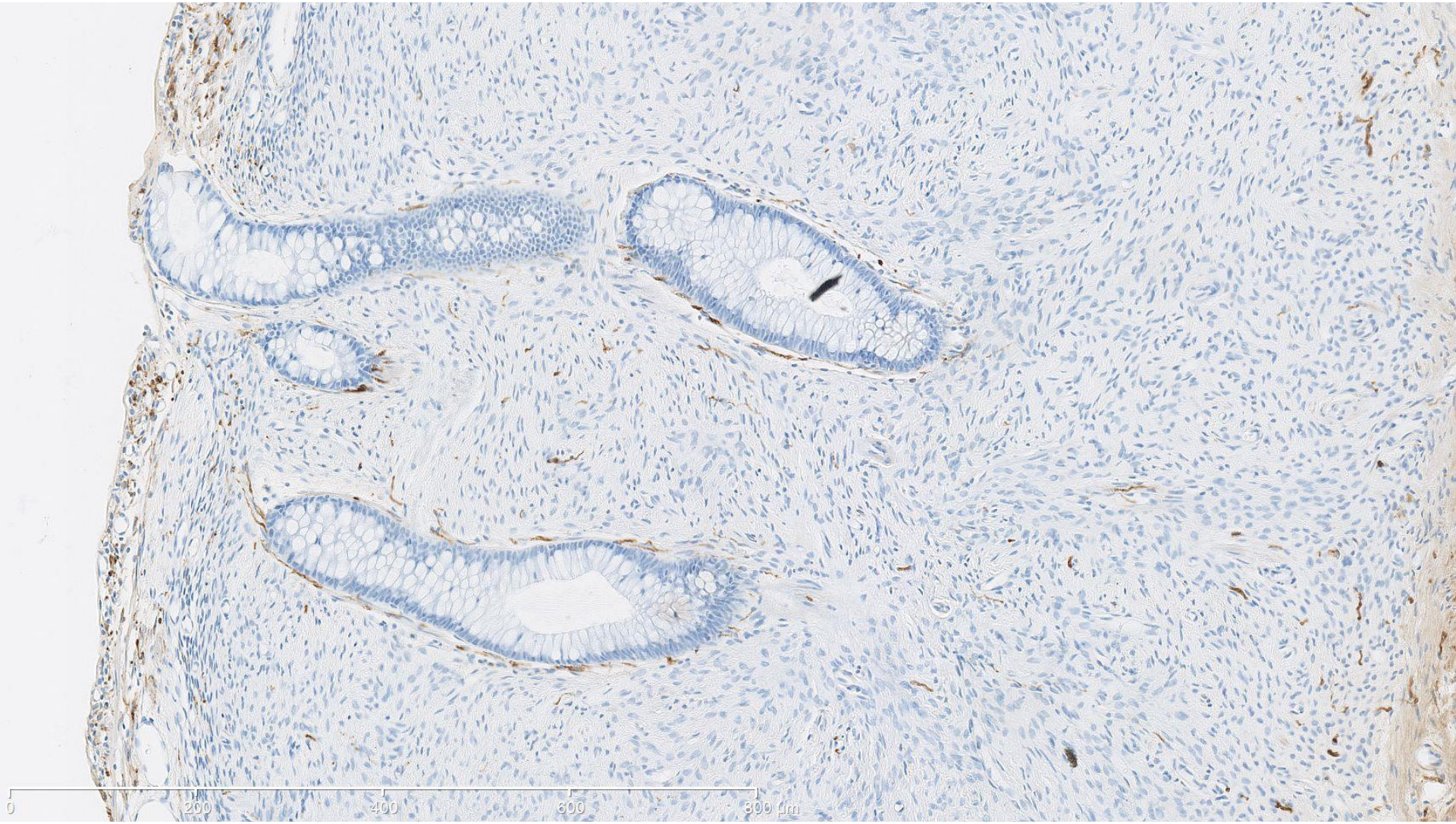
Recently, Hornick et al[5] described 8 cases of mucosal perineurioma of the colon, with typical immunoreactivity for EMA and claudin-1. The authors mention that morphologic features of these mucosal cases are similar to those of so-called fibroblastic polyp (FP) that was described also quite recently.[2,4,7] Comparing the described features of

as follows: 1 in transverse colon, 2 in sigma and 2 in rectosigma. Histologically, all polyps showed previously described features of FP[2,4,7] (Fig. 1). Immunohistochemically (Figs. 1C–E), diffuse positivity for EMA was found in 3 of 5 cases. Claudin-1 was positive in 4 of 5 lesions, and this reactivity was always focal and usually seen around the hyperplastic crypts. Glut-1 was positive strongly in all polyps, again with an accentuation around the crypts. Every case was reactive at least for 2 perineurial cell markers.

Ultrastructurally, the EMA+/claudin+/glut+ lesion was examined. The spindle cells had sparse organelles and long thin cytoplasmic processes (Fig. 2). Although the formalin/paraffin tissue was preserved suboptimaly, many segments of unquestionable external lamina were still seen on the cell processes, sometimes with visible pinocytotic vesicles and primitive cell junctions. This finding is typical for perineurial cell differentiation.[1] Microfilaments with densities typical of myoid cells or desmosomes indicating follicular dendritic cell differentiation were not found.

- asymptomatic solitary polyps
- localized predominantly in the rectosigmoid colon
- Serrated (hyperplastic) crypts were observed on the top or contiguous with the lesion in all cases
- Immunohistochemistry revealed expression of at least one perineurial cell marker (epithelial membrane antigen, claudin-1, and glucose transporter-1
- V600E BRAF mutation in 63% and KRAS mutation in 4%
- "The perineurial stromal component might be derived from modified pericryptic fibroblasts as a consequence of a yet poorly understood epithelial-stromal interaction."

Am J Surg Pathol 2010;34:1663–1671



S-100

Intestinal Perineuriomas

Clinicopathologic Definition of a New Anatomic Subset in a Series of 10 Cases

Jason L. Hornick, MD, PhD and Christopher D. M. Fletcher, MD, FRCPath

Abstract: Benign peripheral nerve sheath tumors are uncommon in the gastrointestinal tract, and perineuriomas have not previously been reported to occur at this anatomic location. In this study, we analyzed the clinicopathologic and immunohistochemical features of 10 perineuriomas arising in the intestine. Eight patients were female and 2 male (median age, 51 years; range, 35–72 years). Eight of the lesions were intramucosal perineuriomas presenting as small sessile polyps detected during colonoscopy; 6 of these 8 patients were asymptomatic and undergoing colorectal cancer screening. The remaining 2 cases were submucosal masses, one each located in the colon and jejunum. Of the mucosal polyps, six were located in the rectosigmoid or sigmoid colon and one each was detected in the descending colon and transverse colon. The polyps ranged from 0.2 to 0.6 cm (median, 0.4 cm) in greatest dimension. The colonic and jejunal masses measured 3 cm and 4.5 cm, respectively. Histologically, the intramucosal perineuriomas were composed of uniform bland spindle cells having ovoid to elongated nuclei and pale indistinct cytoplasm, with no cytologic atypia, pleomorphism, or mitotic activity. The lesions had a fine collagenous stroma, demonstrated irregular borders with the adjacent lamina propria, and entrapped colonic crypts. Five cases exhibited hyperplastic changes in the adjacent or entrapped epithelium. The colonic submucosal tumor was microscopically well circumscribed, whereas the jejunal perineurioma showed focal infiltration through the muscularis propria into the subserosa. The stroma was collagenous in the colonic tumor and predominantly myxoid in the jejunal tumor. The spindle cells in the submucosal perineuriomas demonstrated tapered nuclei and elongated bipolar cytoplasmic processes. All tumors except one were positive for epithelial membrane antigen (EMA); 4 of 10 expressed claudin-1 and 2 of 10 expressed CD34. All tumors were negative for S-100 protein, glial fibrillary acidic protein, neurofilament protein, smooth muscle actin, desmin, caldesmon, KIT, and pan-keratin. Electron microscopy was performed on the tumor lacking EMA expression, revealing typical features of perineurioma, namely, spindle cells with long bipolar cytoplasmic processes and prominent pinocytotic vesicles, surrounded by discontinuous basal lamina. Clinical follow-up was available for 4 patients (median, 34 months; range, 8–53 months). No tumor recurred. In summary, perineuriomas may arise in the intestine, most often as intramucosal lesions detected as colorectal polyps with distinctive histologic features including entrapment of colonic crypts. Distinguishing perineuriomas from other spindle cell neoplasms of the gastrointestinal tract can be facilitated by immunostaining for EMA and claudin-1.

Key Words: perineurioma, schwannoma, neurofibroma, nerve sheath, soft tissue, gastrointestinal tract, colon, polyp

(*Am J Surg Pathol* 2005;29:845–865)

From the Department of Pathology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA.
Reprints: Christopher D. M. Fletcher, MD, FRCPath, Department of Pathology, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115 (e-mail: cfletcher@partners.org).

Benign peripheral nerve sheath tumors uncommonly occur in the gastrointestinal (GI) tract and include ganglioneuromas,[2,3] neurofibromas,[3,9,12] and schwannomas.[2,18,21] Perineuriomas, however, have not previously been reported to arise at this anatomic location. Perineuriomas include soft tissue,[10,15,25] intraneural,[4] and sclerosing[6] variants. The first soft tissue perineurioma was described by Lazarus and Trombetta in 1978 as an intramuscular neurofibroma-like tumor of the calf with ultrastructural features characteristic of perineurial cells, namely, very thin cytoplasmic processes with numerous pinocytotic vesicles, incomplete external lamina, and frequent junctional complexes.[15] Soon after, several studies reported that perineurial cells and derived tumors show immunoreactivity for epithelial membrane antigen (EMA),[1,20,26] which enabled the diagnosis of soft tissue perineurioma to be rendered in the absence of ultrastructural examination. To date, fewer than 50 cases of soft tissue perineurioma have been reported in the literature, most arising in the subcutis,[22] but also occurring in the skin and deep soft tissue. We have recently encountered perineuriomas of soft tissue type arising in the colon and small intestine, most of which presented as mucosal polyps detected at the time of routine colonoscopic screening for colorectal cancer. In this study, we analyzed the clinicopathologic and immunohistochemical features of 10 perineuriomas of the intestine.

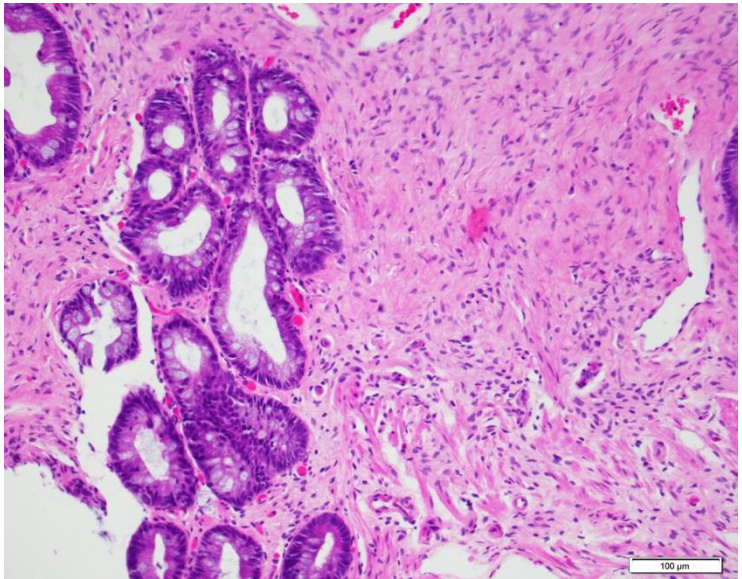
MATERIALS AND METHODS

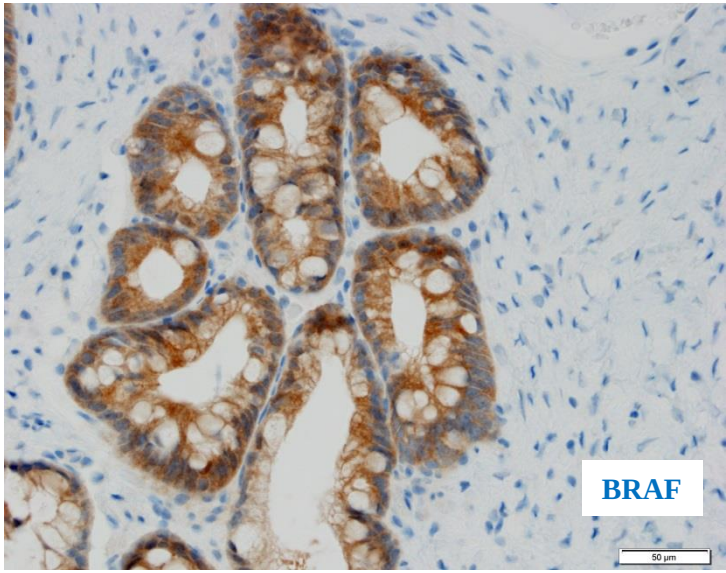
Cases received between 1999 and 2004 were retrieved from the consultation files of one of the authors (C.D.M.F., 4 cases) and the files of the Department of Pathology, Brigham and Women's Hospital, Boston, MA (6 cases). In none of the consult cases was the diagnosis of perineurioma offered. In 1 case, the referring diagnosis was a spindle cell sarcoma. Four-micrometer-thick hematoxylin and eosin-stained sections

Claudin1

- **Intestinal perineurioma**
- **Fibroblastic polyp**

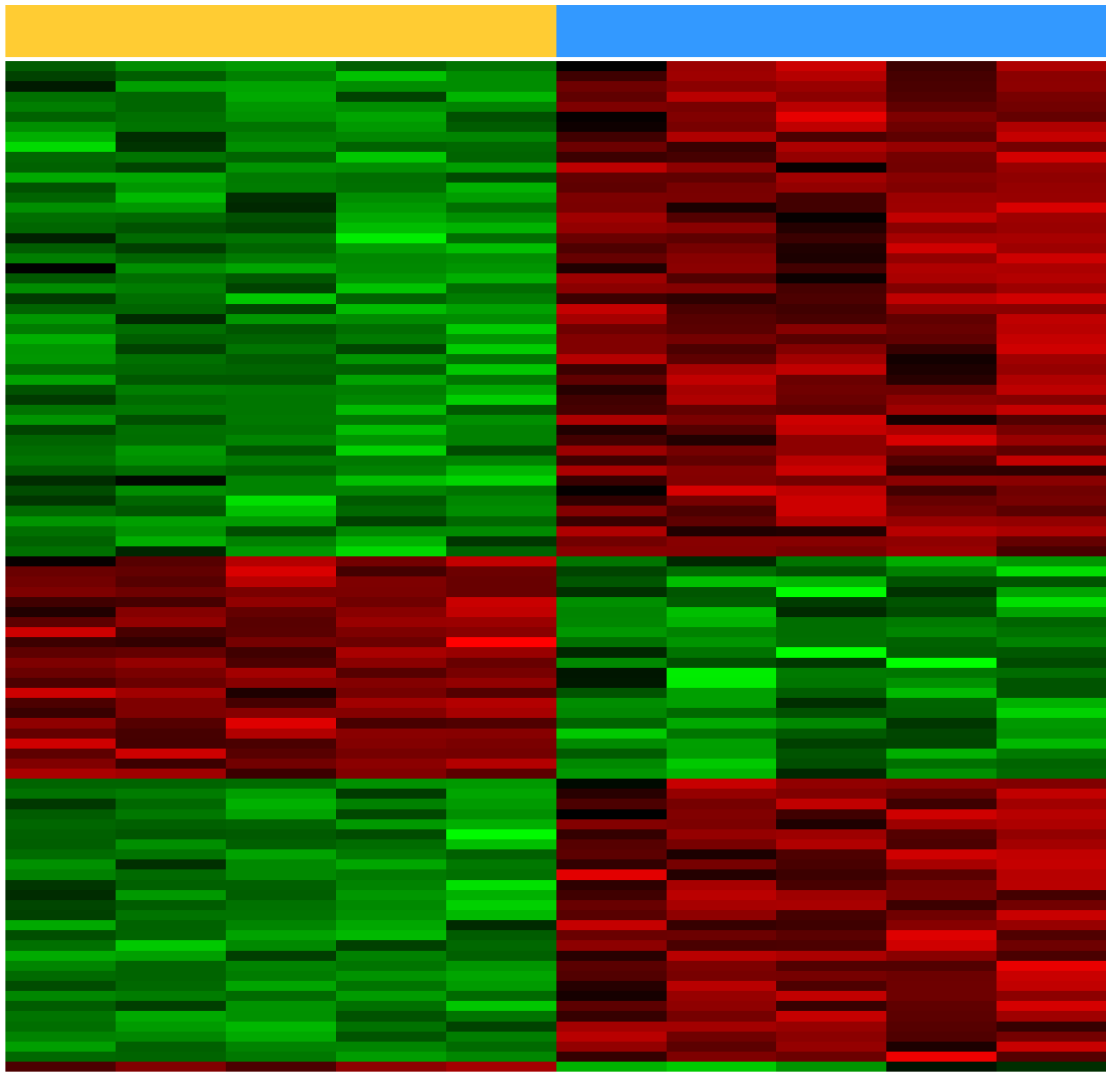
? Or variant of SSA



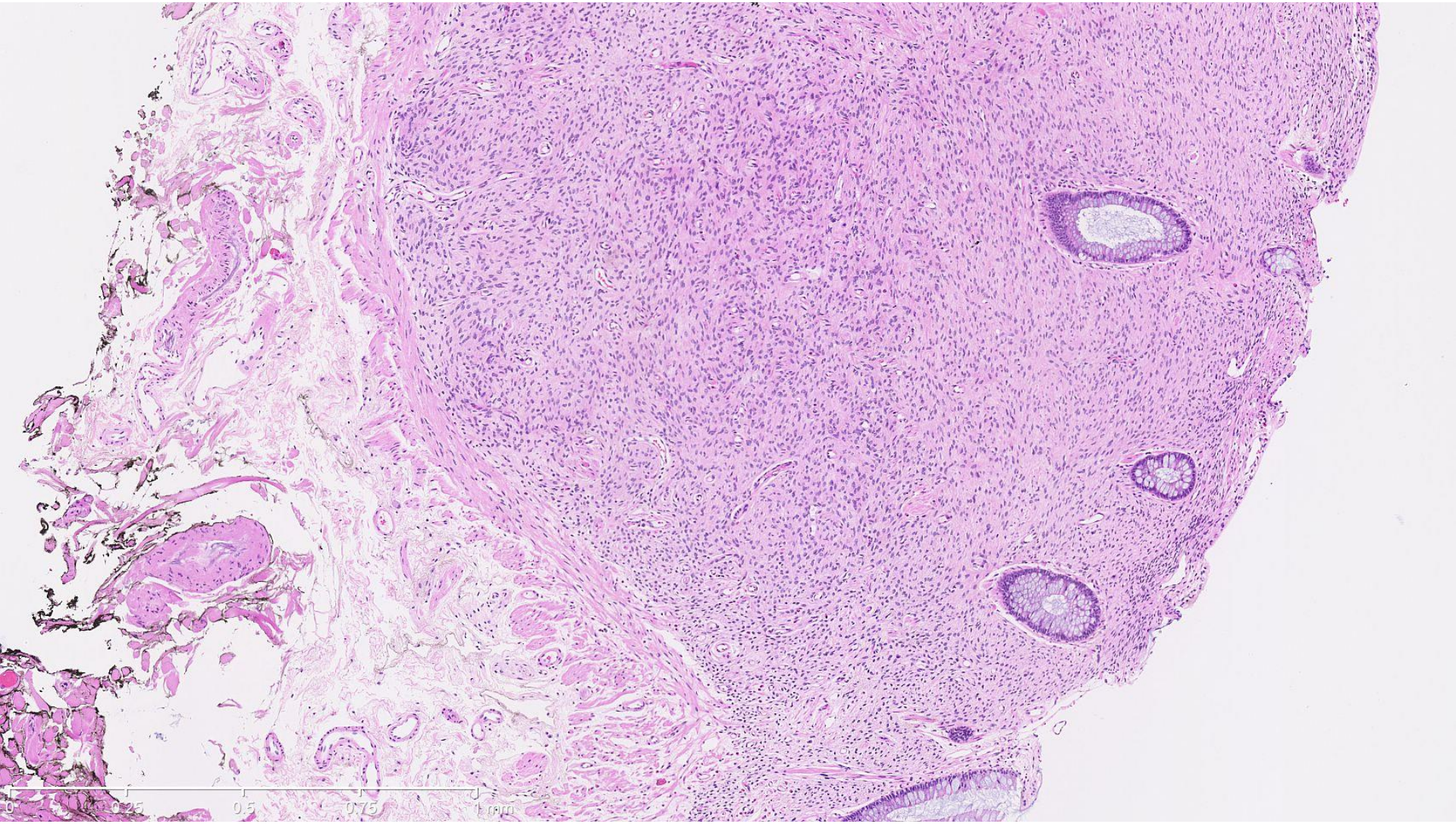


Claudin 1 expression is elevated in colorectal cancer precursor lesions harboring the *BRAF V600E* mutation

Gene expression analysis of Hyperplastic Polyps and Sessile Serrated Adenomas, *Affymetrix platform*



Caruso, M. Ruszkiewicz A, et al. (2014). "Claudin-1 expression is elevated in colorectal cancer precursor lesions harbouring the BRAF V600E mutation." Translational Oncology **7**(4): 456-463.


0
0.25
0.5
0.75
1 mm

- **strong indication of epithelial-mesenchymal interactions in BRAF positive serrated polyps and raises the possibility of epithelial mesenchymal transformation occurring in proportion of serrated polyps**

Colonic Perineuriomas With and Without Crypt Serration

A Comparative Study

Gabriel M. Groisman, MD, Dov Hershkovitz, MD, PhD,† Michael Vieth, MD,‡ and Edmond Sabo, MD†*

Abstract: Colorectal perineuriomas are characterized by a mucosal proliferation of benign stromal cells expressing perineurial markers leading to separation and/or disorganization of the crypts that frequently display a serrated/hyperplastic architecture. Previous studies demonstrated a high prevalence of a *BRAF* p.V600E mutation in perineuriomas with serrated crypts and suggested that perineuriomas without crypt serration may represent an unrelated, different type of polyp. Yet, these molecular analyses included only 2 cases of perineuriomas without

Colorectal perineurioma (also known as fibroblastic polyp) represents a novel type of benign mucosal polyp characterized by a uniform mucosal stromal proliferation of bland, plump spindle cells that leads to separation, entrapment, and disorganization of the colonic crypts. To date, a total of 154 cases have been reported.[1–14] Perhaps the most notable characteristic of this lesion, reported in 108 of 150 cases (72%), is the presence of crypts with a serrated profile embedded

(Am J Surg Pathol 2013;37:745–751)