COWDEN SYNDROME: CLINICAL AND PATHOLOGIC FINDINGS WITH GENETICS UPDATE

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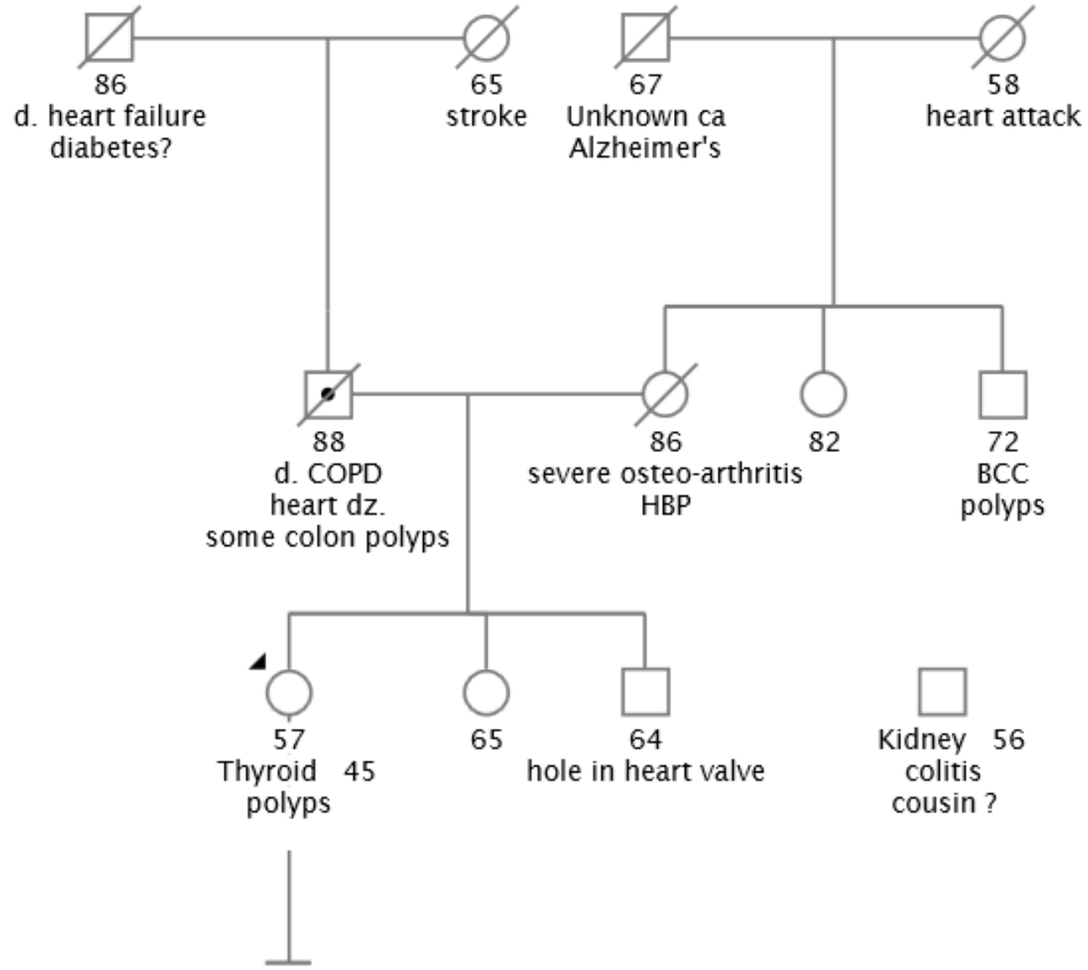
CASE

- 30 year old female underwent colonoscopy for abdominal pain and multiple colon polyps were found.
- Since then she has had several upper and lower endoscopies till now (age 57) with multiple hamartomatous polyps noted on exam.
- Upper endoscopy typically showed multiple gastric polyps, antral nodules and multiple esophageal lesions.
- She has h/o papillary thyroid cancer.
- Forehead cutaneous lesions.
- Right thigh mass - consistent with lipoma.

PEDIGREE



Genetic testing did not identify any mutations.

A diagnosis of Cowden Syndrome was made based on clinical findings.

COWDEN SYNDROME

- Inherited autosomal dominant, multi organ cancer syndrome.
- Prevalence is 1:200,000.
- Increase risk of benign and malignant tumors involving multi organs.
- Included in the spectrum of *PTEN* hamartoma tumor syndrome.
- *PTEN* mutation may only be identified in 25-35% of patients.
- Clinical diagnosis using Major/Minor criteria.

CONSENSUS CLINICAL DIAGNOSTIC CRITERIA

Major criteria

- Breast cancer
- Epithelial thyroid cancer (follicular)
- Macrocephaly (occipital frontal circumference ≥ 97th percentile)
- Endometrial carcinoma
- Gastrointestinal hamartomas ≥ (including ganglioneuromas, but excluding hyperplastic polyps)
- Lhermite–Duclos disease (adult)
- Macular pigmentation of the glans penis
- Multiple cutaneous lesions (any of the following): Multiple trichilemmomas (≥3, at least one biopsy proven), Acral keratosis (≥ 3 palmoplantar keratotic pits and/or acral hyperkeratotic papules), Mucocutaneous neuromas (≥3), Oral papilloma (particularly on tongue and gingiva)- multiple (≥3).

Minor criteria

- Autism spectrum disorder
- Colon cancer
- Esophageal glycogenic acanthosis (≥3)
- Lipomas (43)
- Intellectual disability (IQ ≤ 75)
- Renal cell carcinoma
- Testicular lipomatosis
- Thyroid cancer (papillary or follicular variant)
- Thyroid structural lesion (eg, adenoma, multinodular goiter)
- Vascular abnormalities

An operational diagnosis of CS is made if an individual meets any one of the following criteria:

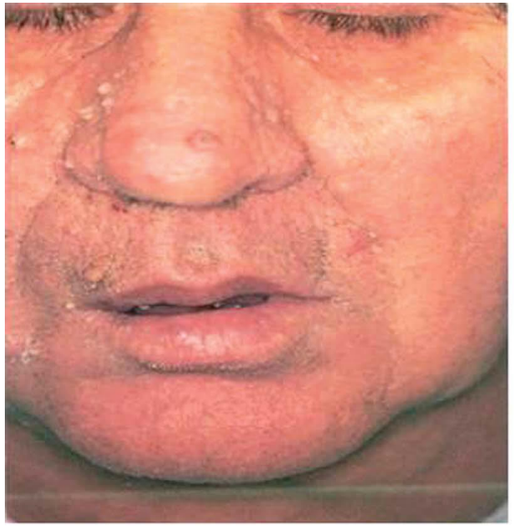
- Three or more major criteria, but one must include macrocephaly, Lhermite–Duclos disease, or gastrointestinal hamartomas.
- Two major and three minor criteria

In a family in which one individual meets the diagnostic criteria for CS listed above, other relatives are considered to have a diagnosis of CS if they meet any one of the following criteria:

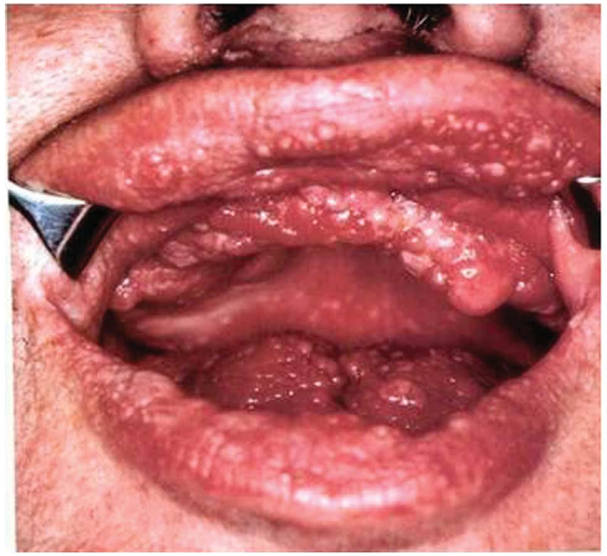
- Any two major criteria
- One major and two minor criteria
- Three minor criteria

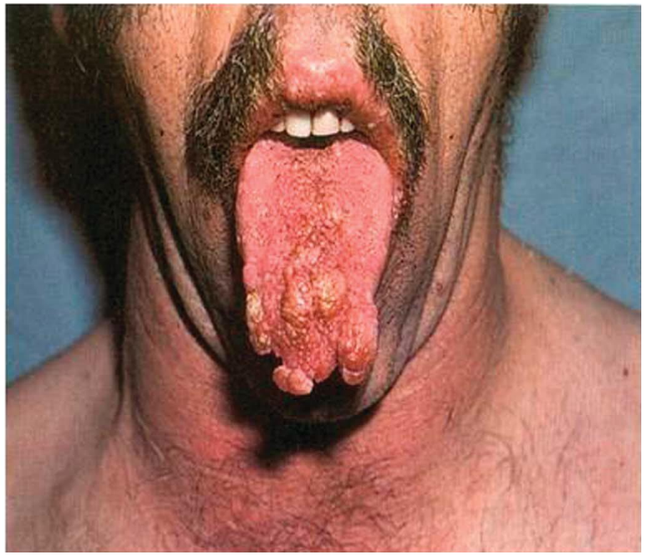
NCCN guidelines 2018

UNIQUE CLINICAL FINDINGS



Facial trichilemmomas





Papillomas of face, lips, tongue, and oral mucosa

Kanth P et al- Am J Gastroenterol. 2017

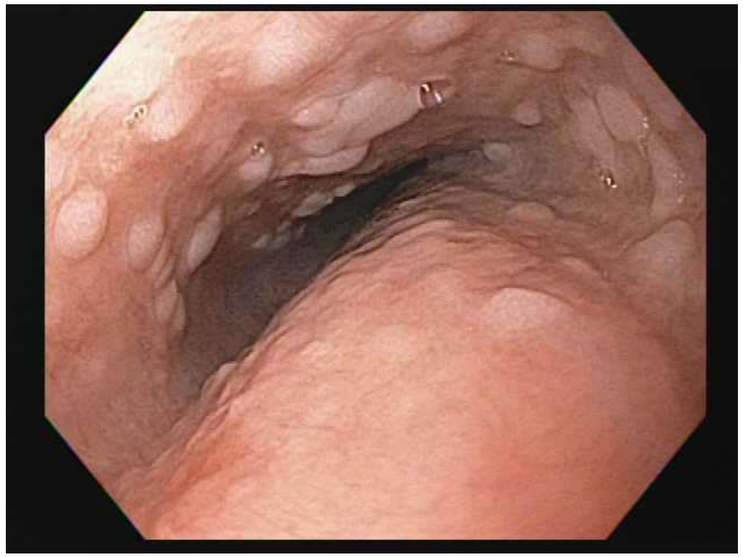
CANCER RISK

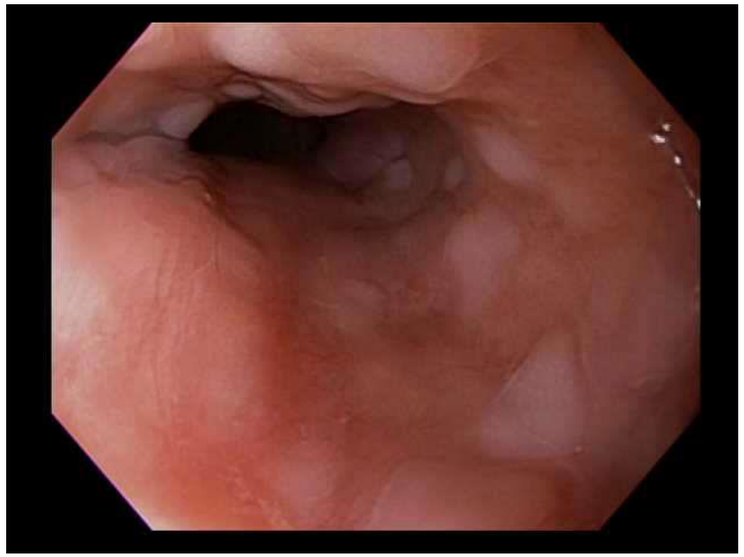
- Breast cancer lifetime risk- 25 to 50%
- Breast cancer usually diagnosed in 40’s (between 40-50 yrs of age).
- Thyroid cancer and Renal cancer – 35%
- Endometrial cancer- 28%
- Colon cancer- 9 to 18%, average age of diagnosis in 40’s

COLON & GI TRACT POLYPS

- Up to 92% of CS patients may have colon polyps.
- Types of polyps- Hamartomatous polyps- include inflammatory/juvenile polyps, expansive lymphoid follicle, ganglioneuromatous polyps and Intramucosal lipoma.
- Hamartomatous polyps may also be found in the stomach, duodenum, and small bowel.
- Finding two or more hamartomatous polyps or any intramucosal lipomas or ganglioneuromas in a patient is a highly prevalent feature of CS.

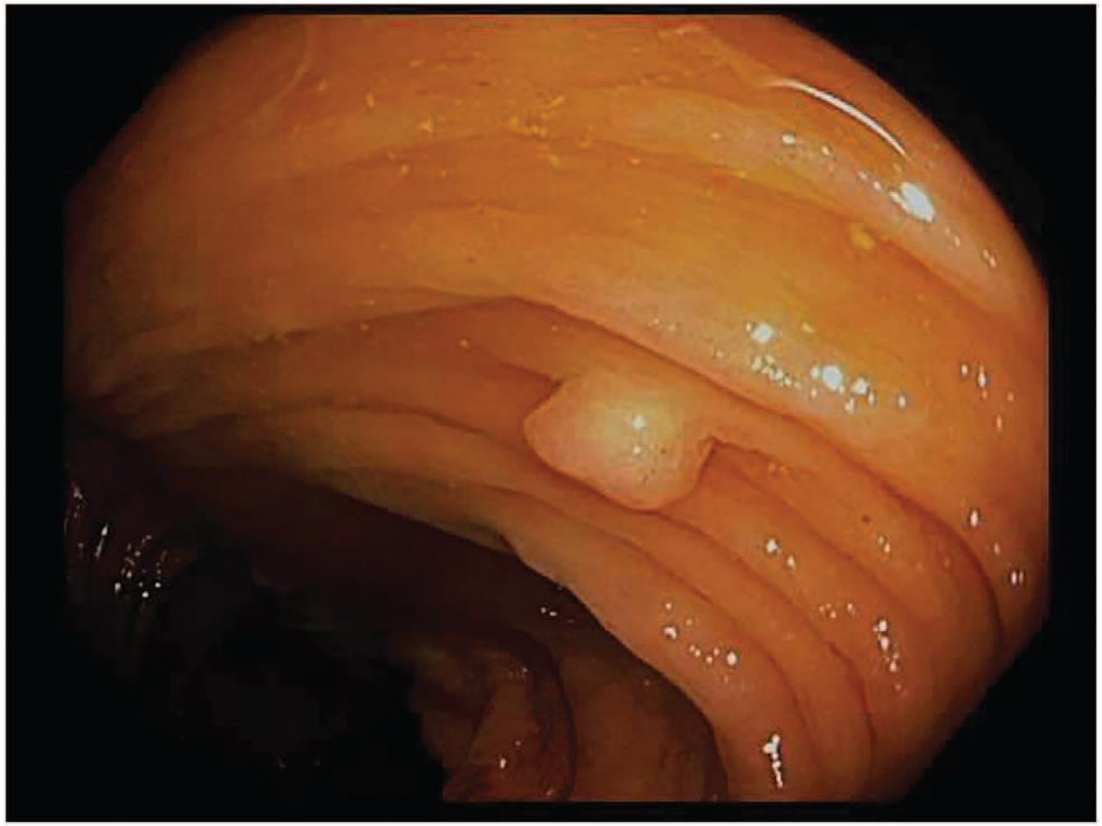
ENDOSCOPY: GLYCOGENIC ACANTHOSIS

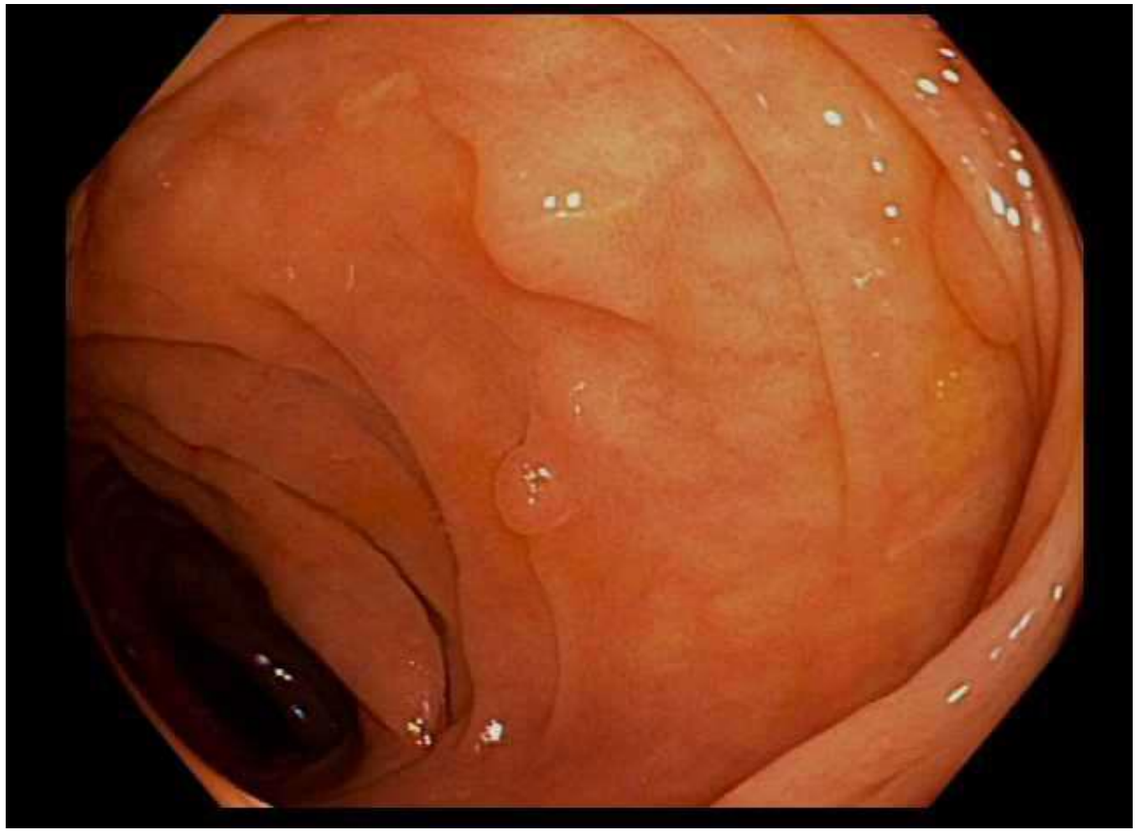




Esophageal benign findings and does not progress to neoplasia.

COLONOSCOPY- HAMARTOMATOUS POLYPS

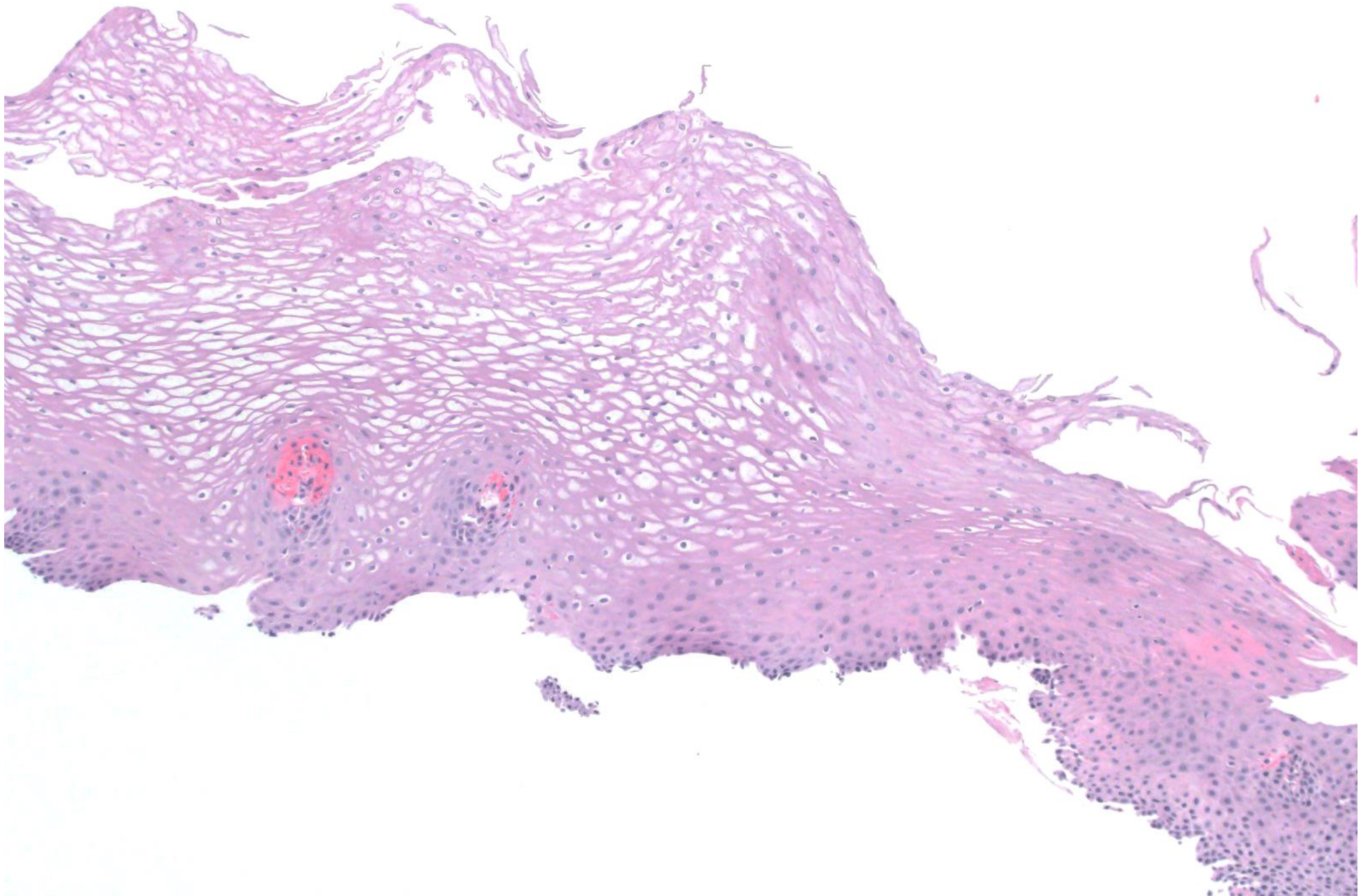


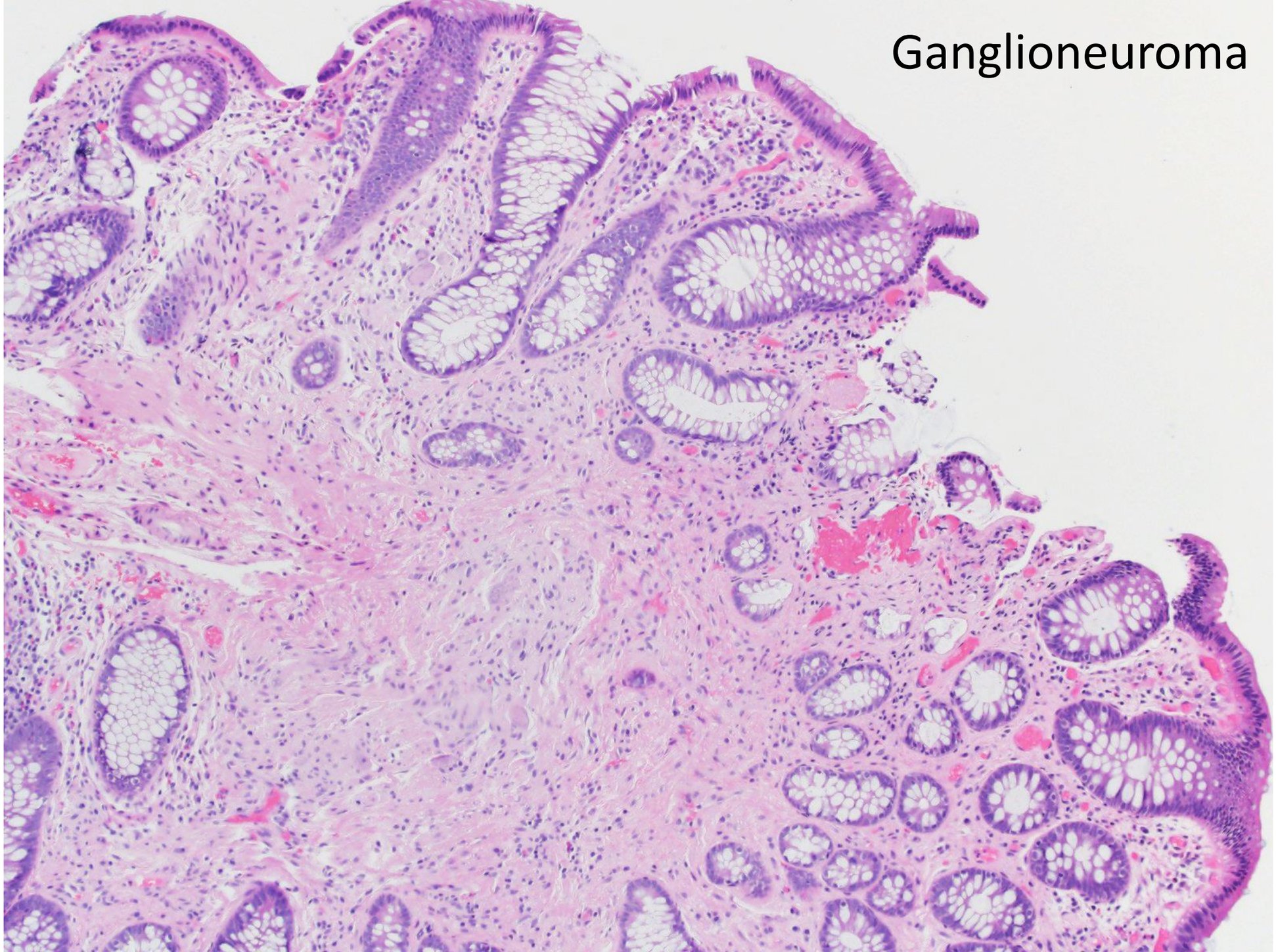


Endoscopically polyps have no unique features and may look like typical adenomas.

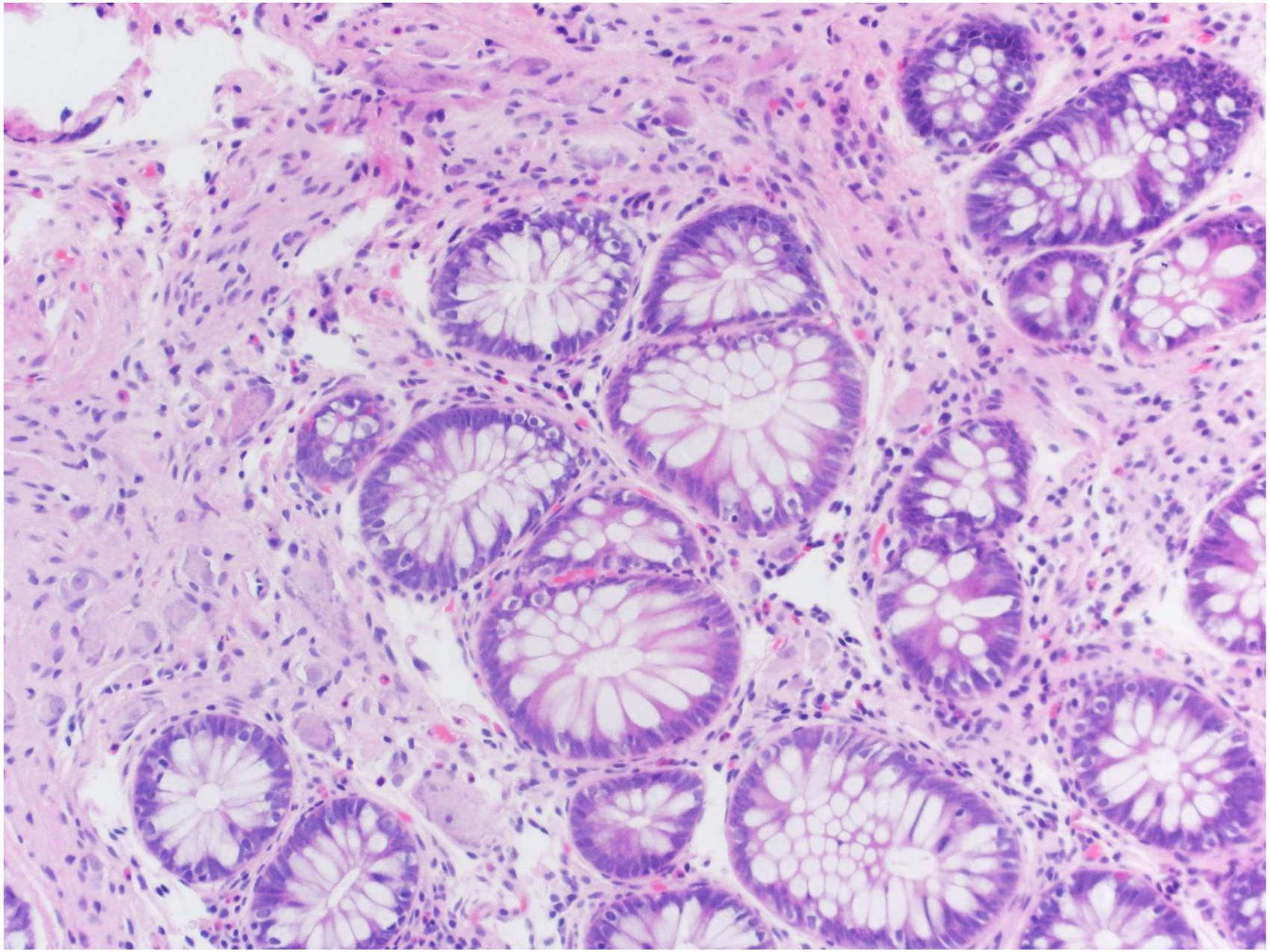
PATHOLOGY OF COWDEN SYNDROME

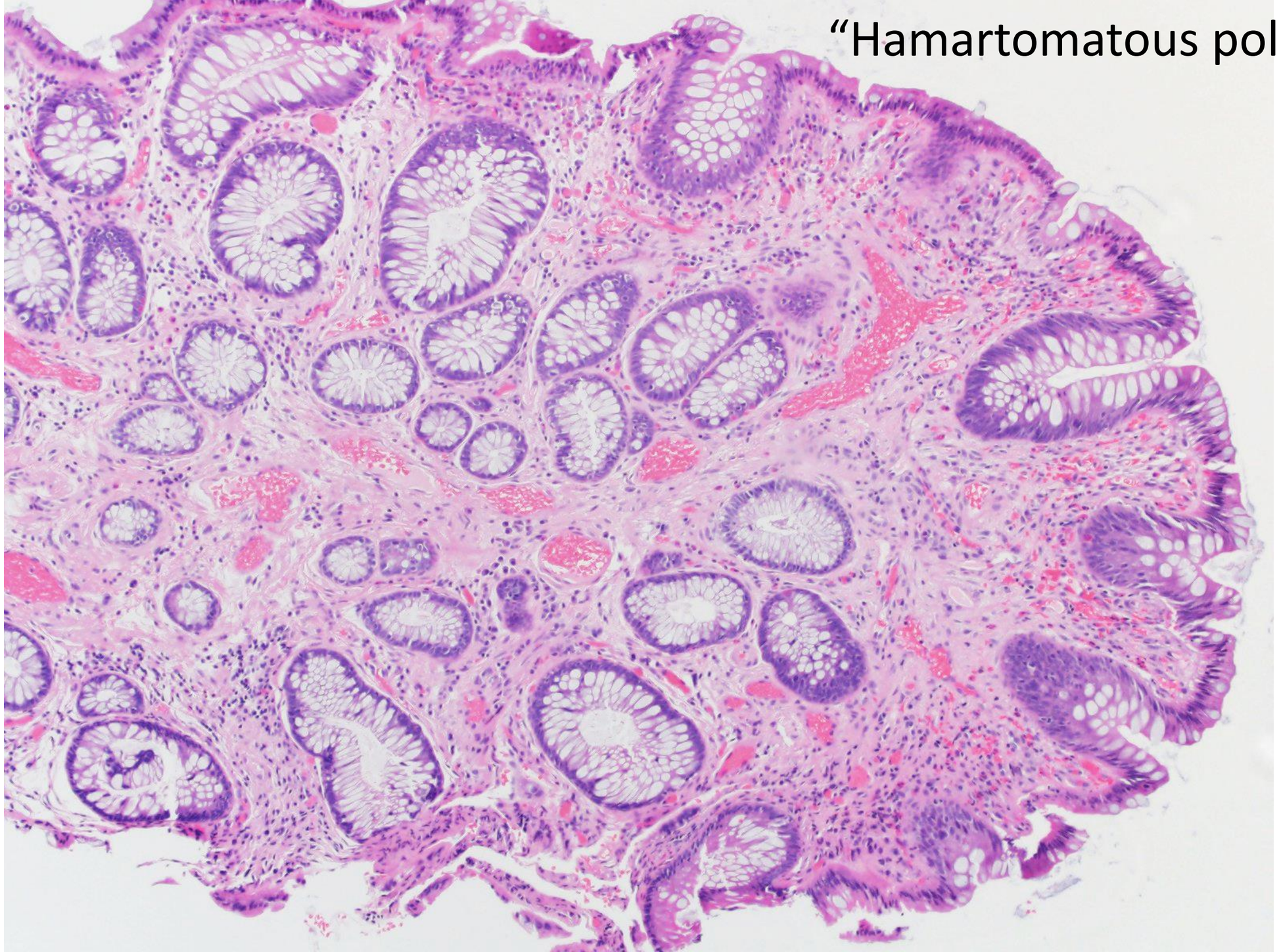
Glycogenic acanthosis



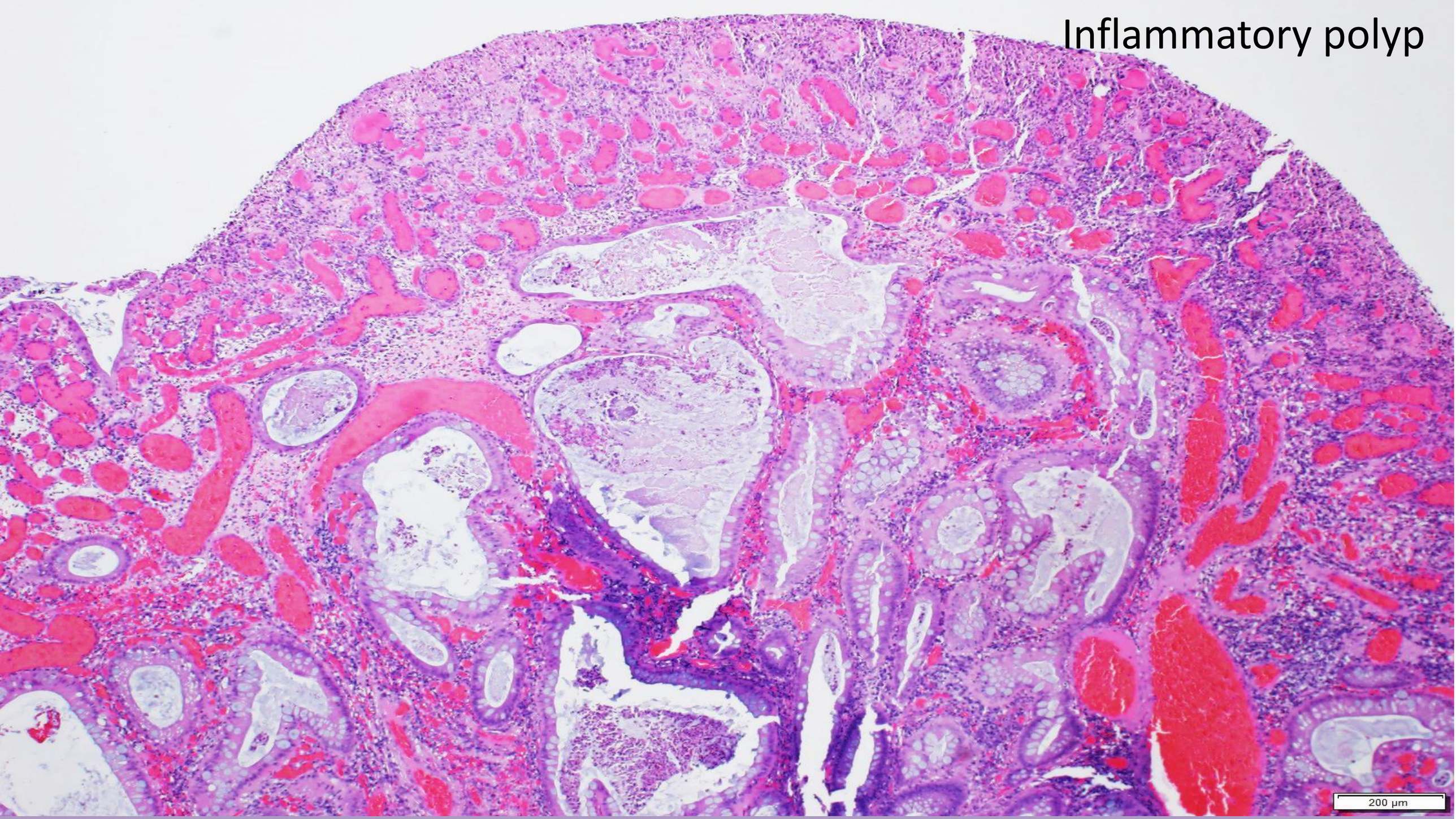

Ganglioneuroma

Ganglioneuroma

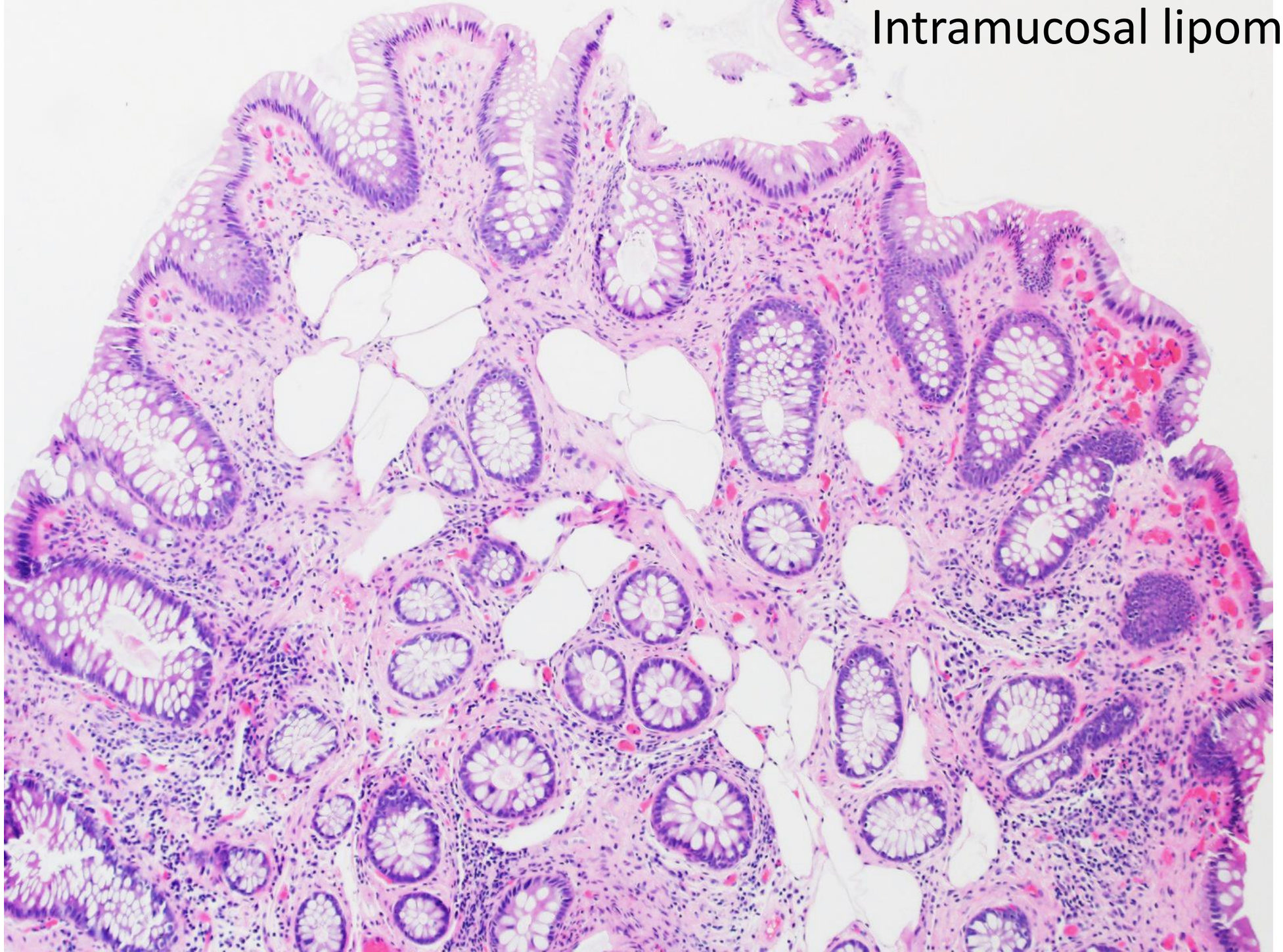



“Hamartomatous polyp”

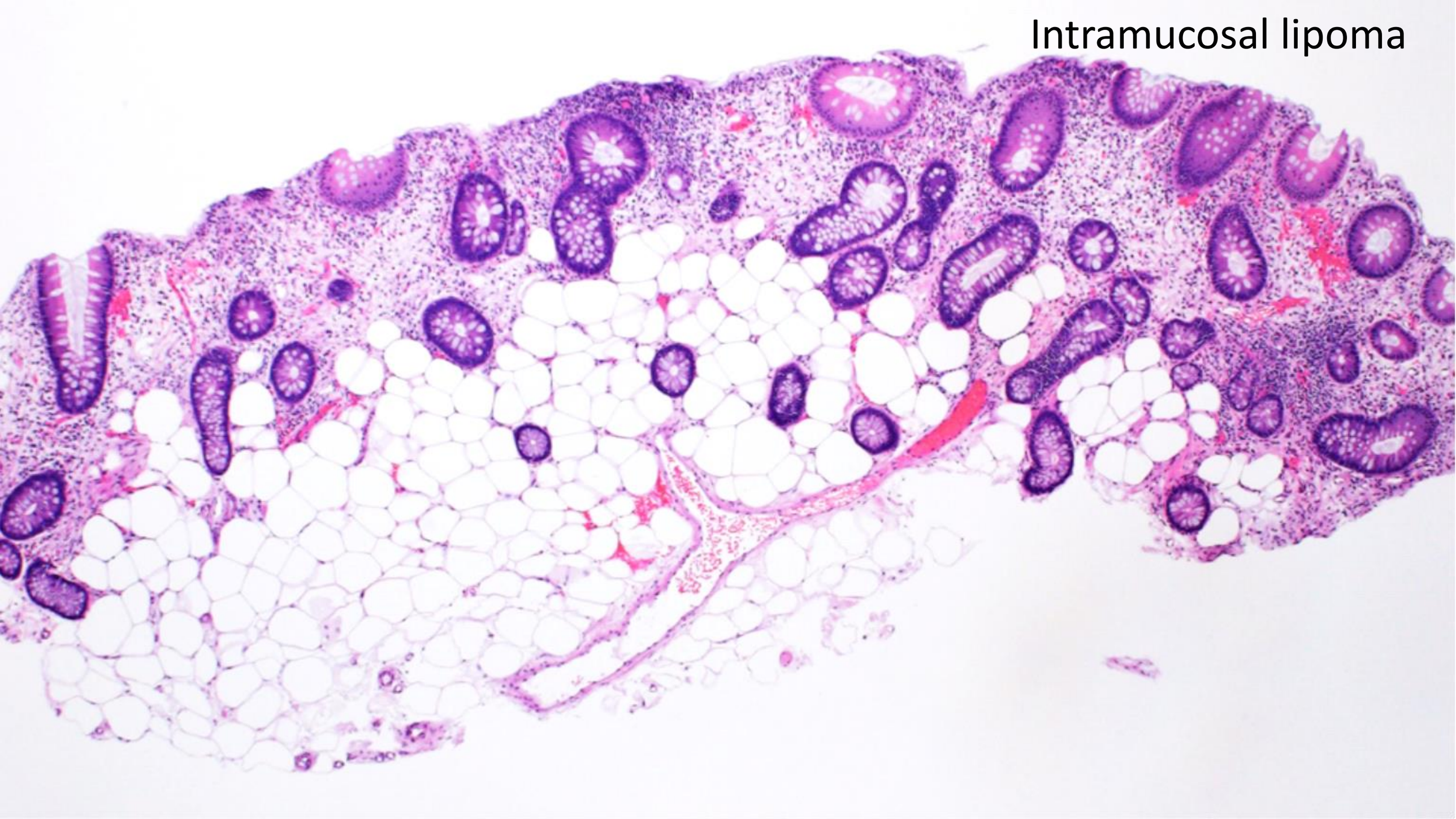
Inflammatory polyp



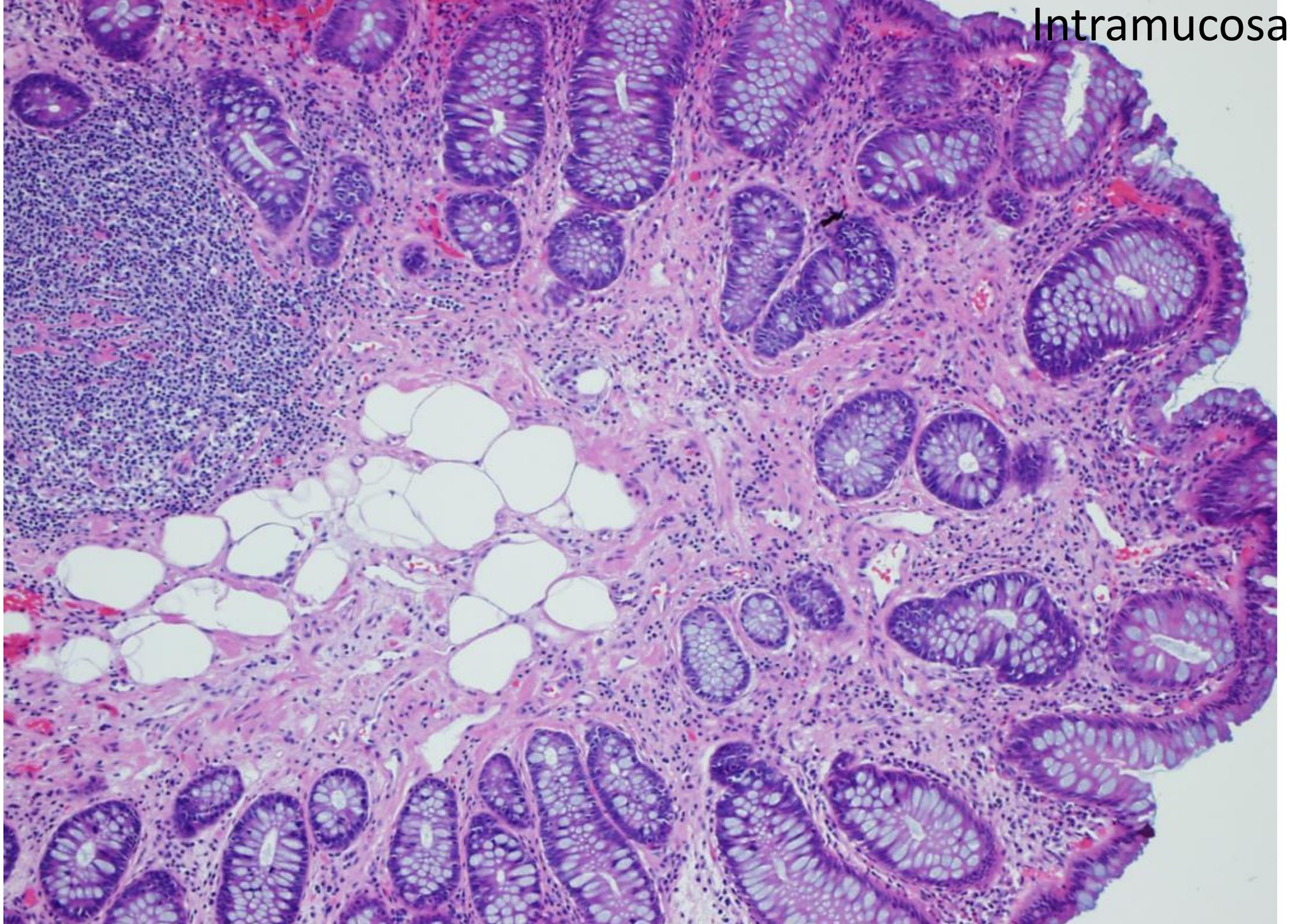
Intramucosal lipoma



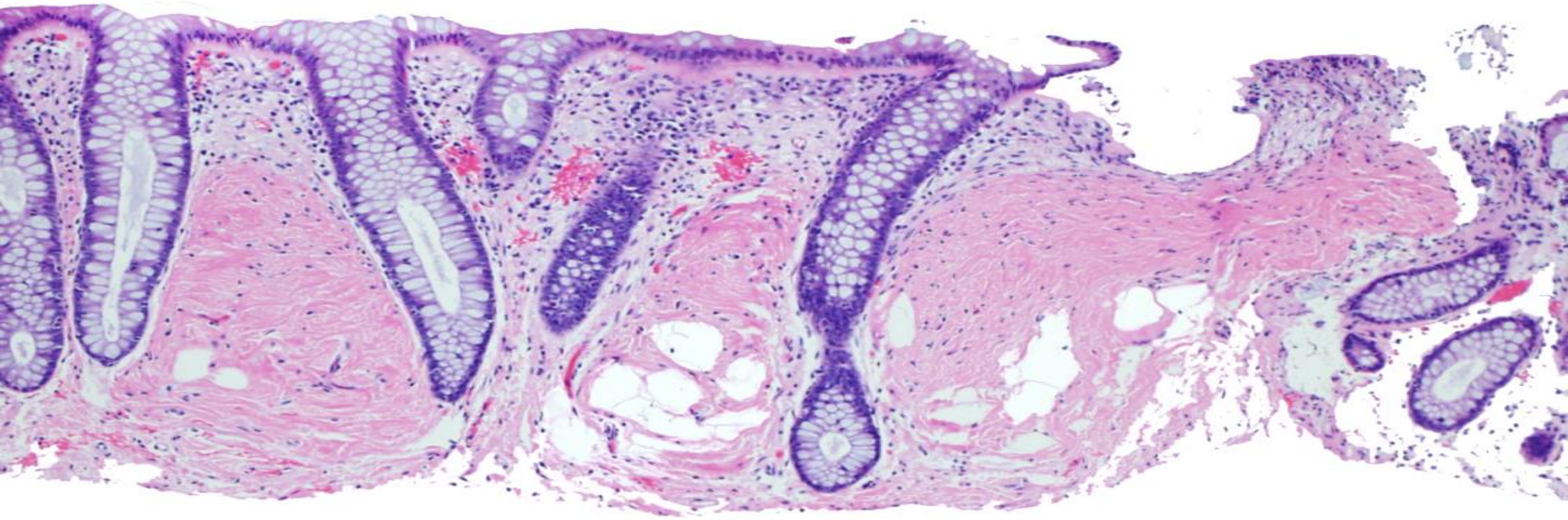
Intramucosal lipoma



Intramucosal lipoma



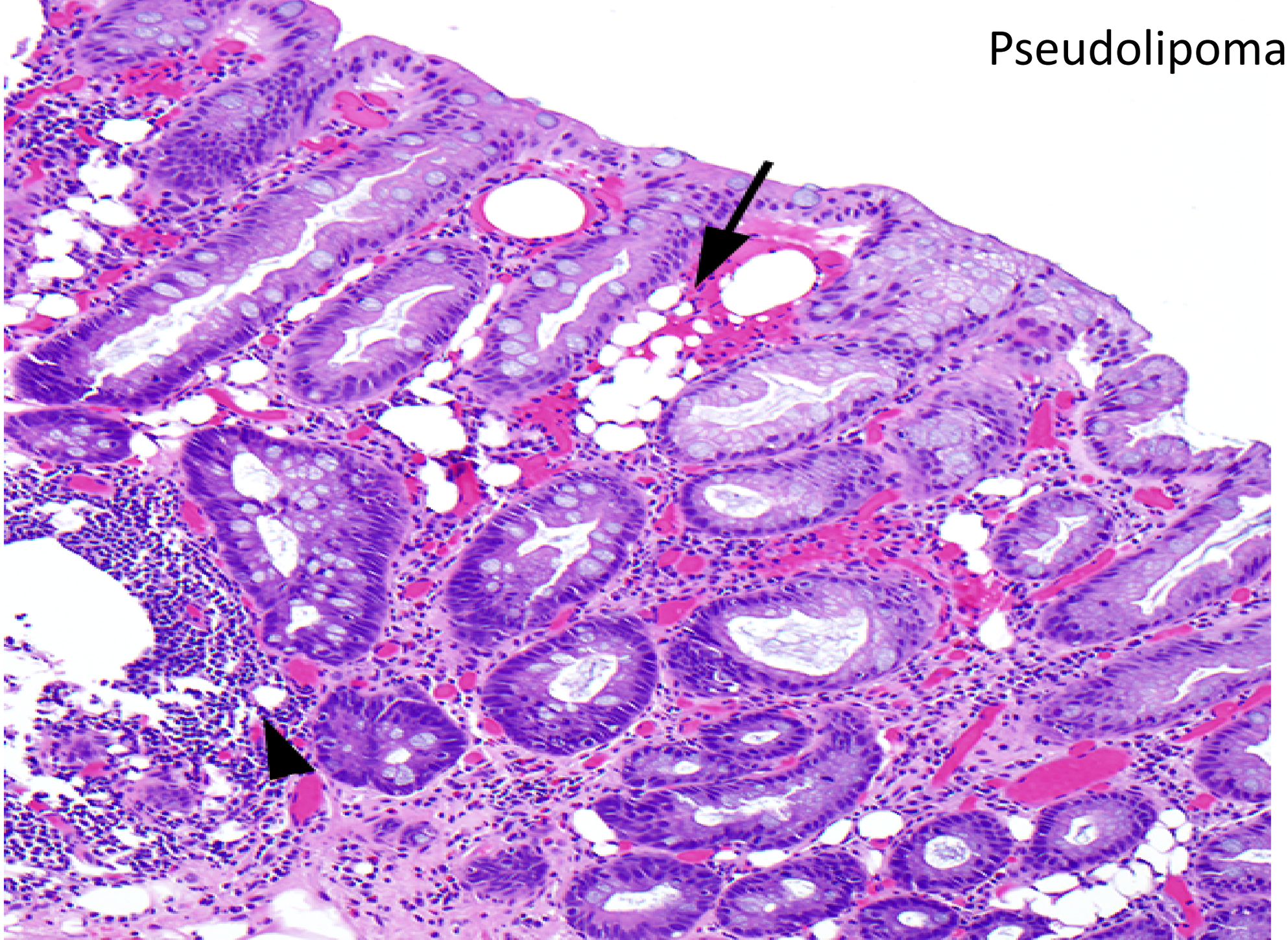
Intramucosal lipoma



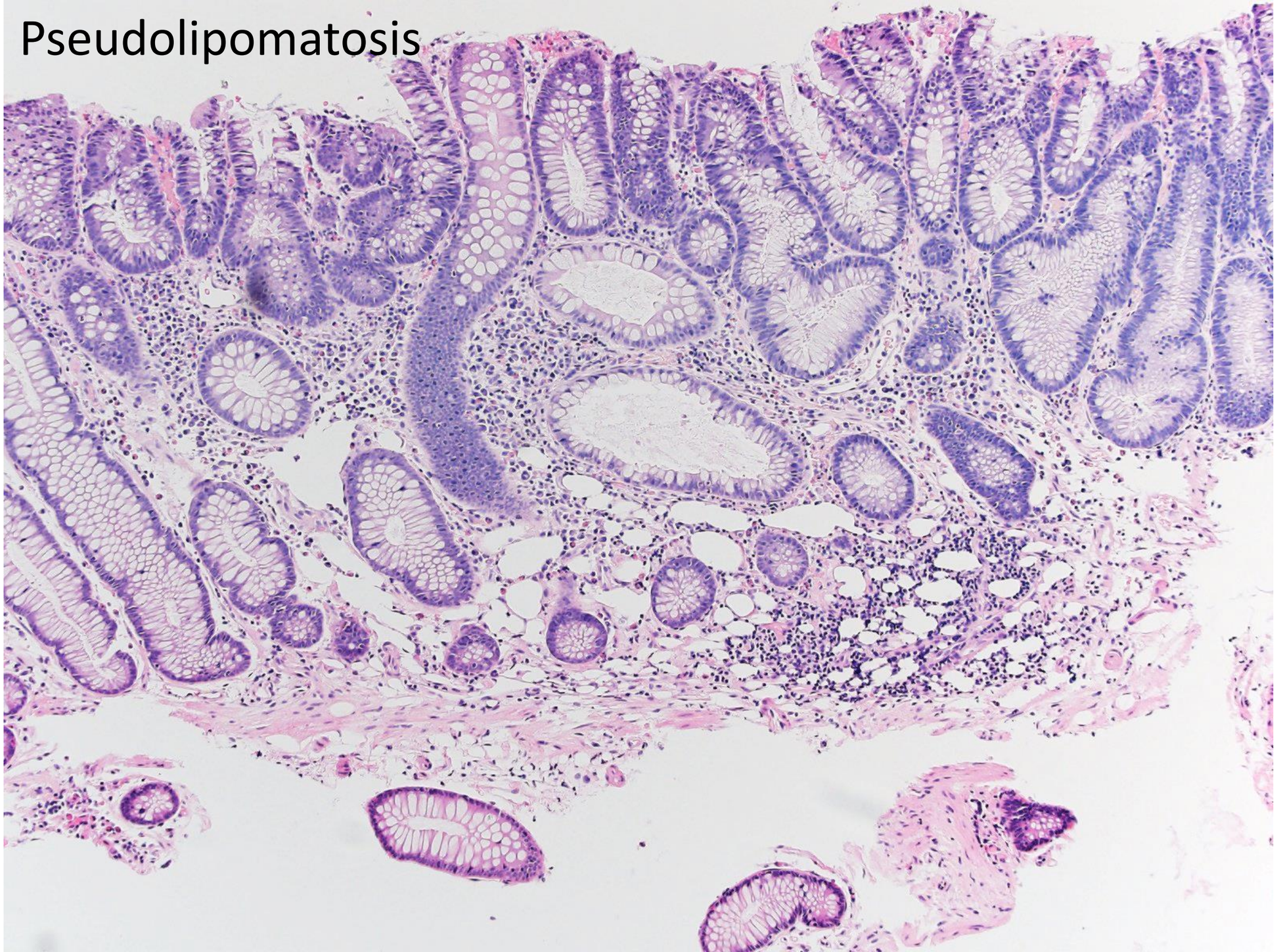
MIMICS OF INTRAMUCOSAL LIPOMA:

- PSEUDOLIPOMATOSIS
- TRICKY S100 INTERPRETATION

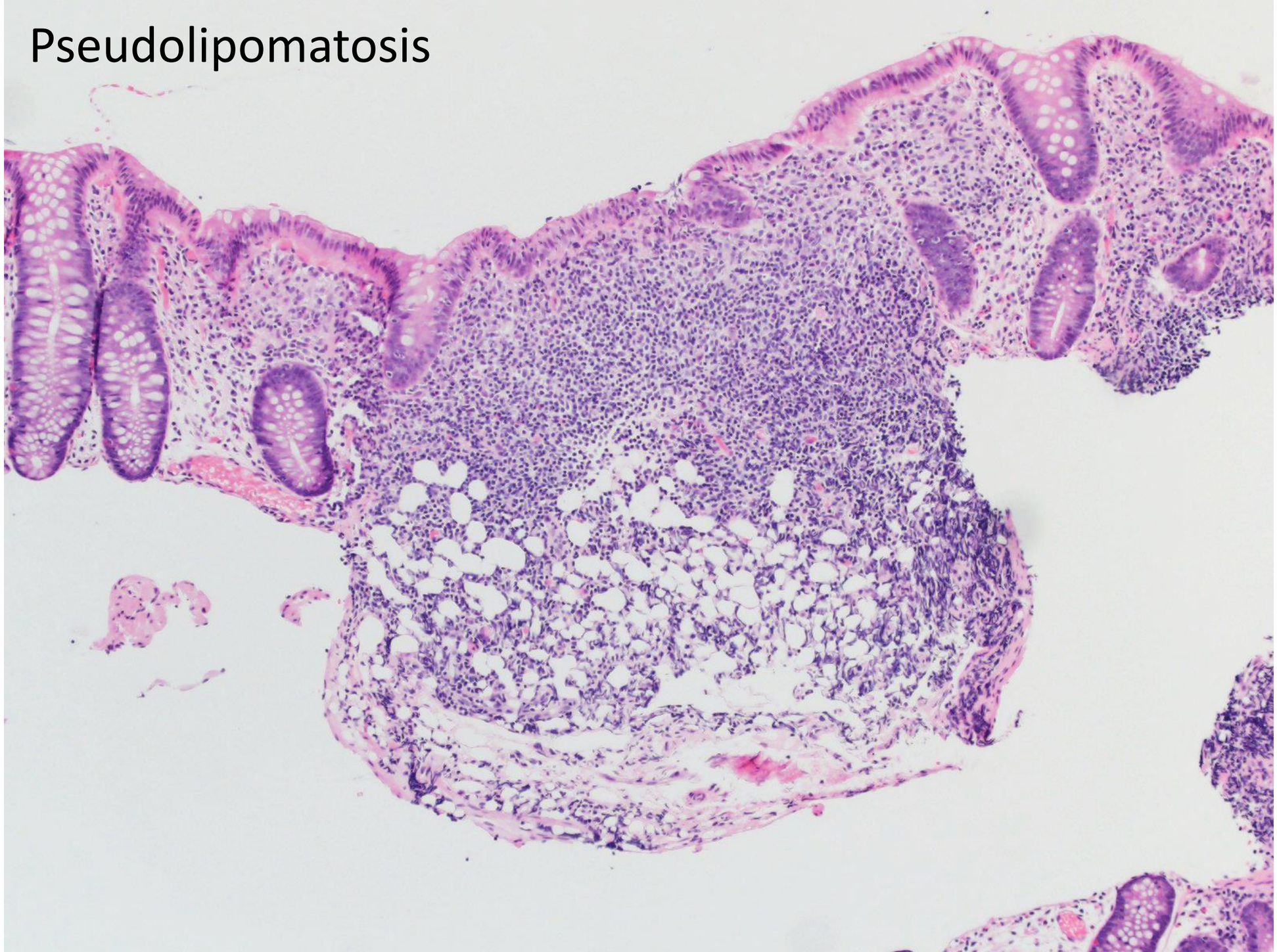
Pseudolipomatosis

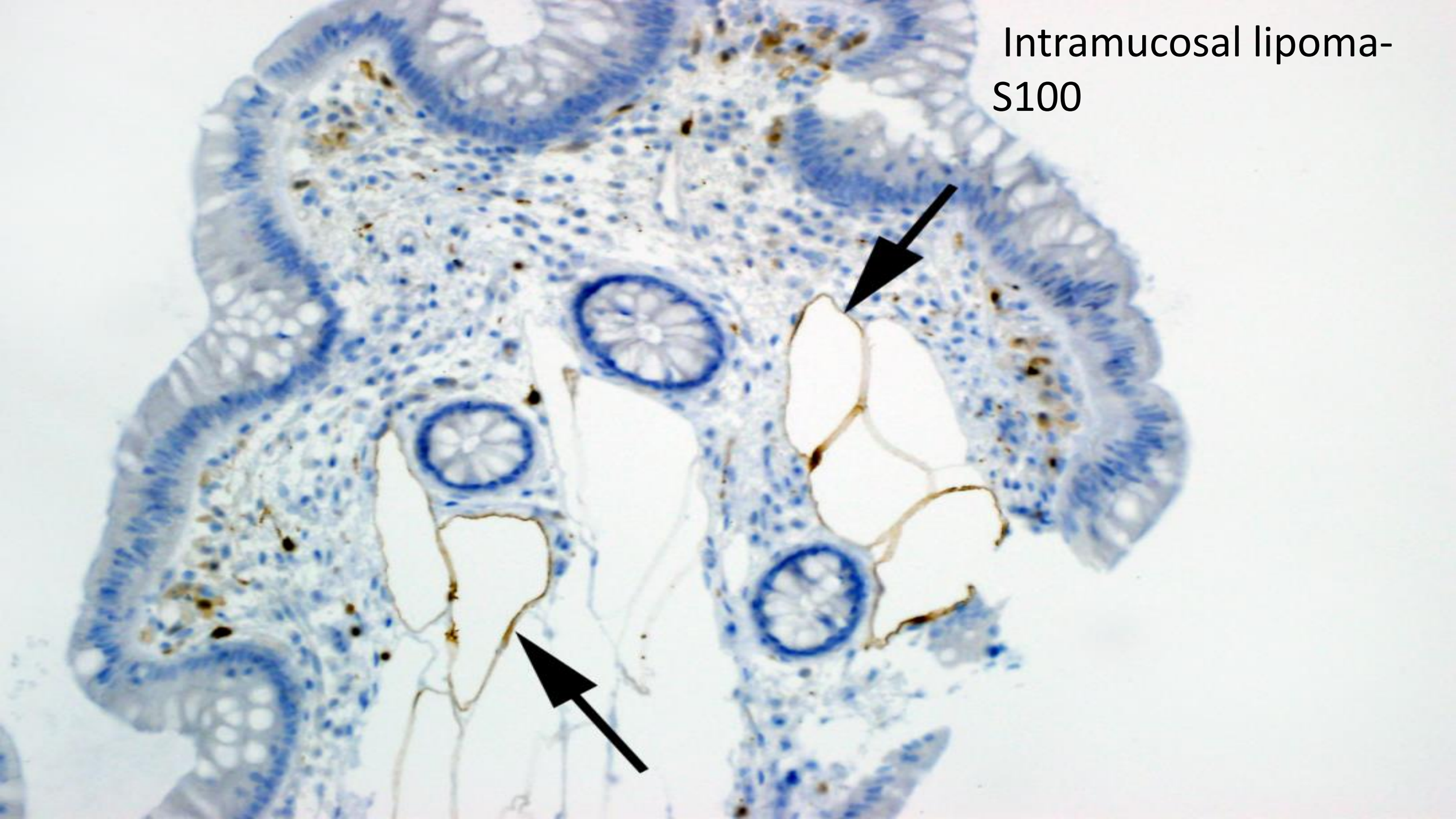


Pseudolipomatosis

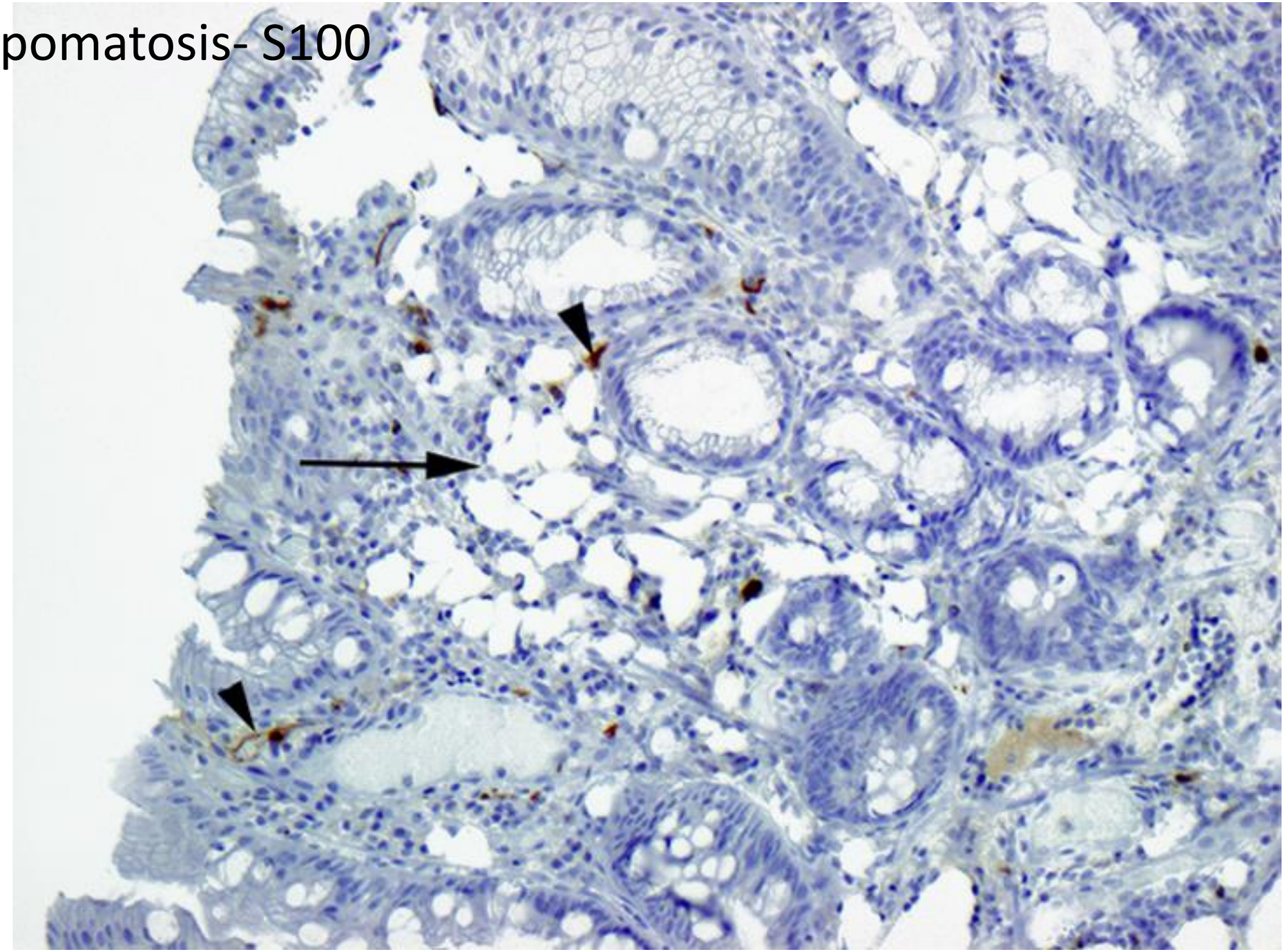


Pseudolipomatosis

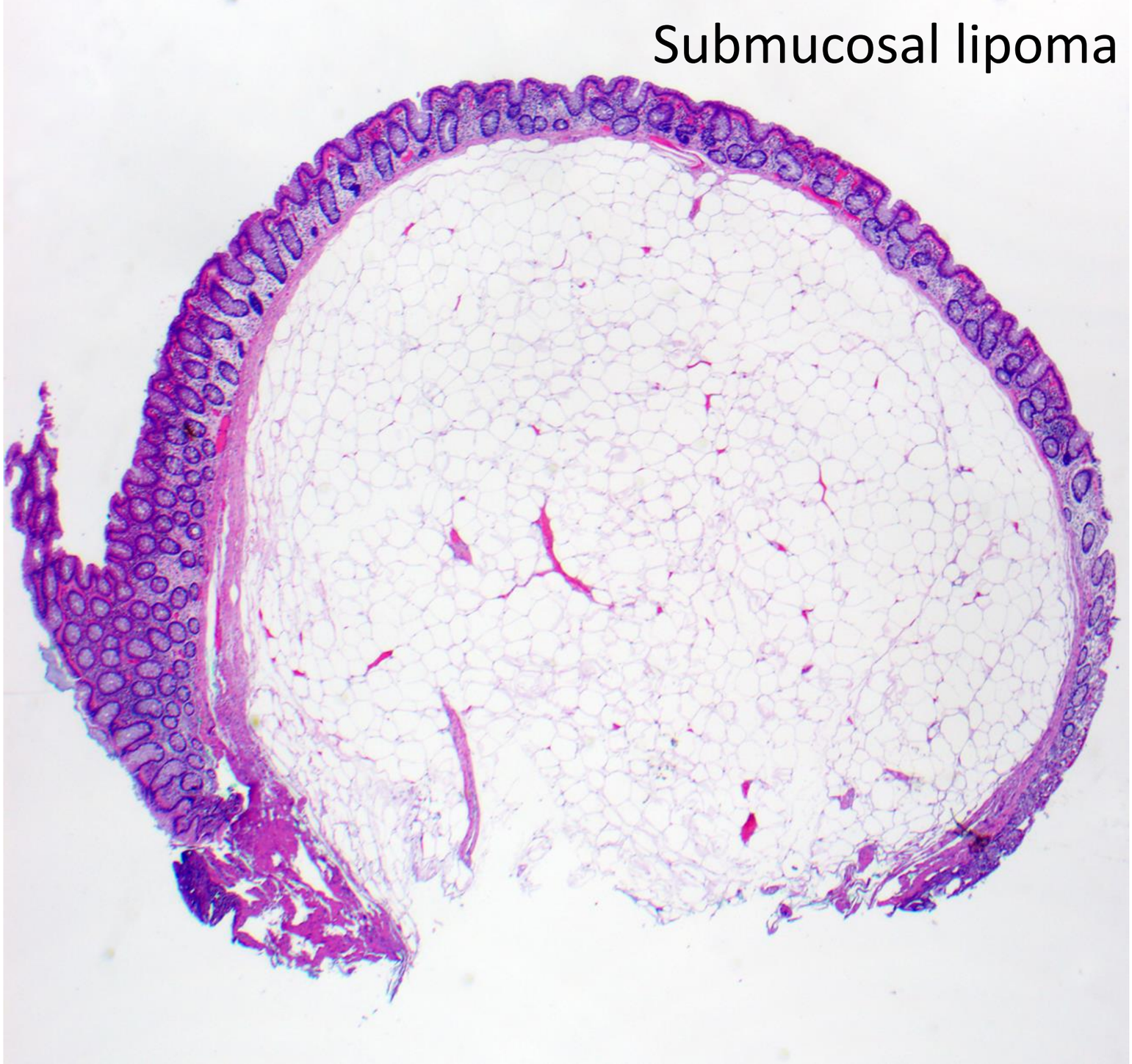



Intramucosal lipoma-
S100

Pseudolipomatosis- S100



Submucosal lipoma



COLONIC POLYPS IN COWDEN SYNDROME

- 90% have colonic polyps; 70% > 50 polyps = polyposis
- Inflammatory/juvenile-type polyps: ***most common*** (95%)
- Lymphoid polyps (63% of patients)
- Ganglioneuromas (53% of patients)
- Adenomas (53% of patients); HP's (32%)
- Intramucosal lipomas (25%)—only in Cowden's, not JP or PJS
- **Admixture** of typical adenomas/HPs + hamartomas
  - ***Highly characteristic of Cowden syndrome: 54-79% of Cowden patients***

Shaco-Levy R, et al. *J Clin Gastroenterol* 2017; Shaco-Levy R, et al. *Hum Pathol* 2016; Stanich PP, et al. *World J Gastroenterol* 2014

ADDITIONAL CASE: 57 YEAR OLD FEMALE

- History of endometrial adenocarcinoma
- Previous colonoscopy noted numerous "hyperplastic polyps"
- Screening colonoscopy
  - 28 polyps identified
  - Intramucosal lipoma
  - Inflammatory-type polyps, lymphoid aggregates
  - Referred to genetic counseling

ADDITIONAL CASE: 57 YEAR OLD FEMALE

- Further clinical examination revealed macrocephaly, multinodular goiter, mental health issues
- Genetic testing revealed a heterozygous pathogenic sequence change in PTEN (c.403A>G)
- Cowden's disease was confirmed based on colonoscopy findings, especially intramucosal lipoma

INTRAMUCOSAL LIPOMAS UNIV OF UT SERIES

IML Type	Number	%
Cowden	5	20%
Possible Cowden	3	12%
Sporadic	17	68%
Total	25	100%

Caveat: retrospective series of GI lipomas in which IML's were likely underdiagnosed; true prevalence of Cowden vs. Sporadic to be determined

ARUP LABORATORIES

Caliskan A, et al. *Mod Pathol*, 2017

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GI INTRAMUCOSAL LIPOMAS

- Subtle, easily overlooked, underdiagnosed?
  - Usually, we disregard "holes" in lamina propria as pseudolipomatosis
- Increased awareness by pathologists and gastroenterologists may be helpful in identifying these patients

Caliskan A, et al. *Mod Pathology*, 2017

PROBLEMS IN COWDEN DIAGNOSIS

- PTEN mutations diagnostic, BUT only 25-35%
  - Dx remains PHENOTYPIC in great majority
  - 55%-90% have affected parent or sibling
- Most phenotypes very common in general population
- Better phenotypic criteria highly sought after clinically: INTRAMUCOSAL LIPOMAS
- Referral to genetic counselors is helpful

SUMMARY

- Intramucosal Lipomas: Early data suggest
  - ~30% Cowden Syndrome
  - ~70% Sporadic
- Mimic: Pseudolipomatosis coli
  - Tiny holes in MALT, S100 Neg
- S100 confirms IML vs. pseudolipomatosis
  - Delicate staining, beware of dendritic cells

CANCER SCREENING- GI CANCERS

- Colon cancer- Colonoscopy screening begins at age 35.
- Earlier screening if symptomatic or an affected family member was diagnosed with CRC before age 40. If so, then screening starts 5 to 10 years earlier than the earliest diagnosis in the family.
- Upper GI screening- Initiate by 35 to 40 years.

Snover D, et al. WHO Classification of Tumors of the Digestive System IARC, Lyon, 2010

CANCER SCREENING- COLON CANCER

- Hamartomatous polyps are usually benign and unclear if they may proceed to dysplasia and cancer.
- Colonoscopy screening every 5 years or depending on number and type of polyps.
- Colectomy indicated when have cancer or high grade lesions.

Snover D, et al. WHO Classification of Tumors of the Digestive System IARC, Lyon, 2010

CANCER SCREENING- BREAST

- Breast exams starting age 25 (every 6-12 months) or 5 to 10 yrs before the earlier breast cancer diagnosis in the family.
- Annual mammogram, consider MRI- Starting 30 to 35 yr or 5-10 yr before cancer diagnosis in the family.
- Discuss option of prophylactic mastectomy.

CANCER SCREENING- ENDOMETRIAL

- No perfect screening.
- Watch for symptoms like abnormal bleeding.
- Consider annual random endometrial biopsies and/or USG starting age 30-35.
- Discuss option of prophylactic hysterectomy once child bearing has completed.

CANCER SCREENING- OTHER

- General- Annual physical exam starting age 18
- Thyroid- Annual thyroid exam and annual USG starting at the time of diagnosis of CS or by age 40.
- Renal USG starting age 40 and every 1-2 years.

VASCULAR ABNORMALITIS

- Brain tumors and vascular malformation affecting any organs are occasionally seen in CS.

- Risk of developing these conditions are not well defined.

ROLE OF GENETIC COUNSELING

- Refer for genetic counseling, family pedigree, clinical history
- Risk calculation for chance of PTEN mutation using Cleveland Clinic's calculator: http://www.lerner.ccf.org/gmi/ccscore/
- Genetic testing- single or multigene panel testing, full sequencing, gene deletion/duplication analysis.
- Discuss cancer risks and screening recommendations.

ROLE OF GENETIC COUNSELING

- Recommendation for genetic testing of family members.

- Provide resources:

a. Cowden's Syndrome Foundation (communities.msn.com/cowdensyndrome/supportinfo.msnw)

b. American Cancer Society (www.cancer.org)

c. The National Alliance of Breast Cancer Organizations (www.nabco.org)

THANK YOU