

# Hamartomatous polyps in Cowden Syndrome

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## - Special Features

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# 41 Patients Cowden/PTEN

- Endoscopies, Colonoscopies
- PTEN mutation status
- Extra-gastrointestinal manifestations
  
- Reviewed
  - Gastrointestinal findings
  - Immunohistochemistry

# PTEN Hamartoma Tumour Syndrome

- AD, ~1 in 20,000
- Multiple hamartomas
- Risk of cancer
- Most cases simplex
- PTEN mutation
- KLLN, SDHB, PIK3CA, AKT1, SEC23B



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## NCCN Guidelines Version 2.2019 Cowden Syndrome/PHTS

### REVISED PTEN HAMARTOMA TUMOR SYNDROME CLINICAL DIAGNOSTIC CRITERIA<sup>®</sup>

#### **MAJOR CRITERIA:**

- Breast cancer
- Endometrial cancer (epithelial)
- Thyroid cancer (follicular)
- GI hamartomas (including ganglioneuromas, but excluding hyperplastic polyps;  $\geq 3$ )
- Lhermitte-Duclos disease (adult)
- Macrocephaly ( $\geq 97$ th percentile: 58 cm for females, 60 cm for males)
- Macular pigmentation of the glans penis
- Multiple mucocutaneous lesions (any of the following):
  - ▶ Multiple trichilemmomas ( $\geq 3$ , at least one biopsy proven)
  - ▶ Acral keratoses ( $\geq 3$  palmoplantar keratotic pits and/or acral hyperkeratotic papules)
  - ▶ Mucocutaneous neuromas ( $\geq 3$ )
  - ▶ Oral papillomas (particularly on tongue and gingiva), multiple ( $\geq 3$ ) OR biopsy proven OR dermatologist diagnosed

#### **MINOR CRITERIA:**

- Autism spectrum disorder
- Colon cancer
- Esophageal glycogenic acanthoses ( $\geq 3$ )
- Lipomas ( $\geq 3$ )
- Intellectual disability (ie, IQ  $\leq 75$ )
- Renal cell carcinoma
- Testicular lipomatosis
- Thyroid cancer (papillary or follicular variant of papillary)
- Thyroid structural lesions (eg, adenoma, multinodular goiter)
- Vascular anomalies (including multiple intracranial developmental venous anomalies)

#### **Operational diagnosis in an individual (either of the following):**

1. Three or more major criteria, but one must include macrocephaly, Lhermitte-Duclos disease, or GI hamartomas; or
2. Two major and three minor criteria.

#### **Operational diagnosis in a family where one individual meets revised PTEN hamartoma tumor syndrome clinical diagnostic criteria or has a *PTEN* pathogenic/likely pathogenic variant:**

1. Any two major criteria with or without minor criteria; or
2. One major and two minor criteria; or
3. Three minor criteria.

## COWDEN SYNDROME/PHTS MANAGEMENT

**WOMEN**

- Breast awareness<sup>1</sup> starting at age 18 y.
- Clinical breast exam, every 6–12 mo, starting at age 25 y or 5–10 y before the earliest known breast cancer in the family (whichever comes first).
- Breast screening
  - ▶ Annual mammography with consideration of tomosynthesis and breast MRI screening with contrast starting at age 30–35 y or 5–10 y before the earliest known breast cancer in the family (whichever comes first).<sup>2,3</sup>
  - ▶ Age >75 y, management should be considered on an individual basis.
  - ▶ For women with a *PTEN* pathogenic/likely pathogenic variant who are treated for breast cancer, and have not had a bilateral mastectomy, screening with annual mammogram and breast MRI should continue as described above.
- Discuss option of risk-reducing mastectomy
  - ▶ Counseling should include a discussion regarding degree of protection, reconstruction options, and risks. In addition, the family history and residual breast cancer risk with age and life expectancy should be considered during counseling.
- Endometrial cancer screening<sup>4</sup>
  - ▶ Encourage patient education and prompt response to symptoms (eg, abnormal bleeding). Patients are encouraged to keep a calendar in order to identify irregularities in their menstrual cycle.
  - ▶ Because endometrial cancer can often be detected early based on symptoms, women should be educated regarding the importance of prompt reporting and evaluation of any abnormal uterine bleeding or postmenopausal bleeding. The evaluation of these symptoms should include endometrial biopsy.
  - ▶ Endometrial cancer screening does not have proven benefit in women with CS/PHTS. However, endometrial biopsy is both highly sensitive and highly specific as a diagnostic procedure. Screening via endometrial biopsy every 1 to 2 years can be considered.
  - ▶ Transvaginal ultrasound to screen for endometrial cancer in postmenopausal women has not been shown to be sufficiently sensitive or specific as to support a positive recommendation, but may be considered at the clinician's discretion. Transvaginal ultrasound is not recommended as a screening tool in premenopausal women due to the wide range of endometrial stripe thickness throughout the normal menstrual cycle.
- Discuss option of hysterectomy<sup>5</sup> upon completion of childbearing and counsel regarding degree of protection, extent of cancer risk, and reproductive desires.
- Address psychosocial, social, and quality-of-life aspects of undergoing risk-reducing mastectomy and/or hysterectomy.

**MEN AND WOMEN**

- Annual comprehensive physical exam starting at age 18 y or 5 y before the youngest age of diagnosis of a component cancer in the family (whichever comes first), with particular attention to thyroid exam.
- Annual thyroid ultrasound starting at time of CS/PHTS diagnosis, including in childhood.
- Colonoscopy, starting at age 35 y unless symptomatic or if close relative with colon cancer before age 40 y, then start 5–10 y before the earliest known colon cancer in the family. Colonoscopy should be done every 5 y or more frequently if patient is symptomatic or polyps are found.
- Consider renal ultrasound starting at age 40 y, then every 1–2 y.
- Dermatologic management may be indicated for some patients.
- Consider psychomotor assessment in children at diagnosis and brain MRI if there are symptoms.
- Education regarding the signs and symptoms of cancer.

**RISK TO RELATIVES**

- Advise about possible inherited cancer risk to relatives, options for risk assessment, and management.
- Recommend genetic counseling and consideration of genetic testing for at-risk relatives.

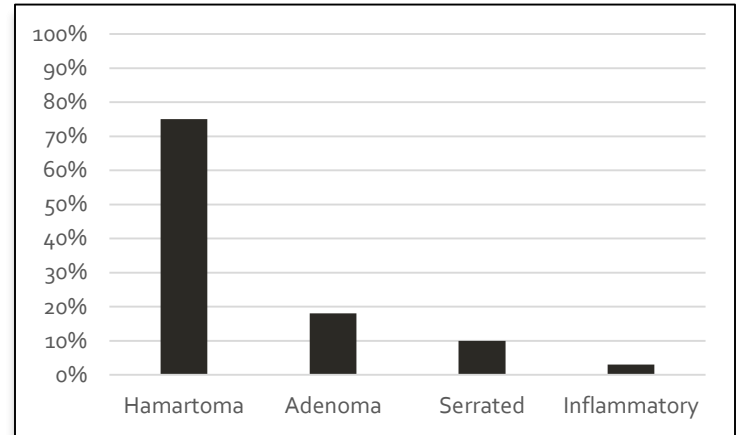
**REPRODUCTIVE OPTIONS**

- For women of reproductive age, advise about options for prenatal diagnosis and assisted reproduction including pre-implantation genetic diagnosis. Discussion should include known risks, limitations, and benefits of these technologies. [See Discussion](#) for details.

- Breast cancer 9 (22%)  
Age 20-81
- Follicular thyroid cancer (2)  
Age 42 and 81
- Endometrial cancer (3)  
Age 32, 47, and 65

# Index Colonoscopy

- 30 (75%) Hamartomatous polyp
- 7 Adenoma
- 4 Serrated
- 1 Inflammatory
  
- Mix of polyp types in 13 (33%)
  
- Hamartoma numbers 1-20, average 4.4



# Surveillance Colonoscopies

- 34 (85%) Hamartomas
- Mix of polyp types 26 (65%)

# Upper Gastrointestinal findings

- 21 patients had upper endoscopies

- Most common findings

Hamartomatous polyps 14 (67%) including 3 ganglioneuromas

Glycogenic acanthosis 11 (52%)

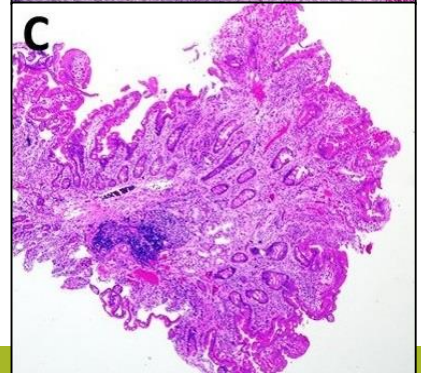
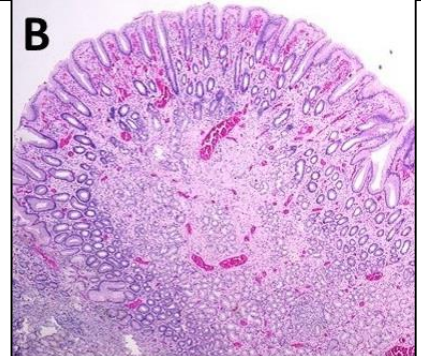
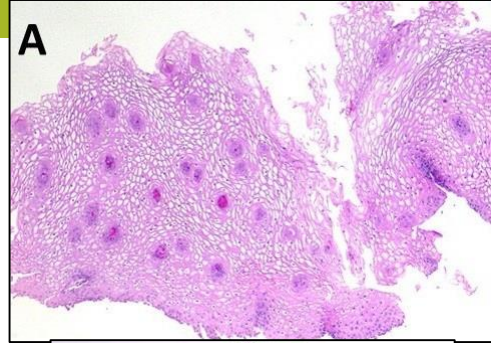
Fundic gland polyp 6

Gastric heterotopia 4

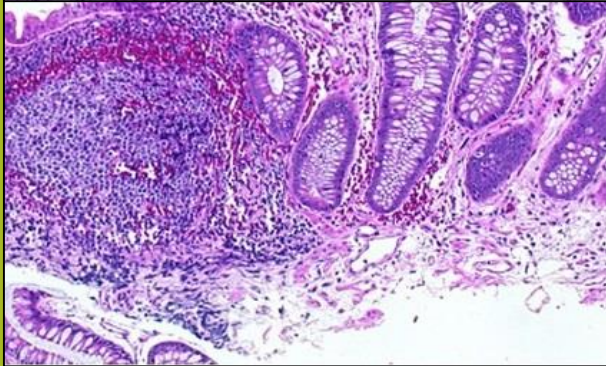
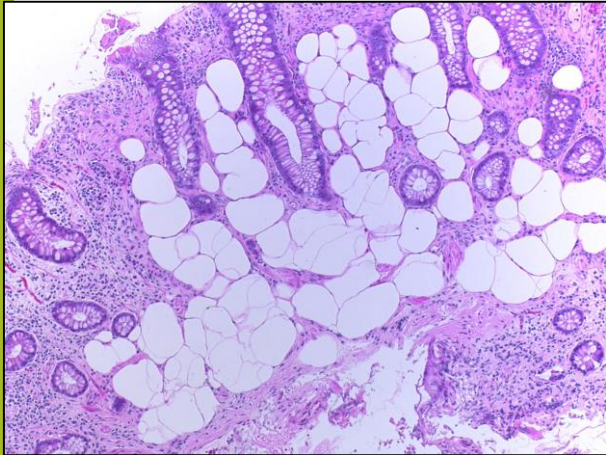
Foveolar hyperplasia 3

Adenomas 2

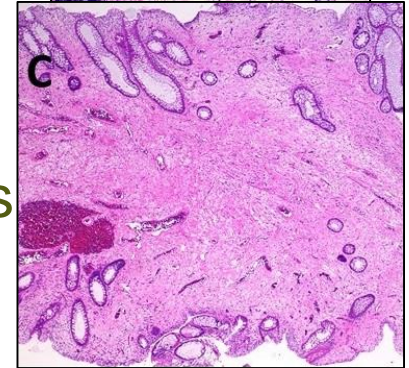
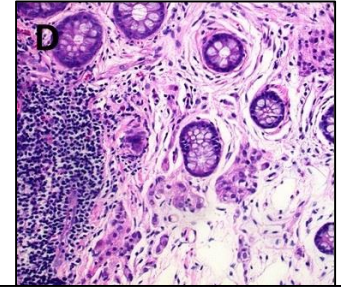
Inflammatory polyps 2



# Special Features of Hamartomatous polyps

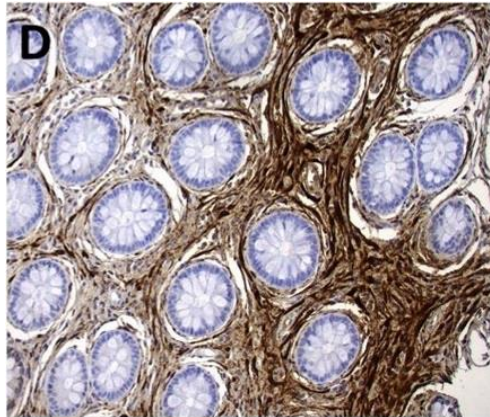
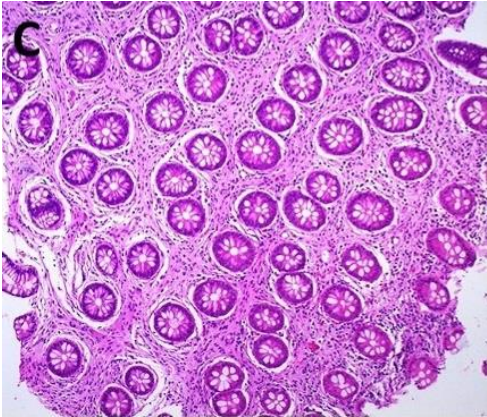
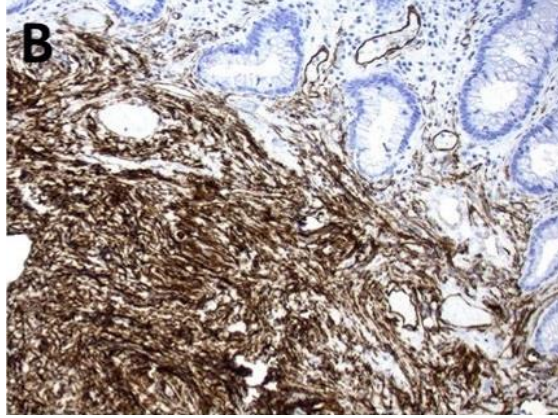
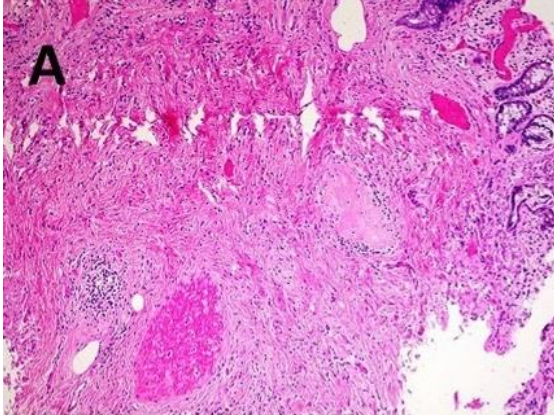


- 16 (53%) at index
- 28 (93%) overall
- Lymphoid follicles
- Intramucosal adipose tissue
- Ganglioneuromatous elements
- Fibrous stroma



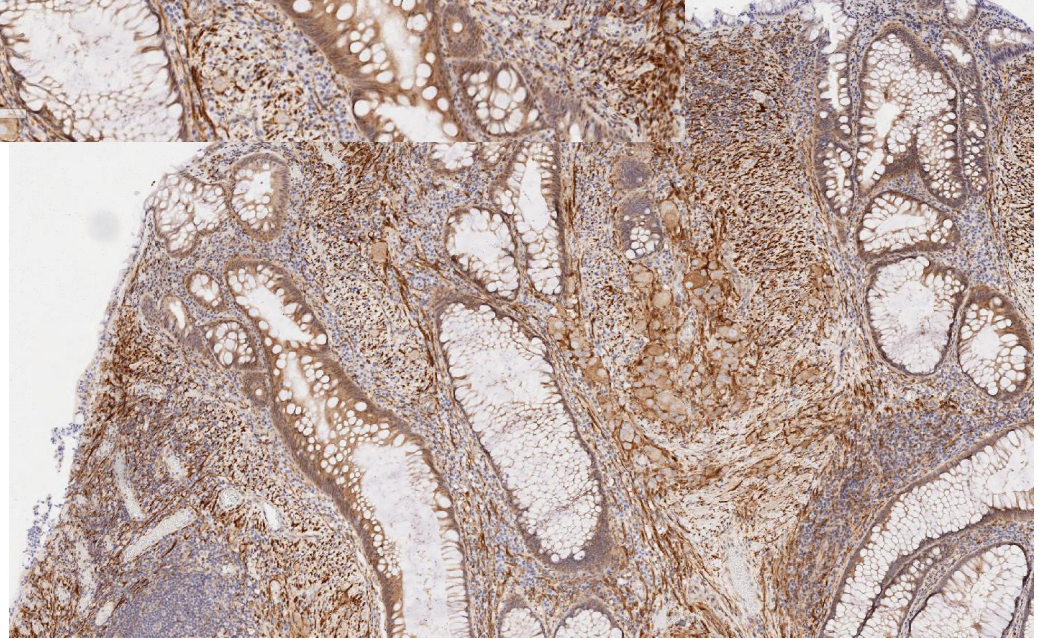
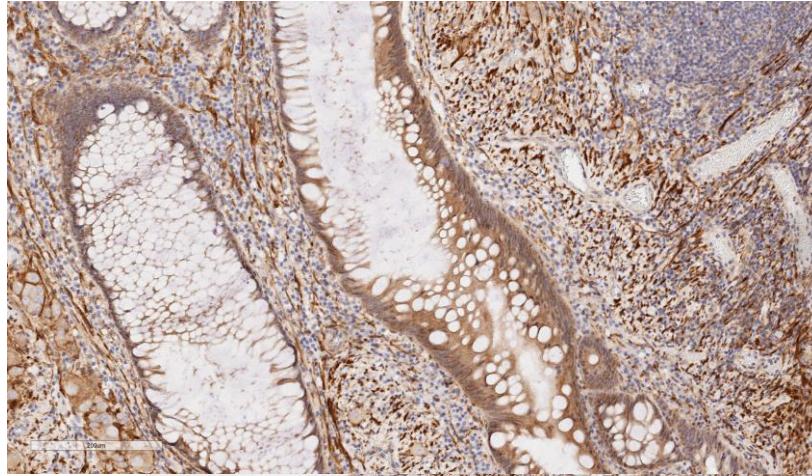
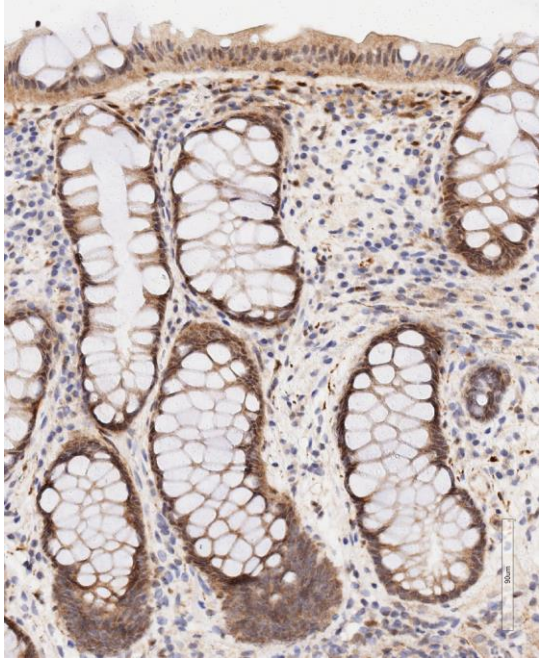


# IHC Hamartomas with no Special Features

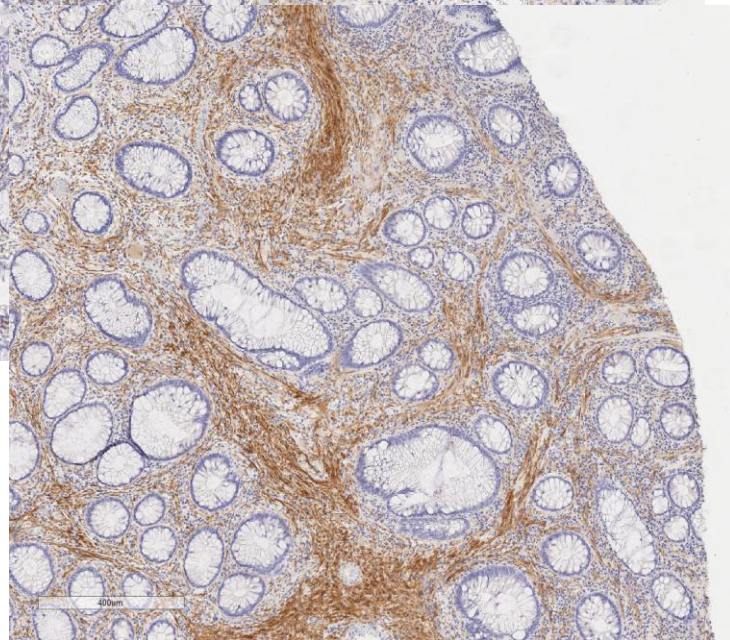
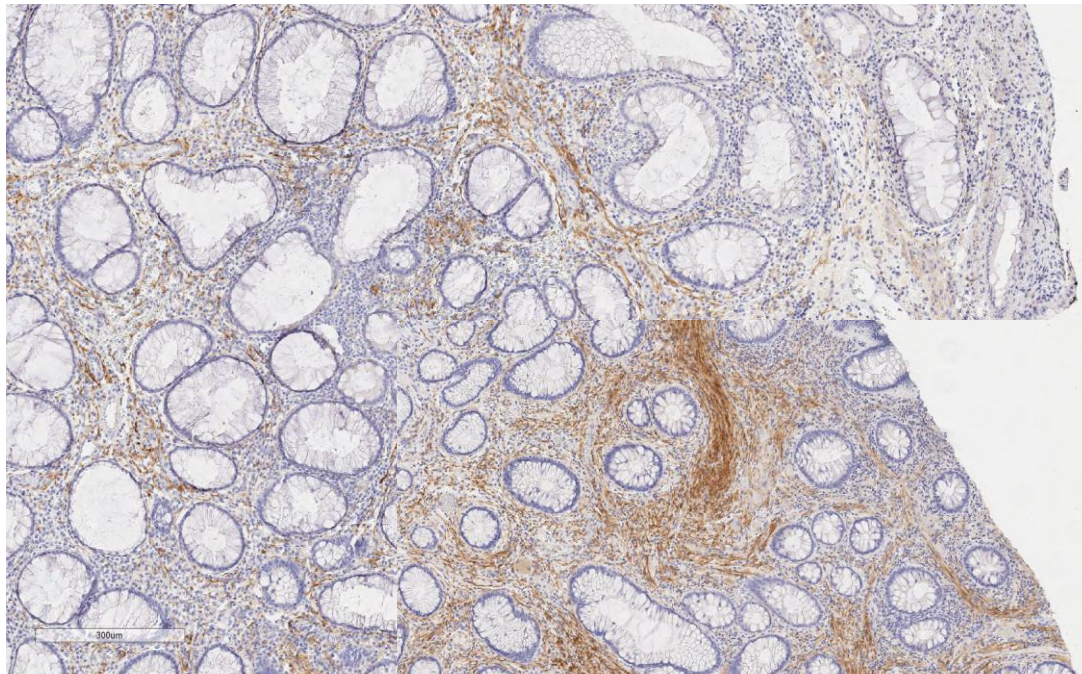
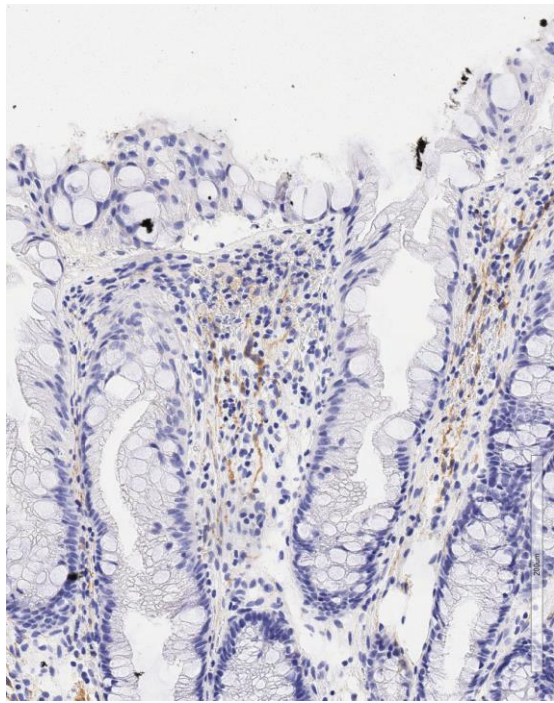


- 12 cases
- CD34 expressed in base of polyp in 9 cases
- S100 highlighted neurites in 8 cases

# PTEN IHC



# PD-L1 IHC



# Things to look out for

- Hamartomas in the colon but also a mixture of polyps
- Upper GI findings
- Special features in Hamartomatous polyps
- Immunohistochemistry may highlight fibrous stroma or neurites