Mesenchymal Tumours of the Upper GI Tract

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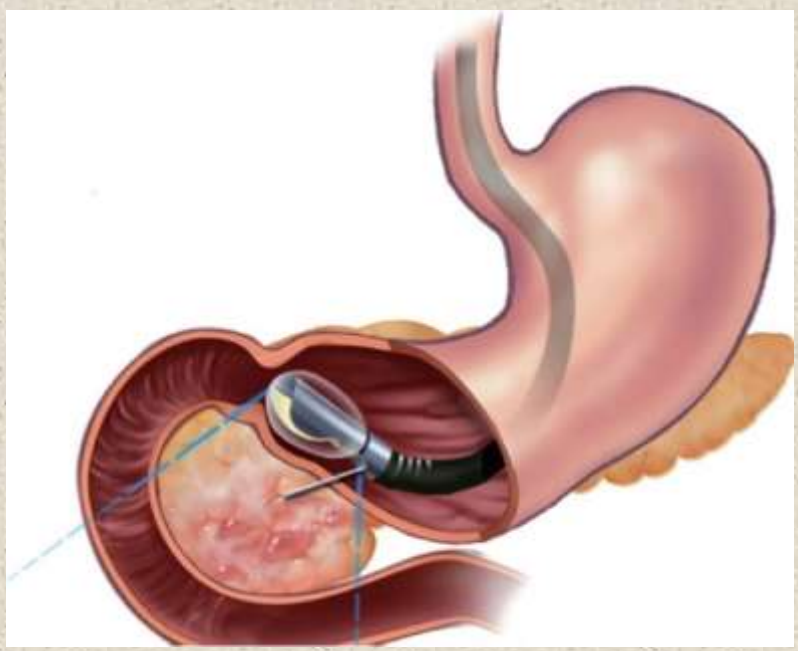
What I'll do

- Minimise listing
- Anatomical divisions – how distally?
- **Updates and practical pointers**
- EUS-FNA (EUS-biopsy)



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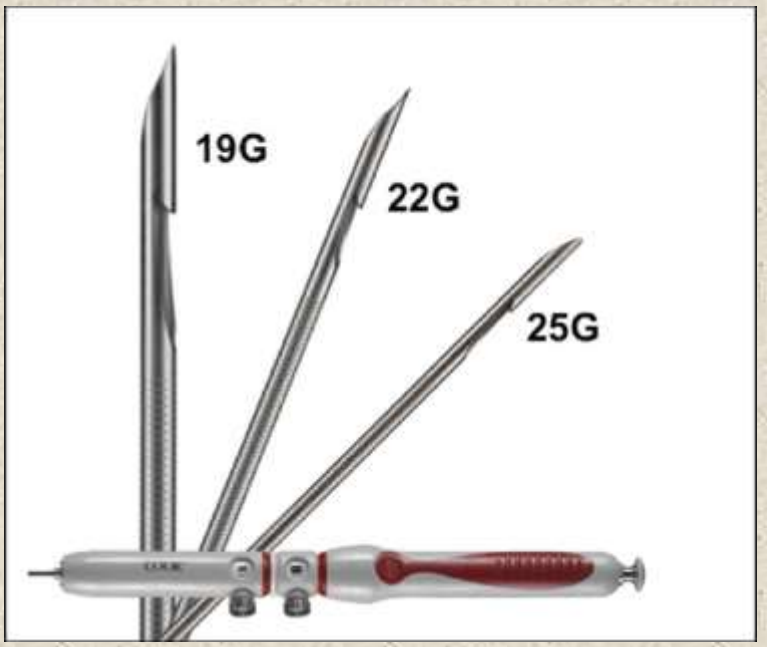
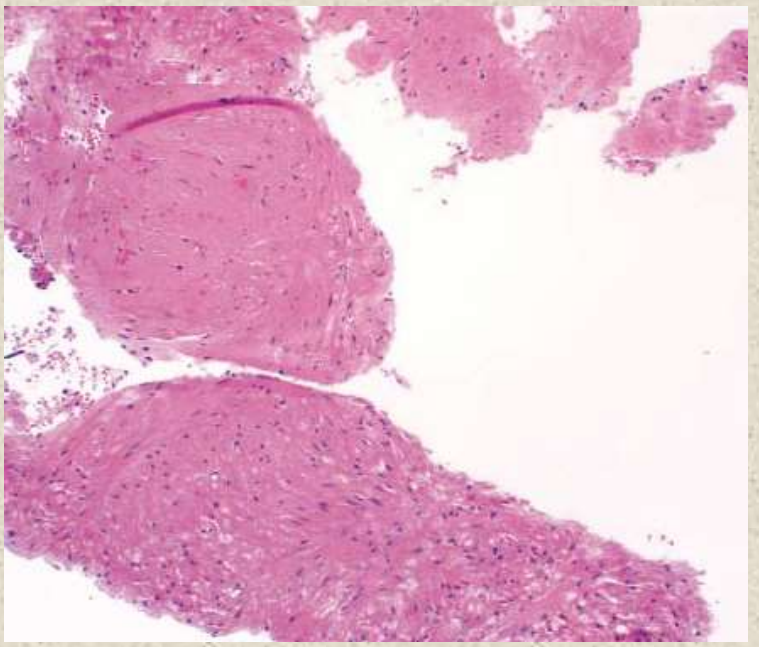


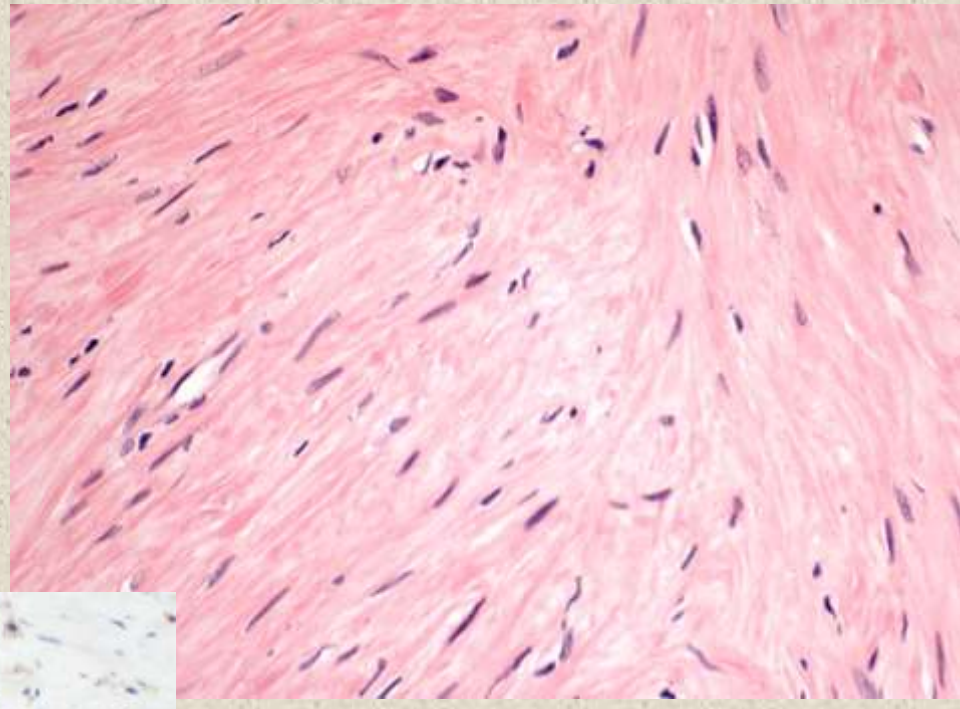


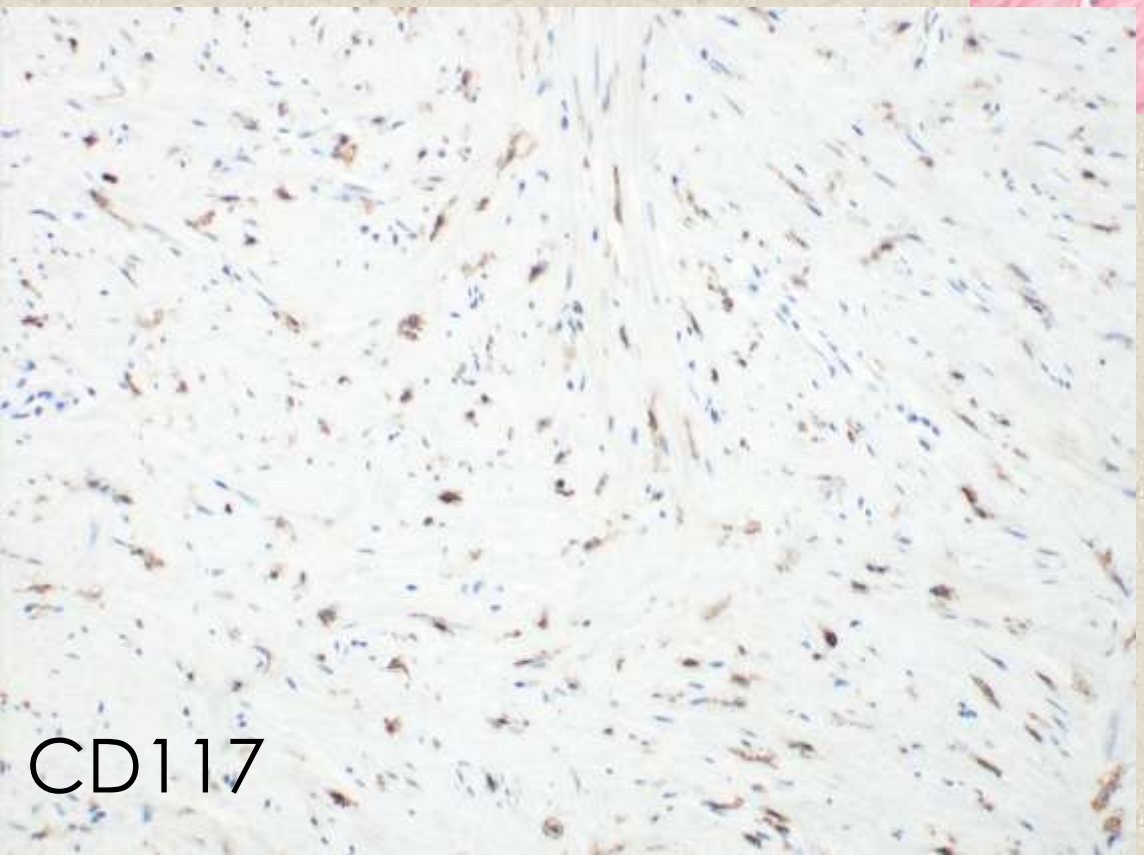
Oesophagus

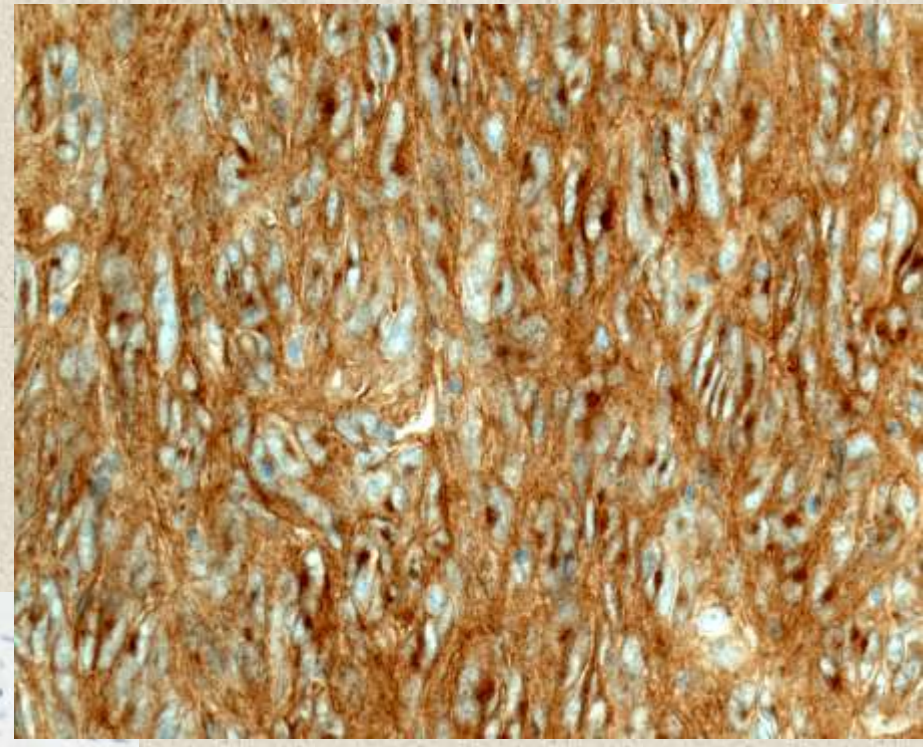
- Smooth muscle tumour (>> GIST)
- Sarcomatoid carcinoma
- *******

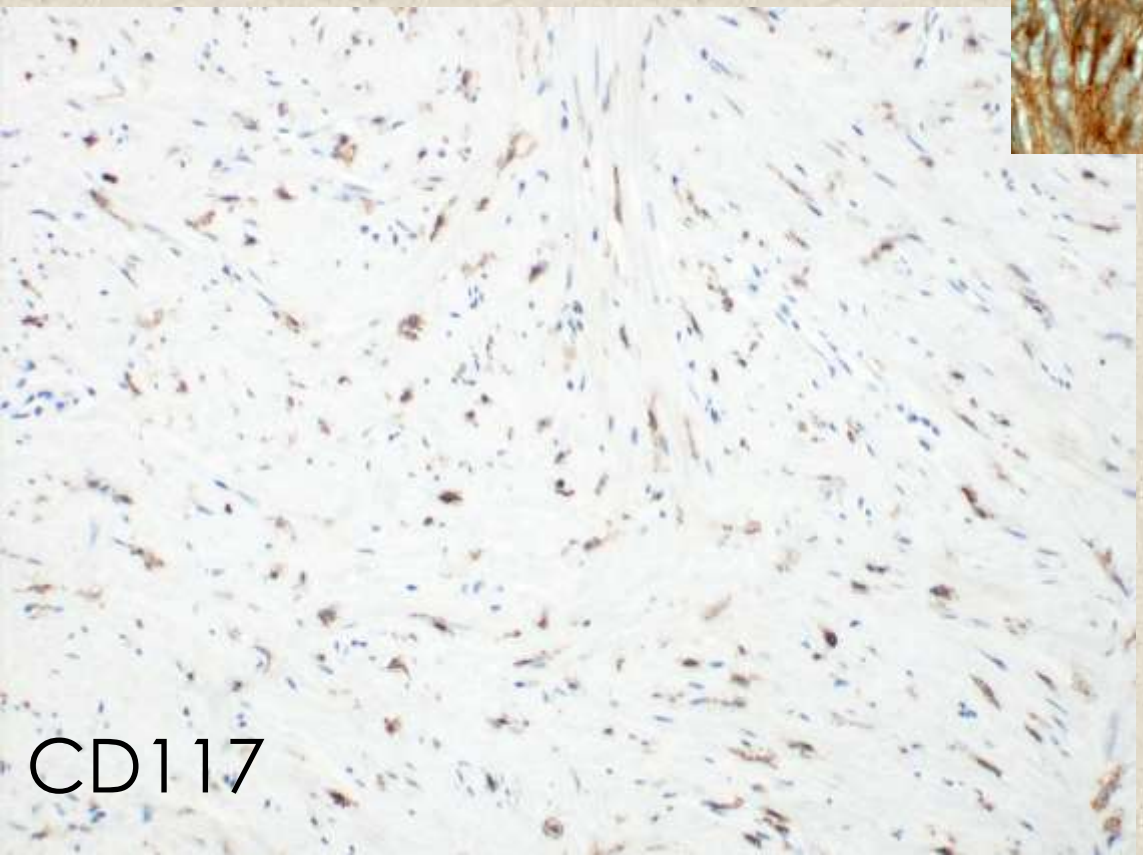
Smooth muscle neoplasms

- Why distinguish from GIST?
  - Excision?
  - Imatinib?
- Immunohistochemistry
  - Beware ICCs
  - Other smooth muscle markers




CD117





CD117

Smooth muscle IHC markers

- Desmin and caldesmon

Smooth muscle IHC markers

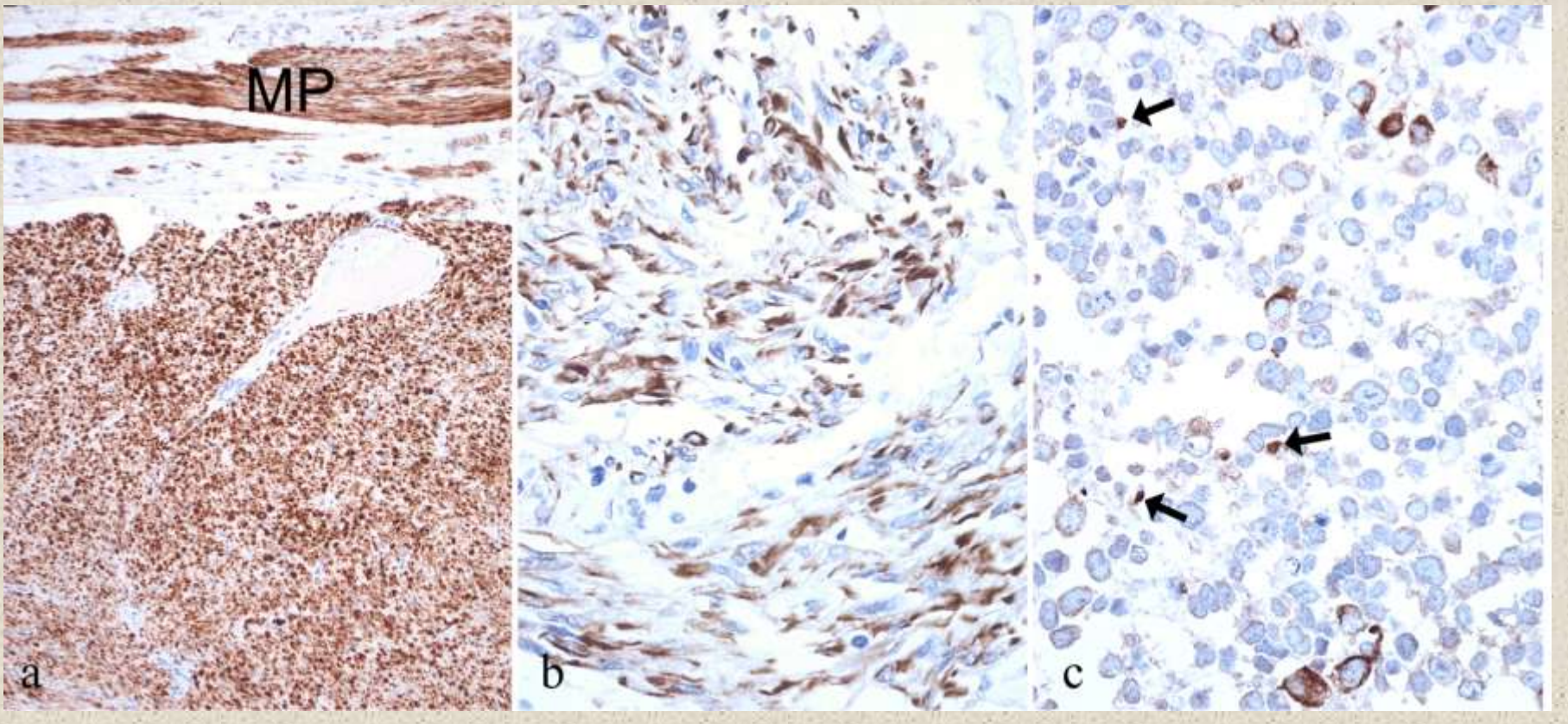
- Desmin and caldesmon
- But PLAP and smoothelin are more specific.

A study of α5 chain of collagen IV, caldesmon, placental alkaline phosphatase and smoothelin as immunohistochemical markers of gastrointestinal smooth muscle neoplasms

Newton ACS Wong, Jenny Wingate, Richard Colling

Wong NACS, *et al*. *J Clin Pathol* 2014;**67**:105–111. doi:10.1136/jclinpath-2013-201797

PLAP IHC - 16 neoplasm types



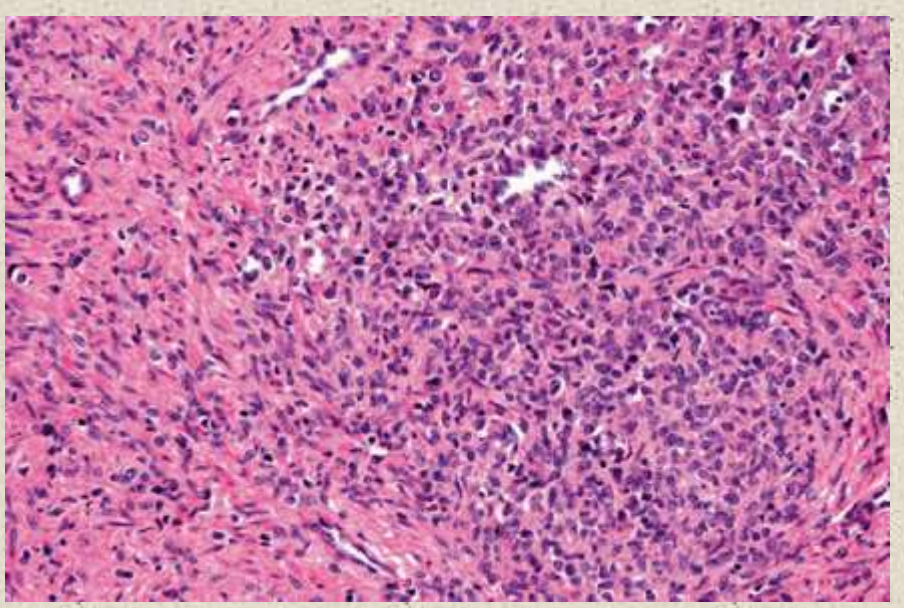
Leiomyoma:	27/27
Leiomyosarcomas:	4/4 (focally reduced)
Angiomyolipoma:	1/5
DSCRT:	1/1

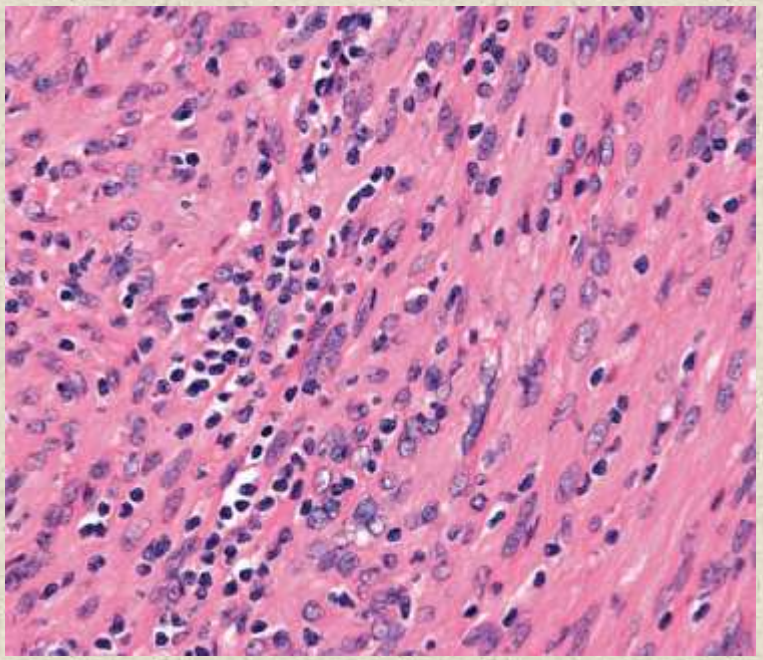
Smooth muscle IHC markers

- Sensitivity: 100% for all three markers
- Specificity:
  - Caldesmon 80%
  - **PLAP** 96%
  - Smoothelin 91%

Smooth muscle neoplasms

- In HIV/AIDS patients, EBV driven smooth muscle neoplasms:
  - less pleomorphism
  - low mitotic count





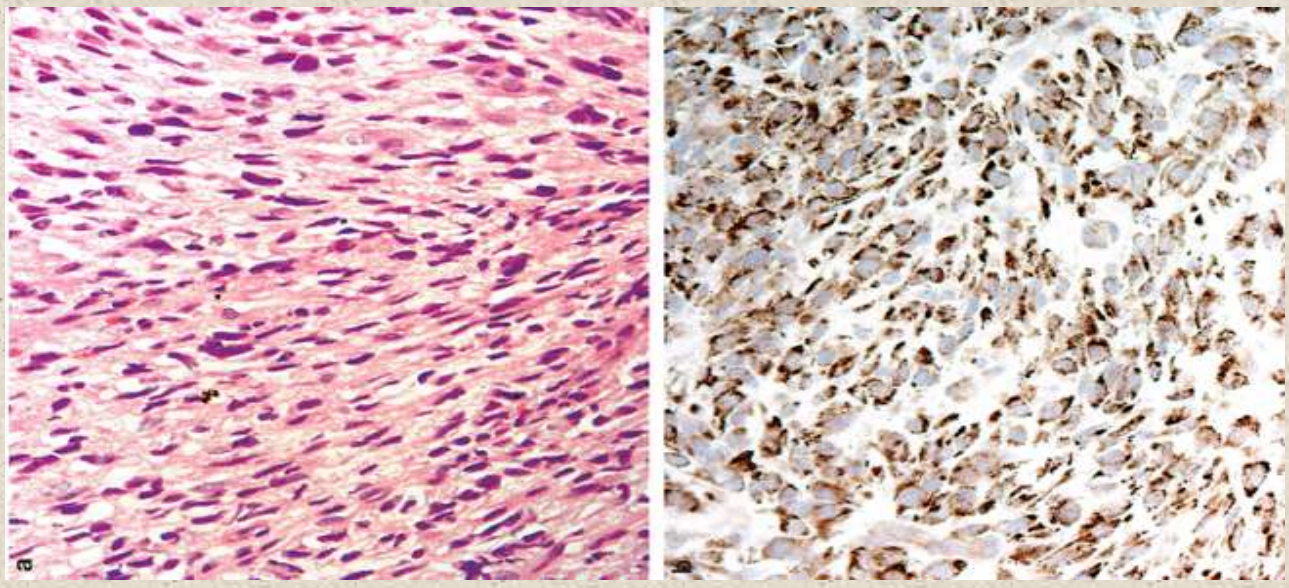
Sarcomatoid carcinoma

- **May express DOG1 and/or CD117**

Histopathology. 2004 Jan;44(1):77-80.

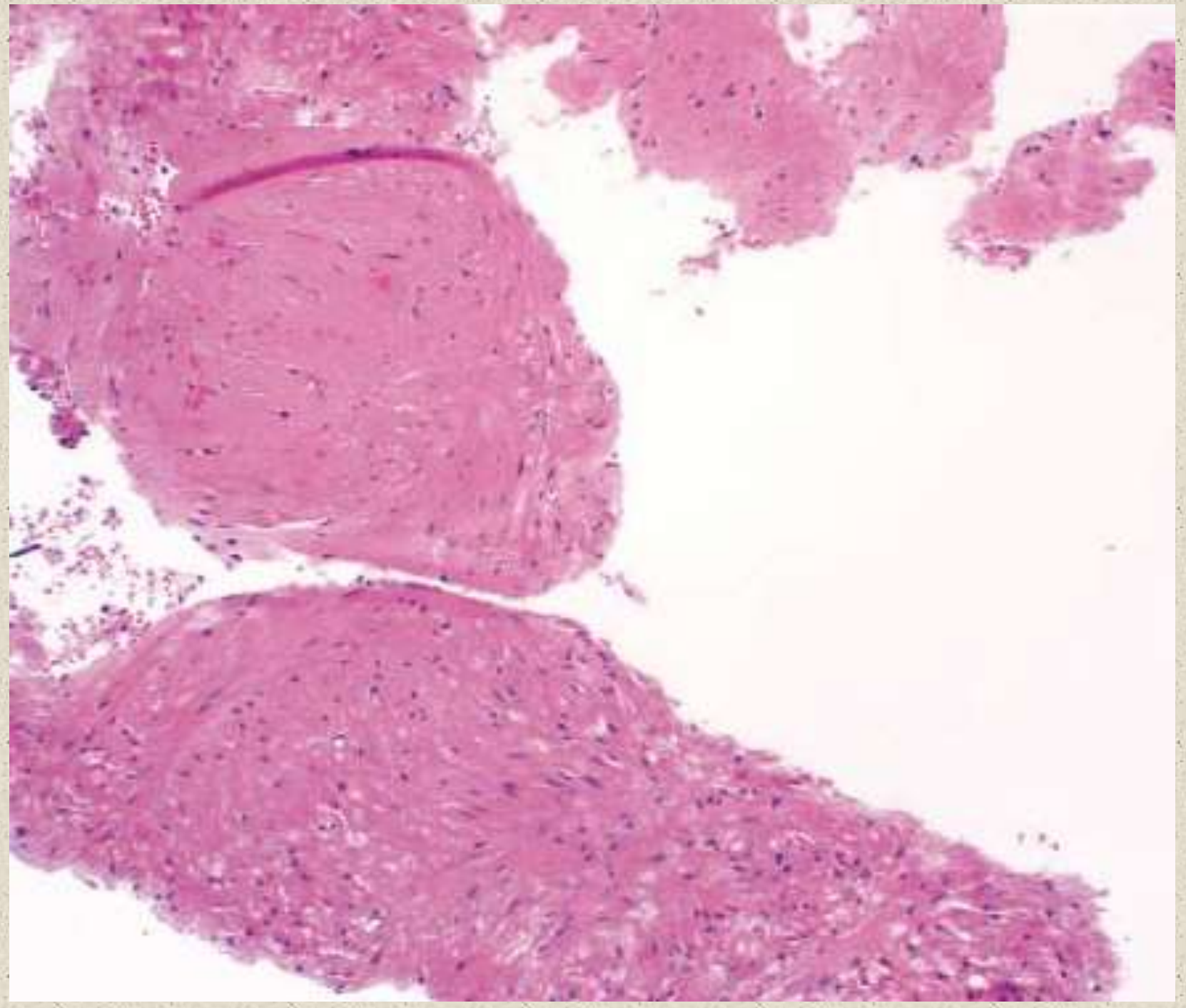
CD117 expression in oesophageal carcinosarcoma: a potential diagnostic pitfall.

Martland GT[1], Goodman AJ, Shepherd NA.



EUS-biopsy

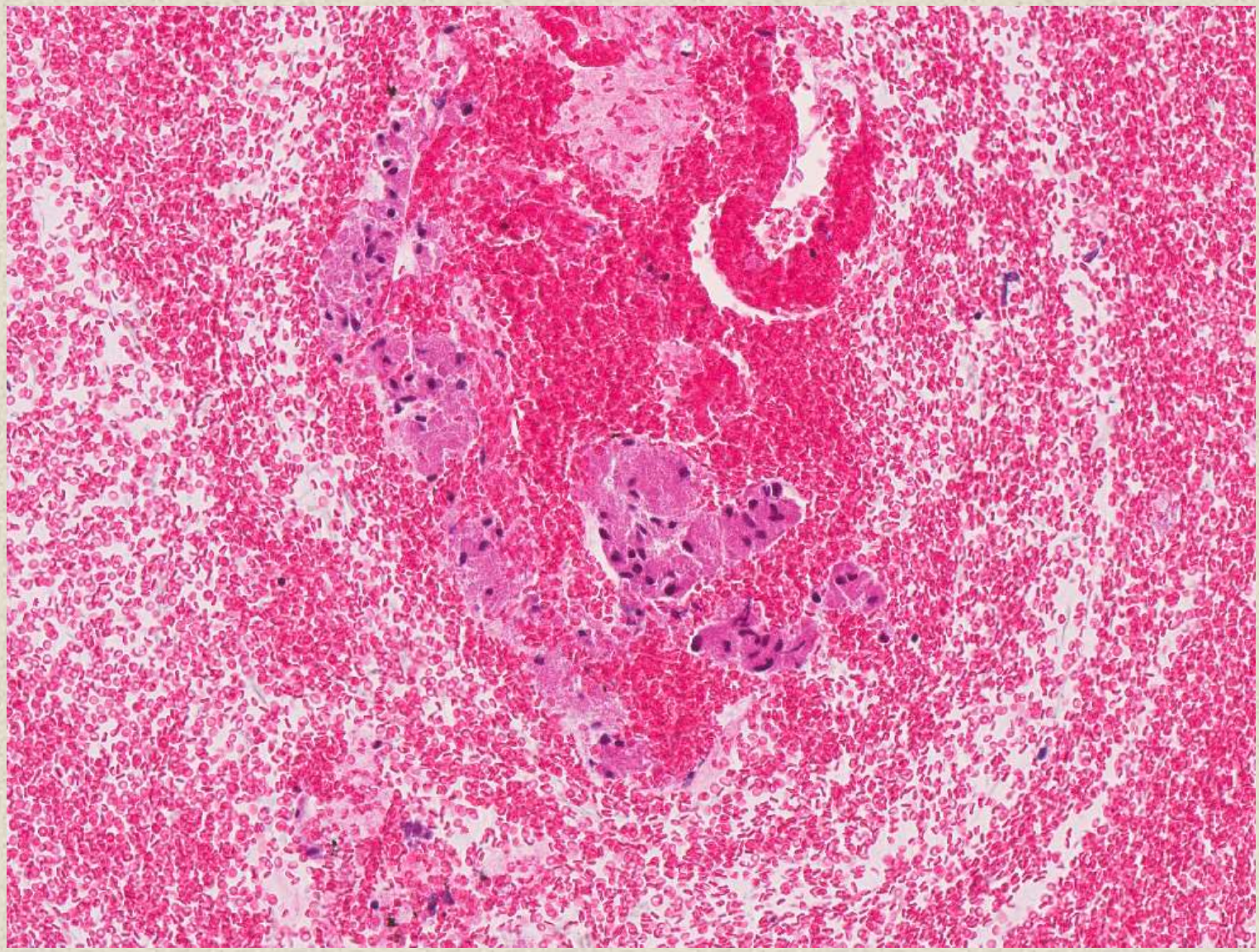
- GIST vs. smooth muscle neoplasm
- Physiological smooth muscle



EUS-biopsy

- GIST vs. smooth muscle neoplasm
- Physiological smooth muscle
- Other submucosal neoplasms

56 yr old woman with a GOJ tumour – normal mucosa. ?GIST. EUS-biopsied:



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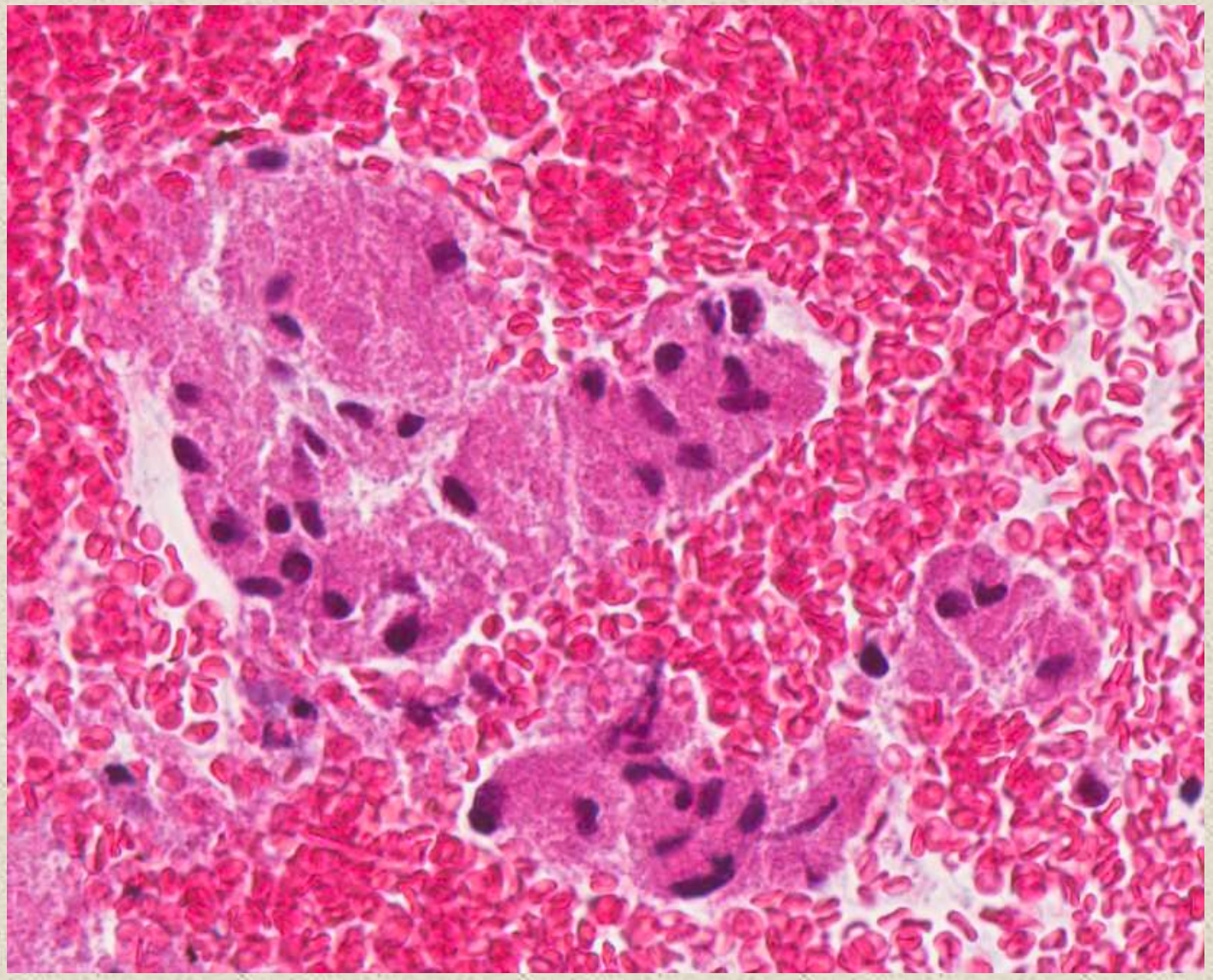

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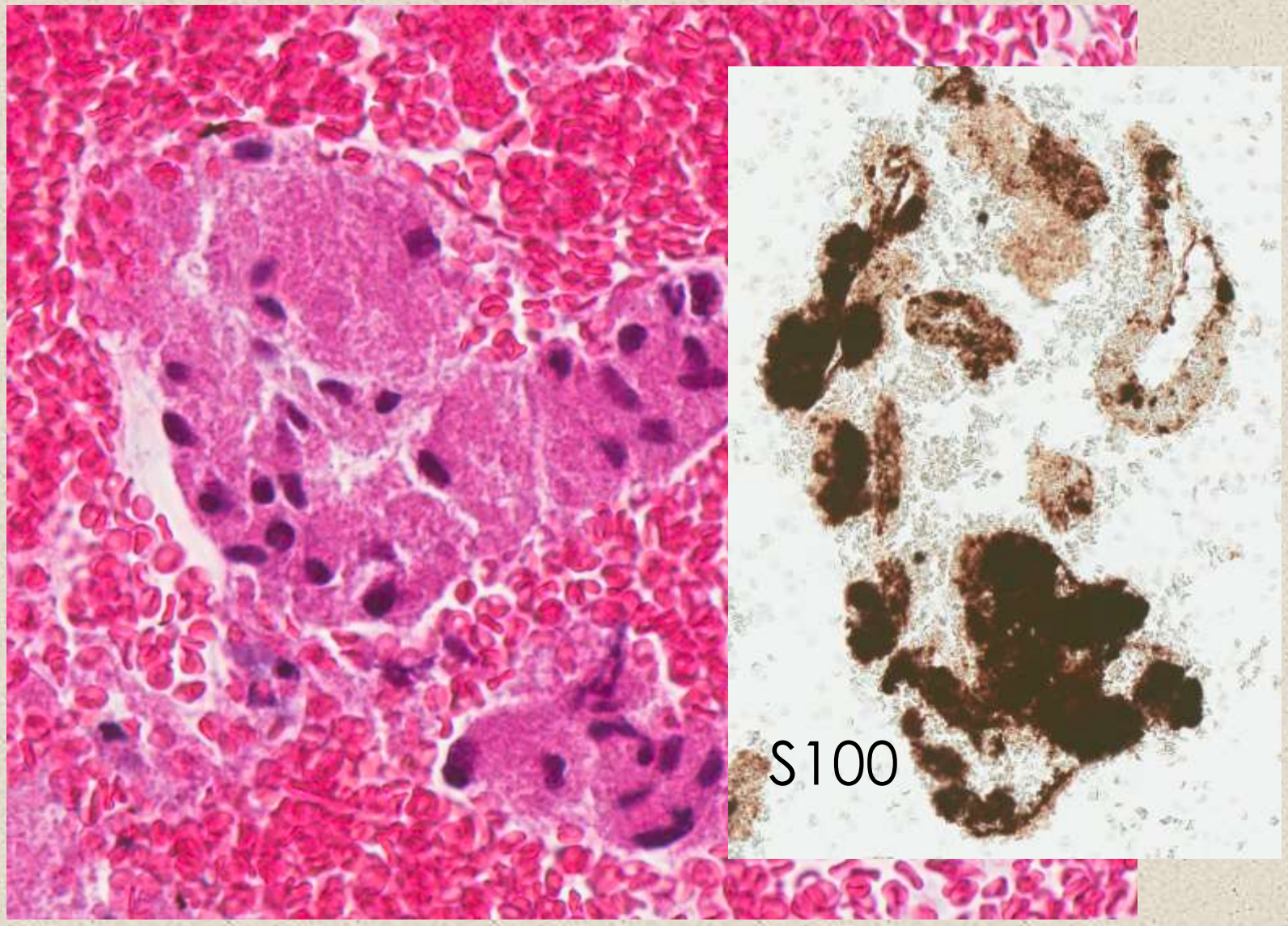
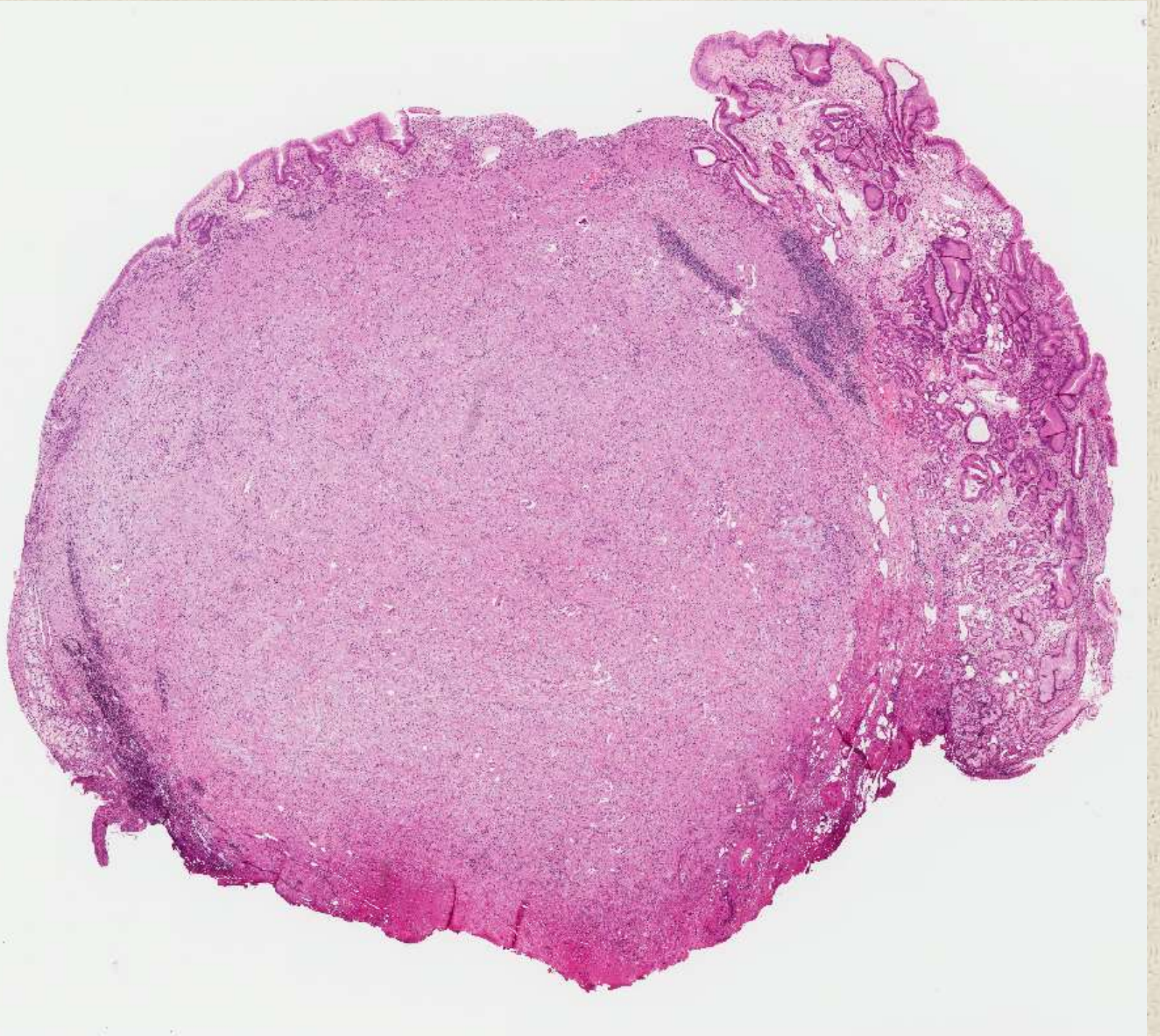
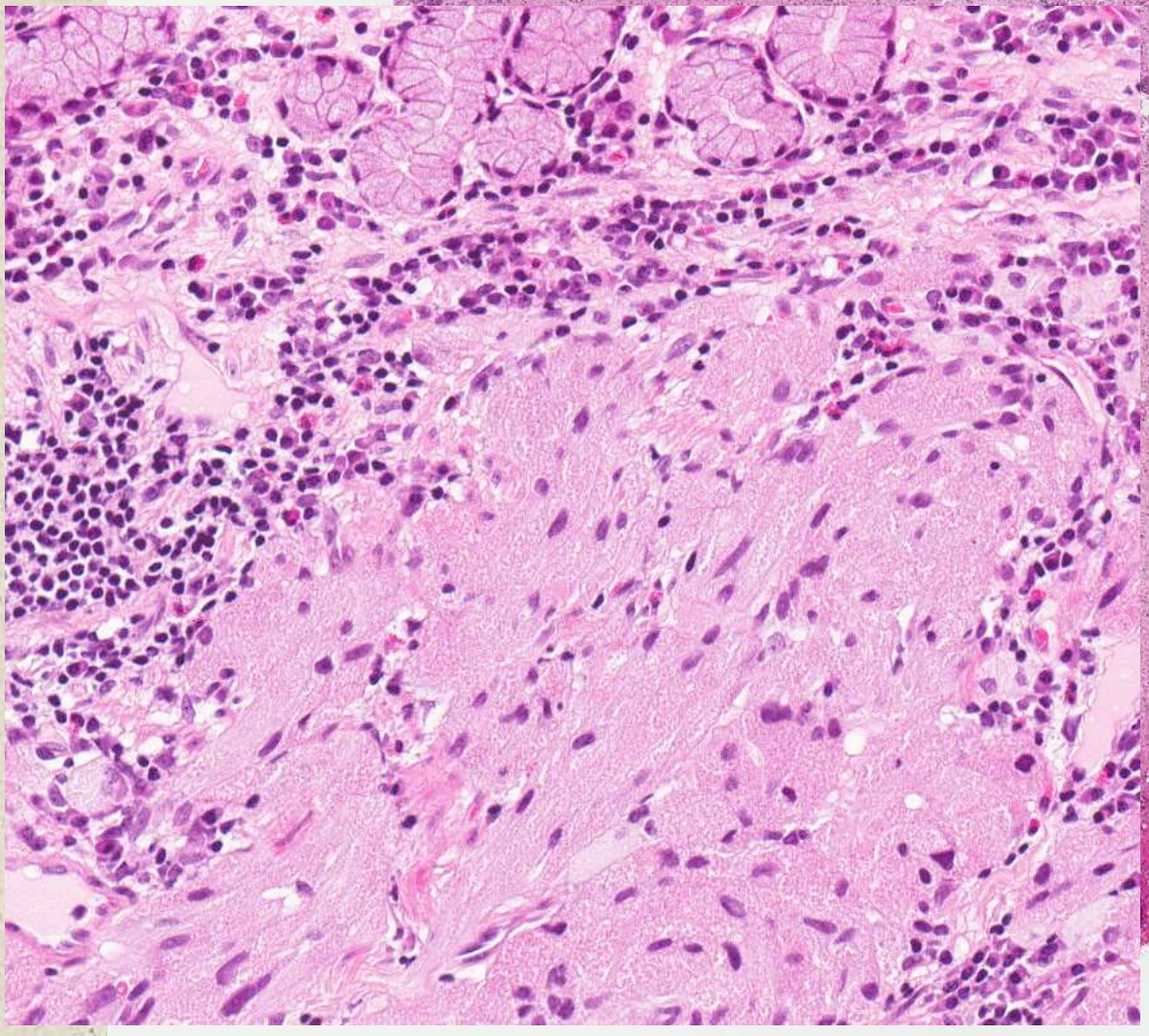
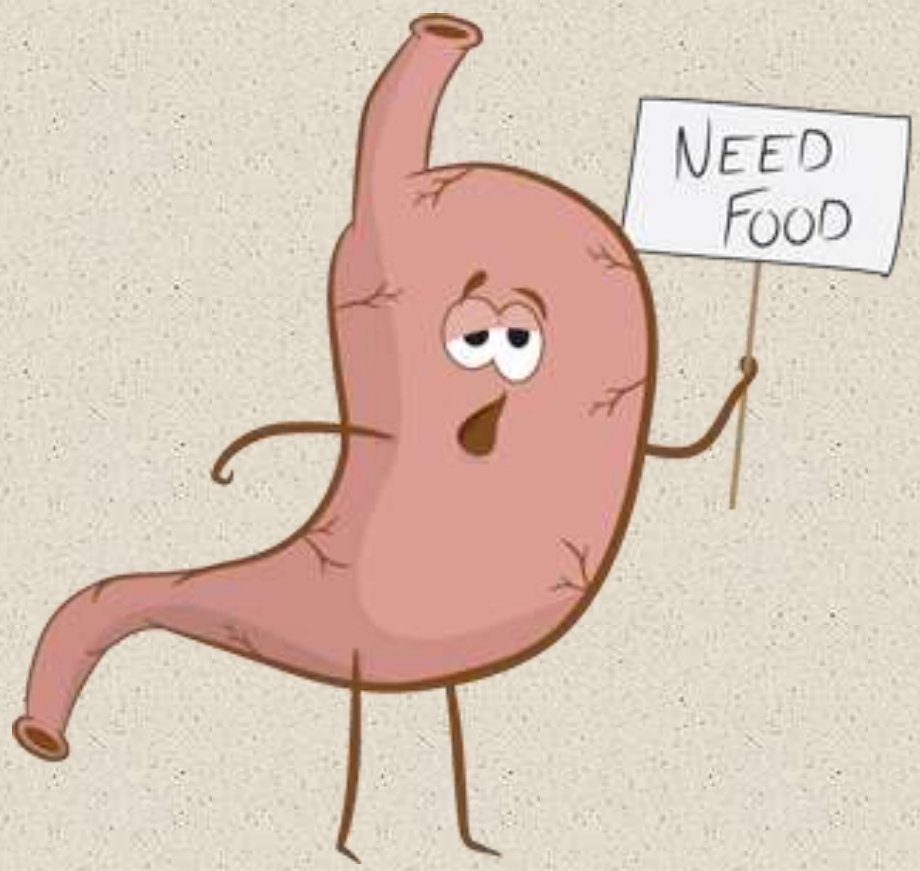




Granular cell tumour



Stomach



- GIST
- Schwannoma
- IFP
- Glomus tumour
- Synovial sarcoma
- IMFT
- Plexiform fibromyxoma

GIST

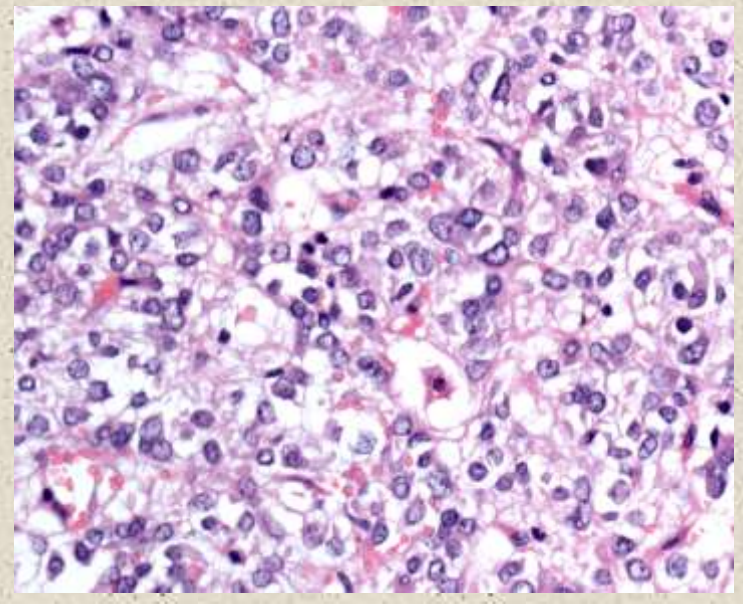
- Is it a CD117 negative GIST?
  - Mainly epithelioid/mixed cell type
  - PDGFRA mutant
  - Gastric/omental

KIT-Negative Gastrointestinal Stromal Tumors

Proof of Concept and Therapeutic Implications

Fabiola Medeiros, MD, Christopher L. Corless, MD,† Anette Duensing, MD,* Jason L. Hornick, MD, PhD,* Andre M. Oliveira, MD,* Michael C. Heinrich, MD,‡ Jonathan A. Fletcher, MD,*§ and Christopher D. M. Fletcher, MD, FRCPath**

(*Am J Surg Pathol* 2004;28:889–894)



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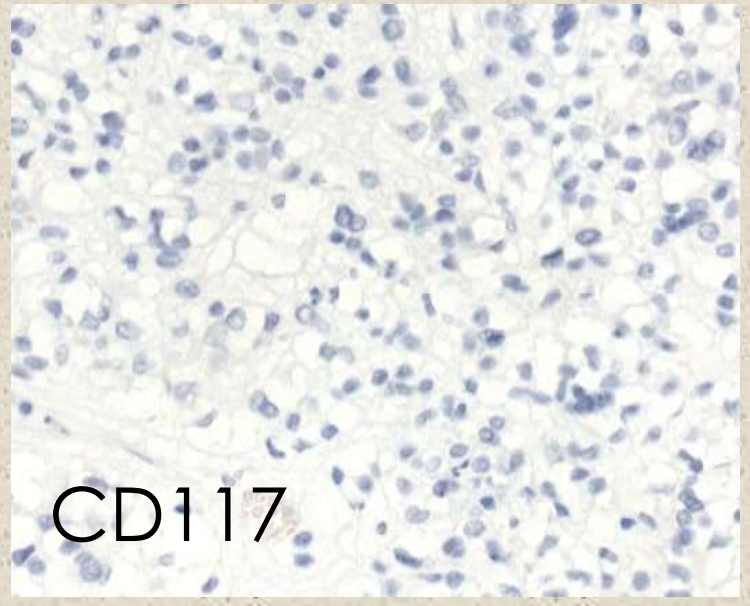
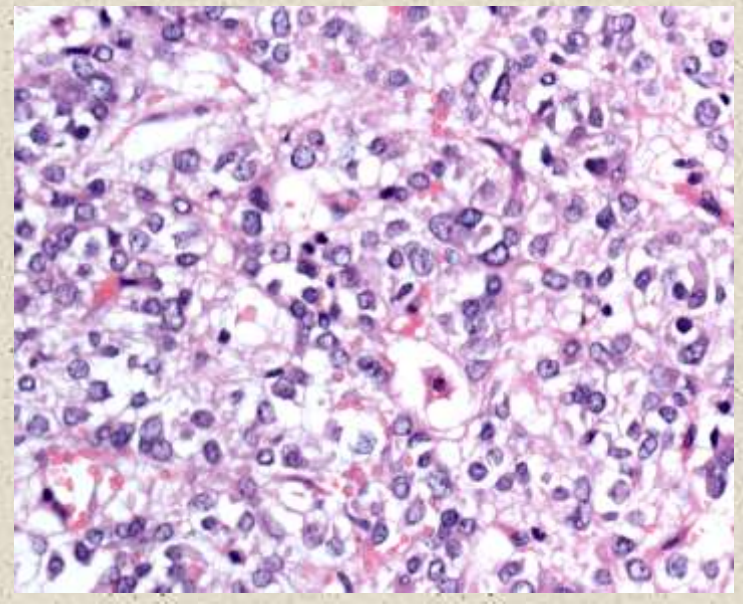

CD117

= ???



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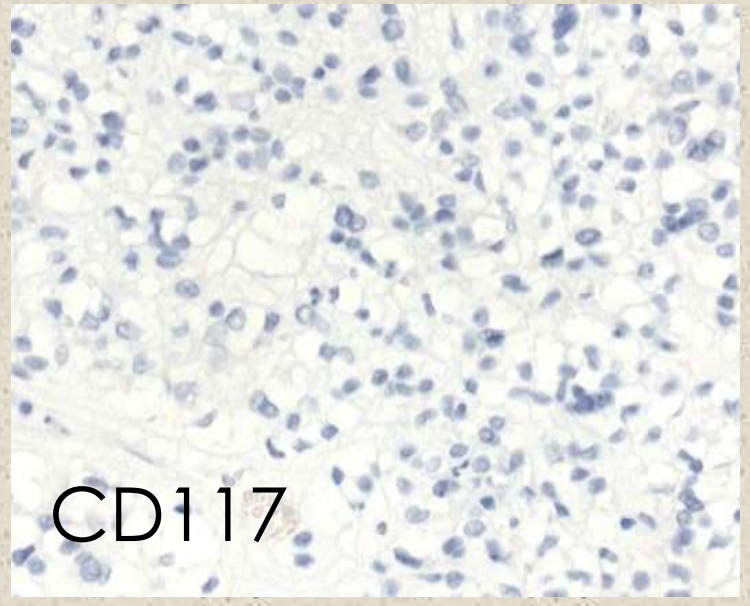

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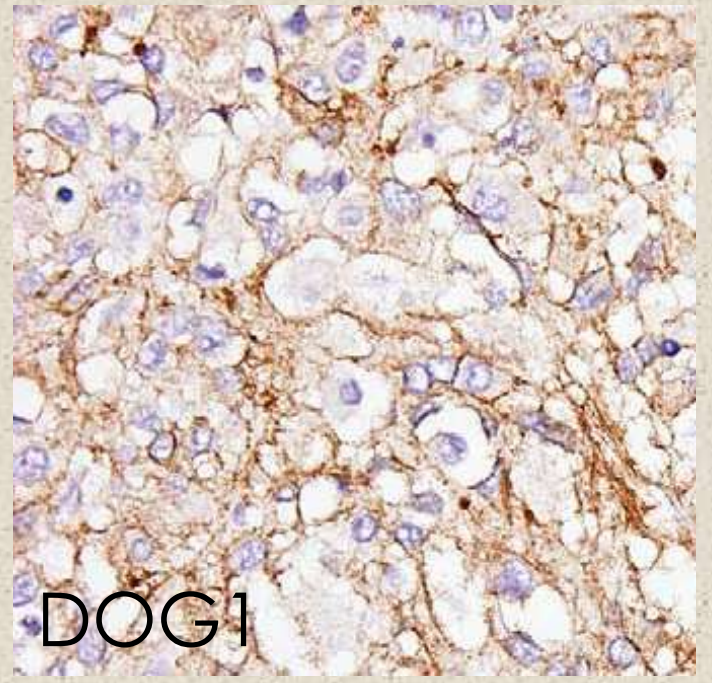
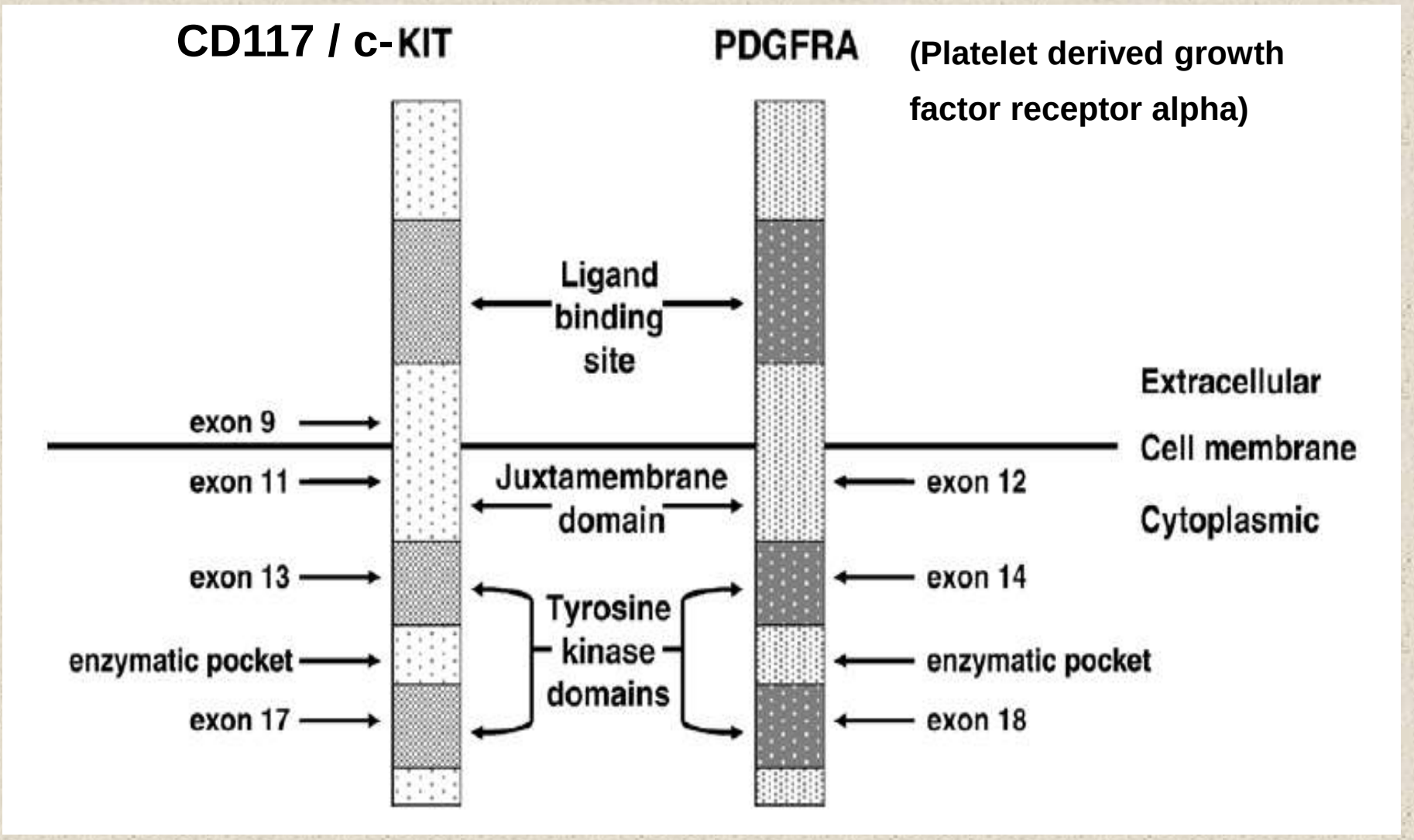
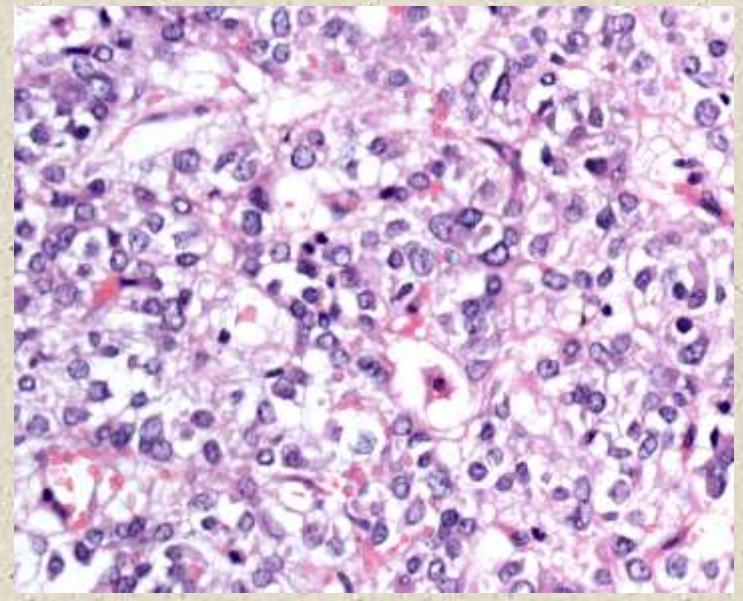


= CD117 neg GIST

Mutations of receptor tyrosine kinase (RTKs)



Hornick *et al*. *Hum Pathol* 2007; **38:** 679.



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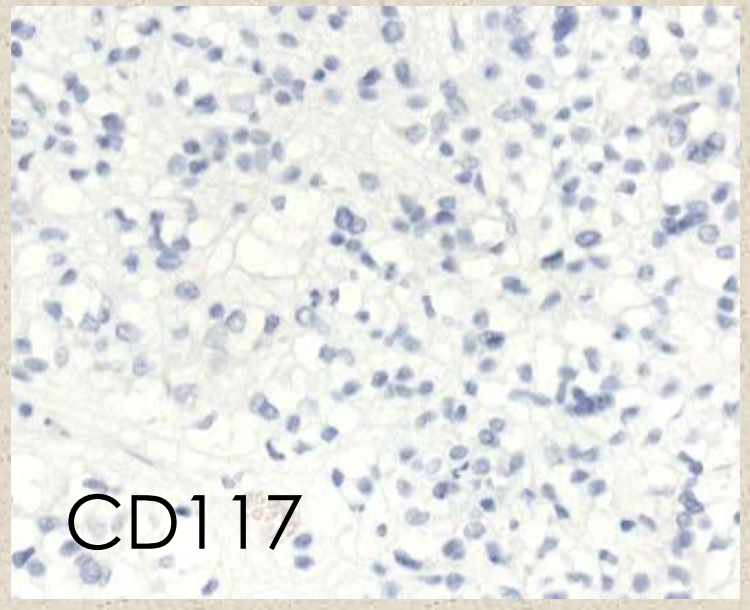
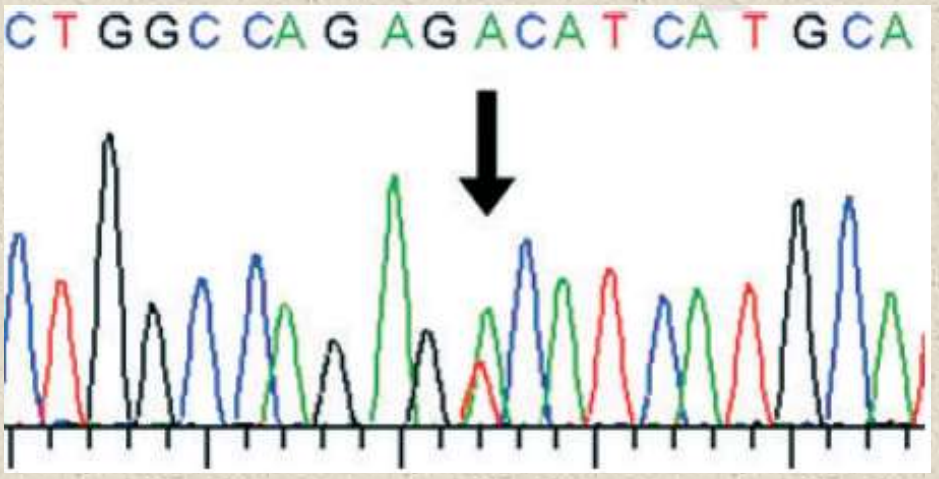
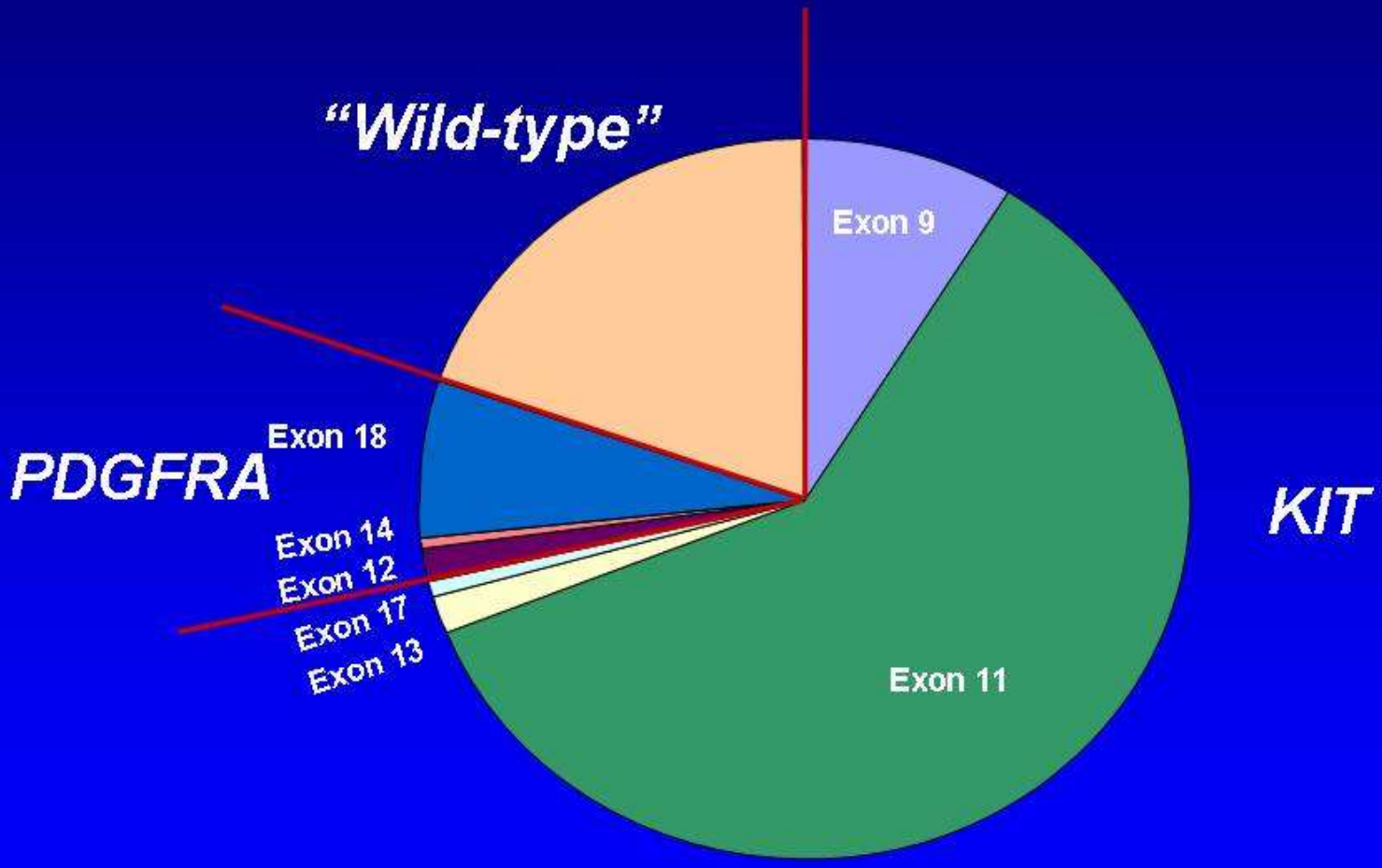


+ ‘D842V’ mutation = CD117 neg GIST



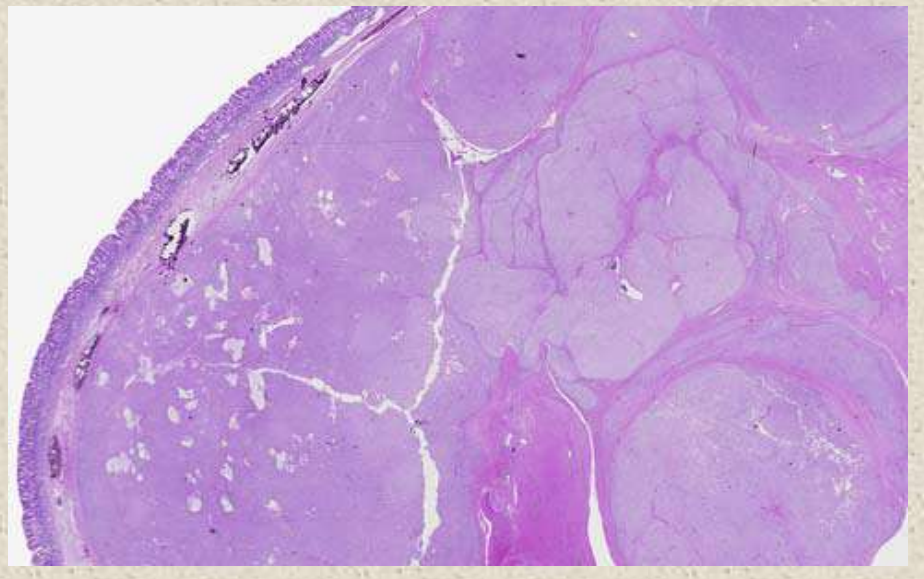
Kinase Mutations in GISTs



Heinrich et al. *J Clin Oncol 21:4342-4349, 2003*
Agaram et al. Genes, Chromosomes & Cancer 47:853–859, 2008
Agaimy et al. J Clin Pathol 2009;62:613–616, 2009

Epithelioid/mixed cell type gastric GISTs

- *PDGFRA* mutant
  - Reduced CD117 expression
  - No age or gender association
- Wild type
  - Do express CD117



- Wild type
  - CD117 expression
  - Stomach
  - Children or young female adults
  - Multinodular/multifocal
  - Nodal and liver metastases
  - Poor response to imatinib
  - Better prognosis

Epithelioid/mixed cell type gastric GIST

- Wild type
  - Paediatric or 'paediatric-like' in adults

Gastrointestinal Stromal Tumors of the Stomach in Children and Young Adults

A Clinicopathologic, Immunohistochemical, and Molecular Genetic Study of 44 Cases With Long-Term Follow-Up and Review of the Literature

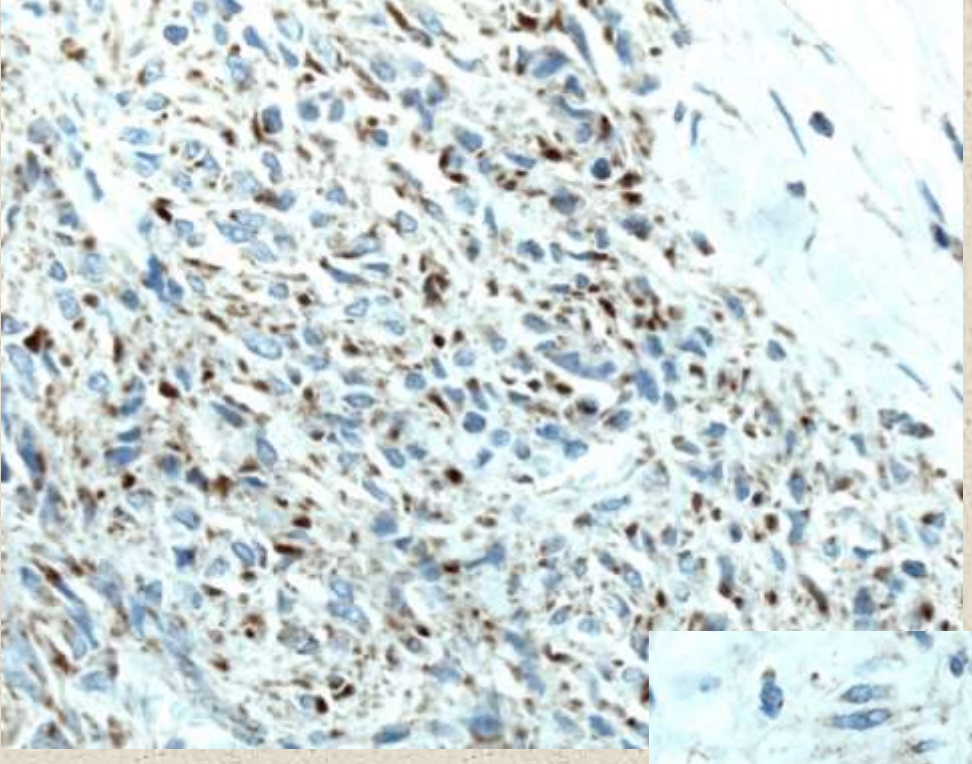
Markku Miettinen, MD, Jerzy Lasota, MD,* and Leslie H. Sobin, MD†*

"Pediatric-type" Gastrointestinal Stromal Tumors in Adults: Distinctive Histology Predicts Genotype and Clinical Behavior

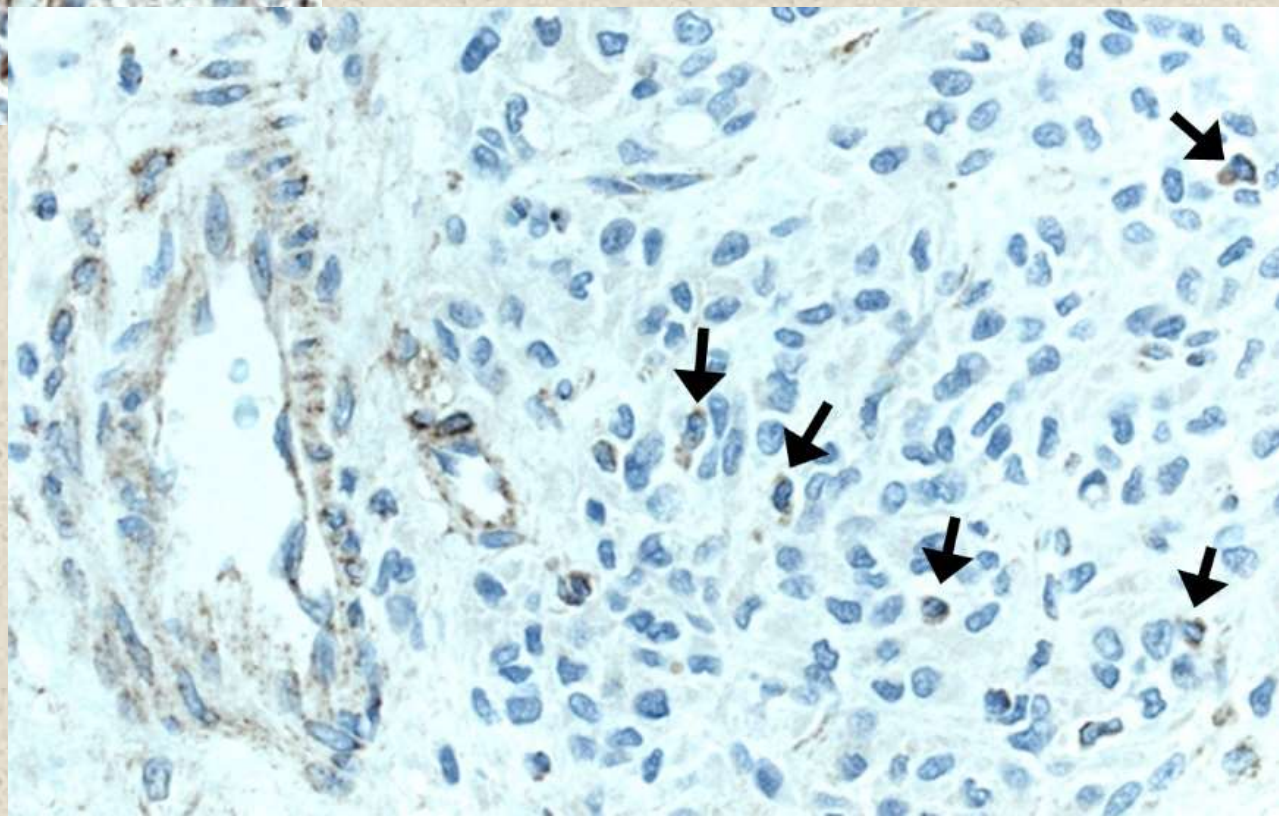
Tanya A. Rege, MD, PhD,† Andrew J. Wagner, MD, PhD,‡ Christopher L. Corless, MD, PhD,§‖ Michael C. Heinrich, MD,‖¶ and Jason L. Hornick, MD, PhD*†*

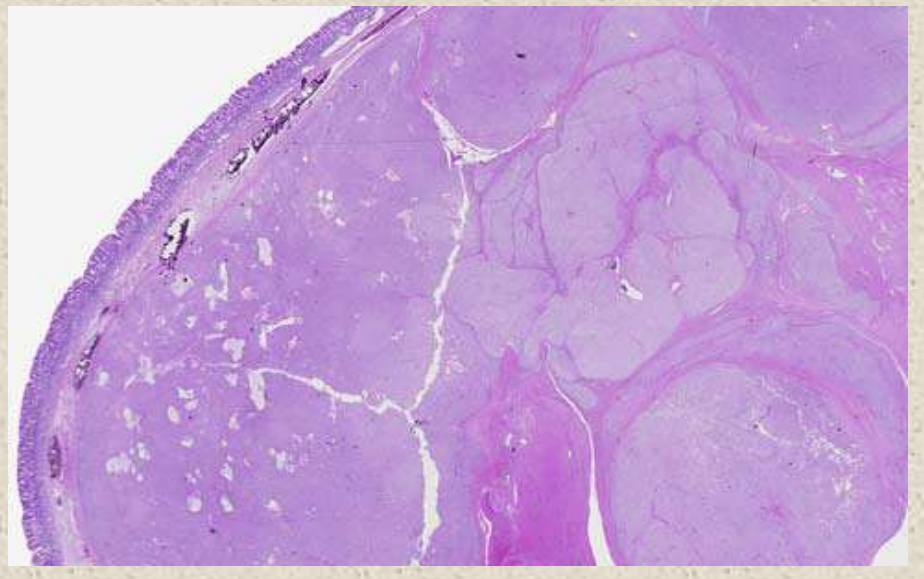
Epithelioid/mixed cell type gastric GIST

- Wild type
  - Paediatric or paediatric-like in adults
  - Could represent Carney triad (no known genetic basis) or Carney-Stratakis (inherited SDH gene mutation)
  - Loss of SDHB protein expression



SDHB

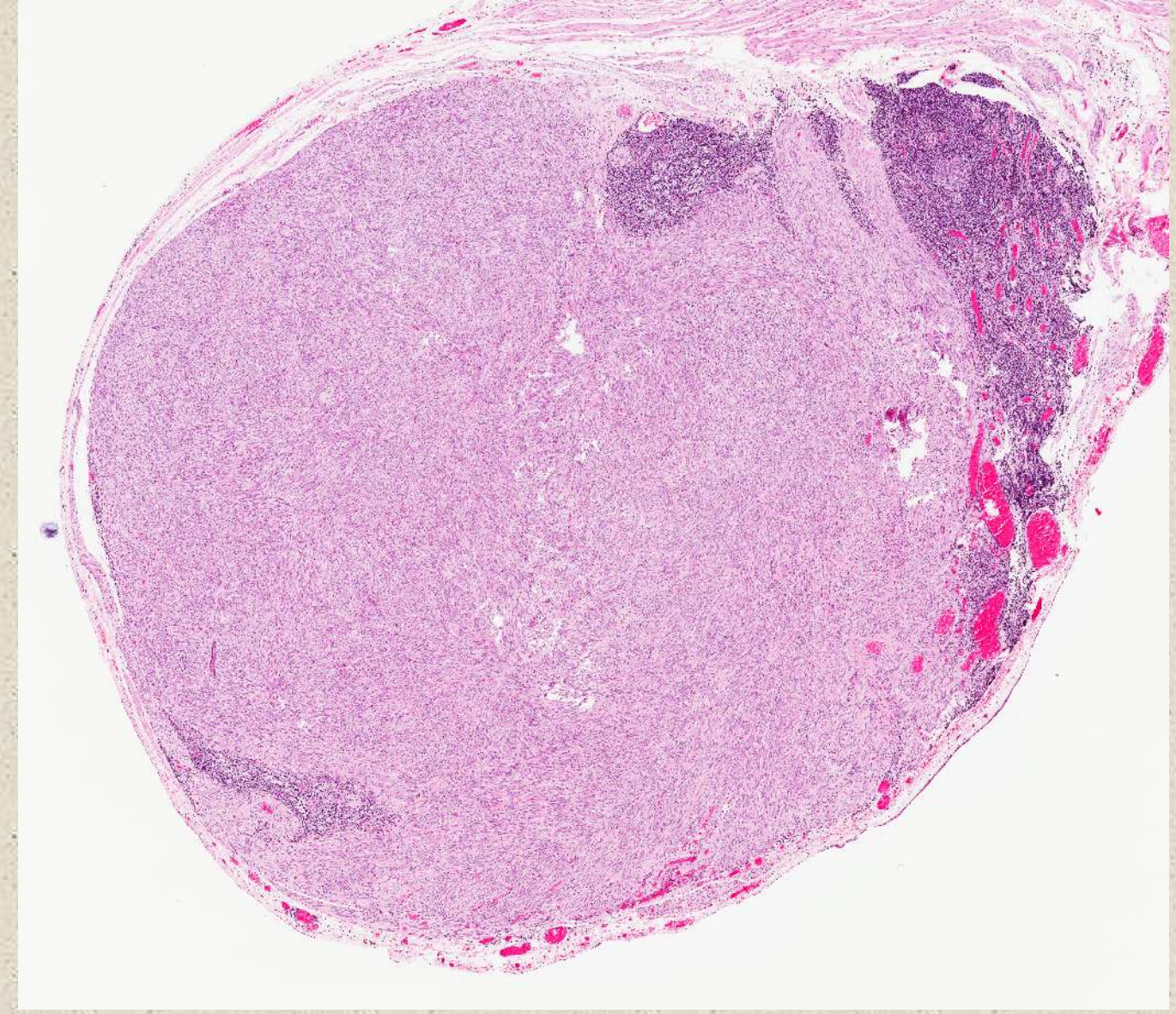


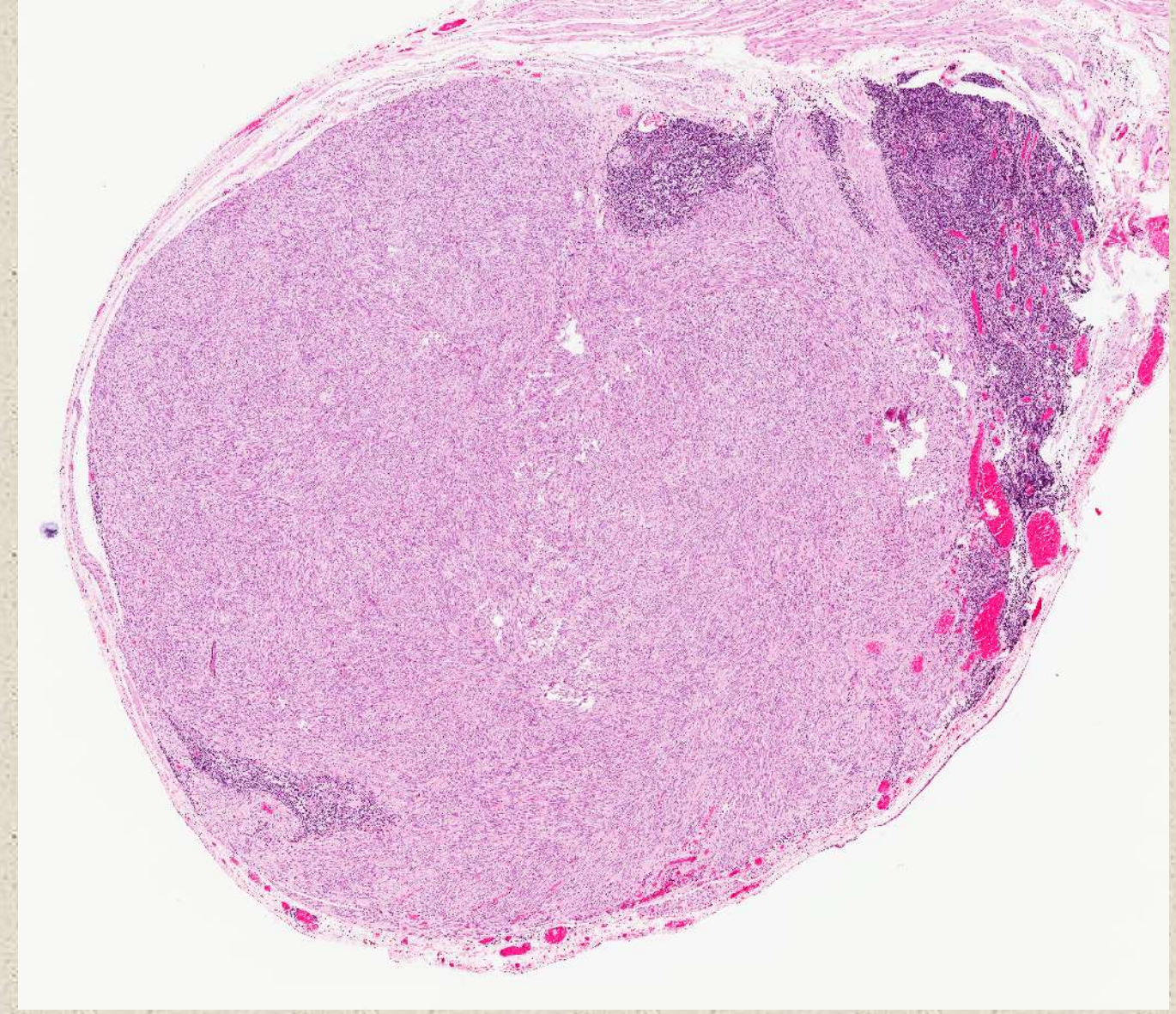


- Wild type
  - CD117 expression
  - Stomach
  - Children or young female adults
  - Multinodular/multifocal
  - Nodal and liver metastases
  - **Poor response to imatinib**
  - **Better prognosis**

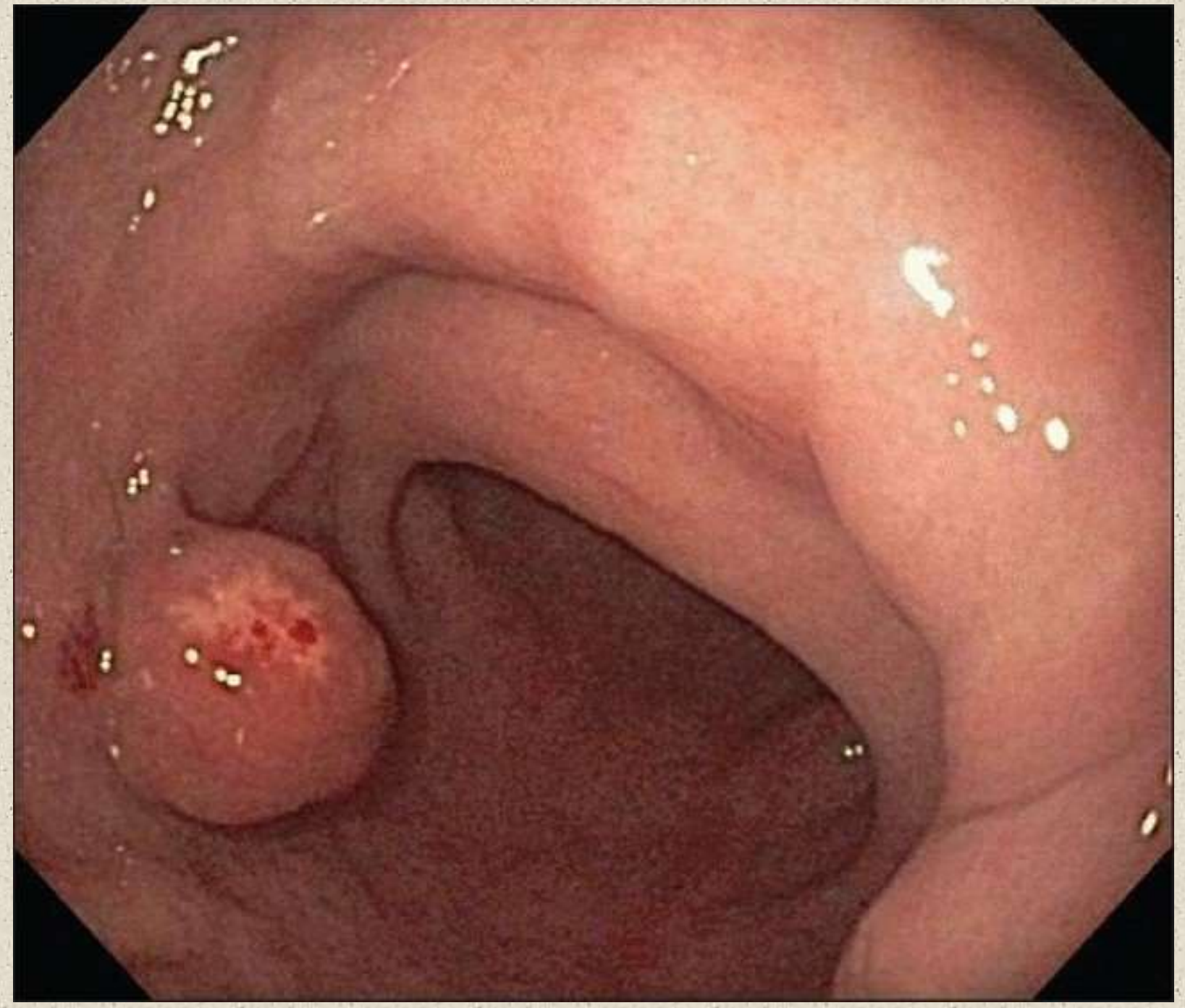
Gastric schwannoma

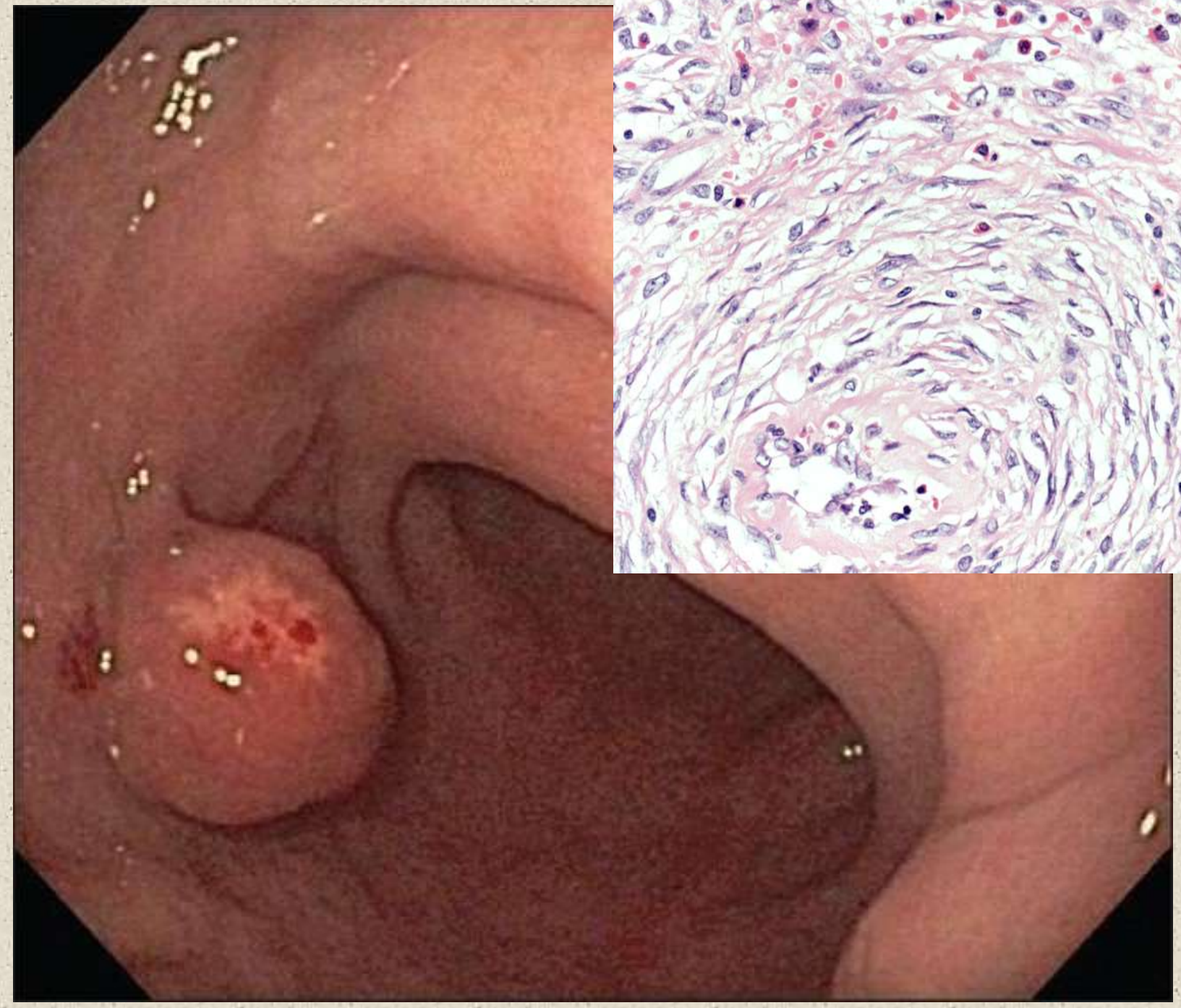
- GISTs ‘never’ show diffuse S100 positivity
- Peripheral lymphoid aggregates but ...





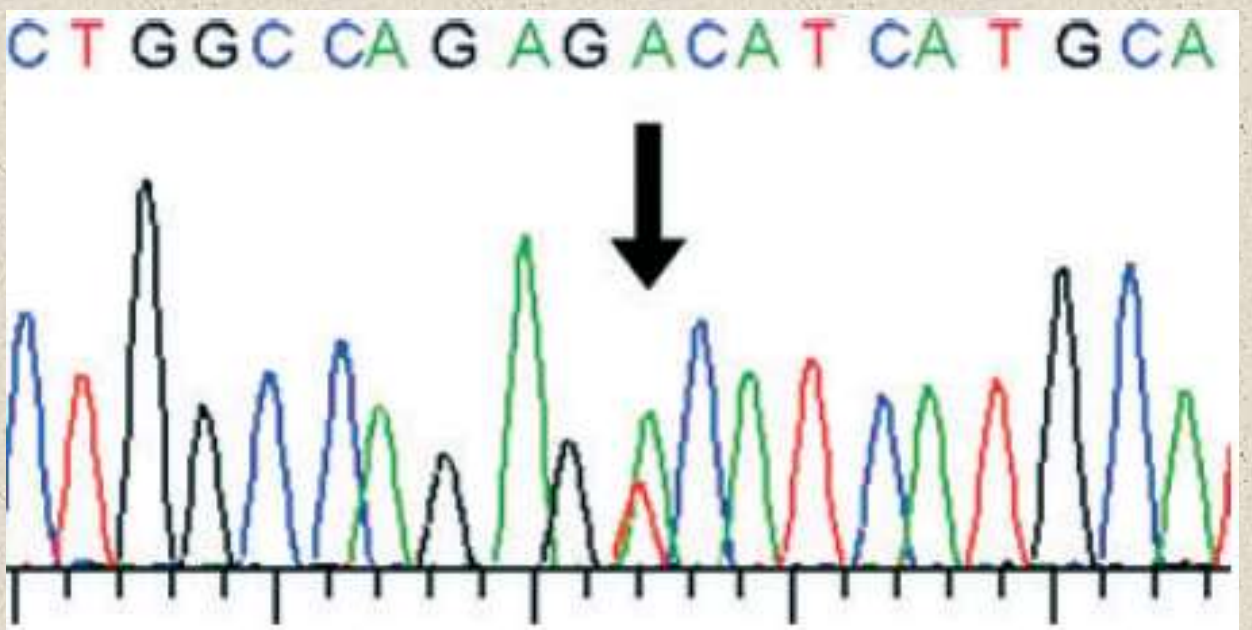
- CD117 and DOG1 diffusely +ve; S100 -ve
- *KIT* exon 11: c.1738_1752dup, p.(His580_Phe584dup)





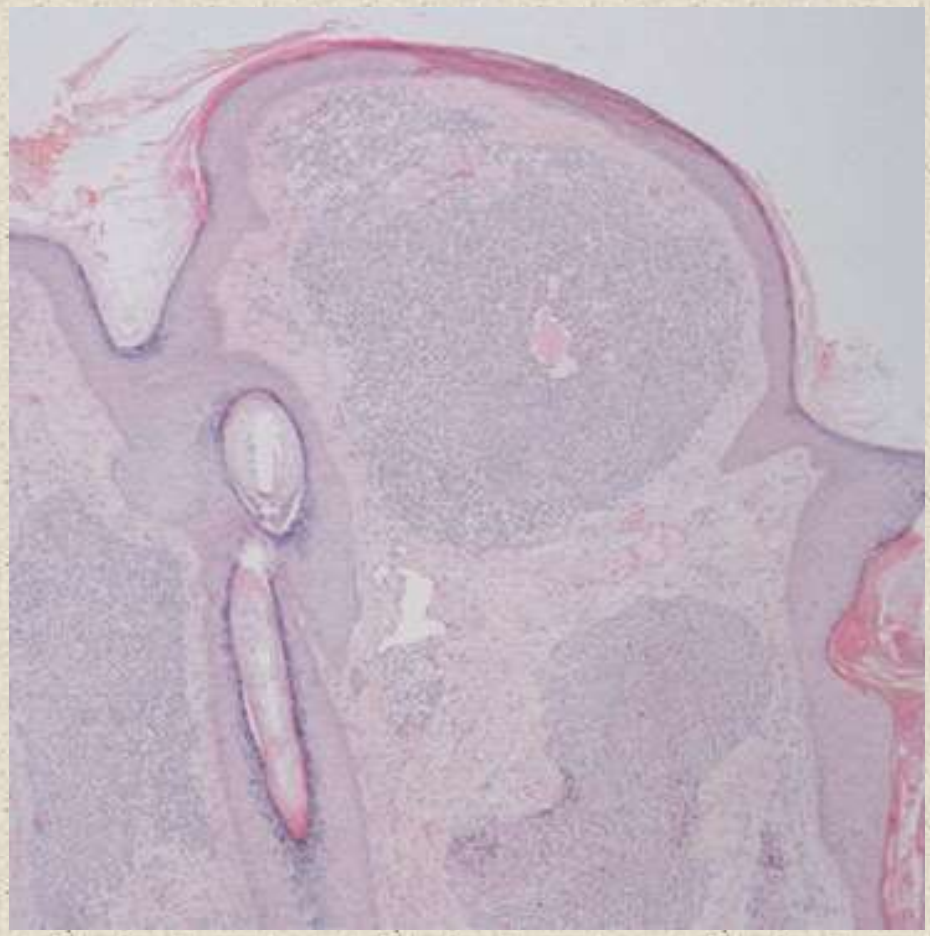
Inflammatory fibroid polyp

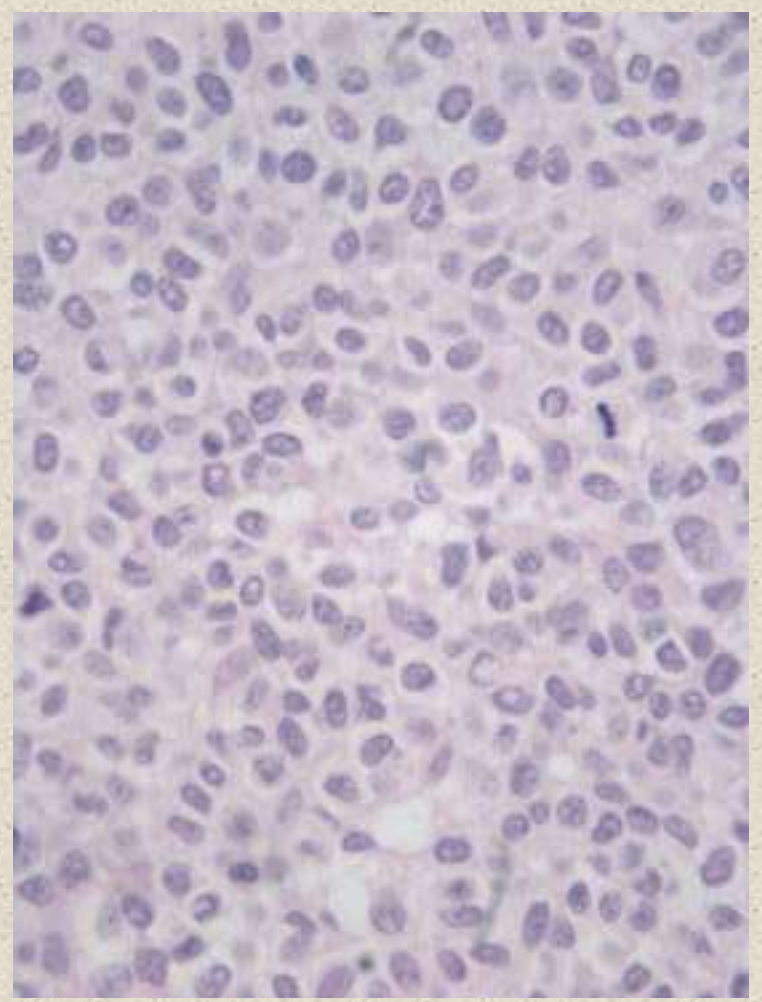
- Up to ¾ may harbour *PDGFRA* mutations



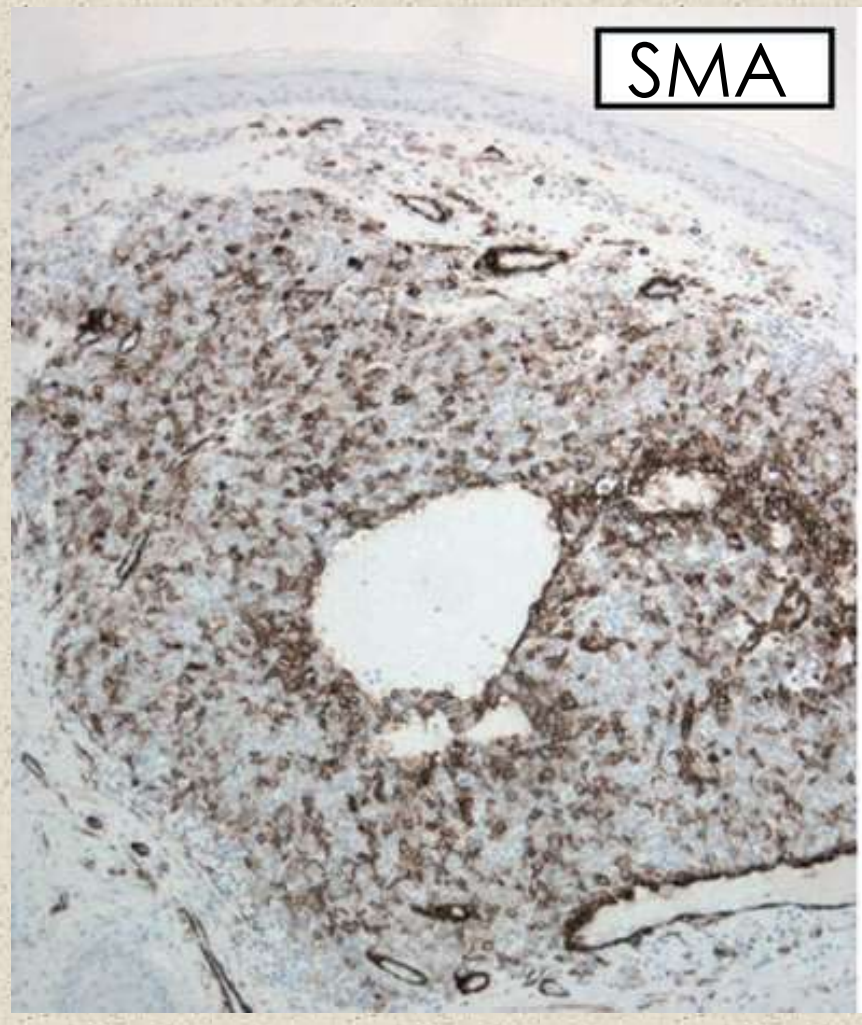
58 yr old man with a previously excised gastric GIST. Scalp tumour excised:

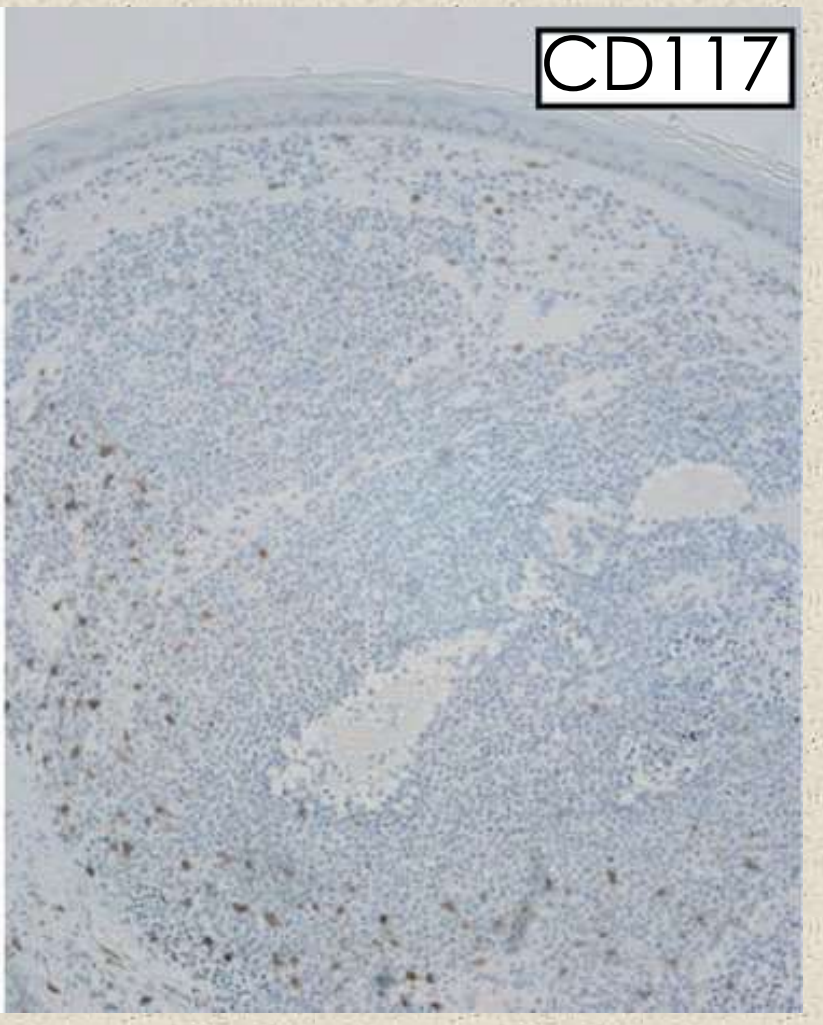
58 yr old man with a previously excised gastric GIST. Scalp tumour excised:



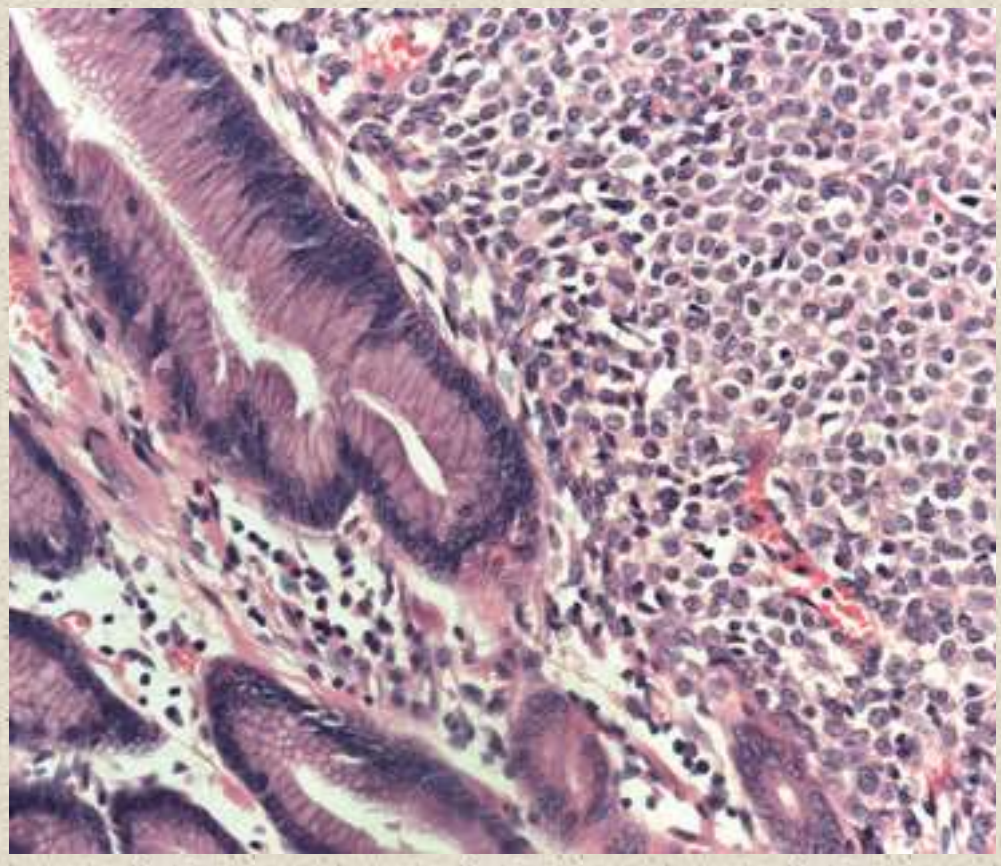


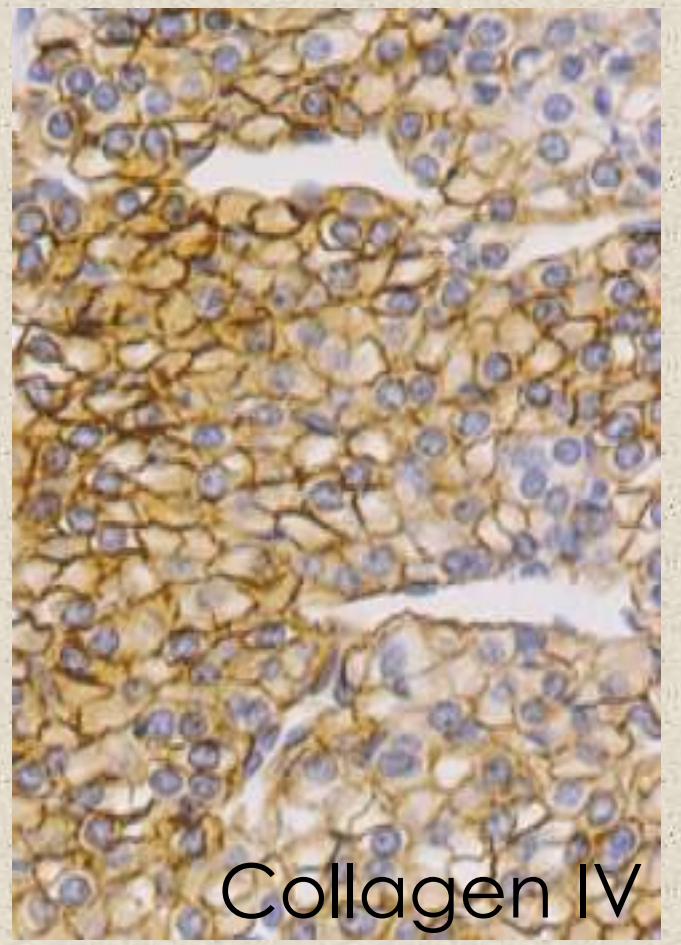
58 yr old man with a previously excised gastric GIST. Scalp tumour excised:





DOG1 and CD34 negative
Wild type for *KIT* and *PDGFRA*





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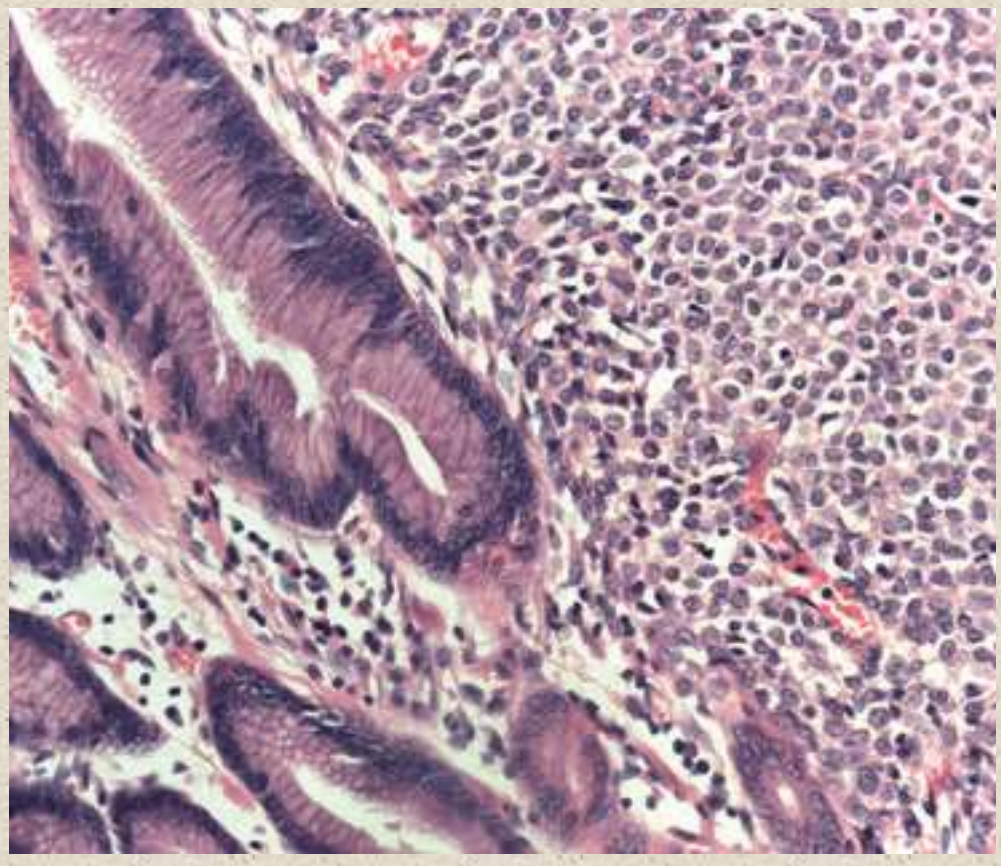
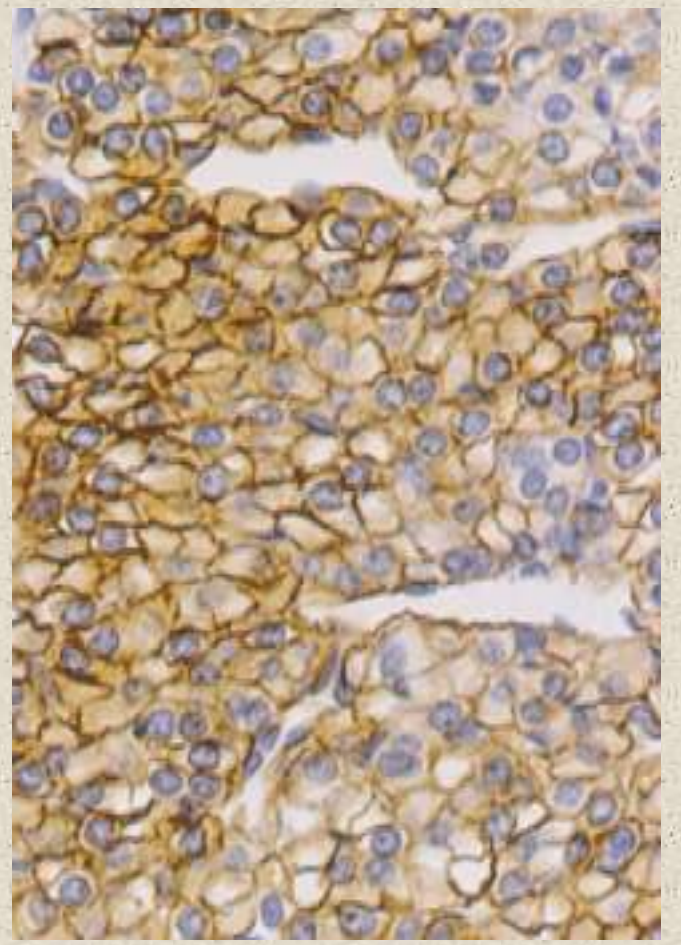
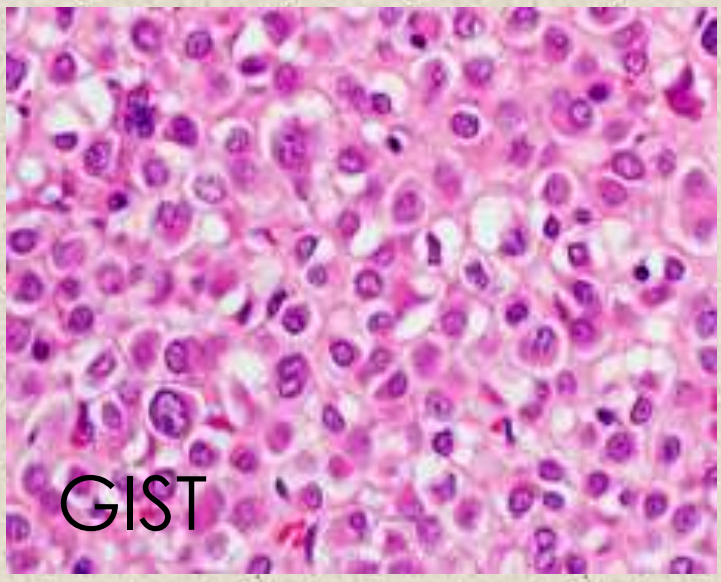


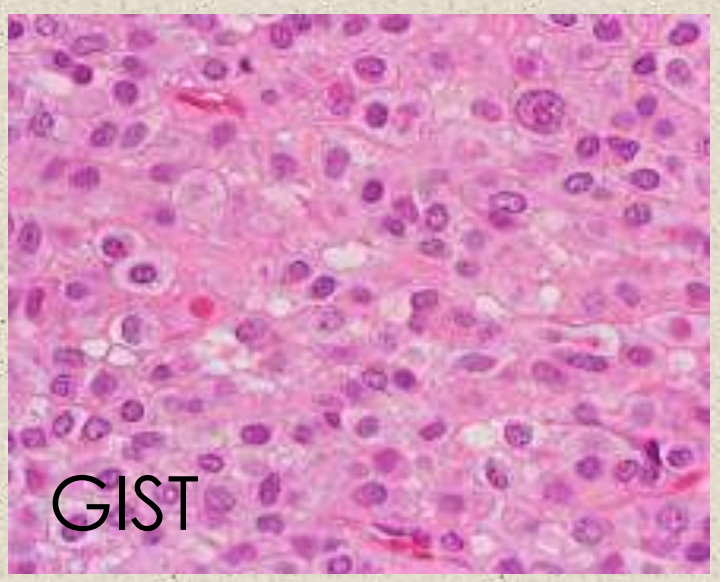


Malignant gastric glomus tumour

Glomus tumour

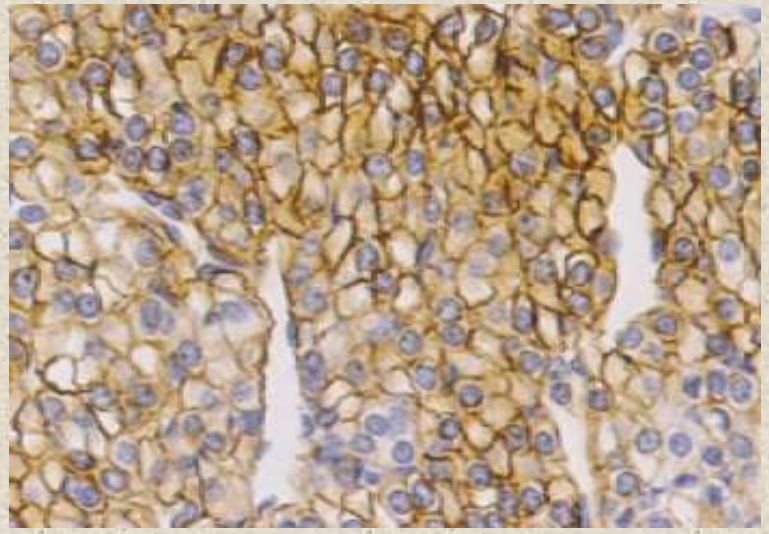
- Very uniform epithelioid cells with prominent cell membranes ... but GIST can too!





Glomus tumour

- Focal SMA positivity with prominent net-like collagen IV / laminin around cells ... but GIST can too (34%!)



- **Lack of CD117, DOG1 and CD34 expressions**

Synovial sarcoma

Histopathology 2015, **66**, 974–981. DOI: 10.1111/his.12593

Abdominal monophasic synovial sarcoma is a morphological and immunohistochemical mimic of gastrointestinal stromal tumour

Newton A C S Wong, Fiona Campbell[1] & Neil A Shepherd[2]

Department of Histopathology, Bristol Royal Infirmary, Bristol, UK, [1]Department of Pathology, Royal Liverpool University Hospital, Liverpool, UK, and [2]Gloucestershire Cellular Pathology Laboratory, Cheltenham General Hospital, Cheltenham, UK

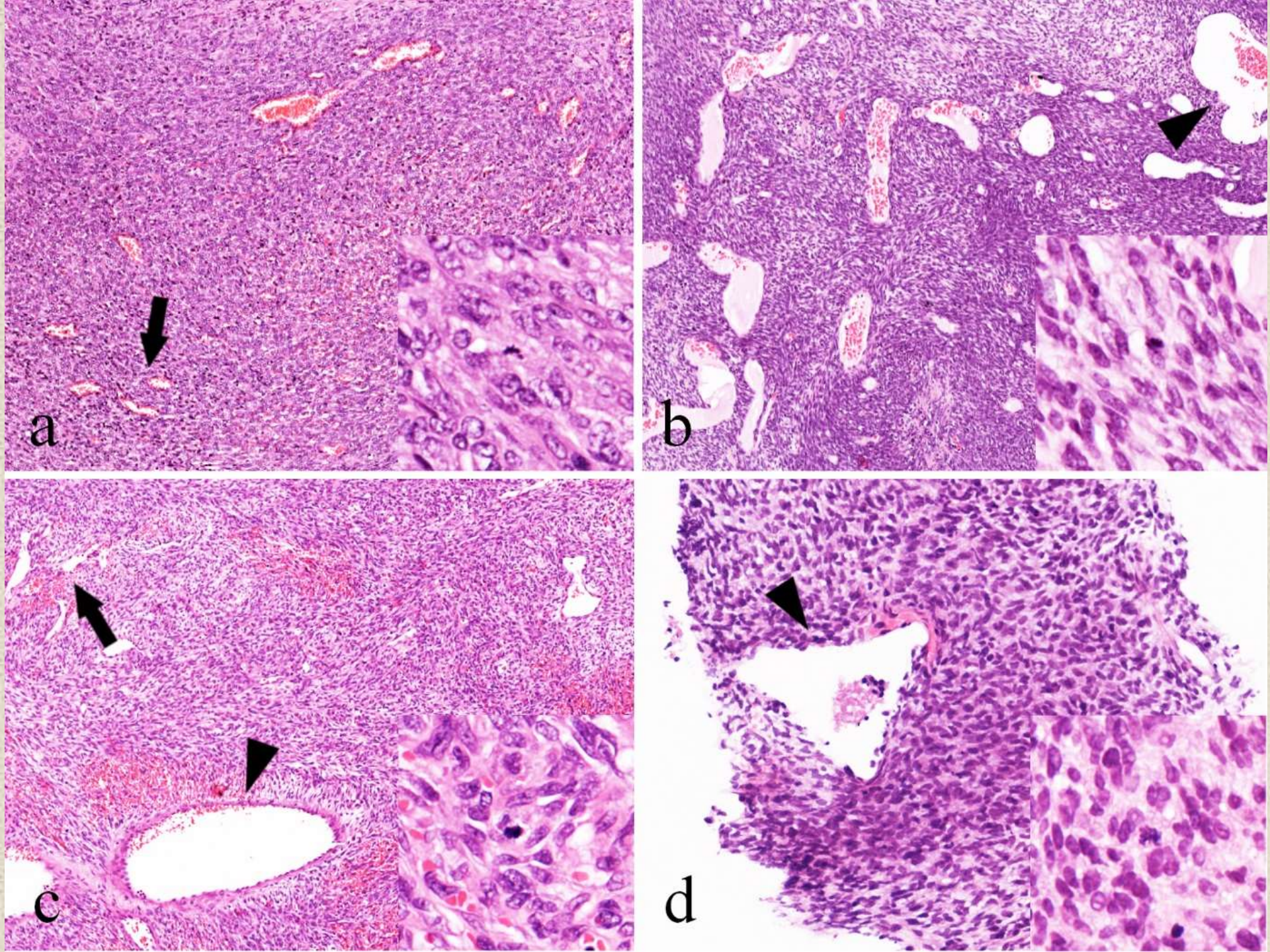
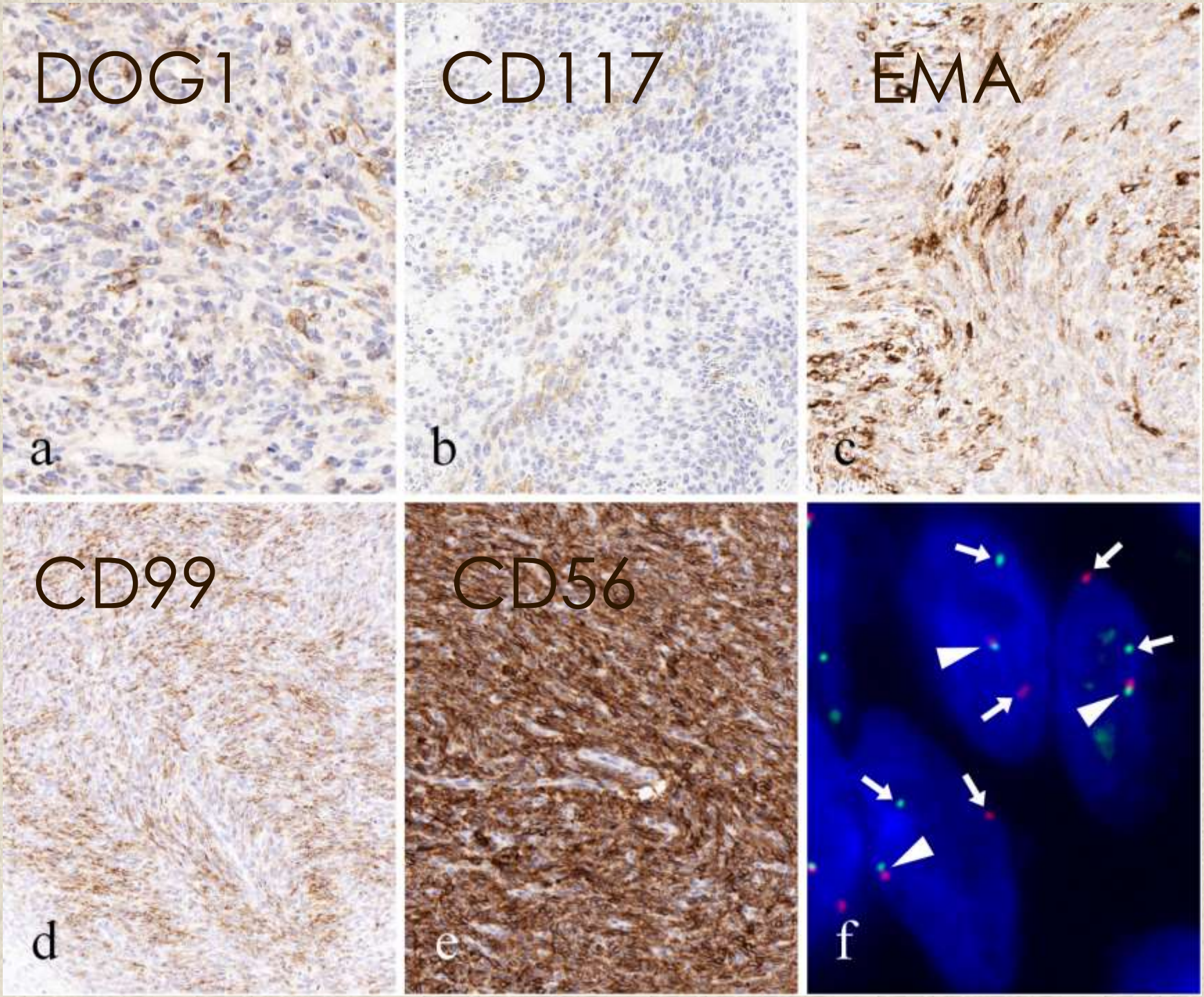
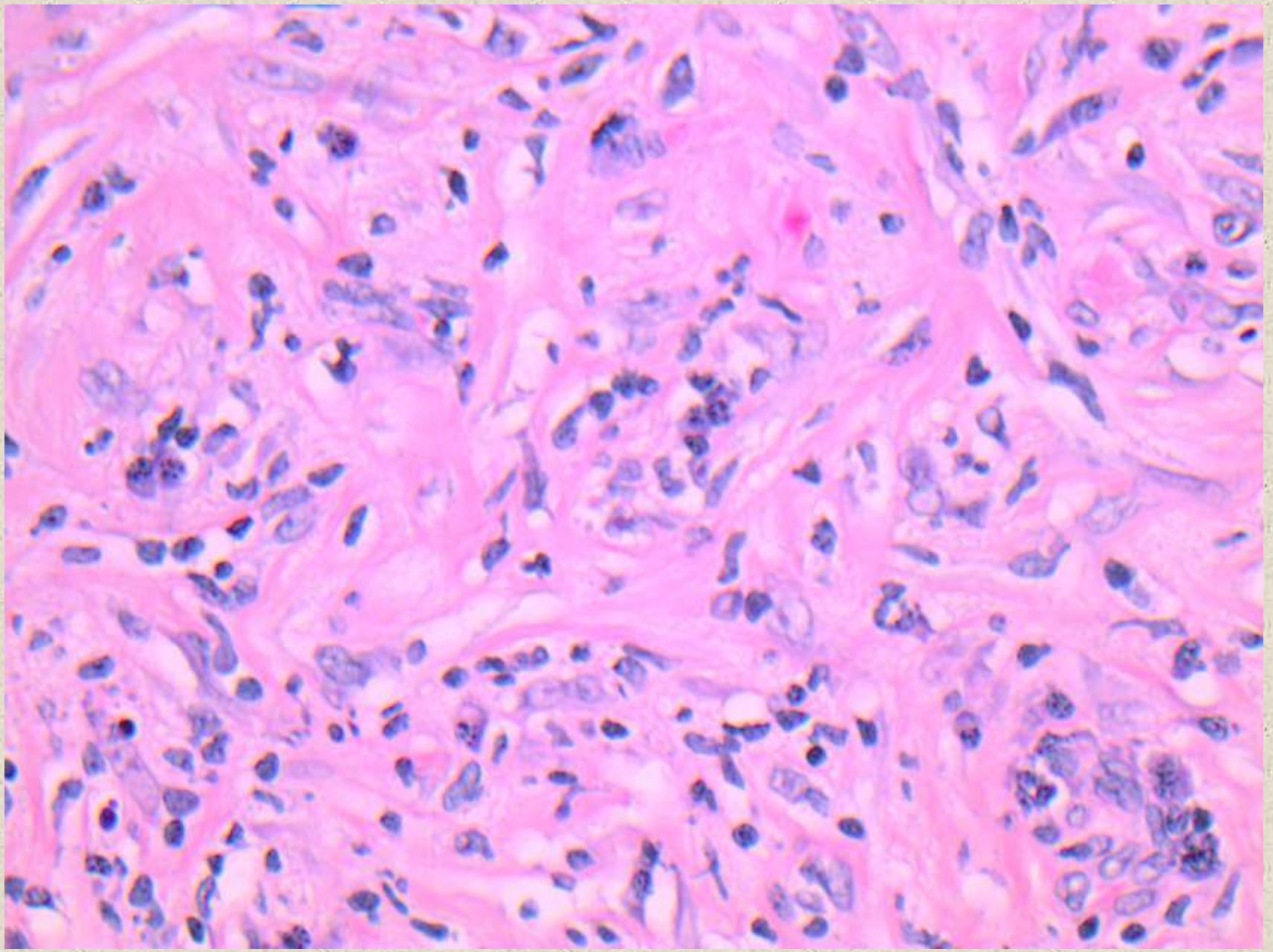

a
b
c
d

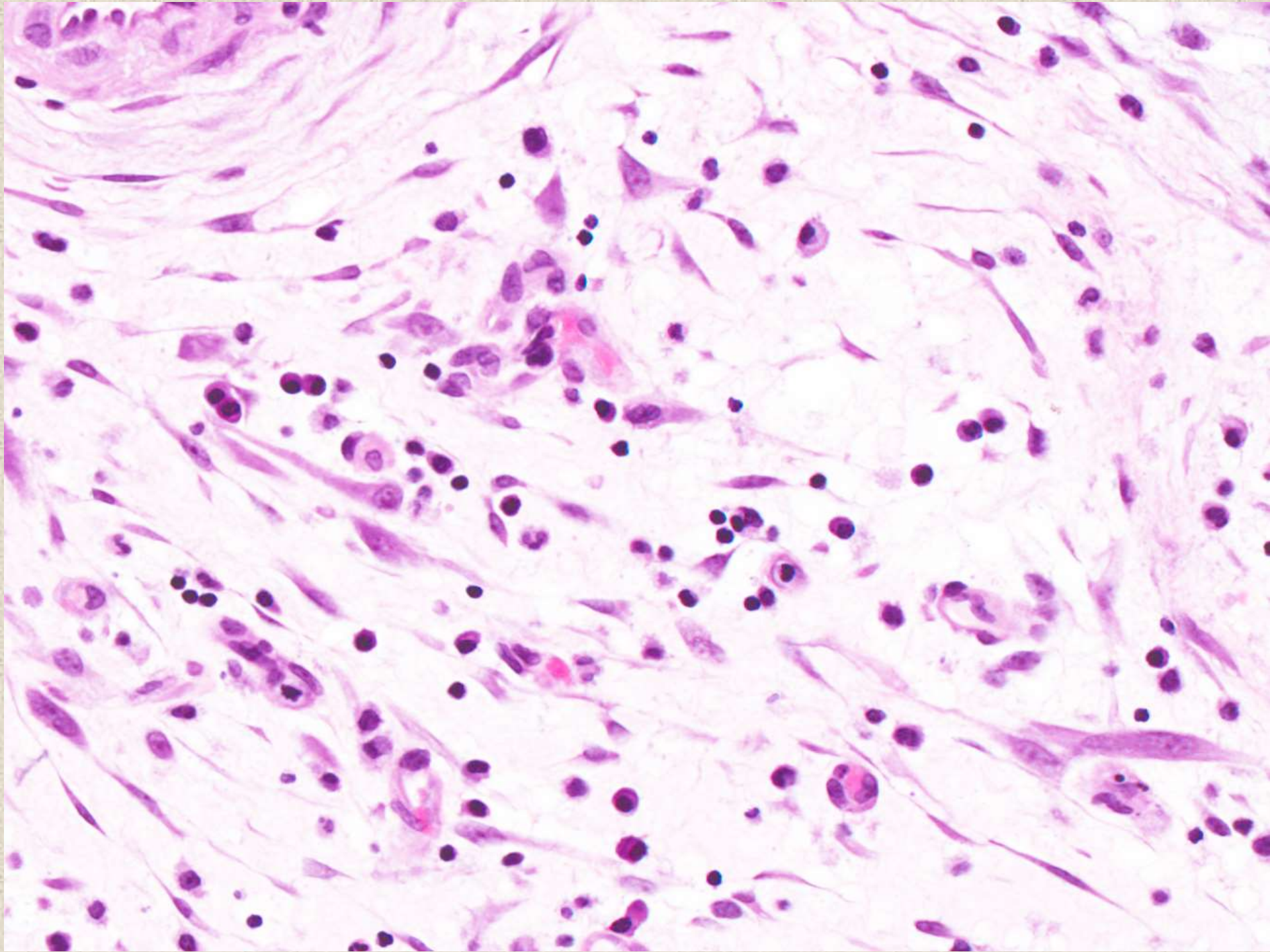
Table 2. Immunohistochemical profiles of the four presented cases of abdominal synovial sarcoma

Immunomarker†	Case 1	Case 2	Case 3	Case 4
CD117	+*	+*	+*	–
DOG1	+*	+	+*	+*
CD34	+	–	–	–
Pancytokeratin	–/+	–	–/+	+
EMA	+	+	+	++
CD99	++	++	++	++
CD56	++	++	++	++
Chromogranin	–	–	–	–
Synaptophysin	–	–	–	–
S100	–	–	–	–
MMC‡	–	–	–	–
SMA	–	–	–	–
Desmin	–	–	–	–


DOG1
CD117
EMA
a
b
c
CD99
CD56
d
e
f

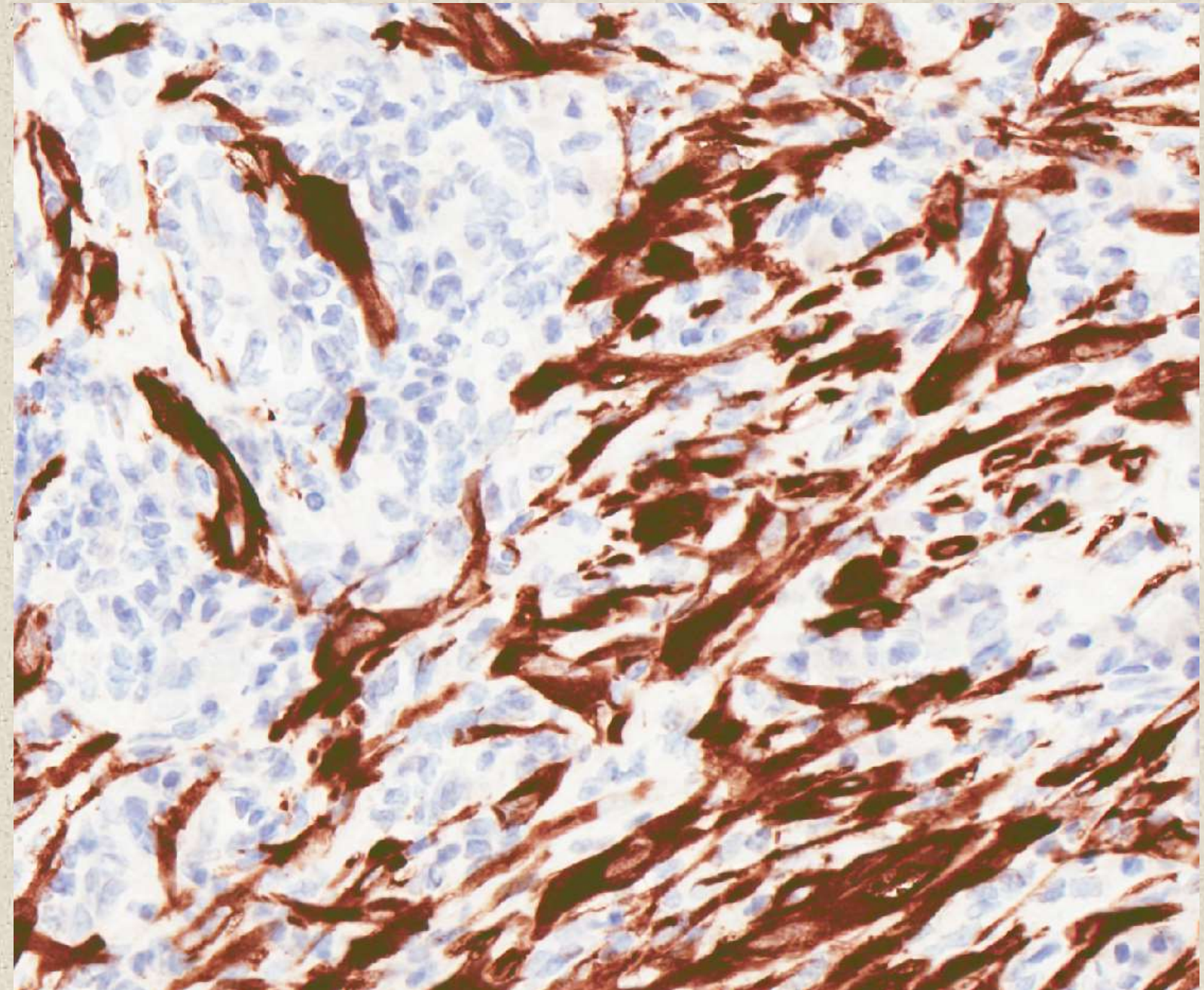
1 yr old girl with a gastric mass.





- Desmin +
- SMA +/-
- CD117 -
- DOG1 -
- Pan CK -

ALK1



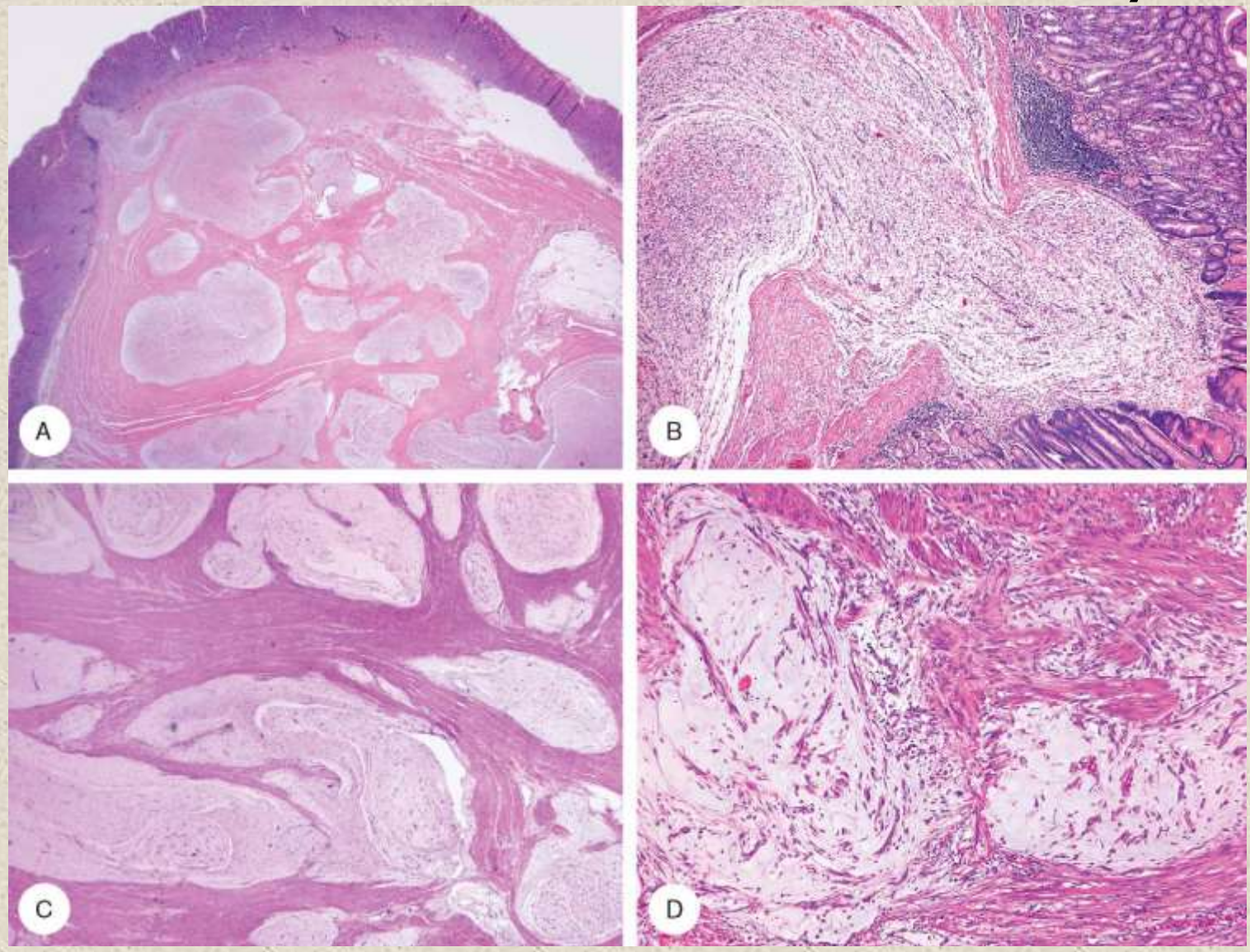
Final diagnosis:

Inflammatory myofibroblastic tumour

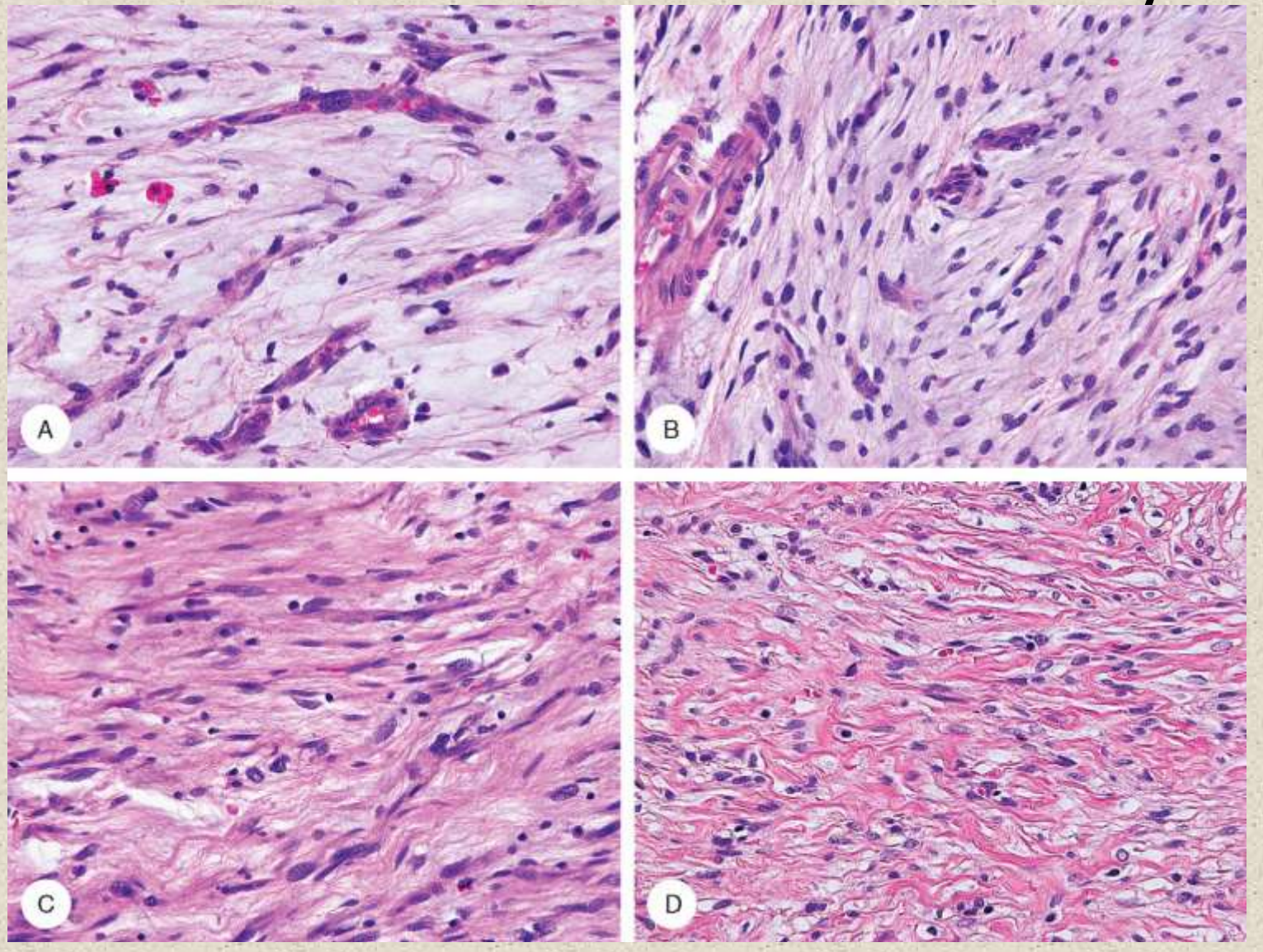
Plexiform fibromyxoma

- aka ‘Plexiform angiomyxoid myofibroblastic tumour of the stomach (PAMTOTS)’; ‘fibroangiomyxoma’.
- 150 GISTs : 1 plexiform fibromyxoma.
- Young-middle aged adults of either sex.
- Non-syndromic.
- Gastric antrum; nowhere else in GIT.

Plexiform fibromyxoma (Miettinen *et al*. *AJSP* 2009; **33:** 1624)



Plexiform fibromyxoma (Miettinen *et al*. *AJSP* 2009; **33:** 1624)

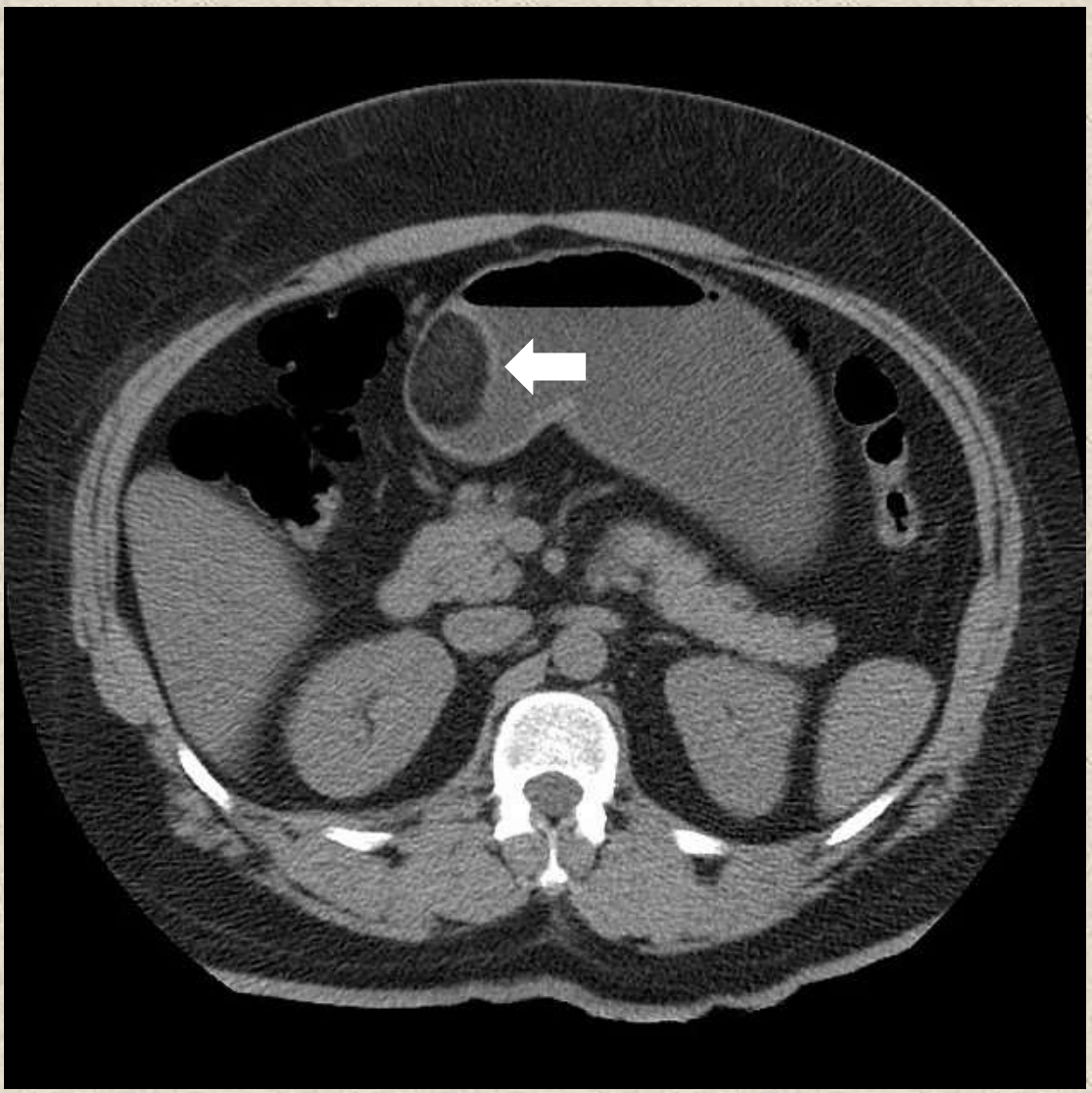


Plexiform fibromyxoma

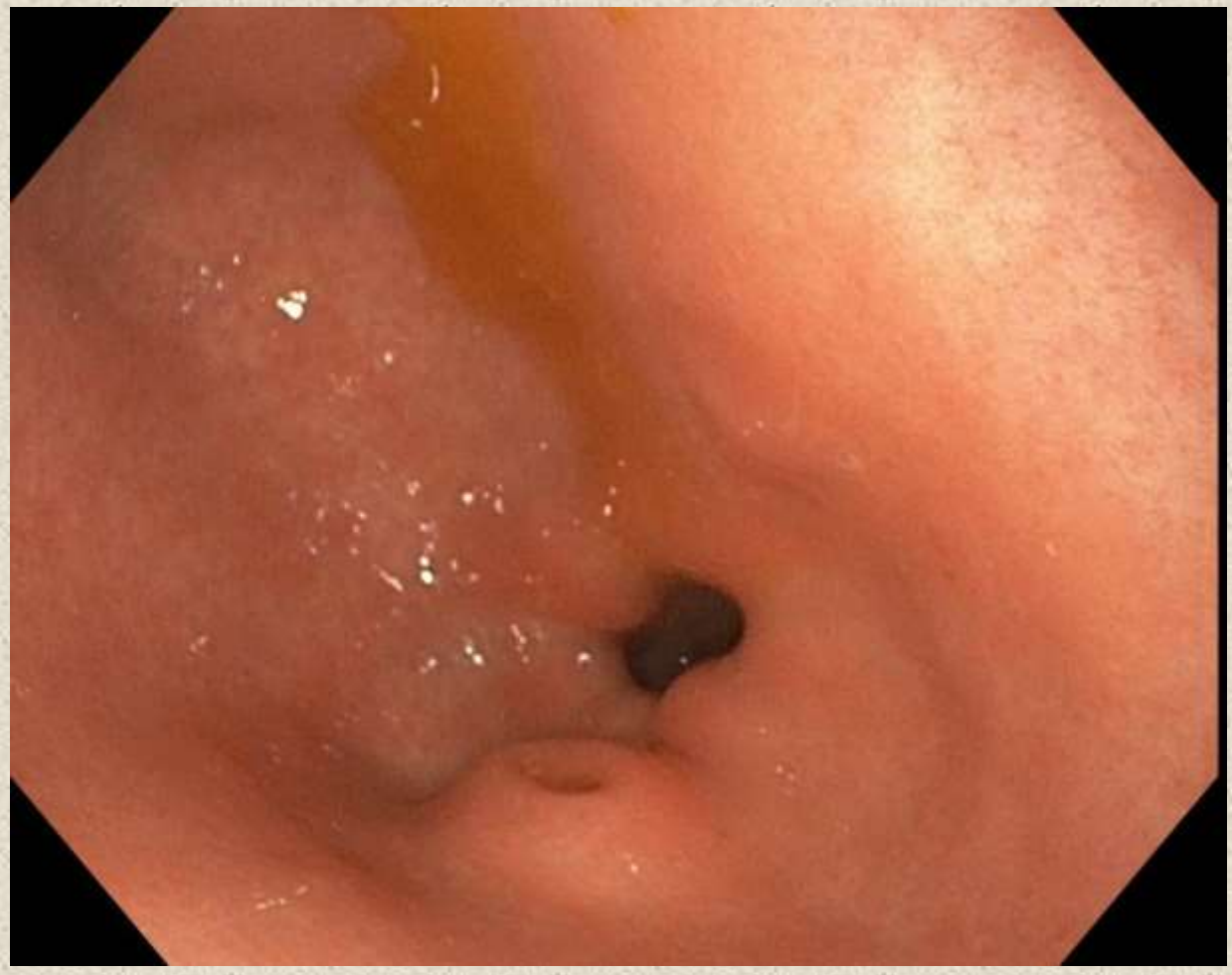
- **SMA+** (8/10 tested) and **CD10+/-** (1/3 tested).
- Negative for CD117, DOG1, CD34, desmin.

EUS-biopsy

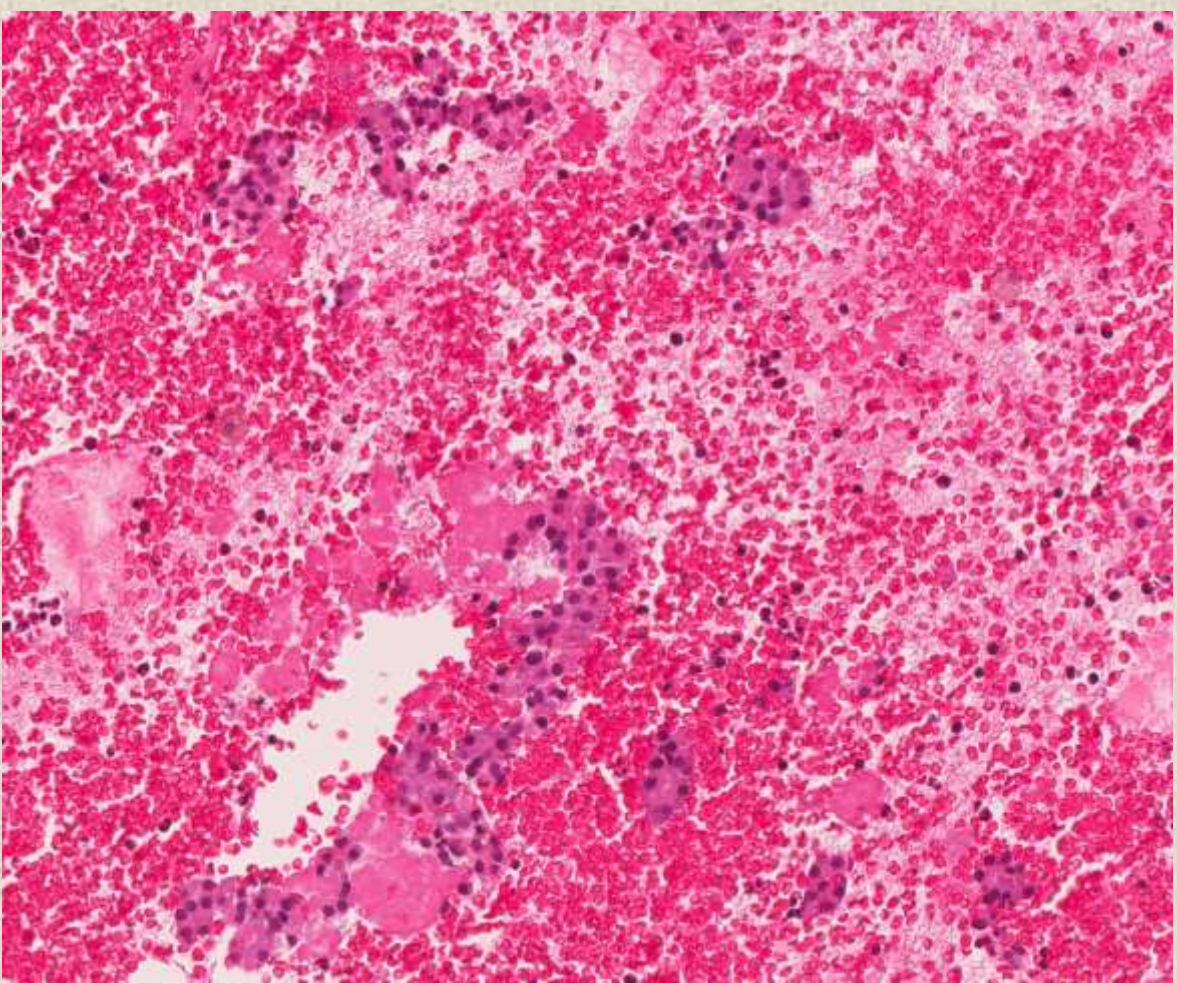
- Lipoma



EUS-biopsy



EUS-biopsy



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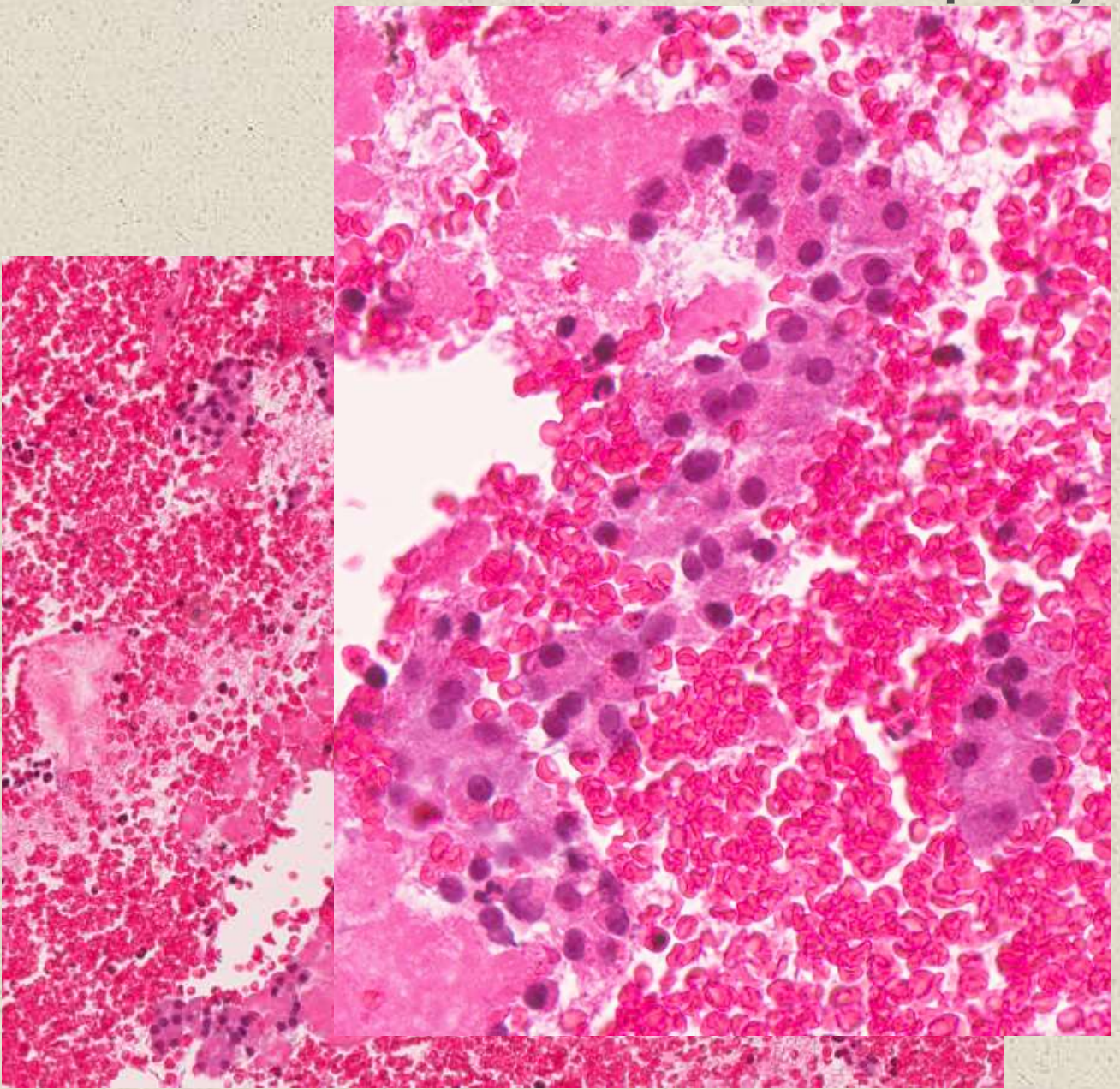
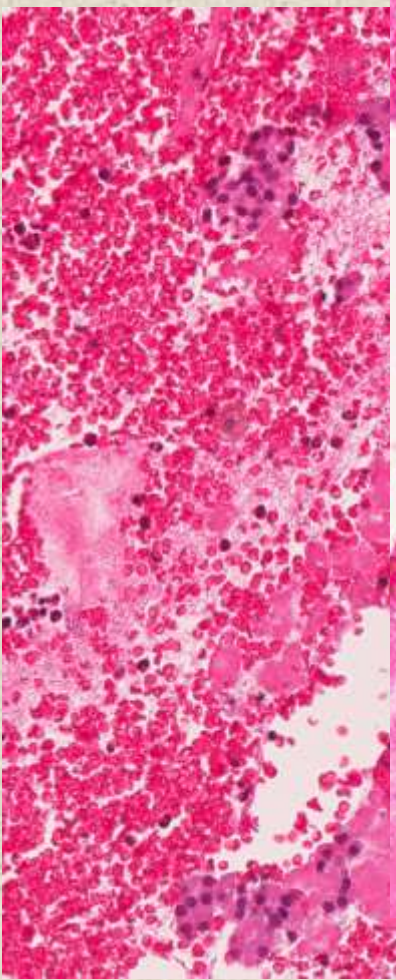
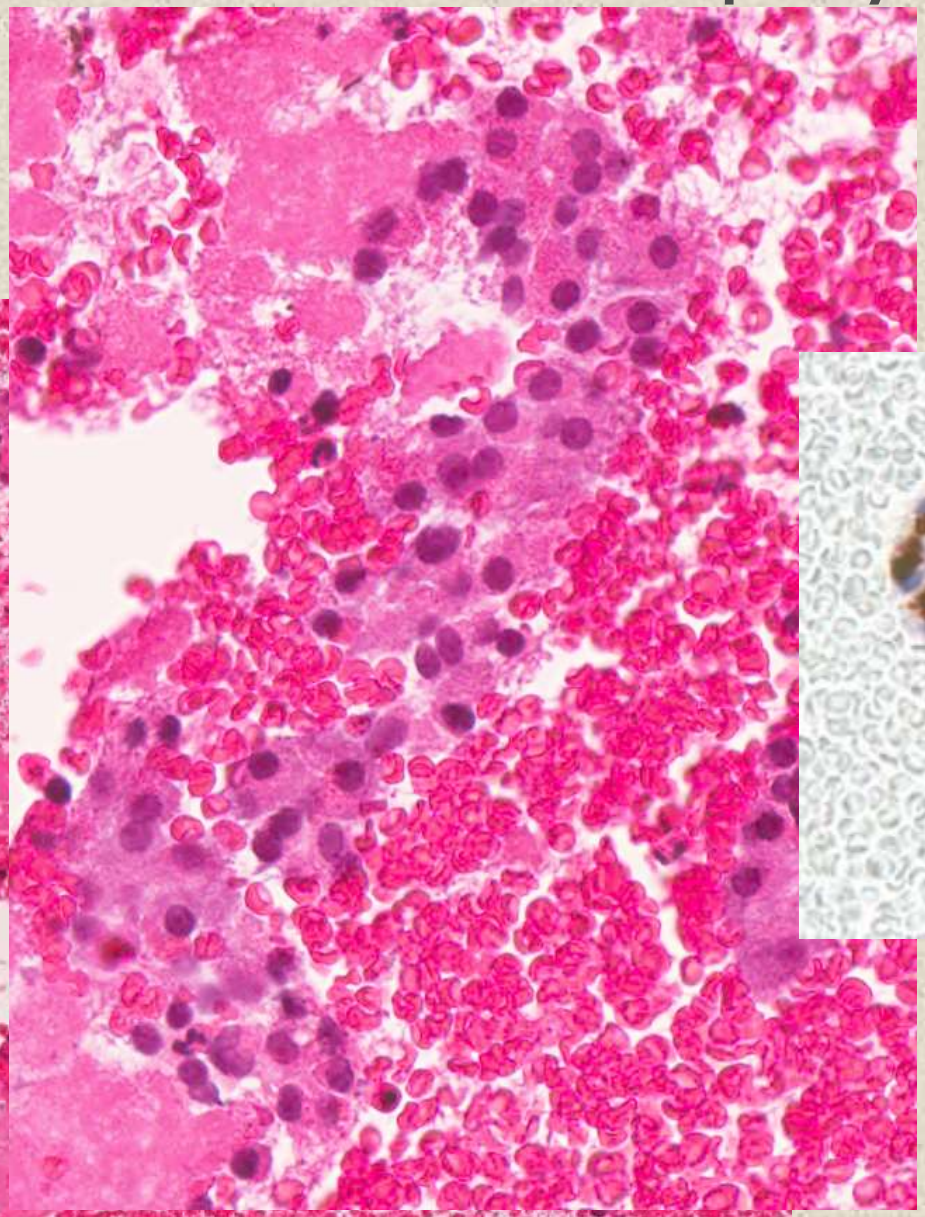
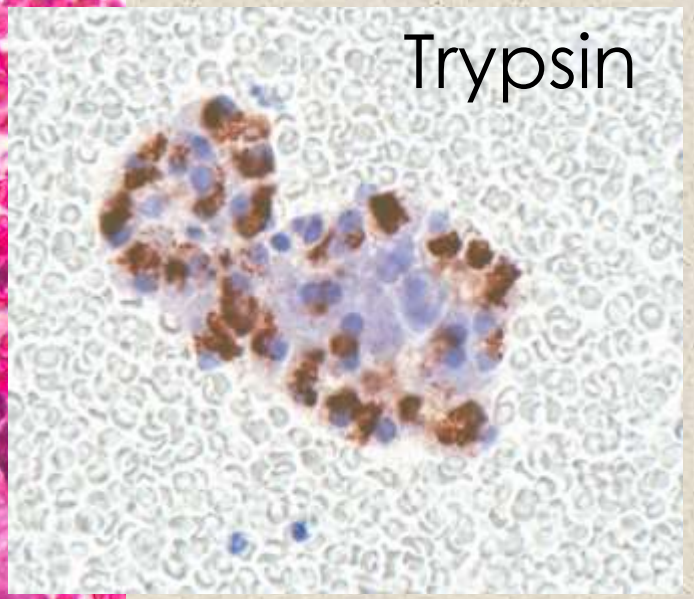


EUS-biopsy







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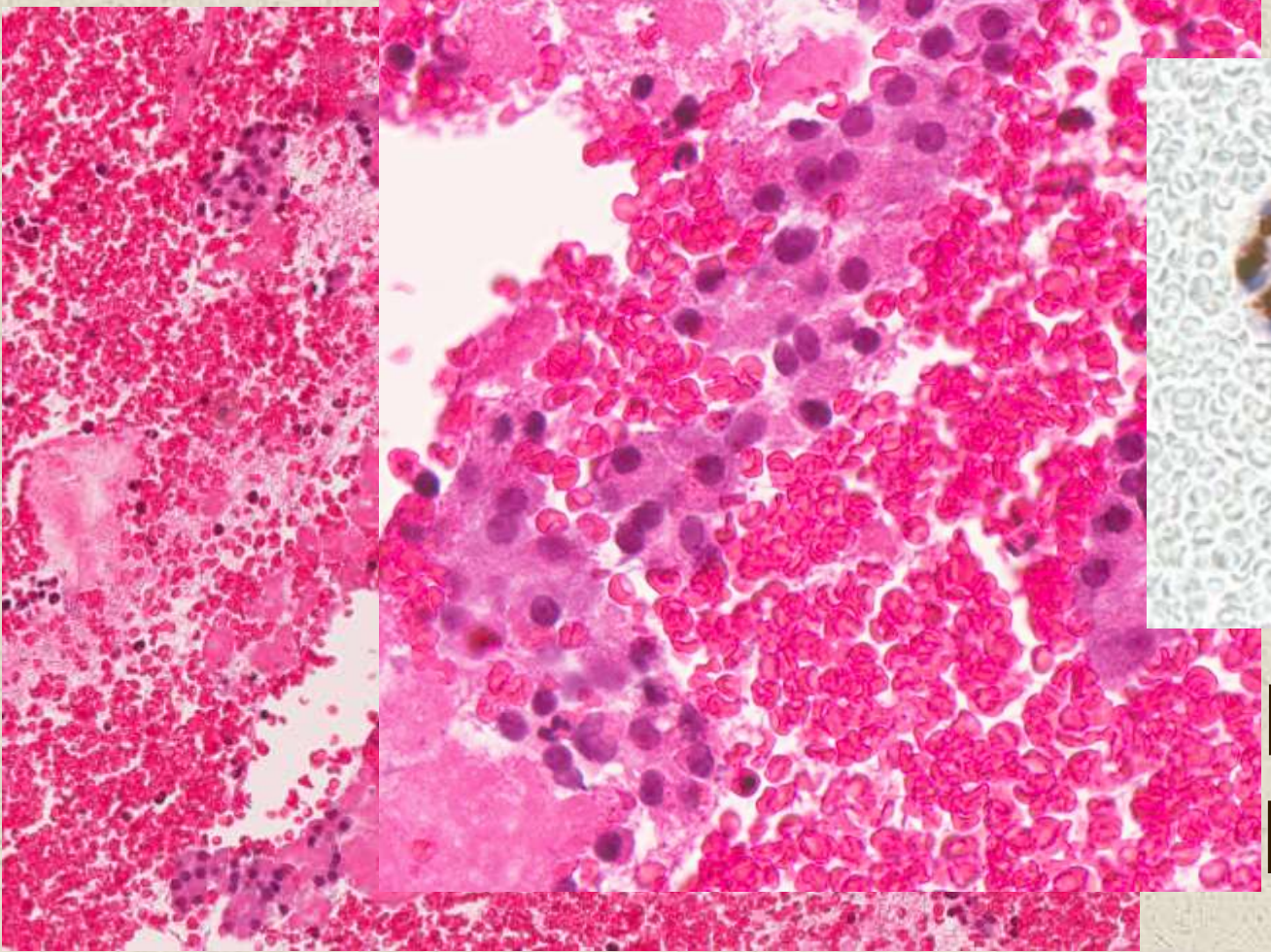
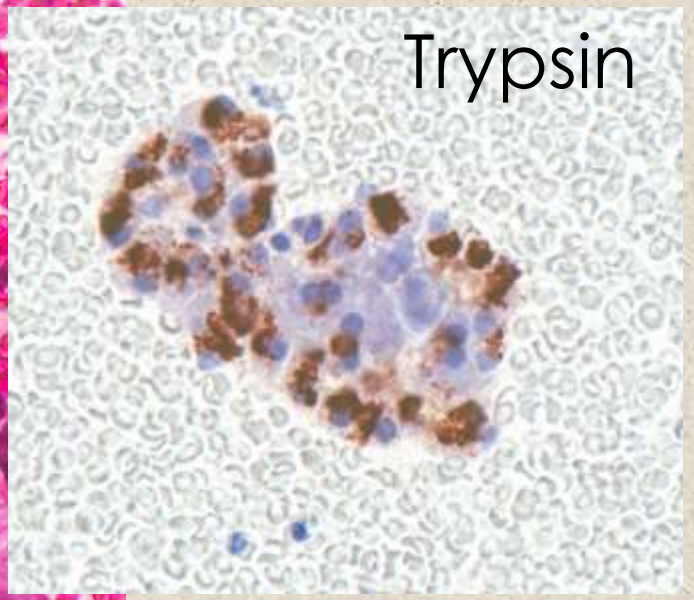
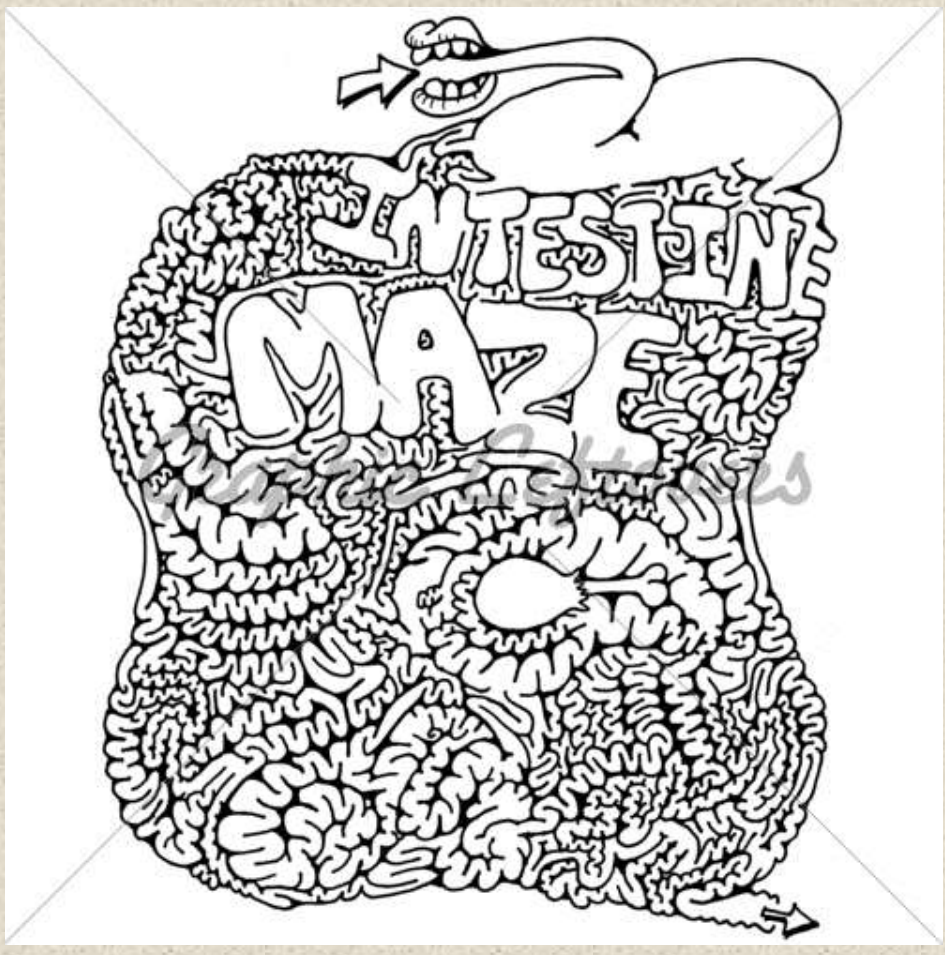




Pancreatic heterotopia

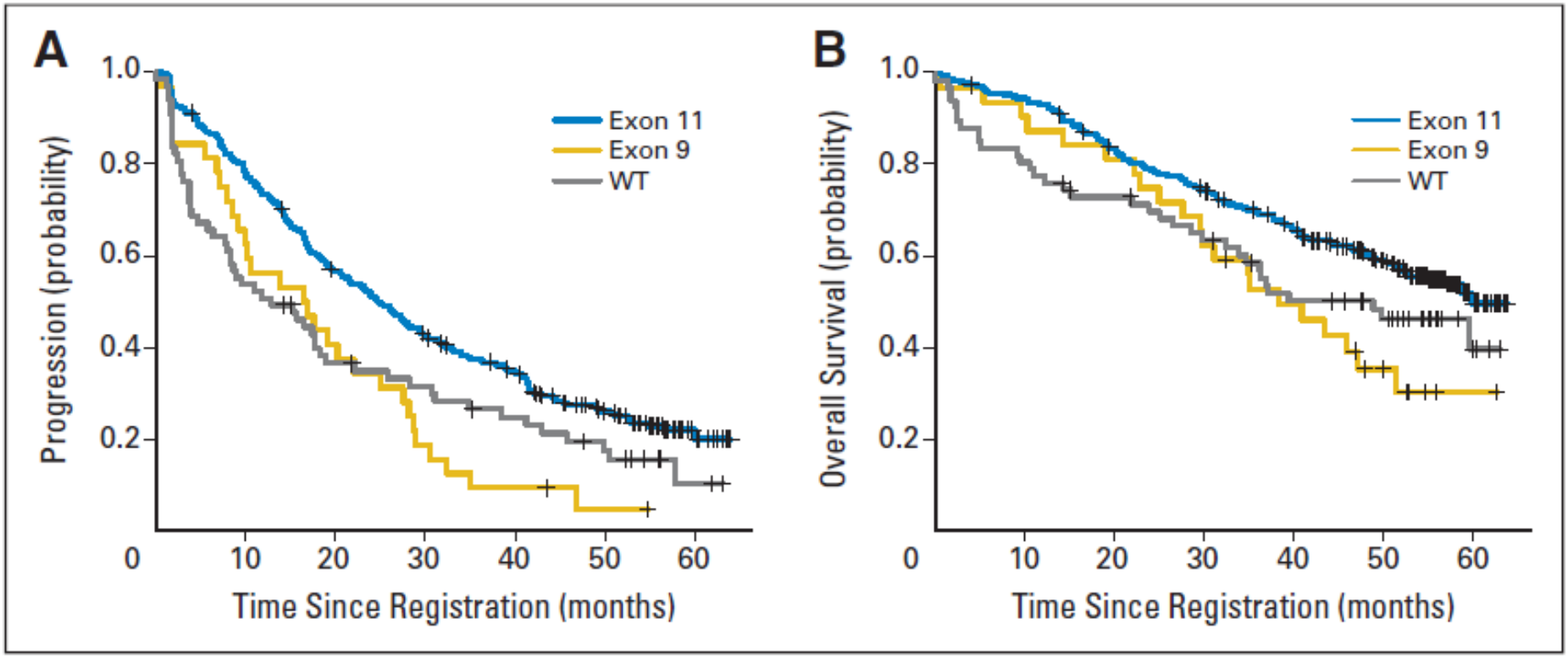
Small intestine

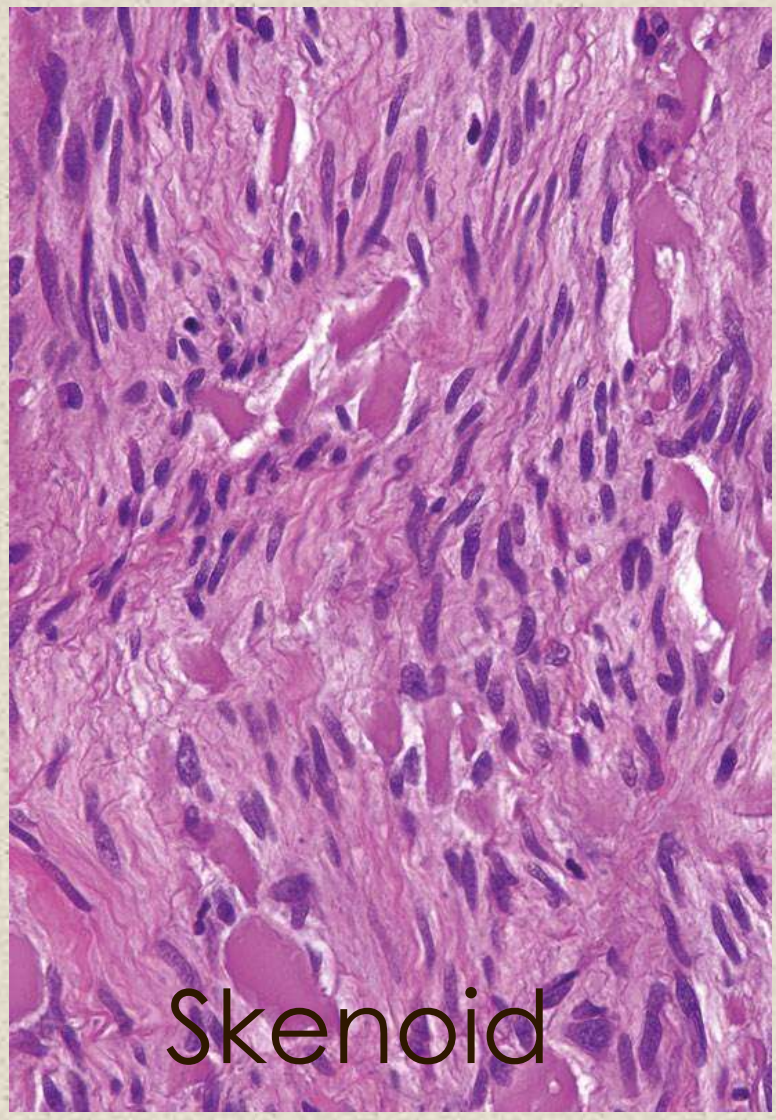


- GIST
- Inflam. fibroid polyp
- Reactive nodular fibrous pseudotumour
- *******

GIST

- KIT exon 9 mutant (relative resistance to imatinib)




Skenoid


Keloid

Reactive Nodular Fibrous Pseudotumor of the Gastrointestinal Tract and Mesentery

A Clinicopathologic Study of Five Cases

Rhonda K. Yantiss, M.D., G. Petur Nielsen, M.D.,
Gregory Y. Lauwers, M.D., and Andrew E. Rosenberg, M.D.

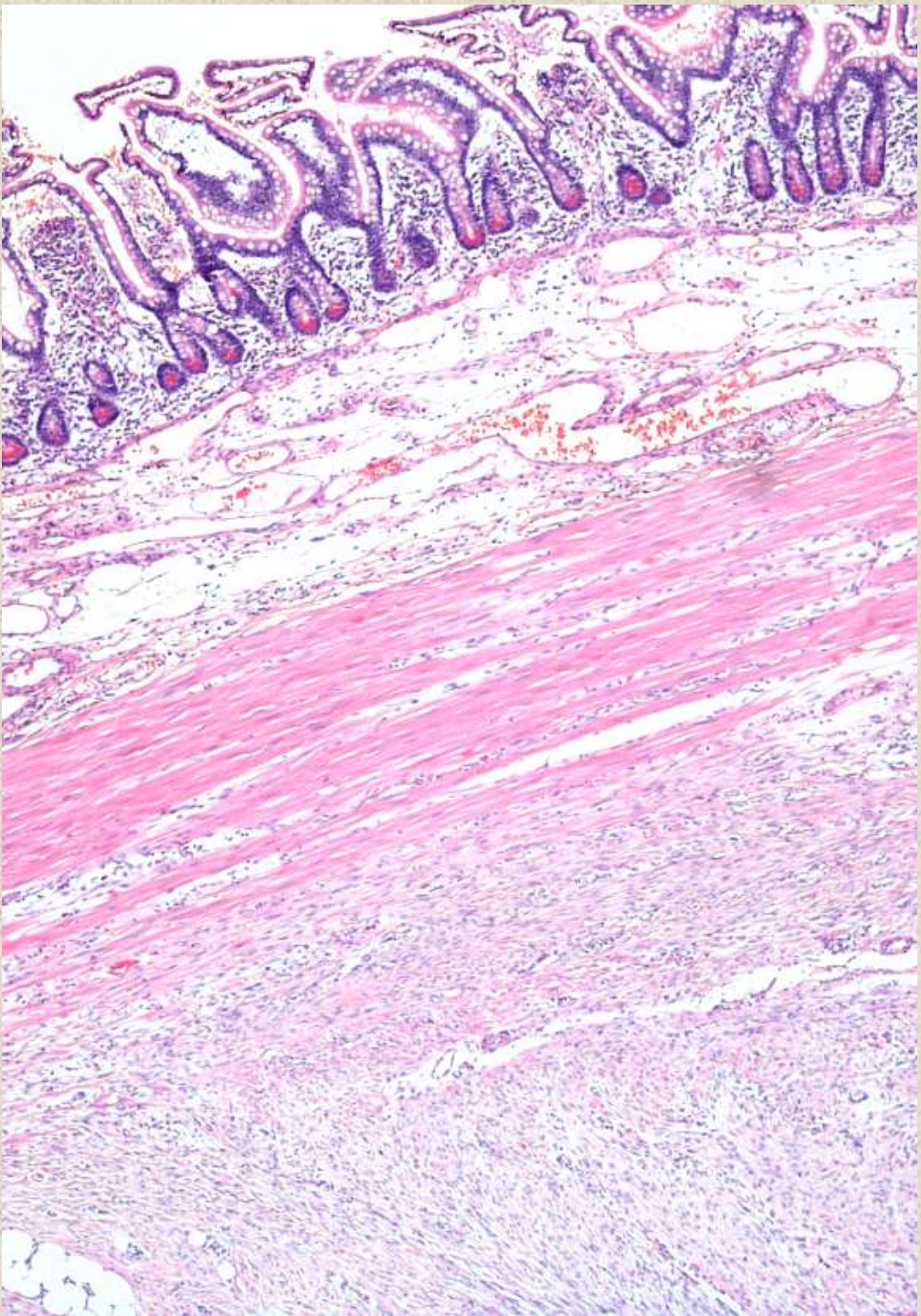
Although the majority of mesenchymal lesions of the gastrointestinal tract are neoplastic in nature, nonneoplastic reactive processes may involve the gastrointestinal tract and mesentery, causing diagnostic confusion with more aggressive neoplasms, such as fibromatosis or gastrointestinal stromal tumors. In this study, we report a series of fibroinflammatory lesions of the gastrointestinal tract that we think represent a relatively cohesive group of tumors and describe the clinical and pathologic features of this entity, which we have termed "reactive nodular fibrous pseudotumor." The tumors affected five patients (four male and one female patient) who ranged in age from 48 to 71 years (mean 56 years). Two patients presented with acute abdominal pain without a significant past medical history, two had incidental lesions discovered during evaluation for other medical conditions, and one was found to have an abdominal mass. Three patients had a history of abdominal surgery. The tumors were multiple in three patients and solitary in two patients. Follow-up was available for four patients. Three patients had no residual disease following surgical resection (mean follow-up 16.3 months) and one patient who had an incomplete surgical resection had stable disease at 26 months. In summary, we report a series of distinct intraabdominal fibroinflammatory pseudotumors that we have collectively termed "reactive nodular fibrous pseudotumors." These lesions are uncommon and may infiltrate the bowel wall, thereby mimicking primary bowel neoplasms or intraabdominal fibromatosis. Recognition of these nonneoplastic lesions is important, as they pursue a benign clinical course, but may be confused with other mesenchymal neoplasms that require more aggressive treatment.

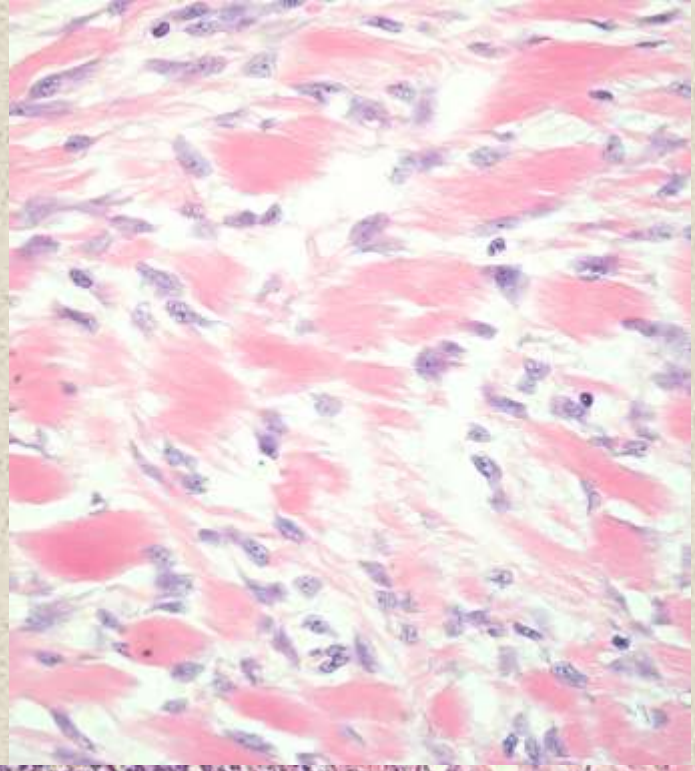
Key Words: Reactive nodular fibrous pseudotumor—Fibroinflammatory tumor—Fibromatosis—Sclerosing mesenteritis—Mesentery—Gastrointestinal tract—Differential diagnosis.

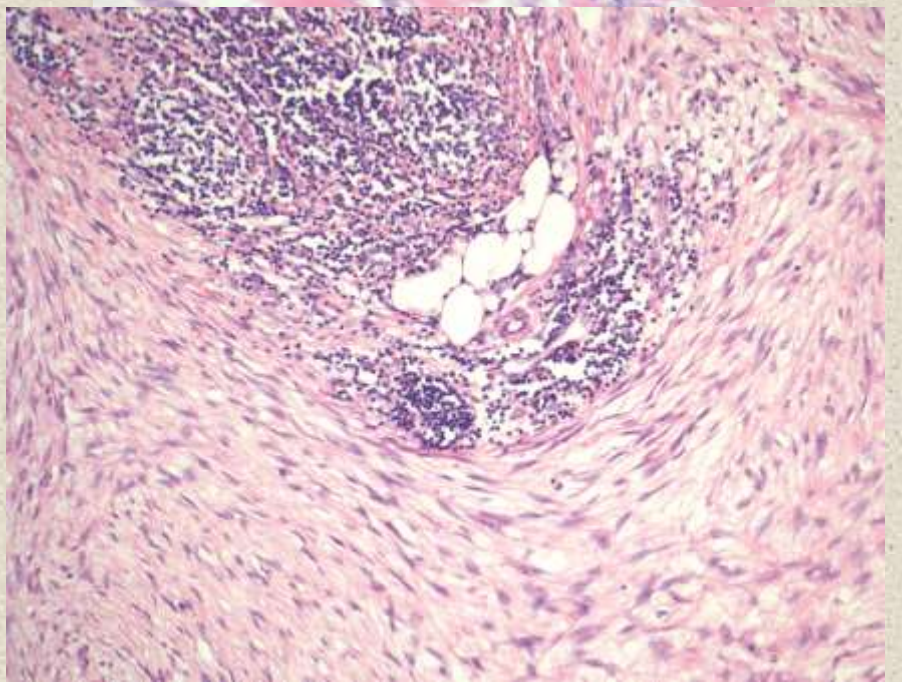
Am J Surg Pathol 27(4): 532–540, 2003.

RNFP

- Hx of intra-abdominal injury.
- **Well circumscribed**.
- **Serosal/subserosal**.
- (Myo)fibroblastic.
- **Keloidal** / collagen bundles.
- Chronic inflammation.







ORIGINAL ARTICLE

Malignant Gastrointestinal Neuroectodermal Tumor: Clinicopathologic, Immunohistochemical, Ultrastructural, and Molecular Analysis of 16 Cases With a Reappraisal of Clear Cell Sarcoma-like Tumors of the Gastrointestinal Tract

David L. Stockman, MD, Markku Miettinen, MD,† Saul Suster, MD,**
Dominic Spagnolo, MBBS, FRCPA, MD,‡§ Hugo Dominguez-Malagon, MD,‖
*Jason L. Hornick, MD, PhD,¶ Volkan Adsay, MD,# Pauline M. Chou, MD, PhD,***
Benhur Amanuel, MBBS, FRCPA,‡§ Peter VanTuinen, PhD, and Eduardo V. Zambrano, MD**

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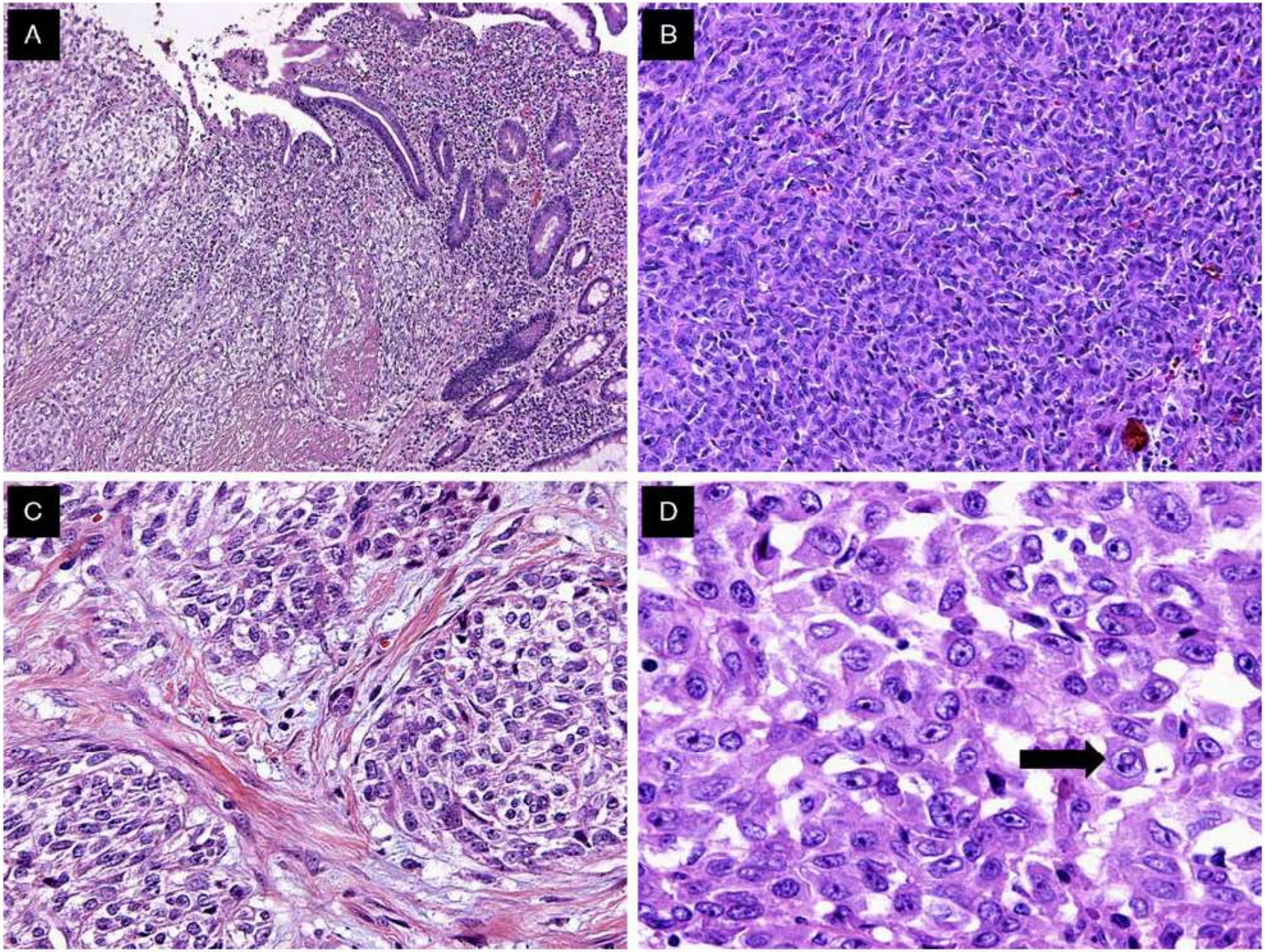
GNET

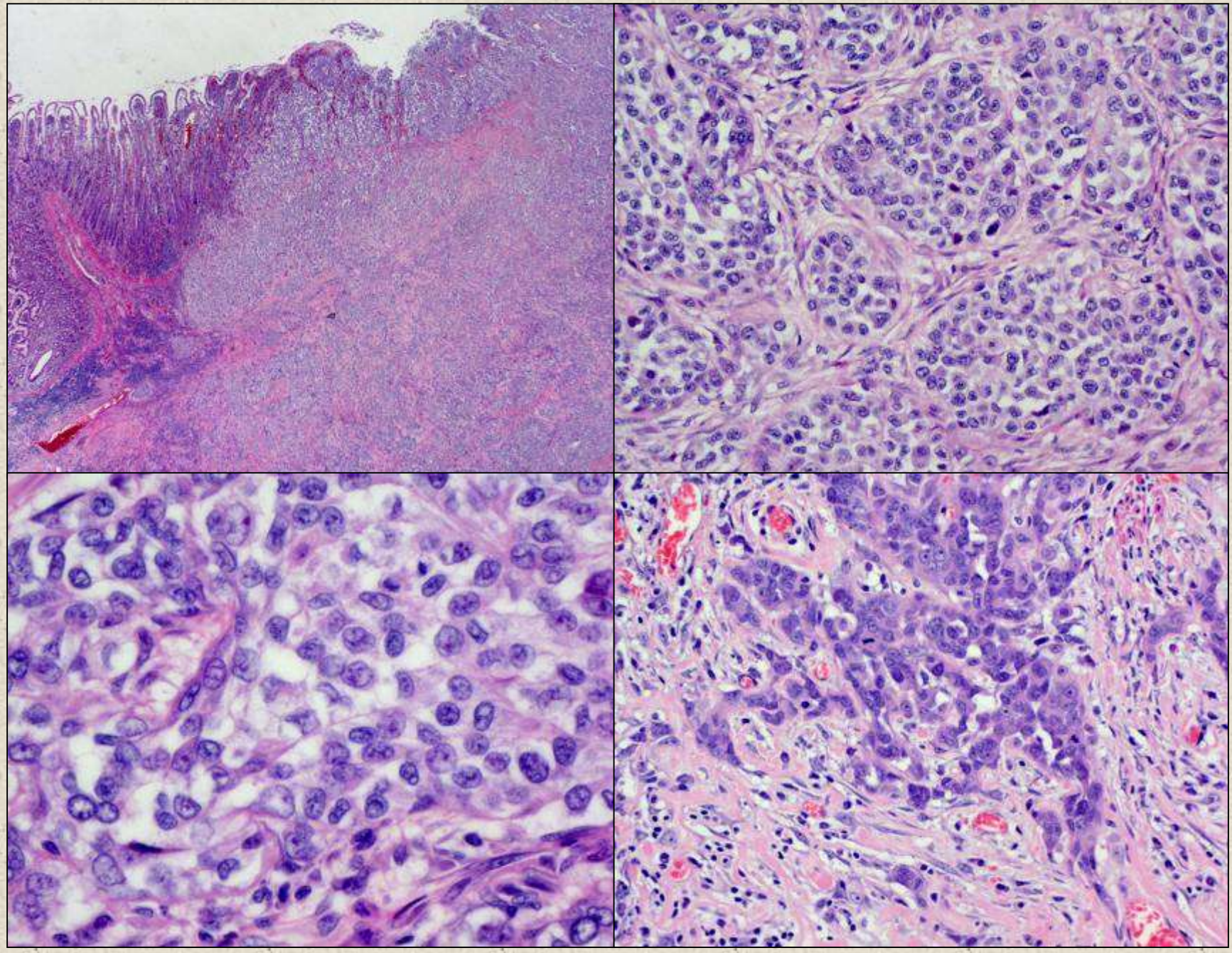
- Clear cell sarcoma-like tumours of the GIT (CCSLTGT)
- NOT to be confused with clear cell sarcoma of soft parts.
- Small bowel >> Stomach and large bowel

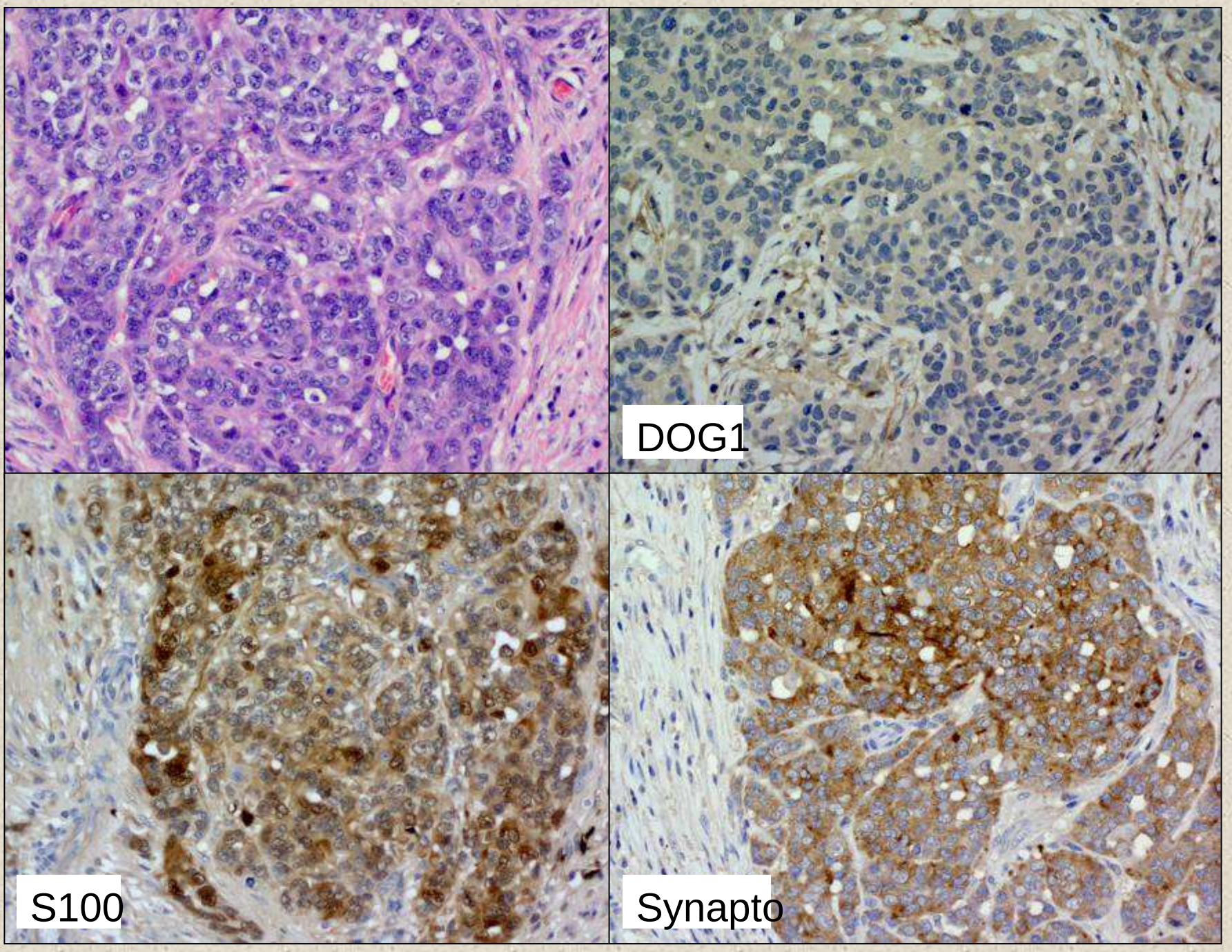

A
B
C
D

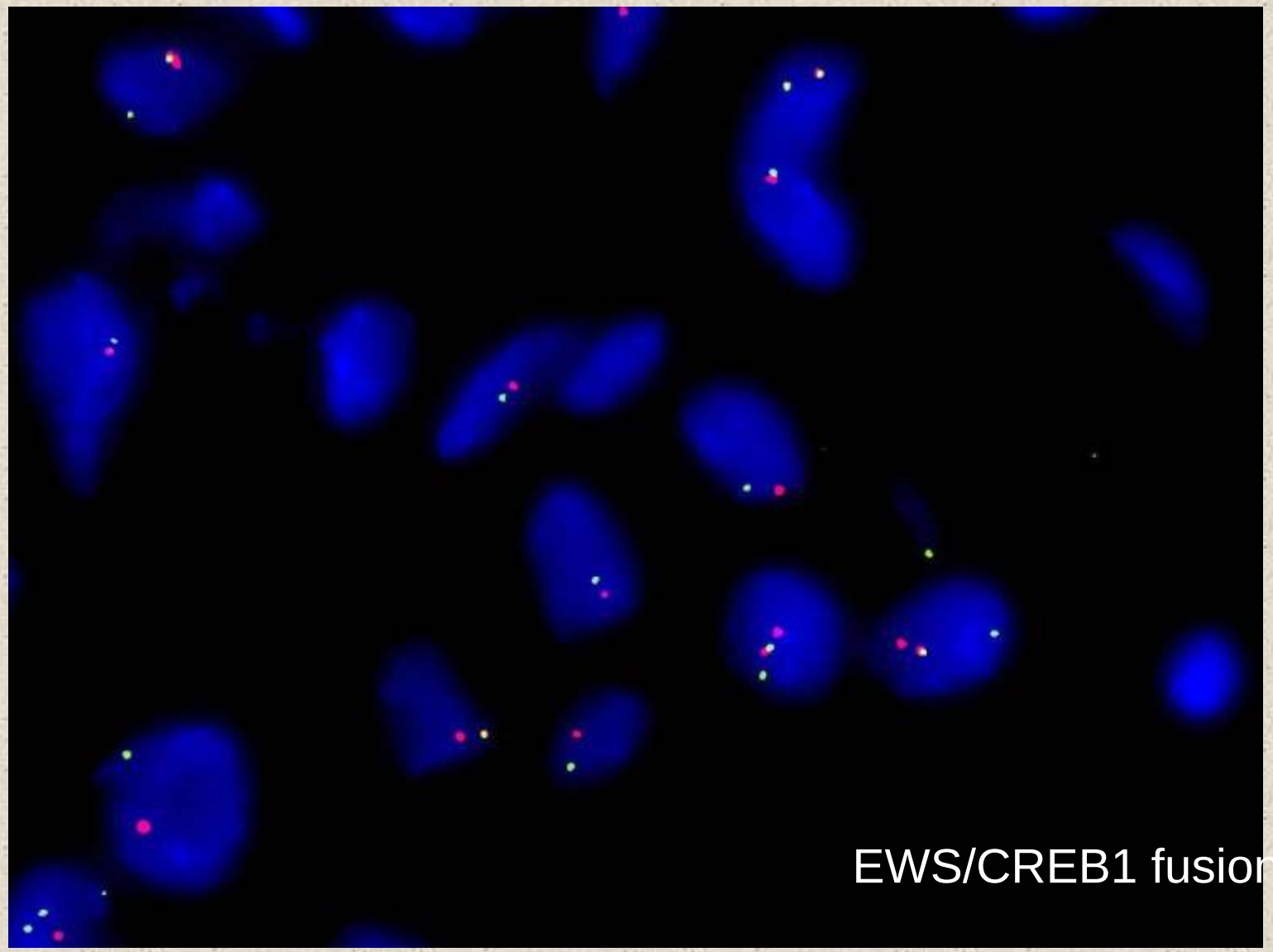
GNET

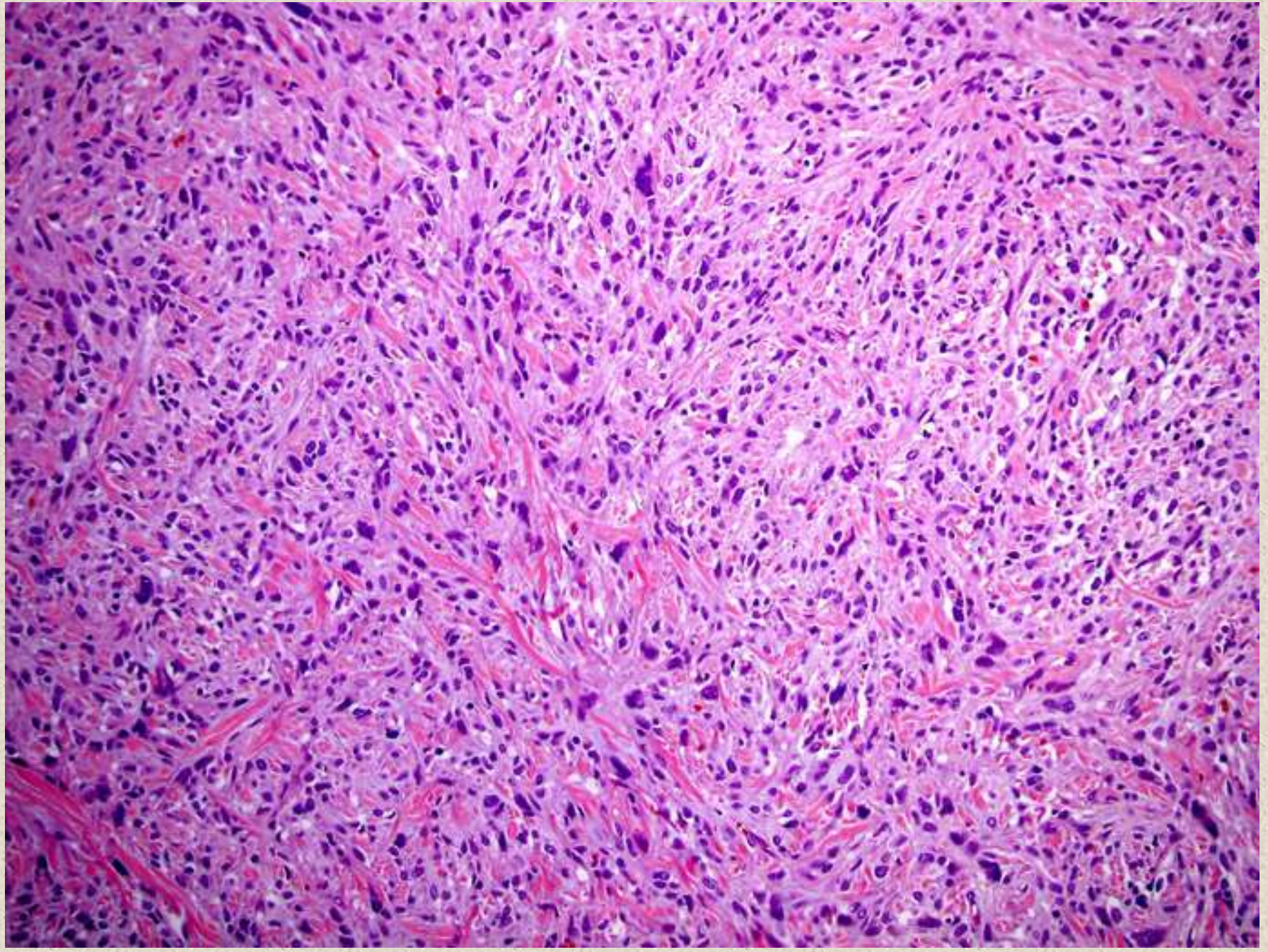
- **S100+** SOX10+
- Variably CD56 + and/or synaptophysin +
- Negative for Melan-A, HMB45, tyrosinase, CD117, DOG1, desmin, SMA.

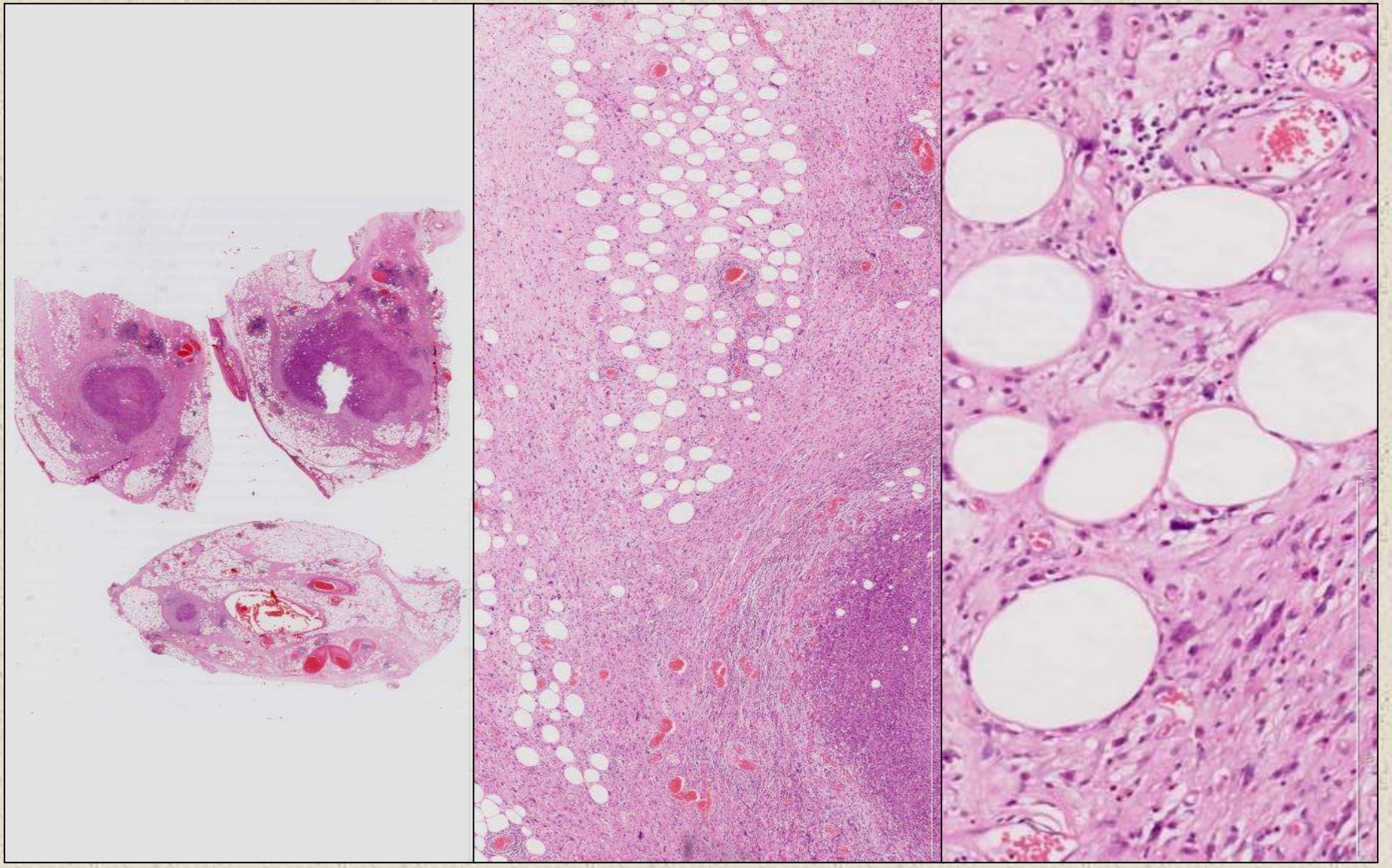
- ***EWS* gene rearrangements** (13 of 14 cases)



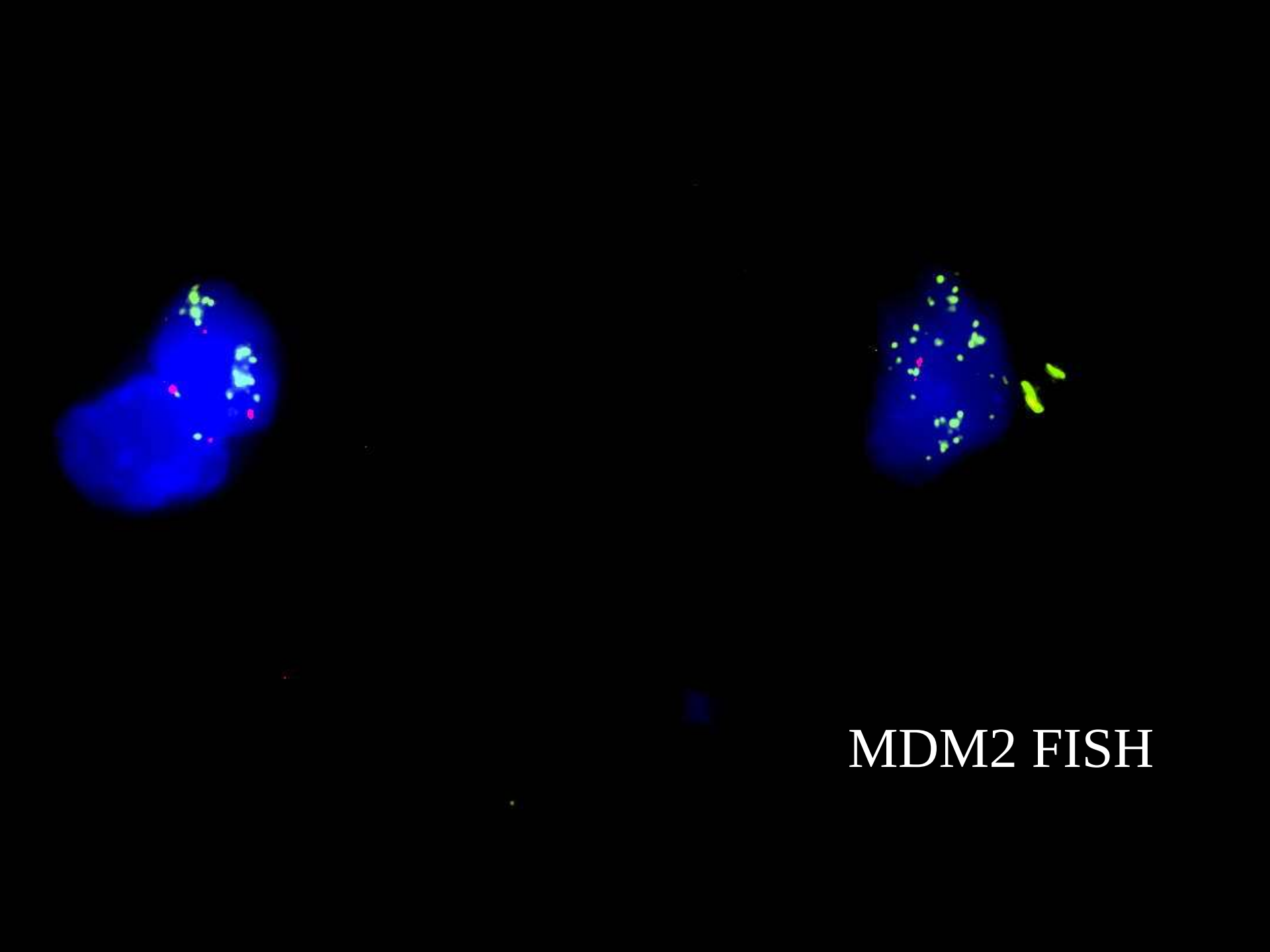

DOG1
S100
Synapto


EWS/CREB1 fusion



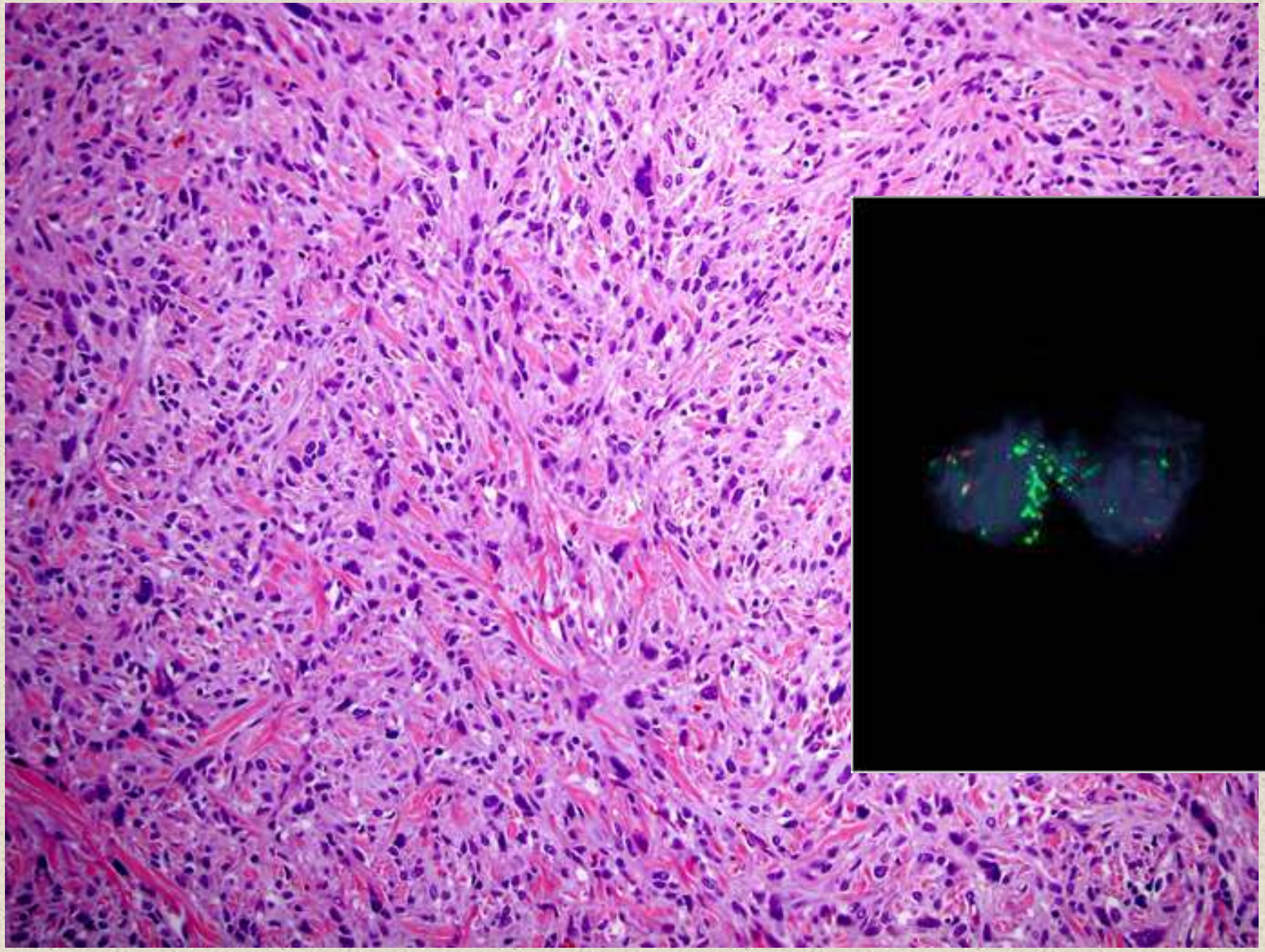


Peri-tumoral tissue


MDM2 FISH

Dedifferentiated liposarcoma

- Older male
- Mesenteric/retroperitoneal.
- Consider if pleomorphic cells with no specific immunophenotype.
- **MDM2 amplification** (FISH).



Summary

- Love mesenchymal neoplasms
- Schmooze your local sarcoma pathologist
- Embrace EUS-biopsies