Mesenchymal GI Tract Lesions

Old Fashioned Morphology and Modern Science

The Secret

- Diagnosing GIT mesenchymal tumors is really about knowing which tumors live in which layers
- For example, inflammatory fibroid polyp (with PDGFRA mutations) is in the submucosa whereas GIST (also with PDGFRA mutations) is in the muscularis propria

Layers – Centered in:

Mucosa

- Some nerve sheath tumors
- “Benign fibroblastic polyp”/perineurioma
- Incidental leiomyomas of muscularis mucosae
- Synovial sarcoma [super rare]
- Mucosal melanoma [anus, esophagus]

Submucosa

- Inflammatory fibroid polyp
- Some benign nerve sheath tumors
- Gangliocytic paraganglioma

Layers – Centered in:

Muscularis propria

- GIST
- GIT schwannoma [with lymphoid cuff]
- Esophageal leiomyomas
- GIT glomus tumors
- Ganglioneuromatosis
- GIT tract clear cell sarcoma

Mesentery

- Desmoid/ fibromatosis
- Inflammatory myofibroblastic tumor
- Sclerosing mesenteritis
- Mesenteric myositis ossificans

Layers

Whevever it wants to

- Metastatic MELANOMA
- Some sarcomatoid carcinomas [such as renal cell ca]

Mesentery

Inflammatory Myofibroblastic Tumor (IMT)

- Pulmonary lesions called “inflammatory pseudotumors” have been recognized for many years and regarded as part of a spectrum of lesions called “plasma cell granulomas”

Terms for IMT

- Inflammatory pseudotumor
- Plasma cell granuloma
- Plasma cell pseudotumor
- Xanthomatous pseudotumor
- Pseudosarcomatous myofibroblastic proliferation
- Inflammatory myofibrohistiocytic proliferation

IMT

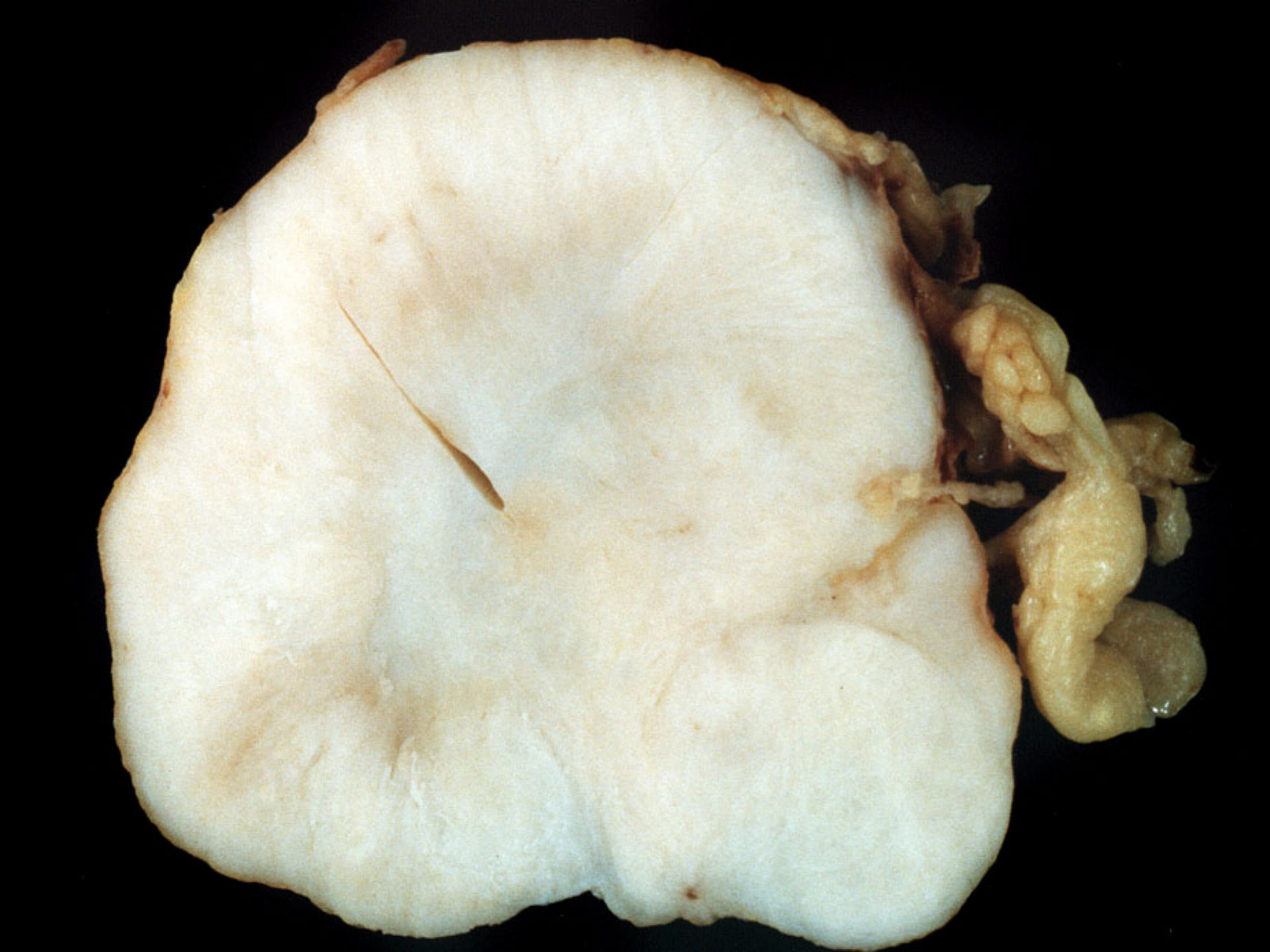
- Subsequently, similar tumors were described in the abdomen and other soft tissue sites.

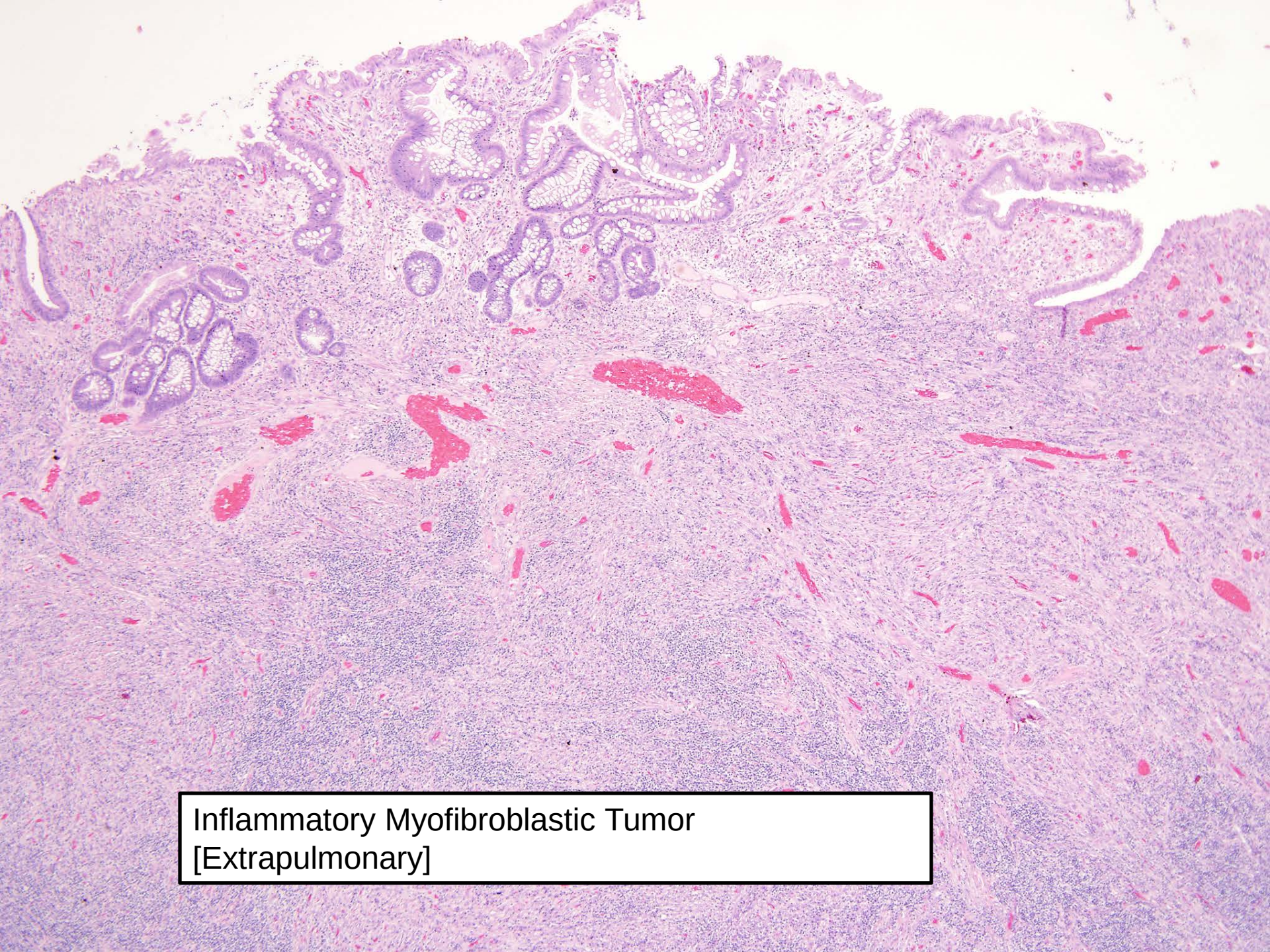
“Inflammatory Fibrosarcoma”

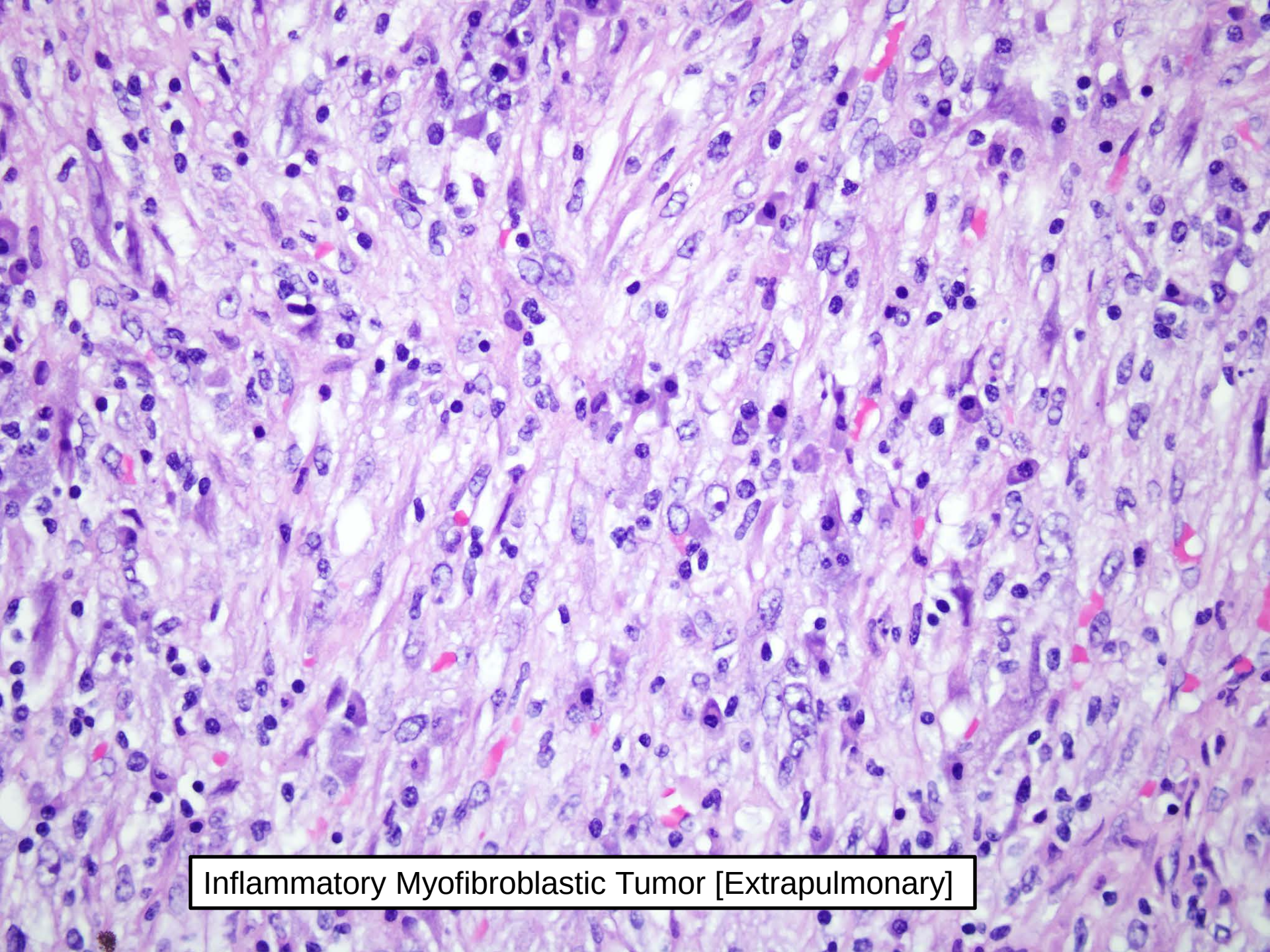
- AFIP series , [Meis and Enzinger 1991], mesentery, omentum and retroperitoneum (over 80% of cases).
- Systemic symptoms.
- Both solitary and multinodular (30%) tumors up to 20 cm in diameter.

Inflammatory Fibrosarcoma

- Myofibroblasts and fibroblasts in fascicles or whorls, and also histiocytoid cells.
- Variable but often marked inflammatory infiltrate
- Immunostaining :smooth muscle actin, cytokeratin.
- 37% recurred and 3 cases (11%) metastasized. A quarter of the patients died of disease.

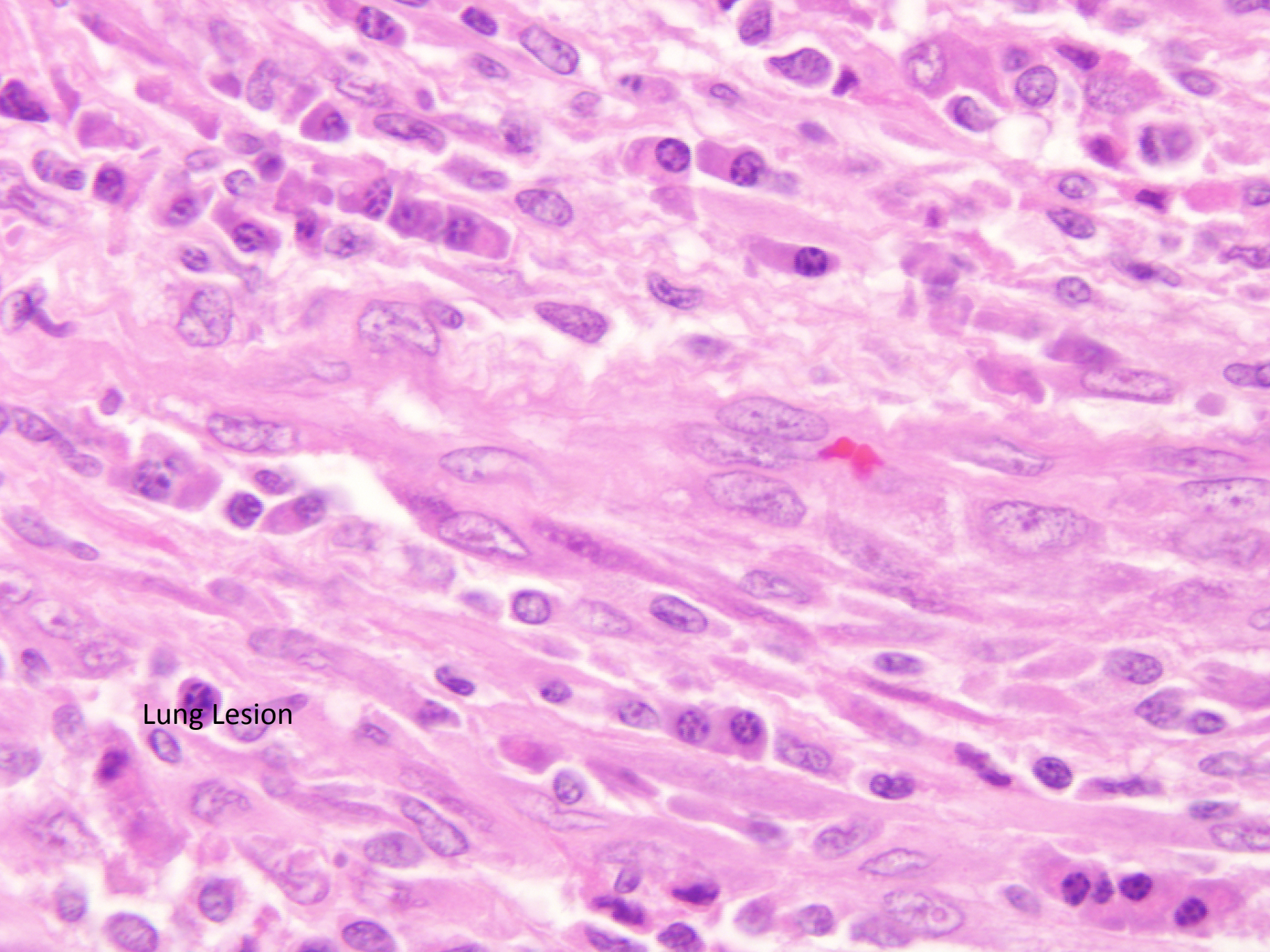


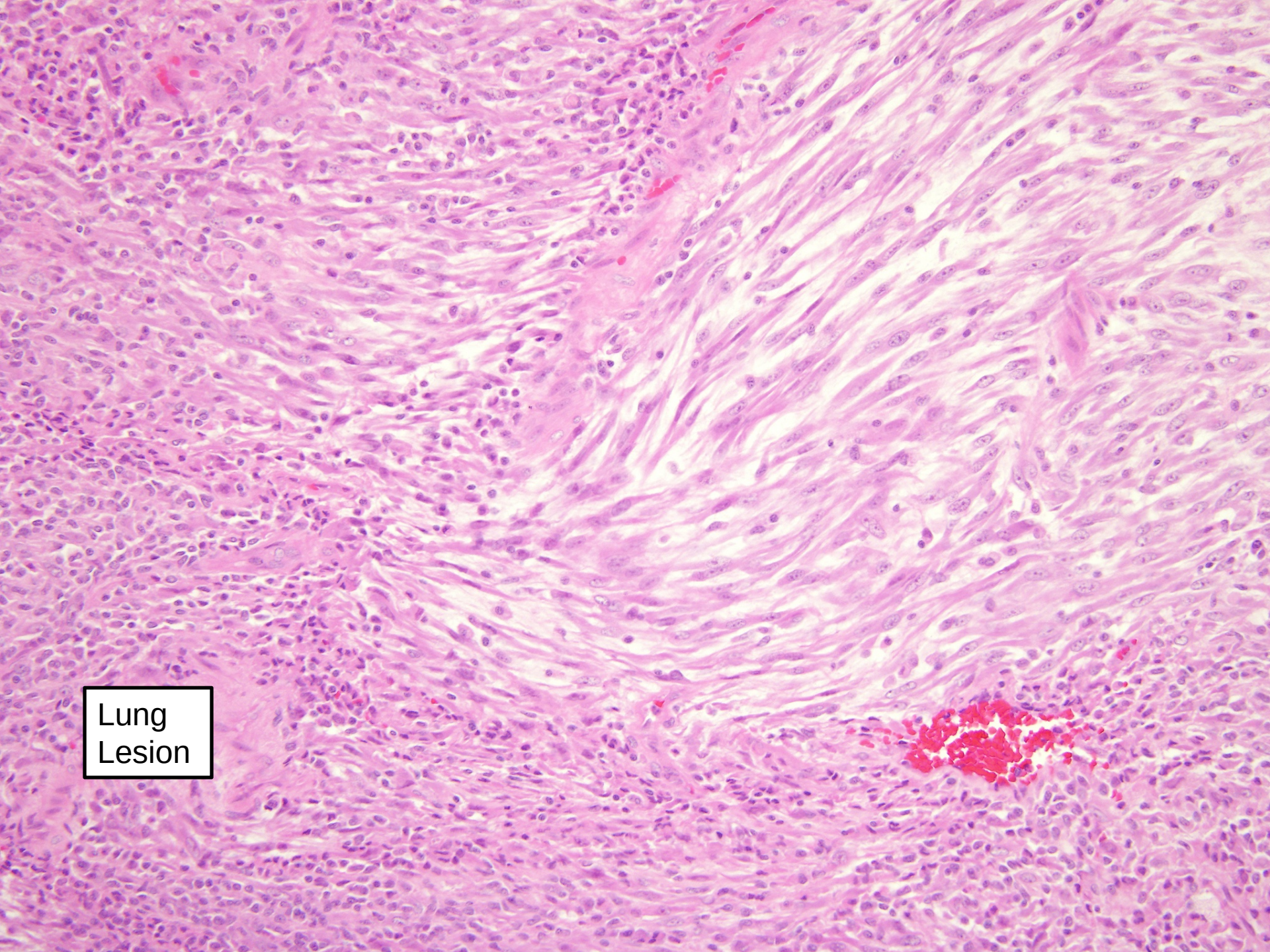

Inflammatory Myofibroblastic Tumor
[Extrapulmonary]

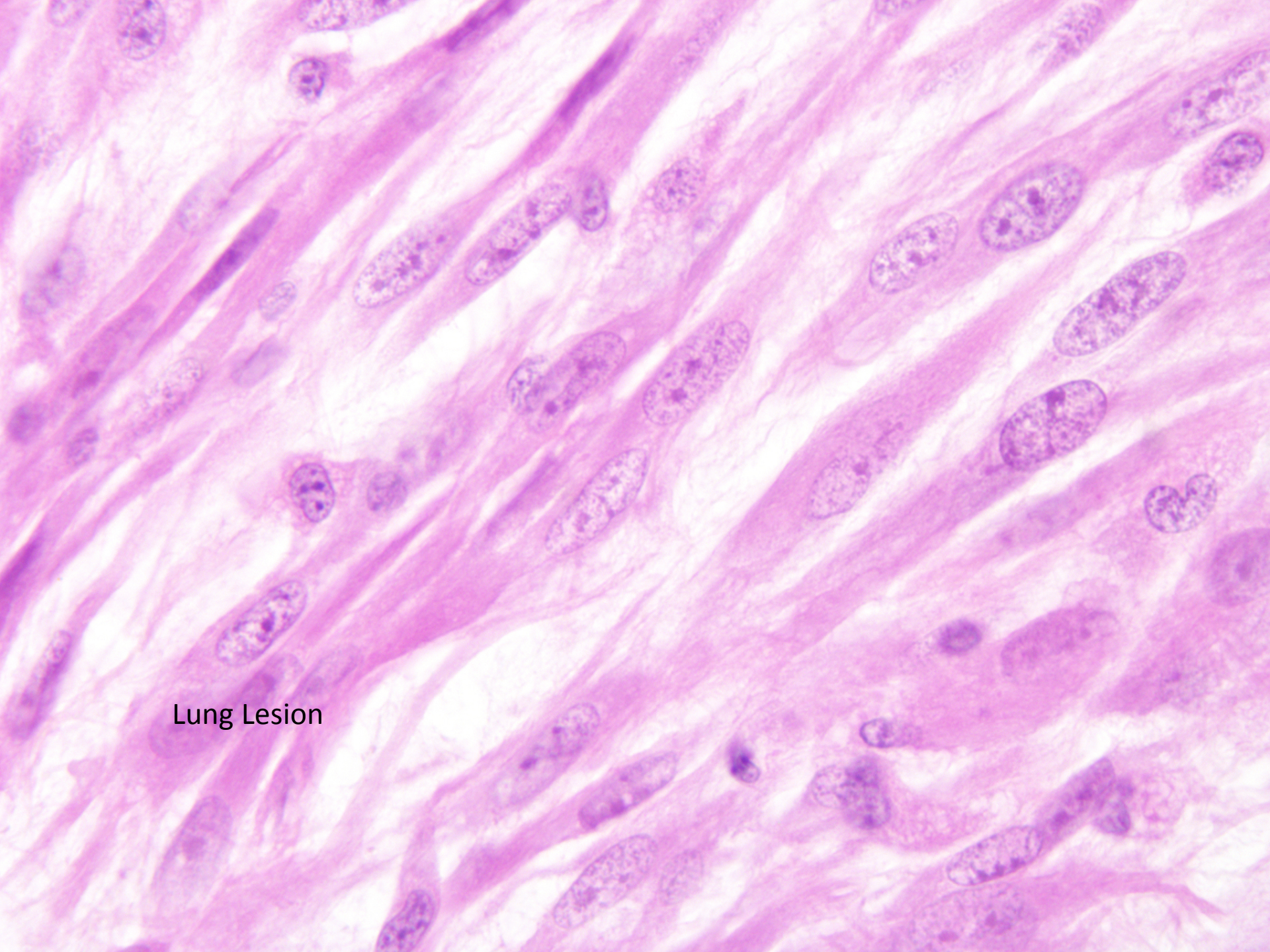

Inflammatory Myofibroblastic Tumor [Extrapulmonary]

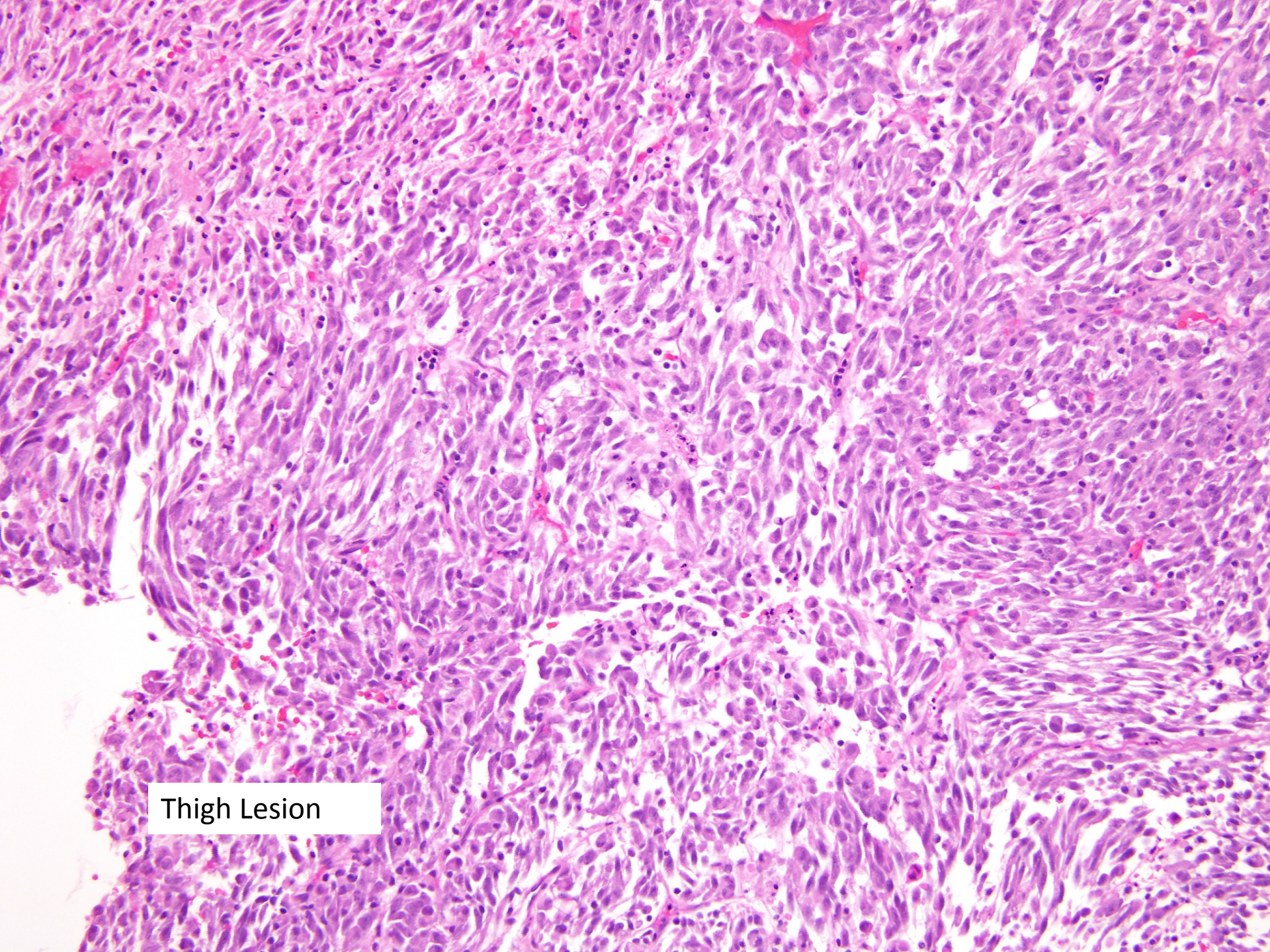
Inflammatory Myofibroblastic Tumor [Extrapulmonary]

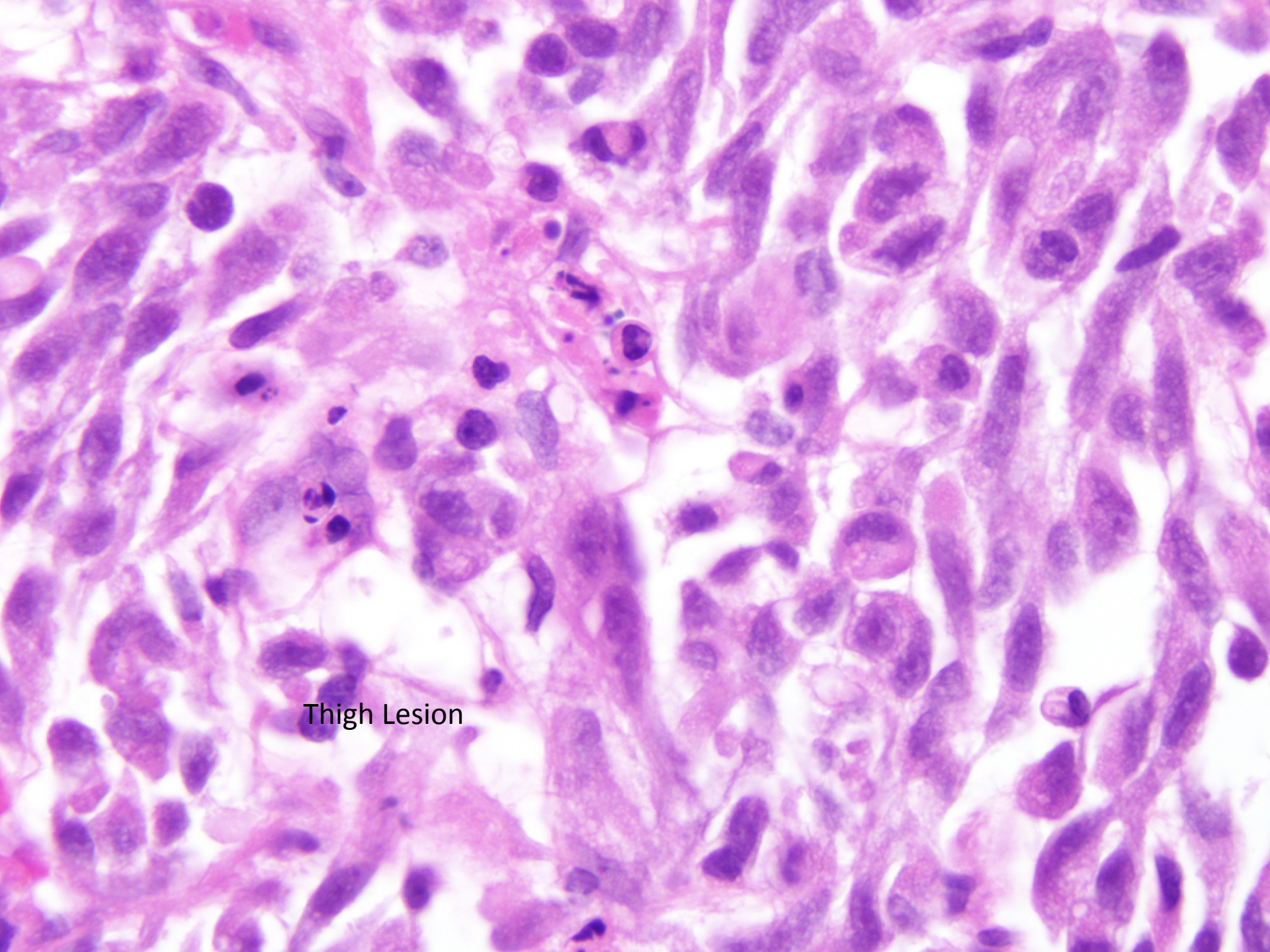
- Coffin et al 1995
- Mostly pediatric cases
- Similar to cases reported by Meis and Enzinger
- ? – Metastatic potential v. multicentricity
- Some cases DO behave aggressively and kill the patient


Lung Lesion


Lung
Lesion


Lung Lesion


Thigh Lesion


Thigh Lesion

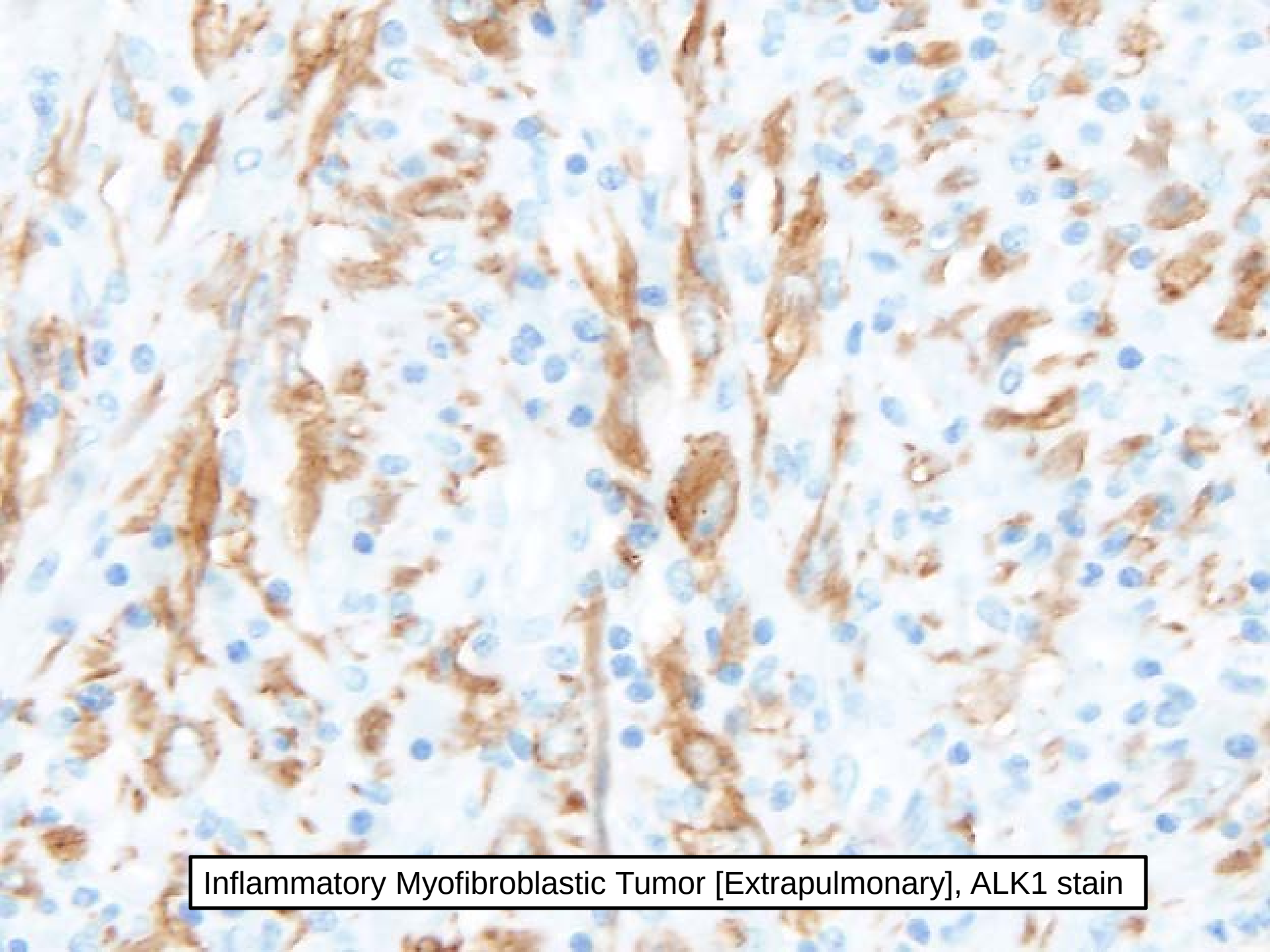
IMT/Inflammatory Fibrosarcoma

- IMT and inflammatory fibrosarcoma of soft tissues have now been recognized as ends of a spectrum of tumors unified by a common molecular profile, which are relatives of lung lesions

- Grouped together by the WHO

IMT; Important Discovery

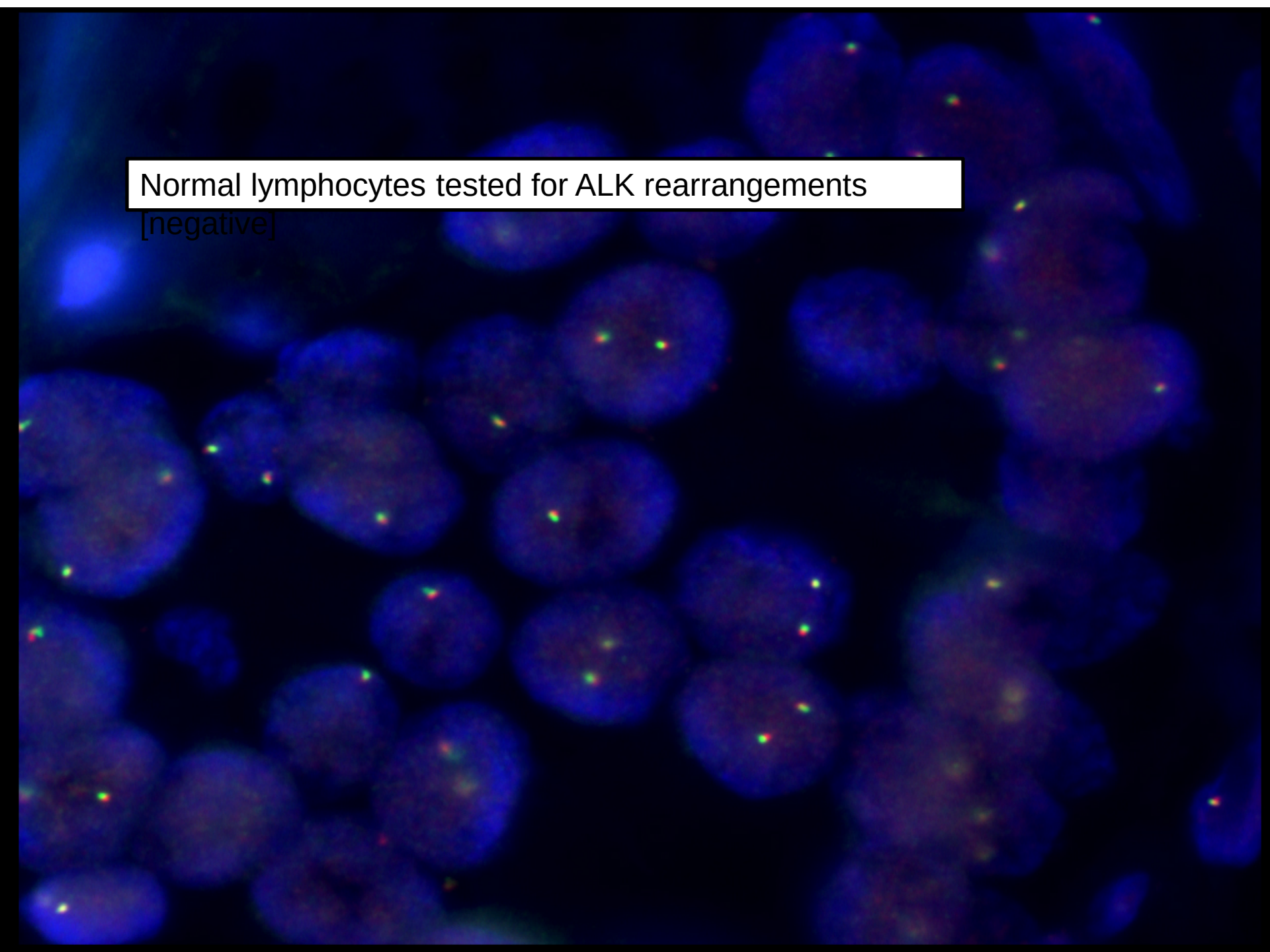
- **Griffin et al [1999] reported 3 IMT with rearrangements at 2p23 involving *ALK* gene**
- **Subsequently, *ALK* shown to be rearranged in a subset of IMTs from many sites**
- **Identified partners including *CLTC* , *RANBP2*, *TPM3* , *TPM4* , *CARS* *ATIC*, and *SEC1L1* .**



Inflammatory Myofibroblastic Tumor [Extrapulmonary], ALK1 stain

ALK FISH

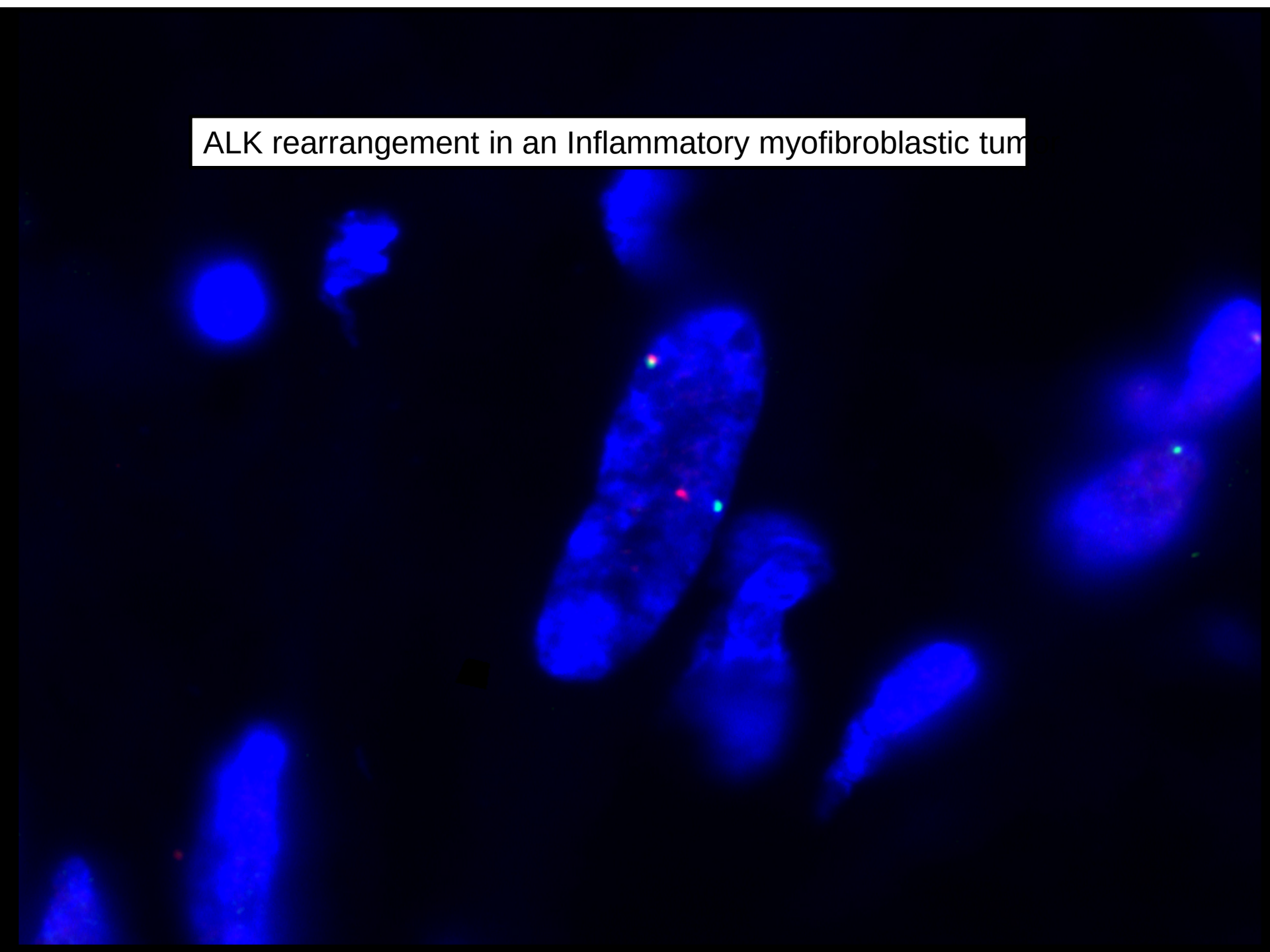
- The FISH test performed for *ALK* is a break apart rearrangement DNA probe.
- Different color fluorescent labels (orange and green) are hybridized to the DNA on either side of the 2p23 breakpoint on chromosome 2.
- The normal, or non-translocated chromosome, has the orange and green signals immediately next to each other, which are sometimes overlapped causing a yellow color to be observed, termed “fused signals or fusions”.
- In the normal control specimen, there are 2 of these fusions (2F) - one for each copy of chromosome 2 - present in each of the nuclei.


Normal lymphocytes tested for ALK rearrangements
[negative]

ALK FISH

- When the 2p23 breakpoint on chromosome 2 is rearranged (involved in a translocation), the orange and green signals are separated, and are visualized as distinct signals more than one signal width apart.

- The abnormal specimen thus has one fusion for the normal chromosome 2, and one orange and one green signal for the rearranged chromosome 2.


ALK rearrangement in an Inflammatory myofibroblastic tum

Targeted Therapy?

- Crizotinib (PF-02341066, Pfizer) - orally bioavailable, ATP-competitive, small-molecule inhibitor of the receptor tyrosine kinases (RTKs) c-Met (also known as hepatocyte growth factor receptor) and anaplastic lymphoma kinase (ALK),
- Used in lung cancer (about 5% of lung cancers have ALK rearrangements) and now IMT!!!
- Butrynski JE, D'Adamo DR, Hornick JL, Dal Cin P, Antonescu CR, Jhanwar SC, Ladanyi M, Capelletti M, Rodig SJ, Ramaiya N, Kwak EL, Clark JW, Wilner KD, Christensen JG, Jänne PA, Maki RG, Demetri GD, Shapiro GI. Crizotinib in ALK-rearranged inflammatory myofibroblastic tumor. N Engl J Med. 2010 Oct 28;363(18):1727-33.
- Ceritinib is a new one validated in lung cancer (N Engl J Med 2014: 370: 1189)

? More Targets for IMT

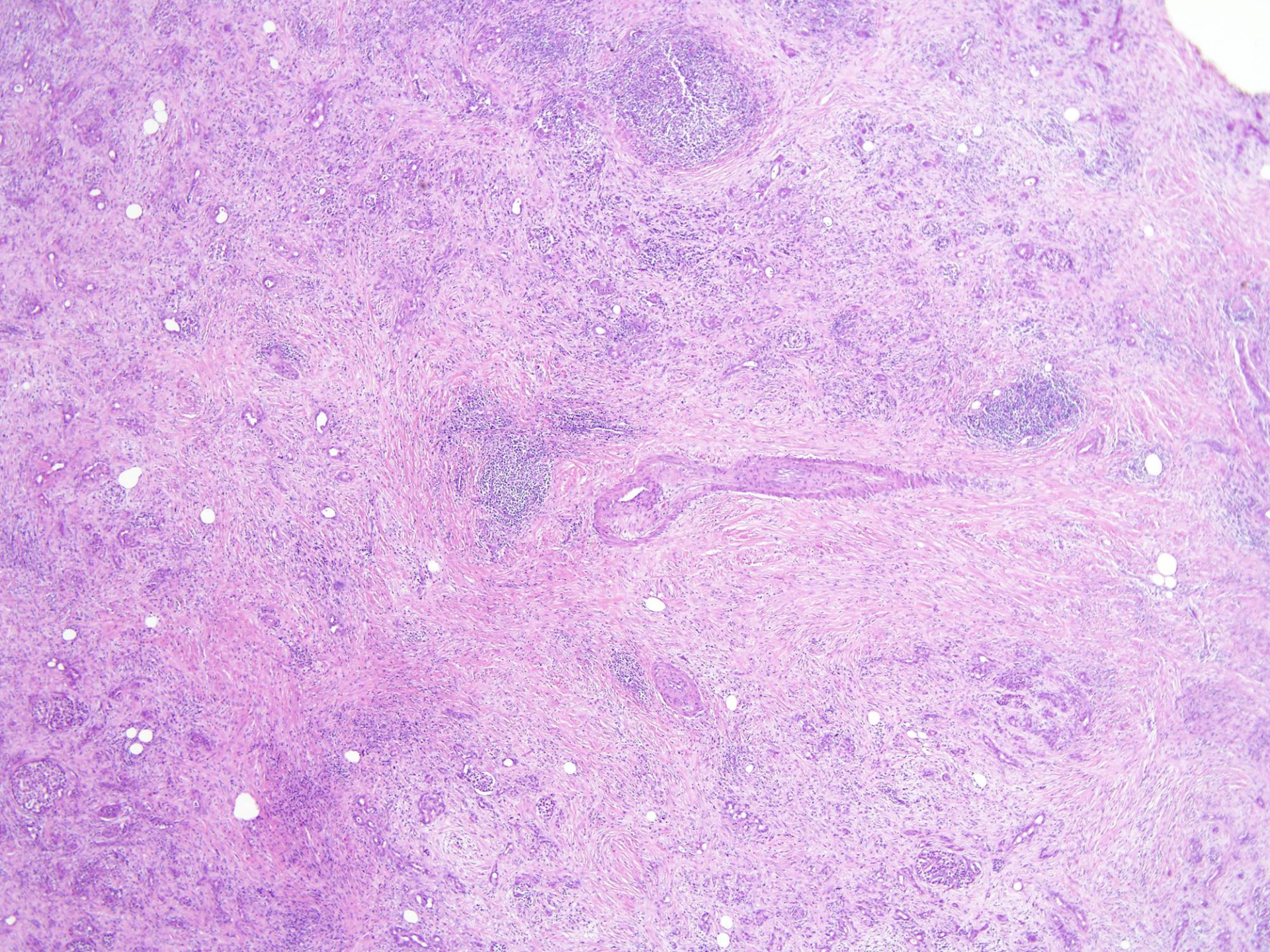
- Several abstracts for USCAP discuss *ROS1* rearrangements as well as *ALK* ones.
- *ROS1* more likely in children (also targetable)

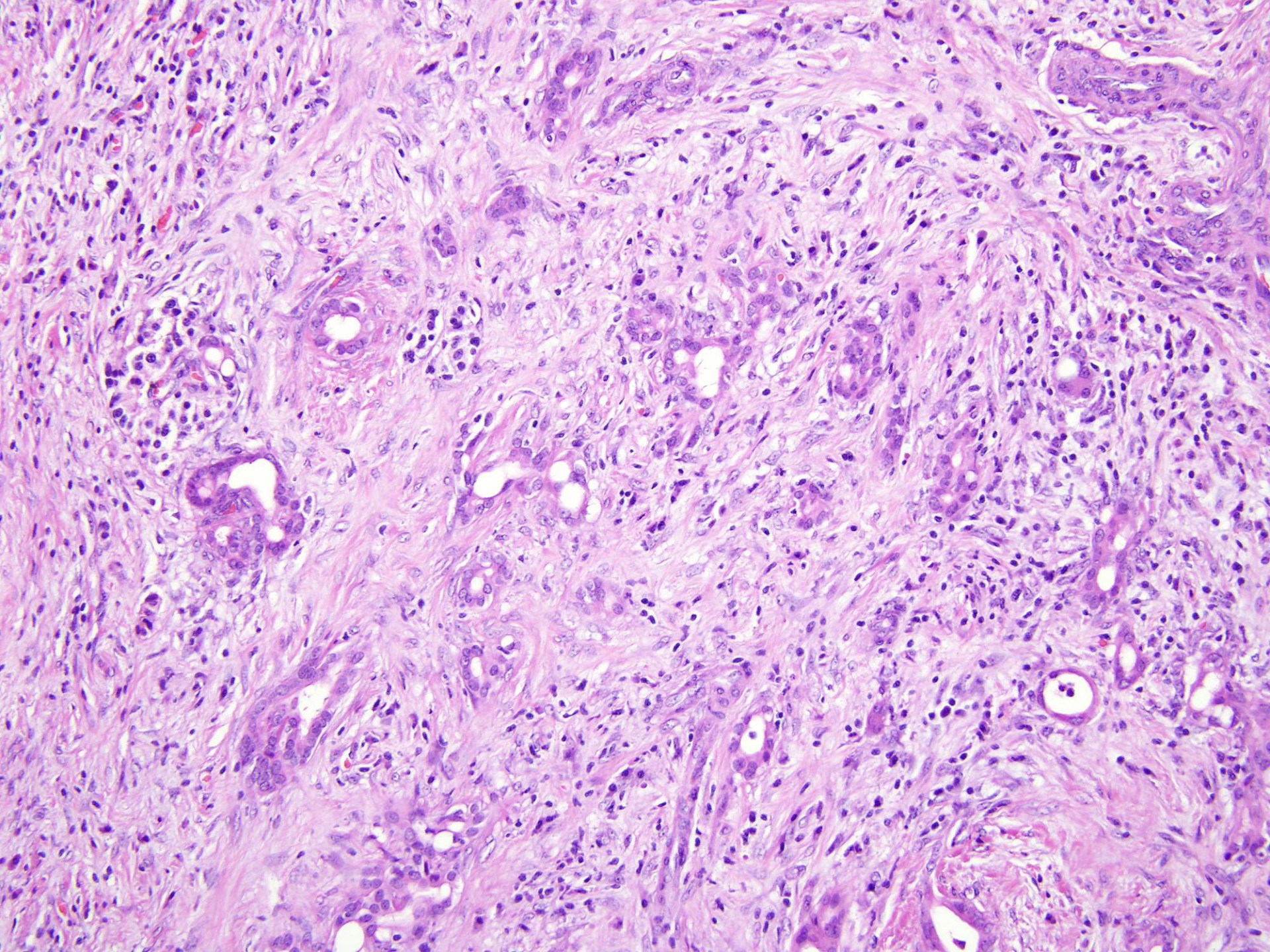
Autoimmune (Lymphoplasmacytic Sclerosing) Pancreatitis

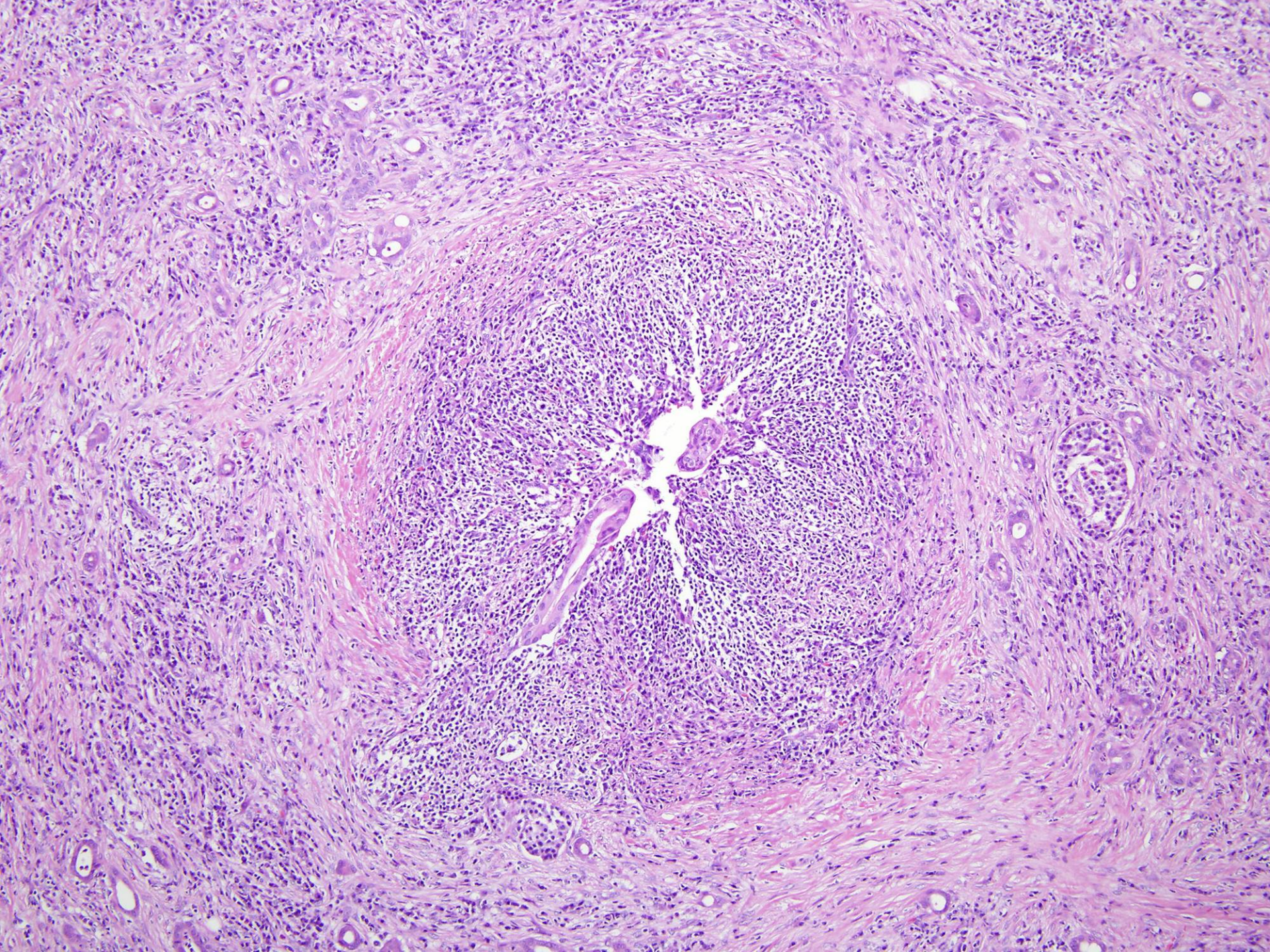
- M;F = 2:1
- Mean age 60 y
- Associated with autoimmune or idiopathic diseases (Sjogren's, PSC, IBD, retroperitoneal fibrosis, thyroiditis)

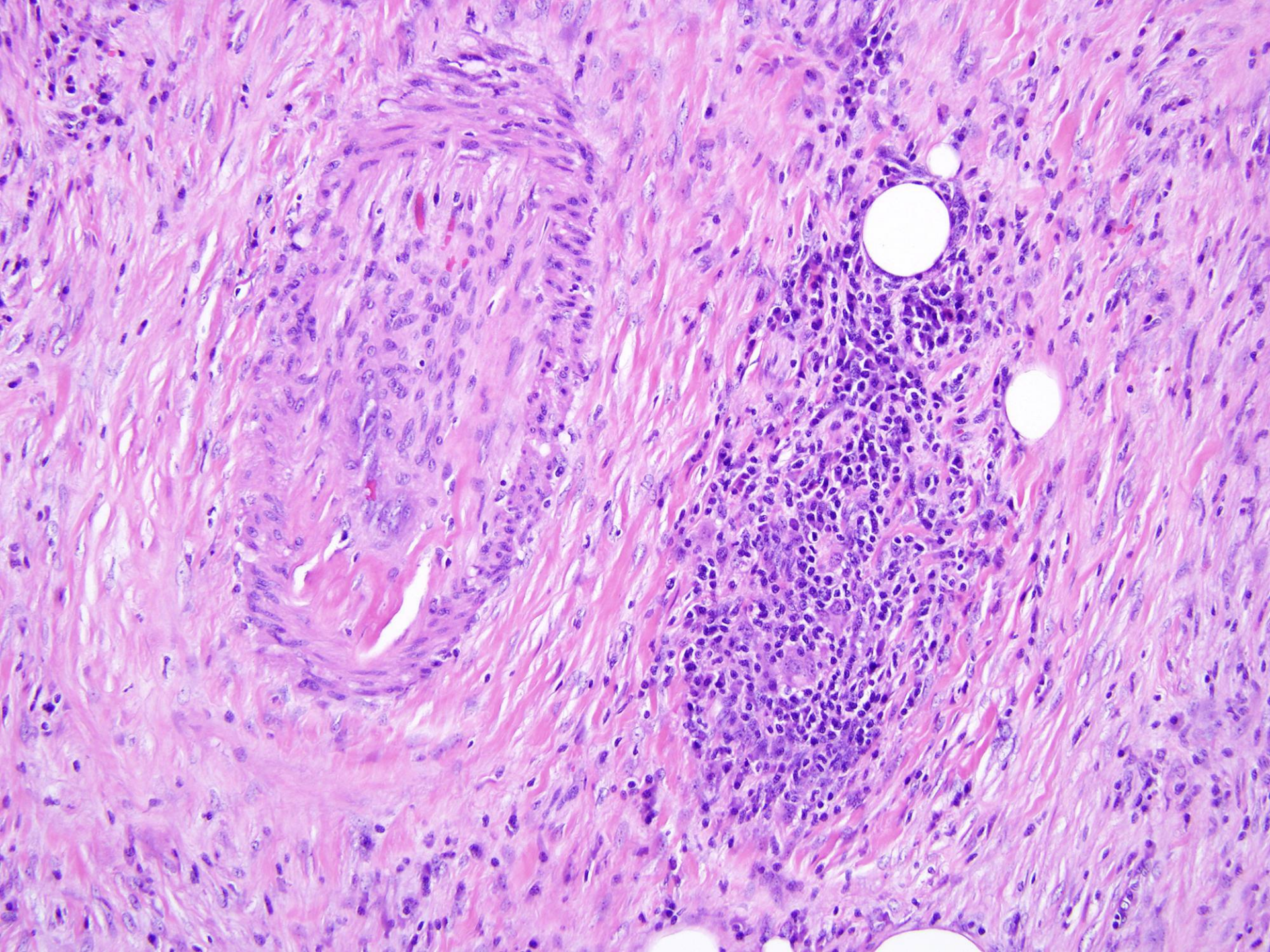
Autoimmune (Lymphoplasmacytic Sclerosing) Pancreatitis - Clinical

- Jaudice, weight loss, abdominal pain
- Diffusely enlarged pancreas without a discrete mass.
- Thickened bile duct
- Lacks features of alcoholic pancreatitis – no pancreatolithiasis or pseudocysts



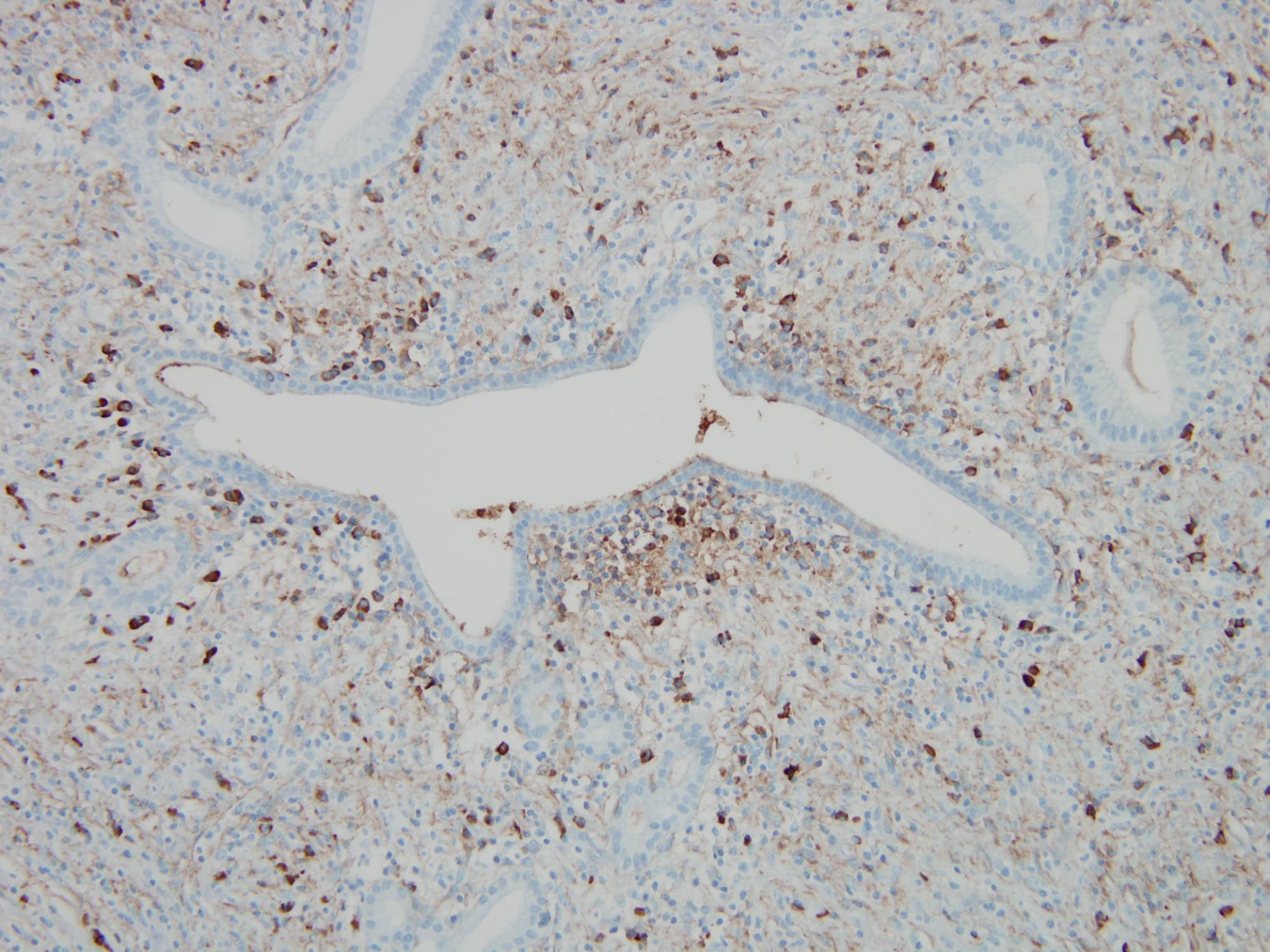






Autoimmune (Lymphoplasmacytic Sclerosing) Pancreatitis - Pathologic

- Most of the lymphocytes are T cells
- >10 IgG4 expressing plasma cells/ hpf



Autoimmune Pancreatitis - Type 1 and 2

Type 1

- Male, jaundiced, older
- More likely to have systemic disease
- Striking interlobular inflammation
- Obliterative phlebitis
- >50 IgG4 labeled cells/hpf, higher serum IgG4

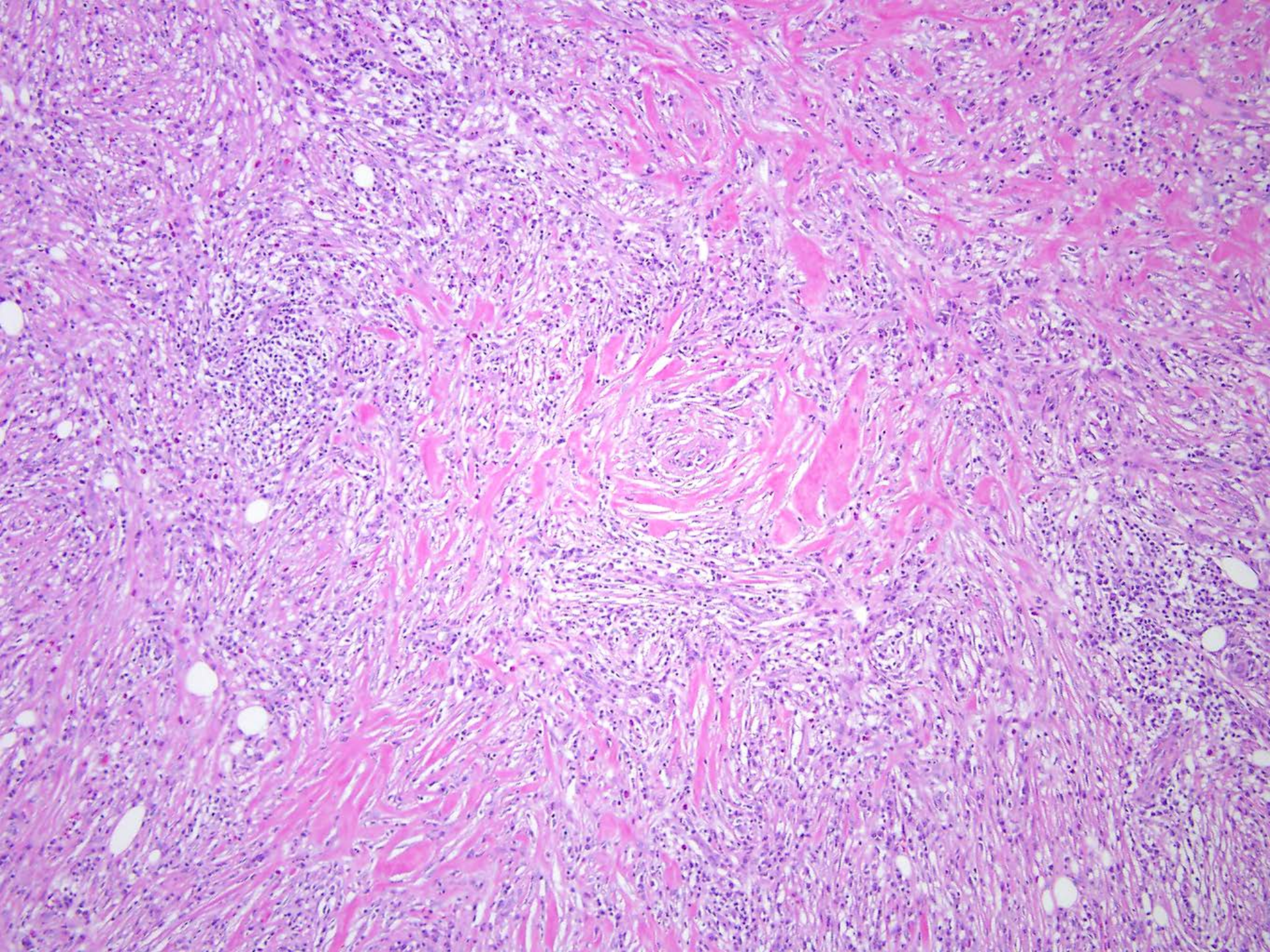
Type 2

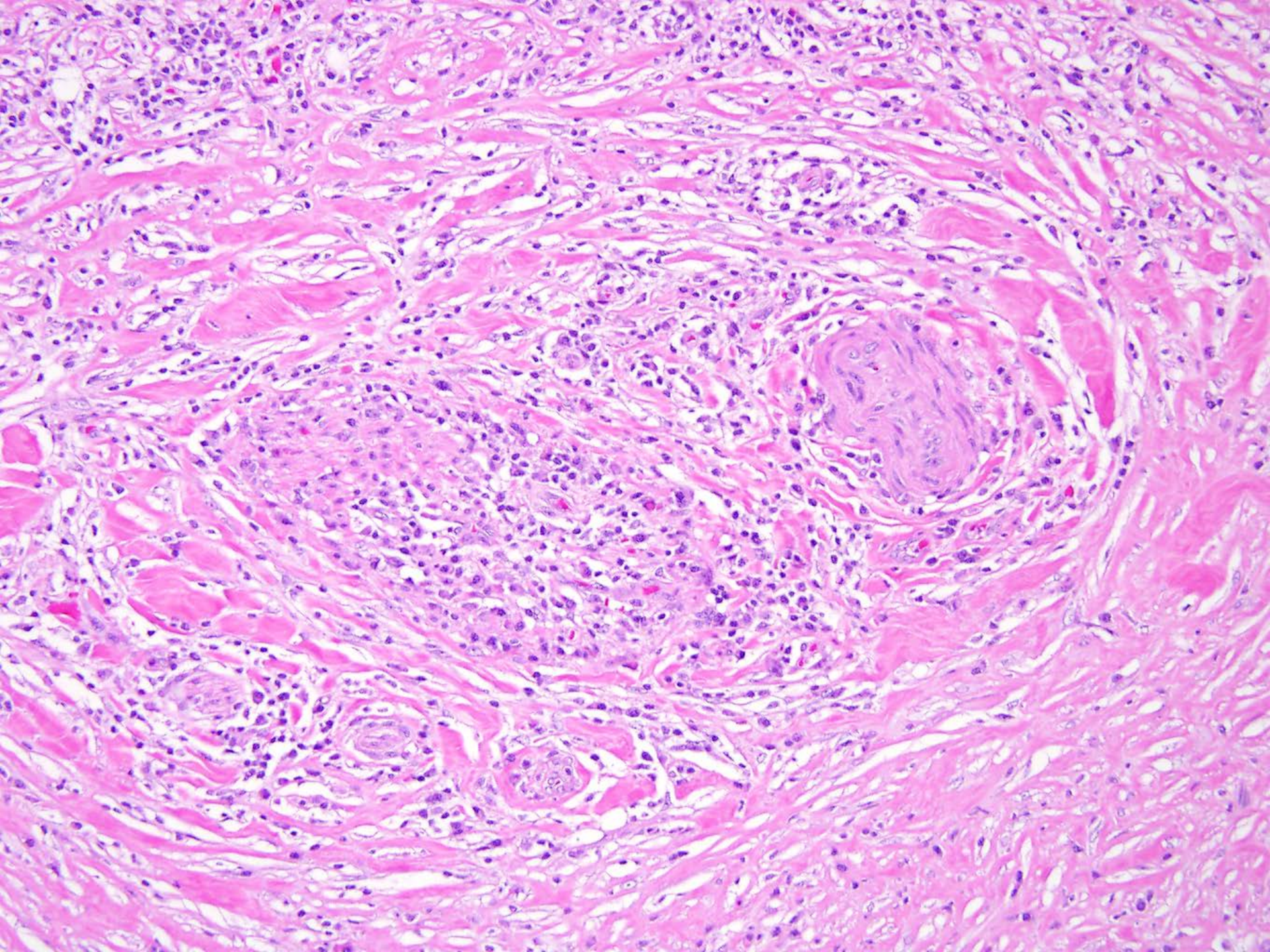
- Abdominal pain
- More duct injury
- Less obliterative phlebitis
- Less systemic disease
- >10 IgG4 labeled cells/hpf

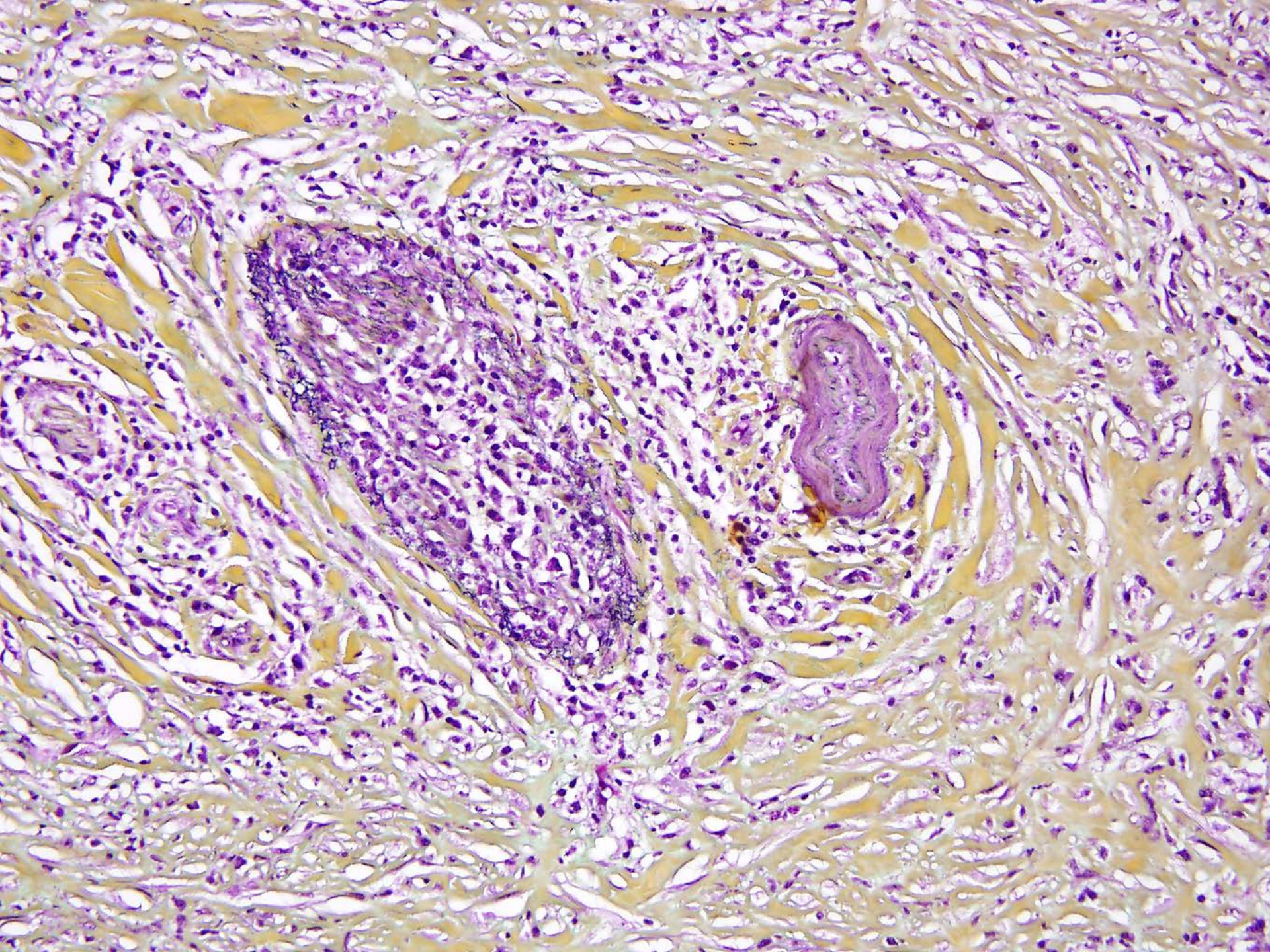
- American Journal of Surgical Pathology. 35(1):26-35, January 2011.

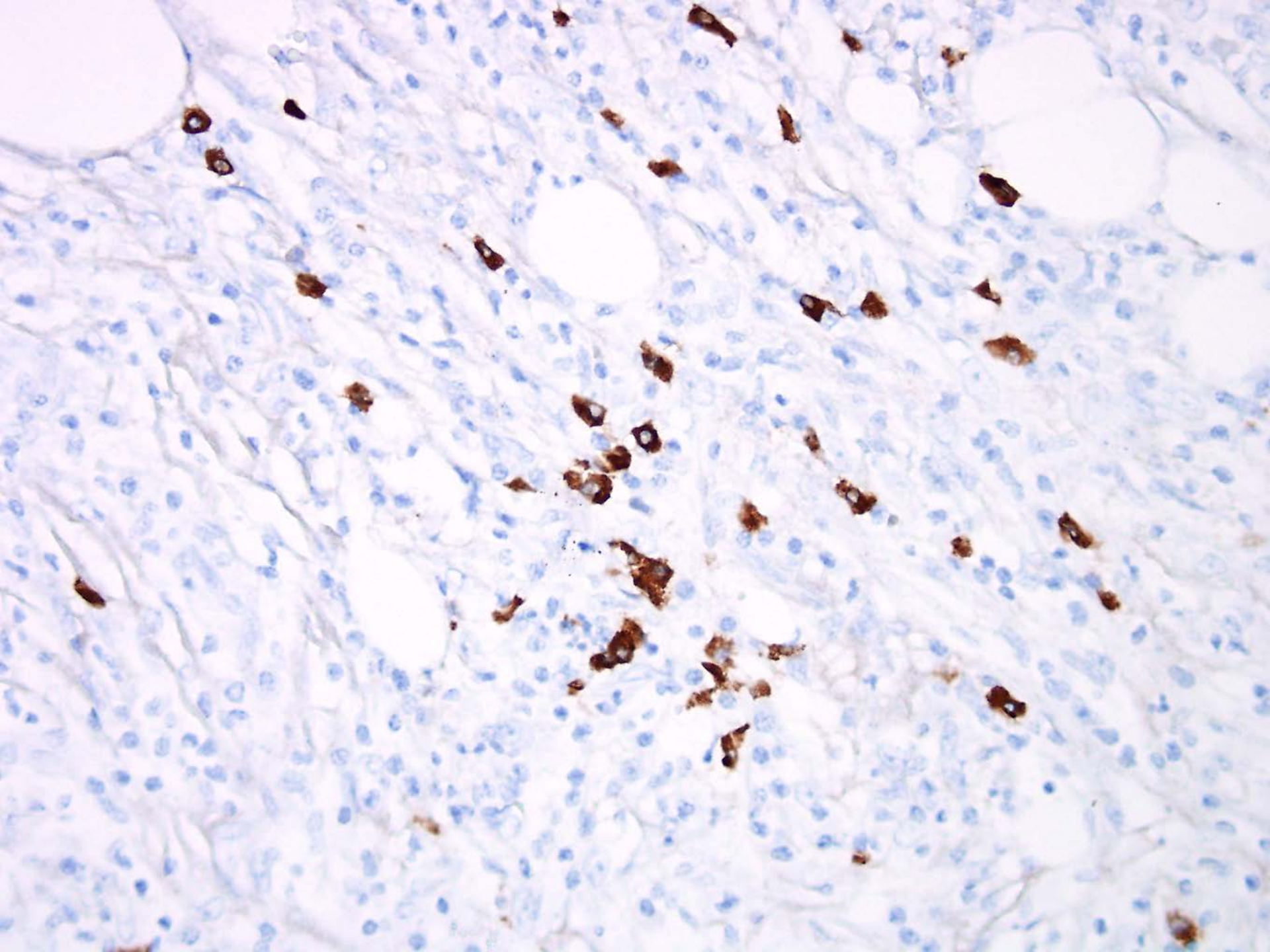
IgG4 Fibrosclerosing Disease

- Fibroinflammatory condition characterized by tumefactive lesions with characteristic histopathologic features
- Dense lymphoplasmacytic infiltrate with abundant IgG4+ plasma cells, storiform fibrosis, obliterative phlebitis and variable presence of eosinophils









IgG4-related Sclerosing Disease

- First described in the pancreas in 1961 as pancreatitis with hyperglobulinemia
- Yoshida invoked “autoimmune pancreatitis” in 1995
- 2001 – Hammamo noted increased serum IgG4 in such persons
- 2003 – Kamisawa noted lots of extrapancreatic sites and other synchronous, metachronous lesions
- Prevalence of about 1/100,000 (Japan)
- Mayo clinic – about 10% of patients with benign pancreatic resections

What causes it?

- No one knows
- Presumably a peculiar immune condition – trigger unknown
- Studies currently strictly observations
- ? Link to H. pylori (Possible link to H. pylori! - Frulloni L, Lunardi C, Simone R, Dolcino M, Scattolini C, Falconi M, Benini L, Vantini I, Corrocher R, Puccetti A. Identification of a novel antibody associated with autoimmune pancreatitis. N Engl J Med. 2009 Nov 26;361(22):2135-42.)

Immunological Basis – Role of T cells

- Naïve T cells differentiate into one of 4 types -
- Th1- responsible for intracellular organisms (Crohn’s disease has this type)
- Th2 – Facilitates humoral response against extracellular pathogens (the type involved in IgG4 disease)
- Tregs (also associated with IgG4 disease)
- Th17 – produce (IL-17) discovered in 2007. They are considered developmentally distinct from Th1 and Th2 cells and excessive amounts thought to play a key role in multiple sclerosis (which was previously thought to be related to Th1 cells), but also psoriasis, autoimmune uveitis, juvenile diabetes, rheumatoid arthritis, and Crohn's disease.

IgG4 Sclerosing disease

- The Th2 response is associated with certain cytokines: interleukin-4, interleukin-5, interleukin-10, interleukin-13, all of which are associated with recruiting eosinophils
- The Tregs probably are the source of the TGF-beta, a protein that promotes fibrosis
- The production of IgG4 is dependent on the T helper type 2 cytokines (IL-5, IL-13). Regulatory cytokines like IL-10 are necessary for class switch of immunoglobulin to IgG4

Conditions Once Regarded as Special Entities now Regarded as IgG4-related

- Autoimmune pancreatitis
- Sclerosing cholangitis
- Mikulicz's syndrome (salivary, lacrimal)
- Riedel's thyroiditis
- Retroperitoneal fibrosis (Ormond's disease)
- Mediastinal fibrosis
- Chronic sclerosing aortitis
- Eosinophilic angiocentric fibrosis (orbit, sinus, nasal cavities)
- Multifocal fibrosclerosis
- Idiopathic hypocomplementemic tubulointerstitial nephritis with extensive tubulointerstitial deposits

Value of Serum IgG4

- Elevated serum IgG4 found in 45-100% of reported patients with these disorders.
- Some studied have included patients with “Type 2 autoimmune pancreatitis (probably not IgG4-related)
- Different testing methods
- Treatment reduces levels

Value of Serum IgG4

- Value of 2 fold over normal in a patient with characteristic organ involvement is valuable with a specificity close 10 100%
- Normal is 140 mg/dl
- Normal serum IgG4 does not exclude the condition

Other diseases that result in elevated ***serum*** IgG4

- Malignancy
- Wegener's granulomatosis
- Churg-Strauss vasculitis
- Allergic diseases
- Parasitic infestations

Disease that have lots of IgG4+ plasma cells in tissue that seem unrelated to IGG4-related sclerosing disease

- Peritumoral cells around cancers
- LYMPHOMAS – especially low-grade and plasmacytic ones (extranodal MALT, follicular)*
- Wegener's granulomatosis
- Parasitic infestations
- Inflammatory bowel disease
- Rosai-Dorfman disease
- Rheumatoid arthritis
- AUTOIMMUNE GASTRITIS
- Inflammatory myofibroblastic tumor (a neoplasm)

*now there are a number of cases reports of lymphomas arising in association with IgG4-related sclerosing disease – they tend to be MALT lymphomas

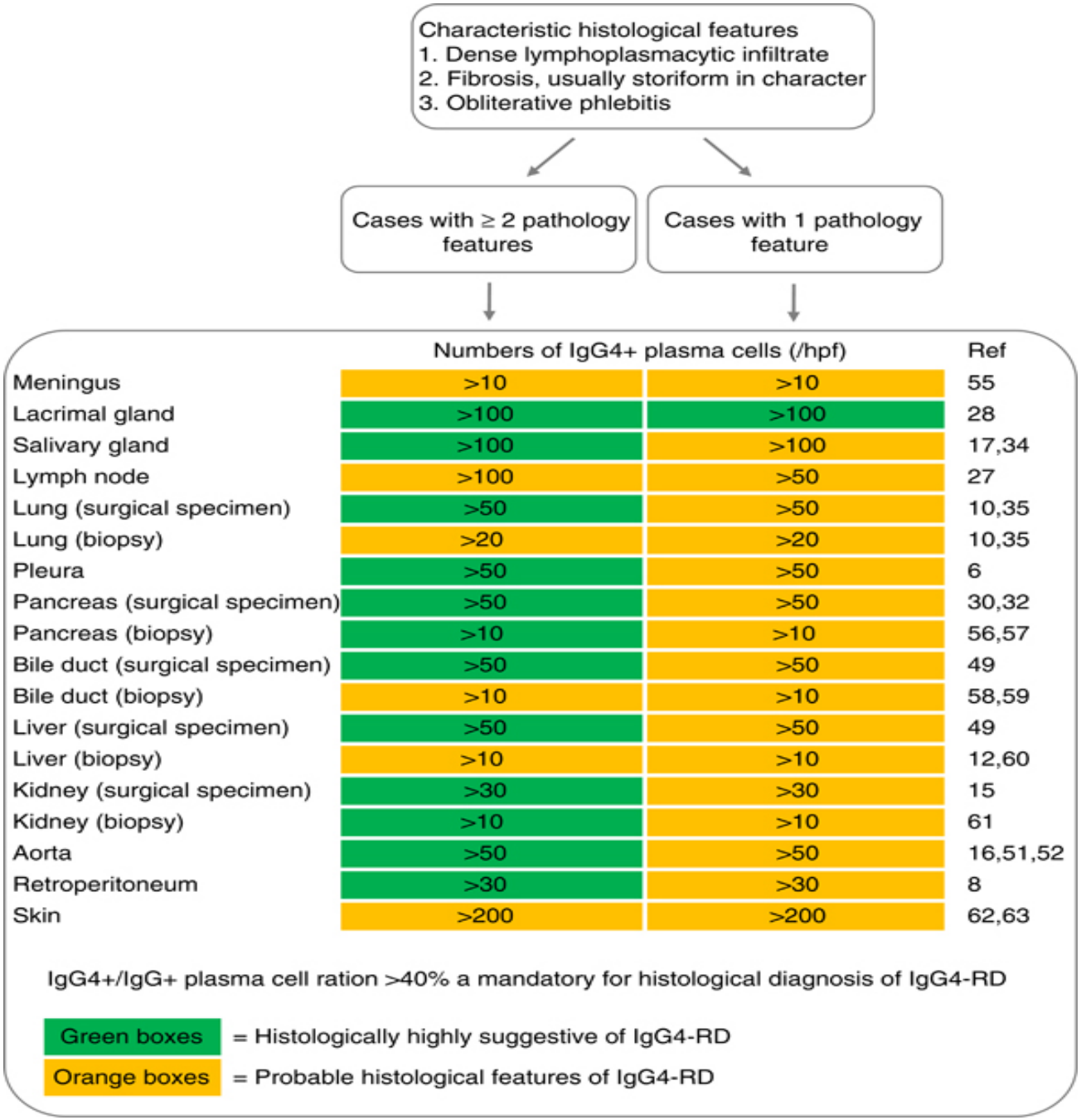
Features Against IgG4related fibrosclerosing disease

- Granulomas
- Abundant neutrophils
- Abscesses
- Necrotizing vasculitis
- CLASSIC IgG4 related disease (with the triad of dense lymphoplasmacytic inflammation, storiform fibrosis, and obliterative phlebitis) is very responsive to steroids. Infections, autoimmune gastritis, and inflammatory myofibroblastic tumors are not.

“Consensus Features” - *Modern Pathology* (2012) **25,** 1181–1192

- MAJOR
- Dense lymphoplasmacytic infiltrate
- Fibrosis, arranged at least focally in a storiform pattern
- Obliterative phlebitis

- MINOR
- Phlebitis without obliteration of the lumen
- Increased numbers of eosinophils



	Numbers of IgG4+ plasma cells (/hpf)		Ref
Meningus	>10	>10	55
Lacrimal gland	>100	>100	28
Salivary gland	>100	>100	17,34
Lymph node	>100	>50	27
Lung (surgical specimen)	>50	>50	10,35
Lung (biopsy)	>20	>20	10,35
Pleura	>50	>50	6
Pancreas (surgical specimen)	>50	>50	30,32
Pancreas (biopsy)	>10	>10	56,57
Bile duct (surgical specimen)	>50	>50	49
Bile duct (biopsy)	>10	>10	58,59
Liver (surgical specimen)	>50	>50	49
Liver (biopsy)	>10	>10	12,60
Kidney (surgical specimen)	>30	>30	15
Kidney (biopsy)	>10	>10	61
Aorta	>50	>50	16,51,52
Retroperitoneum	>30	>30	8
Skin	>200	>200	62,63

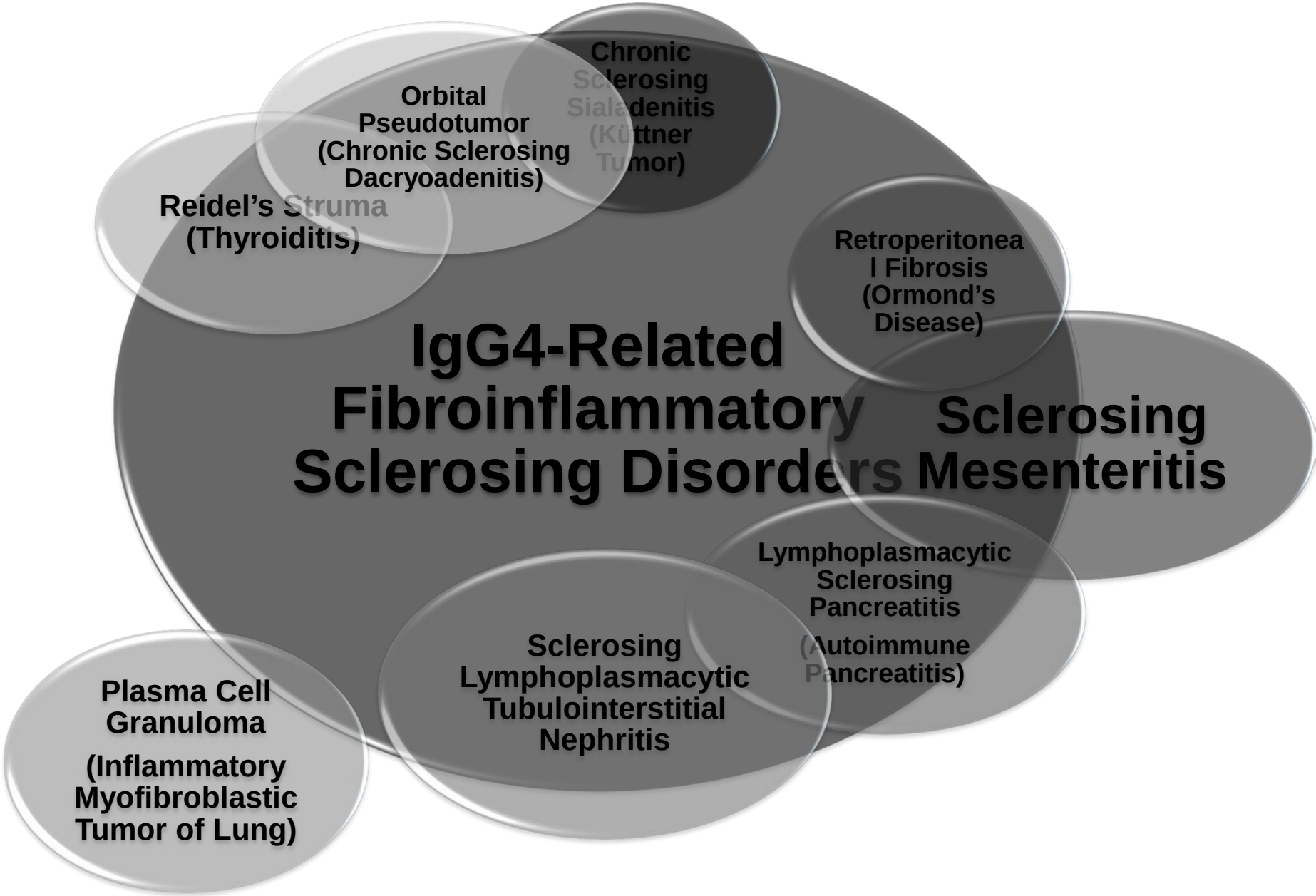
IgG4+/IgG+ plasma cell ration >40% a mandatory for histological diagnosis of IgG4-RD

Green boxes = Histologically highly suggestive of IgG4-RD

Orange boxes = Probable histological features of IgG4-RD

IgG4-related disease

- Remains poorly understood
- Steroid-responsive
- Overlap with other immune disease
- IgG4 can also be found associated with other conditions that are malignant or infectious so important to insist on the histology criteria before managing with steroids


IgG4-Related Fibroinflammatory Sclerosing Disorders
Chronic Sclerosing Sialadenitis (Küttner Tumor)
Orbital Pseudotumor (Chronic Sclerosing Dacryoadenitis)
Reidel's Struma (Thyroiditis)
Retroperitoneal Fibrosis (Ormond's Disease)
Sclerosing Mesenteritis
Lymphoplasmacytic Sclerosing Pancreatitis (Autoimmune Pancreatitis)
Sclerosing Lymphoplasmacytic Tubulointerstitial Nephritis
Plasma Cell Granuloma (Inflammatory Myofibroblastic Tumor of Lung)

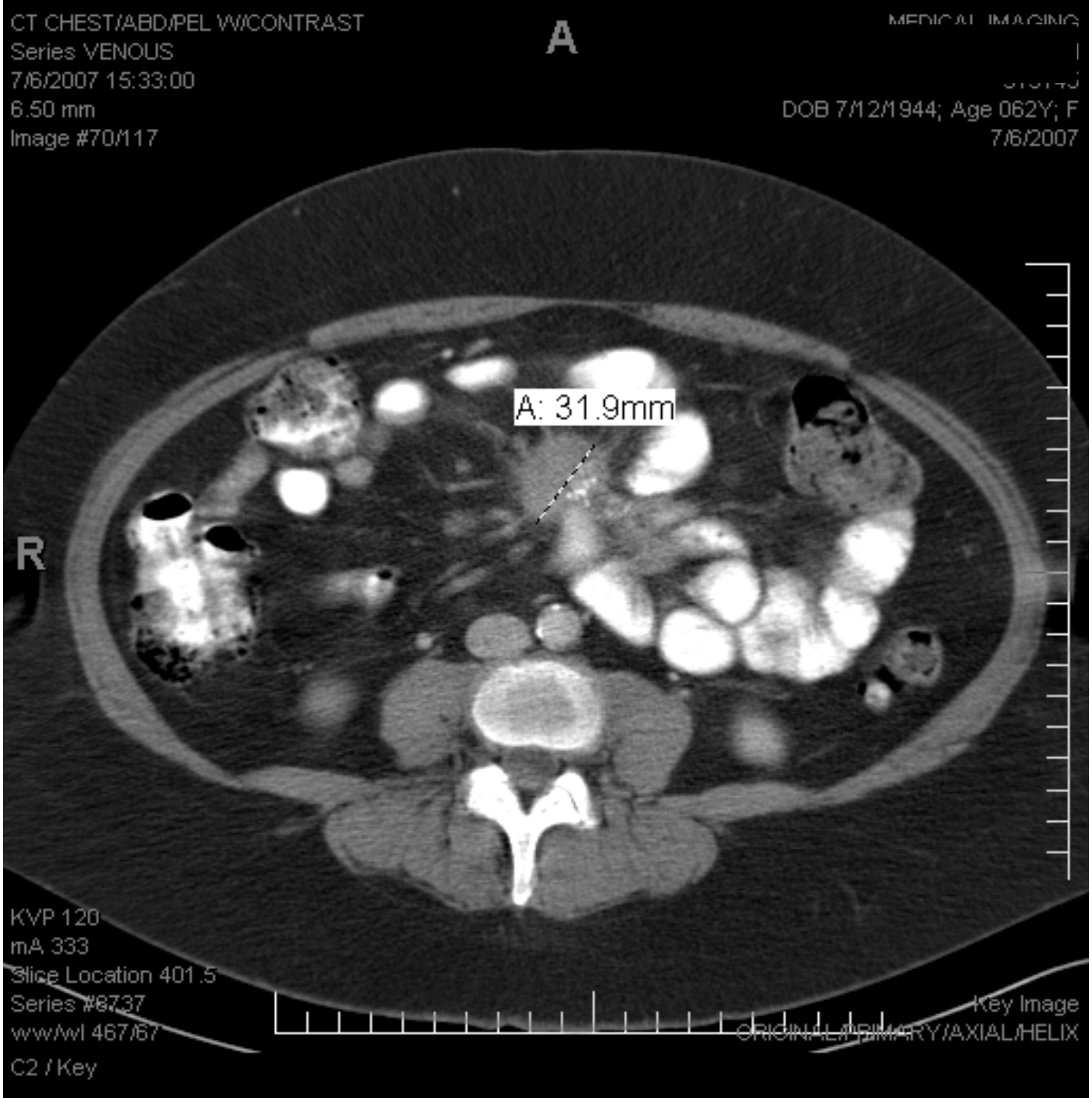
Sclerosing mesenteritis

- Commonly affects small bowel mesentery
- Isolated mass in 80% of patients (multiplicity in 20%)

Emory TS, Monihan JM, Carr NJ, Sobin LH. Sclerosing mesenteritis, mesenteric panniculitis and mesenteric lipodystrophy: a single entity? *Am J Surg Pathol* 1997;**21**;392-8.

Sclerosing mesenteritis

- Fibrous bands infiltrating and encasing fat lobules
- Associated inflammatory infiltrate (lymphocytes, plasma, eosinophils)
- Vasculitis absent [not true anymore]
- Few neutrophils
- Unknown etiology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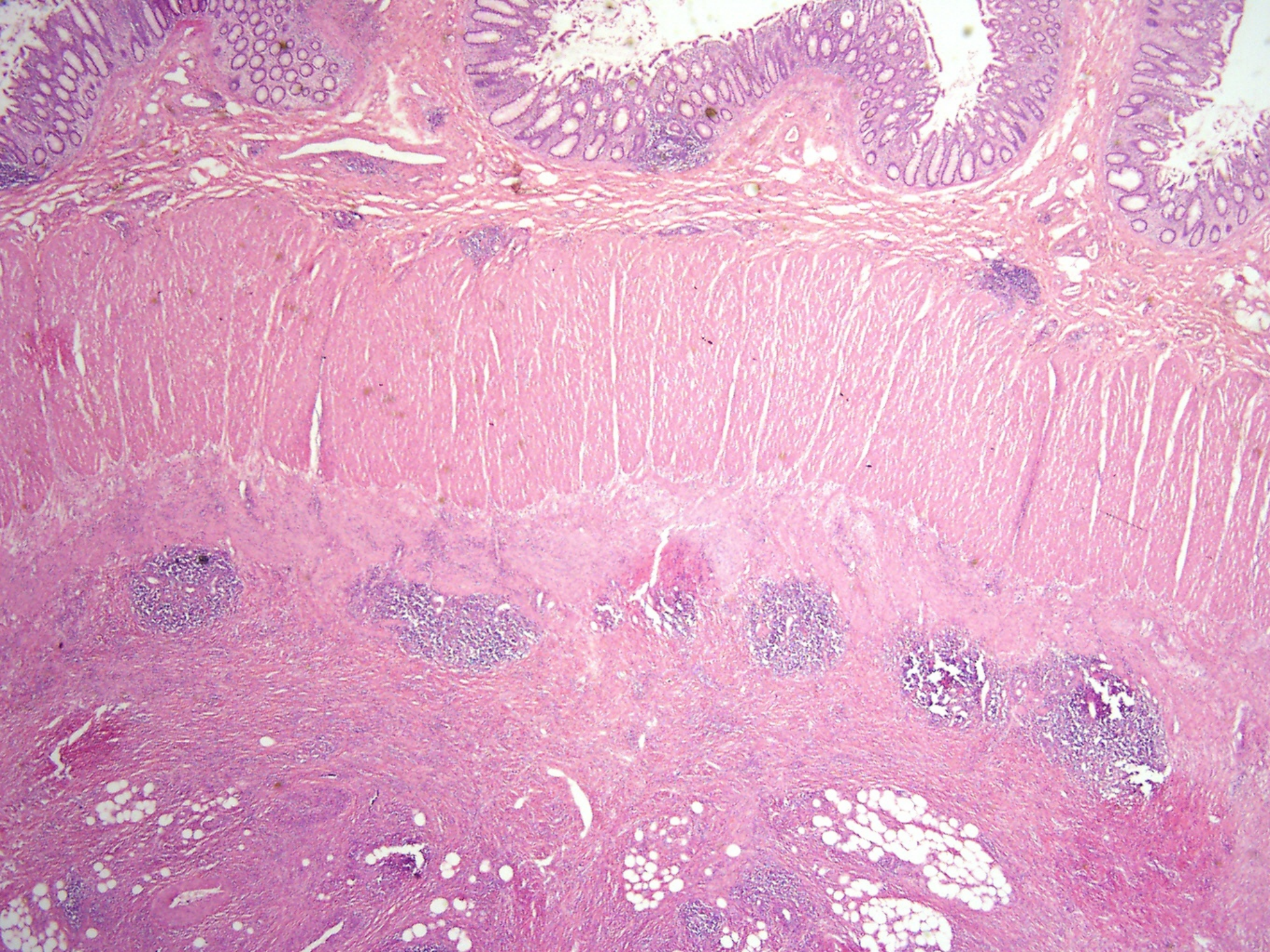
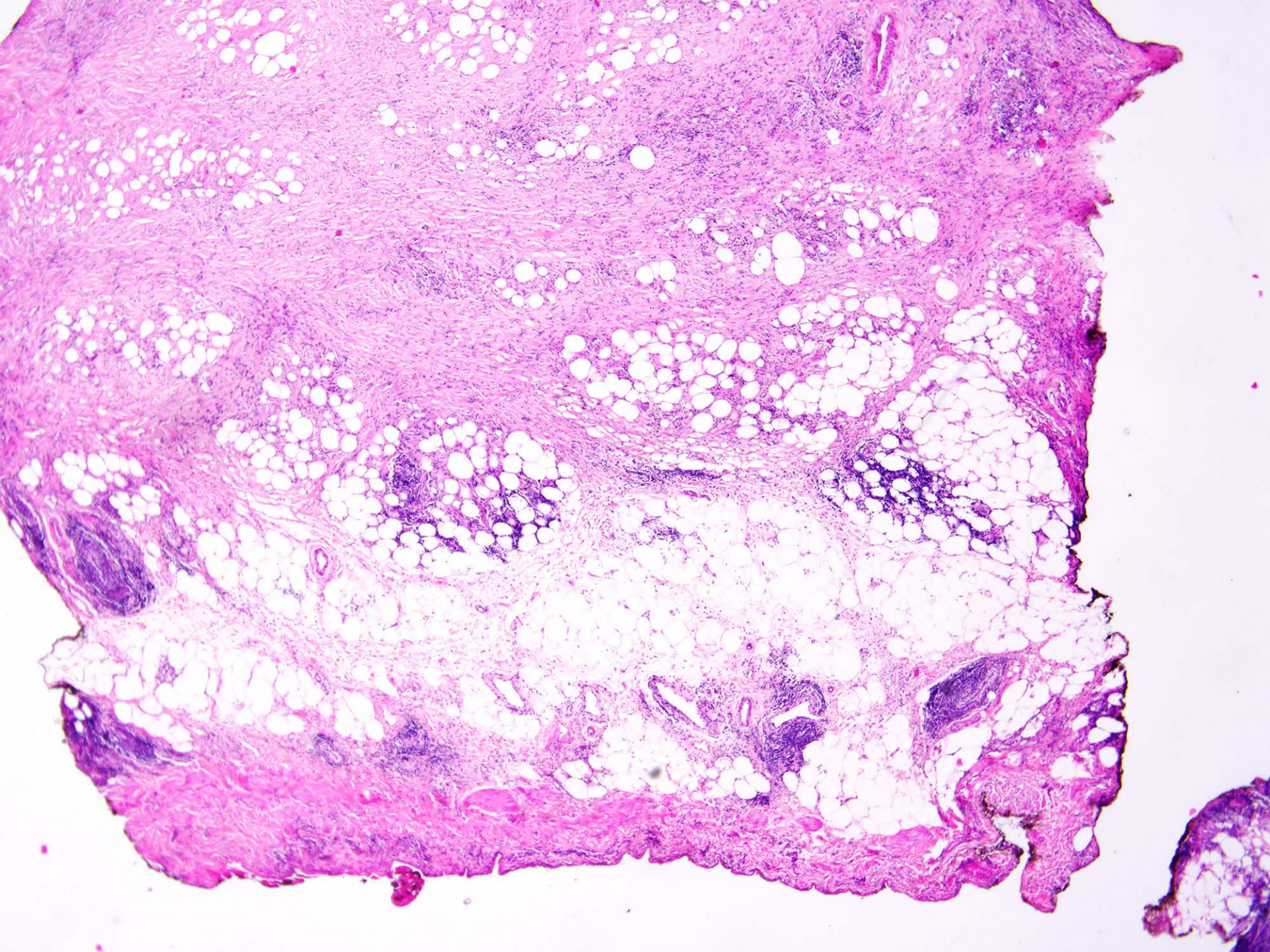
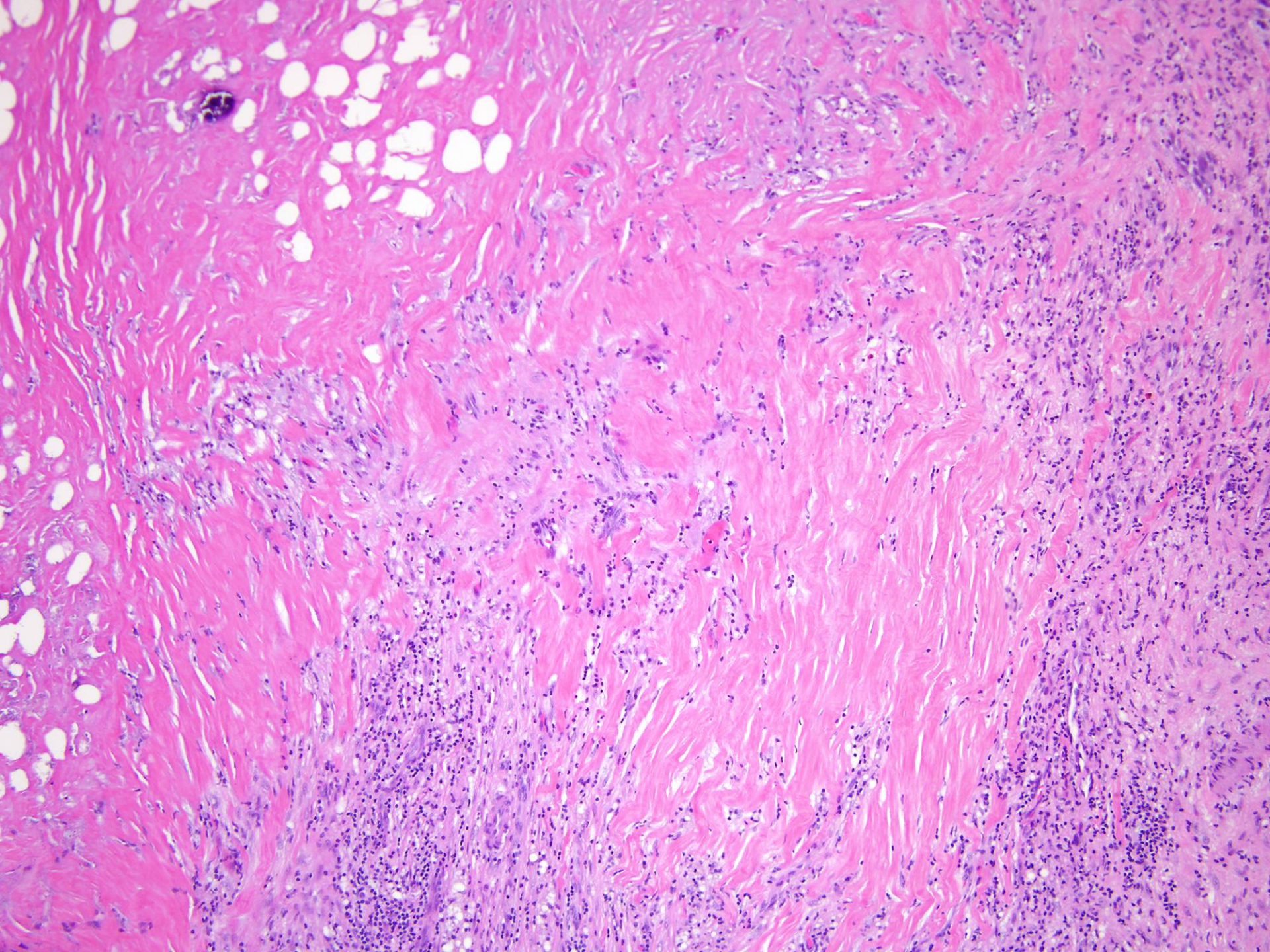
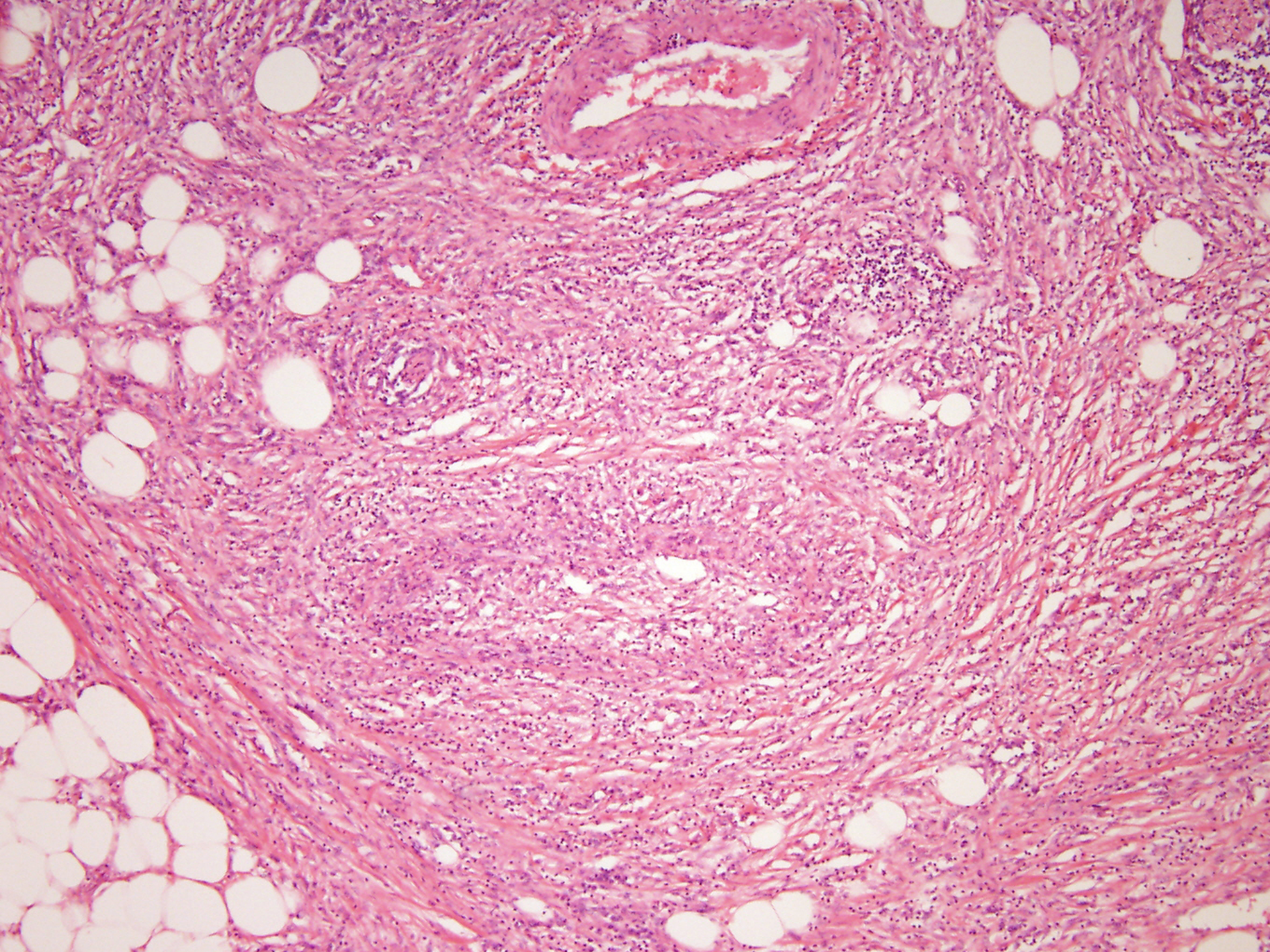
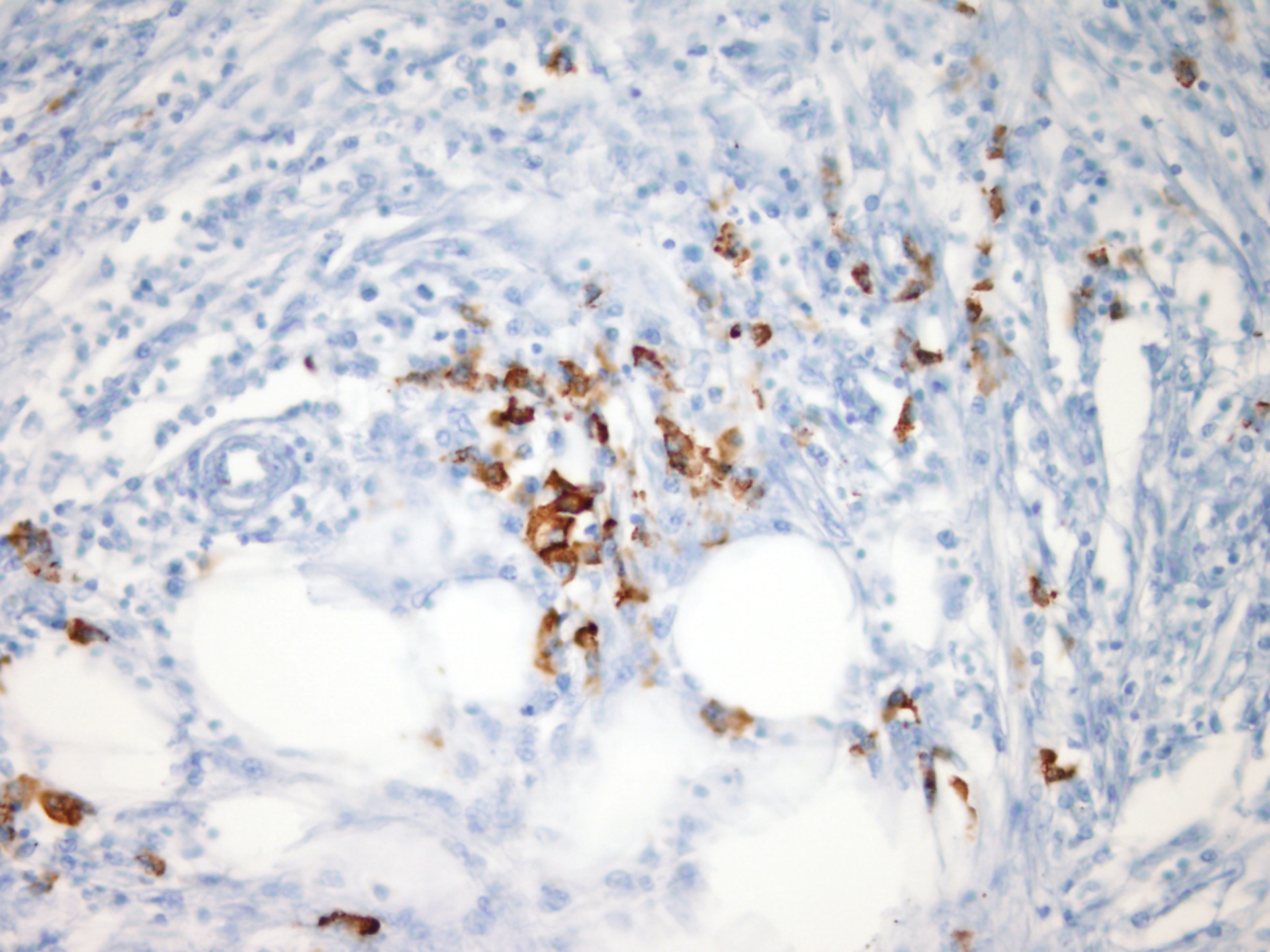


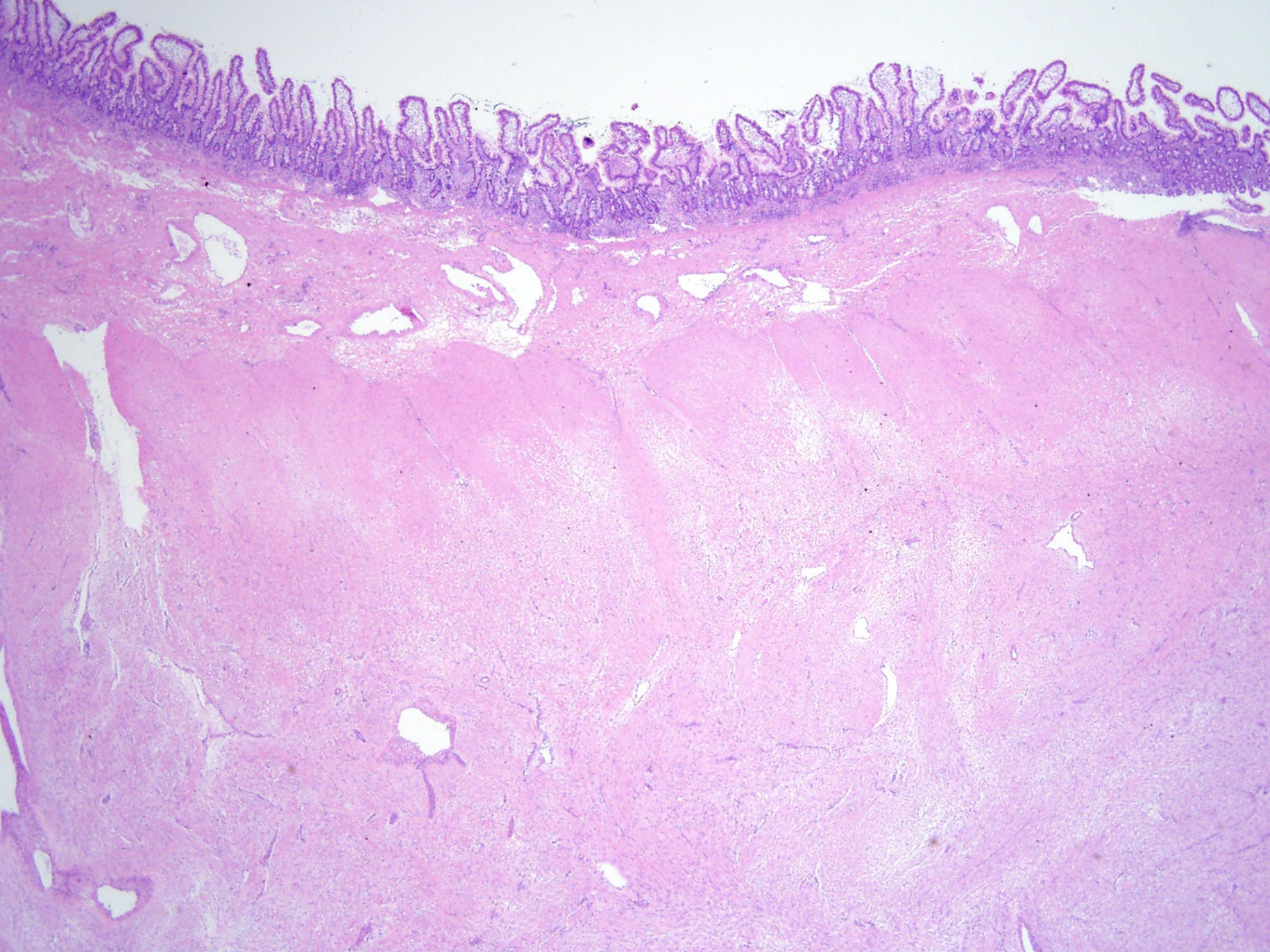


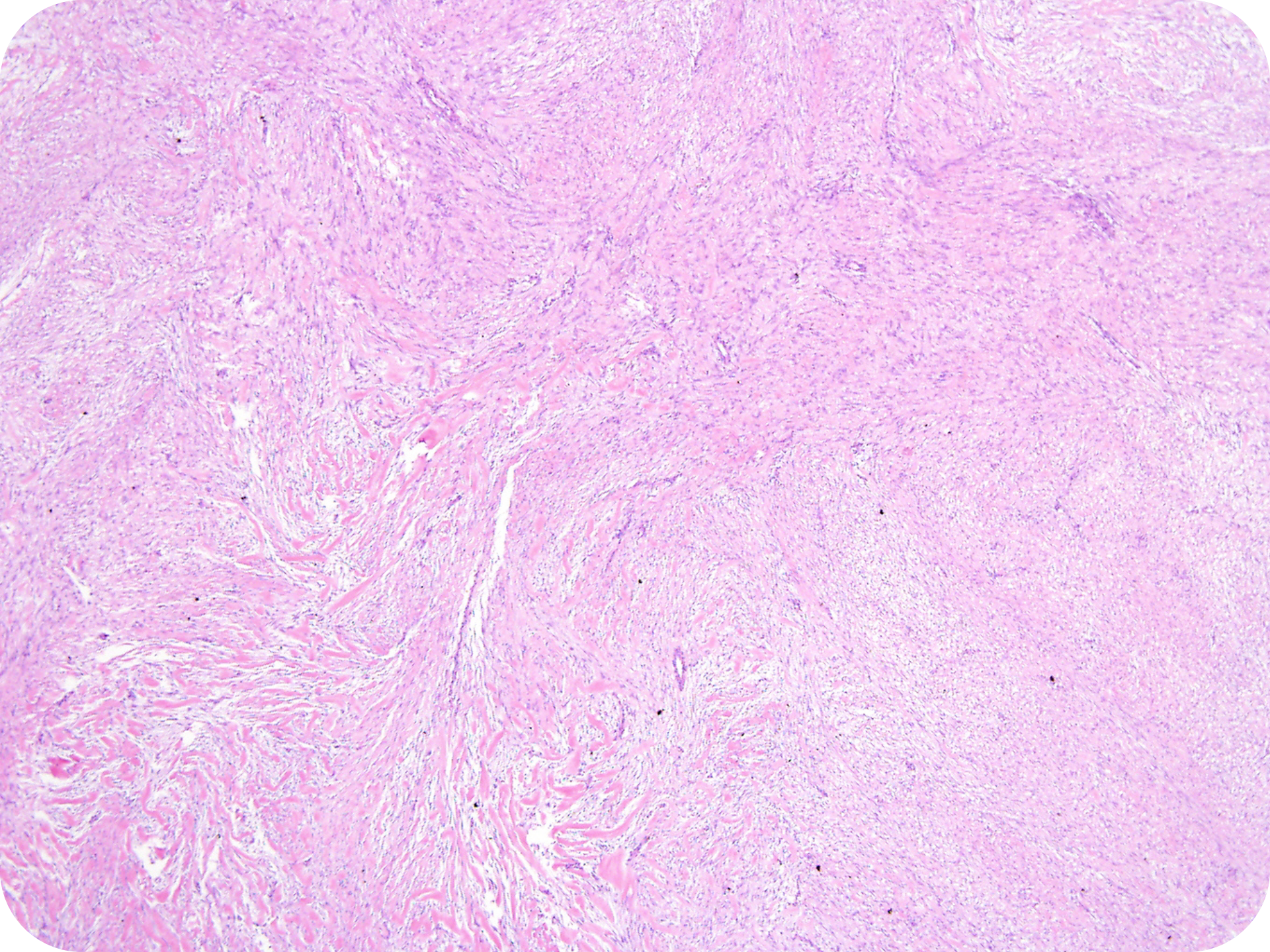


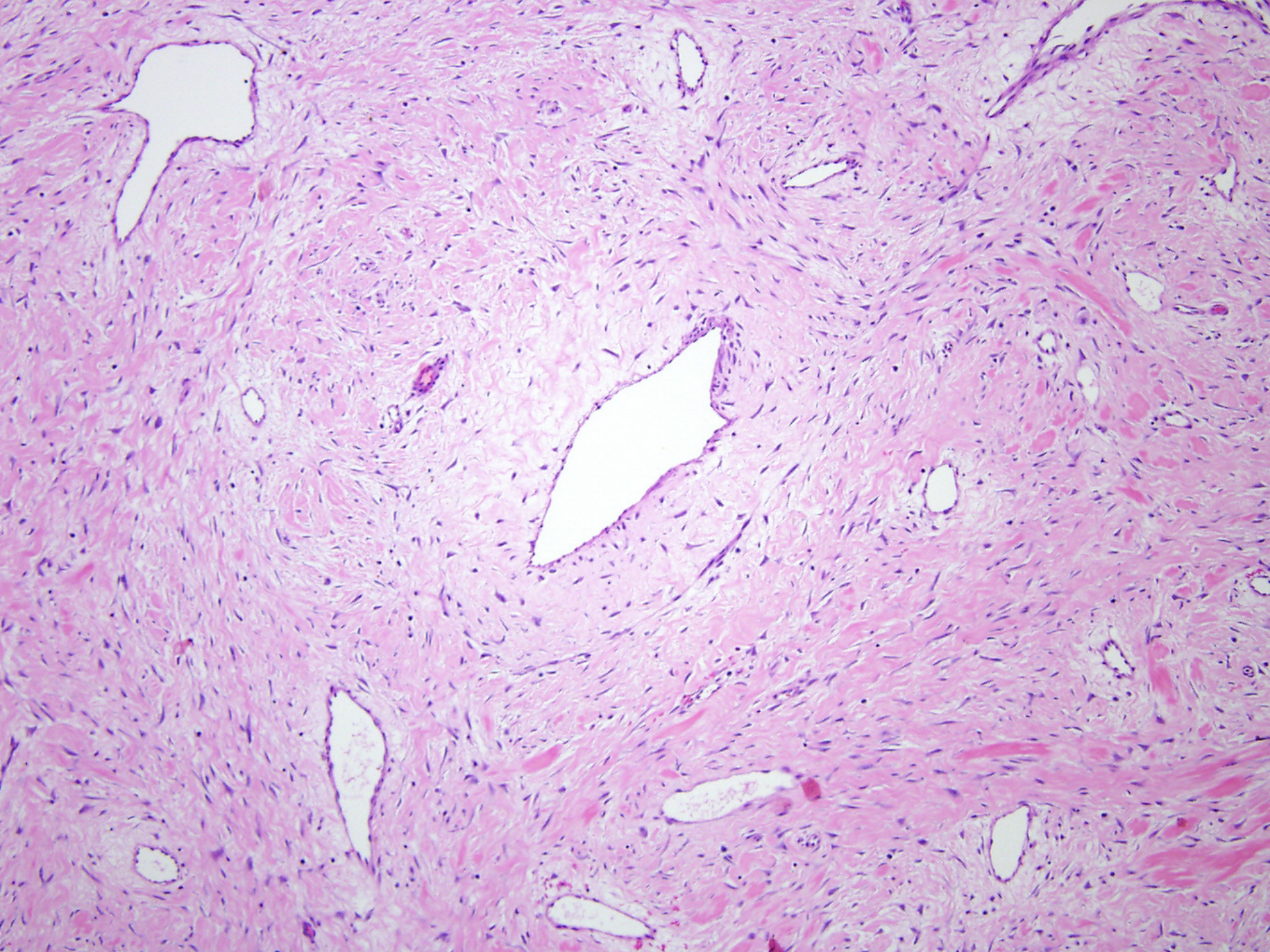


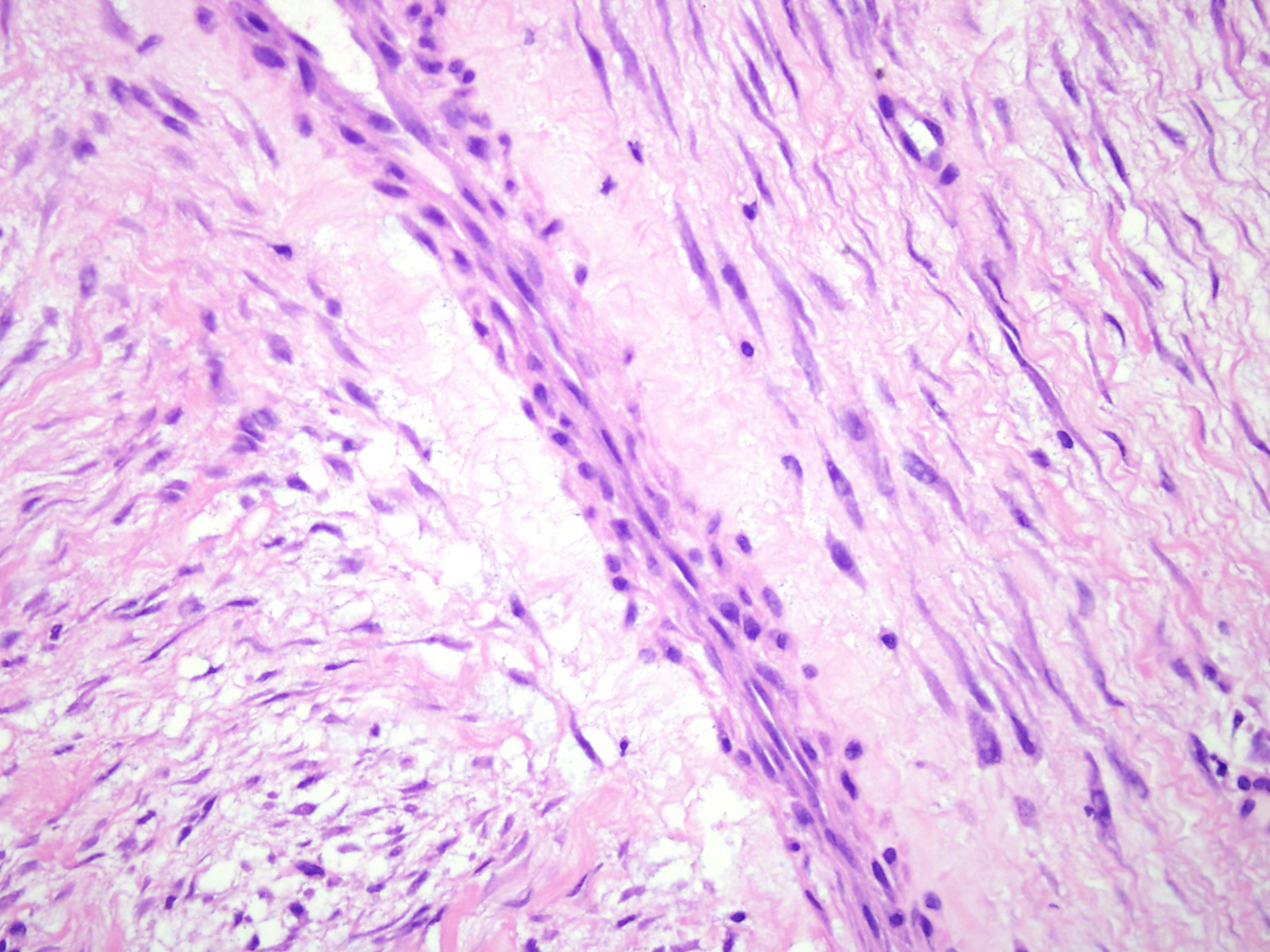


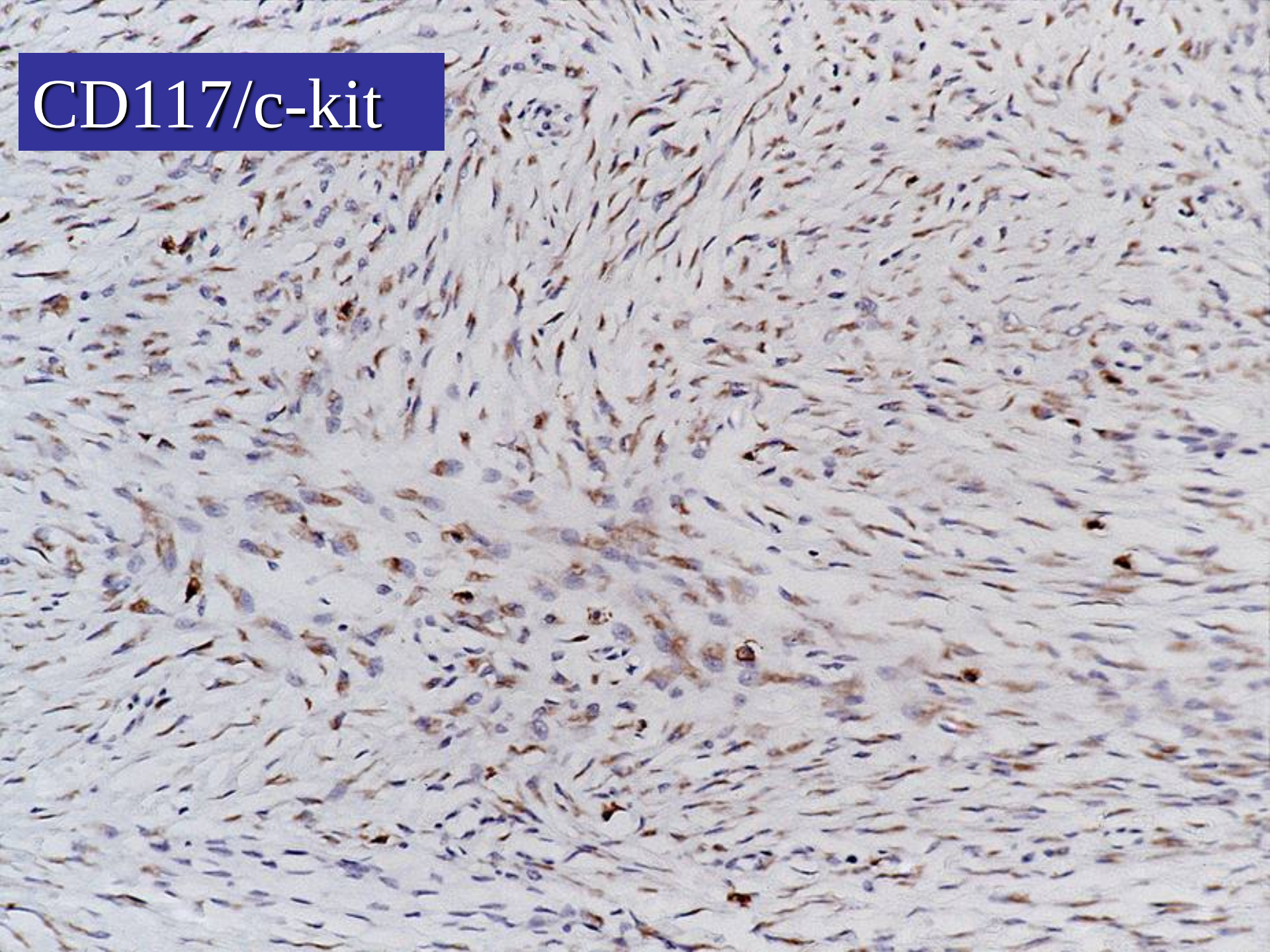
A 9cm mass was excised from the jejunal wall and mesentery of a 33 year old woman.









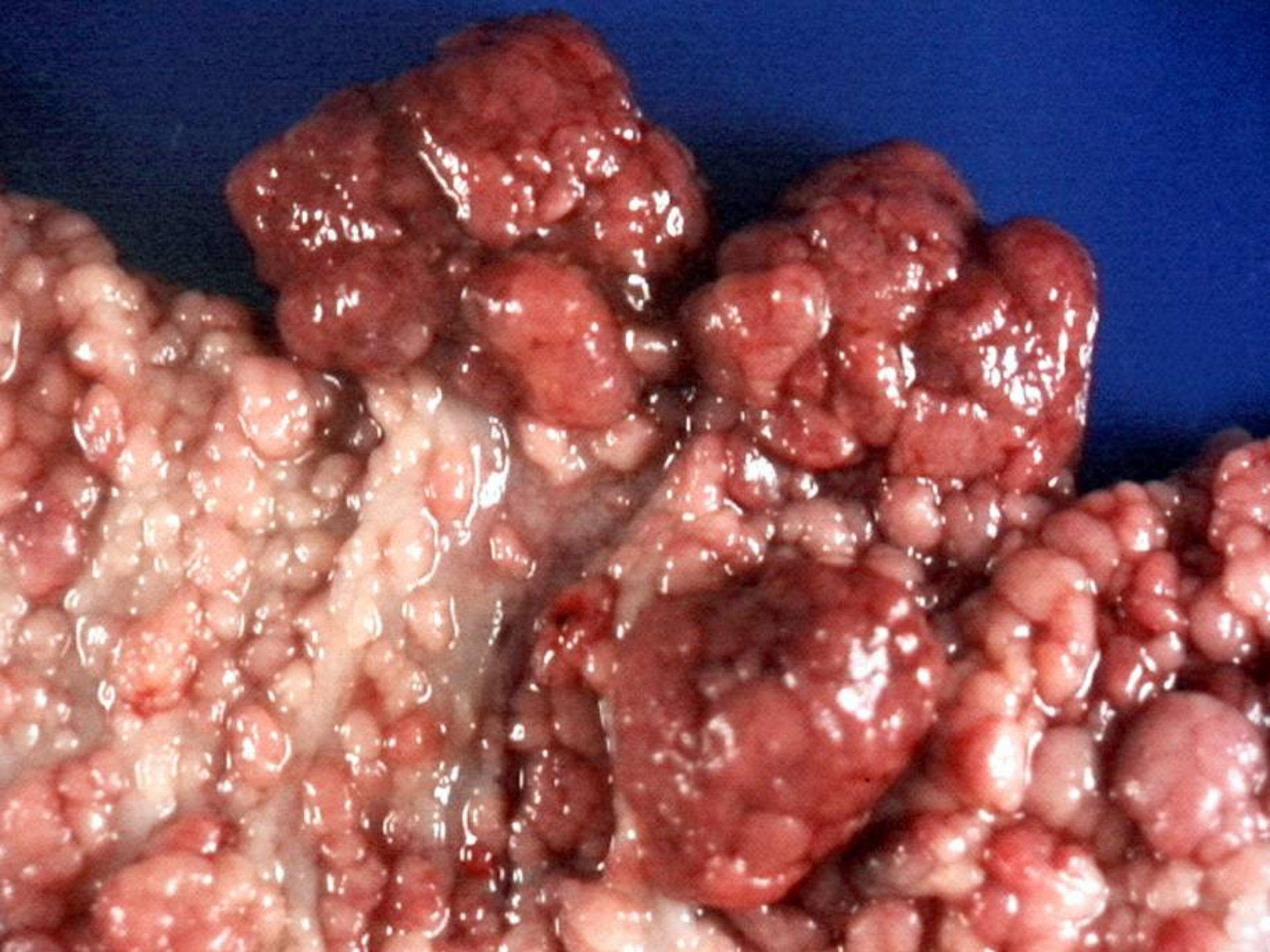

CD117/c-kit

Diagnosis: Mesenteric Fibromatosis

Mesenteric Fibromatoses

- May be a component of Gardner syndrome (FAP)

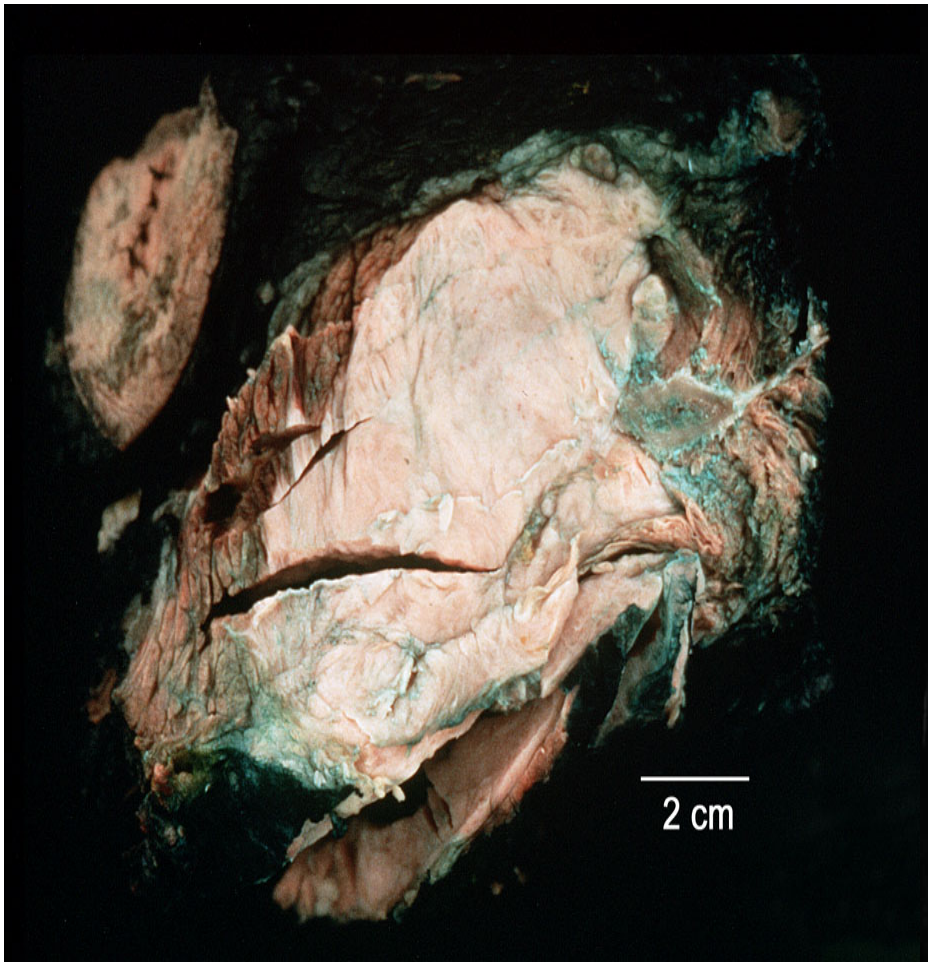
- Virtually all familial fibromatoses have associated *APC* gene mutations



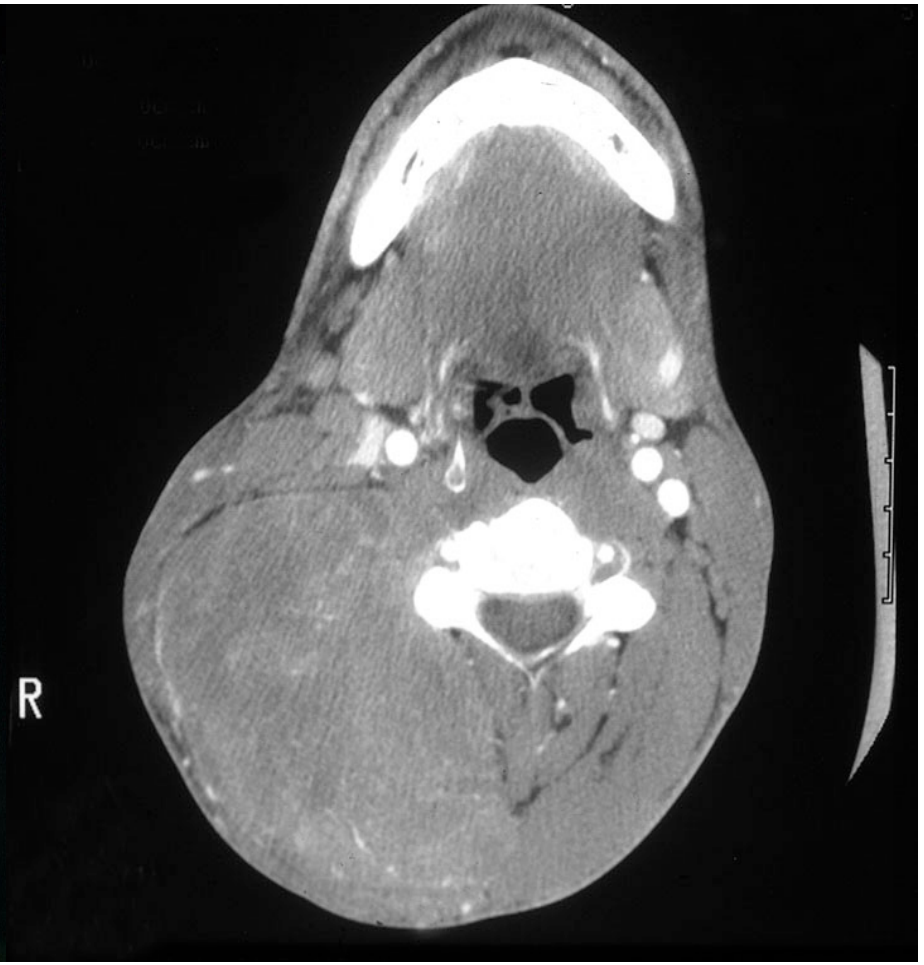
Fibromatoses - Clinical

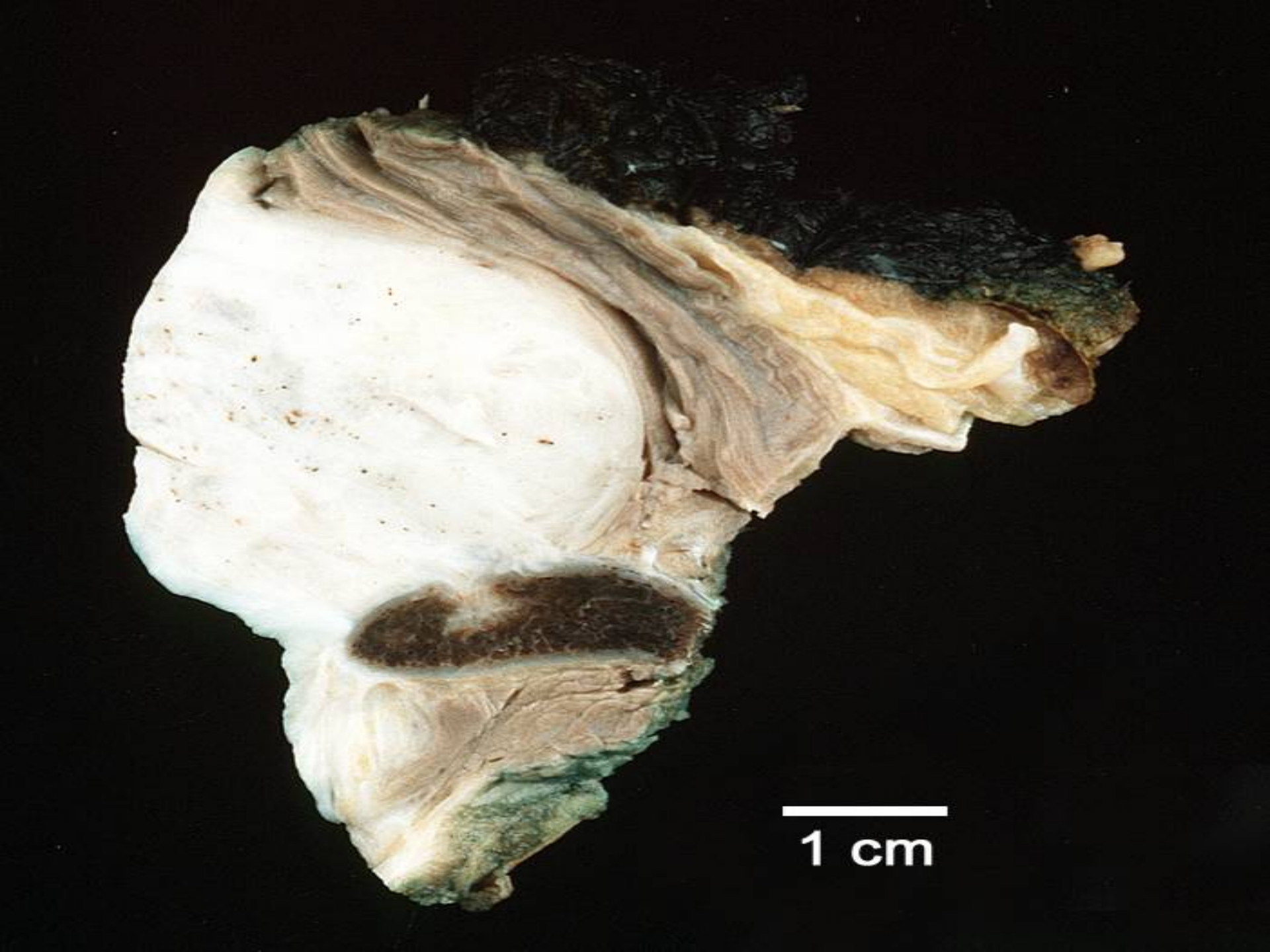
- 2-4 individuals per million per year.
- In children, equal gender incidence, mostly extra-abdominal.
- Puberty – age 40 usu in females [estrogen driven] and in abdominal wall.
- Older adults – mostly extra-abdominal – equal gender incidence.
- Associated with FAP and APC gene alterations.

Fibromatosis of Shoulder In Young Woman



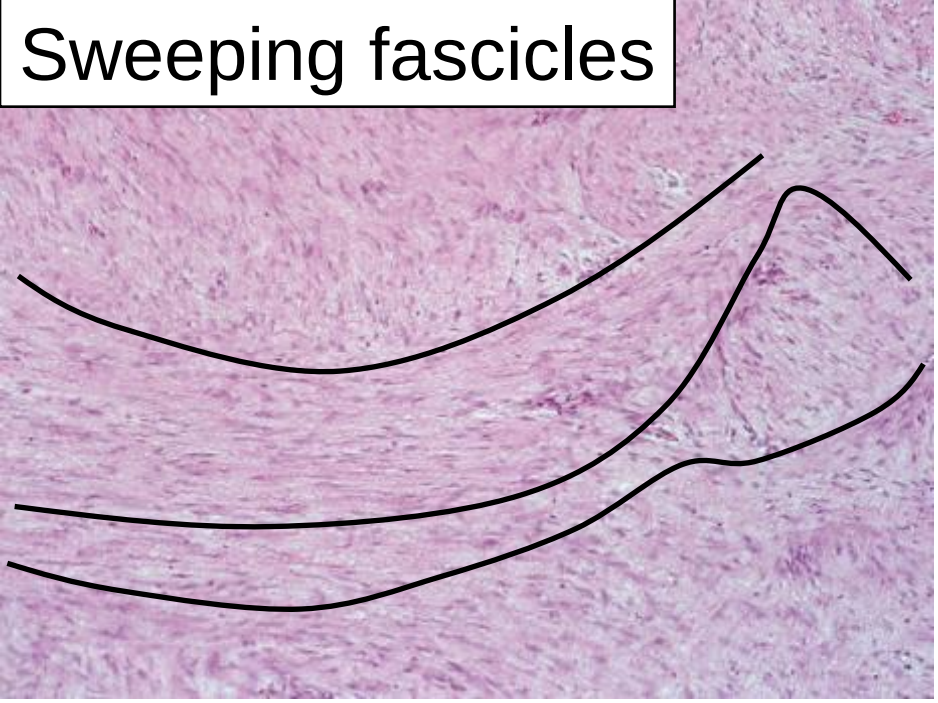
Imaging Study of Fibromatosis in Elderly Man

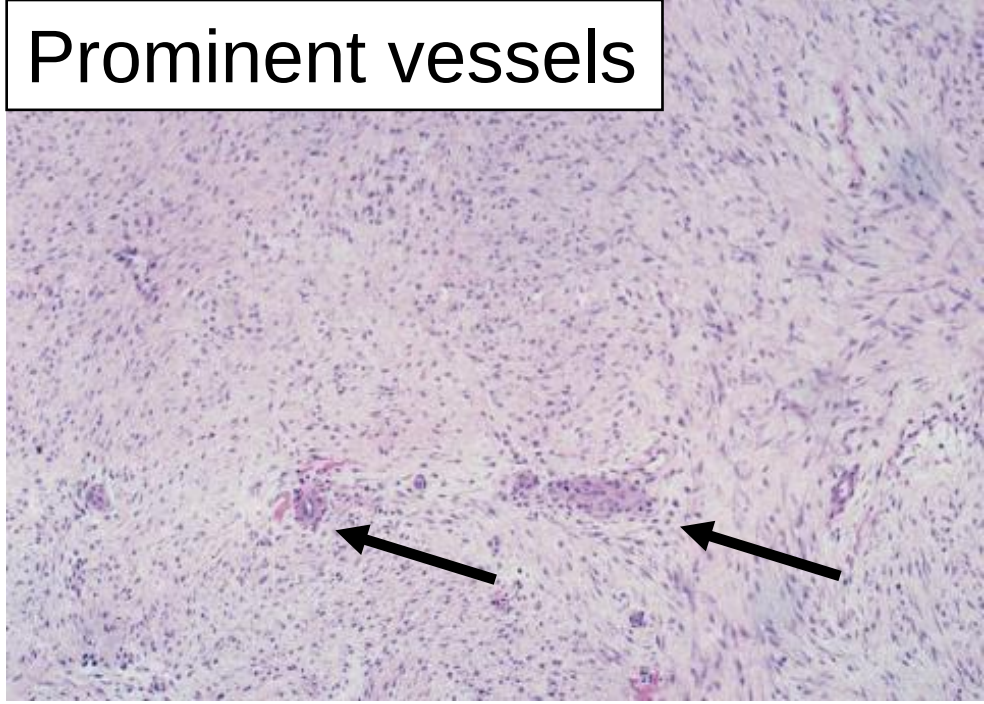


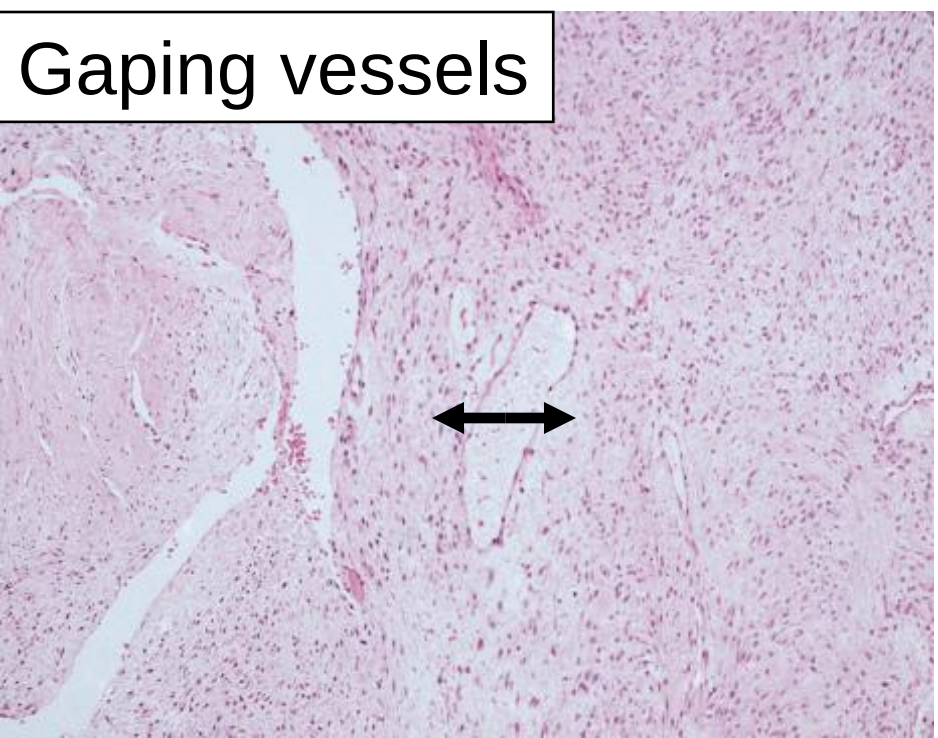

1 cm

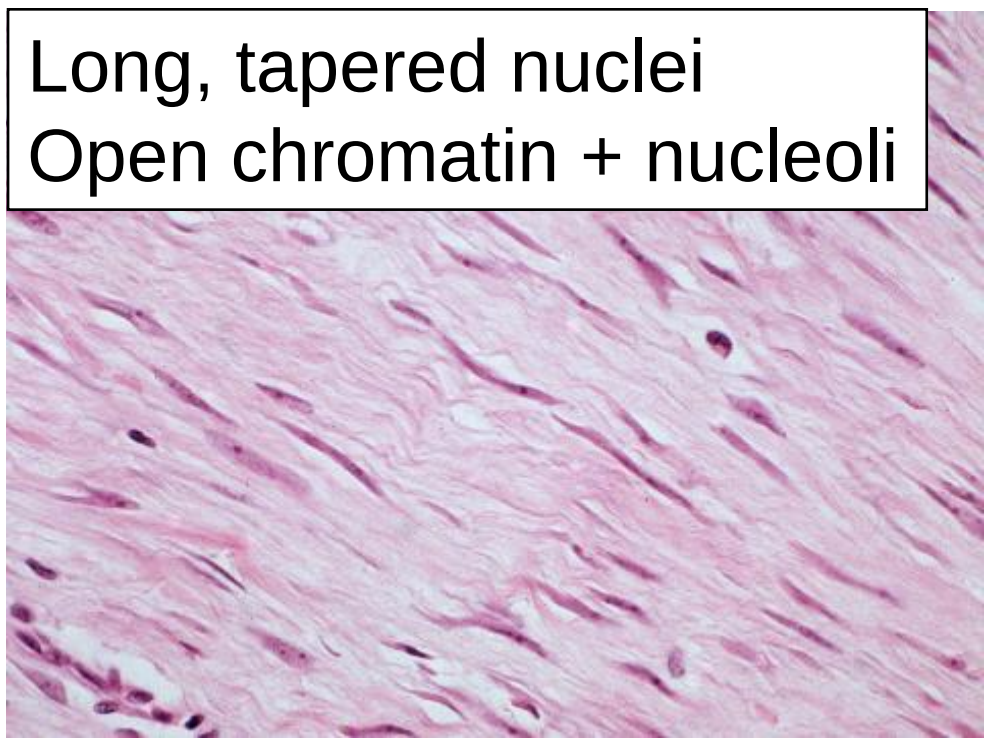
Features of Fibromatoses

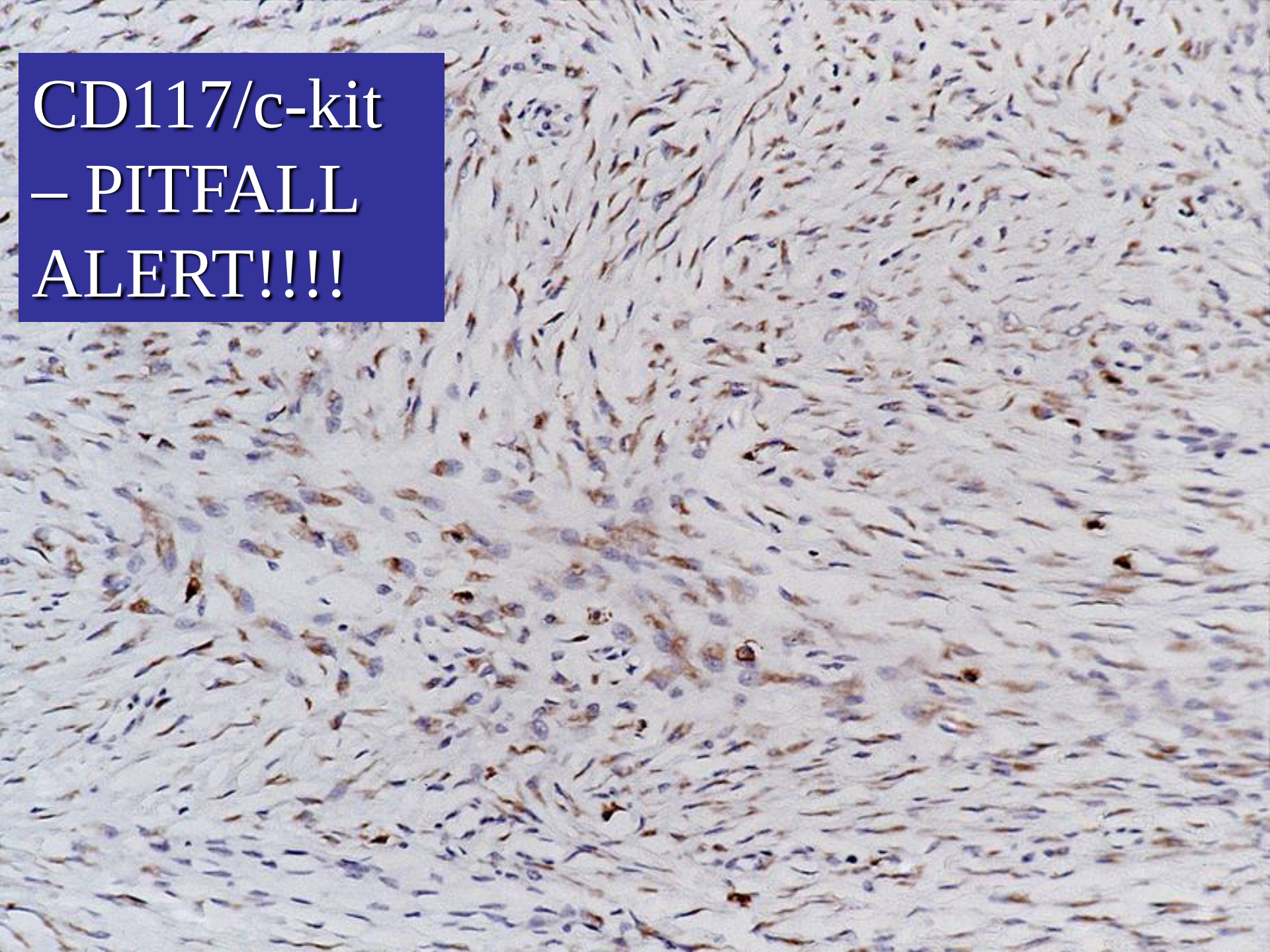
- Sweeping Fascicles of Fibroblasts
- Infiltrative Growth Pattern
- Characteristic Vascular Pattern


Sweeping fascicles


Prominent vessels

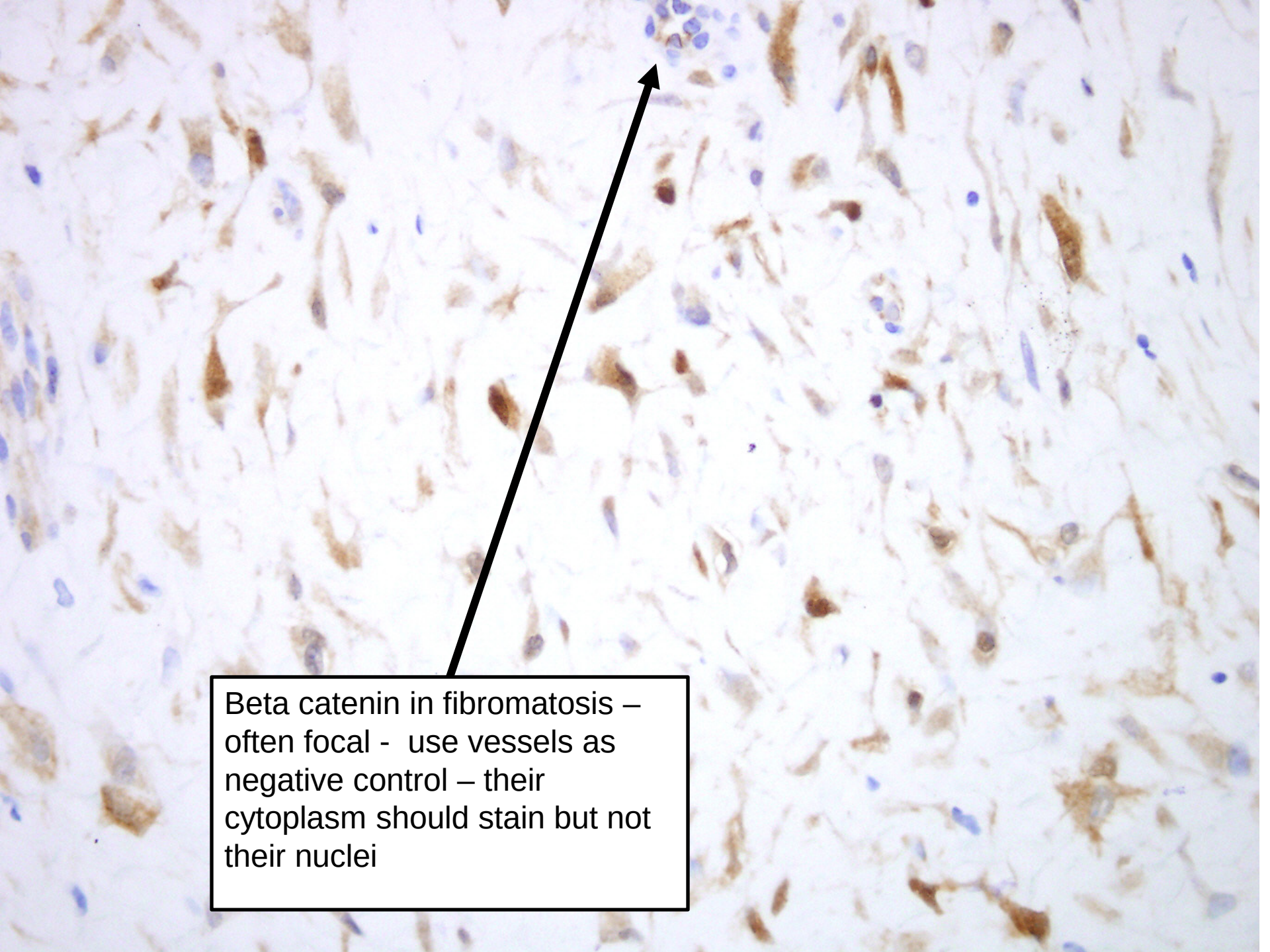

Gaping vessels


Long, tapered nuclei
Open chromatin + nucleoli


CD117/c-kit
– PITFALL
ALERT!!!!

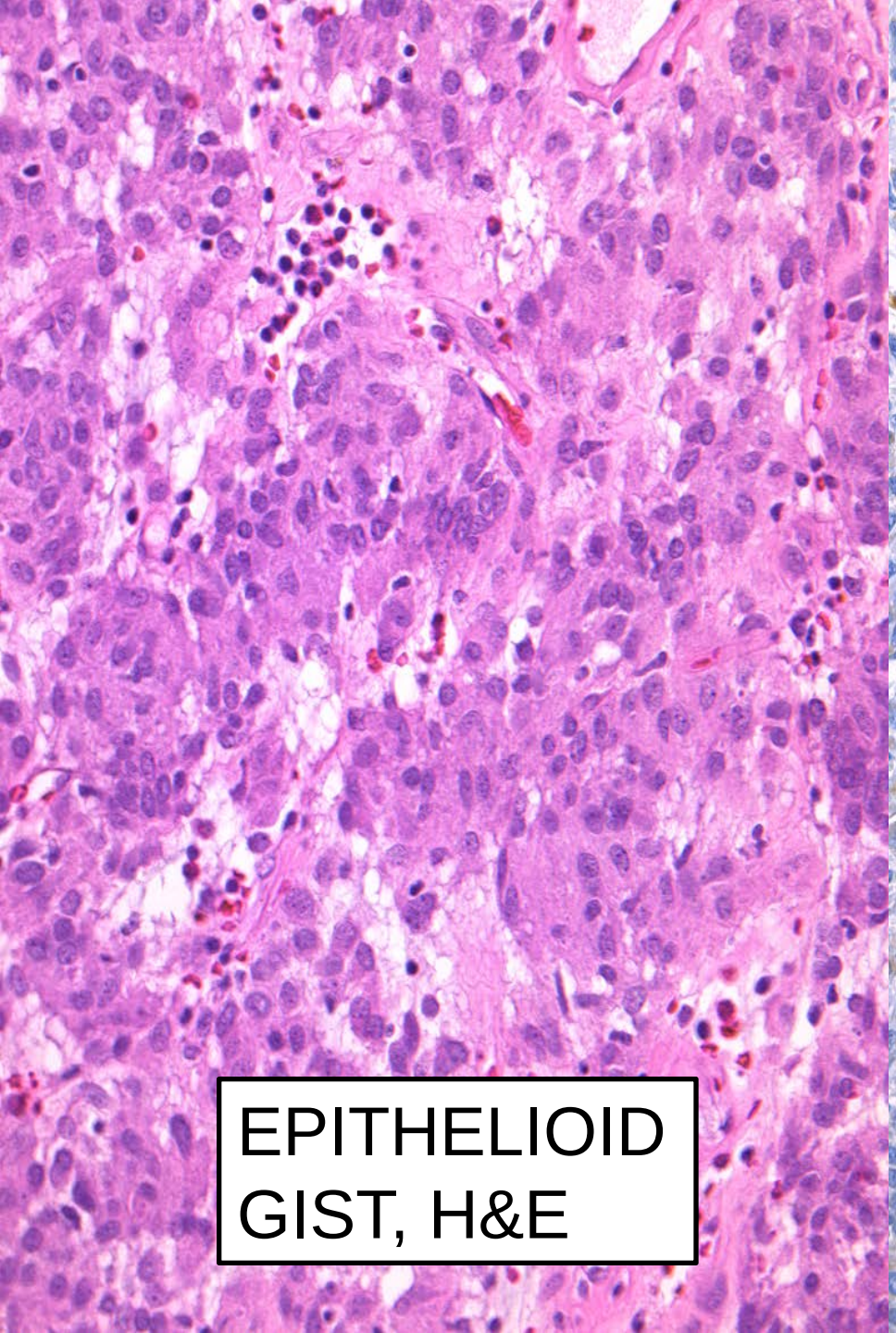
β catenin in Fibromatoses

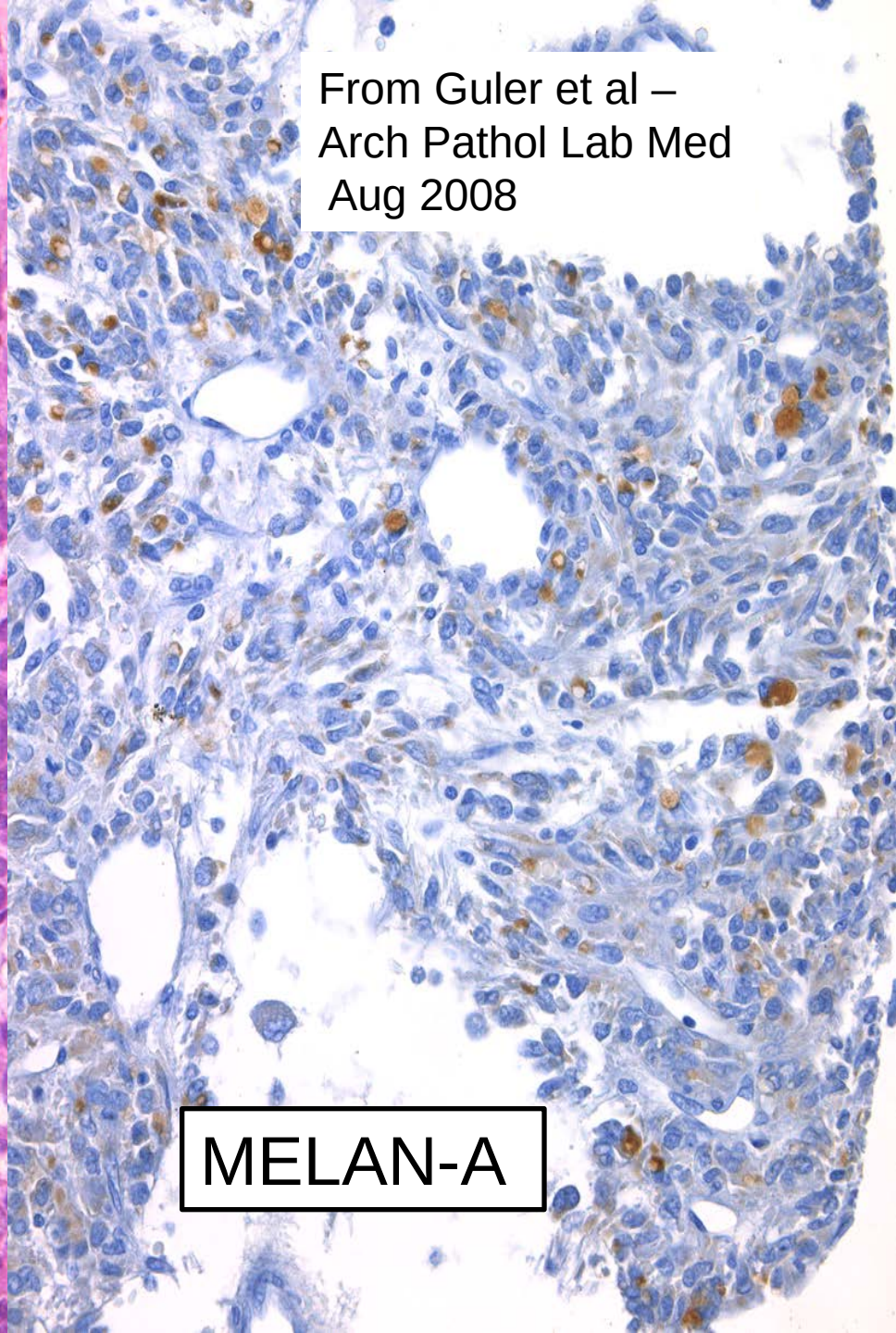
- Accumulates in nucleus
- NOT detected in GISTs

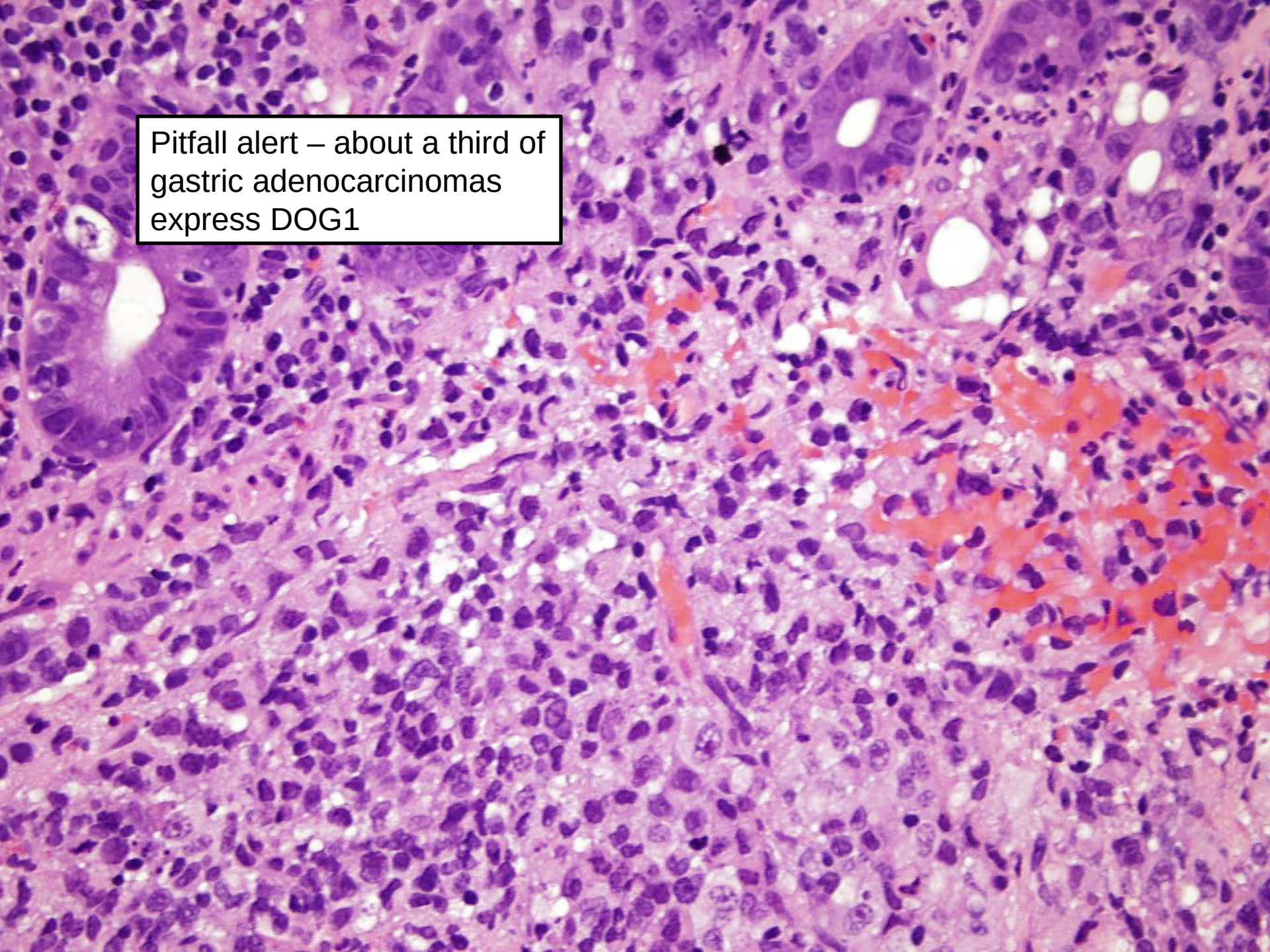

Beta catenin in fibromatosis – often focal - use vessels as negative control – their cytoplasm should stain but not their nuclei

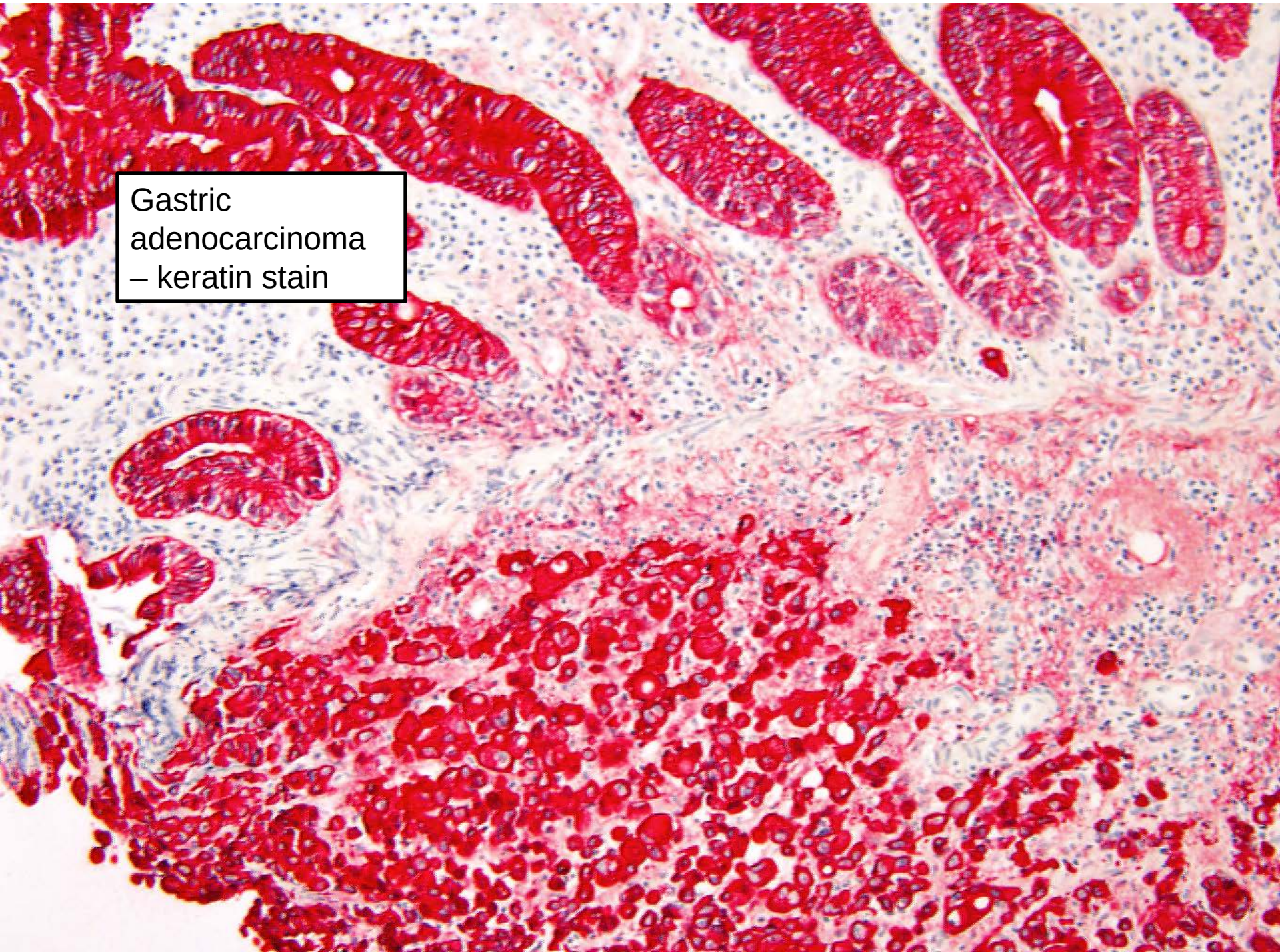
Another Immuno Tip – Pitfall alert

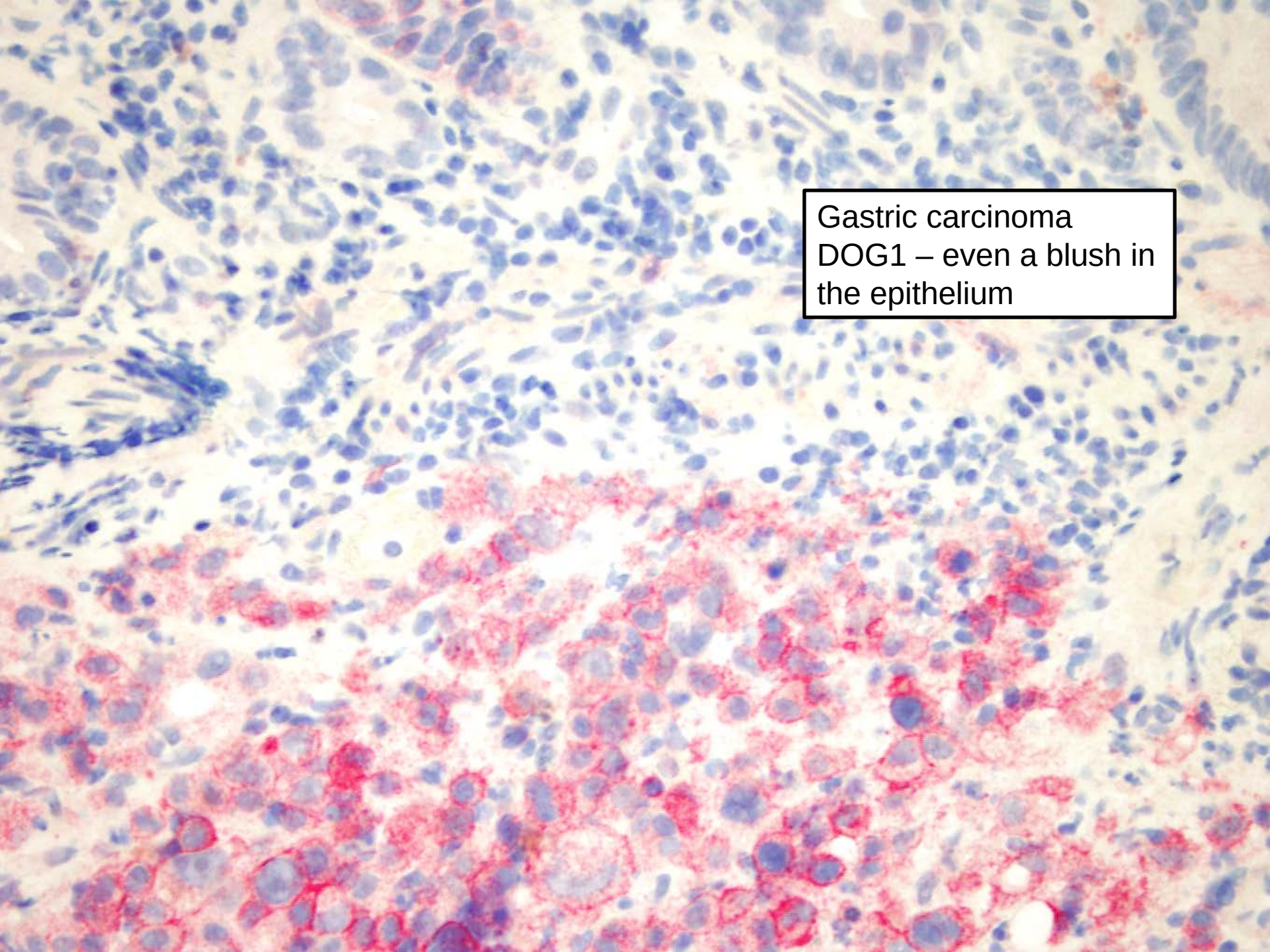
- About 30-40% of epithelioid GISTS stain with MELAN-A [but not HMB45]
- In our hands these expressed CD34 [most melanomas do not] and lacked S100 [most melanomas have S100].


EPITHELIOID
GIST, H&E

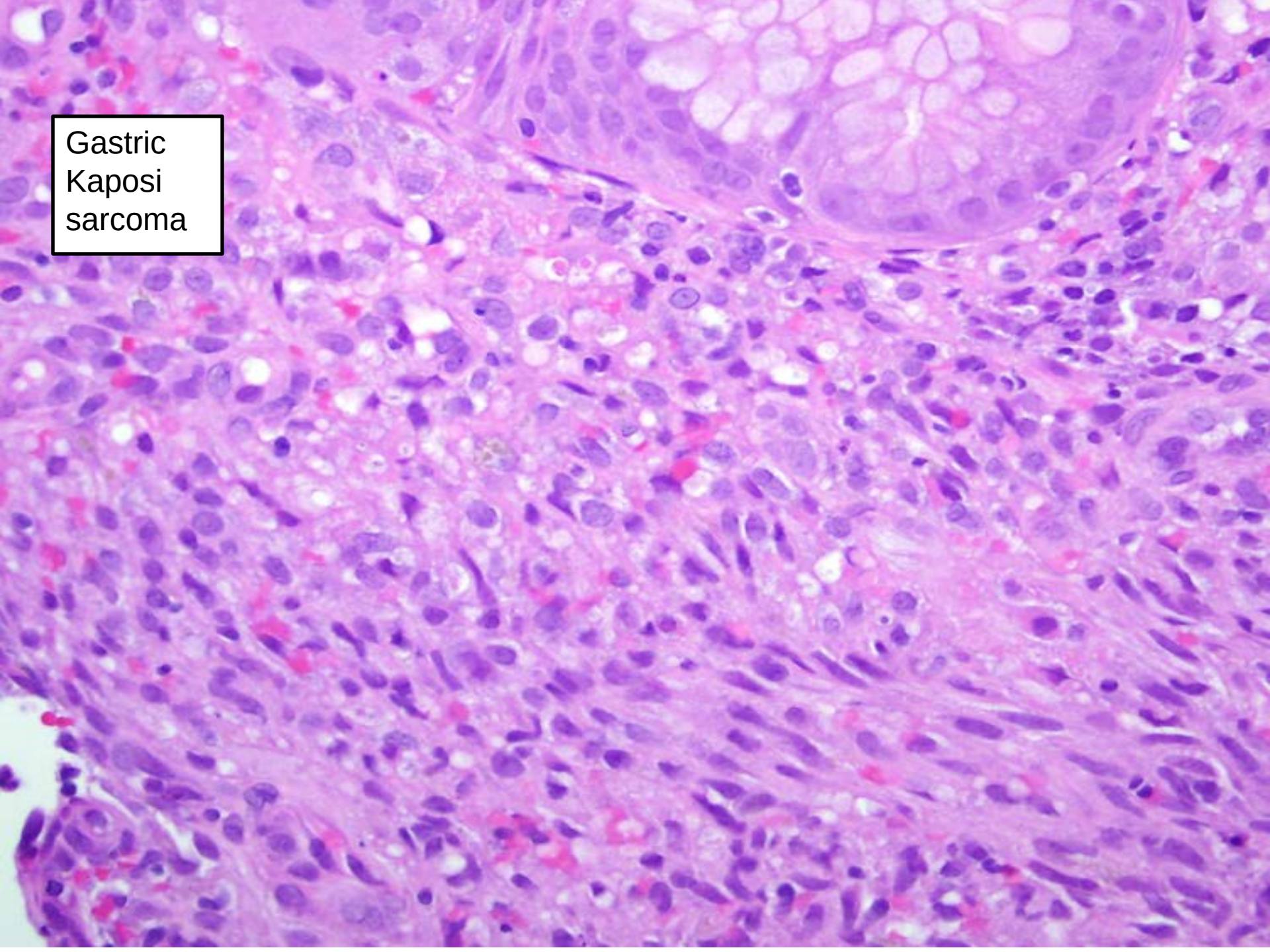

From Guler et al –
Arch Pathol Lab Med
Aug 2008
MELAN-A

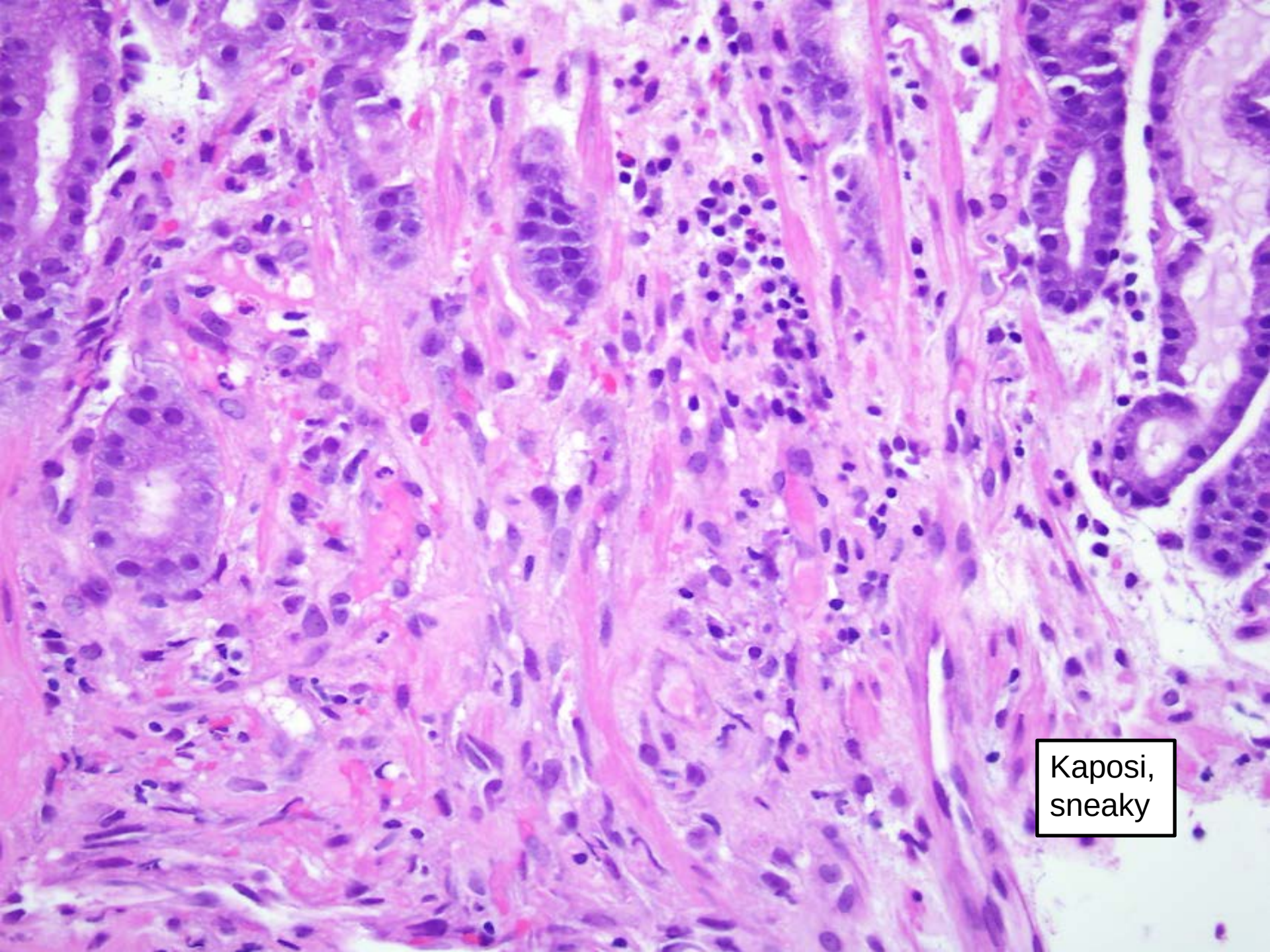

Pitfall alert – about a third of gastric adenocarcinomas express DOG1

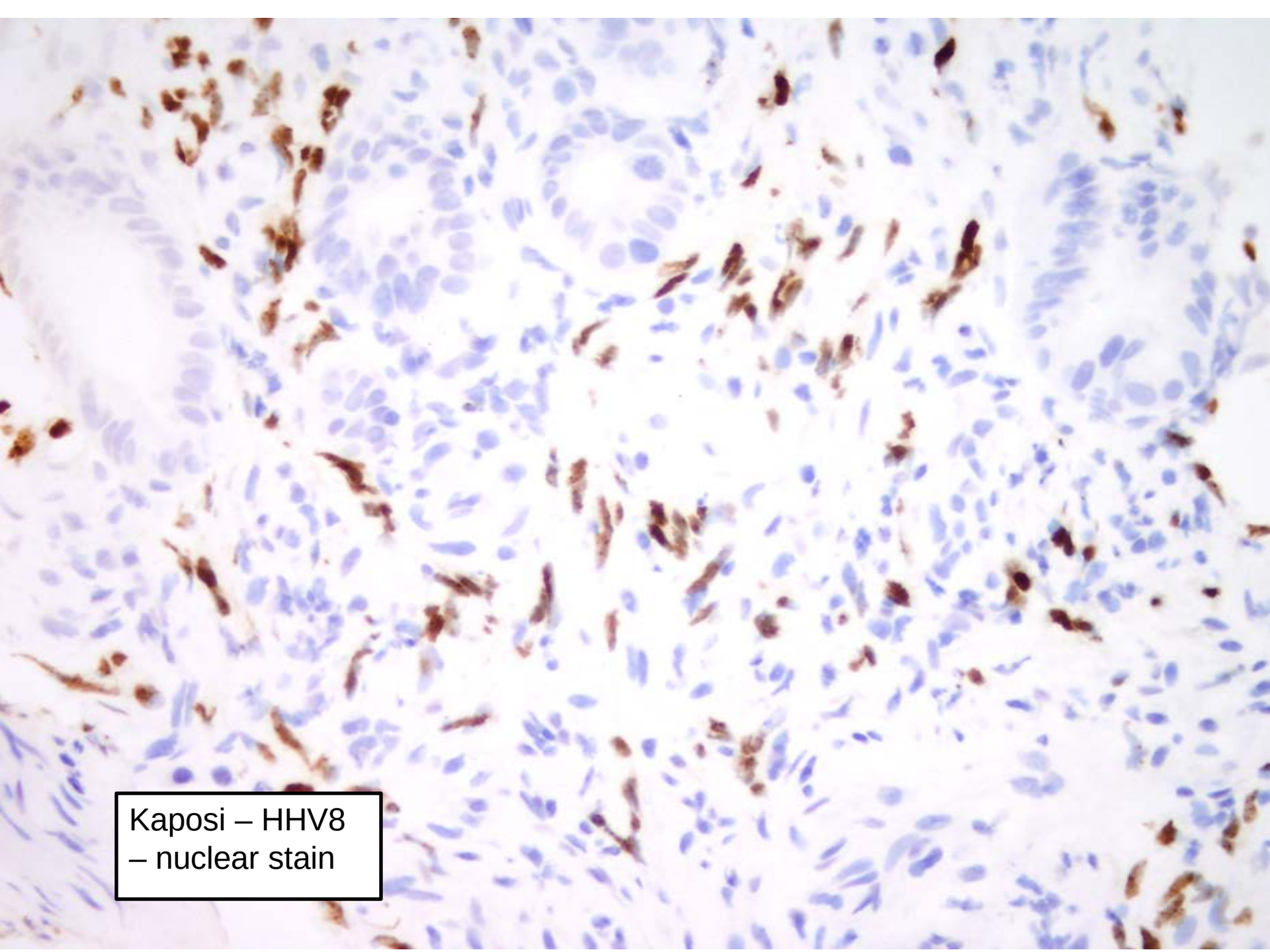

Gastric adenocarcinoma – keratin stain

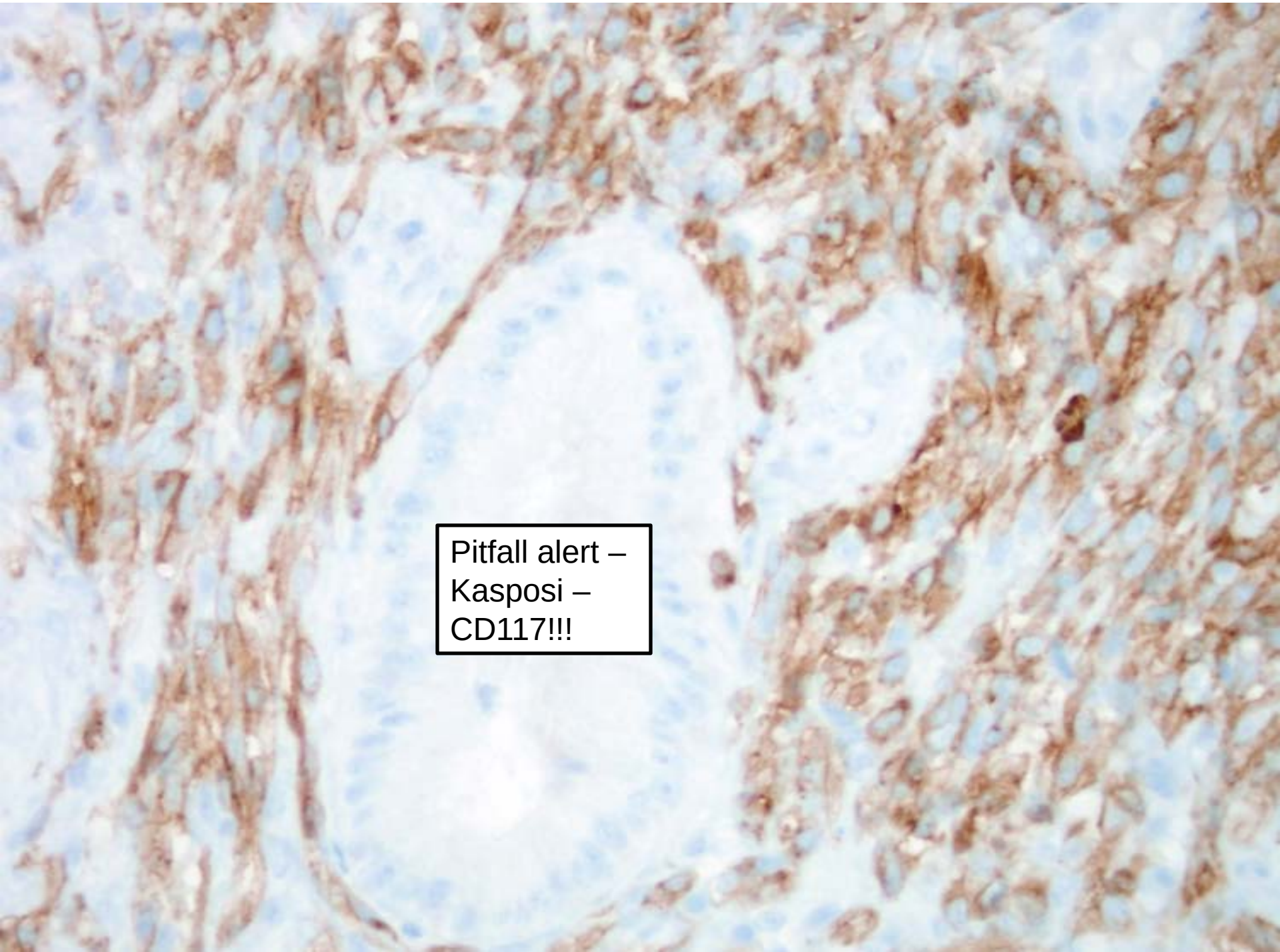

Gastric carcinoma
DOG1 – even a blush in the epithelium

Another pitfall


Gastric
Kaposi
sarcoma


Kaposi,
sneaky


Kaposi – HHV8
– nuclear stain


Pitfall alert –
Kasposi –
CD117!!!

Emperor of The Muscularis Propria

GIST –

Stromal tumors of GI tract

of spindle or epithelioid morphology, which are typically immunohistochemically positive for

kit (CD117)

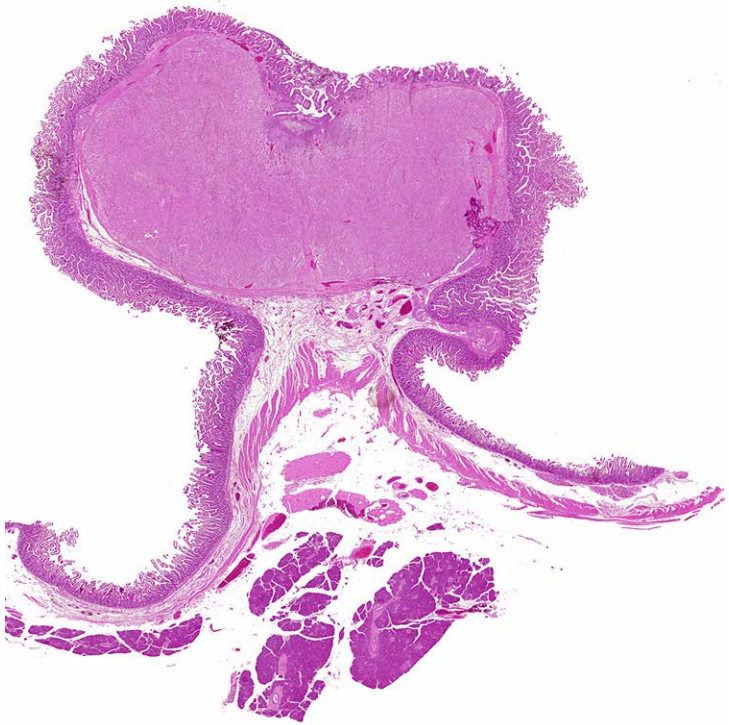
Identical tumors arise in

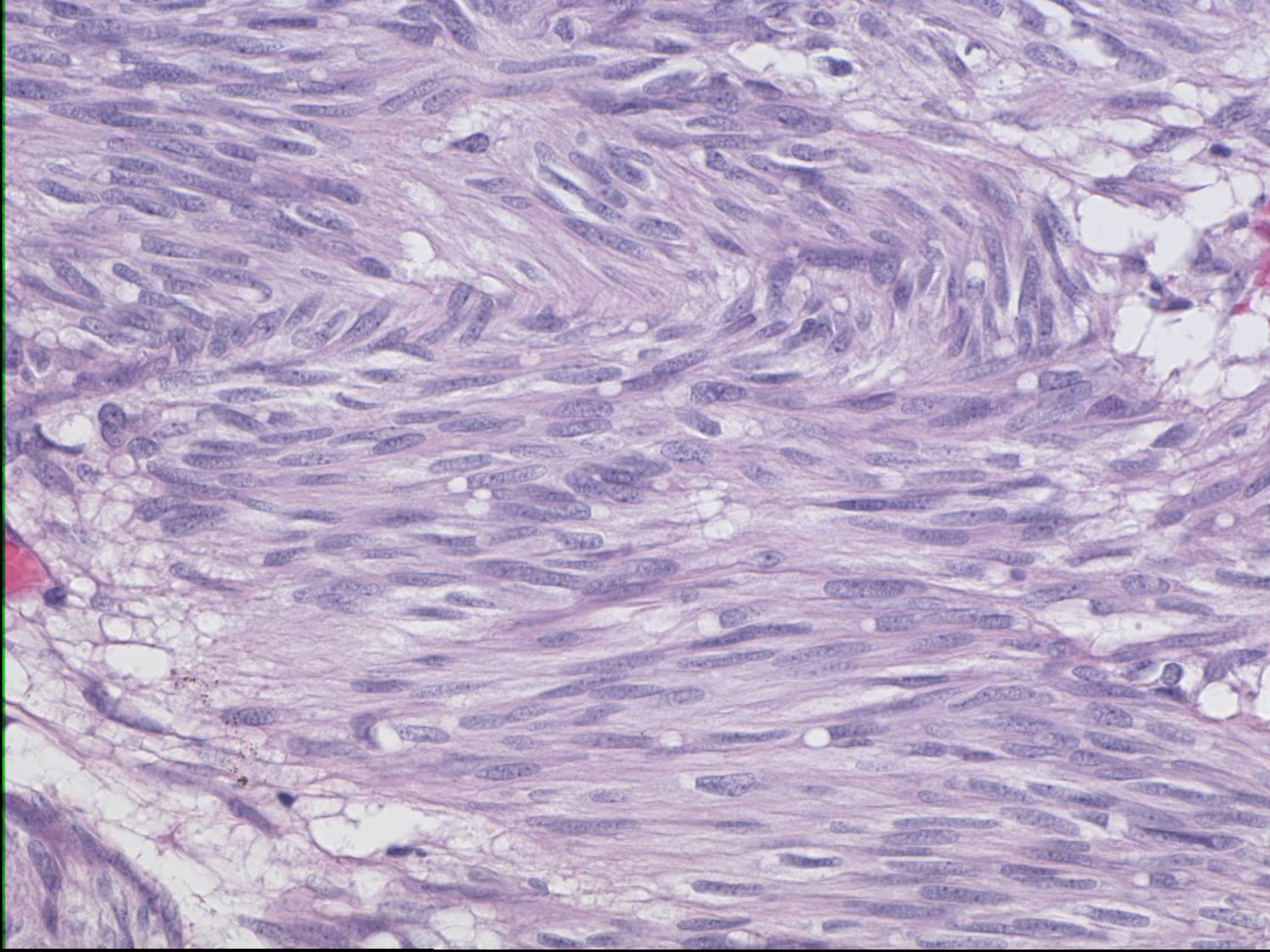
omentum, mesentery, retroperitoneum

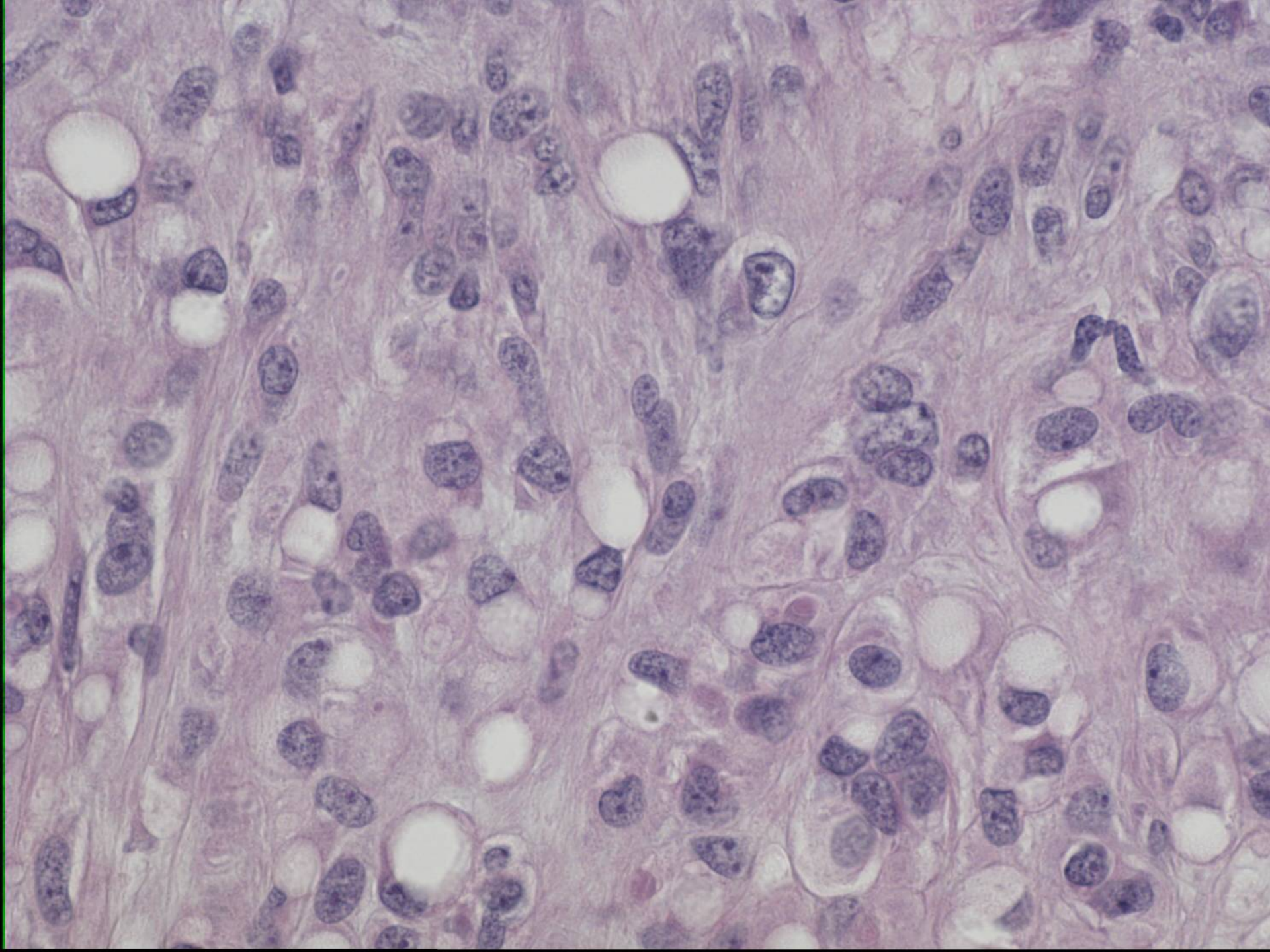
bladder, gall bladder

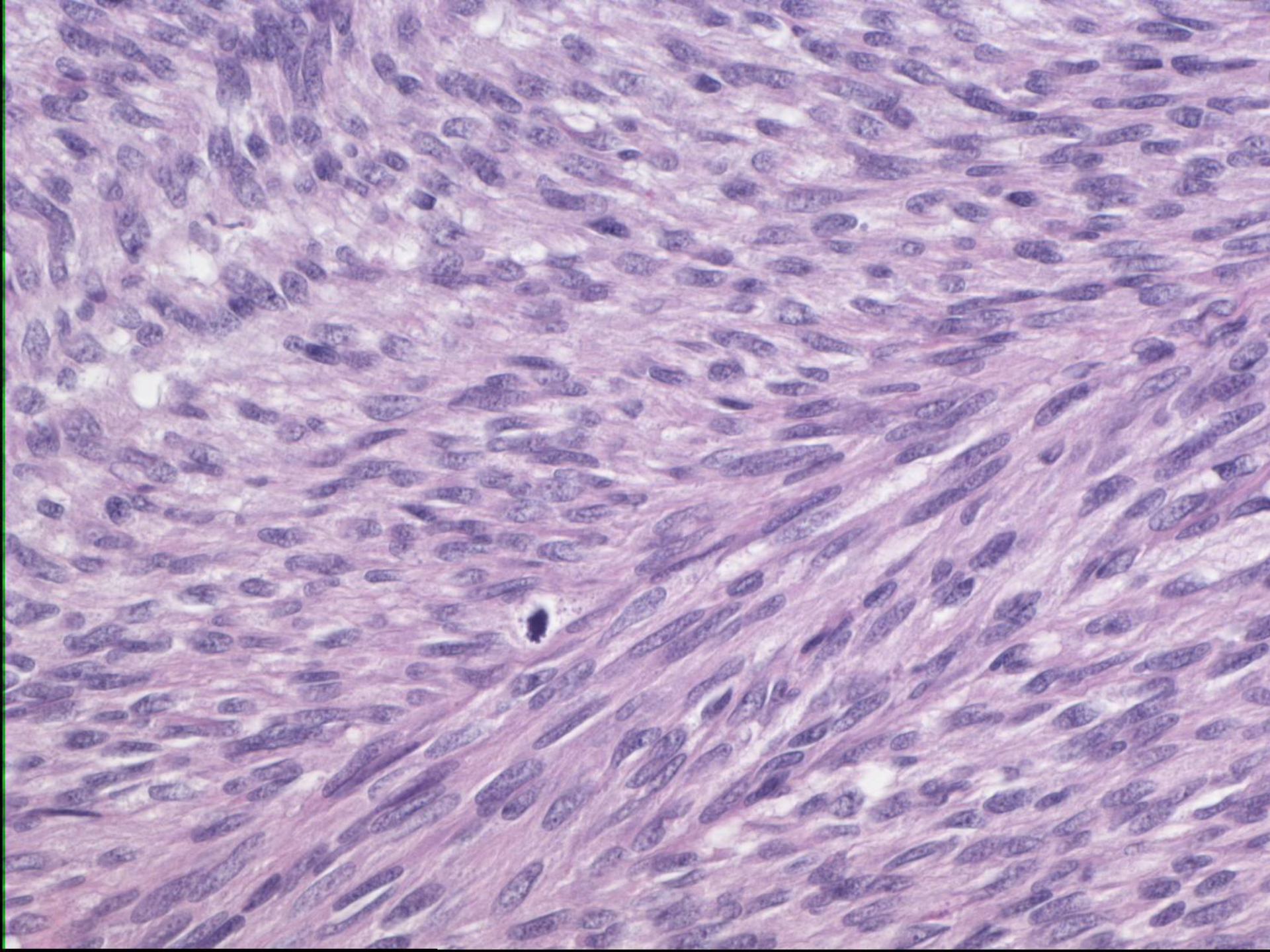
GIST

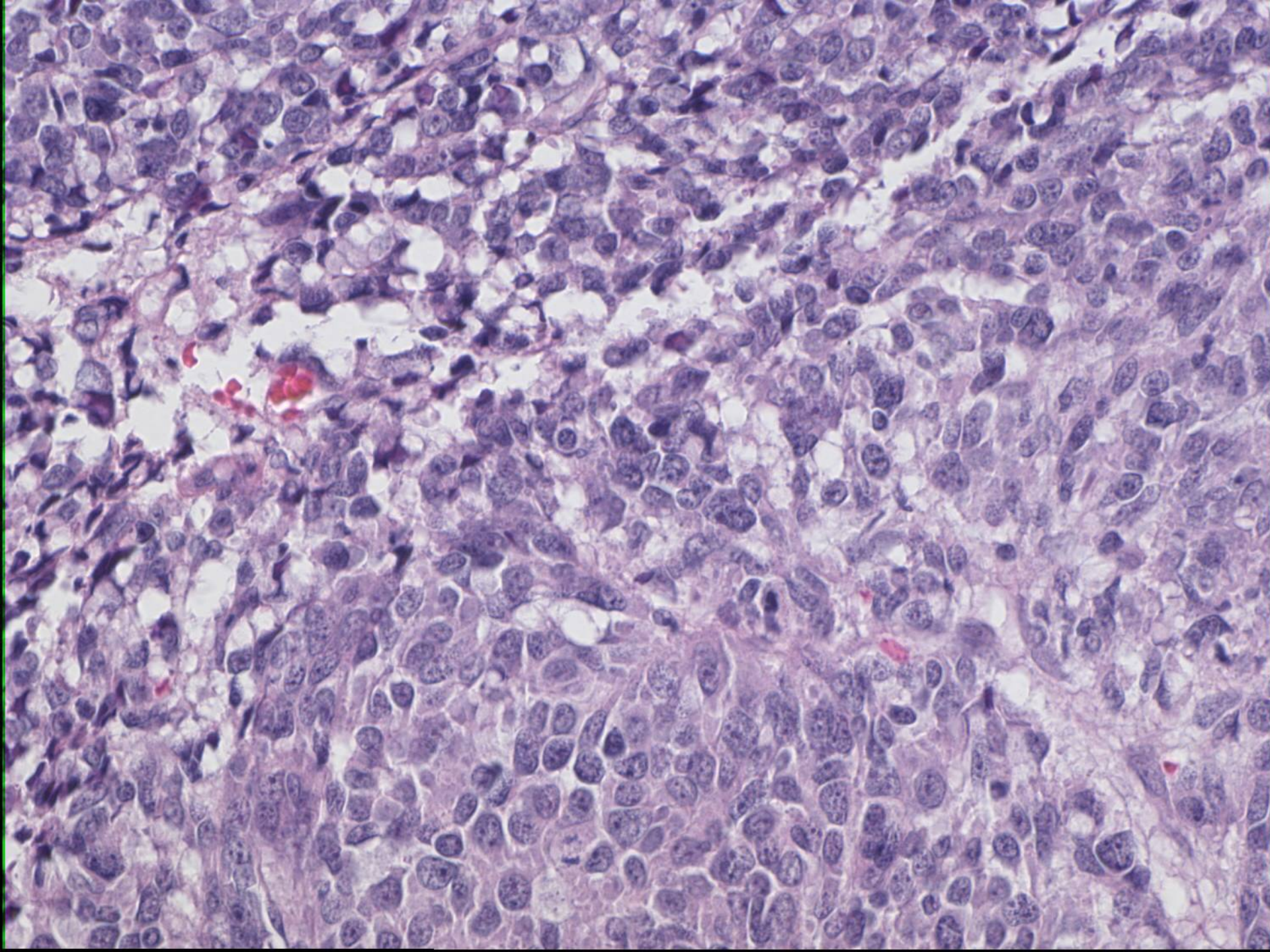
- 5-10% of all sarcomas
- 5,000/yr in US
- 1% of GI malignancy
- M > F >50 yrs
- Pain, bleeding, mass
- Incidental
- Metastasis





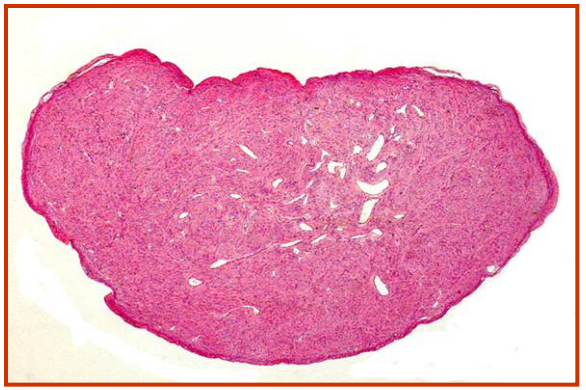






GIST: Associations

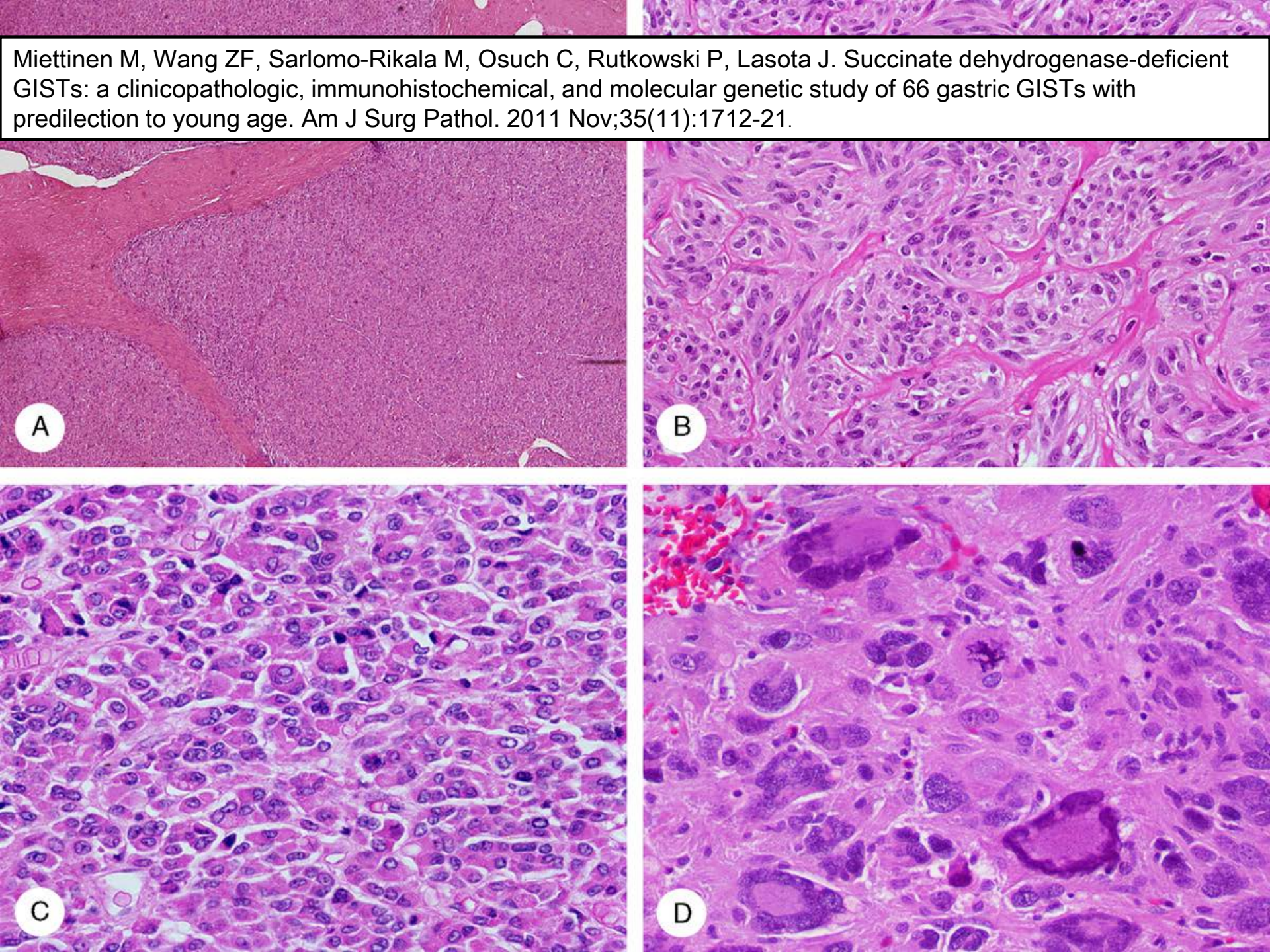
- Familial, multiple
  germline c-kit mutation (11) or
  PDGRFA mutation
- NF-1
  NF-1 product/c-kit interaction
  [lack kit mutations but stain with
  kit antibodies]
- Carney's triad:
  epithelioid GIST
  paraganglioma
  pulmonary chondroma



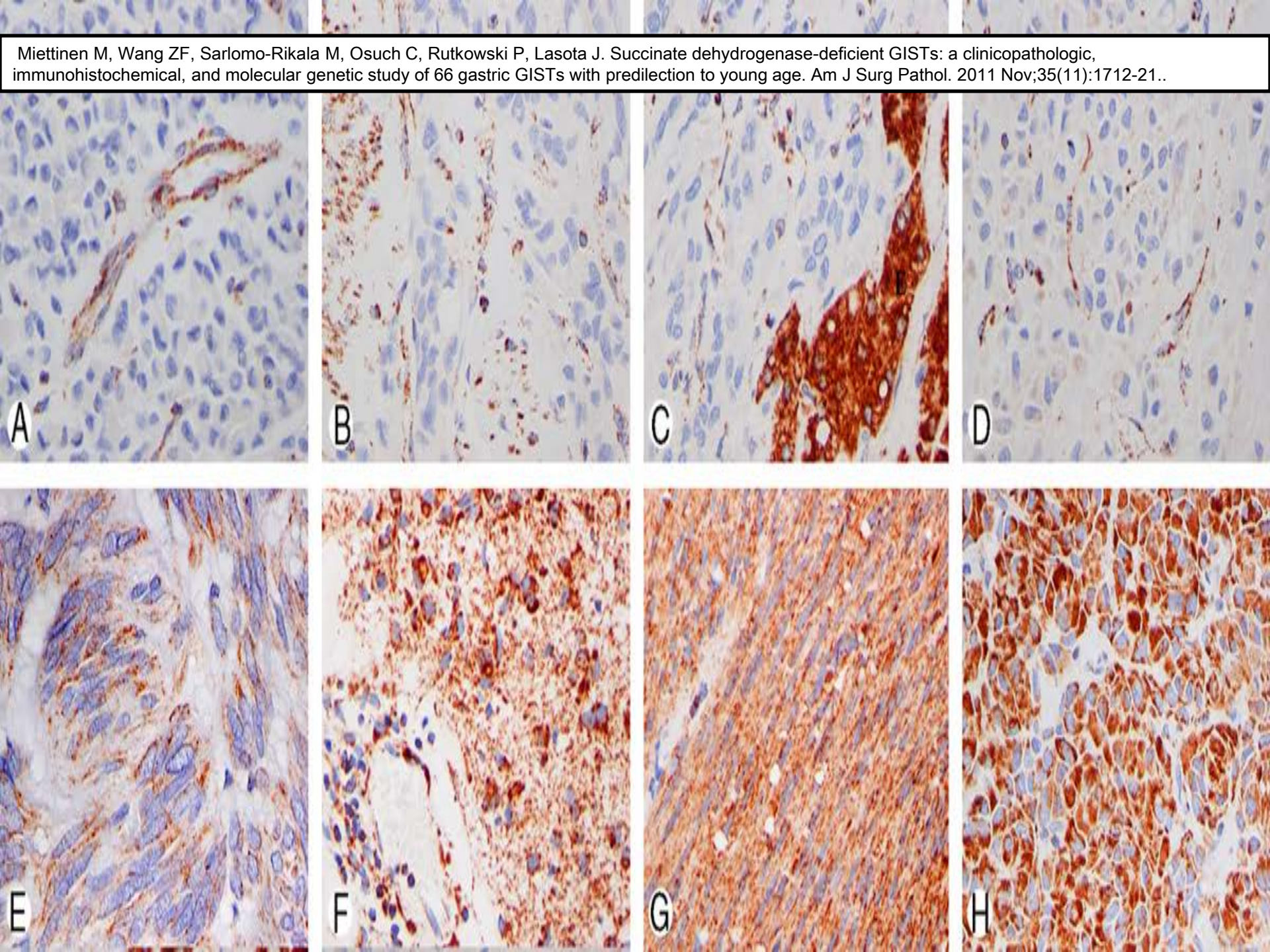
Family of *KIT* wild type GISTS – All Stain With KIT/DOG1 Immunostains

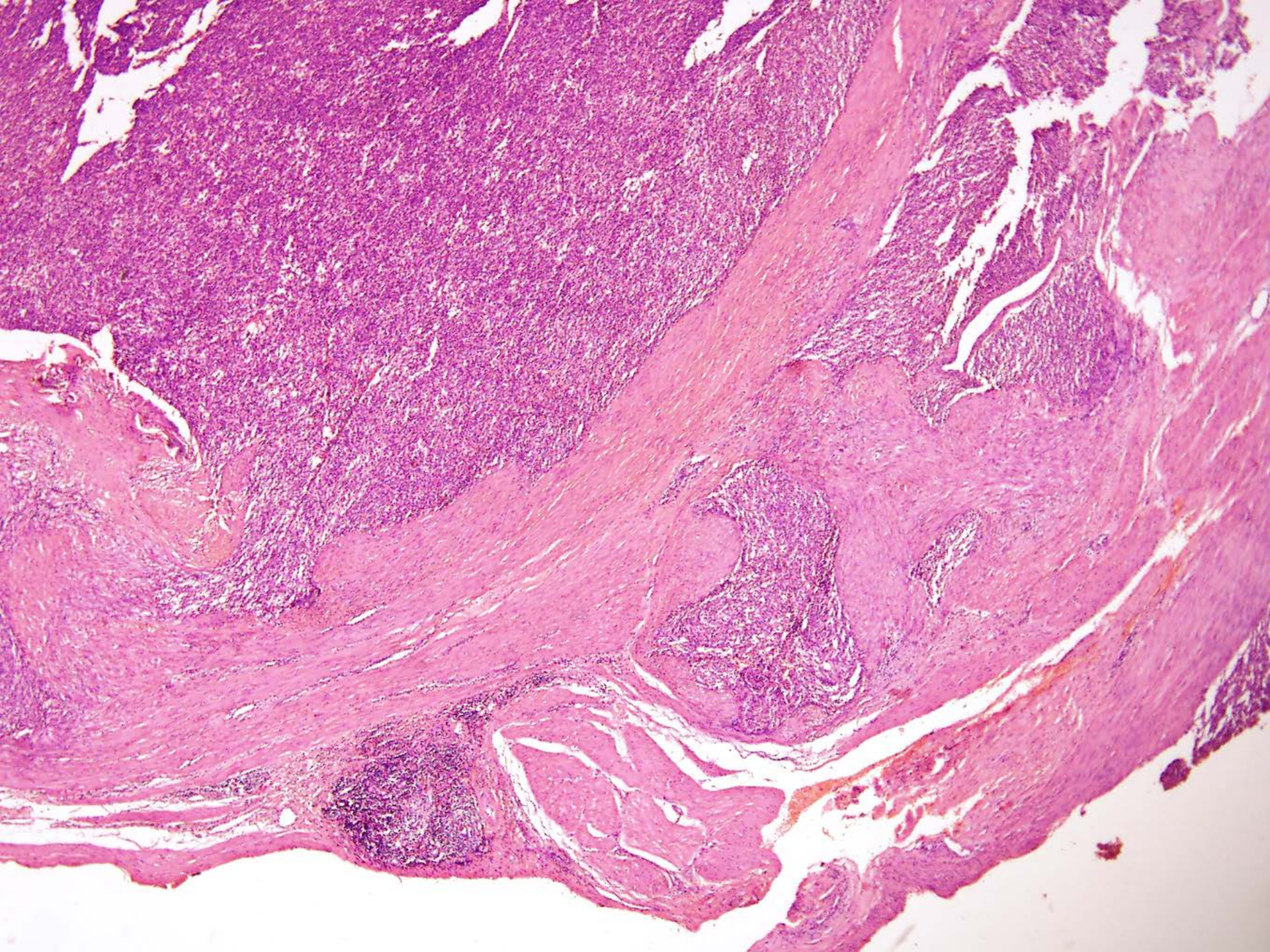
- NF1-associated
- Succinate dehydrogenase deficient ones:
  - About 7% of all GISTS (one study says 15%*)
  - Most pediatric cases
  - Gastric location
  - Often epithelioid with plexiform growth; LN mets; indolent course; no response to imatinib
  - Associated with Carney triad, Carney-Stratakis syndrome (GISTs and paraganglioma; affected families with germline mutations in either SDHB, SDHC or SDHD)

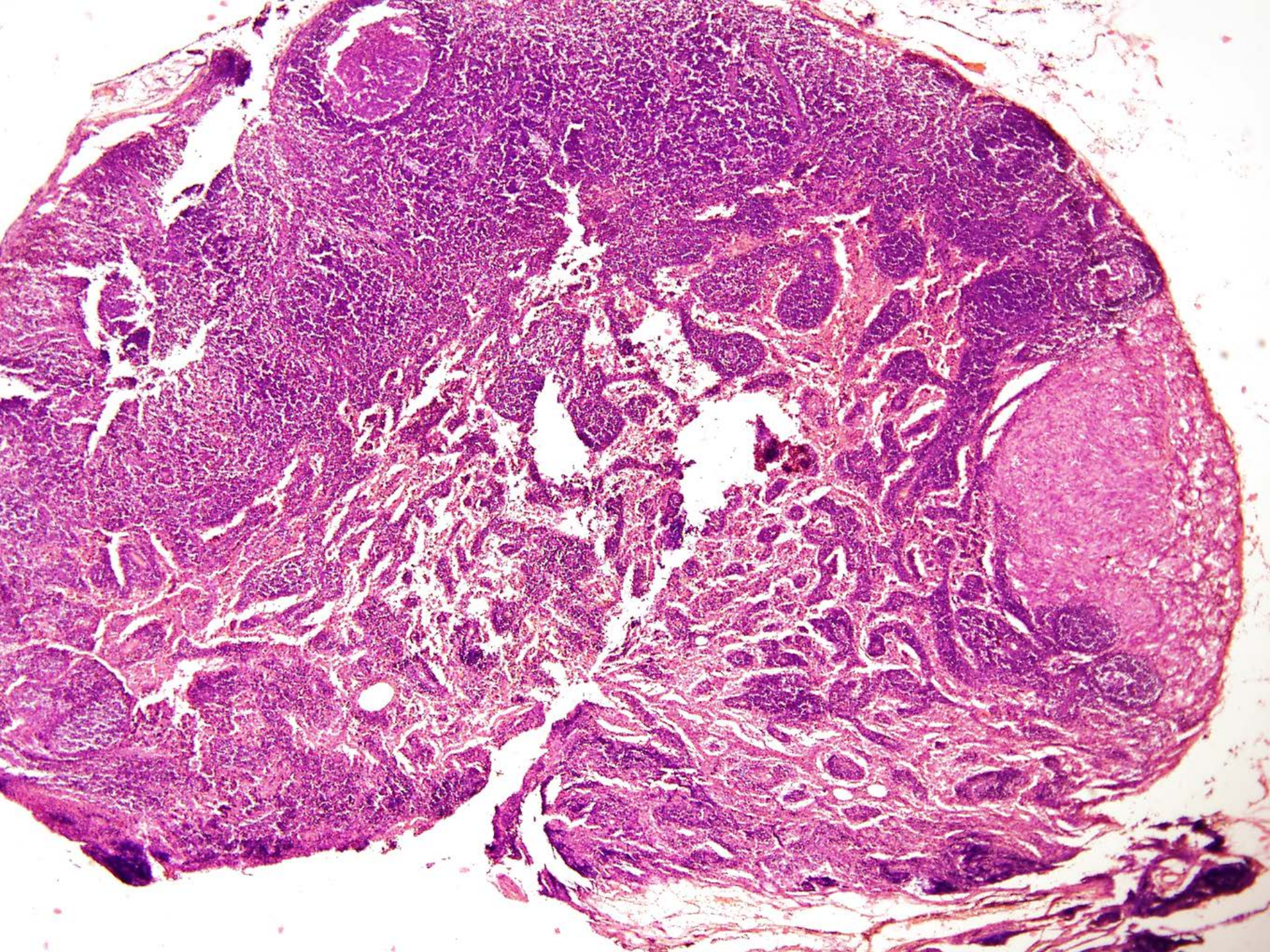
Miettinen M, Wang ZF, Sarlomo-Rikala M, Osuch C, Rutkowski P, Lasota J. Succinate dehydrogenase-deficient GISTs: a clinicopathologic, immunohistochemical, and molecular genetic study of 66 gastric GISTs with predilection to young age. Am J Surg Pathol. 2011 Nov;35(11):1712-21.



Miettinen M, Wang ZF, Sarlomo-Rikala M, Osuch C, Rutkowski P, Lasota J. Succinate dehydrogenase-deficient GISTs: a clinicopathologic, immunohistochemical, and molecular genetic study of 66 gastric GISTs with predilection to young age. Am J Surg Pathol. 2011 Nov;35(11):1712-21..

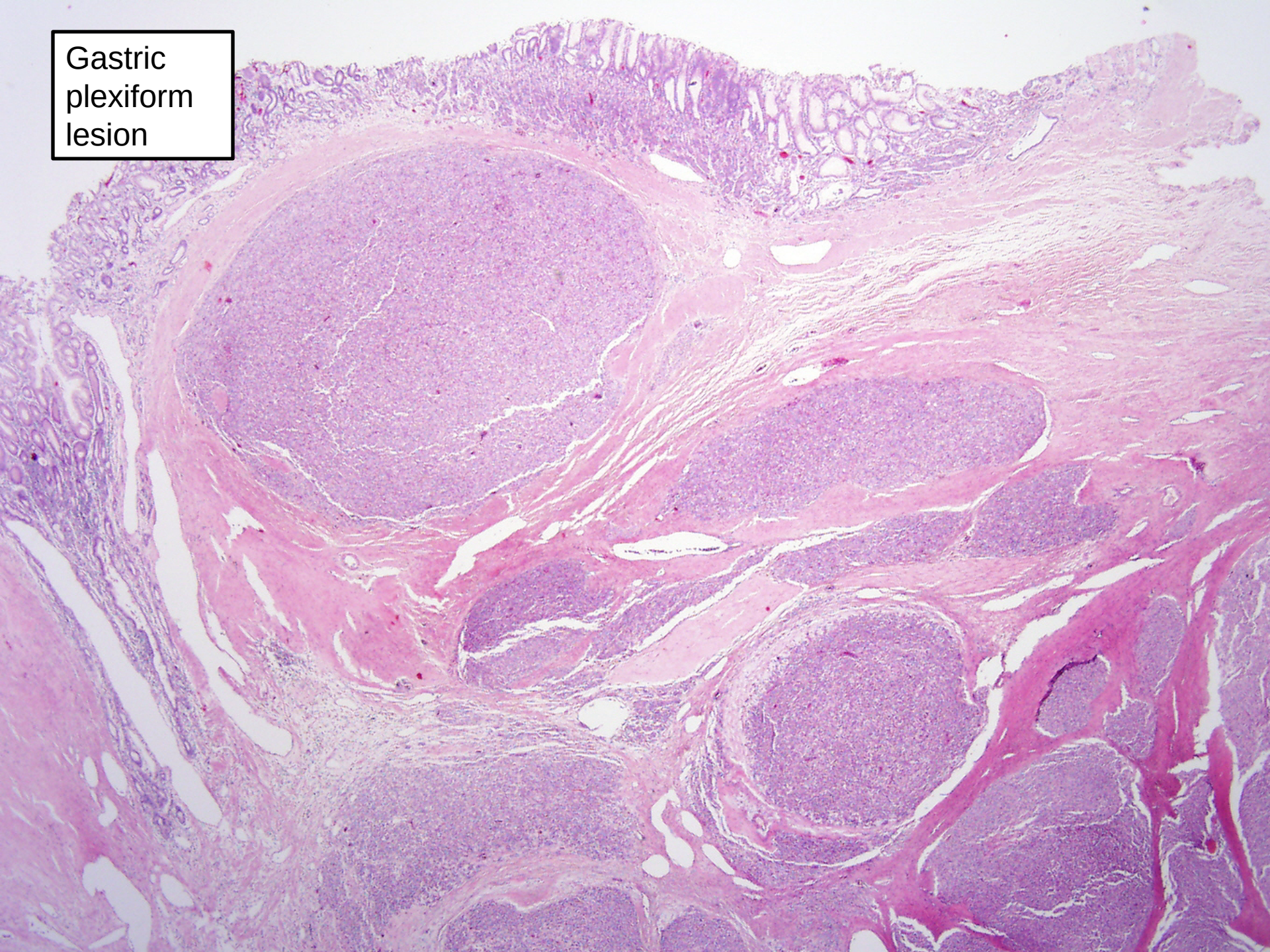


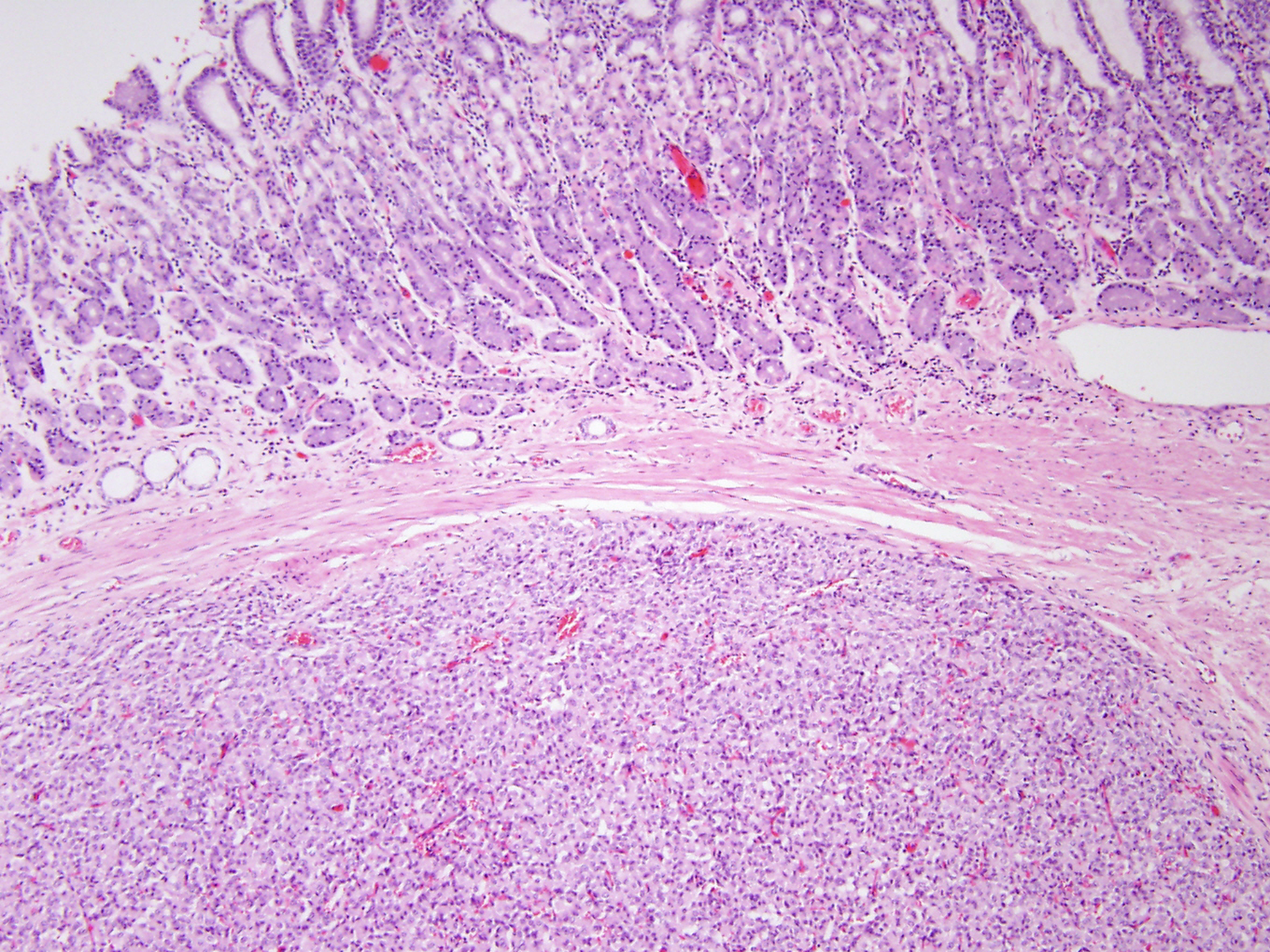


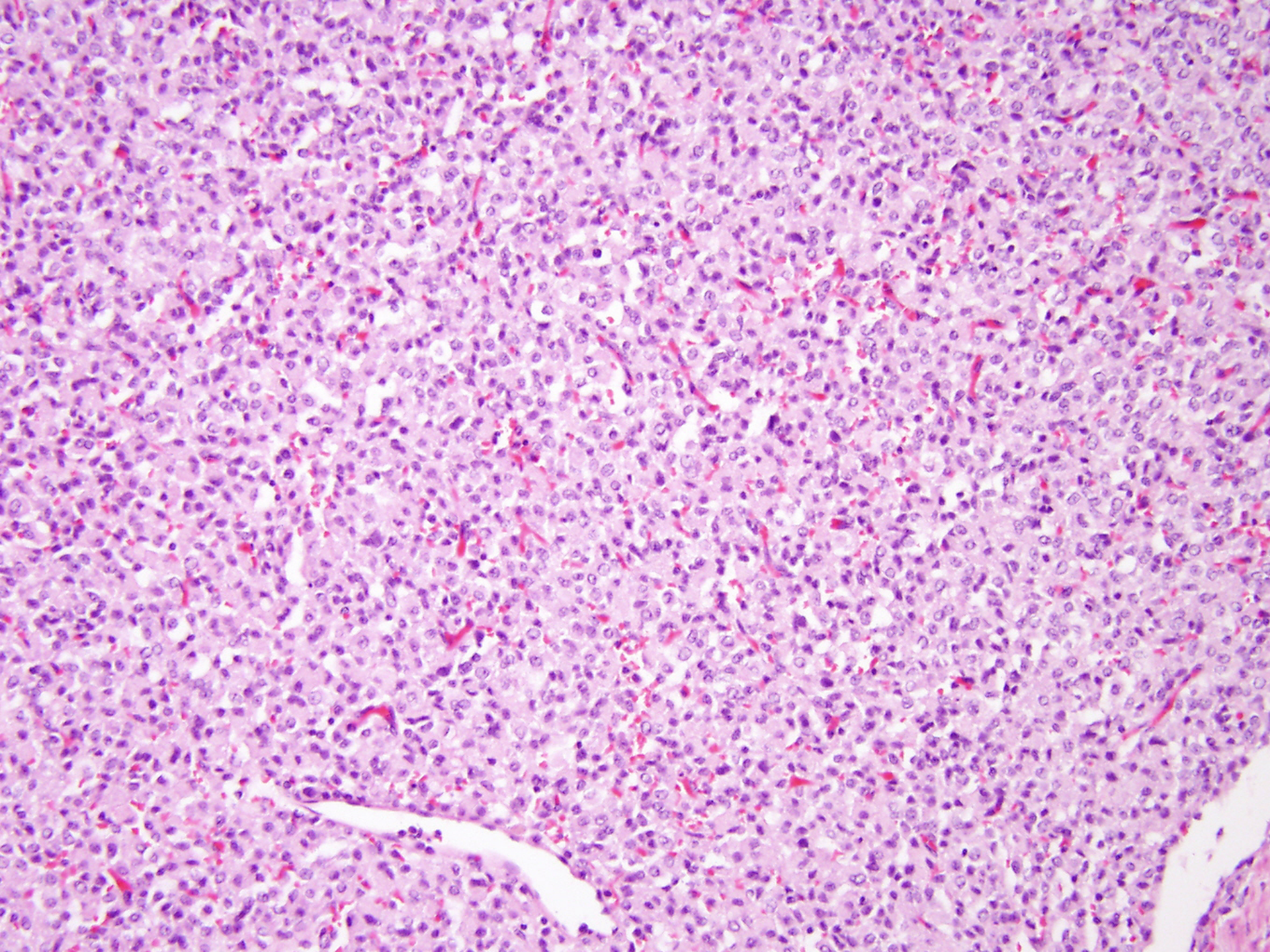


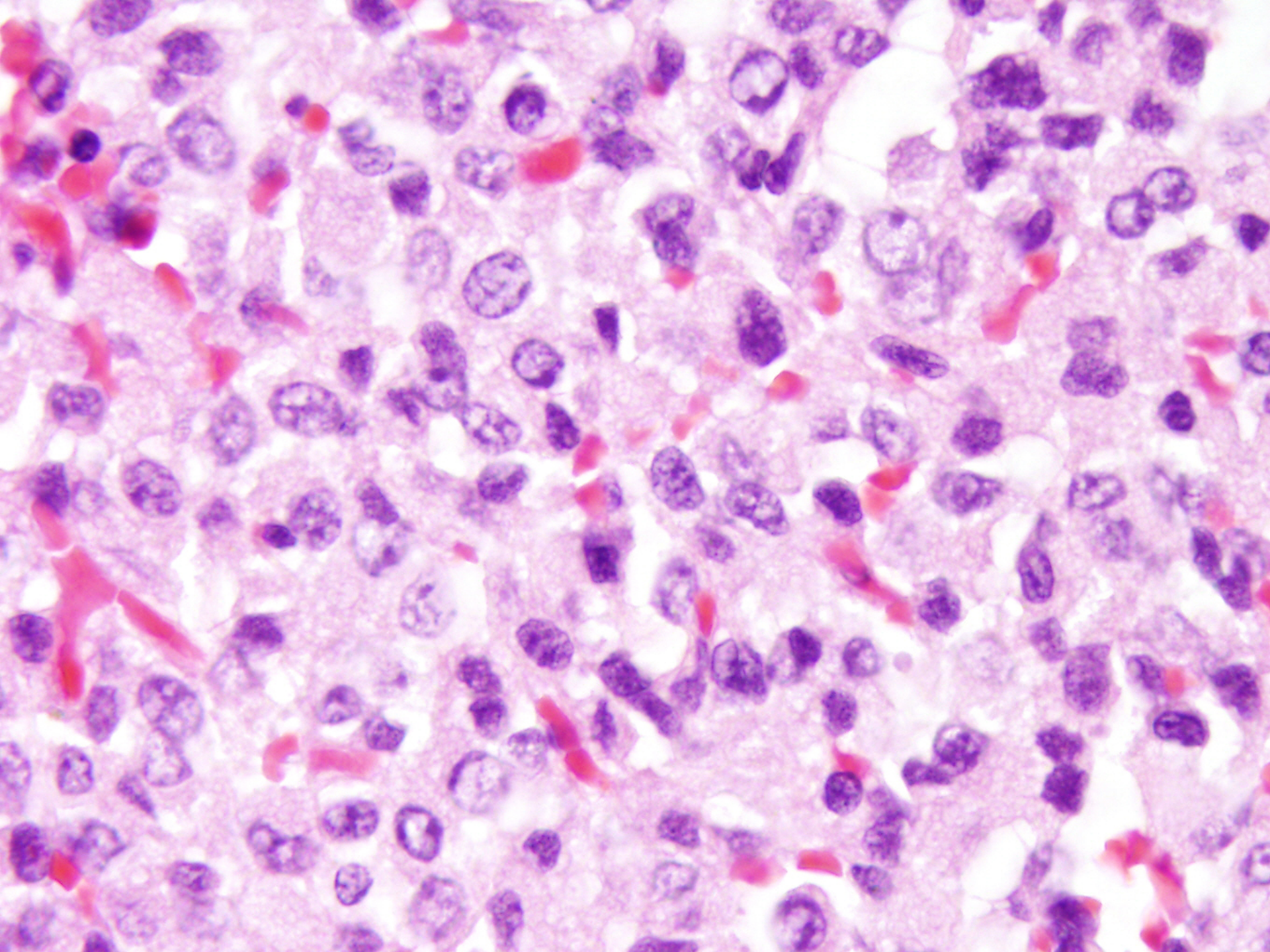
Case

- 40 year old woman. She had had a tumor resected from her stomach as a child and had had spread to lymph nodes. Each time she had an operation. She presented with a new gastric mass


Gastric
plexiform
lesion

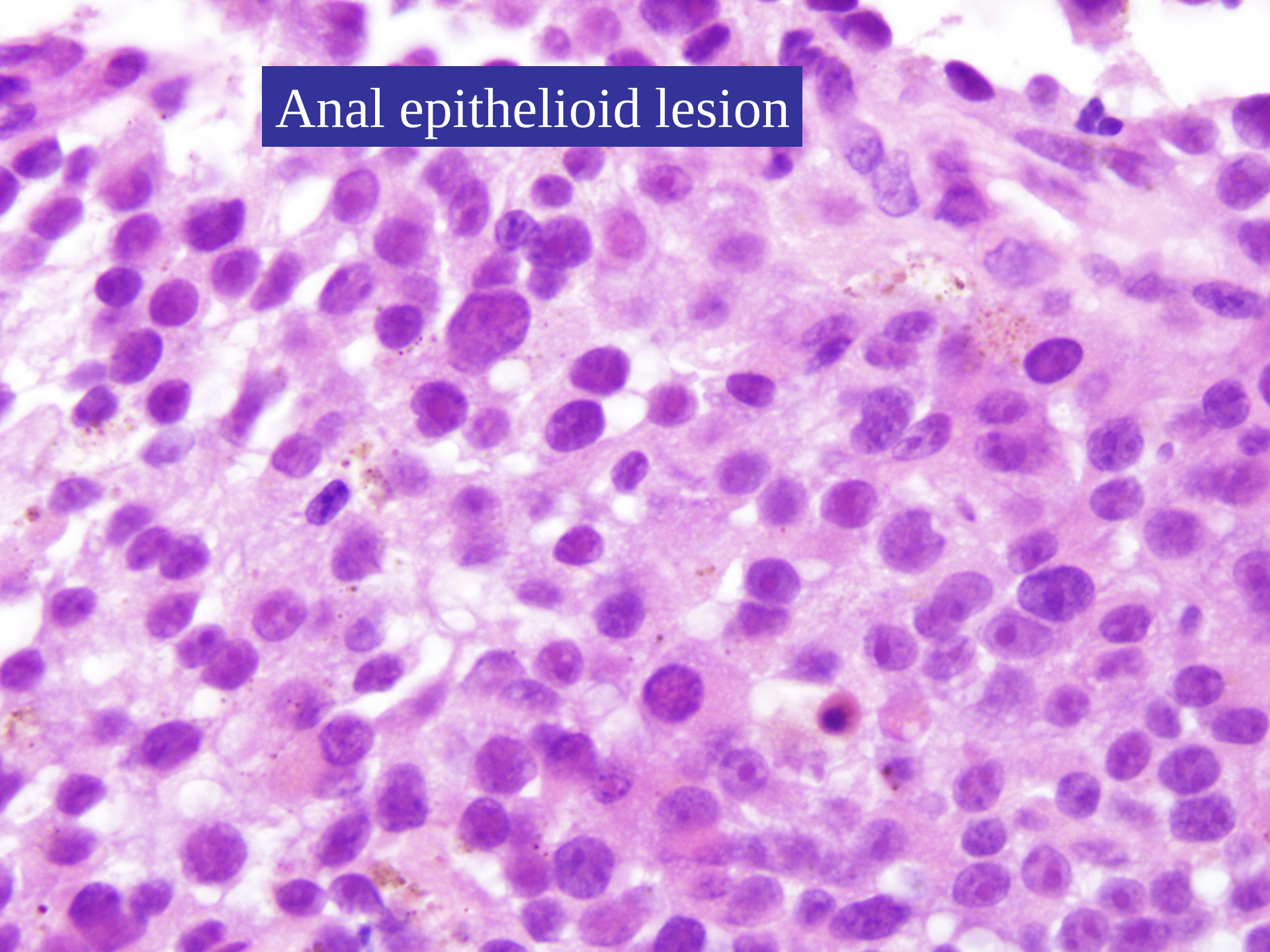


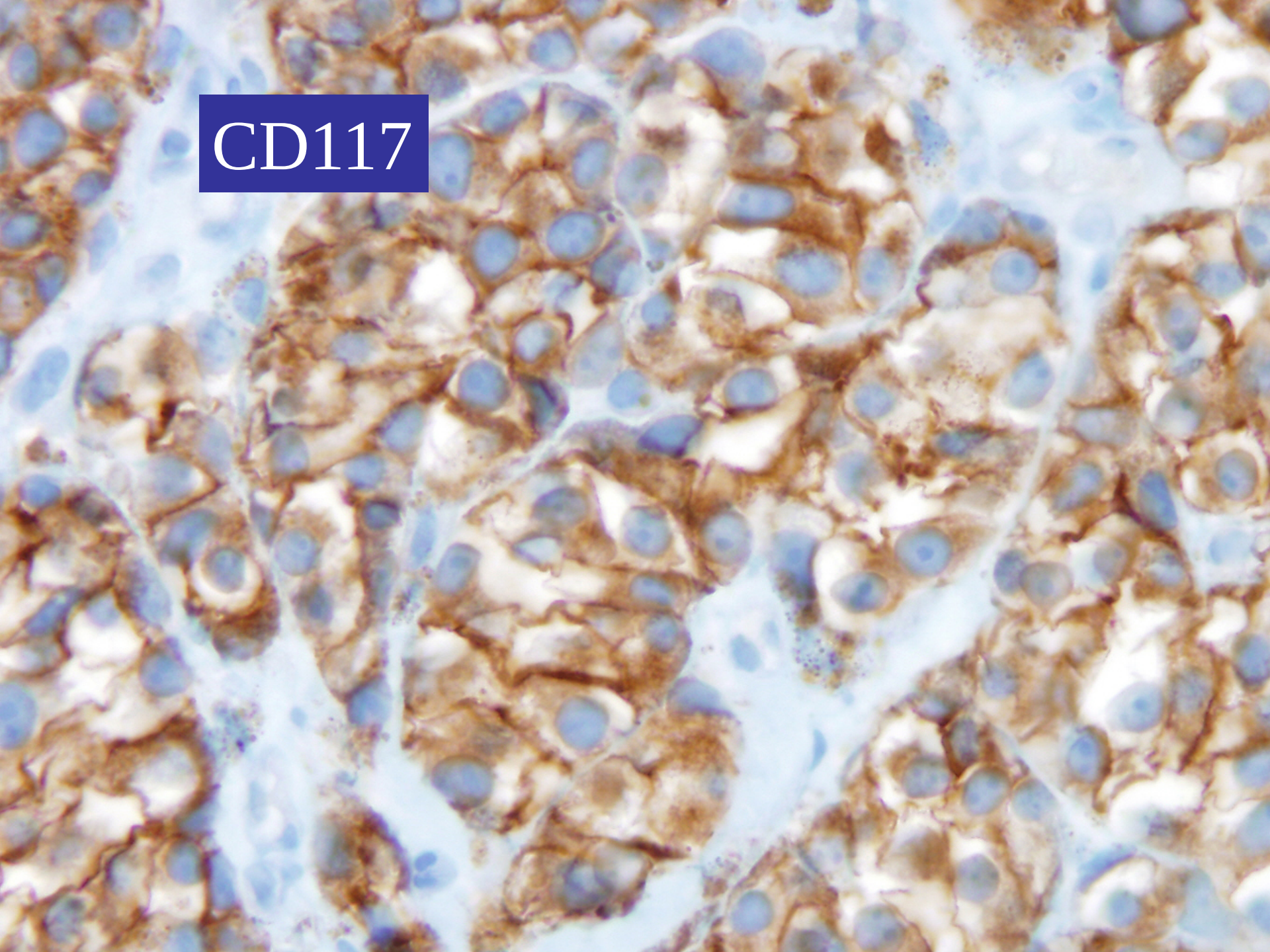


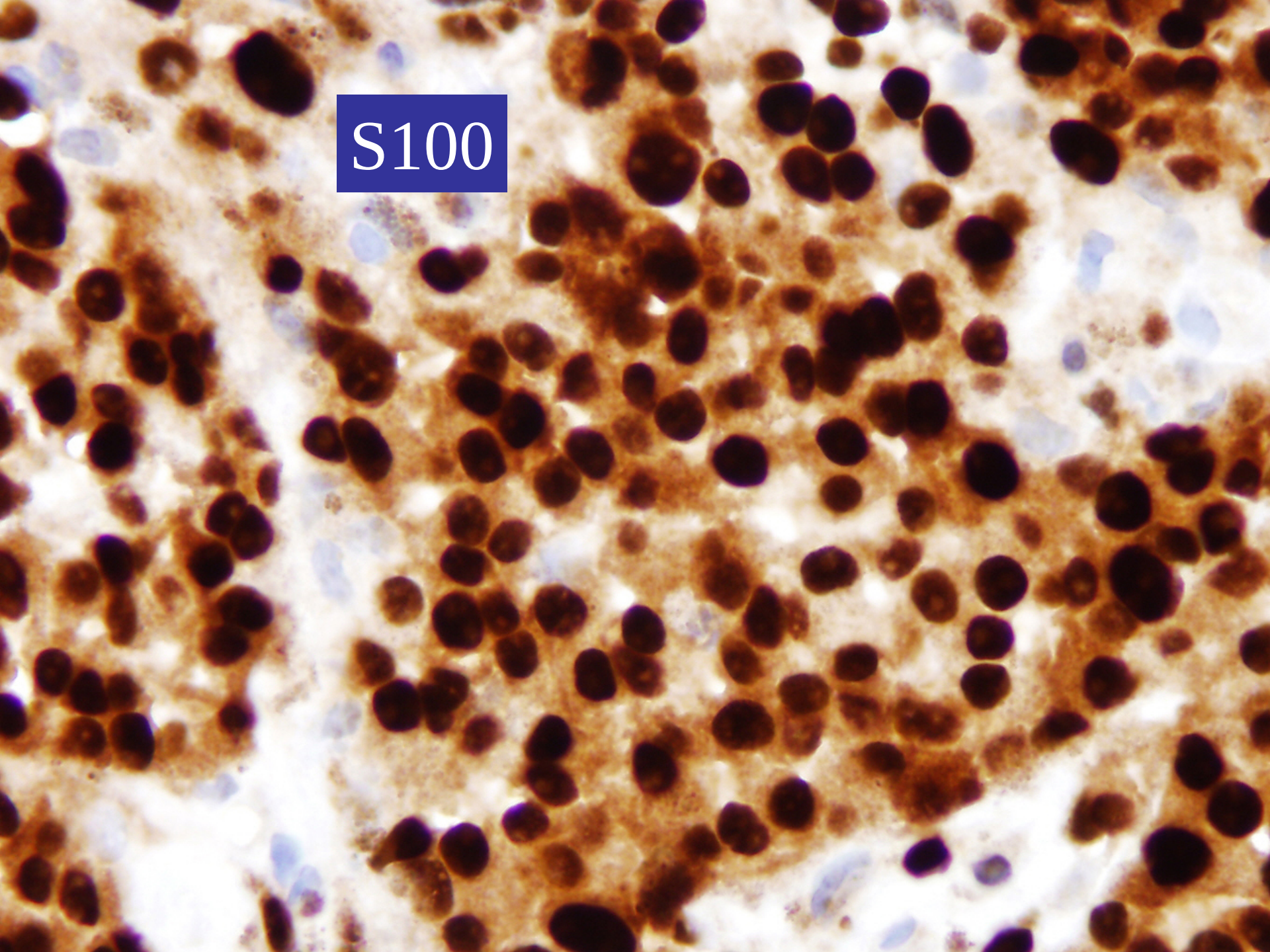


More SDH deficient tumors

- Renal cell carcinoma with characteristic morphology (weird flocculent cytoplasmic inclusions)
- Pheochromocytoma/ paraganglioma


Anal epithelioid lesion


CD117


S100

Something submucosal

Inflammatory Fibroid Polyp (IFP)

- First described by J Vaněk
- 6 lesions, all in stomach (antrum/pylorus-5)

Vaněk J. Gastric submucosal granuloma with eosinophilic infiltration. *Am J Pathol* 1949;**25**;397-411.

IFP

- Present term coined in early 1950's

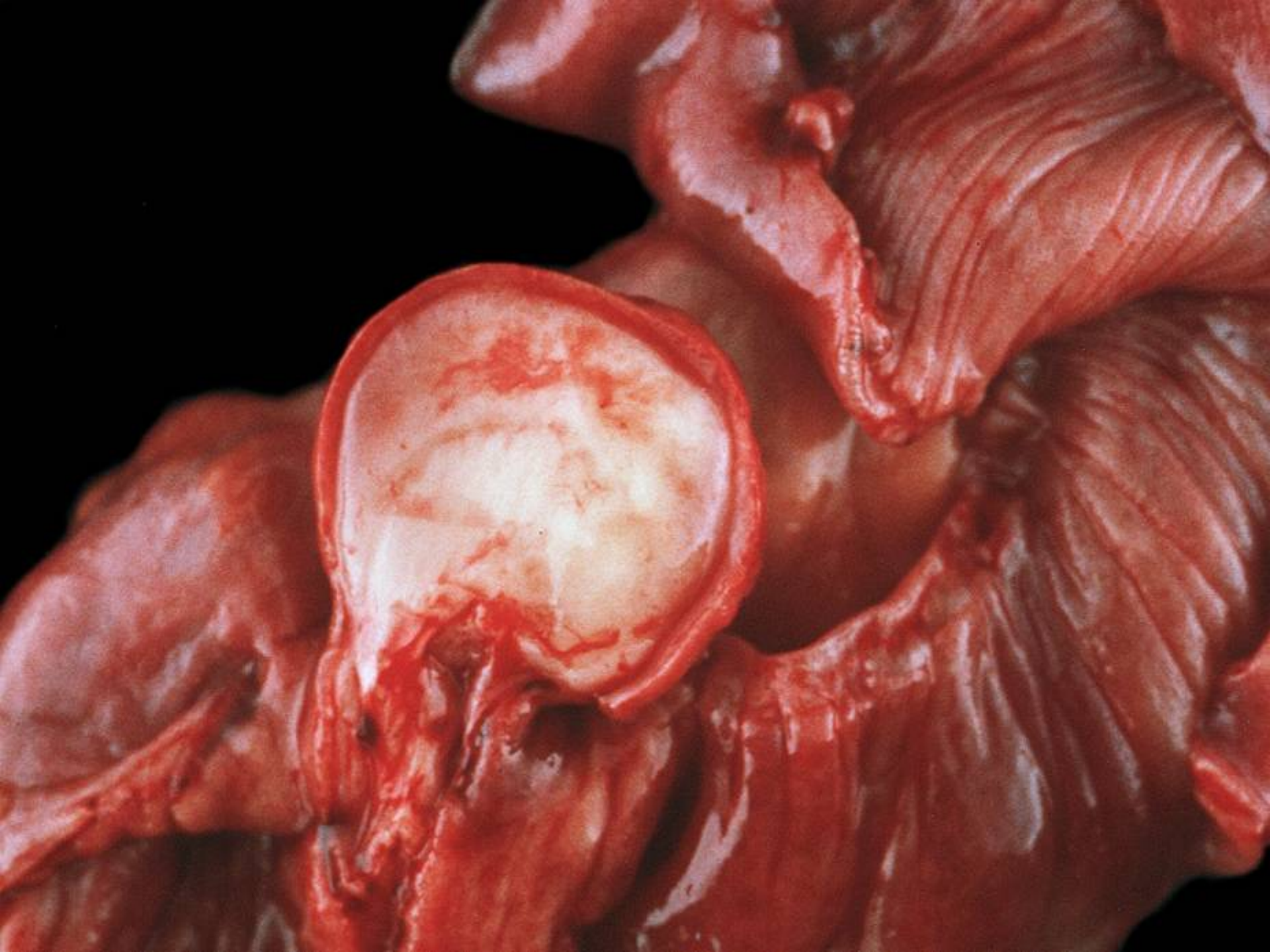
Helwig E, Ranier A. Inflammatory fibroid polyps of the stomach. *Surg Gynecol Obstets* 1953;**96**;355-67.

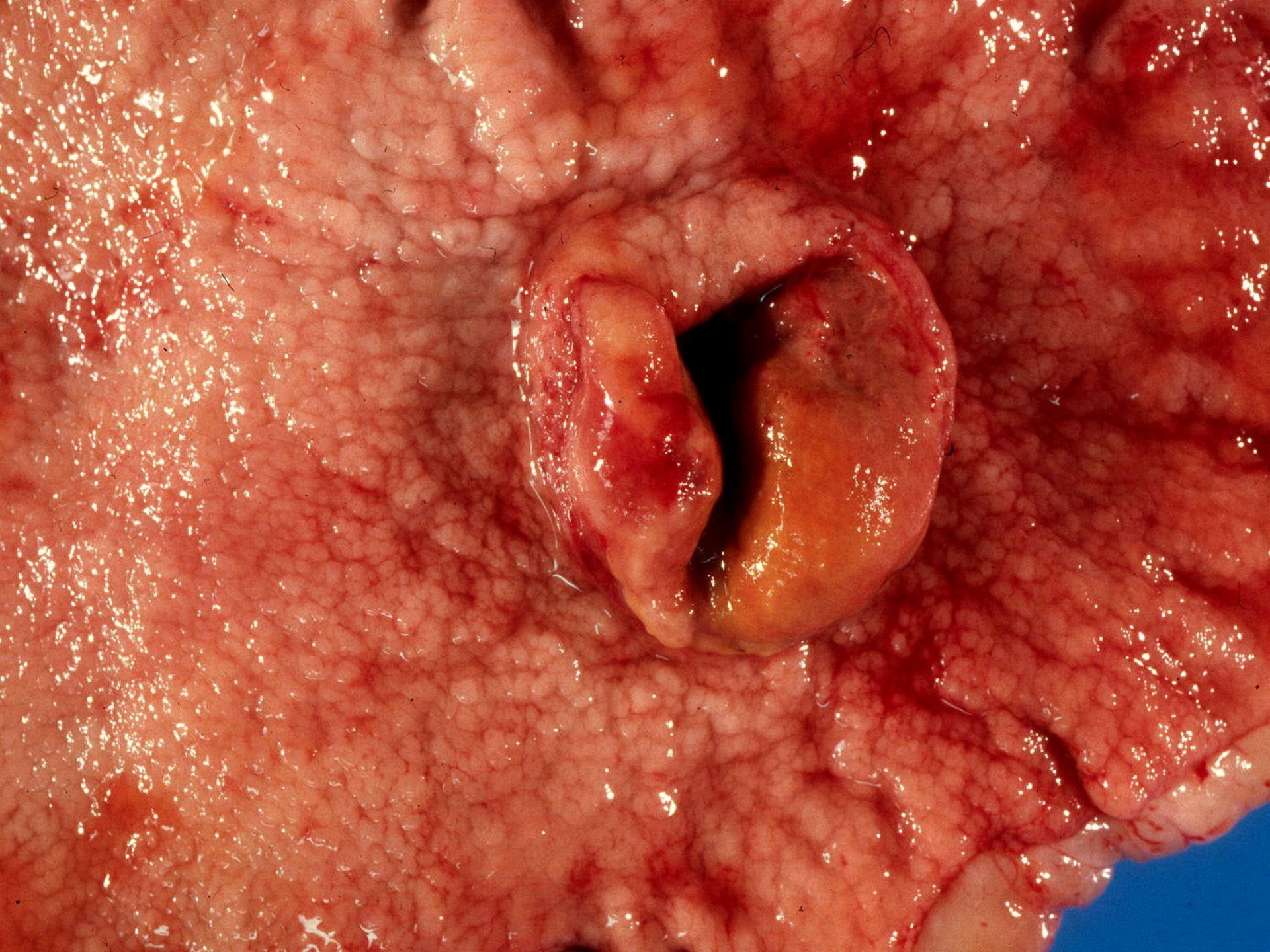
IFP Location

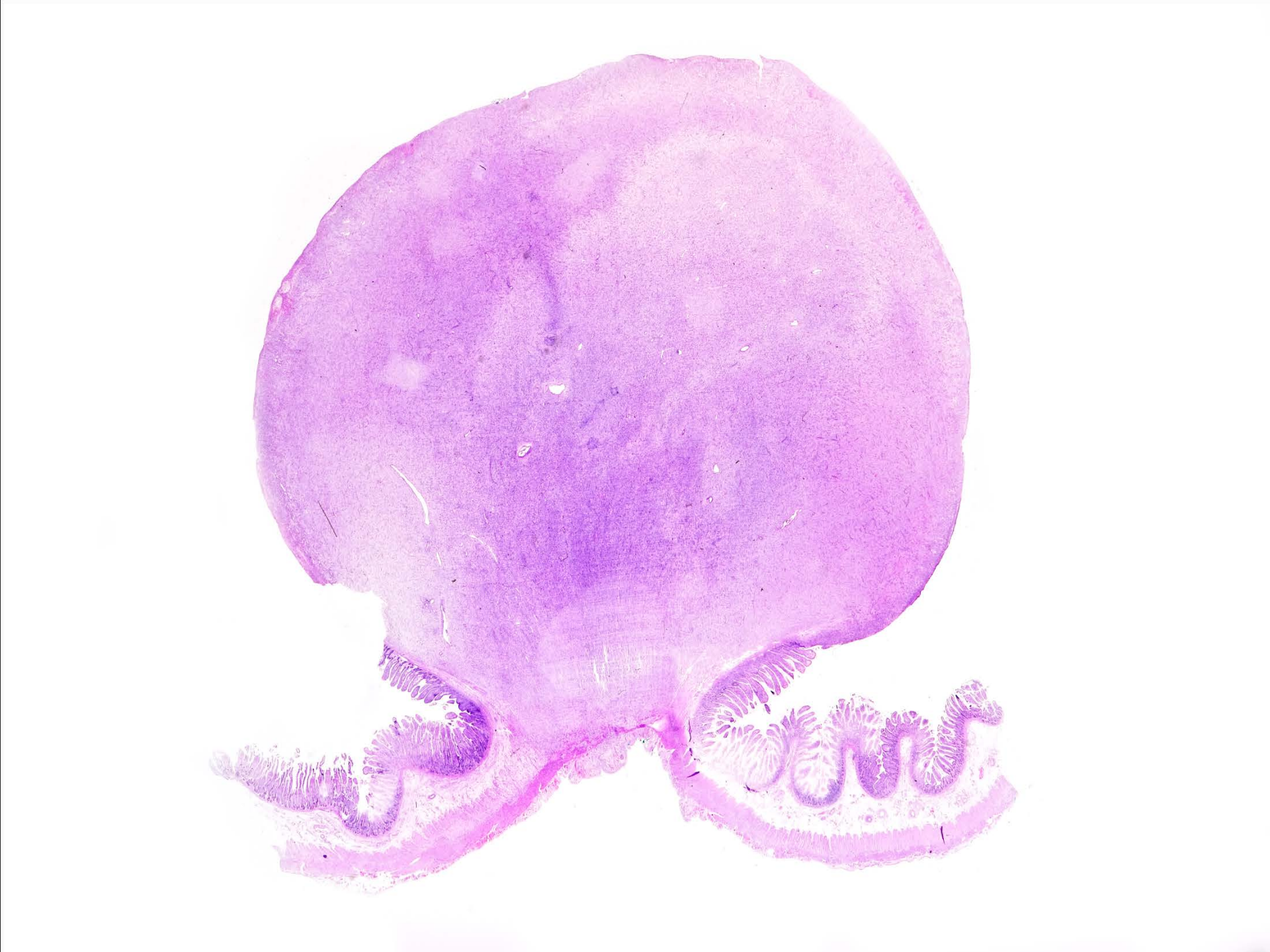
- Vast majority in stomach
- @1% of all gastric polyps
- Always in adults (60-80yrs)

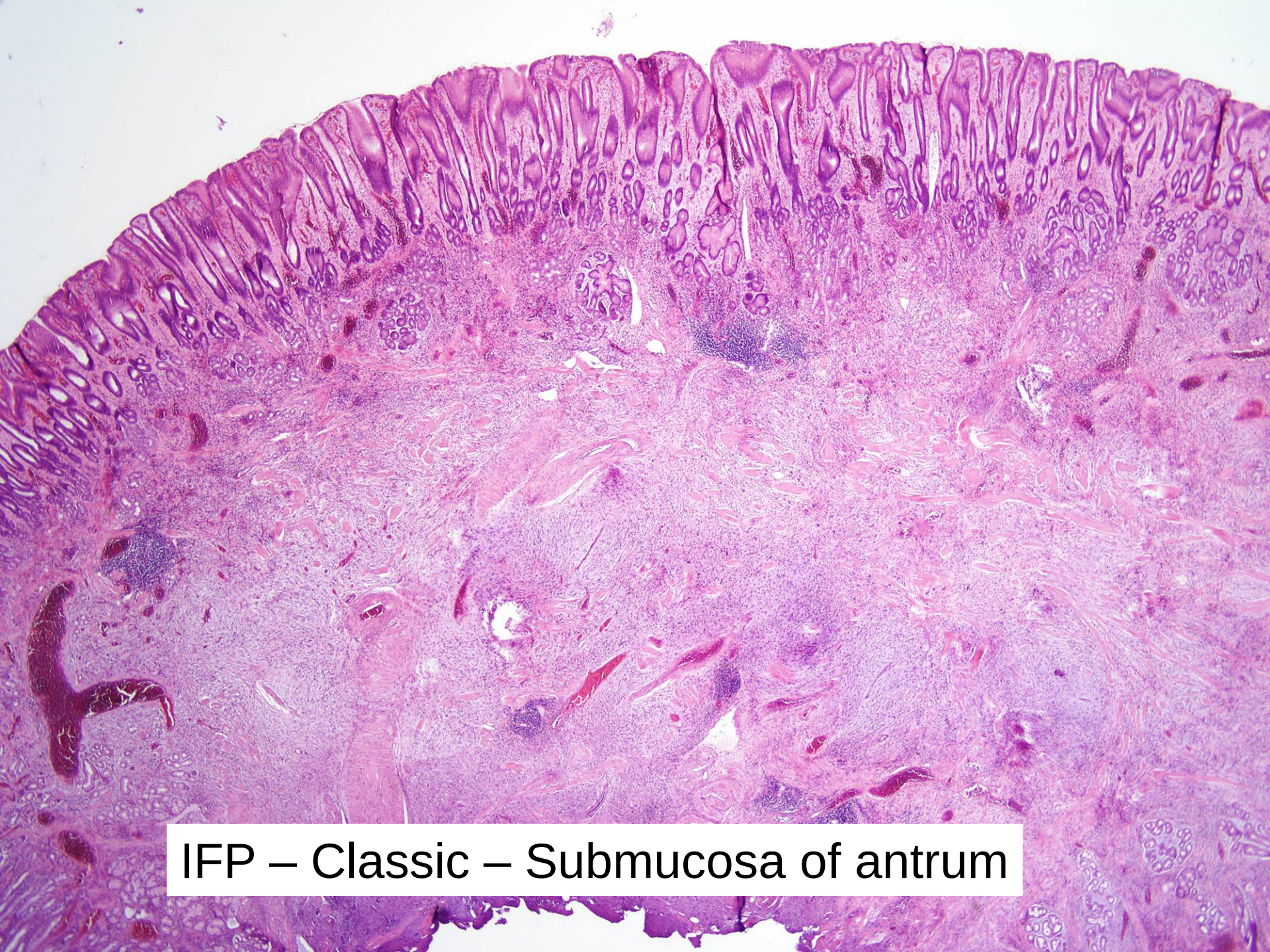
IFP- Endoscopic Appearance

- Smooth submucosal lesions
- Surface ulceration/erosion in about 1/3 of cases
- Presentation is site specific

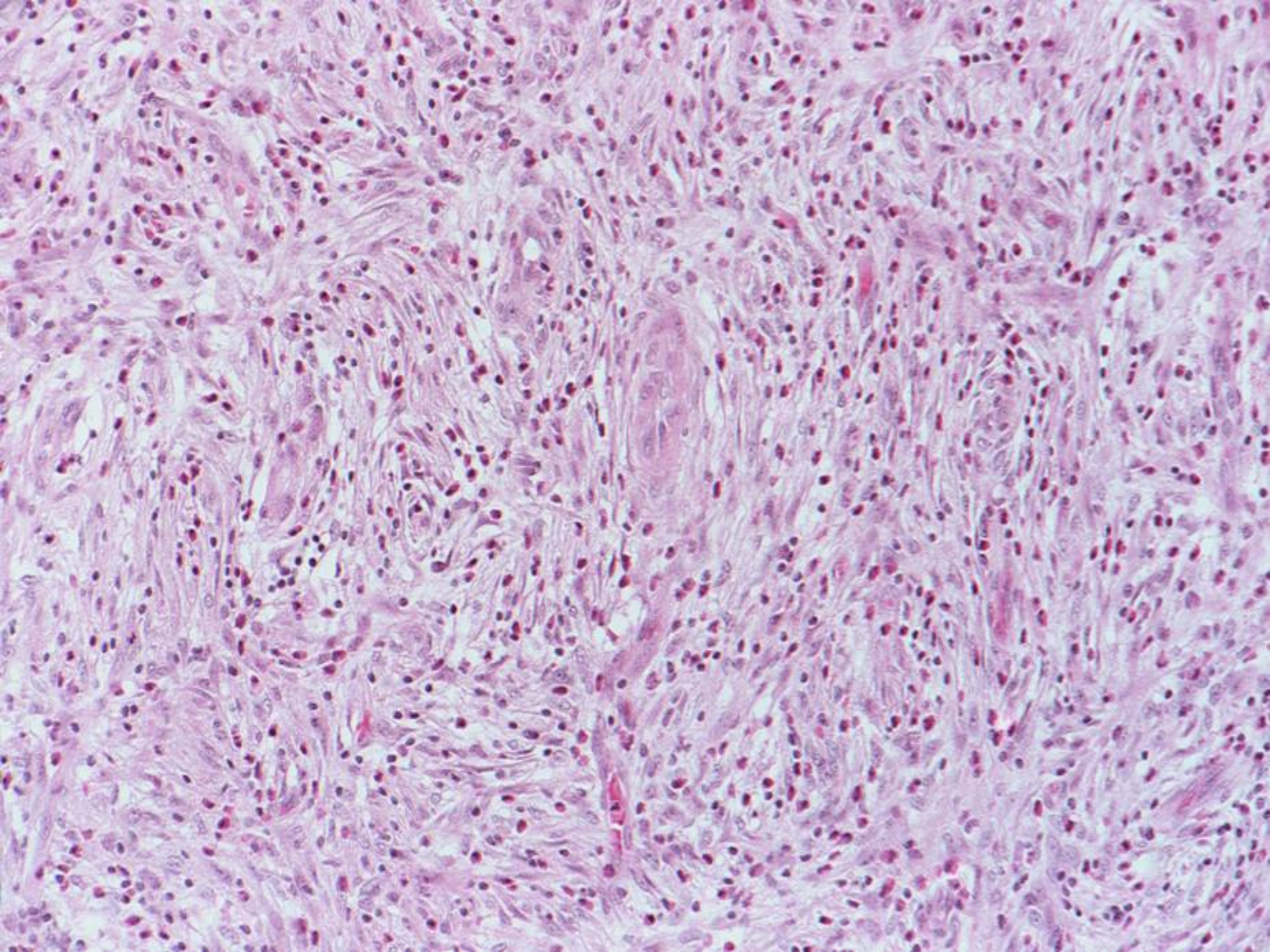


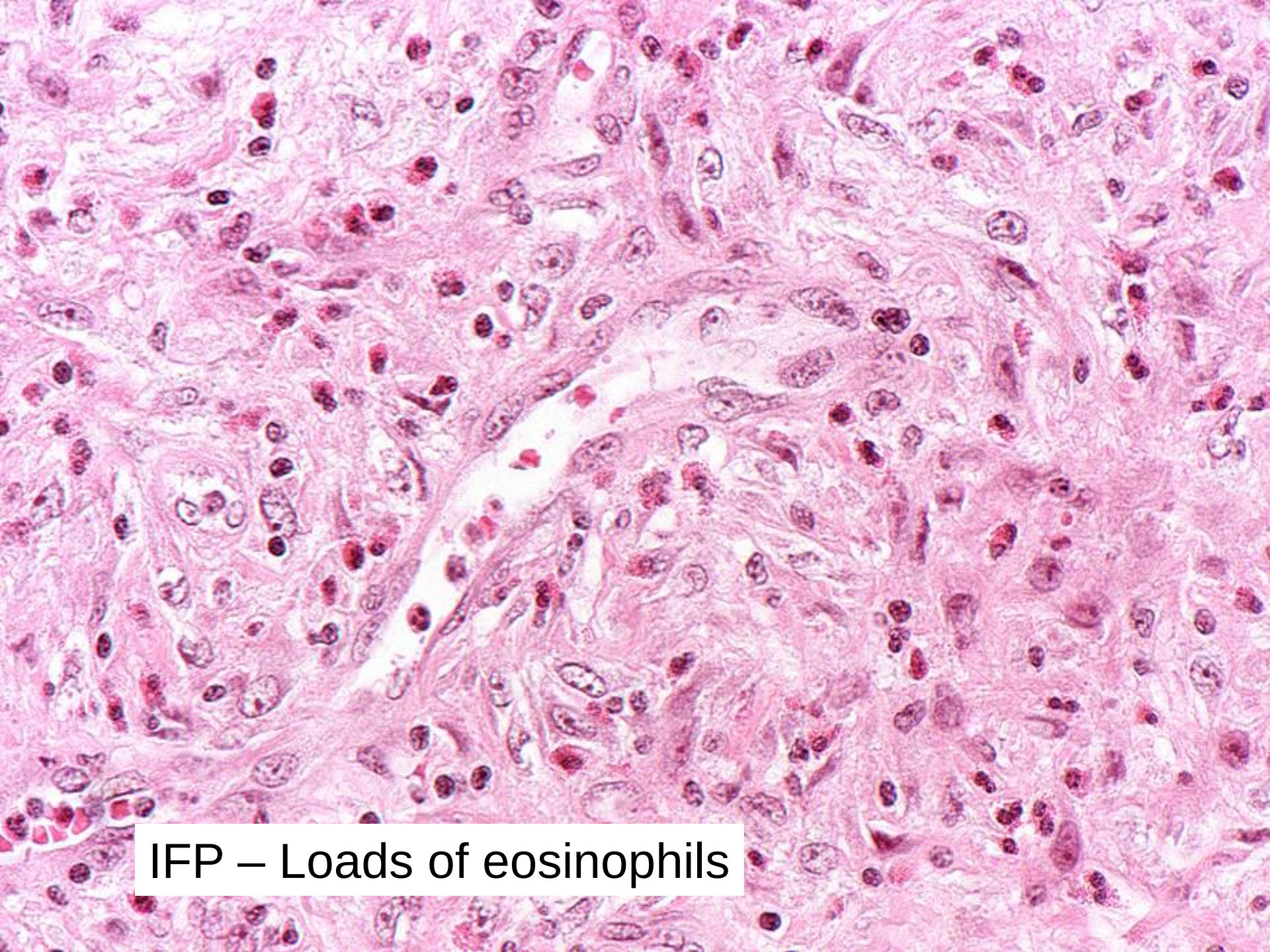


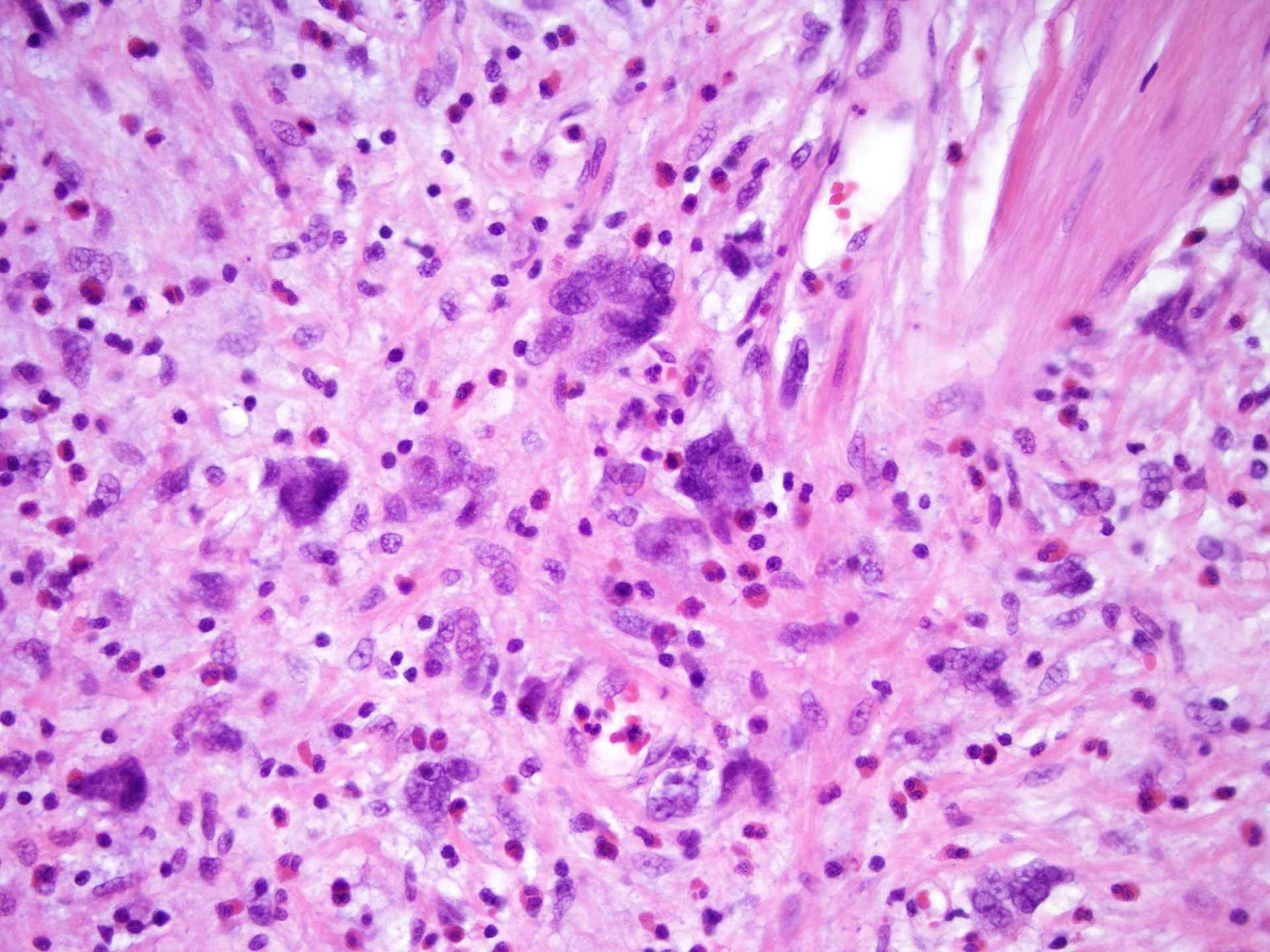




IFP – Classic – Submucosa of antrum




IFP – Loads of eosinophils



IFP- Pathogenesis

- Believed reactive in past – now known to have *PDGFRA* mutations (just like some GISTs – but ALWAYS benign)
- One family with these tumors in 3 generations of women (“Devon polyposis”)
- Diploid flow cytometry.
- Japanese examples associated with gastric ca (not western ones, coincidence?)

IFP- Immunohistochemistry

- Fibroblastic/myofibroblastic
- Variable actin, negative S100
- Consistent CD34 (less striking in large tumors)
- NO CD117/c-kit/DOG1


CD34

Translocation sarcomas in the GI tract

- Synovial sarcoma
- Clear cell sarcoma of GI tract
- Ewings/PNET
- Whatever! Even low-grade fibromyxoid sarcoma
- Can require correlation with molecular techniques to diagnose
- Fortunately all are rare

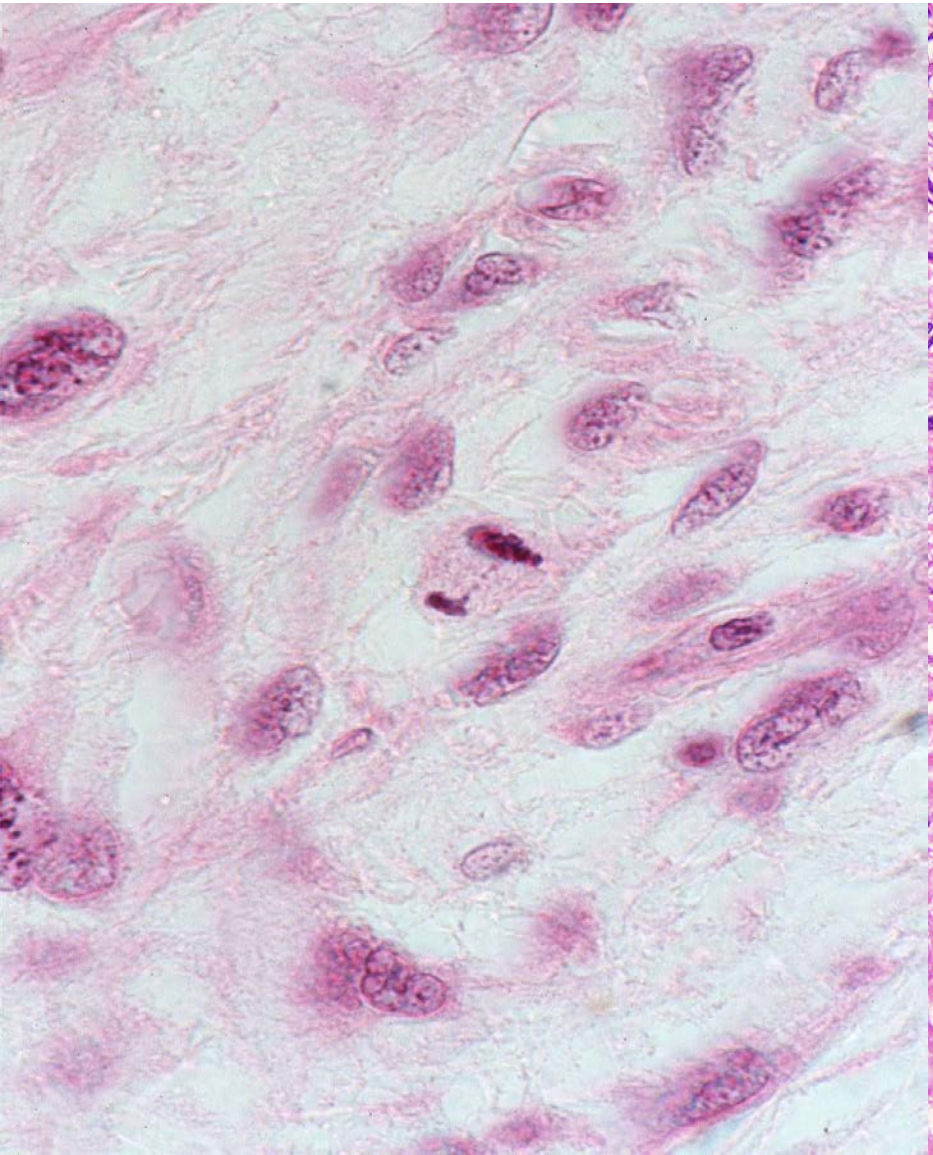
Important Clue

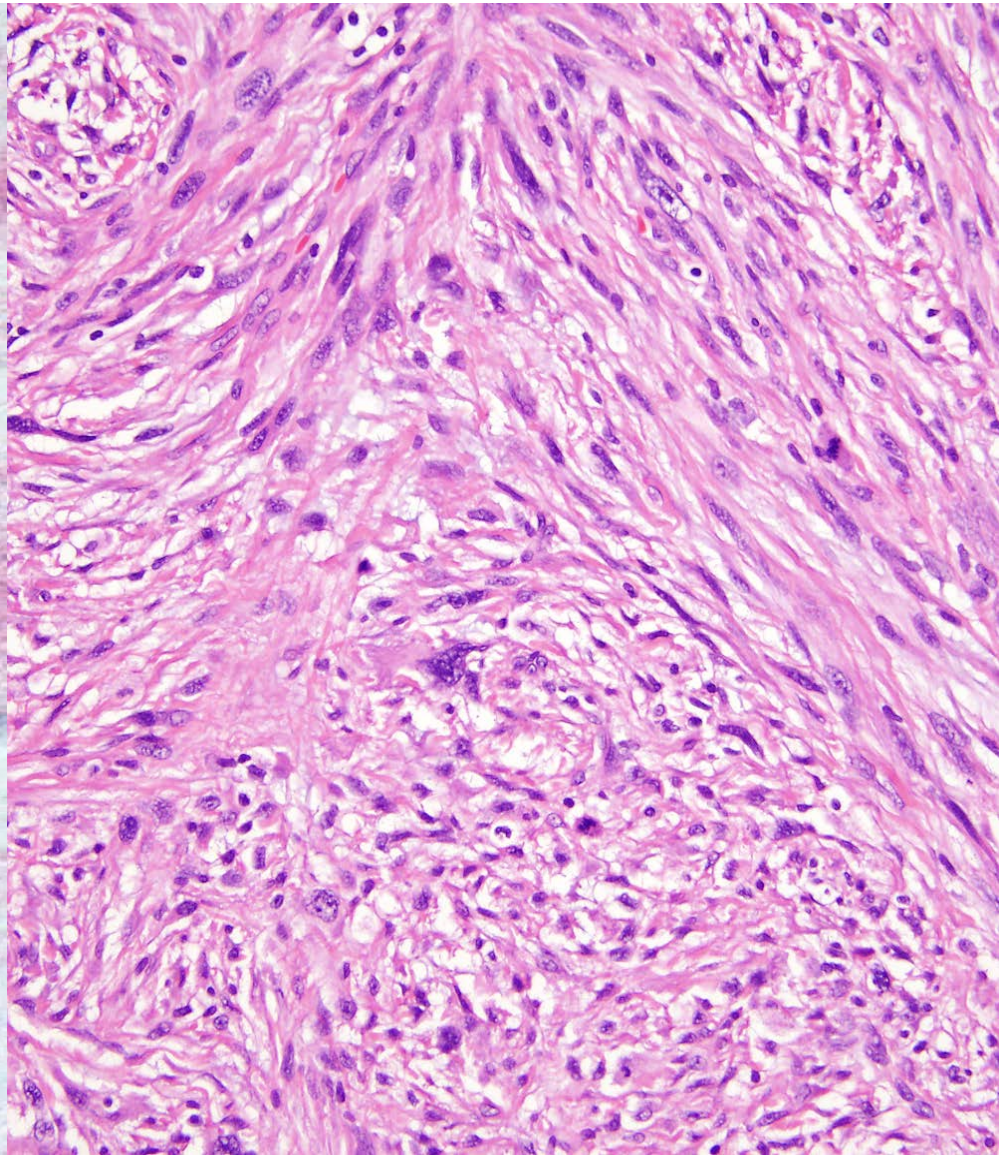
Sarcomas associated with characteristic translocations are NOT pleomorphic, have uniform regular nuclei, and lack atypical mitoses.

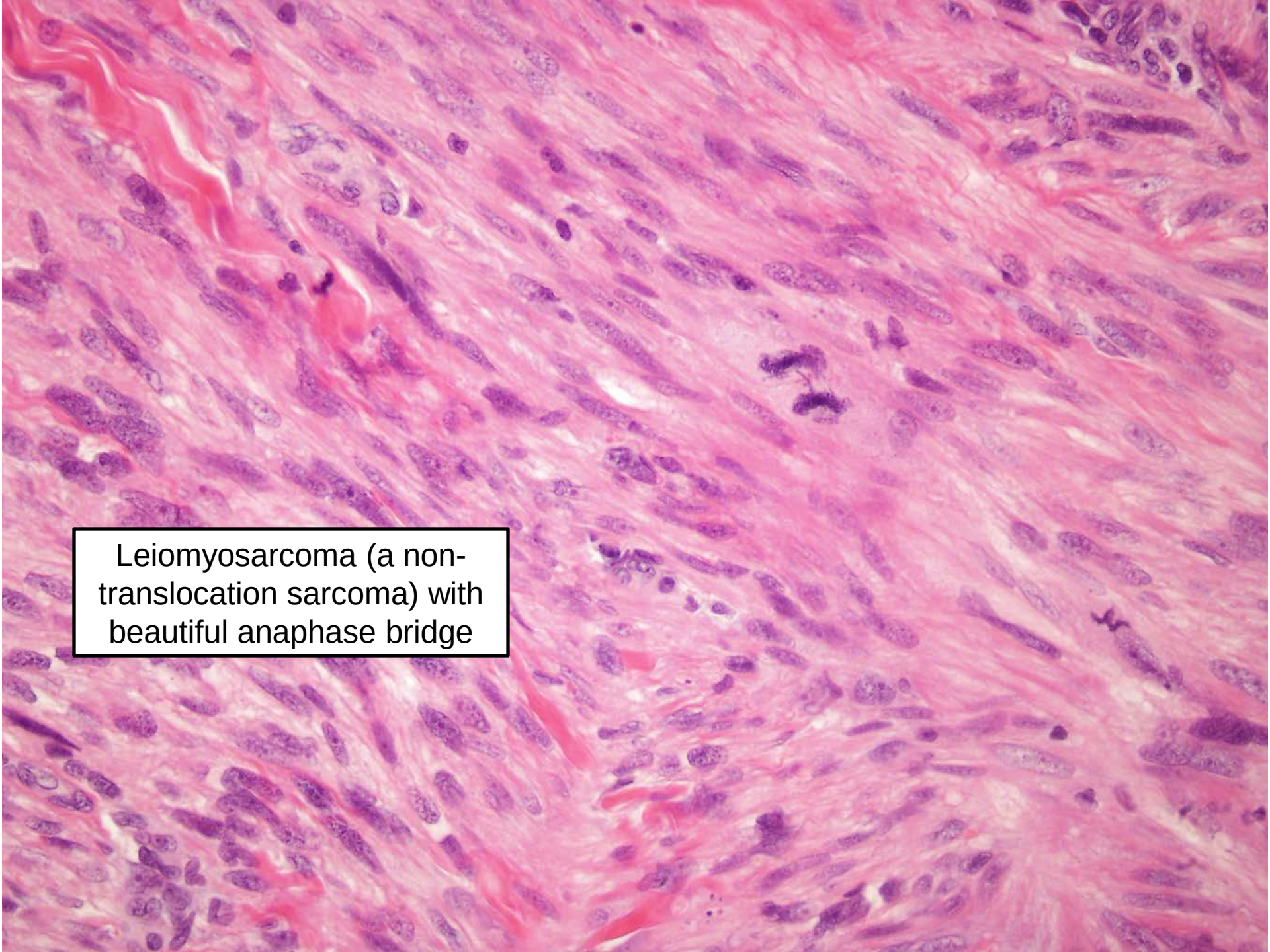
CHROMOSOMAL TRANSLOCATIONS ESTABLISHED CYTOGENETICALLY AND THE CORRESPONDING GENE CHANGES

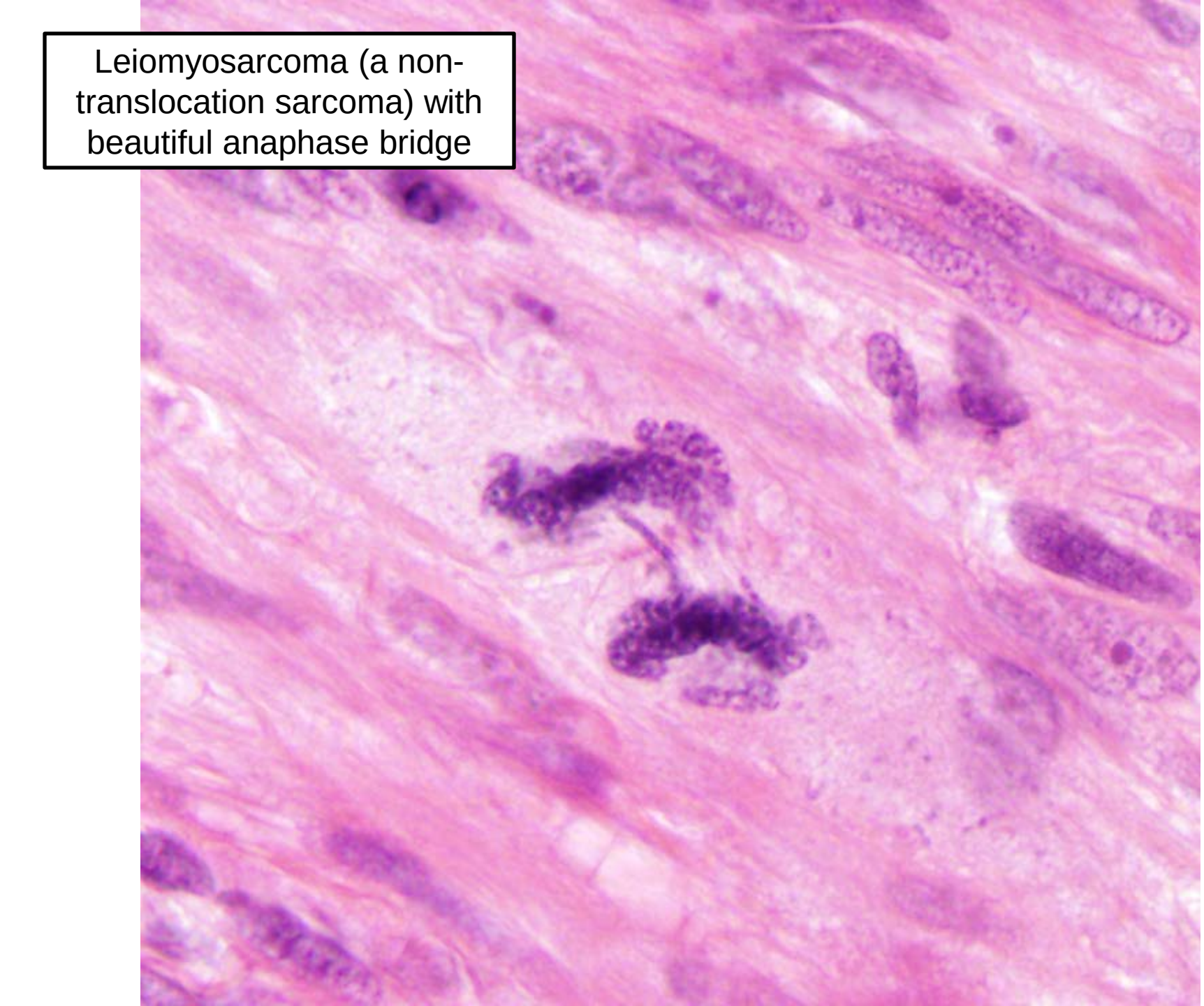
Tumors	Translocation	Gene changes
Alveolar rhabdomyosarcoma	t(2;13)(q35;q14)	PAX3-FKHR
	t(1;13)(p36;q14)	PAX7-FKHR
Alveolar soft part sarcoma	t(X;17)(p11.2;q25)	ASPL-TFE3
Clear cell sarcoma (malignant melanoma of soft parts)	t(12;22)(q13;q12)	ATF1-EWS
Congenital fibrosarcoma and mesoblastic nephroma	t(12;15)(p13;q25)	ETV6-NTRK3
Dermatofibrosarcoma protuberans (giant cell fibroblastoma)	t(17;22)(q22;q13)	COL1A1-PDGFB
Desmoplastic small round cell tumor	t(11;22)(p13;q12)	WT1-EWS
Endometrial stromal sarcoma	t(7;17)(p15;q21)	JAZF1-JJAZ1
Ewing sarcoma and peripheral primitive neuroectodermal tumors	t(11;22)(q24;q12)	EWS-FLI1
	t(21;22)(q22;q12)	EWS-ERG
	t(7;22)(p22;q12)	EWS-ETV1
	t(17;22)(q12;q12)	EWS-E1AF
	t(2;22)(q33;q12)	FEV-EWS
Inflammatory myofibroblastic tumor	t(2;19)(p23;p13.1)	ALK-TPM4
	t(1;2)(q22-23;p23)	TPM3-ALK
Myxoid chondrosarcoma, extraskeletal	t(9;22)(q22;q12)	EWS-CHN(TEC)
	t(9;17)(q22;q11)	RBP56-CHN(TEC)
	t(9;15)(q22;q21)	TEC/TCF12
Myxoid liposarcoma	t(12;16)(q13;p11)	TLS(FUS)-CHOP
	t(12;22)(q13;q12)	EWS-CHOP
Synovial sarcoma	t(X;18)(p11;q11)	SYT-SSX1
		SYT-SSX2
Low-Grade Fibromyxoid Sarcoma	t(7;16)(q33;p11)	FUS-BBF2H7

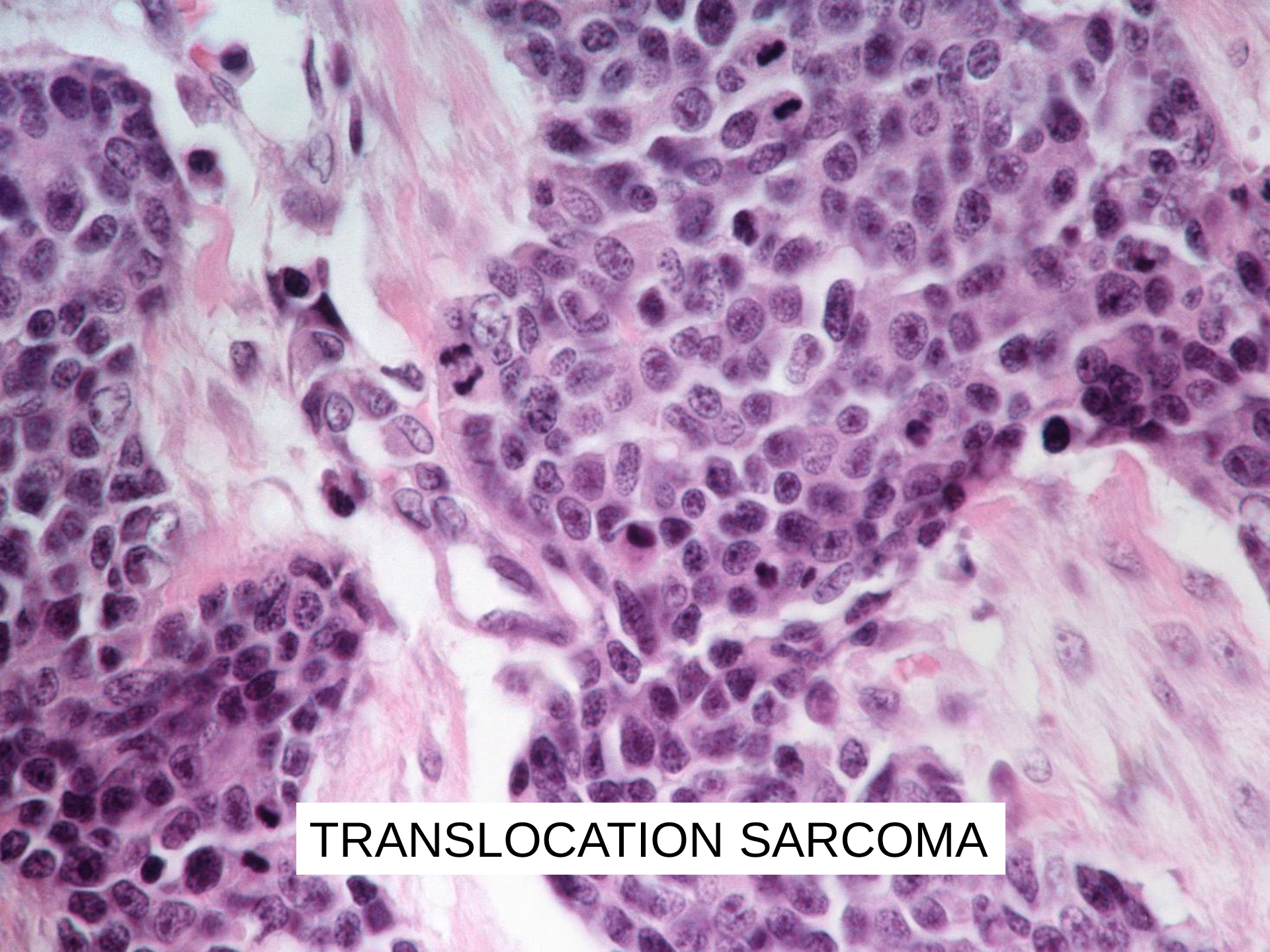
HIGH GRADE PLEOMORPHIC SARCOMA



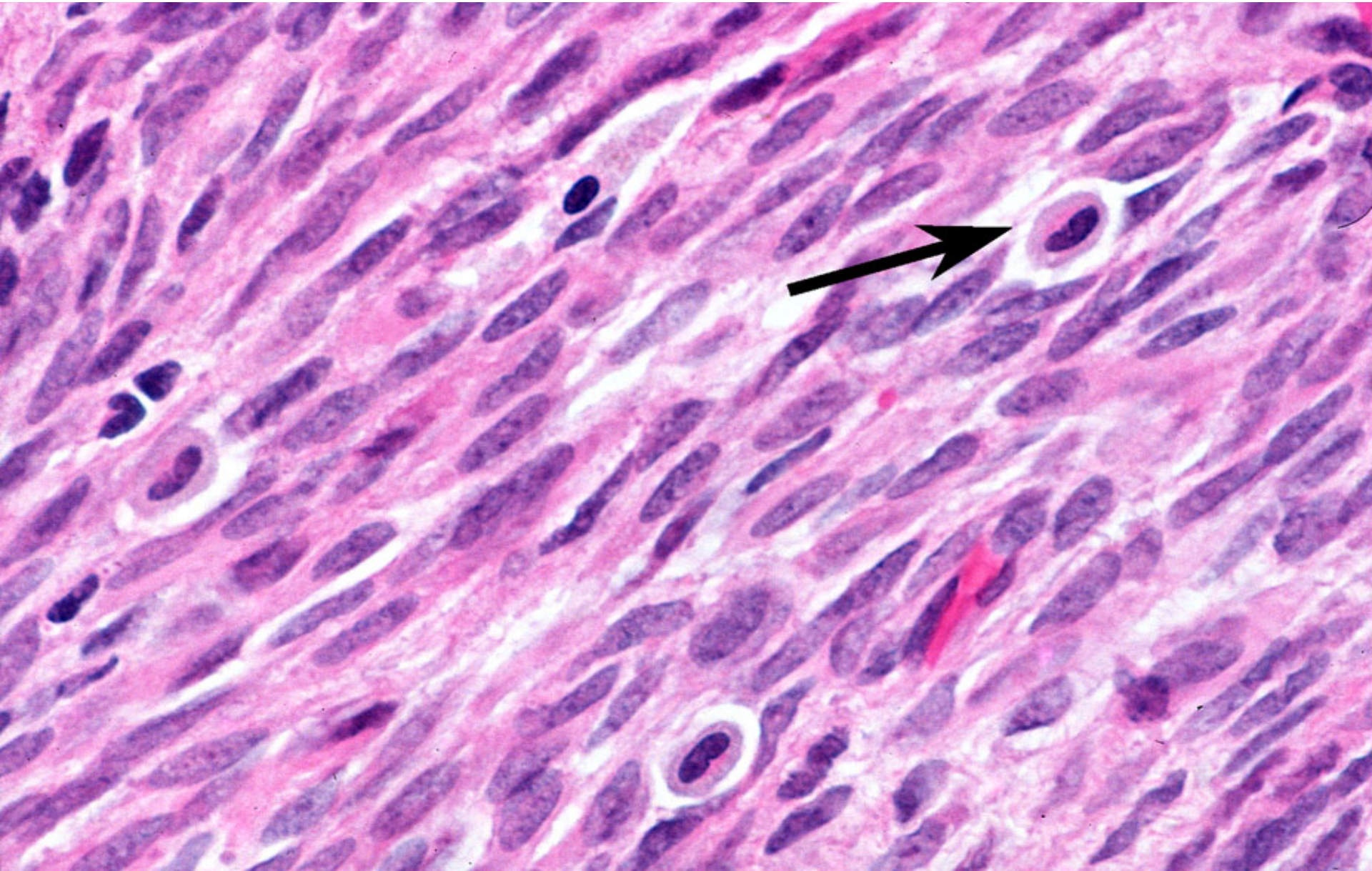


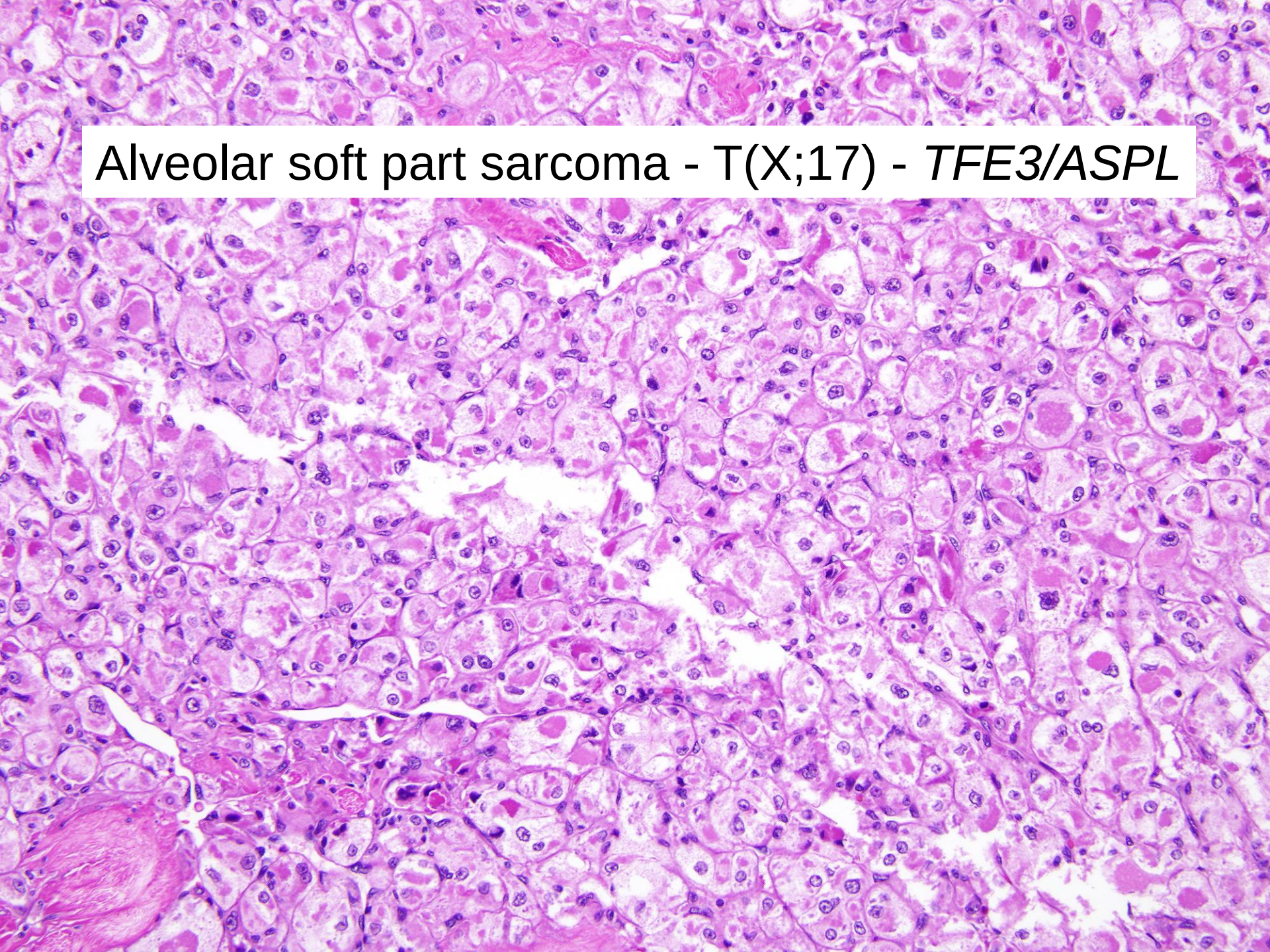

Leiomyosarcoma (a non-translocation sarcoma) with beautiful anaphase bridge

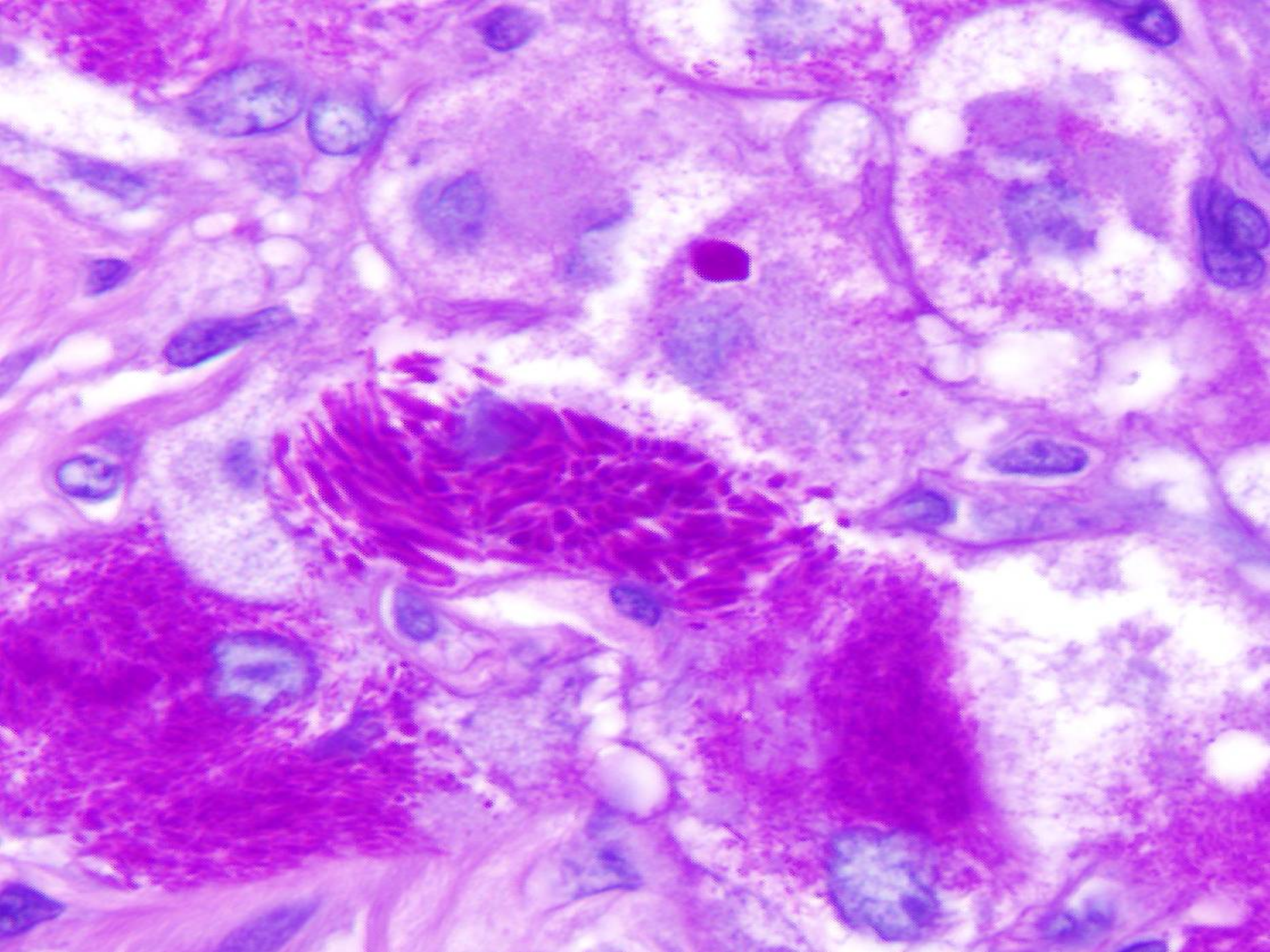

Leiomyosarcoma (a non-translocation sarcoma) with beautiful anaphase bridge


TRANSLOCATION SARCOMA

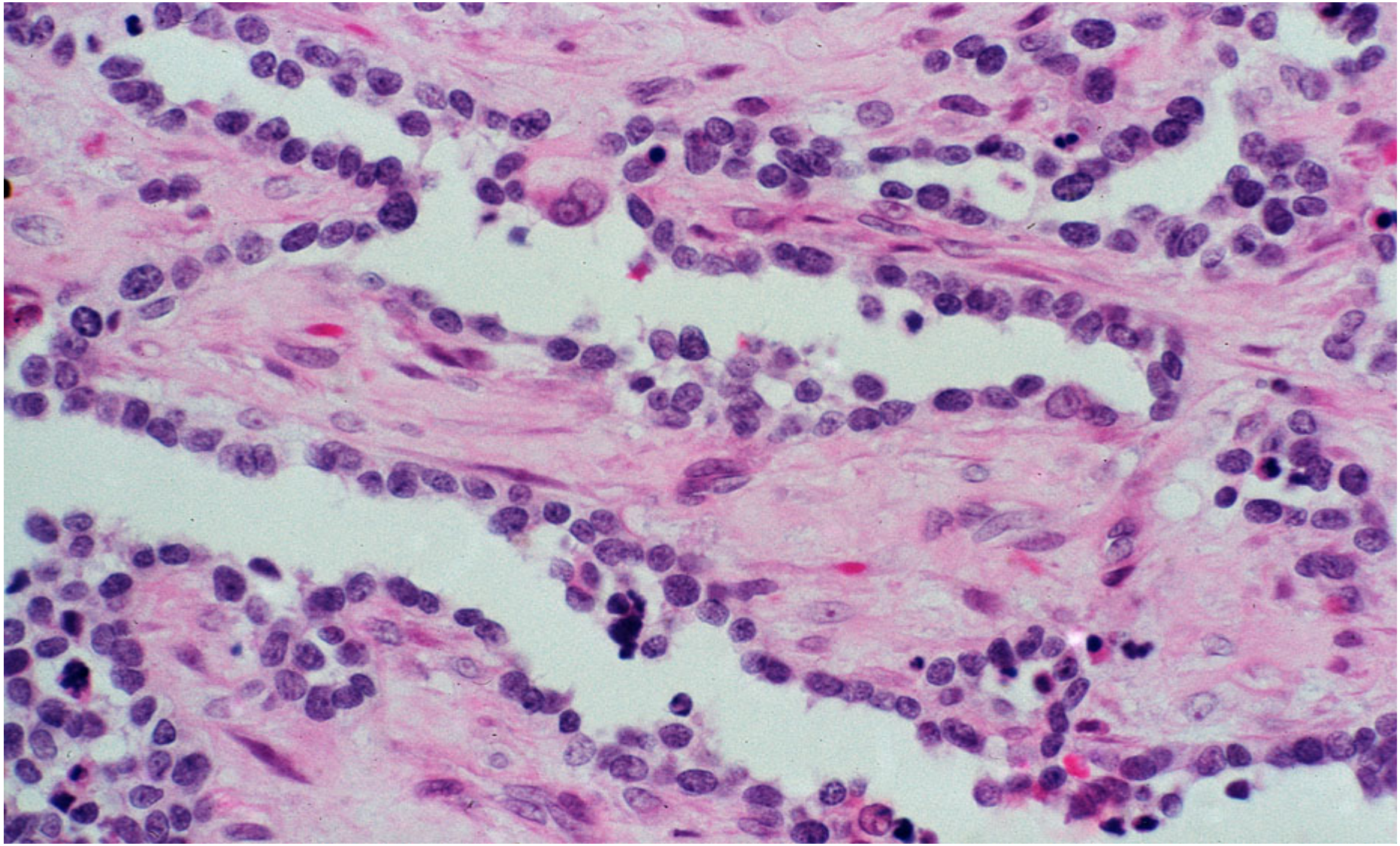
Synovial Sarcoma – Monophasic; t(X;18) – SYT-SSX1 or SYT-SSX2 (mast cell indicated by arrow)



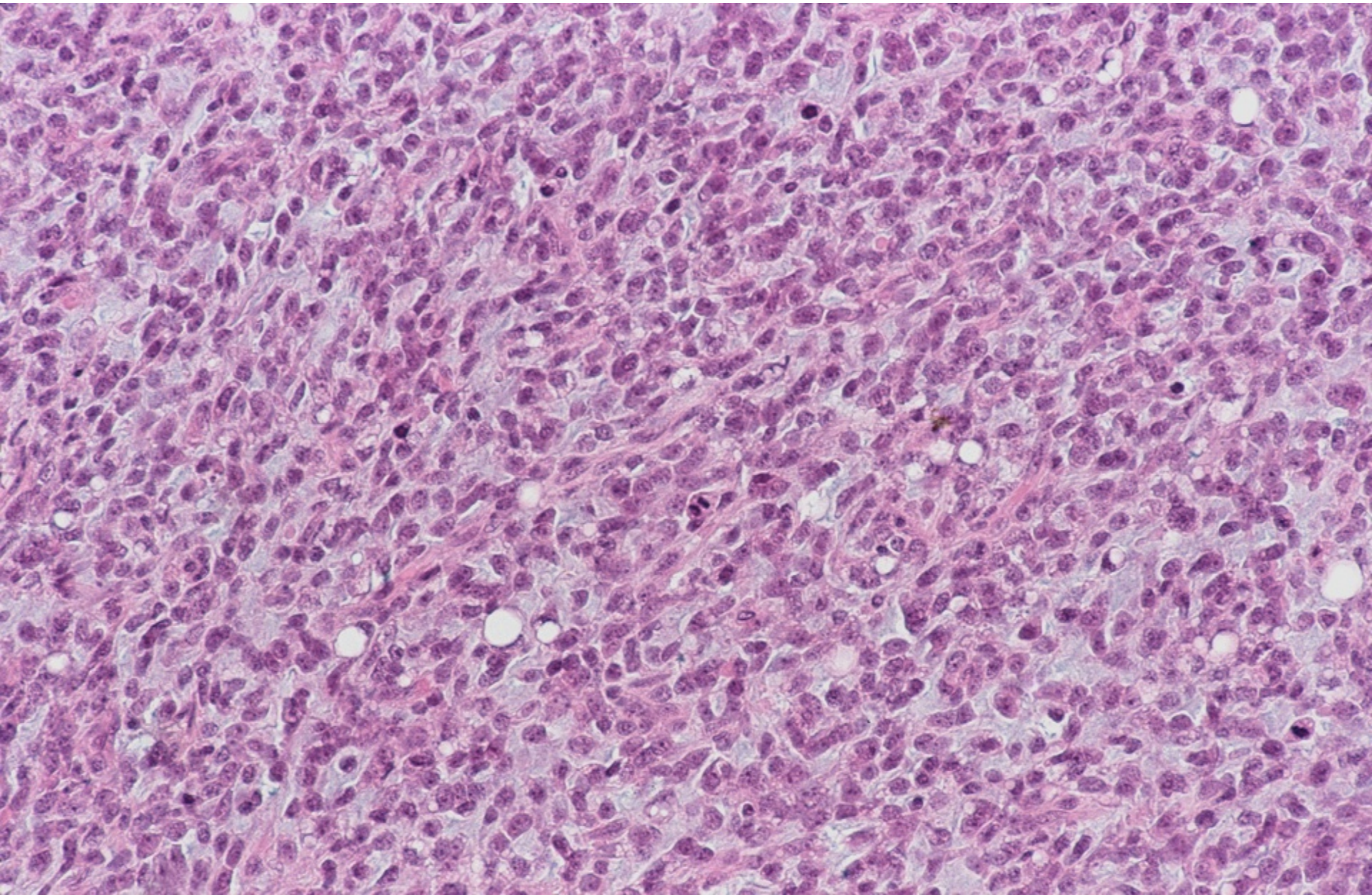

Alveolar soft part sarcoma - T(X;17) - *TFE3/ASPL*

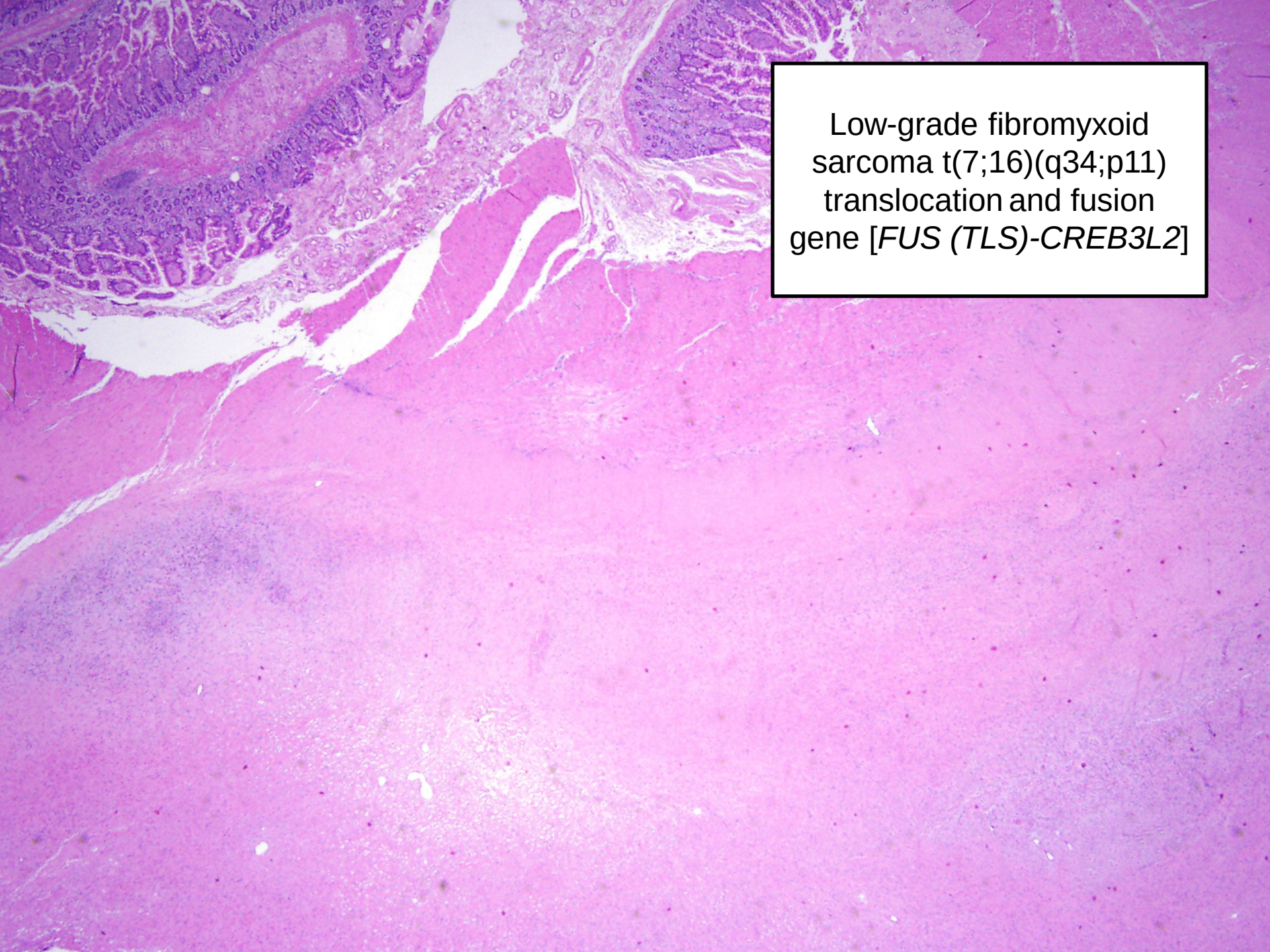


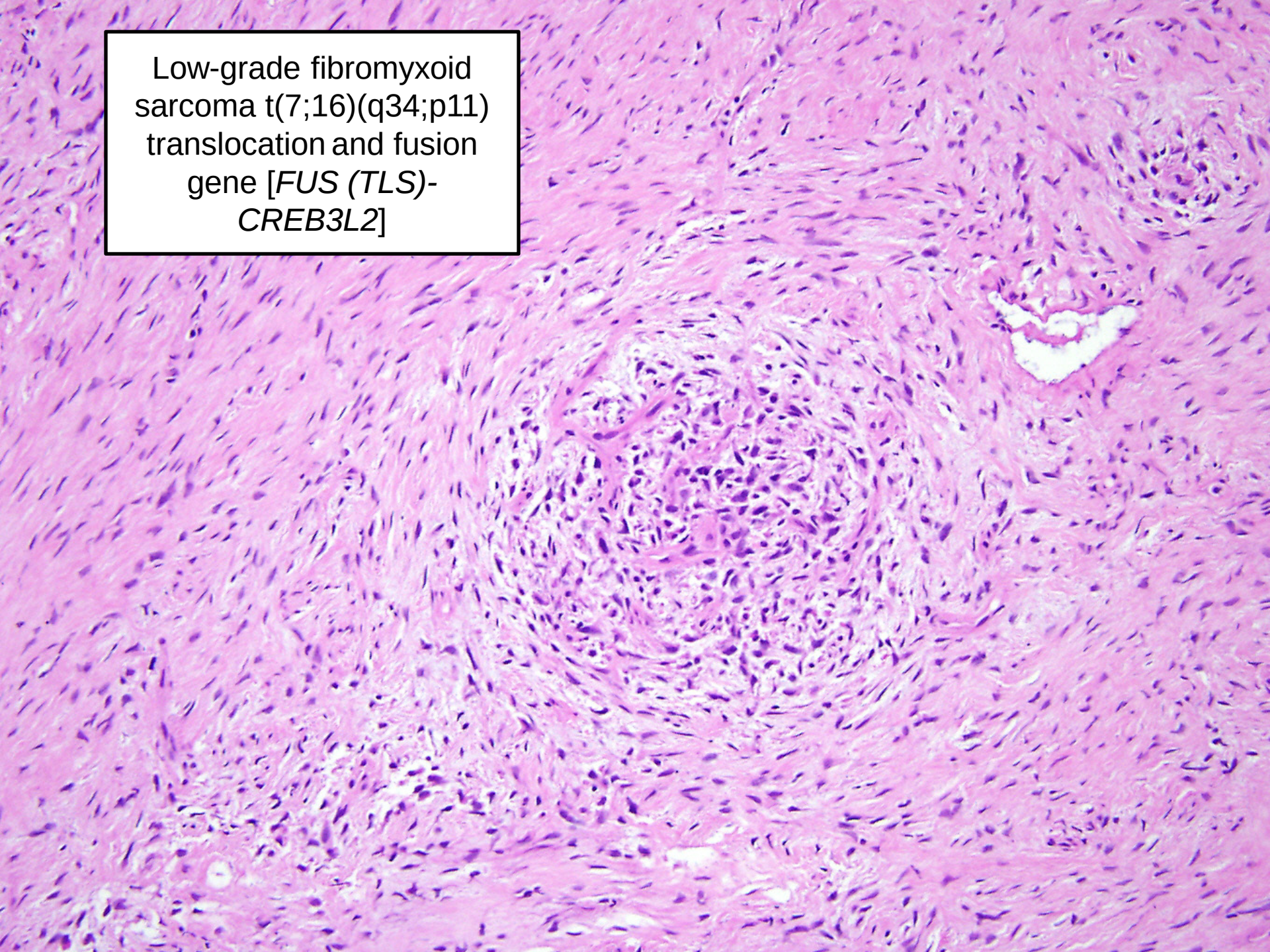
Alveolar Rhabdomyosarcoma; t(2;13) –*PAX3-FKHR* (*FOXO1*) Or t(1:13) – *PAX7 – FKHR (FOXO1)*



Round Cell Lipsarcoma – t(12;22) – *TLS(FUS)* – *CHOP* (*DDIT3*) T(12;22) – *EWS-CHOP (DDIT3)*




Low-grade fibromyxoid sarcoma t(7;16)(q34;p11) translocation and fusion gene [*FUS (TLS)-CREB3L2*]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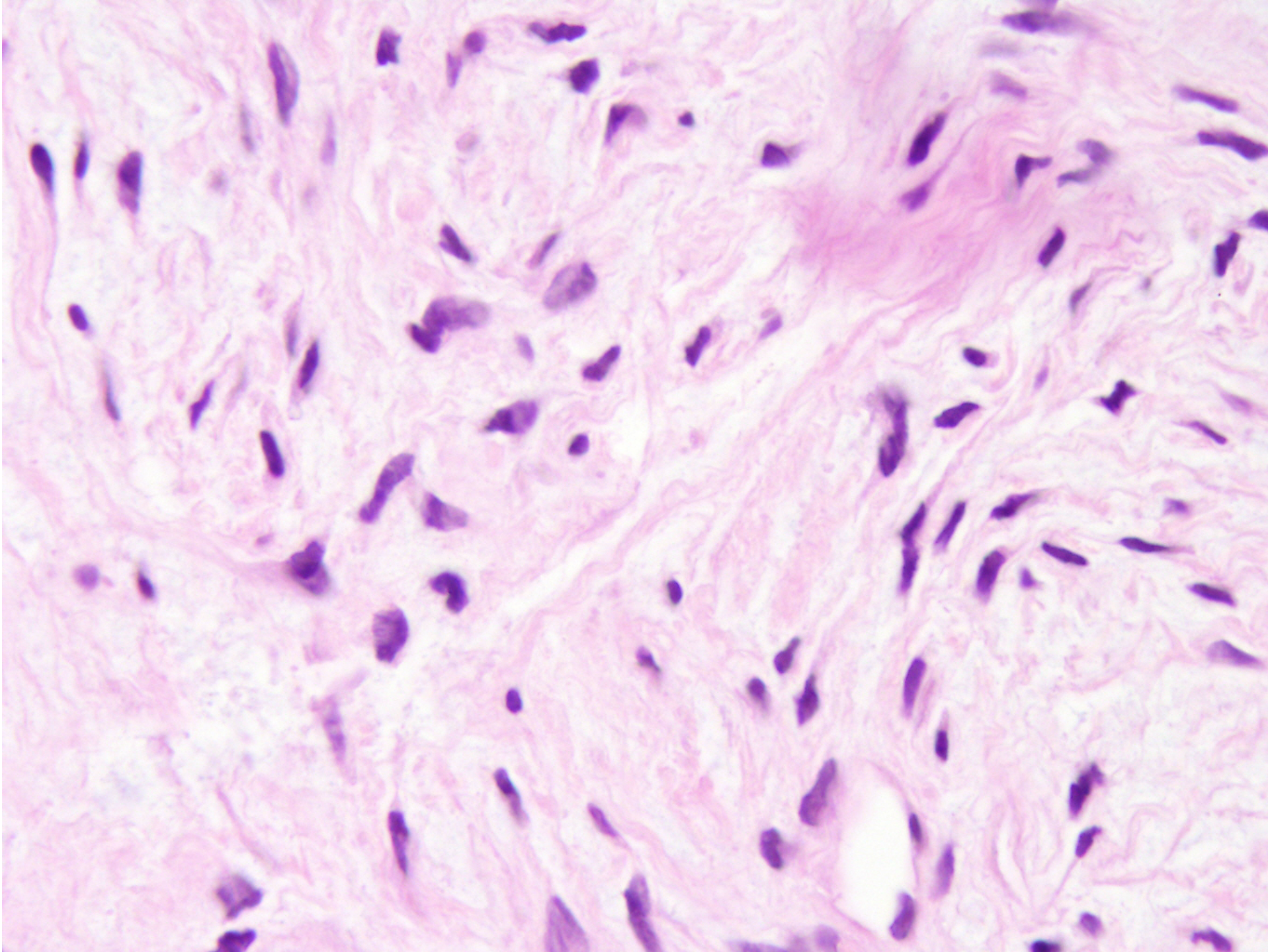
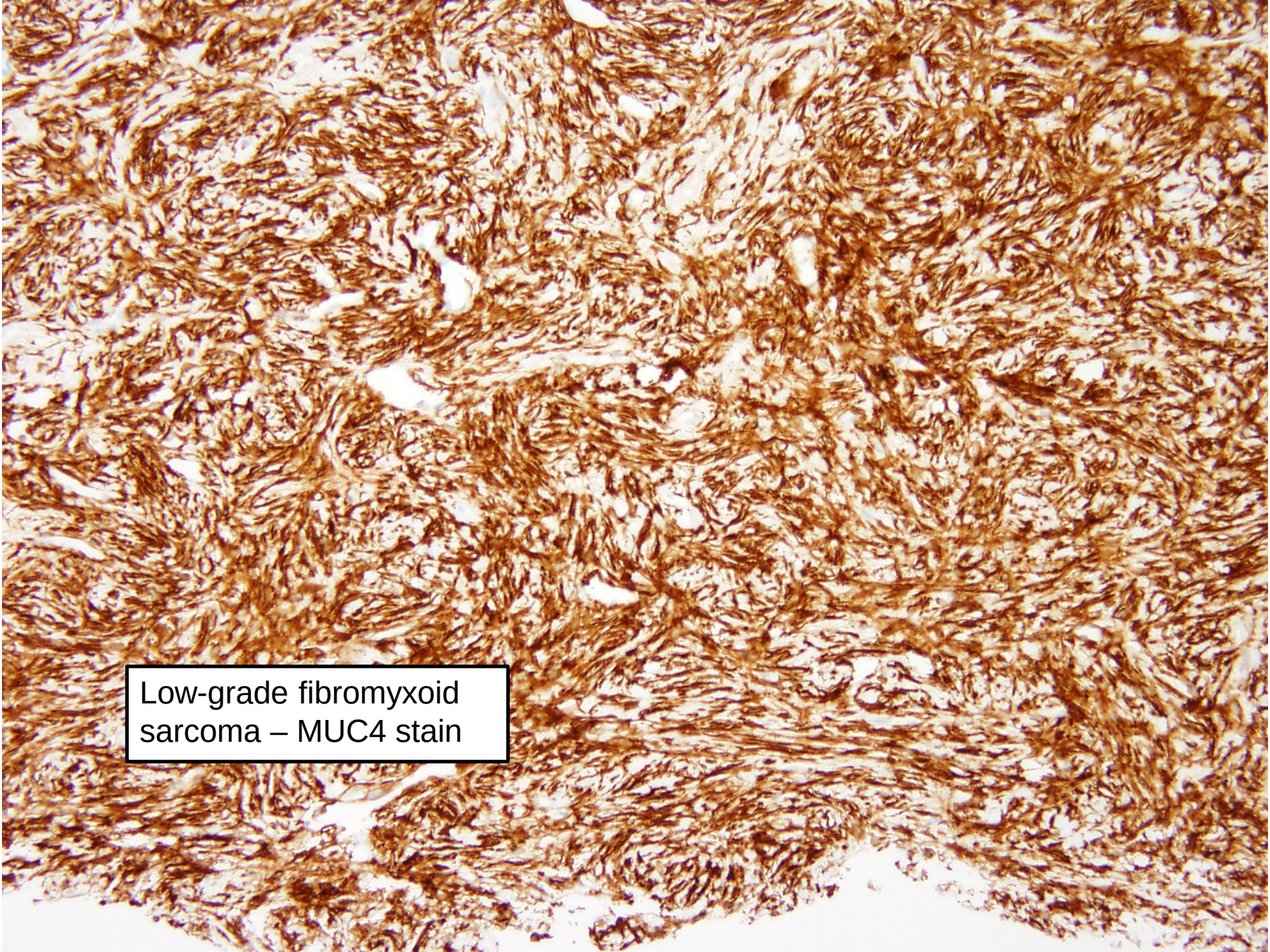
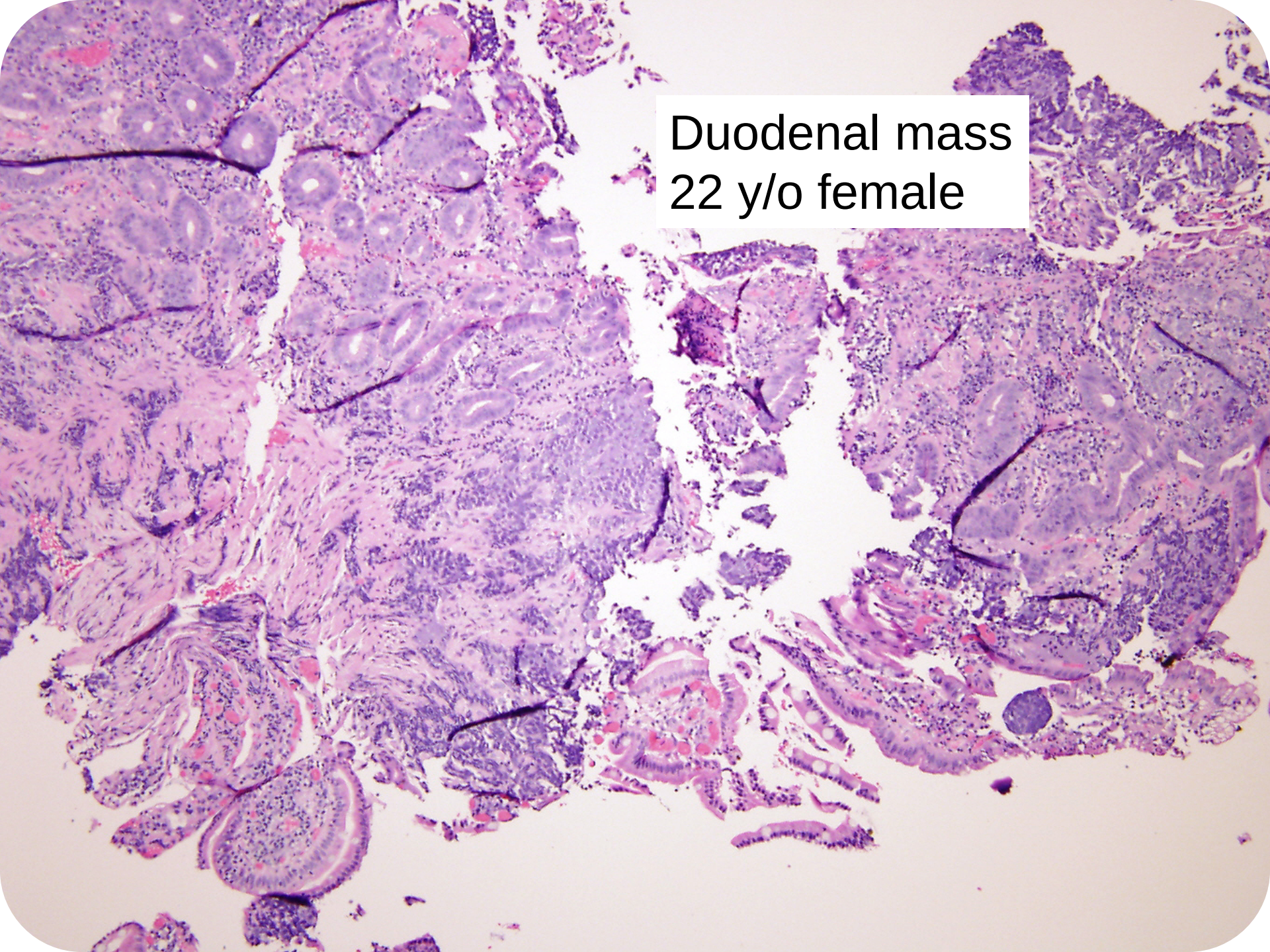
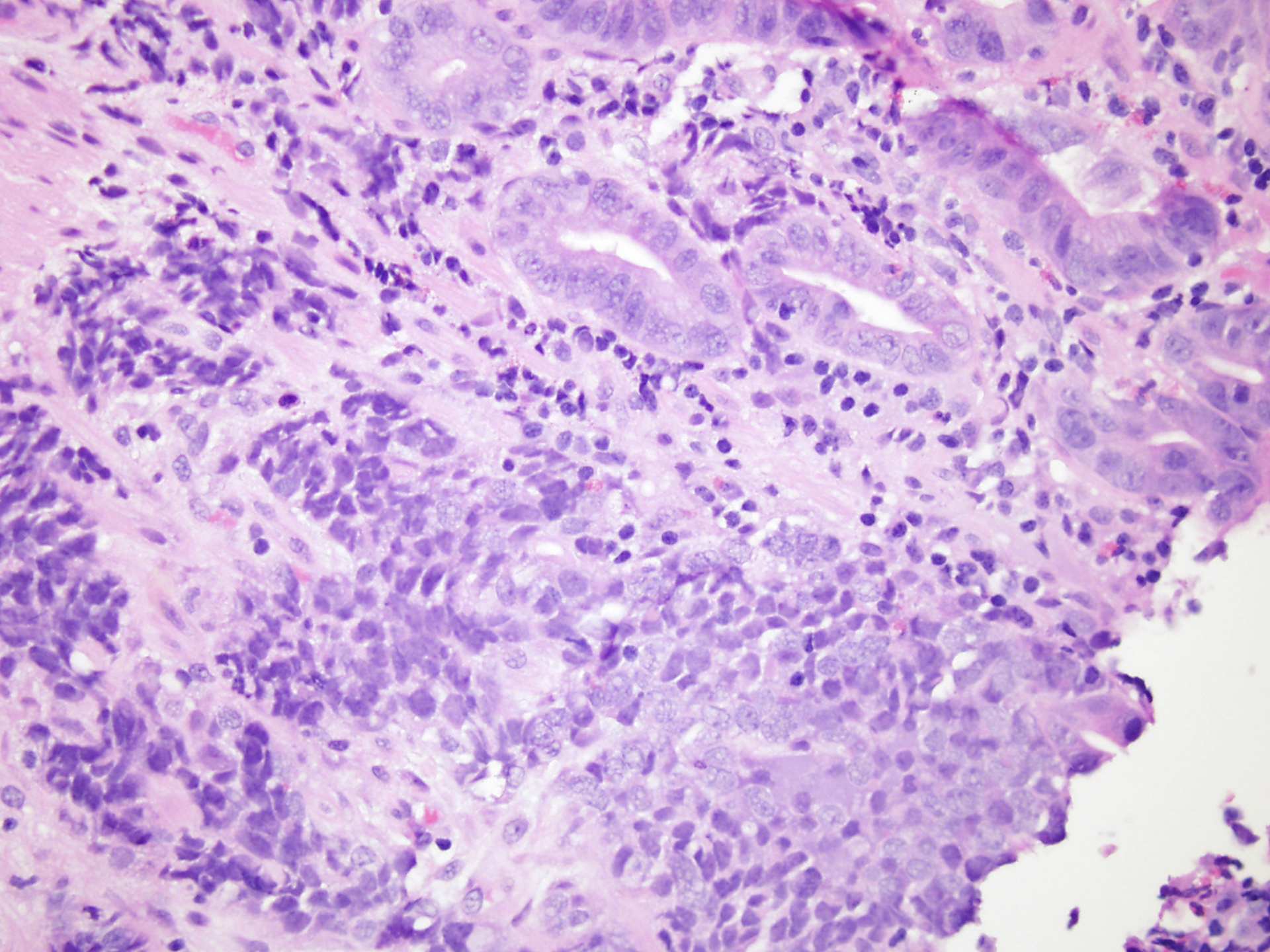


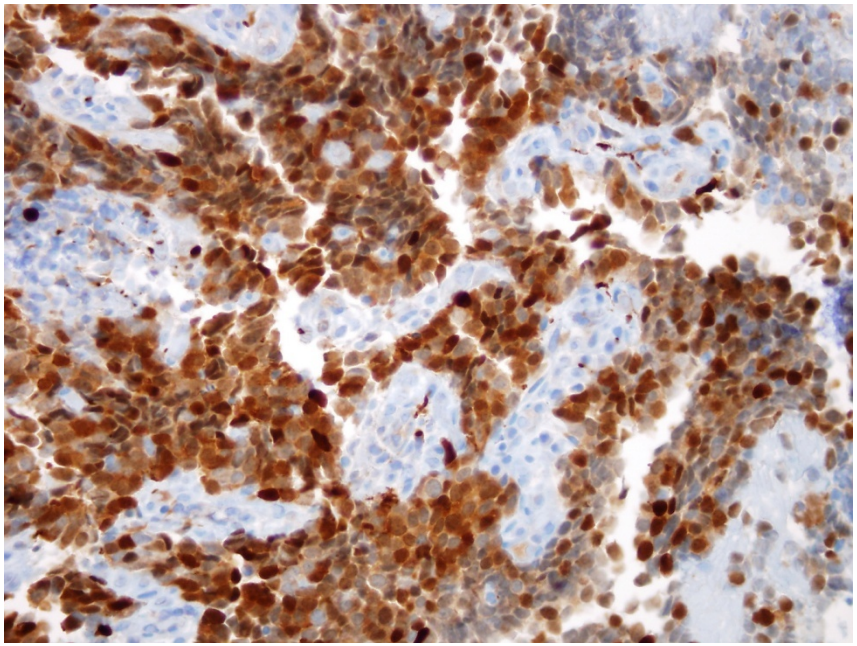

Low-grade fibromyxoid
sarcoma – MUC4 stain


Duodenal mass
22 y/o female

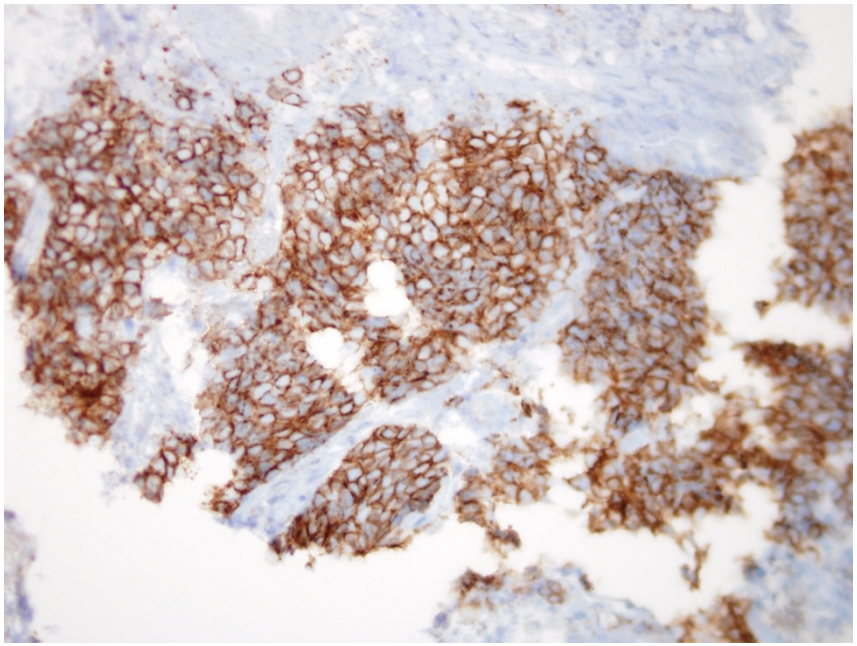


Duodenal mass,22 y/o female

S100 protein



CD99

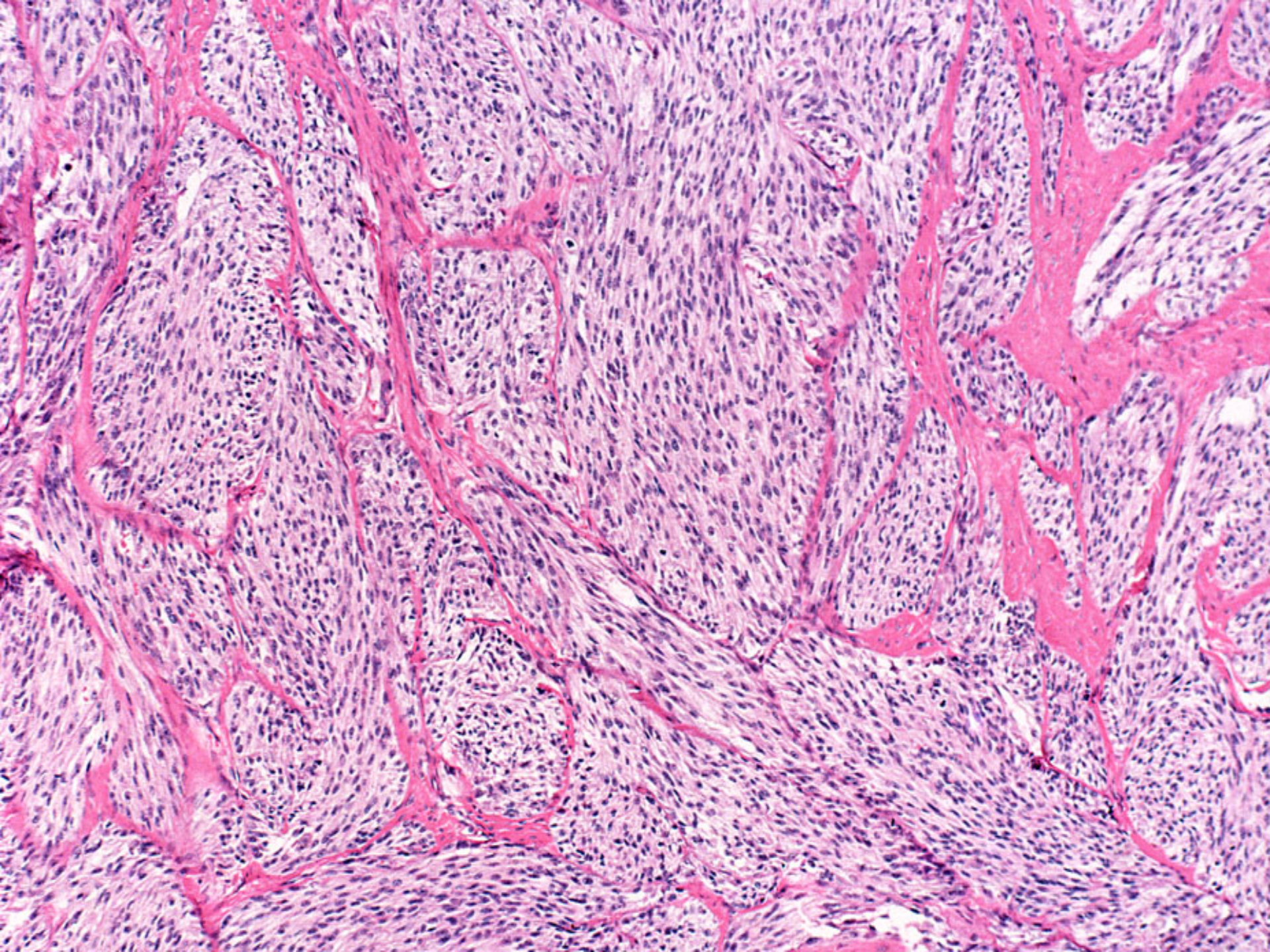


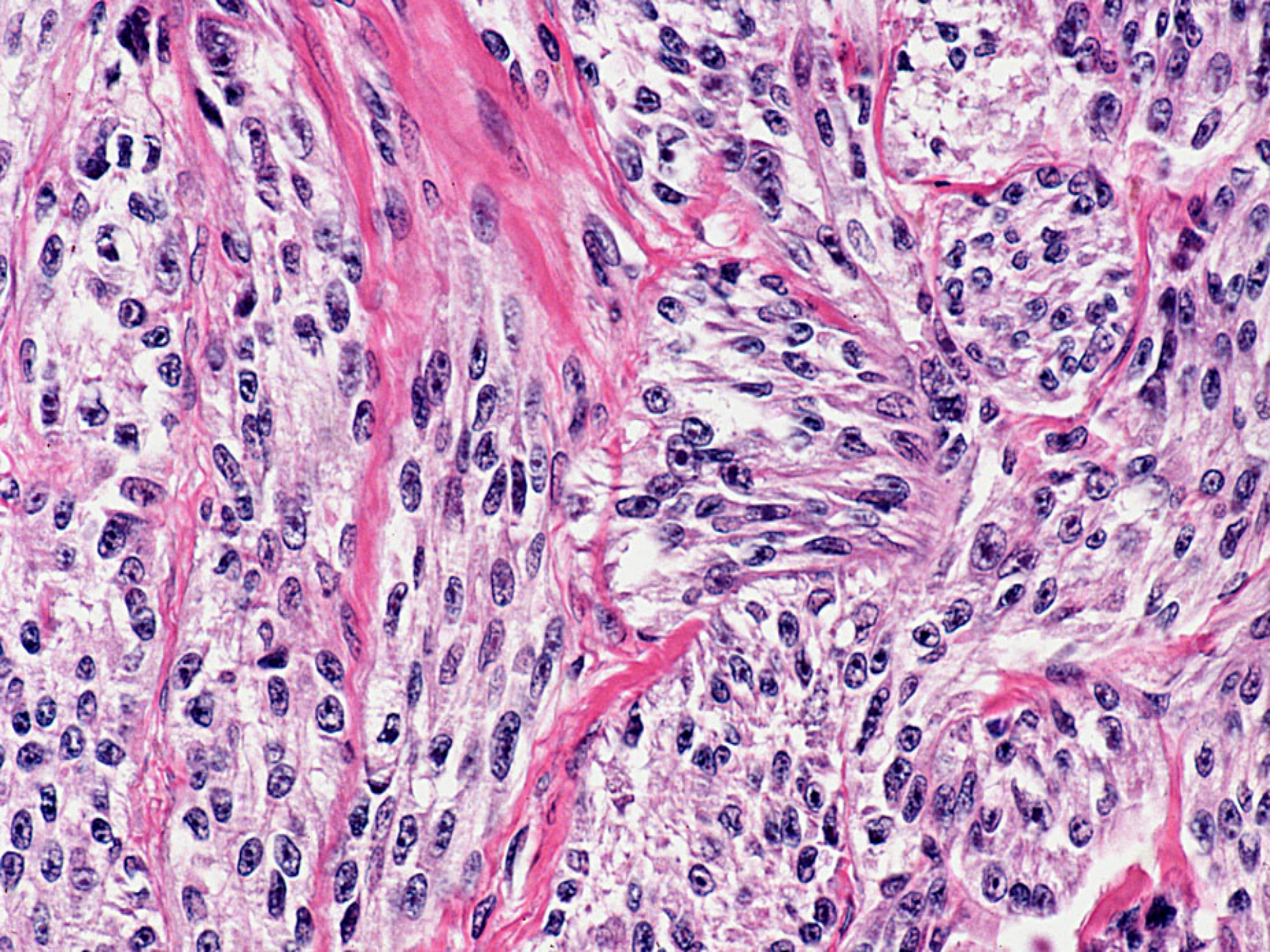
DDx

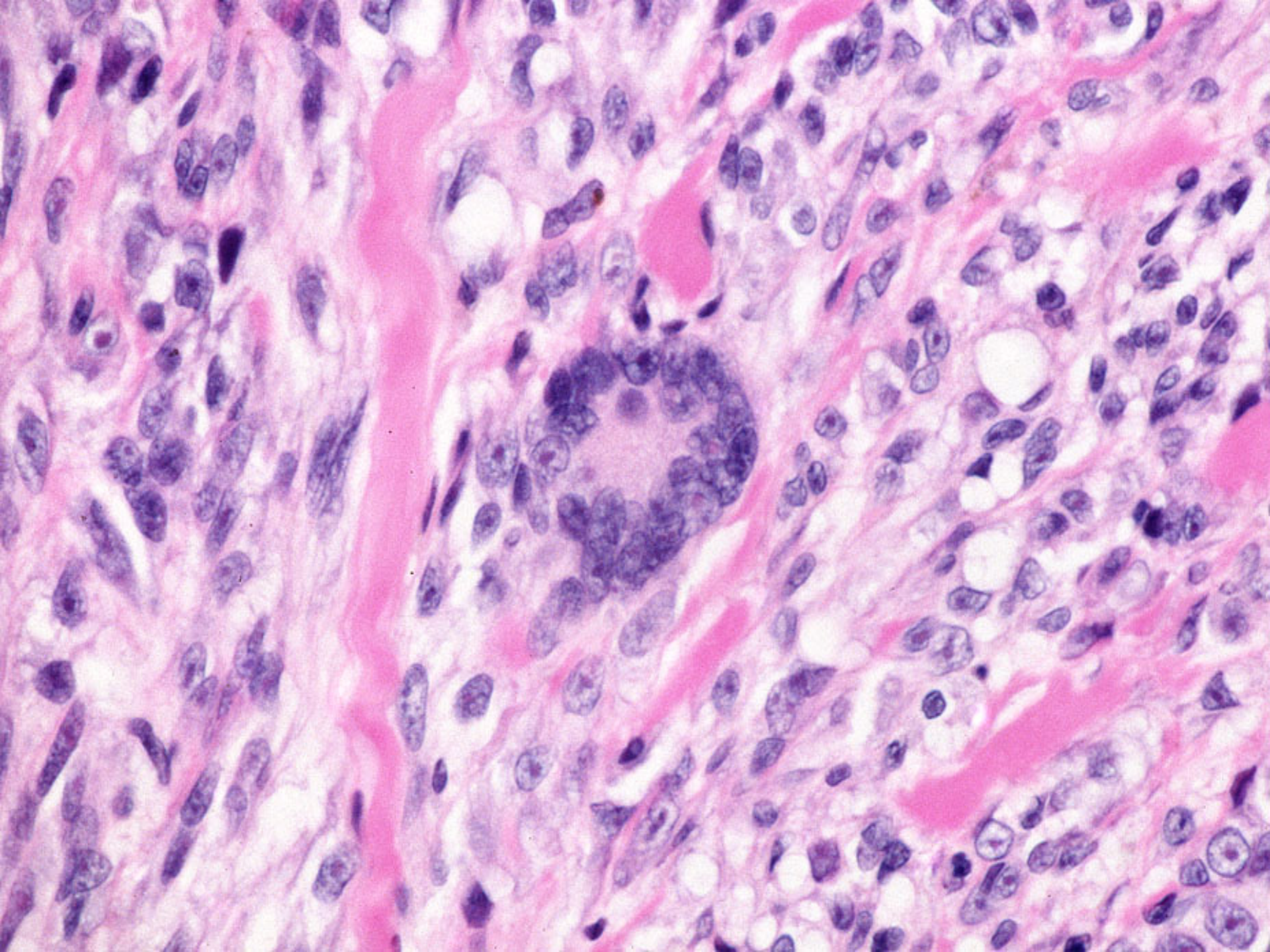
- Clear cell sarcoma of GIT – not impossible –can have CD99 labeling (*EWS- ATF1)*
- Ewings/PNET of GIT – possible – can have S100 protein labeling (*EWS-FLI1)*
- Metastatic melanoma – possible
- Need to use PCR rather than FISH to separate first 2

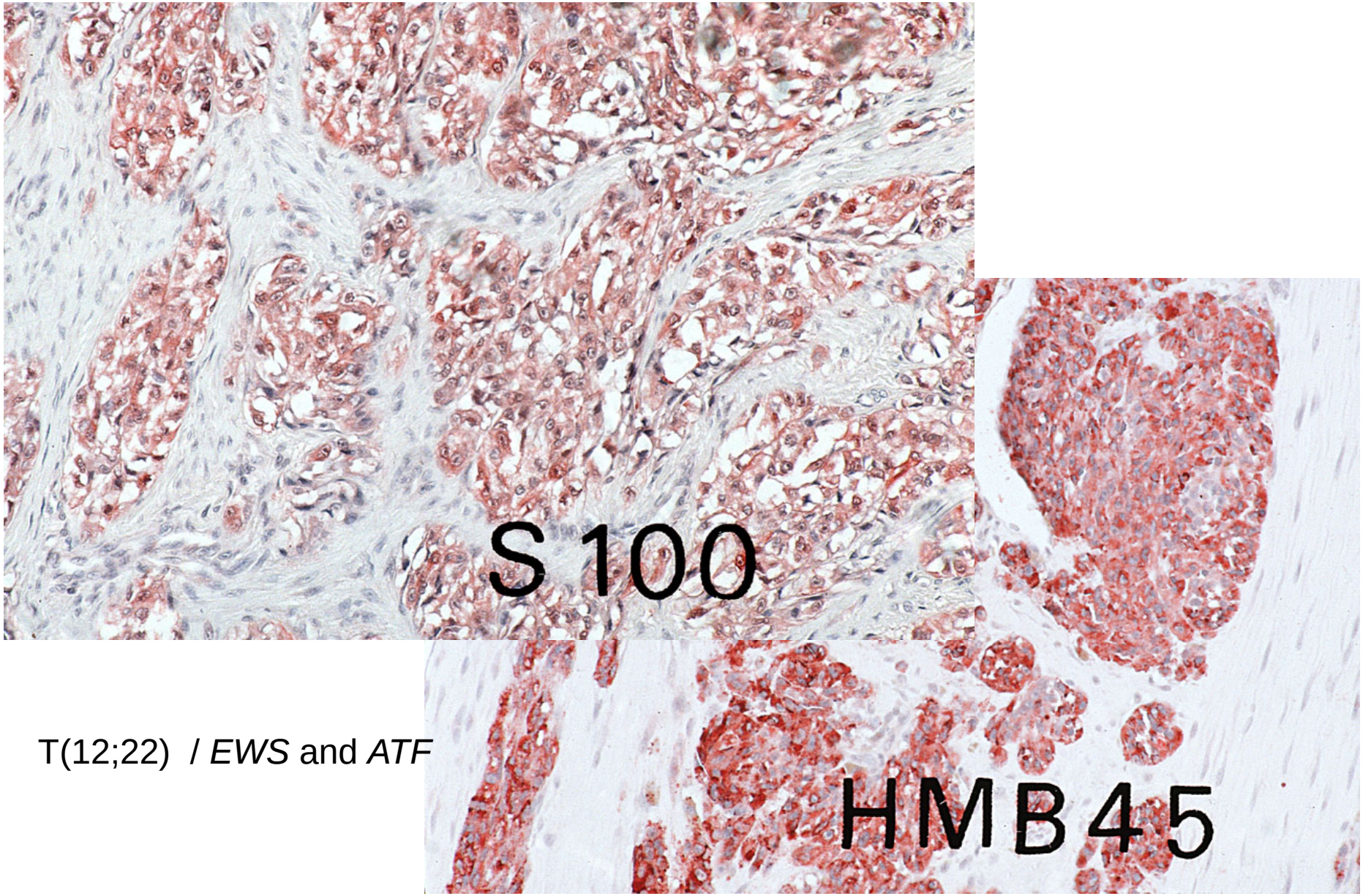
Clear cell sarcoma of soft tissue

- Young adults
- Tendon sheaths and aponeuroses
- Packeted morphology
- Labels with S100 protein, HMB45, lacks kit labeling
- Characteristic translocation t(12;22)(q13;q12), resulting in a *EWS-ATF1* fusion

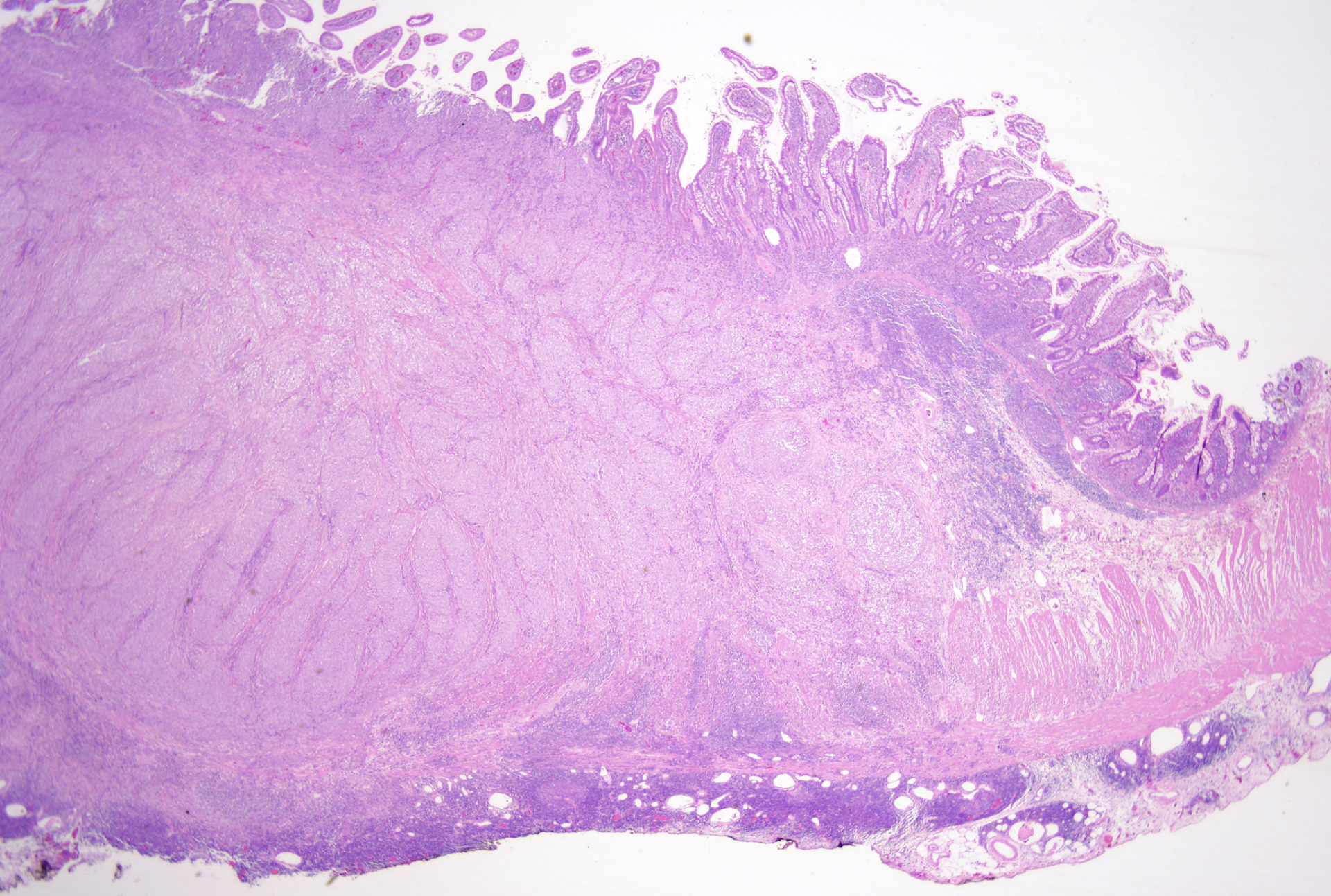




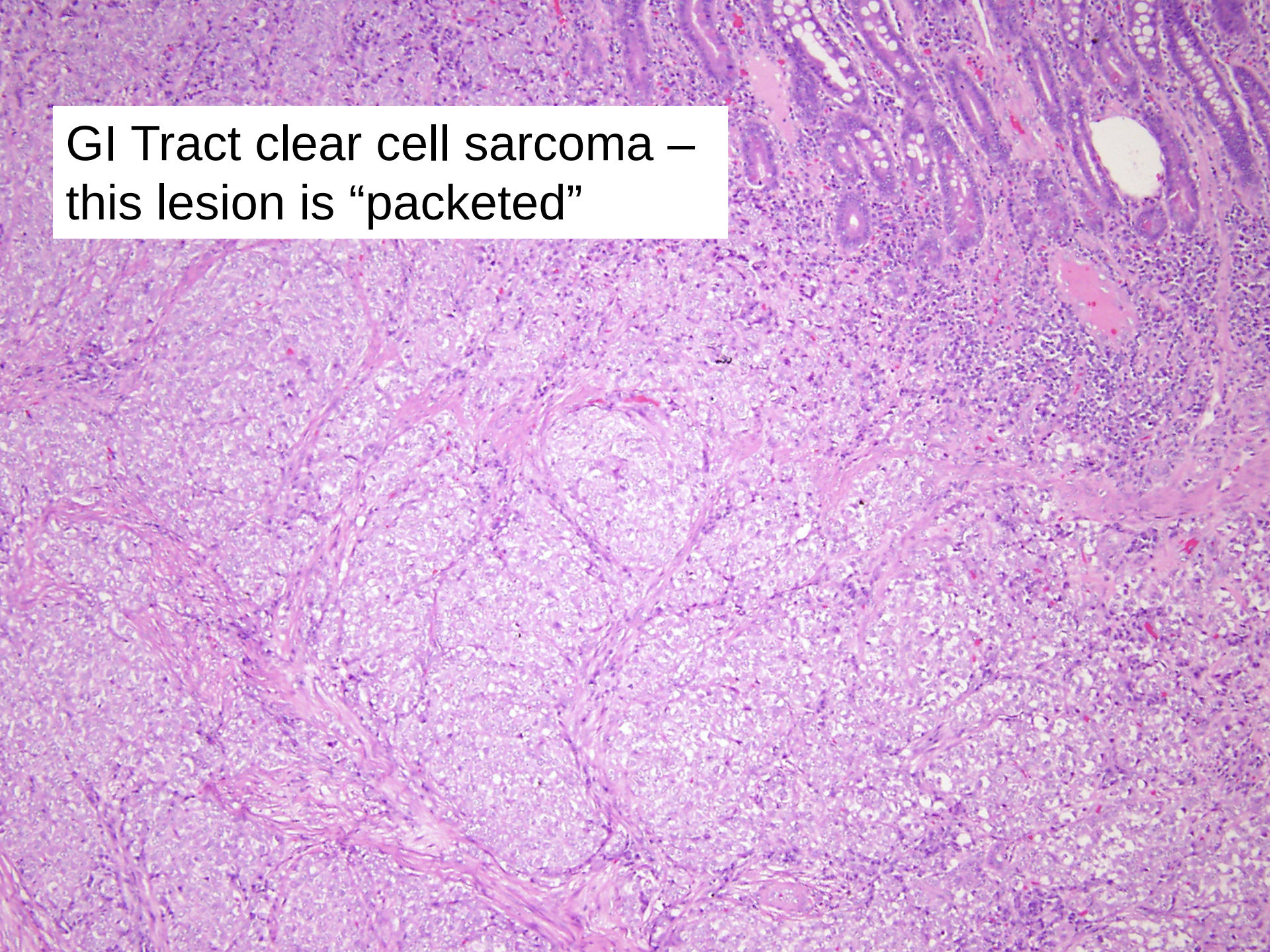


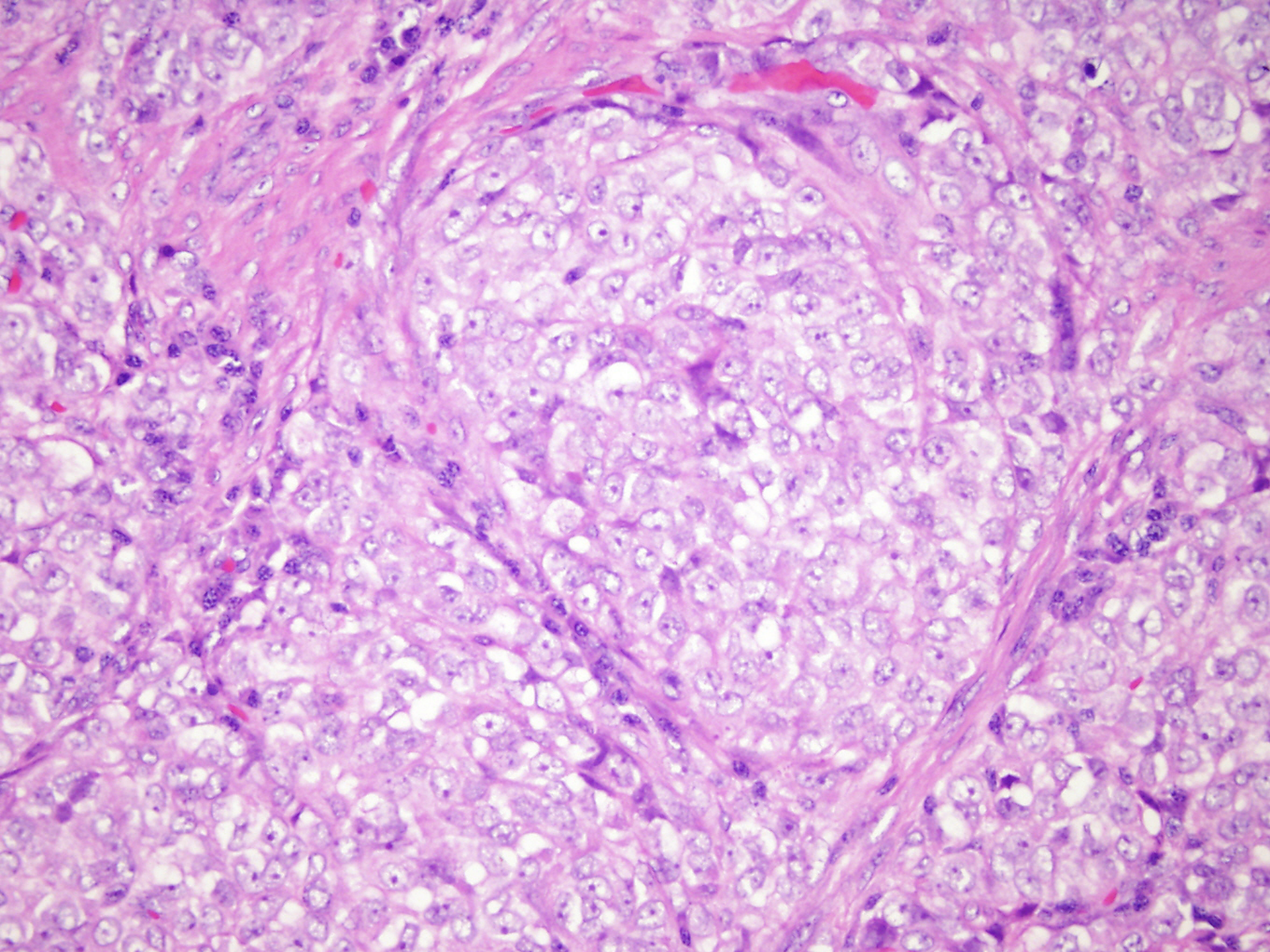


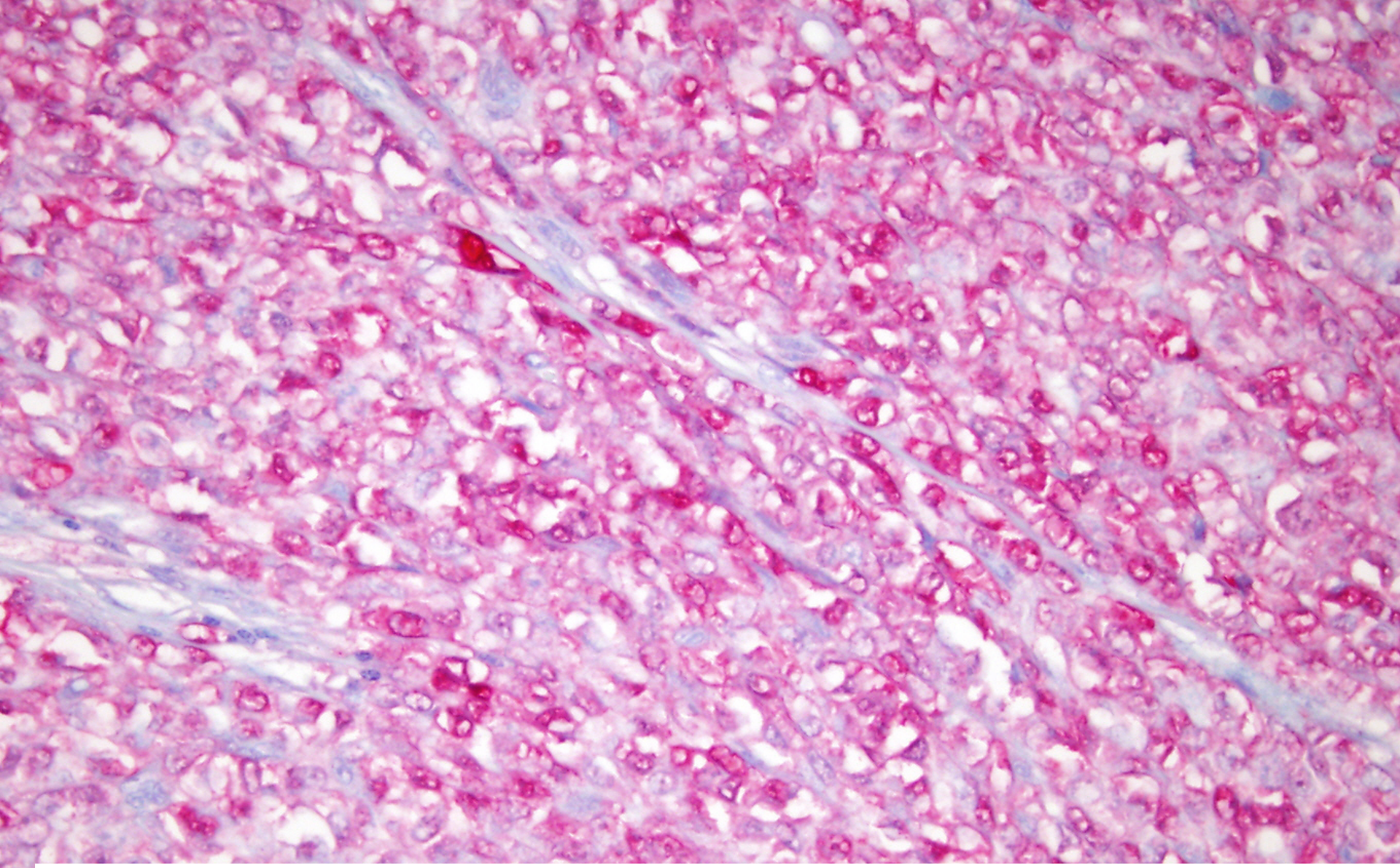
T(12;22) / *EWS* and *ATF*



GI Tract clear cell sarcoma


GI Tract clear cell sarcoma –
this lesion is “packeted”

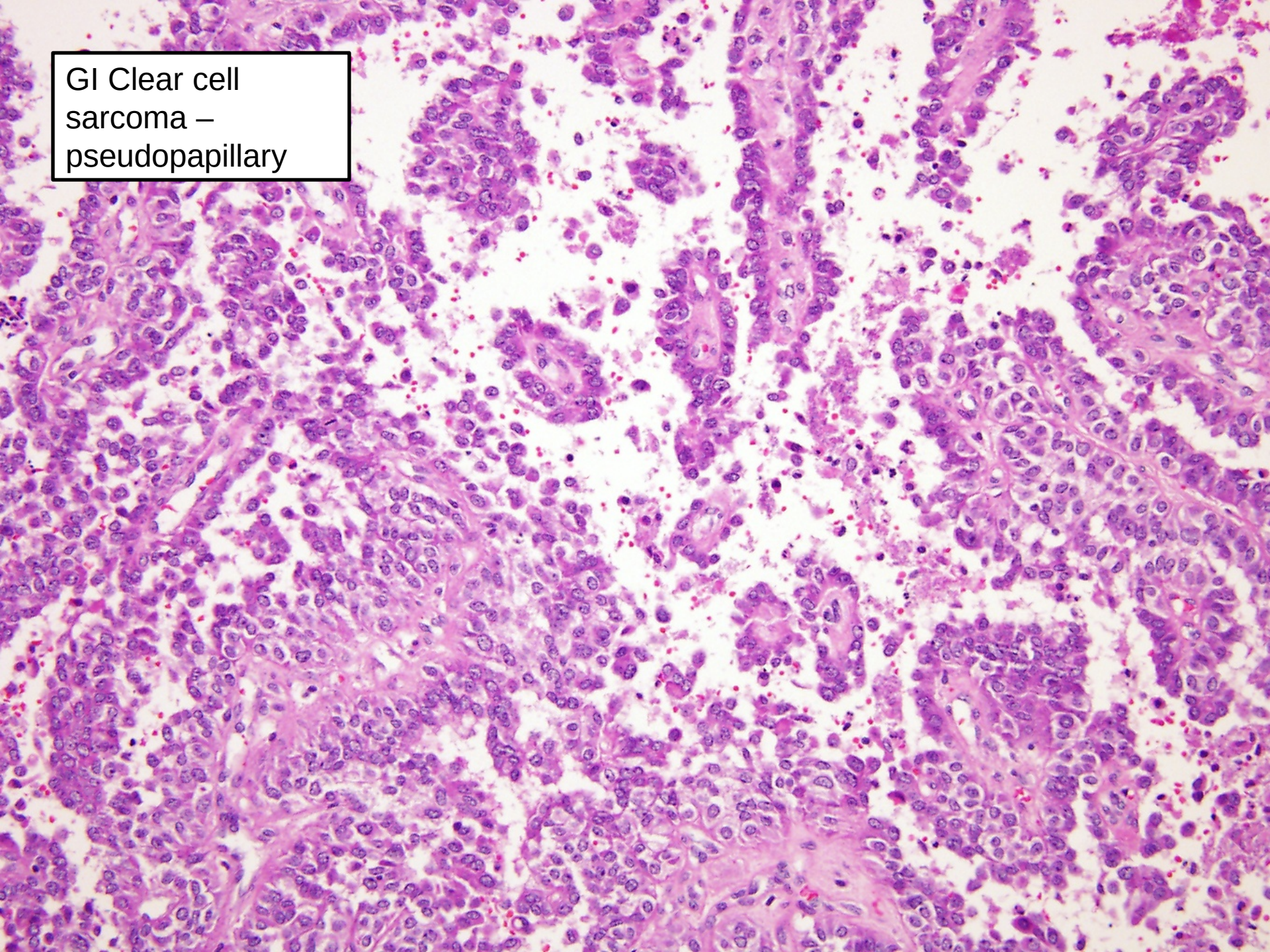


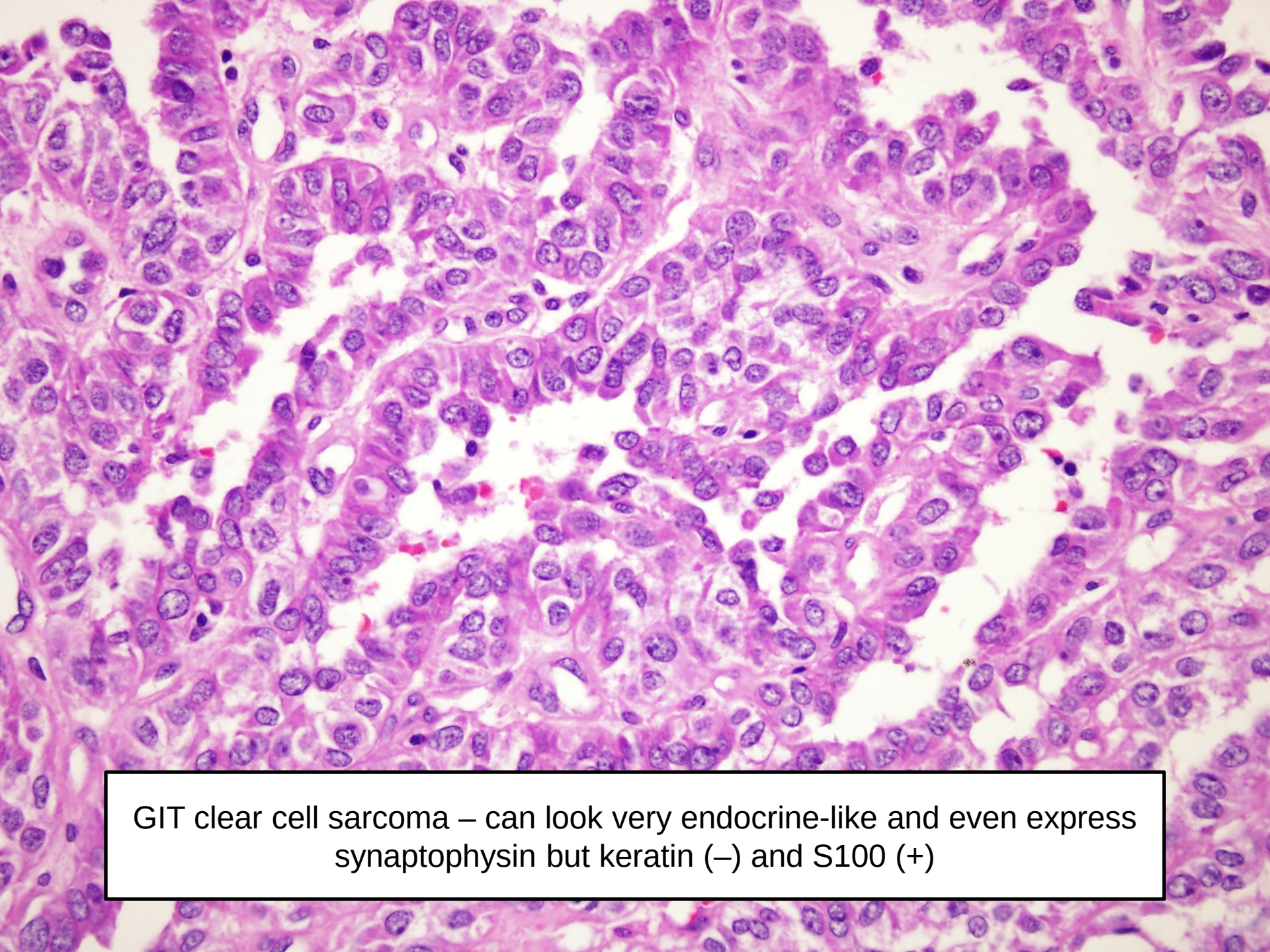


GI Tract clear cell sarcoma – this case was HMB45 negative– Probably has a variant fusion *EWS – CREB1* rather than classic *EWS – ATF1*

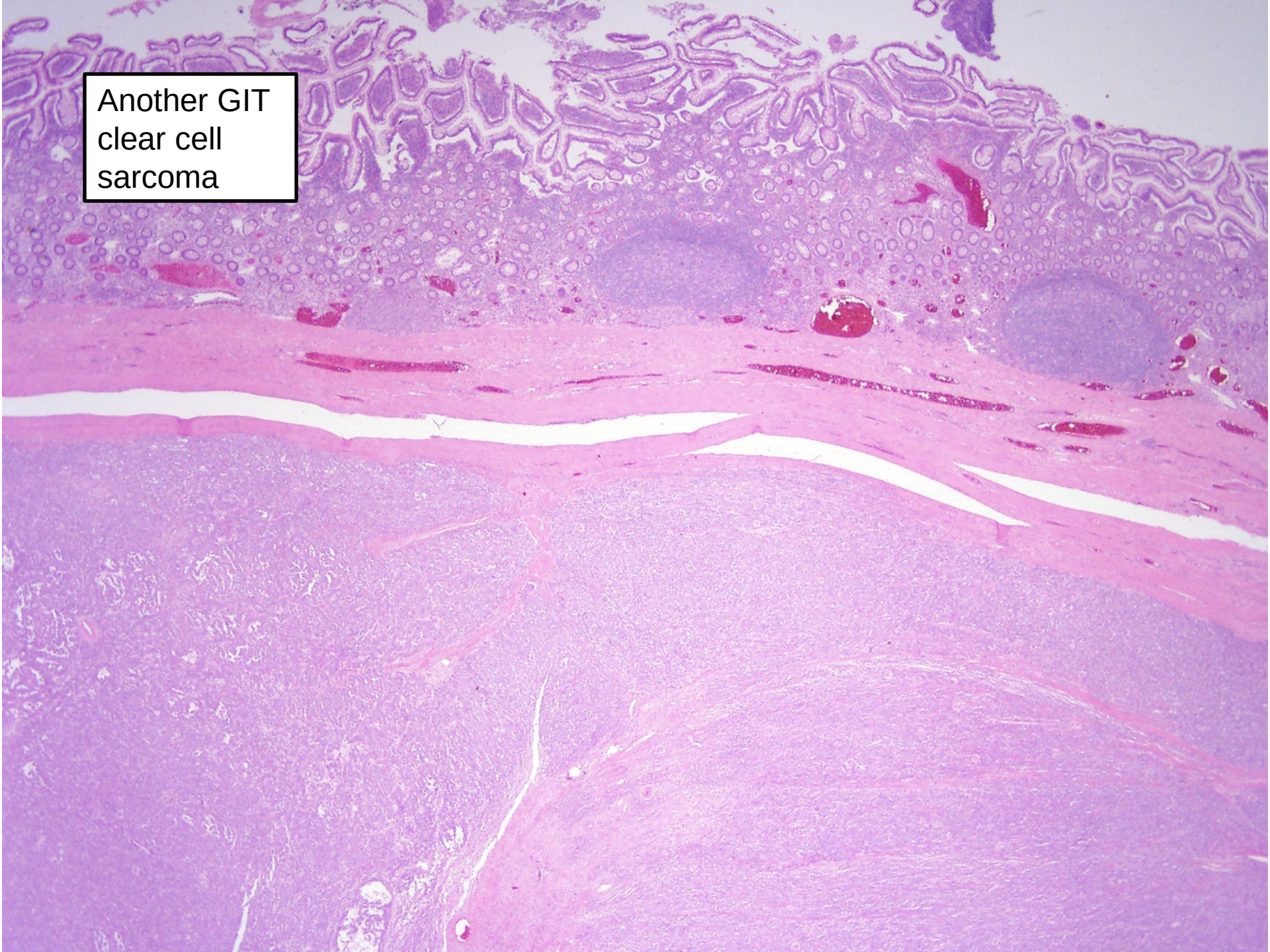
What about GIT Clear cell sarcoma?

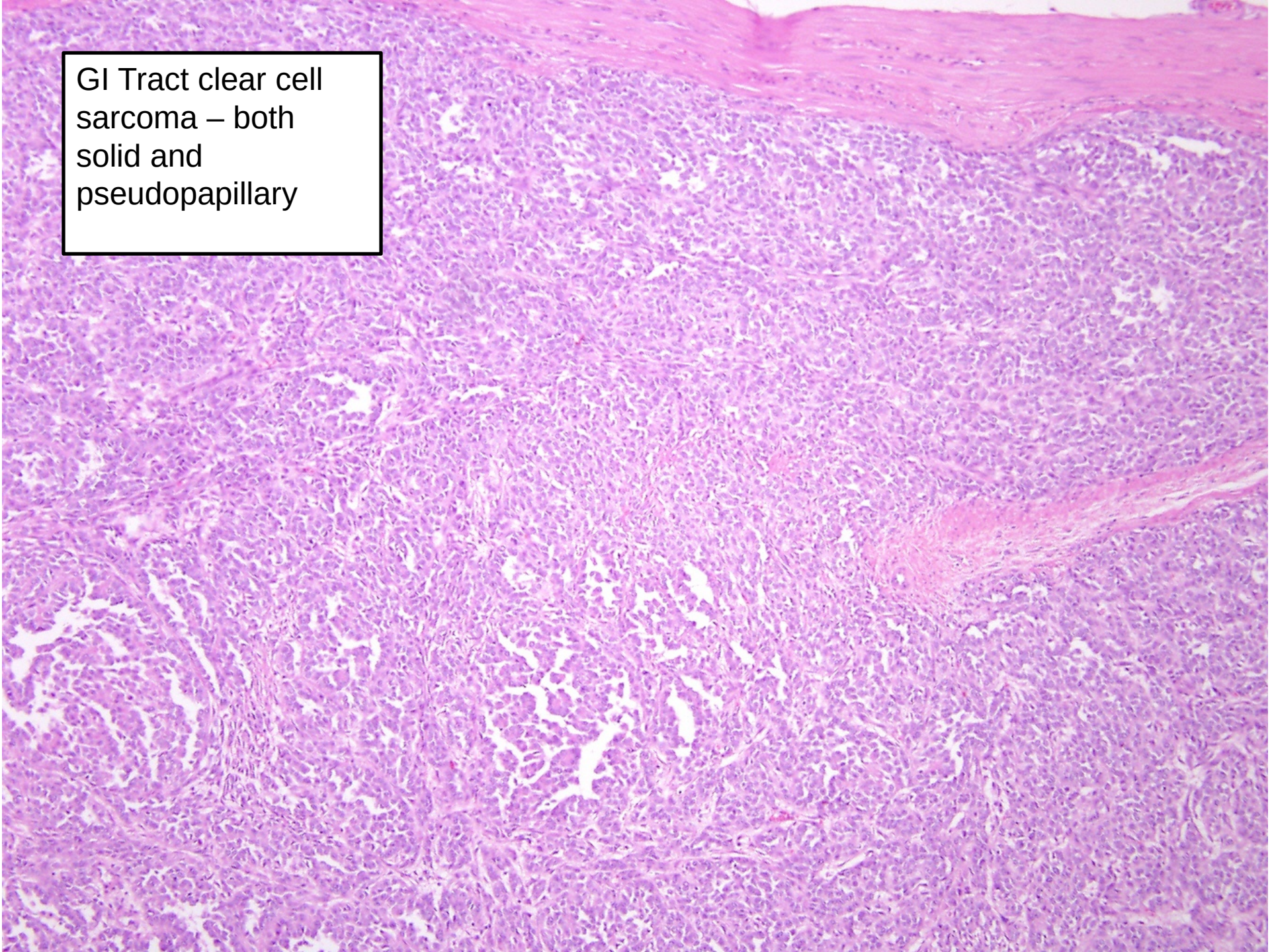
- Antonescu et al EWS-CREB1: a recurrent variant fusion in clear cell sarcoma--association with gastrointestinal location and absence of melanocytic differentiation. Clin Cancer Res. 2006 Sep 15;12(18):5356-62.
- Covinsky et al. EWS-ATF1 fusion transcripts in gastrointestinal tumors previously diagnosed as malignant melanoma. Hum Pathol. 2005 Jan;36(1):74-81.
- Lyle et al. Gastrointestinal melanoma or clear cell sarcoma? Molecular evaluation of 7 cases previously diagnosed as malignant melanoma. Am J Surg Pathol. 2008 Jun;32(6):858-66.
- Stockman DL, Miettinen M, Suster S, Spagnolo D, Dominguez-Malagon H, Hornick JL, Adsay V, Chou PM, Amanuel B, Vantuinen P, Zambrano EV. 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. Am J Surg Pathol. 2012 Jun;36(6):857-68.

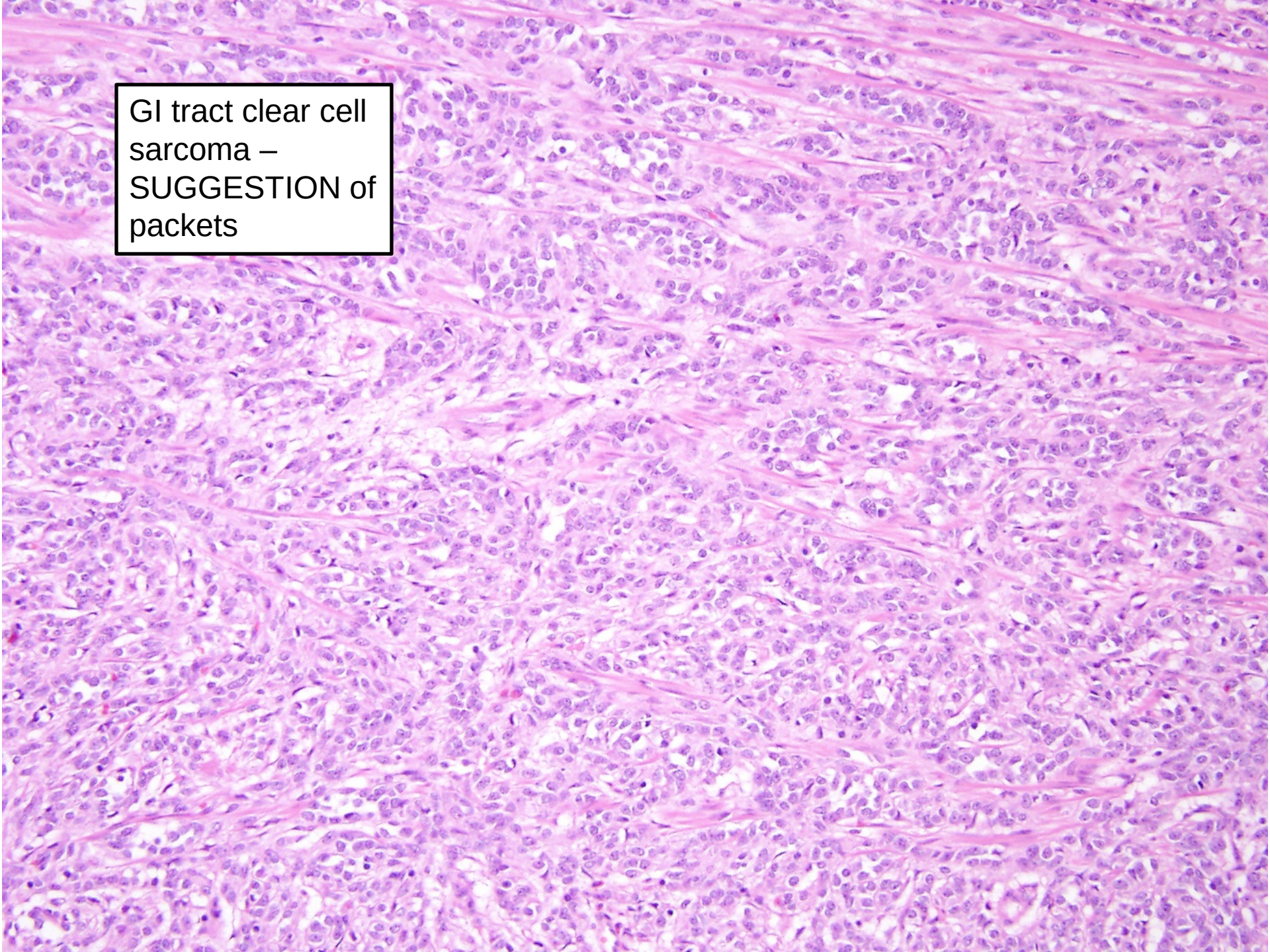

GI Clear cell sarcoma – pseudopapillary

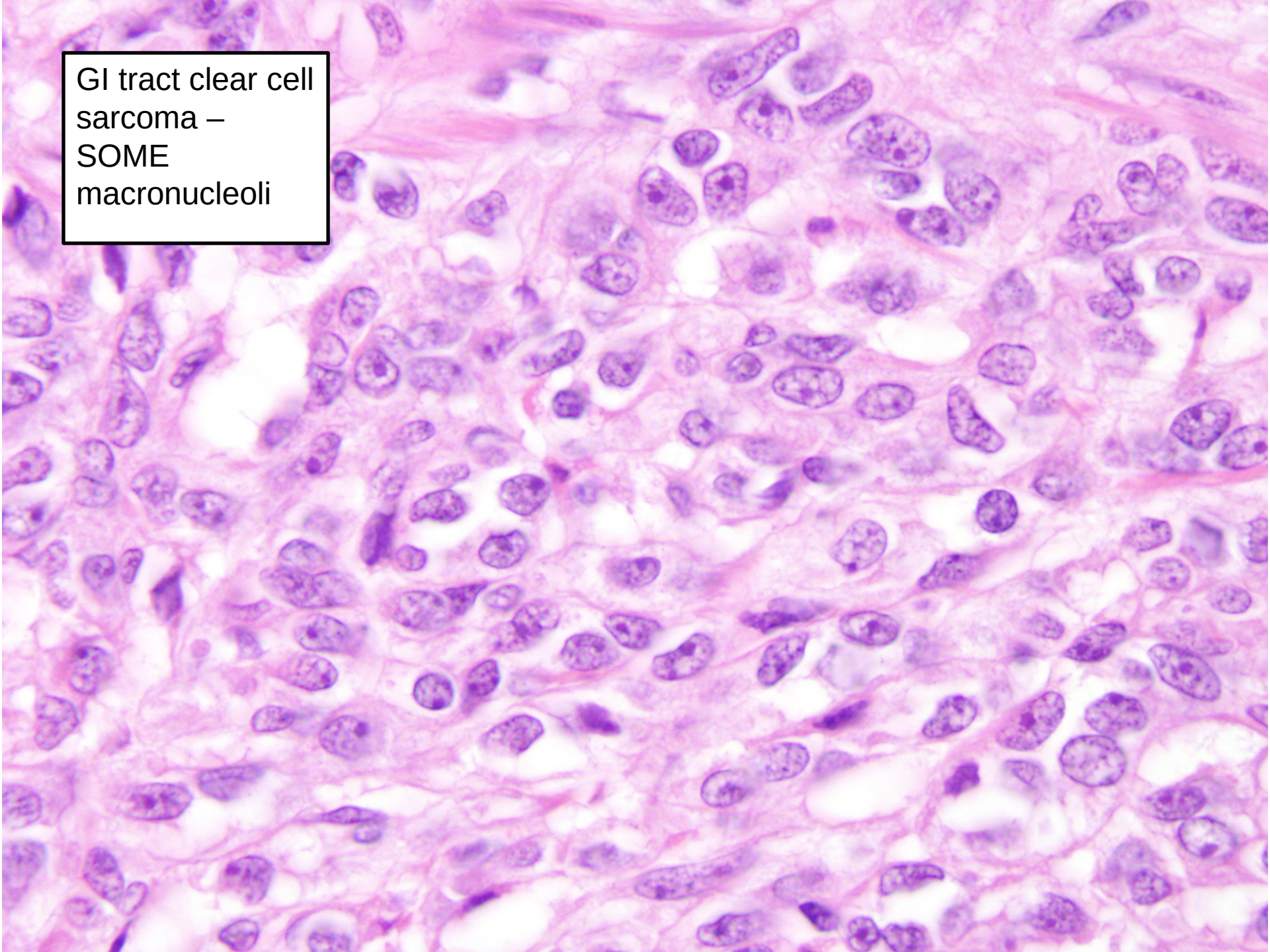


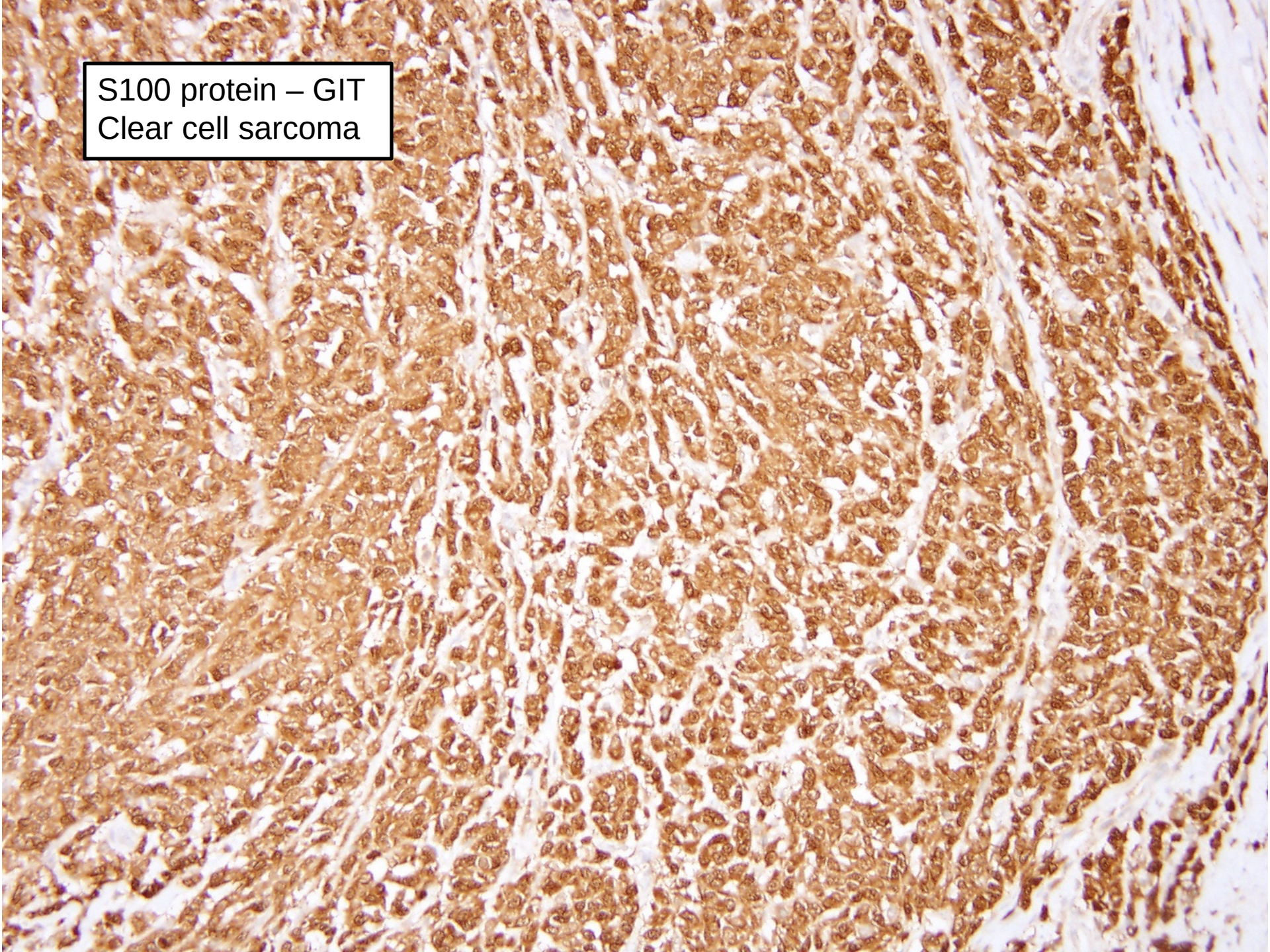
GIT clear cell sarcoma – can look very endocrine-like and even express synaptophysin but keratin (–) and S100 (+)


Another GIT
clear cell
sarcoma


GI Tract clear cell sarcoma – both solid and pseudopapillary


GI tract clear cell sarcoma – SUGGESTION of packets

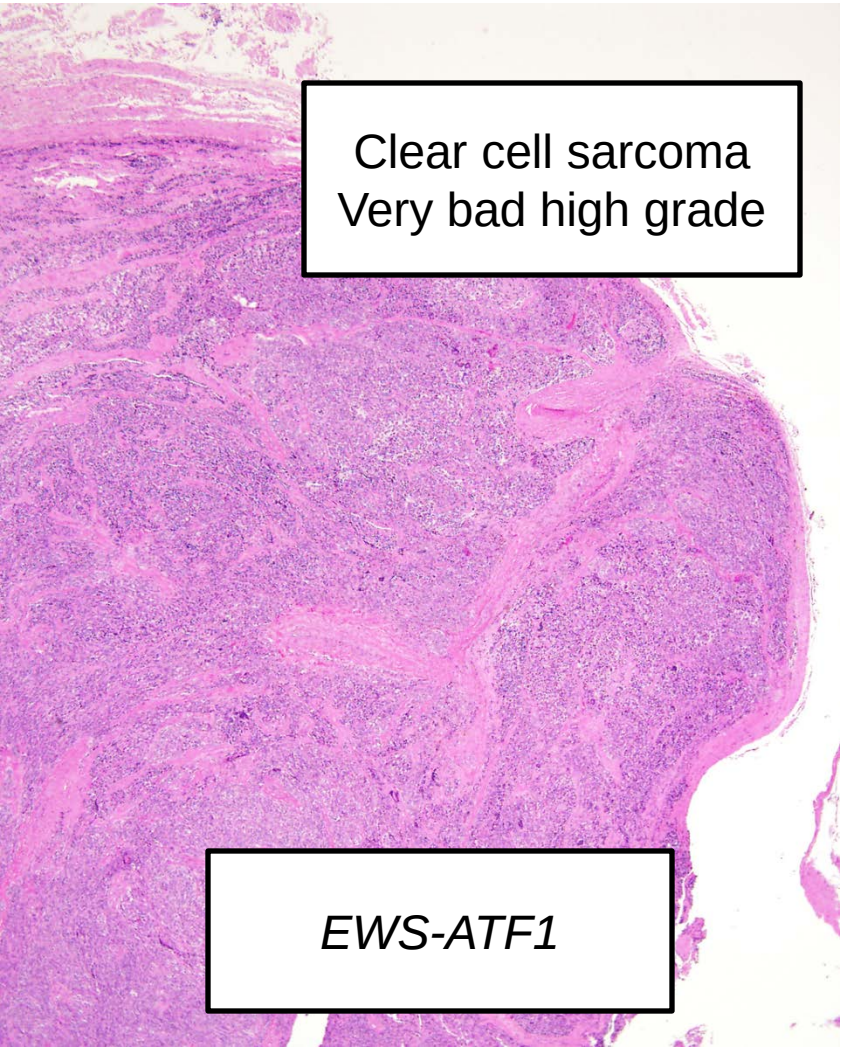

GI tract clear cell sarcoma – SOME macronucleoli

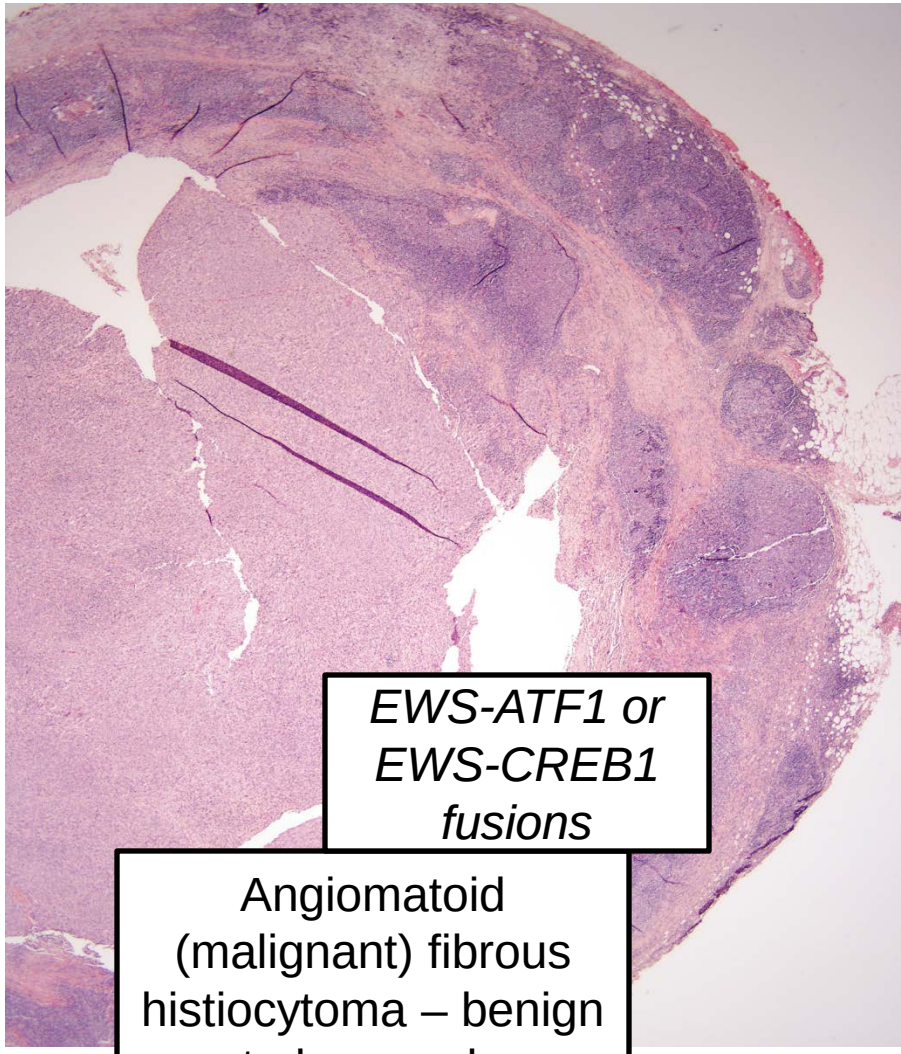

S100 protein – GIT
Clear cell sarcoma

GI Tract Clear Cell Sarcoma

- Horrible prognosis – mean survival 32 months in small series
- Early spread to nodes, liver

By the way…..


Clear cell sarcoma
Very bad high grade
EWS-ATF1


EWS-ATF1 or EWS-CREB1 fusions
Angiomatoid (malignant) fibrous histiocytoma – benign to low-grade

Back to our case

It was shown to have an *EWS-FLI1* rearrangement and was diagnosed as EWING's/PNET

Spindly Things in The GI Tract [and elsewhere]

- Attention to morphologic principles and knowledge of a few pitfalls allows a logical approach to these lesions.
- We have an opportunity to greatly impact patient care.


GIST AVE.