



Uterine Mesenchymal Neoplasms, Soundbites

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MD Anderson
~~Cancer~~ Center
Making Cancer History®

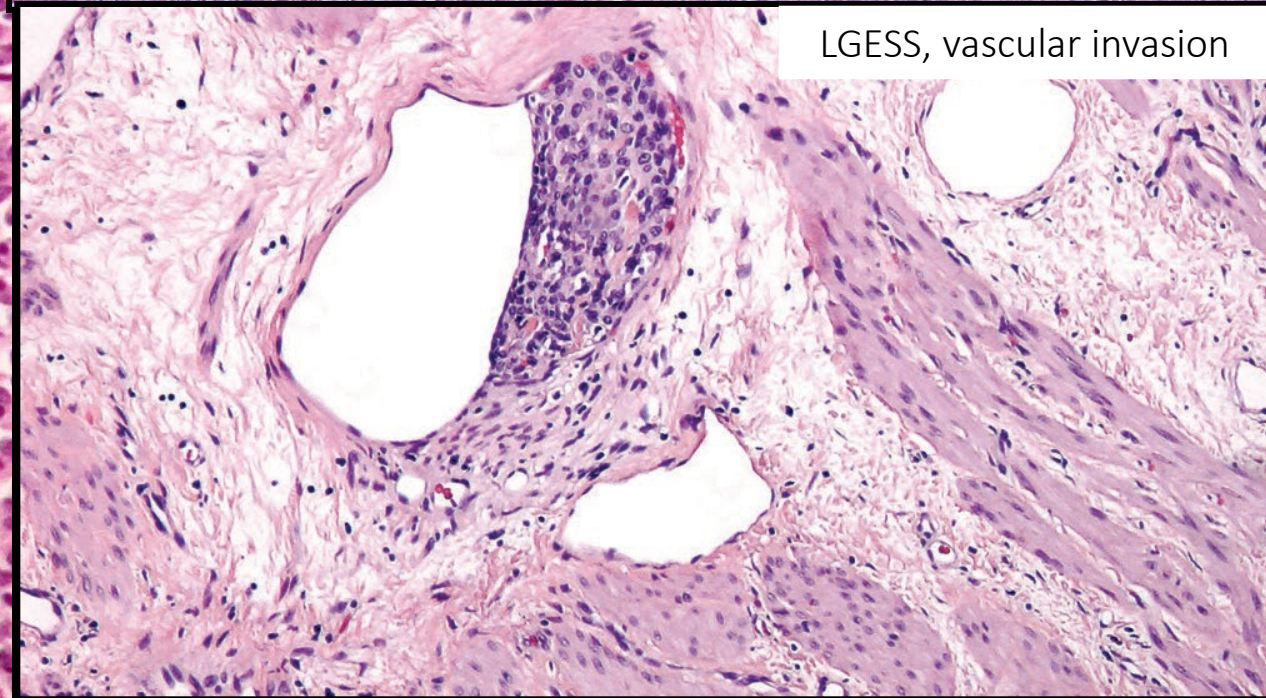
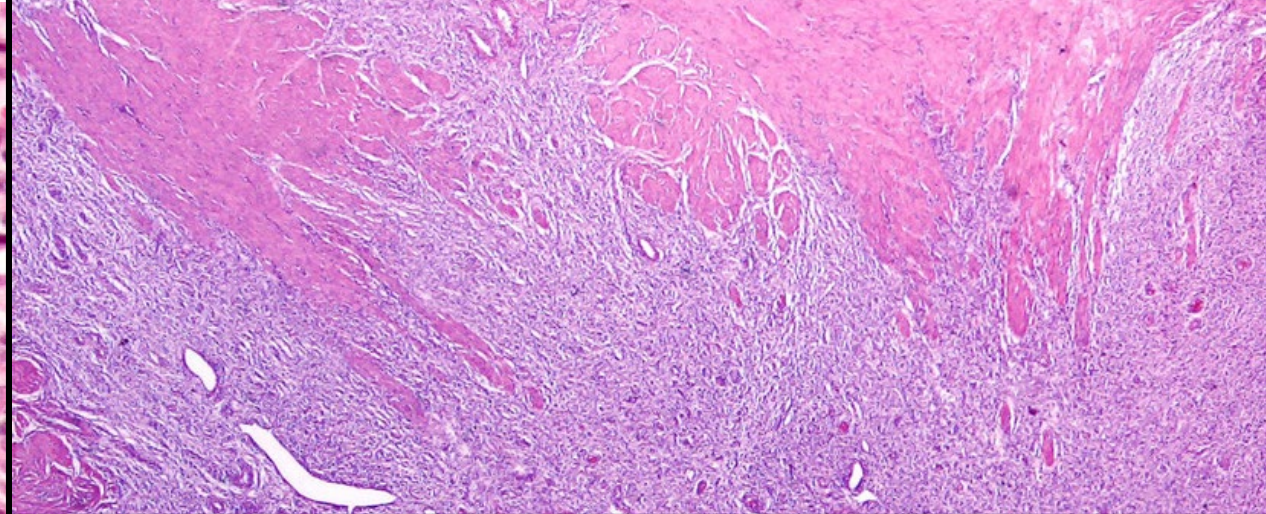
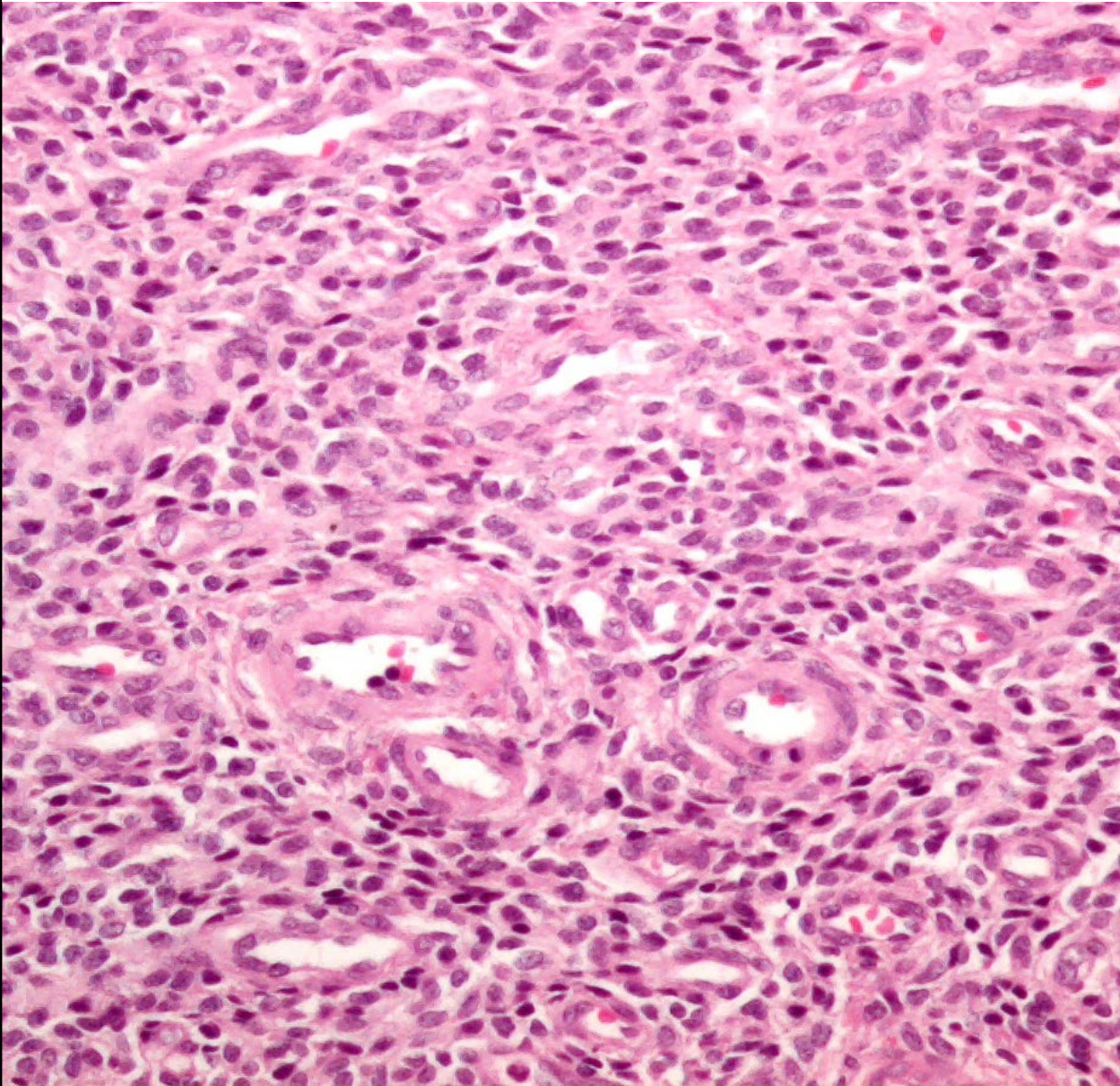
Soundbites

- ESS
 - Low grade and high grade
- Smooth muscle tumors with nuclear atypia
- PEComa
- Uterine sarcomas with NTRK Fusion

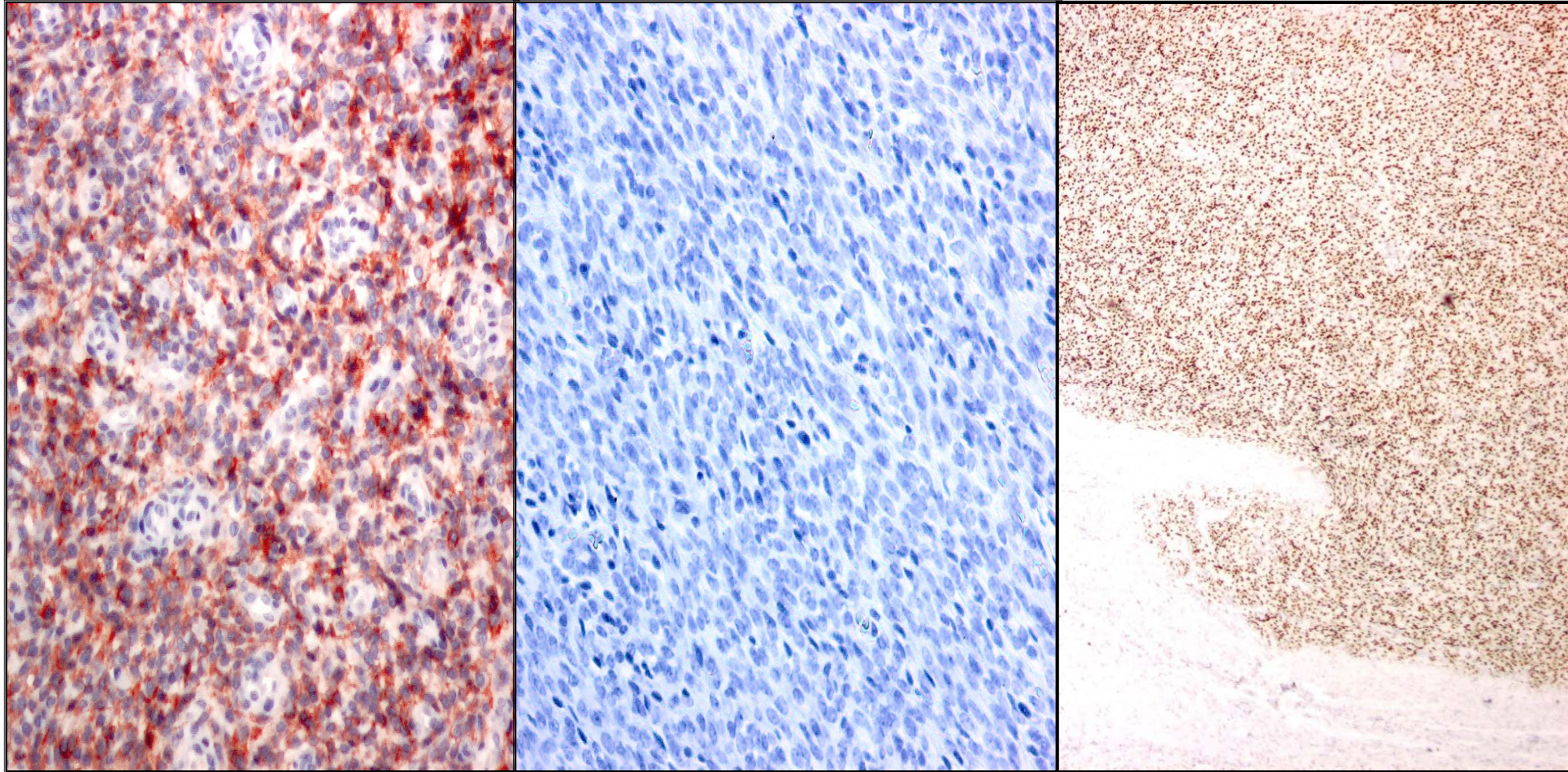
LGESS: Cells with uniform oval or round nuclei with scanty or moderate amount of amphophilic or eosinophilic cytoplasm
Small blood vessels similar to spiral arterioles

LGESS, infiltration of myometrium

LGESS, vascular invasion



LGESS, Immunoperoxidase Studies



CD 10 +

Caldesmon, SMMS-1 and
HDAC8 negative

ER+, PR+ ,WT-1+

Desmin and SMA can be +

LGESS, Genetic Abnormalities

t (7;17) (p15;q21)



JAZF1-SUZ12 (JJAZ1)
fusion gene
Most common (48% of the cases)

t (6;7) (p21;p15)



JAZF1-PHF1
fusion gene
Second most common

The *PHF1* gene* can also fuse with *EPC1* and *MEAF6*. * ESS with sex-cord like diff

Other translocations



ZC3H7B-BCOR fusion gene
MBTD1-CXorf67 fusion gene

LGESS, Prognosis

Typically, an indolent tumor with a tendency to have late recurrences

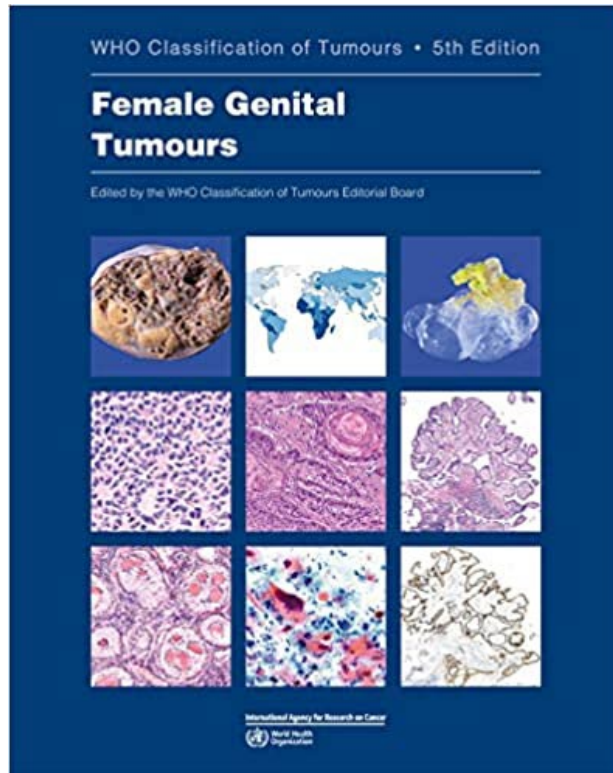
Figo Stage	Recurrence Rate	Survival Rate
I	36%	92%
III-IV	76%	66%

Chang et al,1990

LN mt	19 -33%
Adnexal mt	13%

Dos Santos LA, et al, 2011; Riopel et al, 2004

High Grade Endometrial Stromal Sarcoma

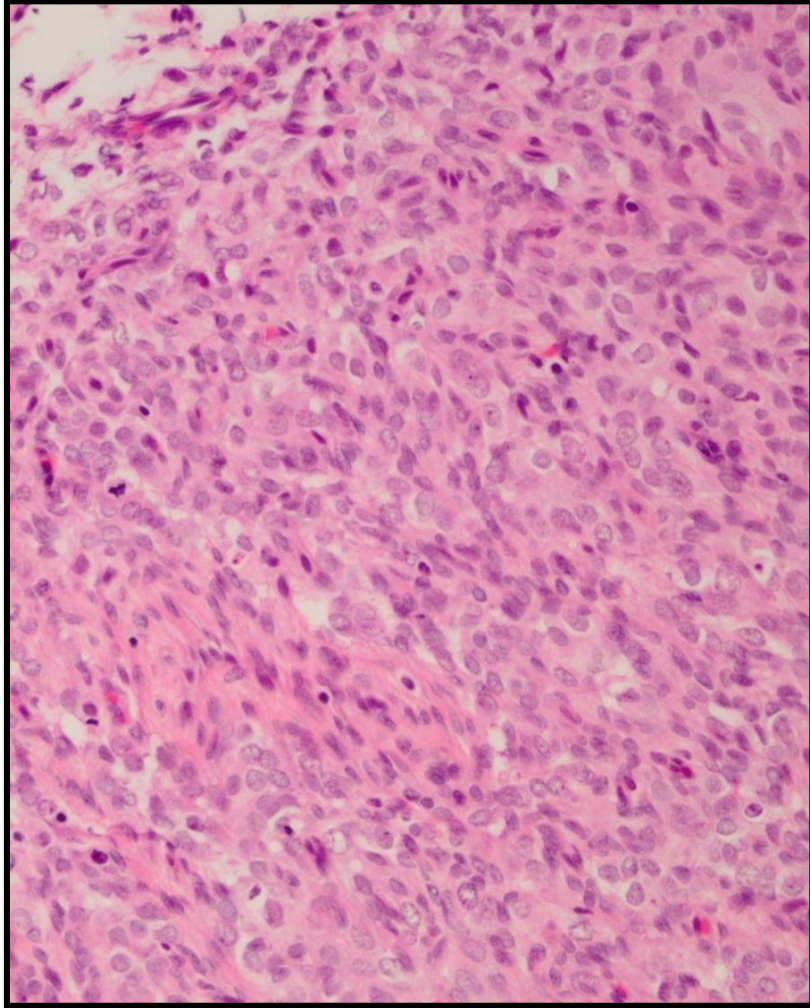


2020

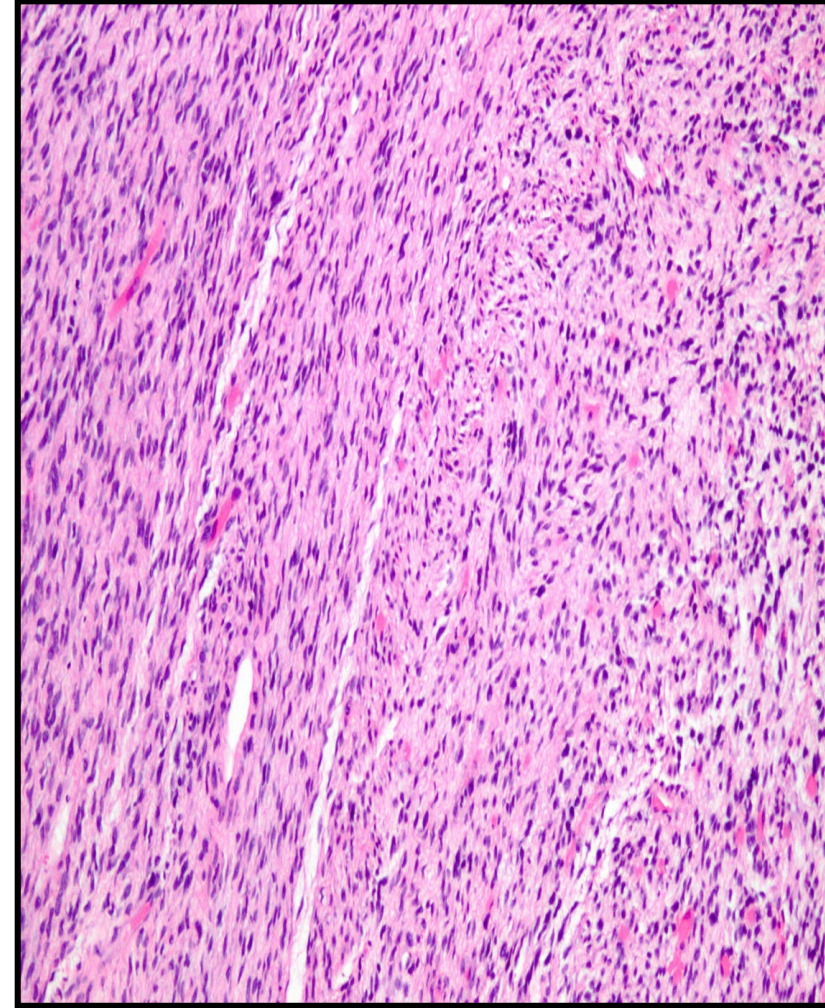
Definition

A malignant endometrial stromal tumor with uniform high grade, round and/or spindle morphology, sometimes with a low-grade component (conventional or fibromyxoid)

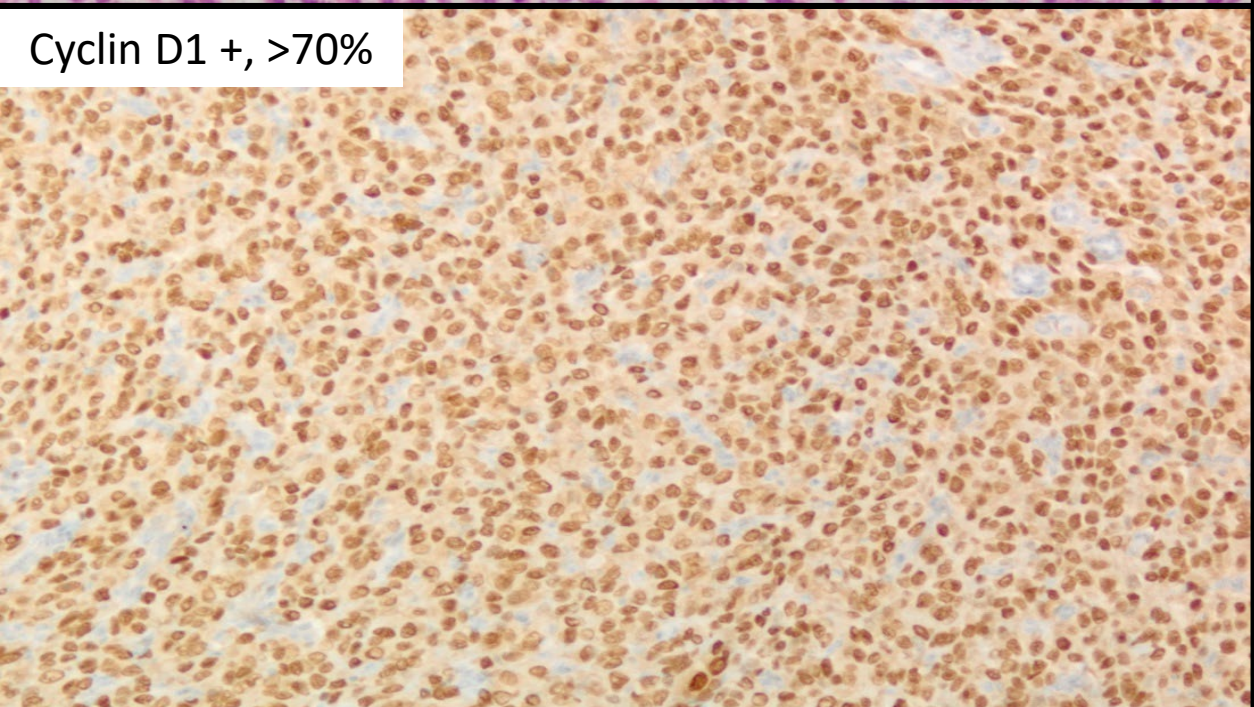
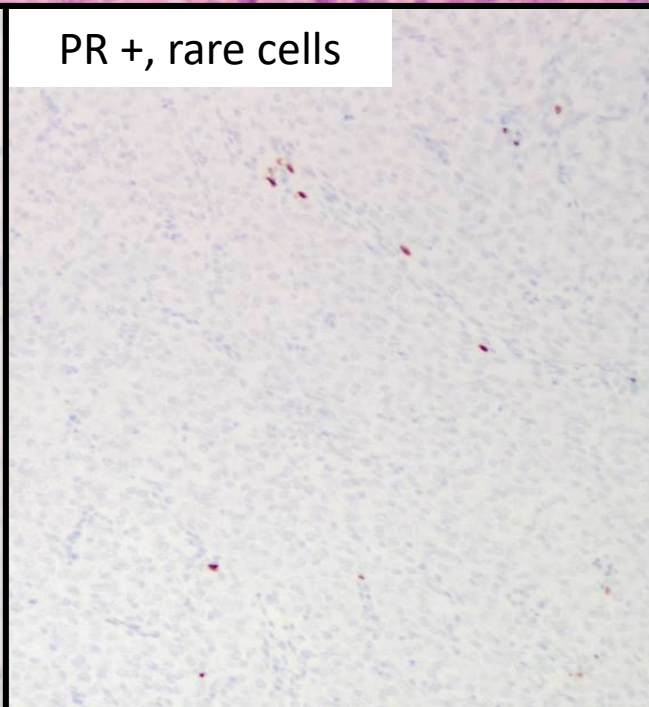
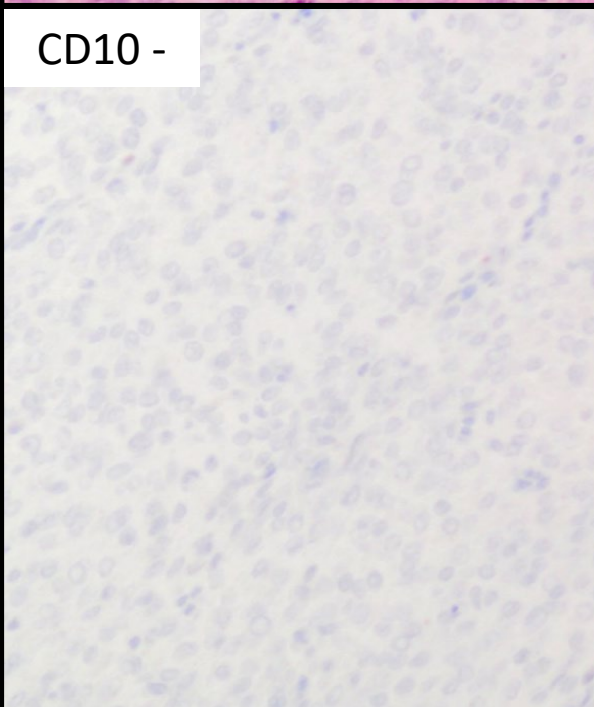
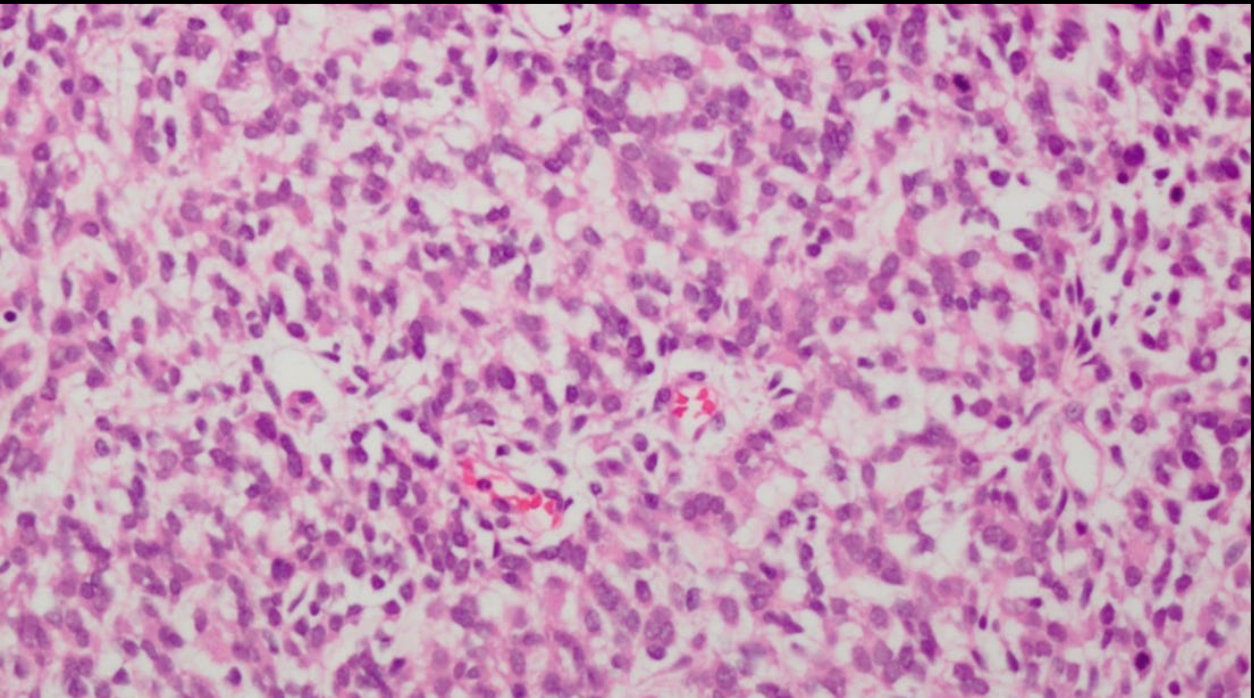
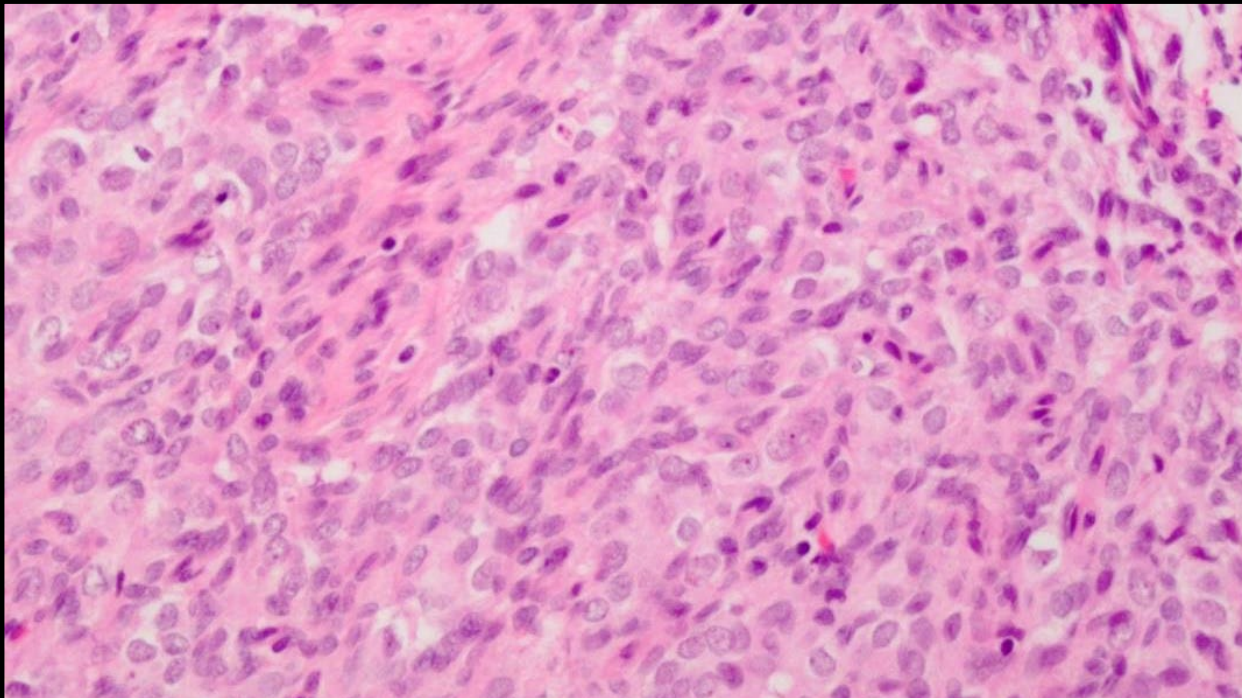
YWHAE-NUTM2 Endometrial Stromal Sarcoma



Nested pattern with round cells



Spindle cells



CD10 -

PR +, rare cells

Cyclin D1 +, >70%

YWHAE- NUTM2 Endometrial Stromal Sarcoma

- High grade component is negative for DOG-1, but it can be positive for:
 - BCOR
 - c-KIT (no *KIT* mutations)
 - CD56
 - CD99

How to tell these two tumors apart?

Low Grade ESS (<i>JAZF1</i> -rearranged ESS)	High Grade ESS (<i>YWHAE-NUTM2</i> fusion)
Smooth nuclear membrane	Irregular nuclear membrane
MI, usually < 5 mitoses/10 HPFs	MI >10 mitoses/10HPFs
Biphasic pattern is rare	Biphasic pattern is frequent (round and spindle cell components)

How to tell these two tumors apart?

Low Grade ESS (*JAZF1*-rearranged ESS)

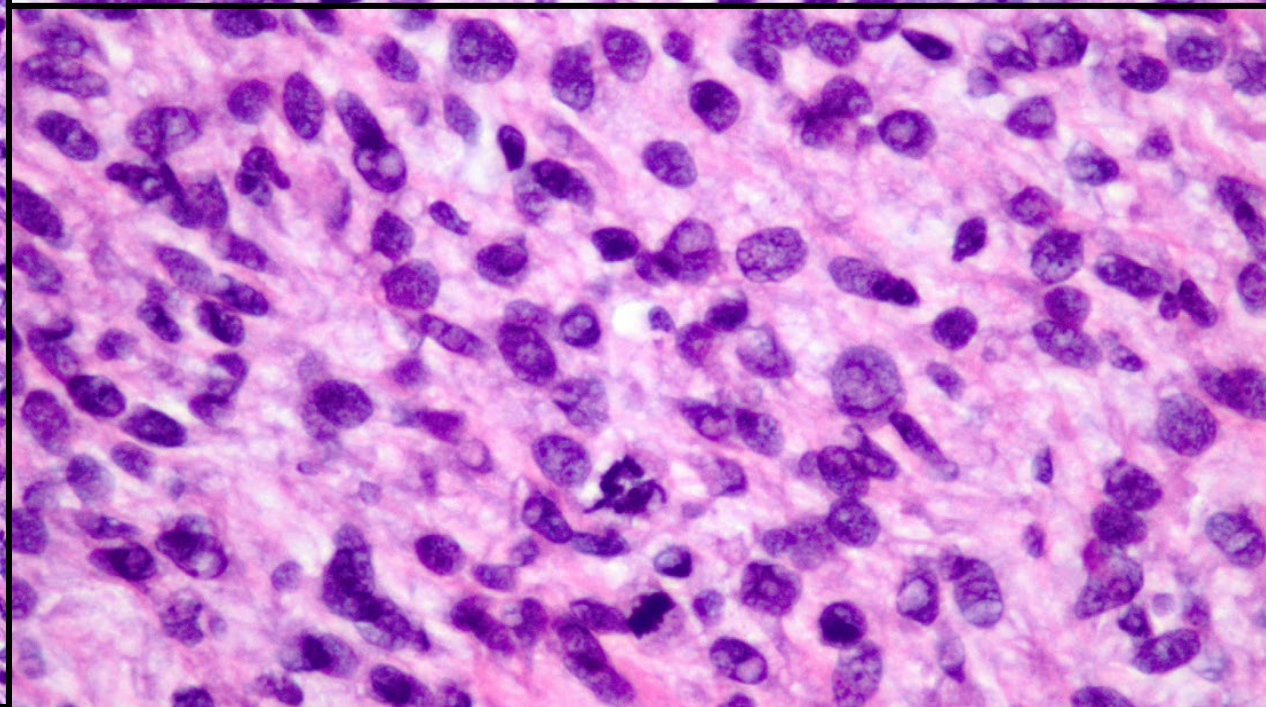
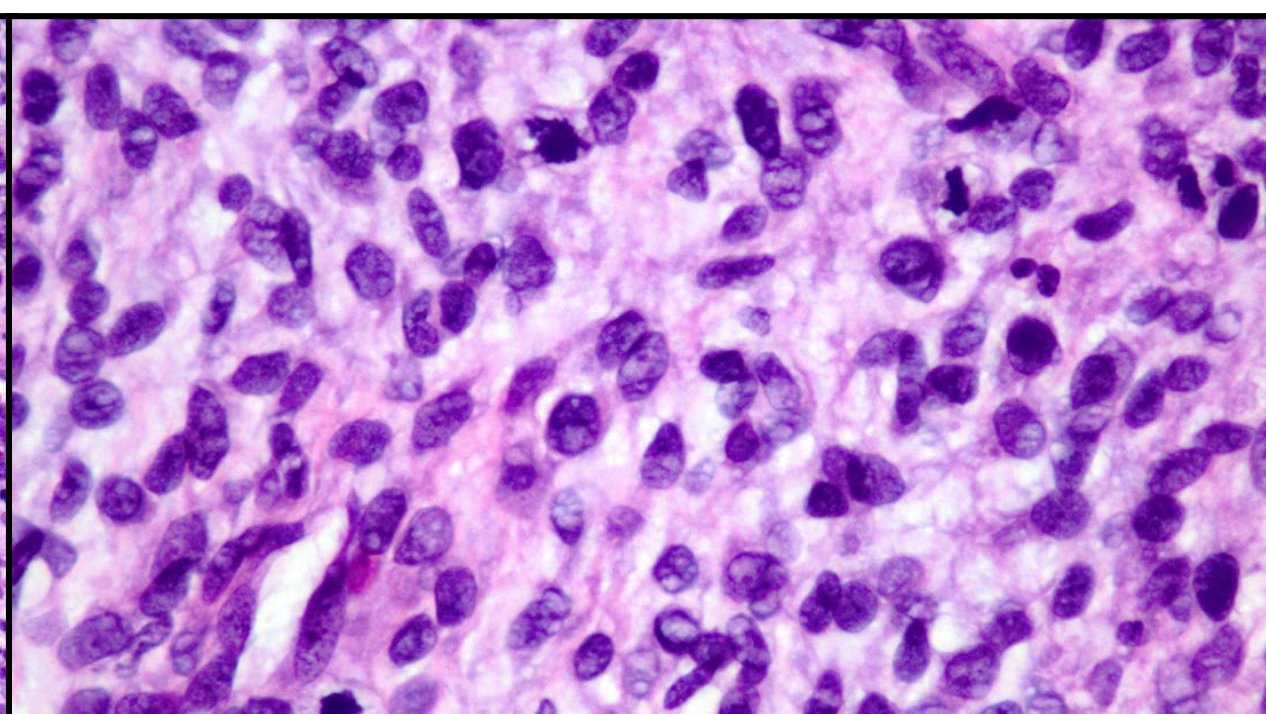
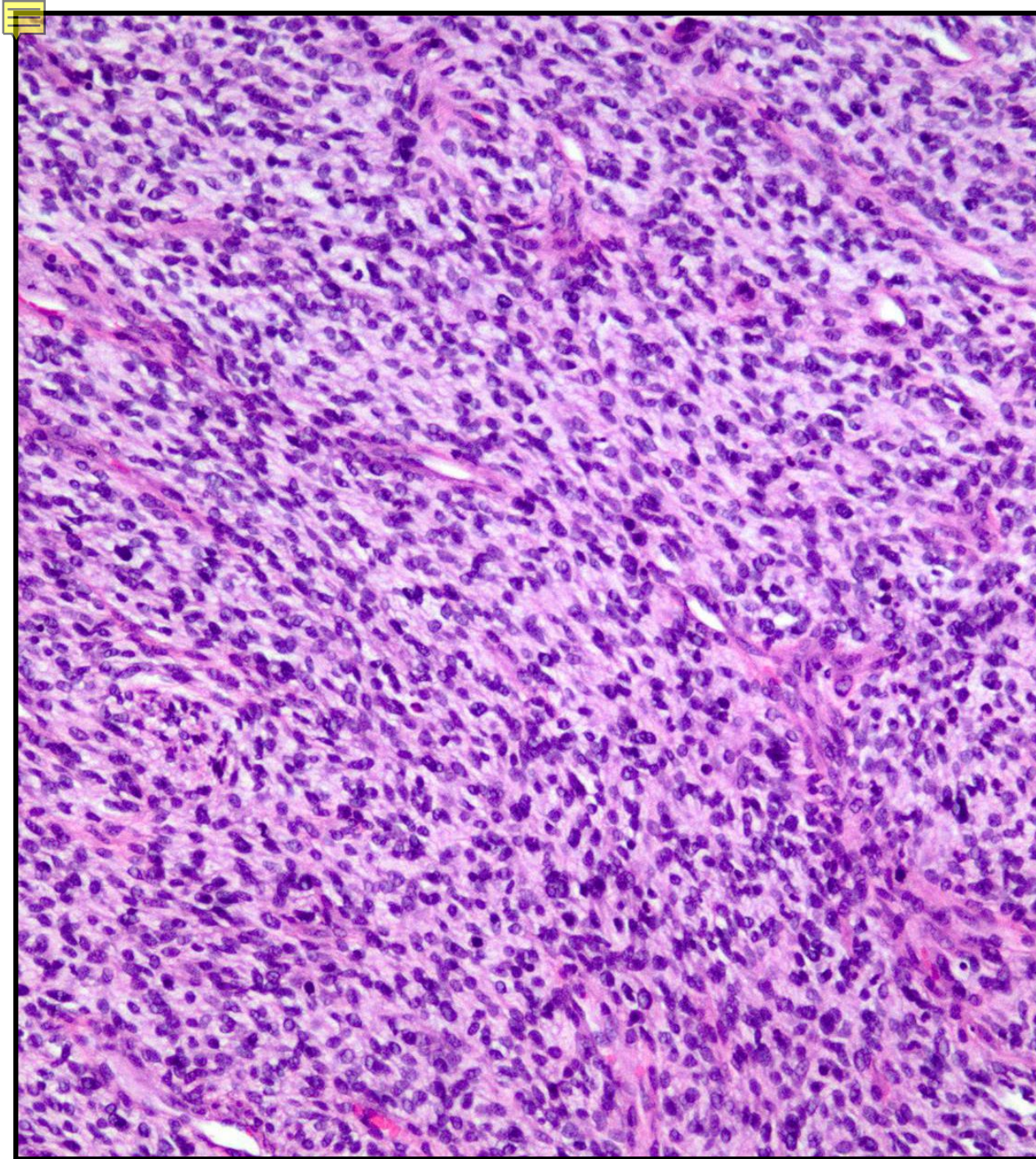
IHC:

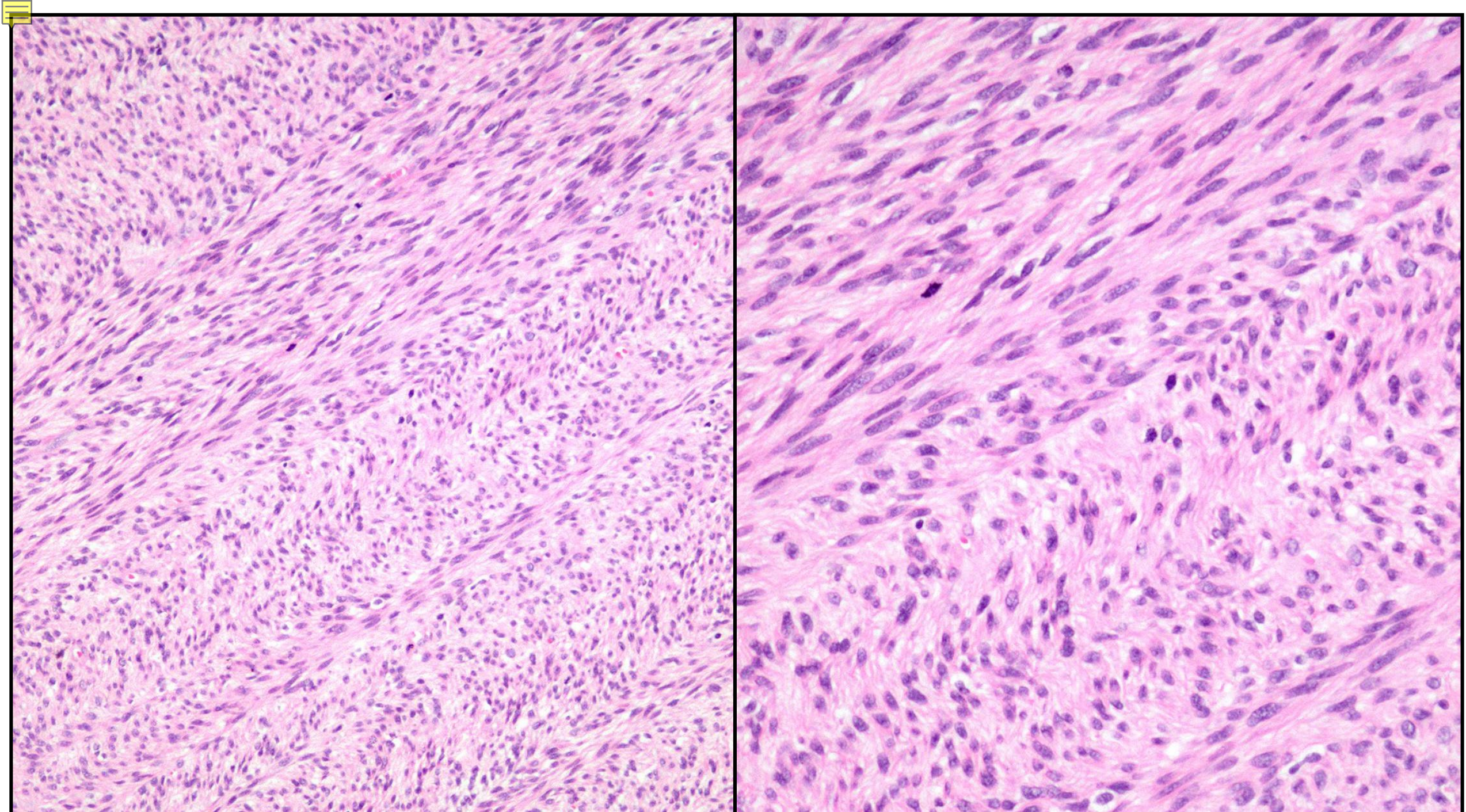
- CD10+
- ER +
- PR+
- Cyclin D1, - or + < 50% of the cells

High Grade ESS (*YWHAЕ-NUTM2* fusion)

IHC:

- Round cell component
 - CD10 –
 - ER – or focally + (< 5%)
 - PR – or focally + (<5%)
 - Cyclin D1 + ≥ 70% of the cells
- Spindle cell component
 - CD10 +
 - ER +
 - PR +
 - Cyclin D1 – or +, up to 50% (weak expression)





CLINICAL DATA: TSH BSO IN 40'S FOR LEIOMYOMAS, NOW WITH ELEVATED SOLITARY MASS, PRE-OP
DIAGNOSIS: PELVIC MASS

SPECIMEN: PELVIC MASS

FROZEN SECTION DIAGNOSIS:
LOW-GRADE SPINDLE CELL LESION; WITH GROSS DEGENERATIVE AREAS. (AO)

GROSS DESCRIPTION: BS:snc

Received in formalin labeled with the patient's name and "pelvic mass" is a 15.2 x 11.5 x 8.5 cm rubbery portion of tissue weight 947 g. The external surface is smooth, intact and exhibits a tan-pink-red heterogeneous appearance. The cut surfaces are tan and faintly trabeculated with a slippery and whorled/striated appearance. There are areas of tan-yellow softening (consistent with necrosis). Areas of necrosis occupy less than 10% of the overall mass. Representative sections are submitted for frozen section diagnosis. The frozen section remnant tissue is entirely submitted in cassette 1. Additional representative sections, including the areas of necrosis, are submitted in cassettes 2-10.

MICROSCOPIC DIAGNOSIS:

PELVIC MASS RESECTION: ENDOMETRIAL STROMAL SARCOMA, MEASURING 15.2 X 11.5 X 8.5 CM (SEE NOTE).

NOTE: The mass is well circumscribed and composed of a bland spindle cell proliferation with mild cytologic atypia and foci of necrosis and hemorrhage. Many mitotic figures (approximately greater than 40 per 10 HPF) with a high proliferation index on MIB-1 immunohistochemical stains are identified. No significant nuclear pleomorphism or anaplasia is seen. The immunohistochemical stain results are as follows:

ADDENDUM:

The patient has been seen in consultation at [redacted] University Medical Center for reported recurrent pelvic mass. The histologic sections and representative paraffin block of the pelvic mass ([redacted]) have been further examined by Dr. [redacted] at [redacted] who rendered the following diagnosis with further comments:

"MOST CONSISTENT WITH MALIGNANT SOLITARY FIBROUS TUMOR. (SEE COMMENT).

COMMENT: Histologic sections show sheets of spindle cells arranged in a fascicular, woven architecture. The cells are elongated with ovoid nuclei, nuclear enlargement and delicate indistinct cytoplasm. We count up to 13 mitotic figures per 10 high power fields. Necrosis is abundant. The provided immunohistochemical stains show patchy positivity with CD10 and ER. They are negative for AE1/AE3, S100, desmin, SMA, myogenin, CD117, HMB-45 and PR. MIB1 shows an elevated proliferation index.

Immunohistochemistry prepared at [redacted] on sections from the provided paraffin tissue block show the lesional cells are negative for desmin, caldesmon, CD10 and HMB-45. STAT6 demonstrates moderate to strong staining in most nuclei, providing support for solitary fibrous tumor. Positive STAT6 may also be seen in leiomyosarcoma, undifferentiated pleomorphic sarcoma, dedifferentiated liposarcoma, GIST, MPNST and synovial sarcoma; however we do not have any findings to support those entities.

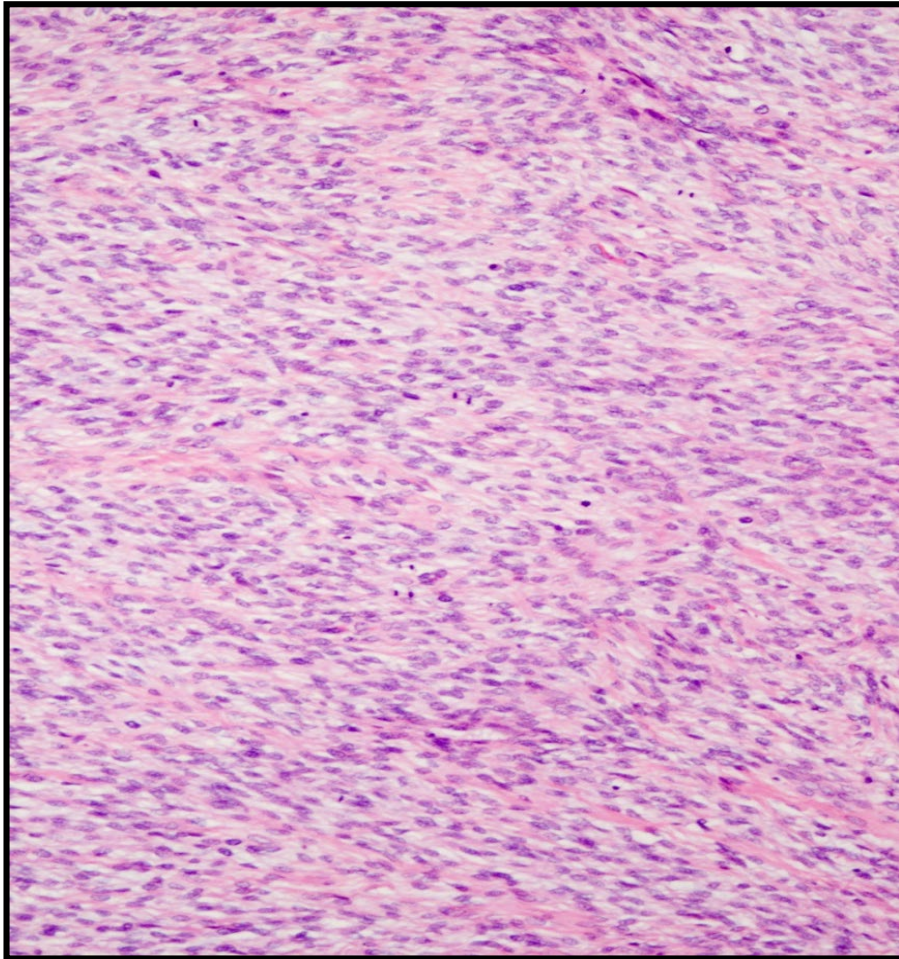
We consider this lesion a malignant solitary fibrous tumor, which recur and metastasize. This assessment is based on increased mitotic figures greater than 4 mitotic figures per 10 HPFs, tumor necrosis, infiltrative margins and large size >10 cm). Positive surgical margin and high mitotic rate are the

STAIN	RESULT
CD10	Positive
Estrogen Receptor	Positive
Progesterone Receptor	Negative
MIB-1	Positive, high proliferation index
Desmin	Negative
Muscle specific actin	Negative
Myogenin	Negative
CD117 (c-kit)	Negative
S-100	Negative
SMB45	Negative
Keratin AE1/AE3	Negative

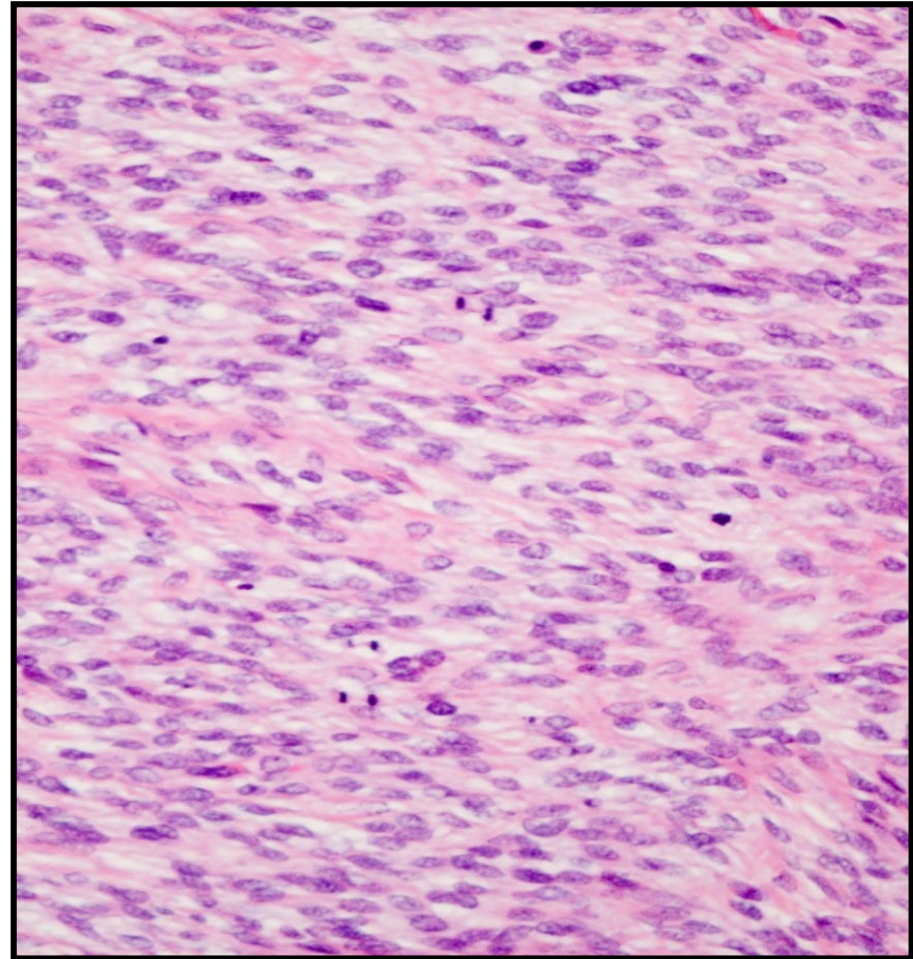
Immunohistochemical stain with beta-Catenin is pending and will be reported in an addendum.

High Grade ESS (*ZC3H7B-BCOR* Gene Fusion) with Abundant Myxoid Stroma – Mimicking Myxoid Leiomyosarcoma

Spindle Cells in Fascicles

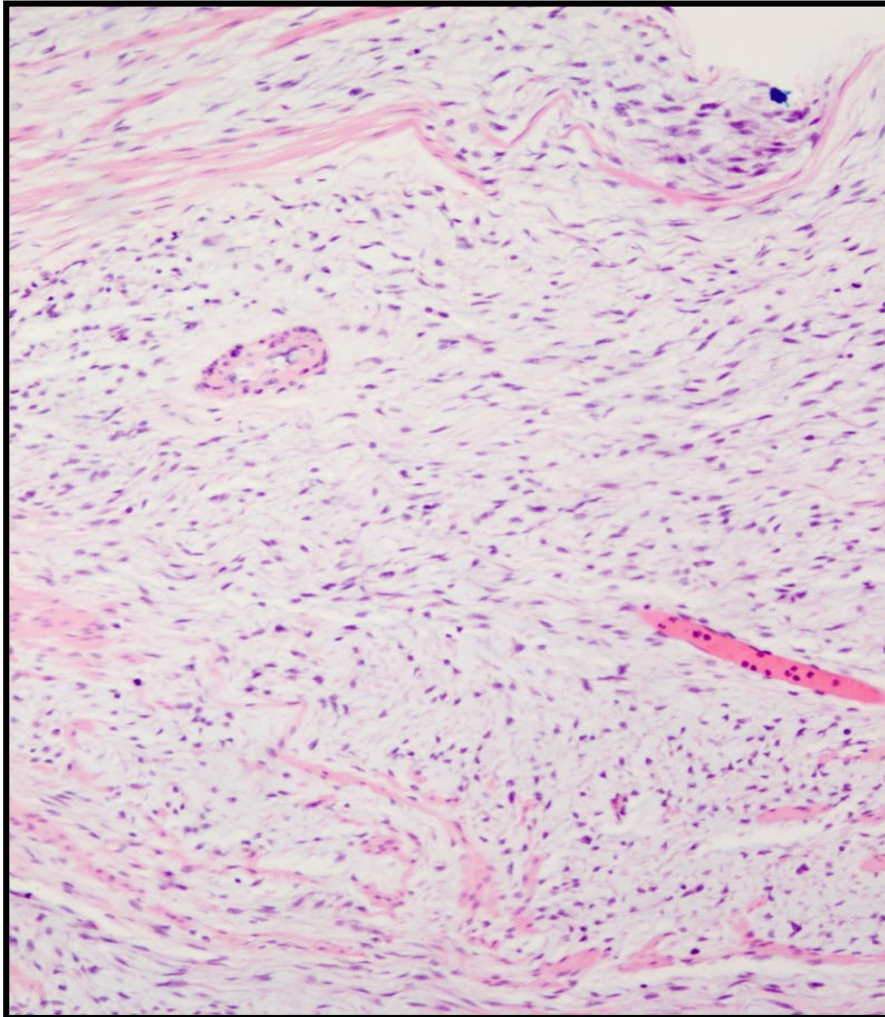


Numerous Mitotic Figures

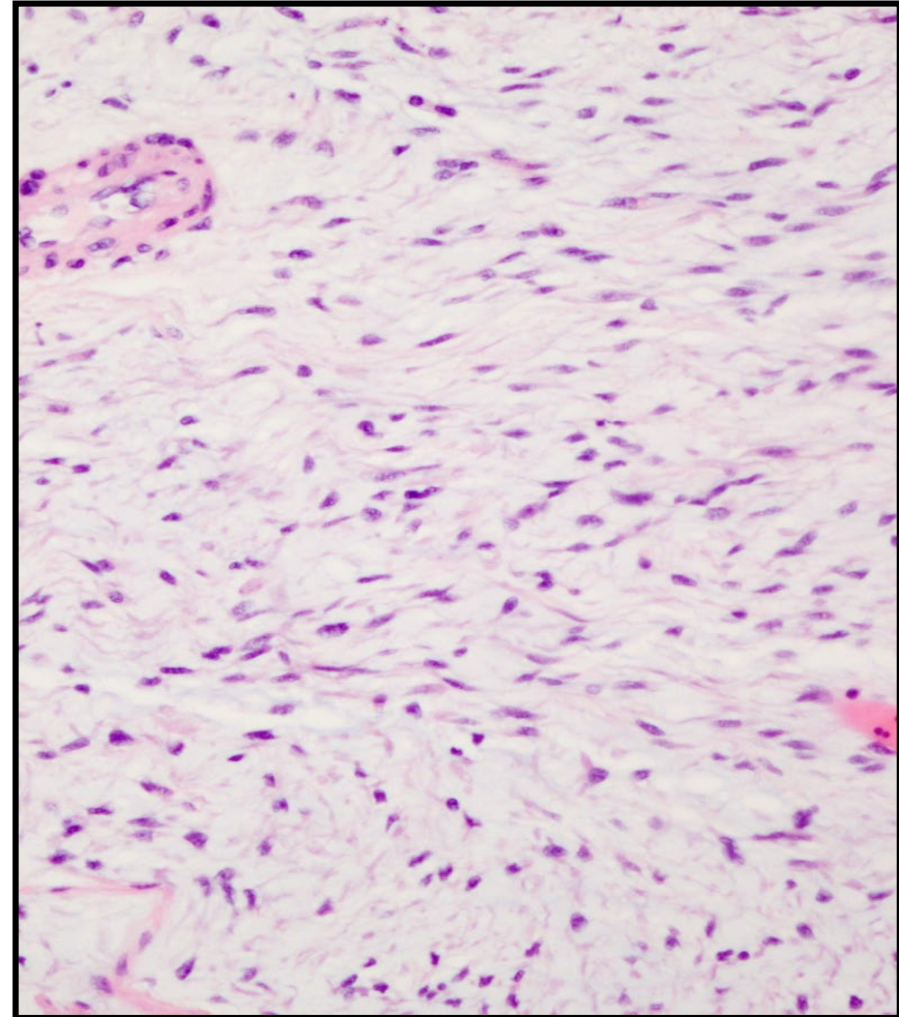


High Grade ESS (*ZC3H7B-BCOR* Gene Fusion) with Abundant Myxoid Stroma – Mimicking Myxoid Leiomyosarcoma

Spindle cells in myxoid stroma

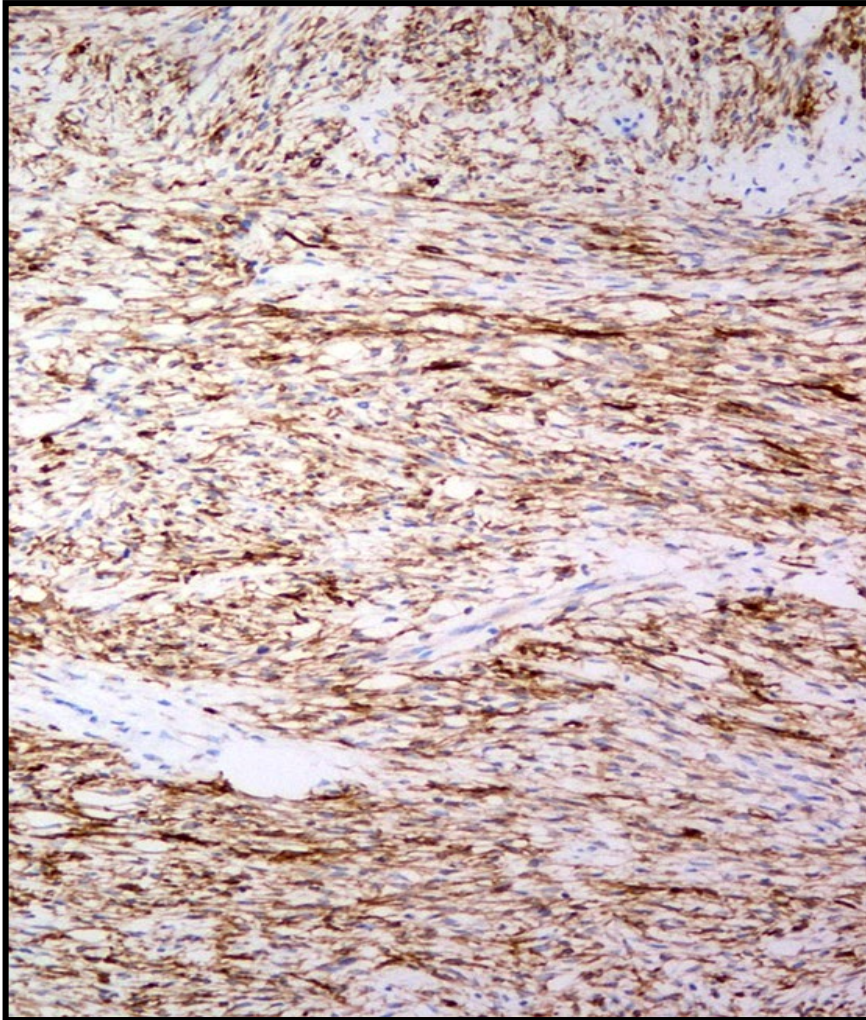


Spindle cells in myxoid stroma

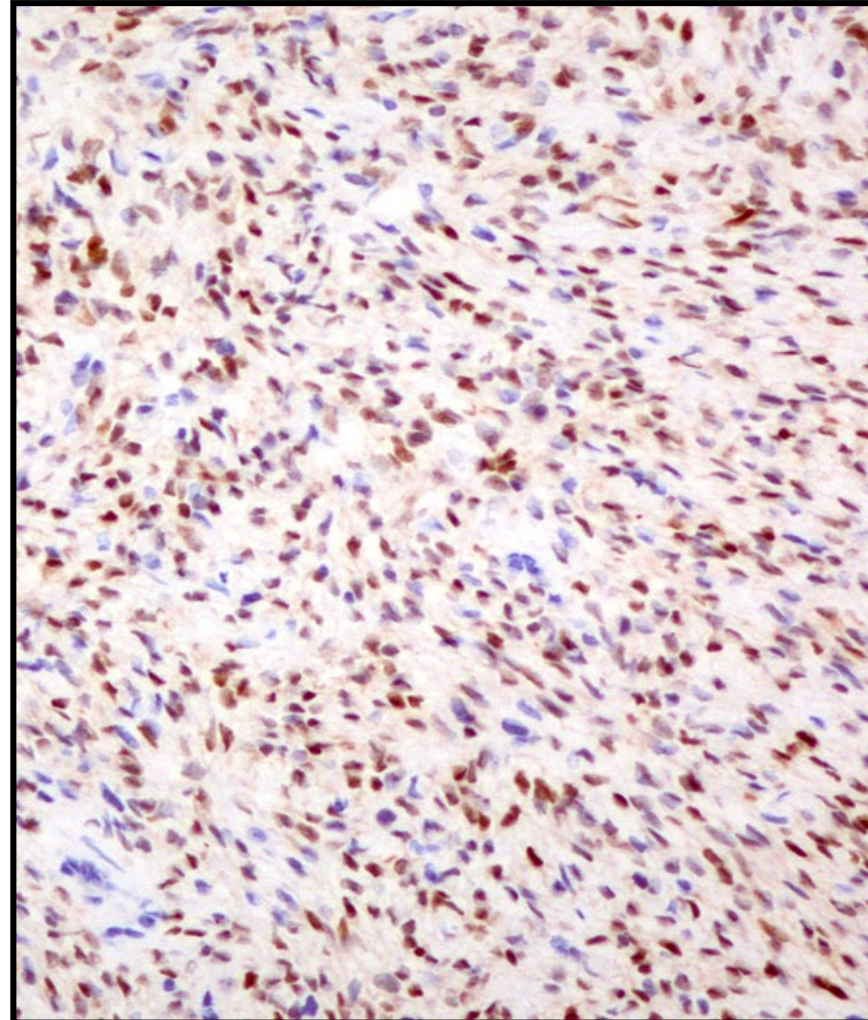


High Grade ESS (*ZC3H7B-BCOR* Gene Fusion) with Abundant Myxoid Stroma – Mimicking Myxoid Leiomyosarcoma

CD10 +



Cyclin D1 +

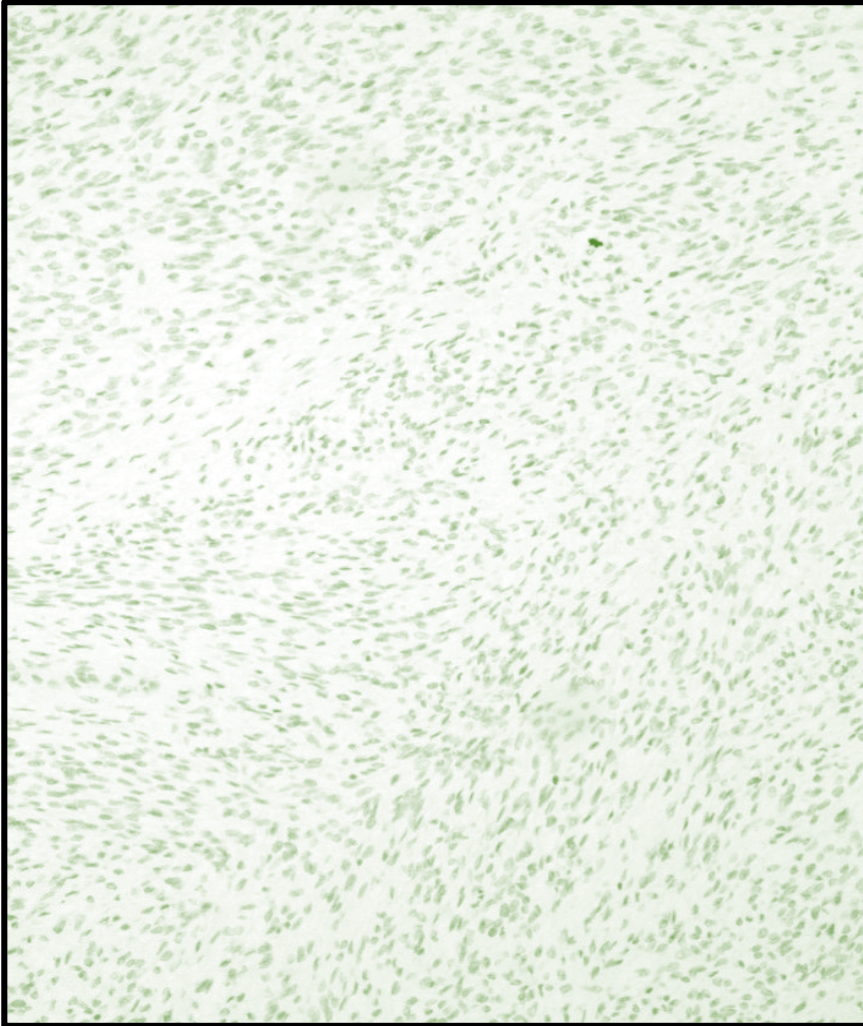


ER/PR: -/+ (F)

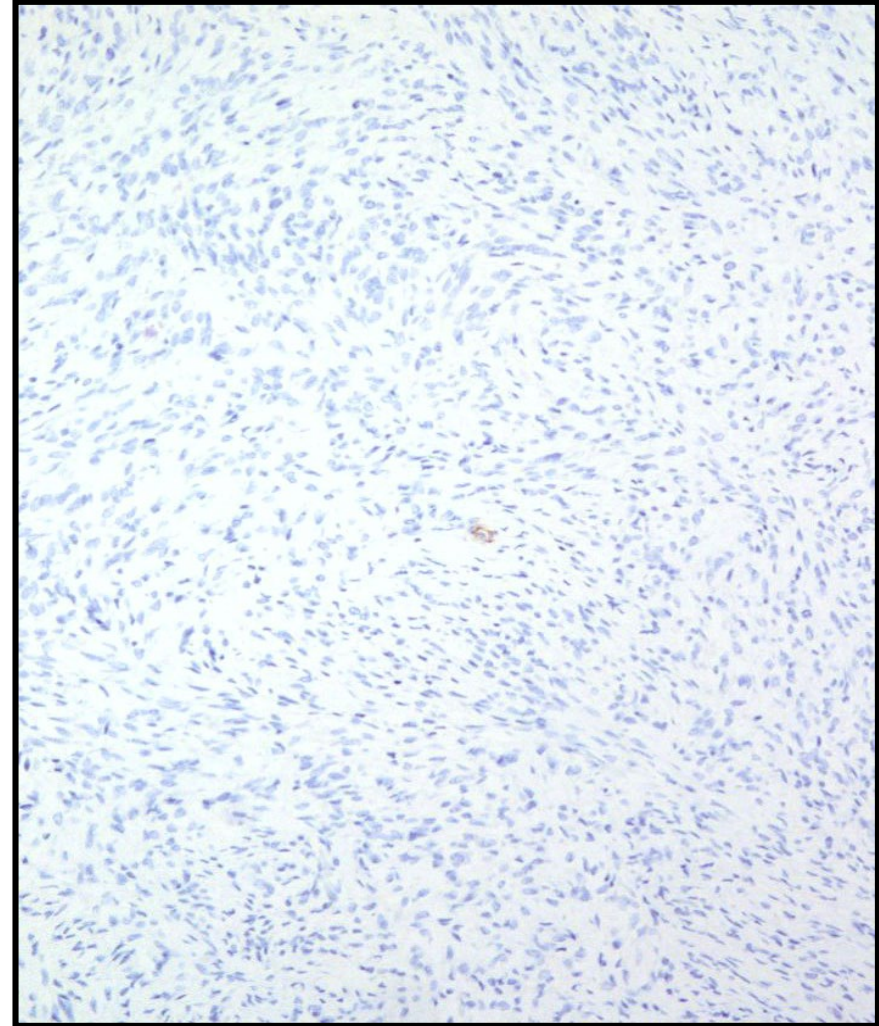
BCOR: variable

High Grade ESS (*ZC3H7B-BCOR* Gene Fusion) with Abundant Myxoid Stroma –Mimicking Myxoid Leiomyosarcoma

Desmin -

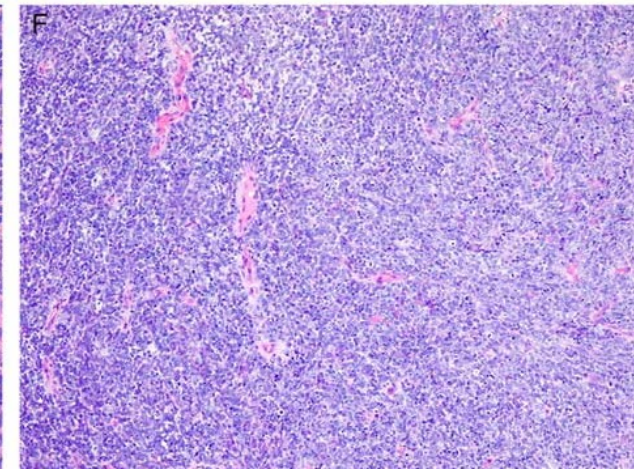
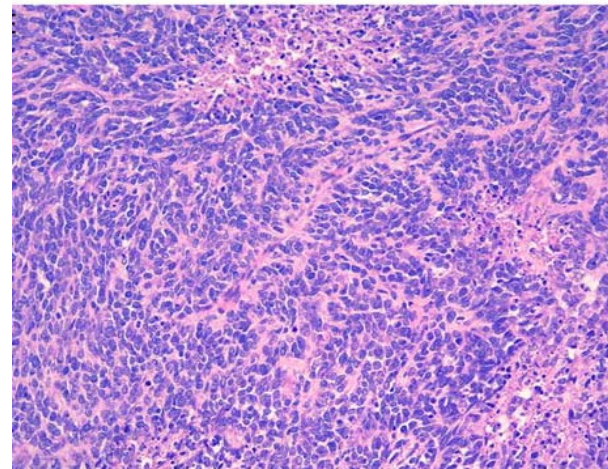
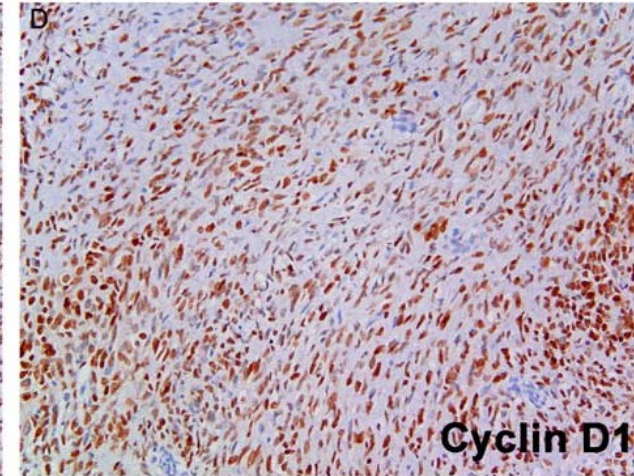
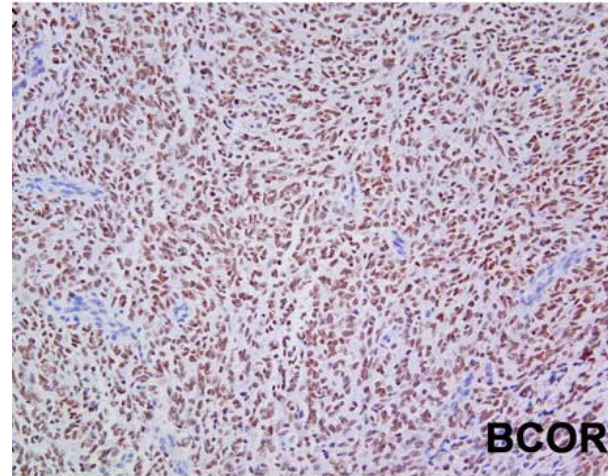
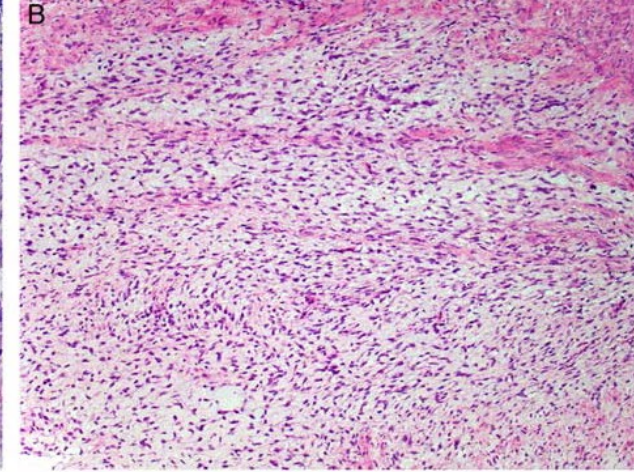
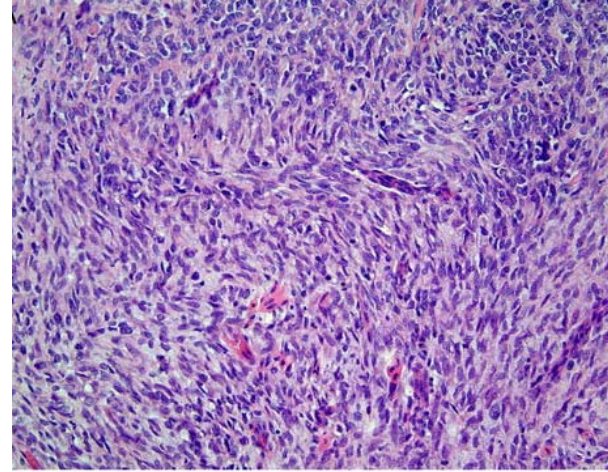


SMMS-1 - and Caldesmon +/- F



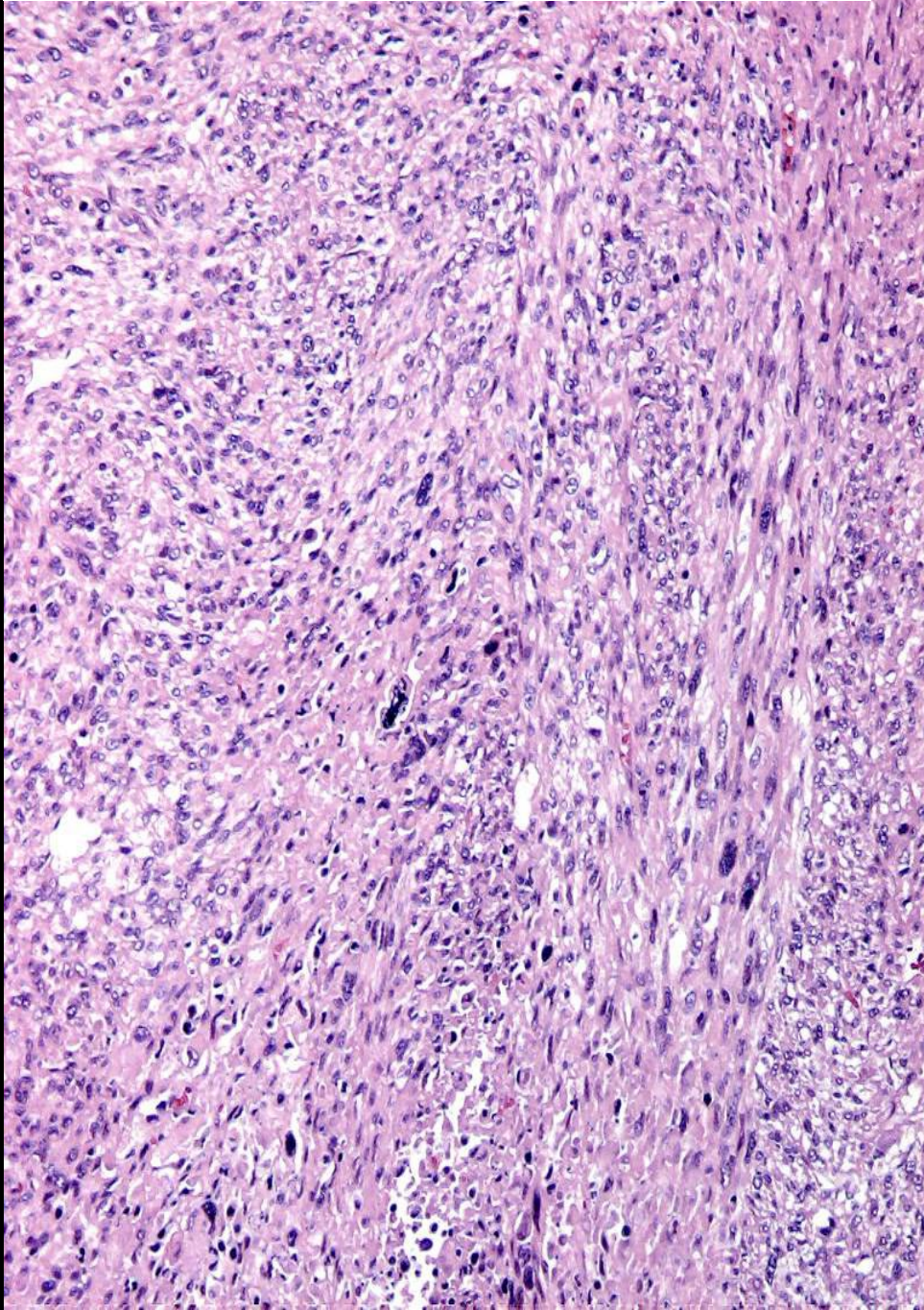
High Grade ESS with *BCOR* Internal Tandem Duplication (*BCOR* ITD)

- IHC:
 - CD10 + (F/D)
 - ER/PR -
 - *BCOR* +, D
 - Cyclin D1 +, D
 - Desmin -/+
 - Caldesmon -

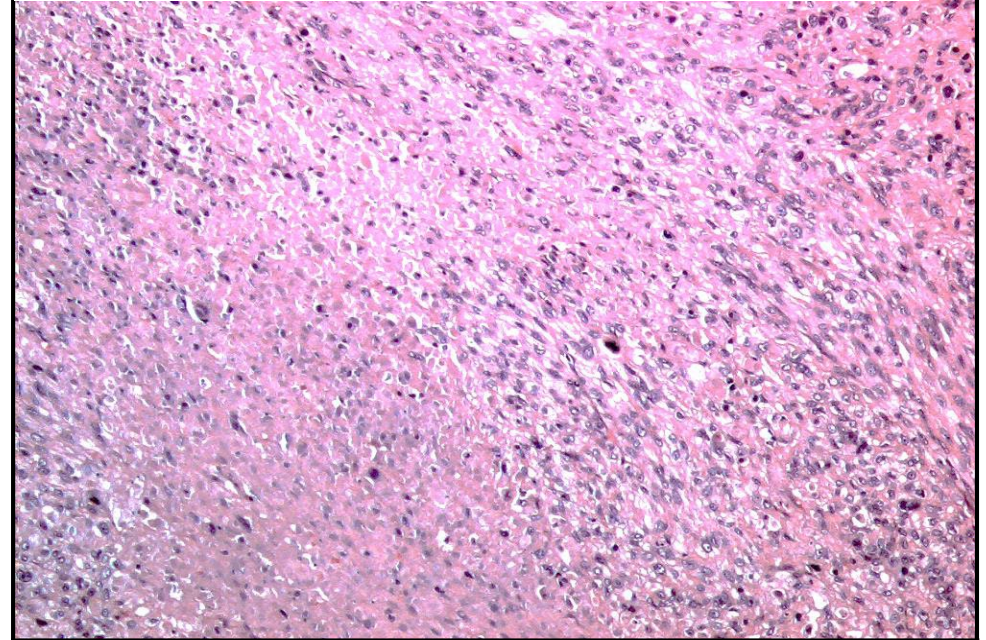


Leiomyosarcoma

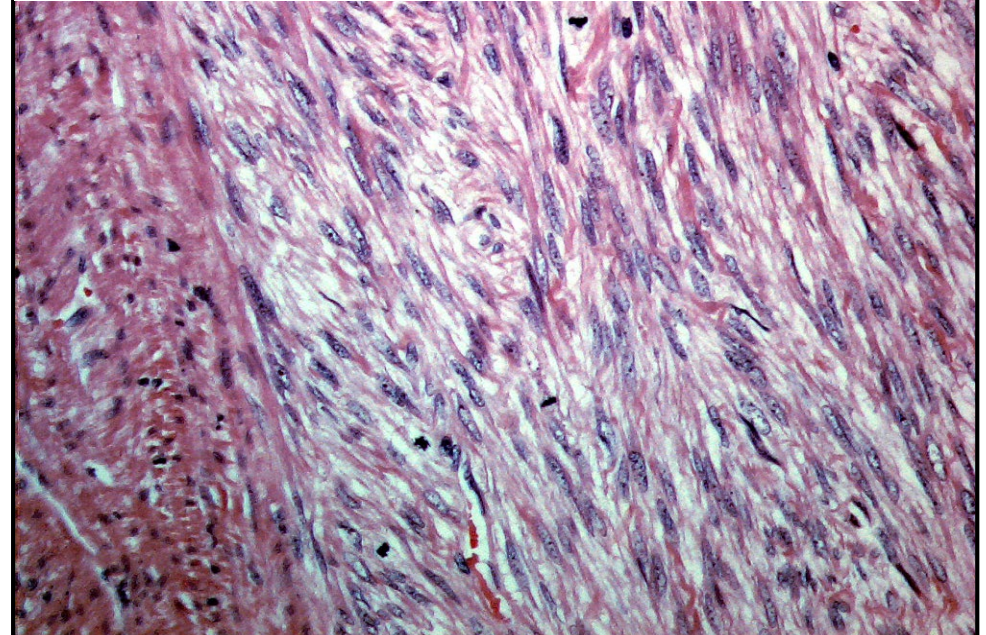
Diffuse significant cytologic atypia



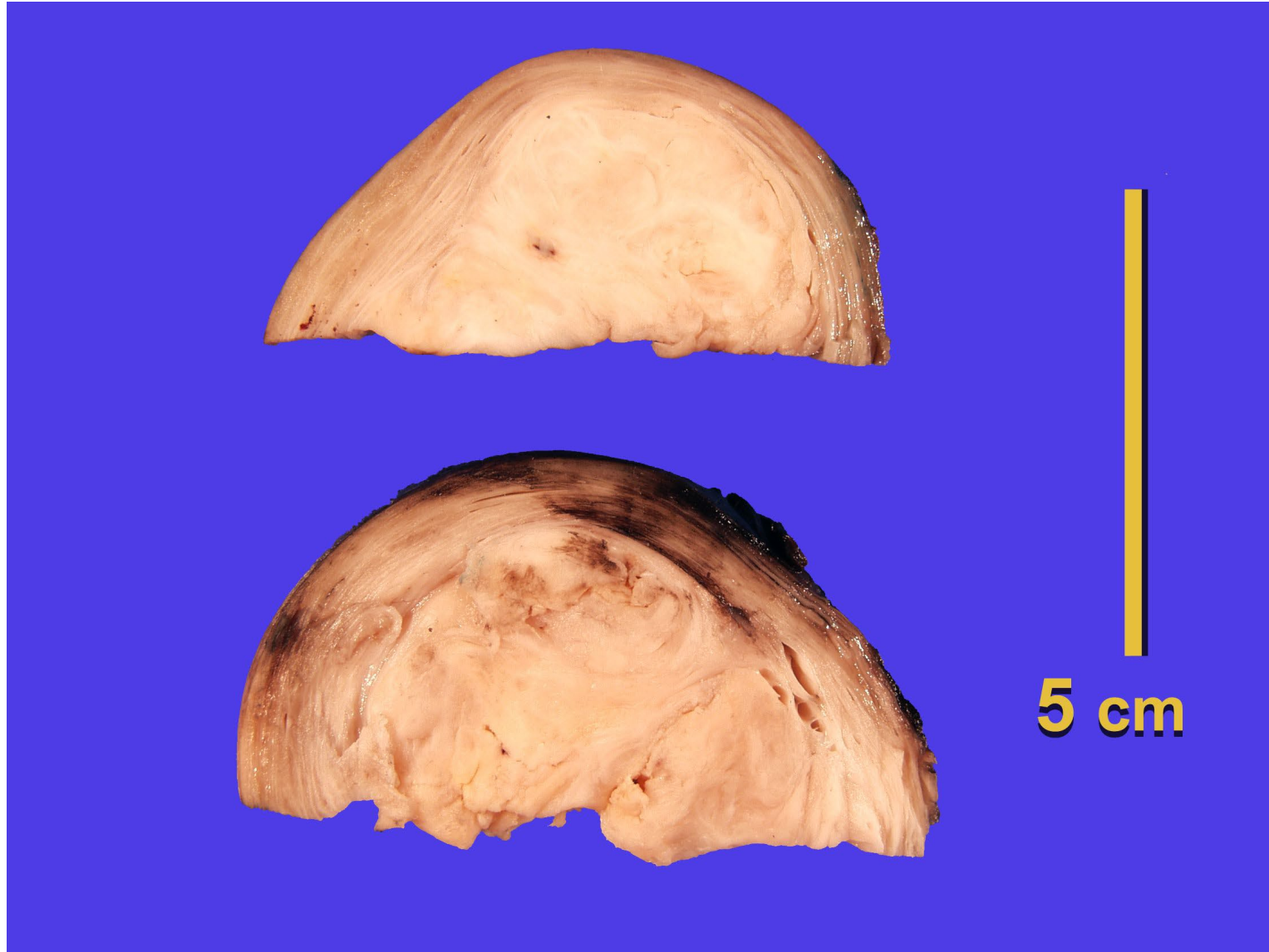
Coagulative tumor cell necrosis



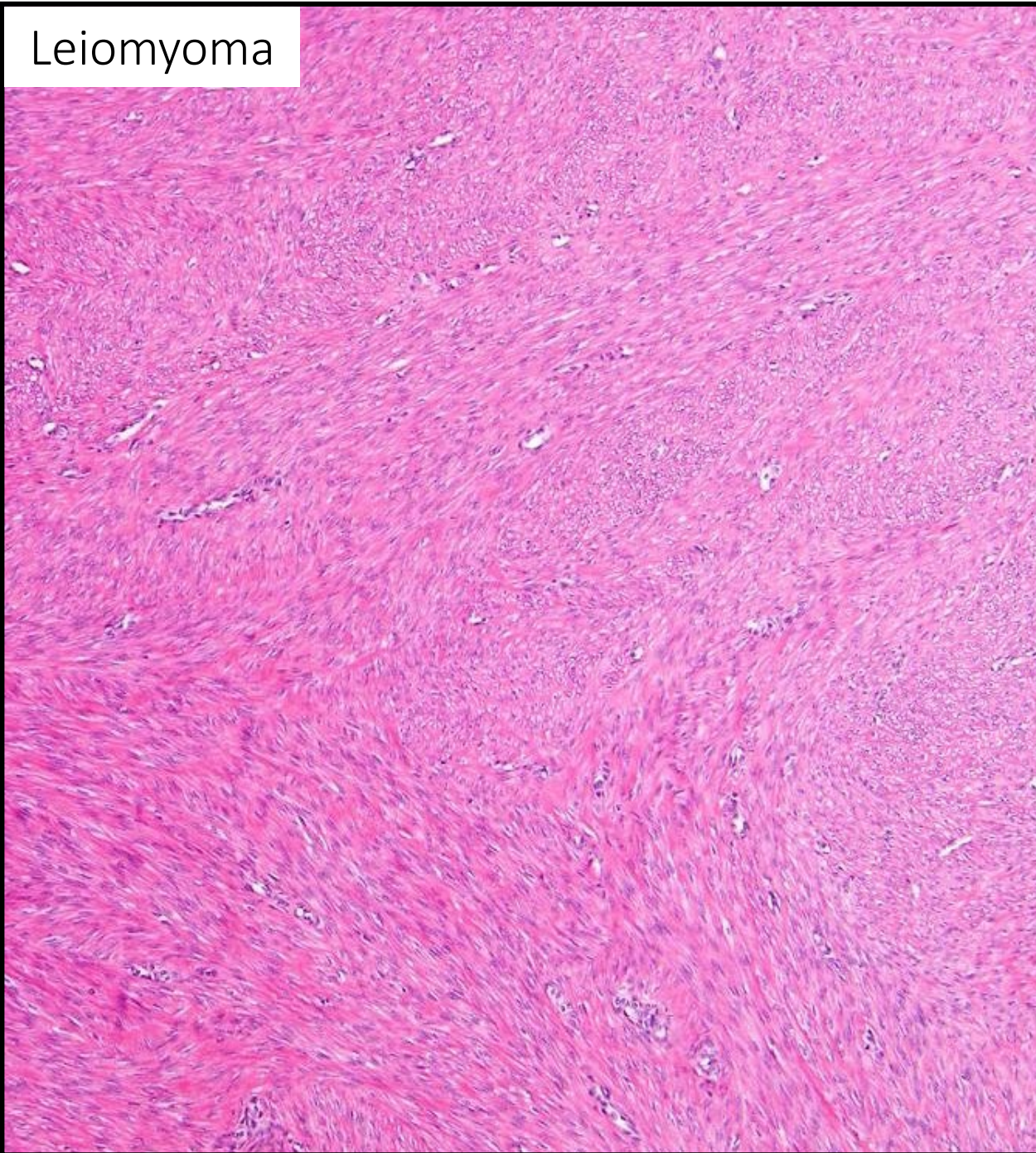
Mitotic index ≥ 10 mitoses per 10 HPFs



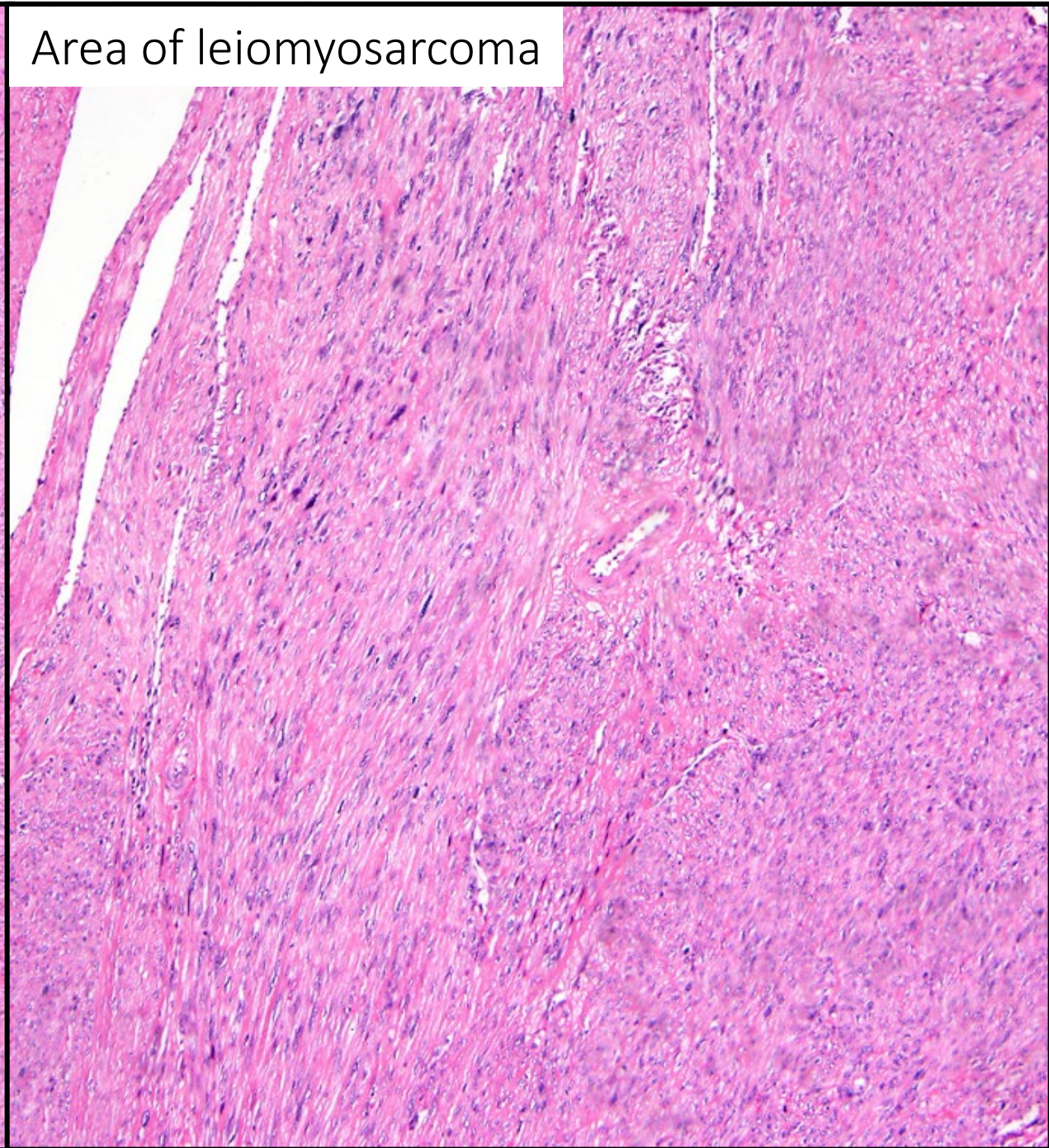
Focal Leiomyosarcoma in a Leiomyoma

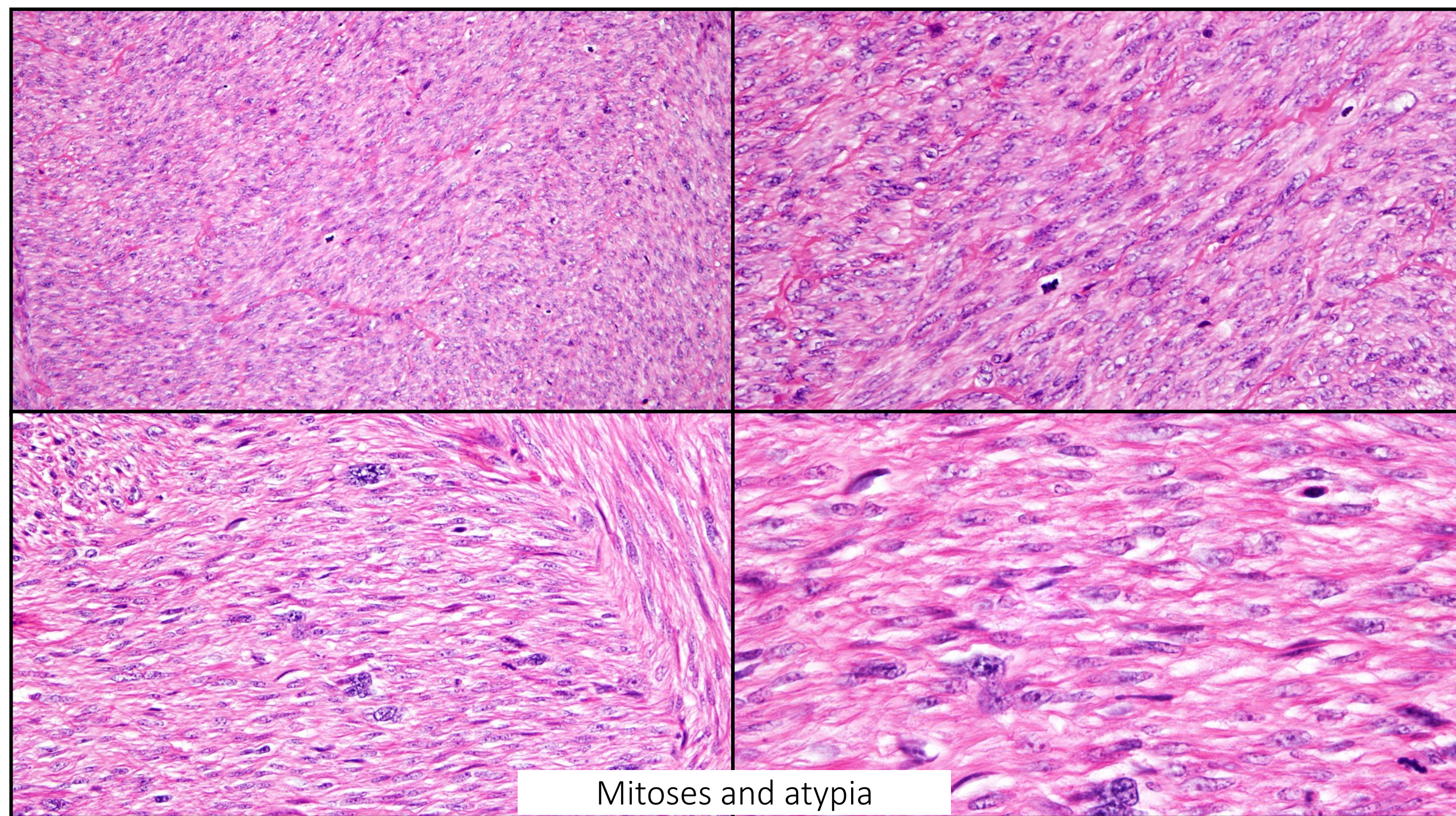


Leiomyoma



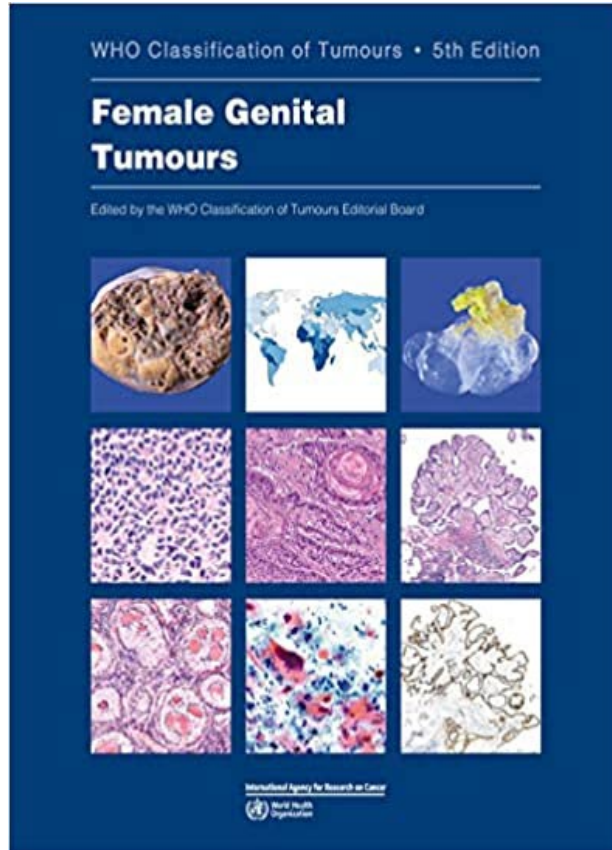
Area of leiomyosarcoma





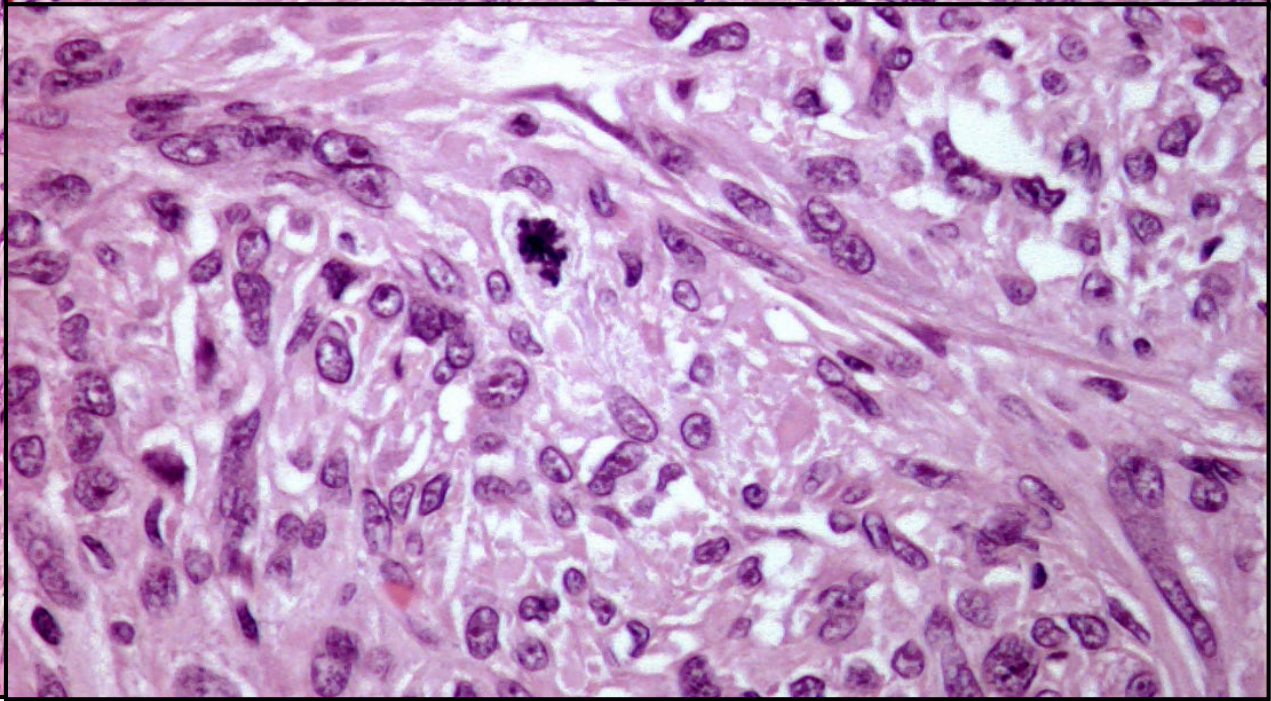
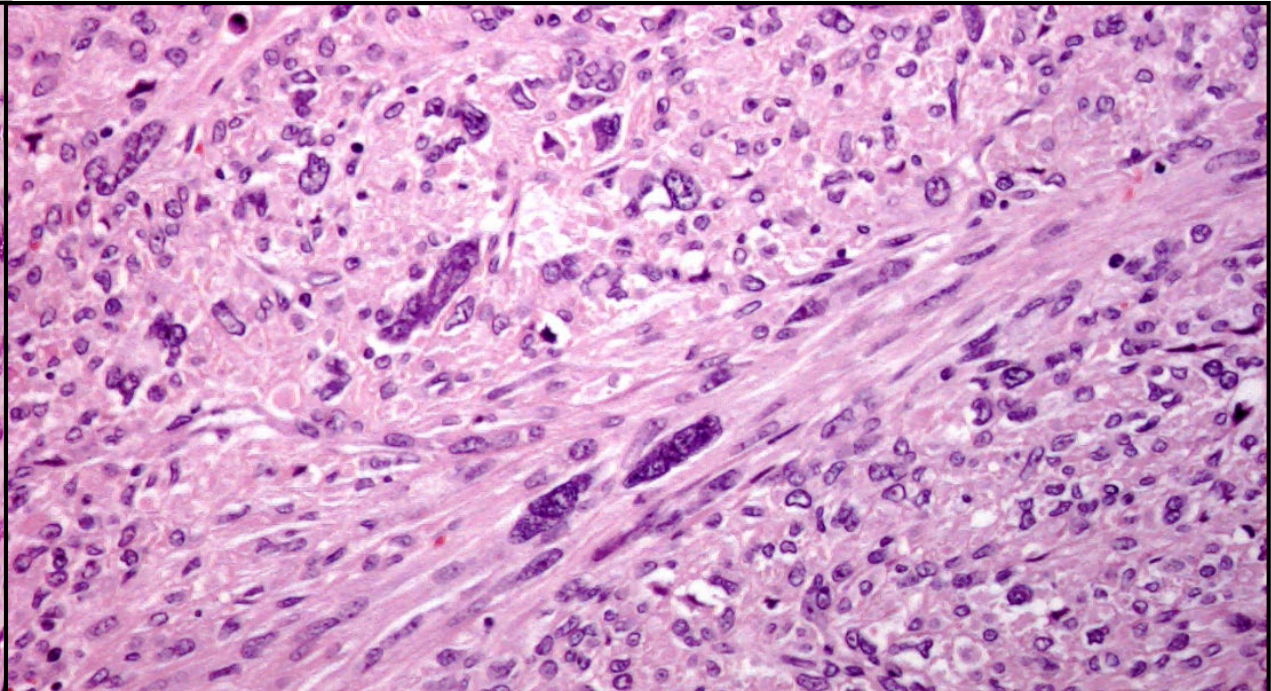
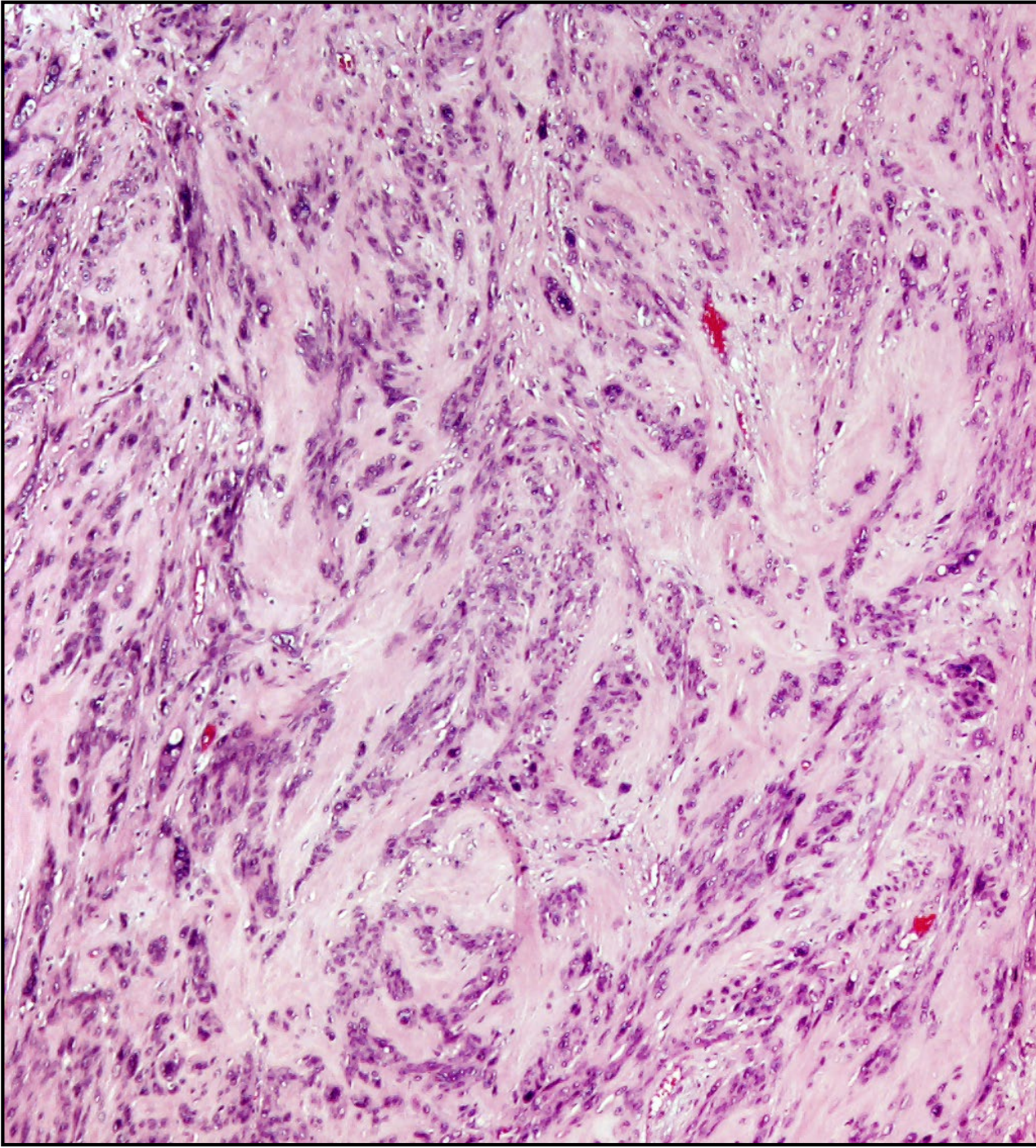
Mitoses and atypia

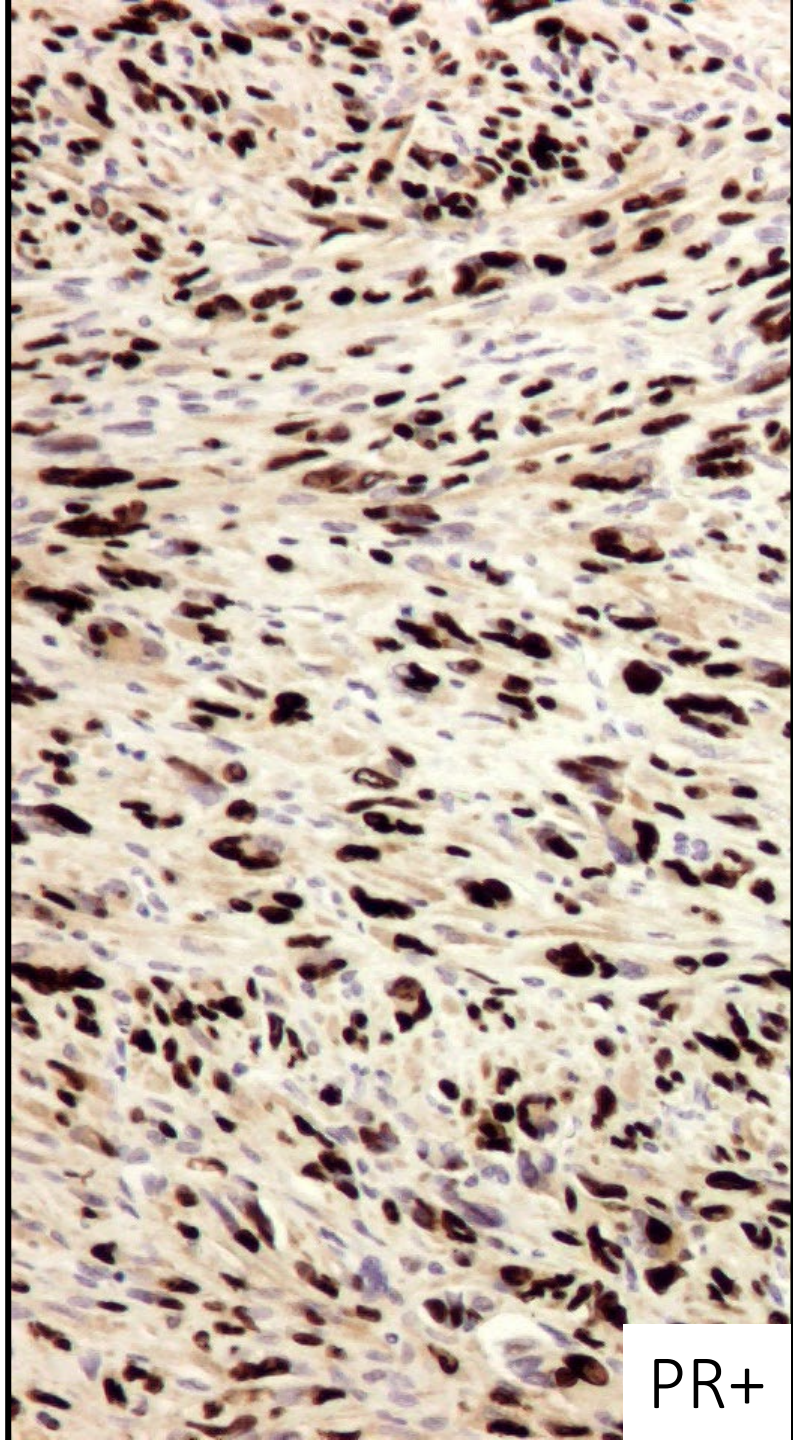
Leiomyoma with Bizarre Nuclei (Symplastic Leiomyoma)



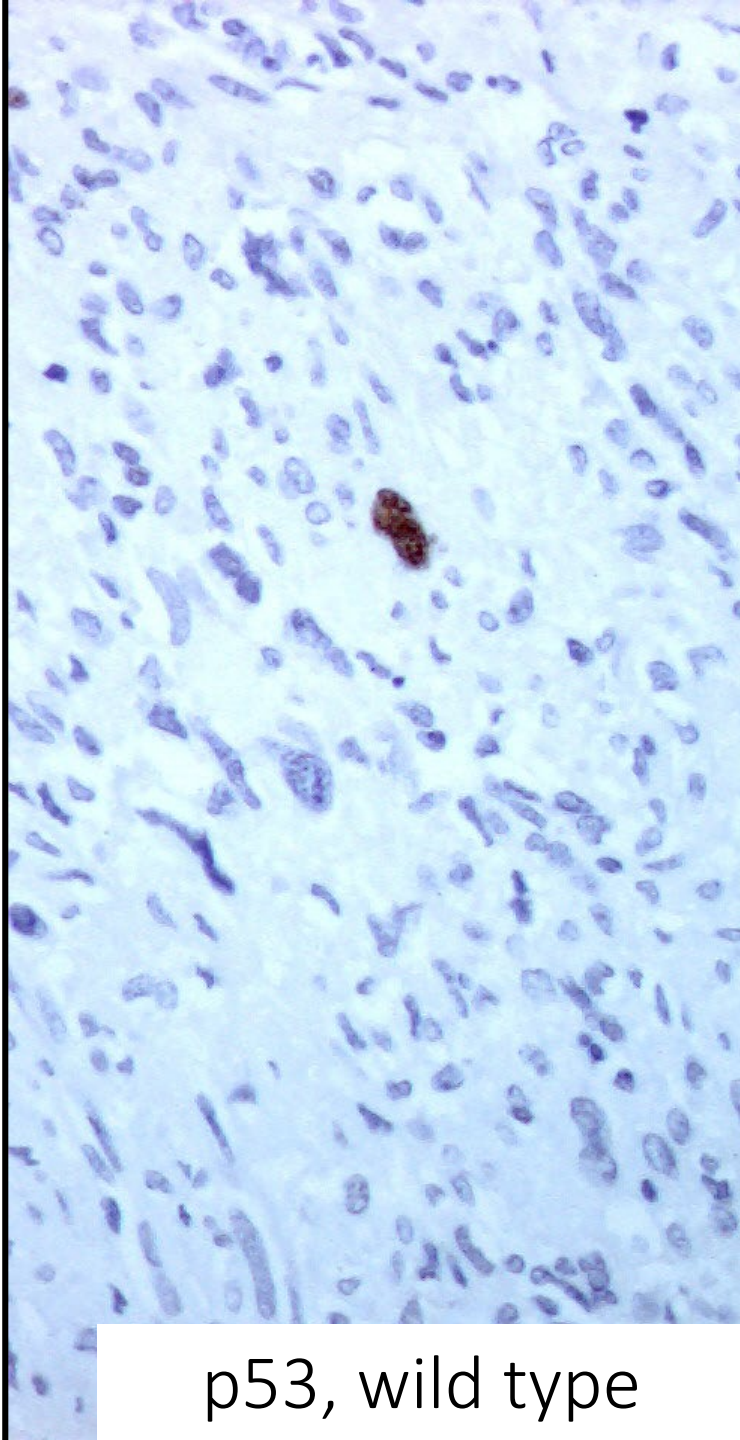
2020

- Background of typical leiomyoma
- Bizarre cells in focal, multifocal or diffuse distribution
- Bizarre cells
 - Mononucleated or multinucleated
 - Smudged chromatin
 - Intranuclear cytoplasmic pseudoinclusions variably present
 - Low mitotic activity (< 5 mitoses per 10 HPFs)
 - Numerous karyorrhectic nuclei

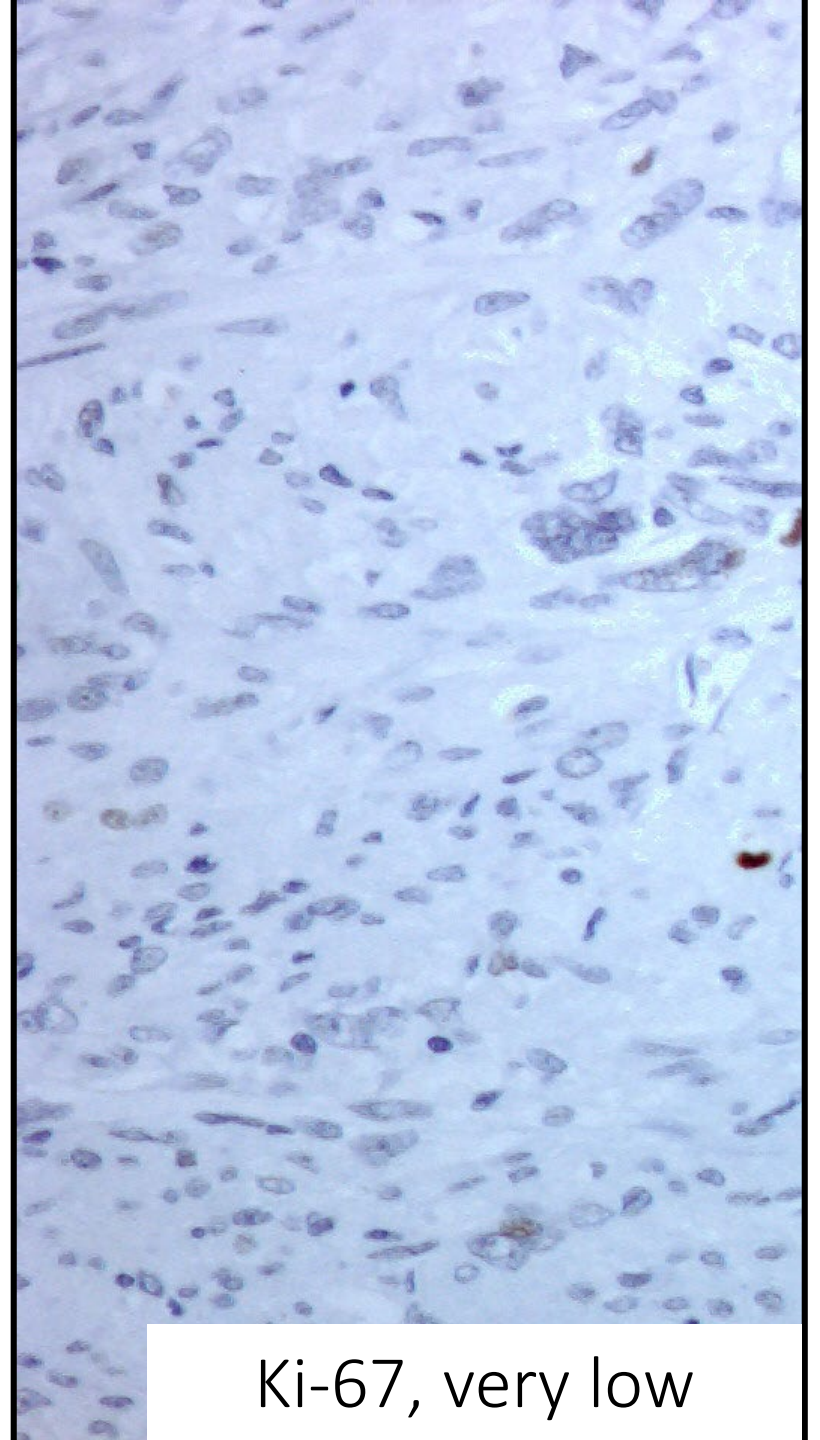




PR+



p53, wild type



Ki-67, very low

Atypical Leiomyomas of the Uterus *A Clinicopathologic Study of 51 Cases*



*Amy Ly, MD, Anne M. Mills, MD, Jesse K. McKenney, MD, Bonnie L. Balzer, MD, PhD,
Richard L. Kempson, MD, Michael R. Hendrickson, MD, and Teri A. Longacre, MD*

(Am J Surg Pathol 2013;37:643–649)

Low rate of extrauterine, intra-abdominal recurrence
($< 2\%$) and negligible risk for distant metastasis

Uterine Leiomyomas With Bizarre Nuclei *A Clinicopathologic Study of 59 Cases*



Sabrina Croce, MD, Robert H. Young, MD,† and Esther Oliva, MD†*

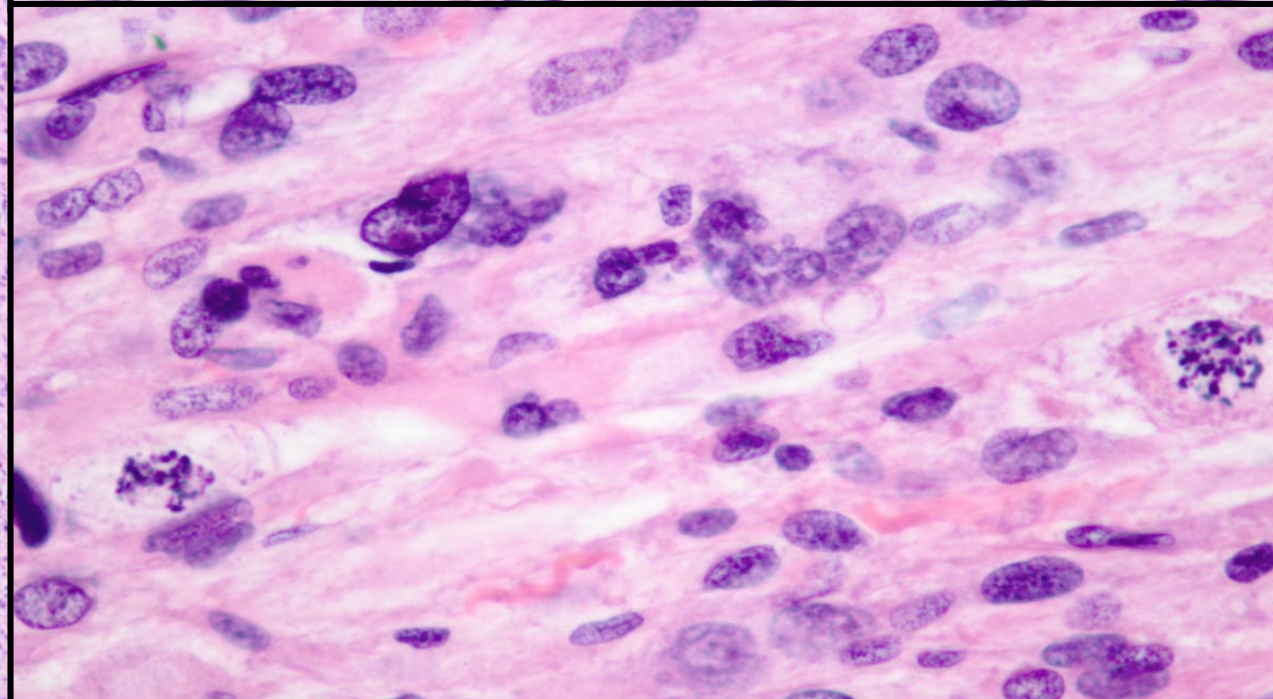
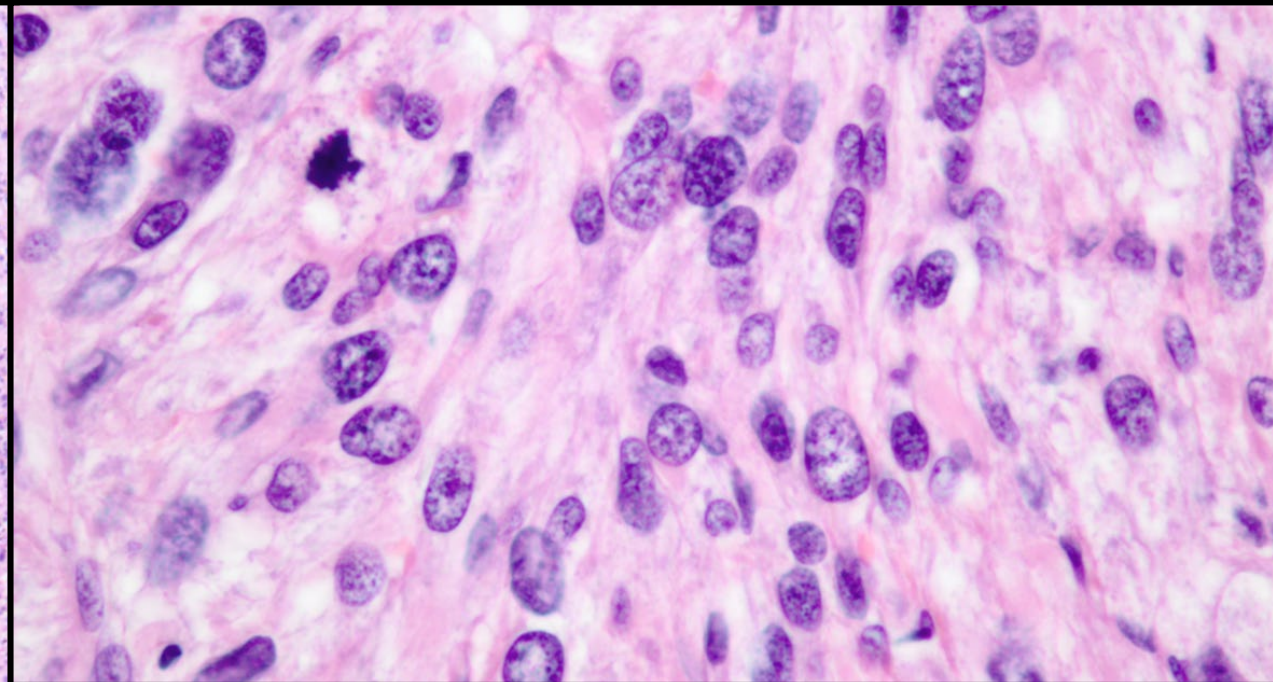
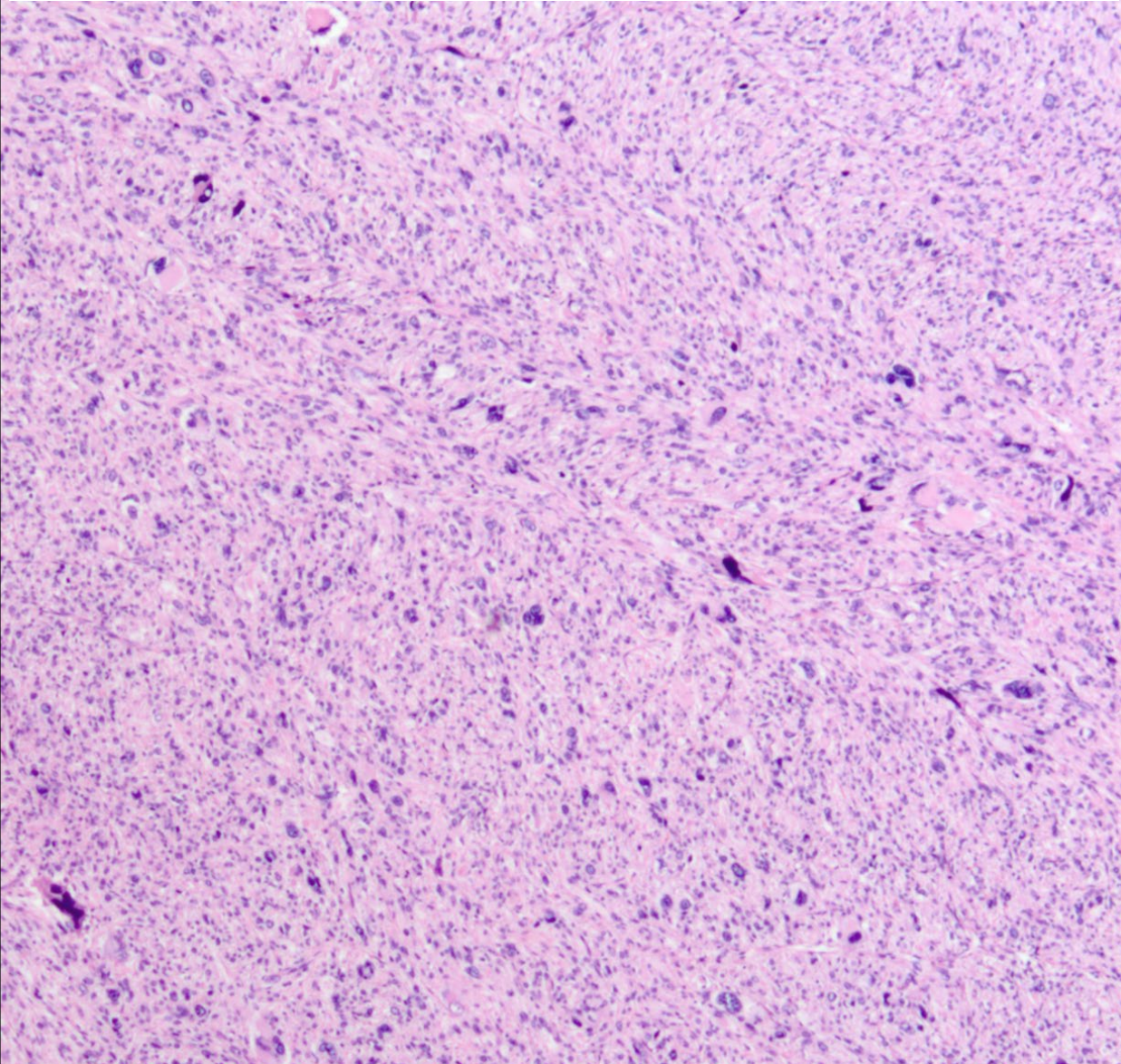
(Am J Surg Pathol 2014;38:1330–1339)

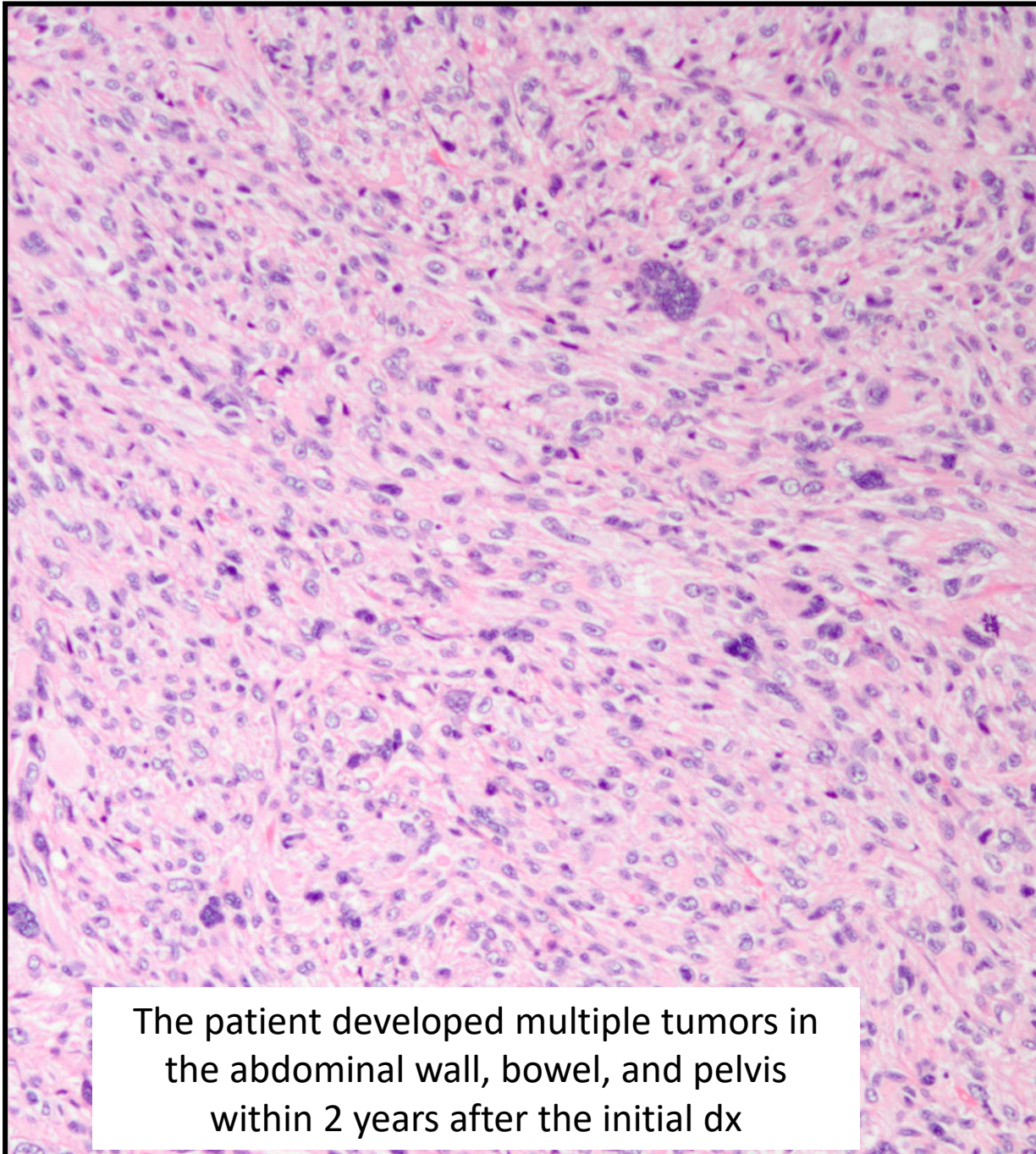
No recurrences

Be Careful with the Diagnosis of Atypical Leiomyoma with a Low Risk of Recurrence, A Cautionary Tale

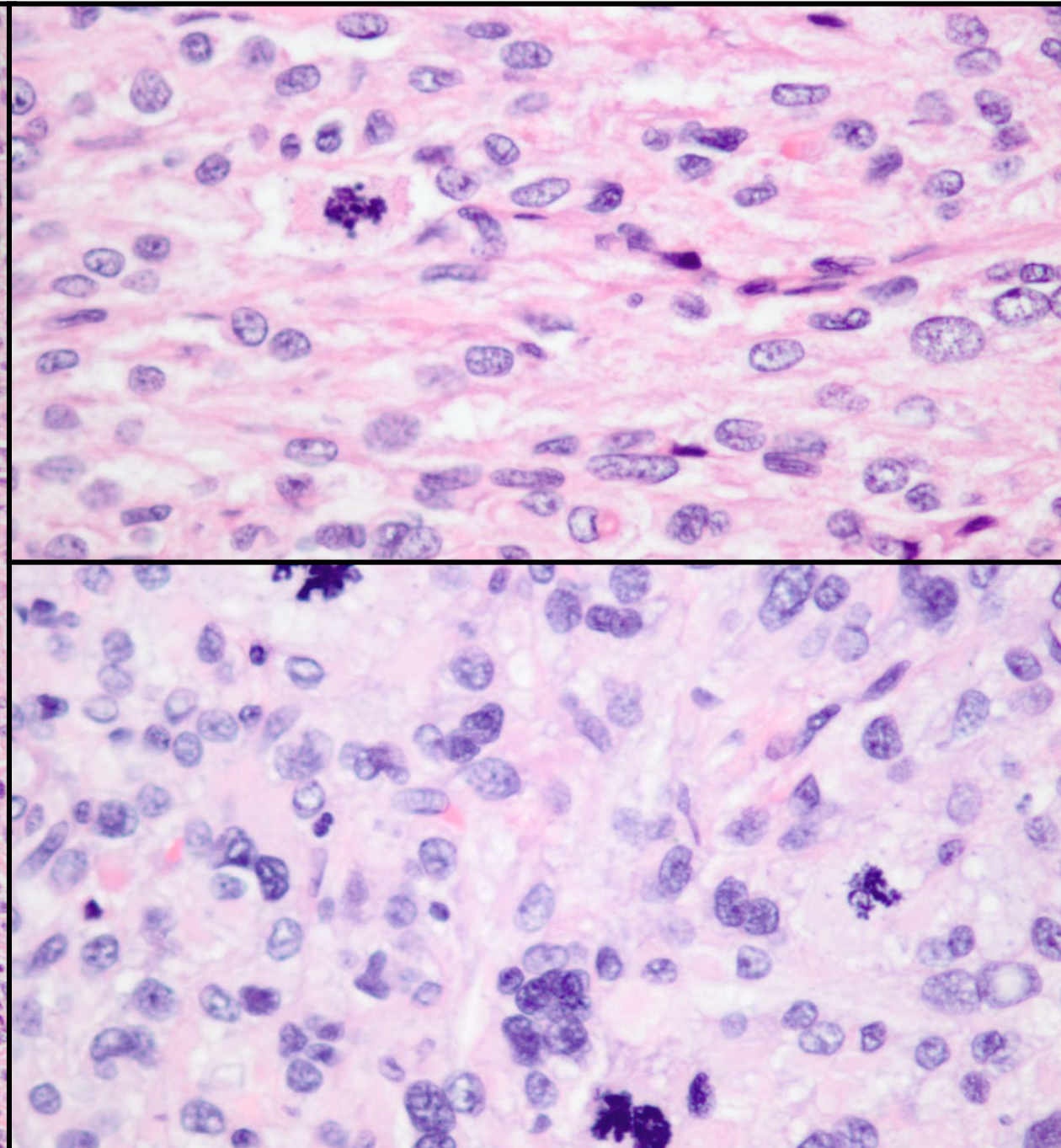
- A 45 year-old woman underwent an abdominal supracervical morcellated hysterectomy
 - The specimen measured 22 x 20 x 6 cm in aggregate
 - It contained a 15 x 13 x 6 cm aggregate of tan, white whorled nodular tissue with yellow, soft areas

Nuclear pleomorphism, up to 15 mitoses per 10HPFs. The latter seen only in 1 slide and missed in the initial review by 2 gyn pathologists. Case signed as “ Atypical Leiomyoma”

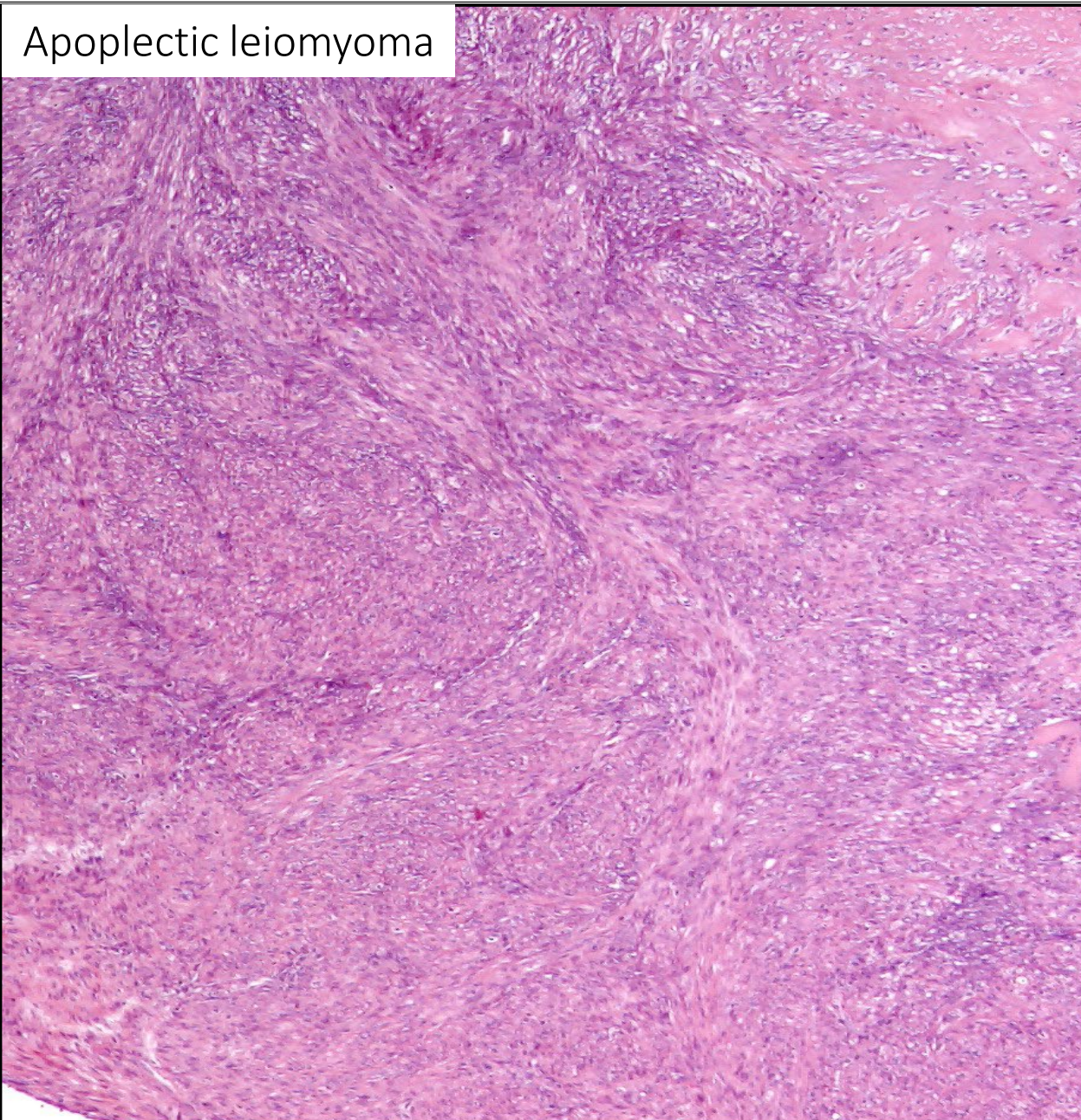




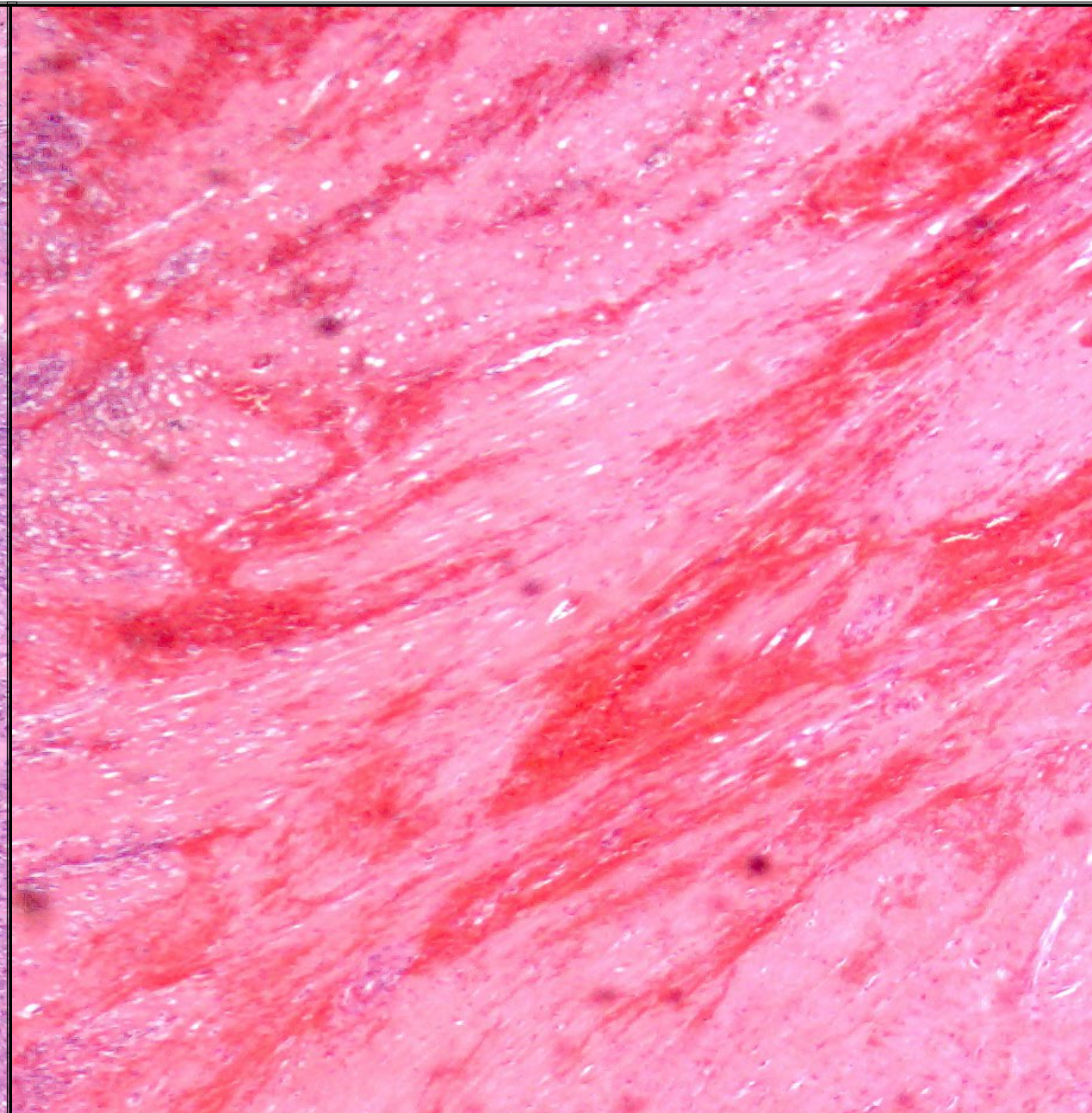
The patient developed multiple tumors in the abdominal wall, bowel, and pelvis within 2 years after the initial dx



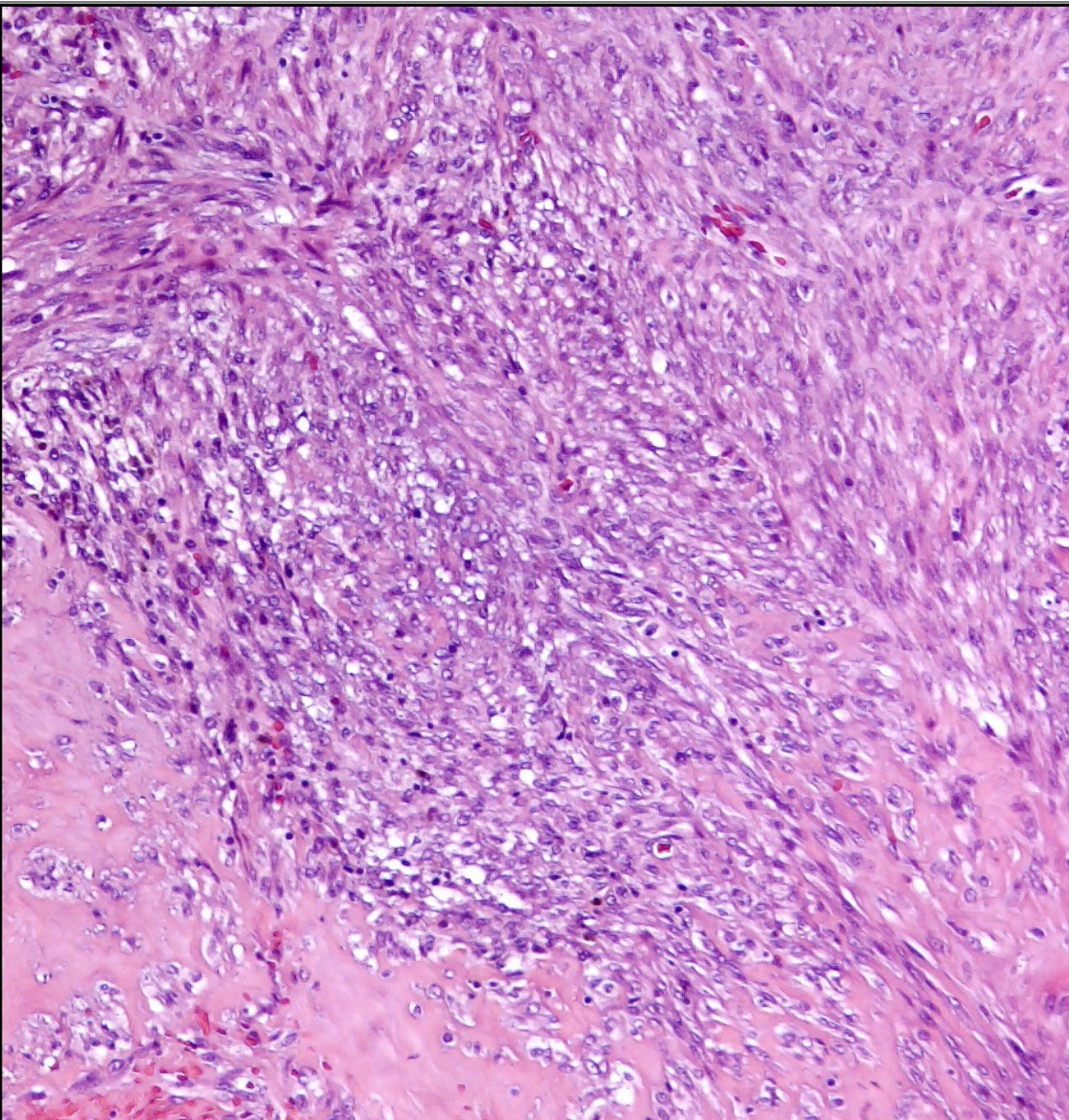
Apoplectic leiomyoma



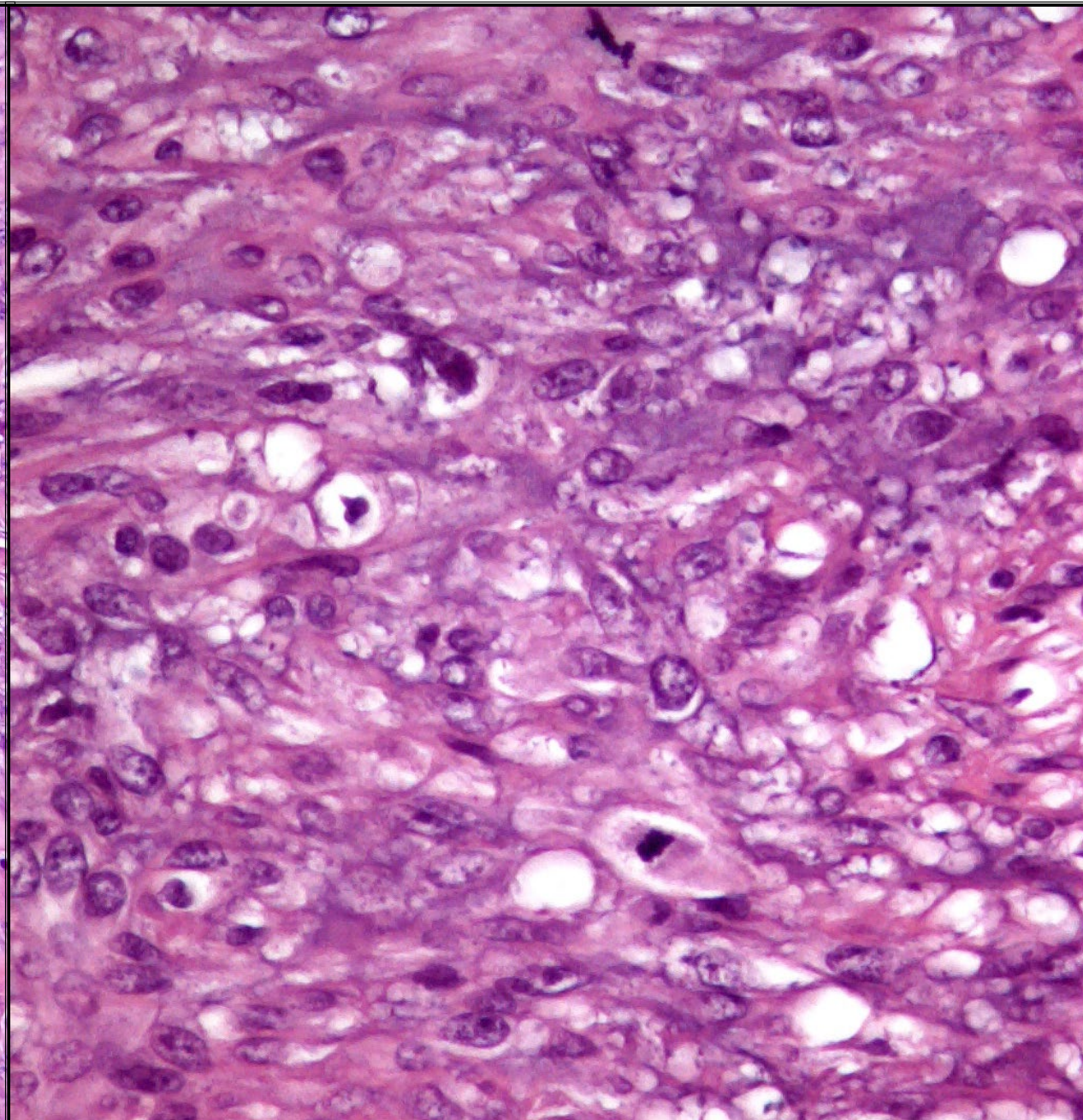
Cellular areas



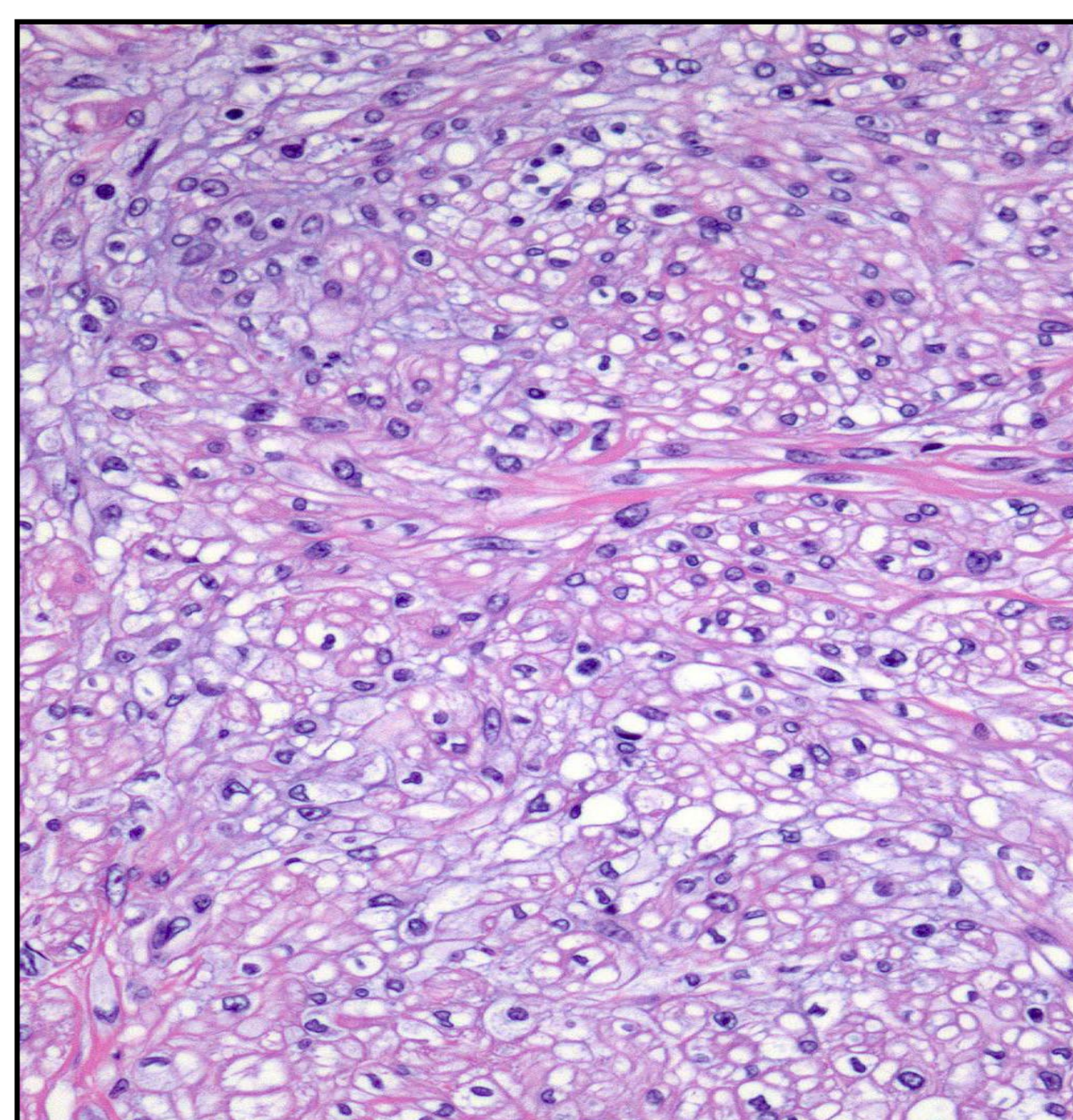
Multiple foci of necrosis and hemorrhage



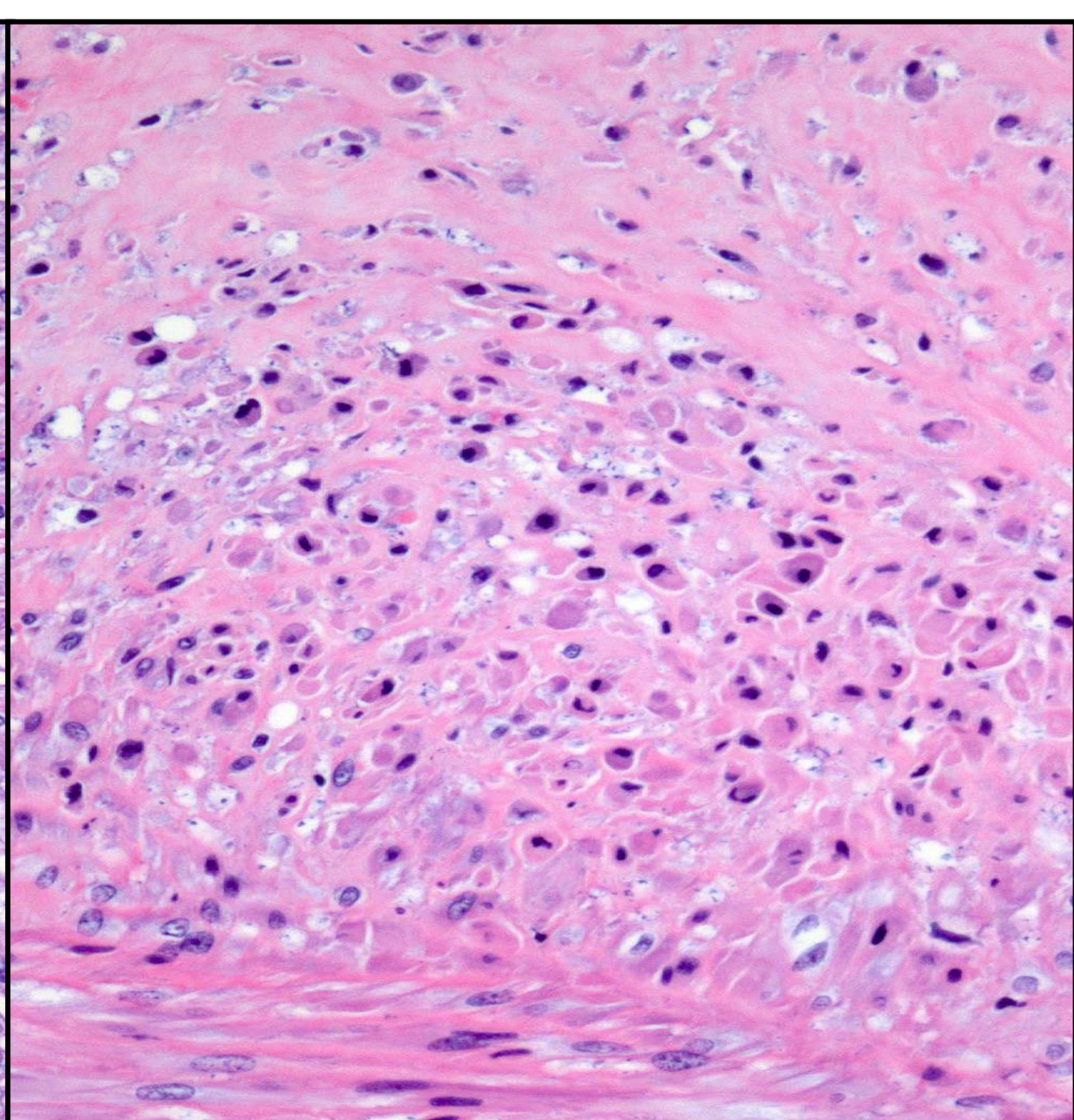
Mildly atypical cells



MI, up to 14 mitoses per 10 HPFs

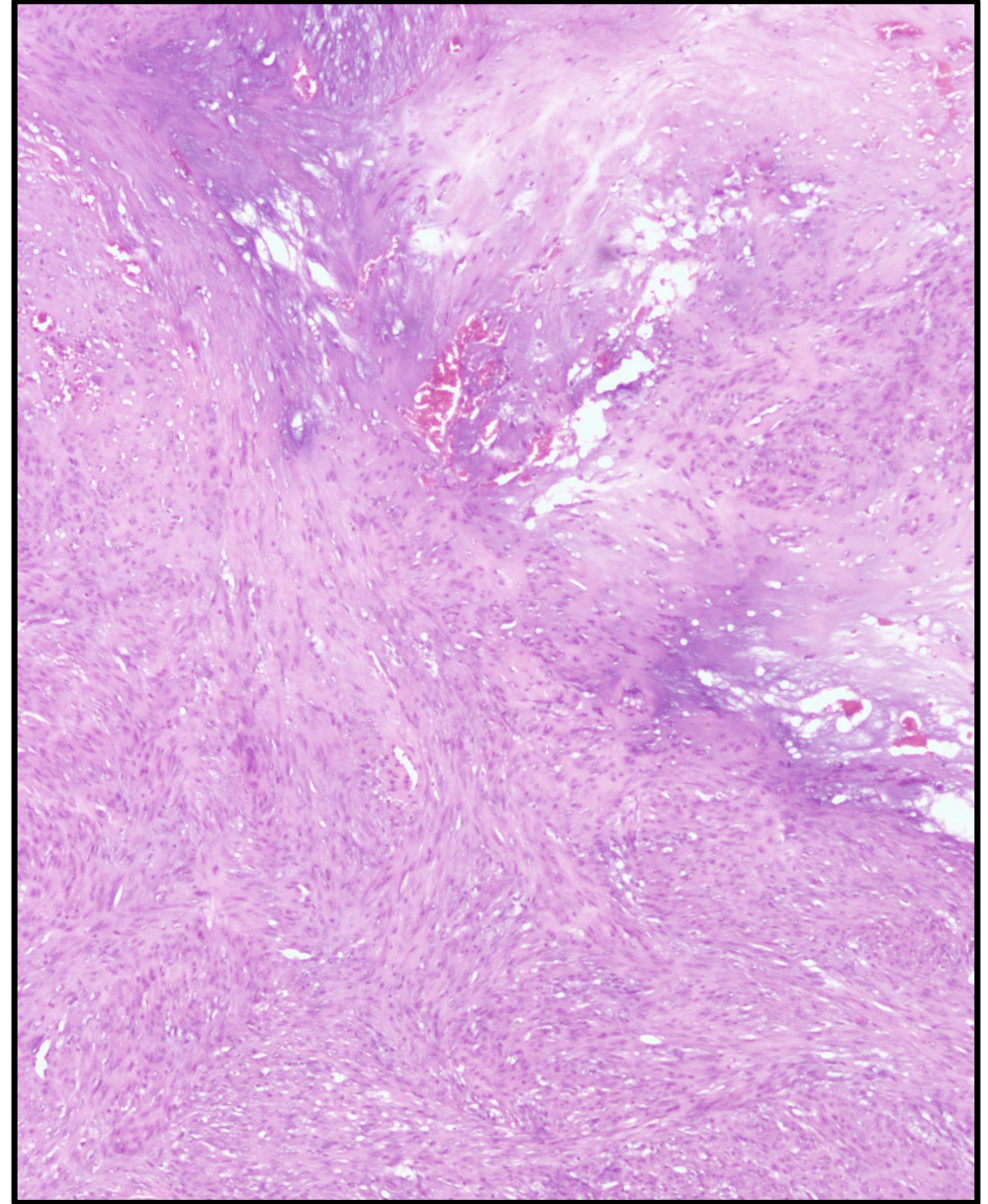
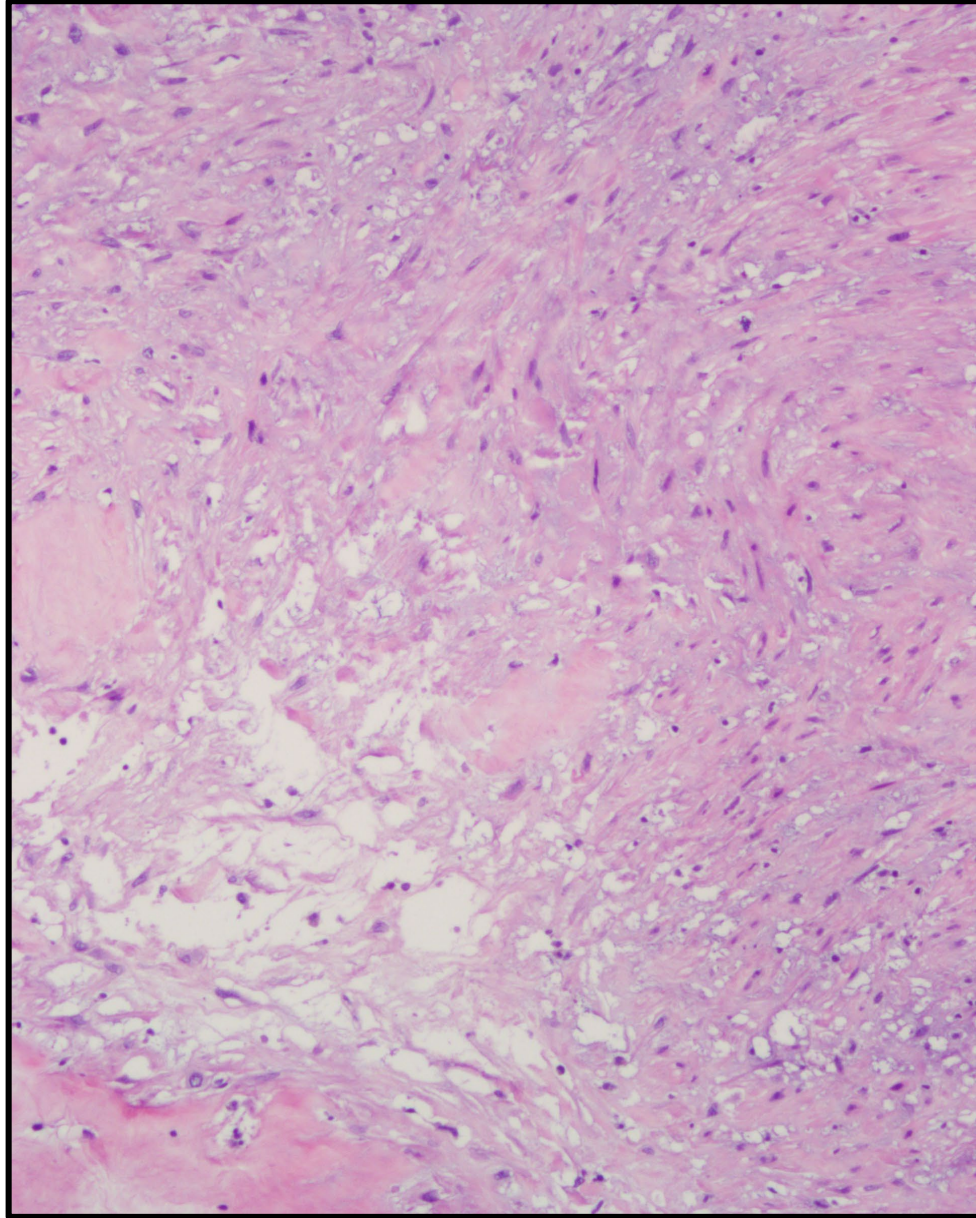


Epithelioid cells



Pyknosis

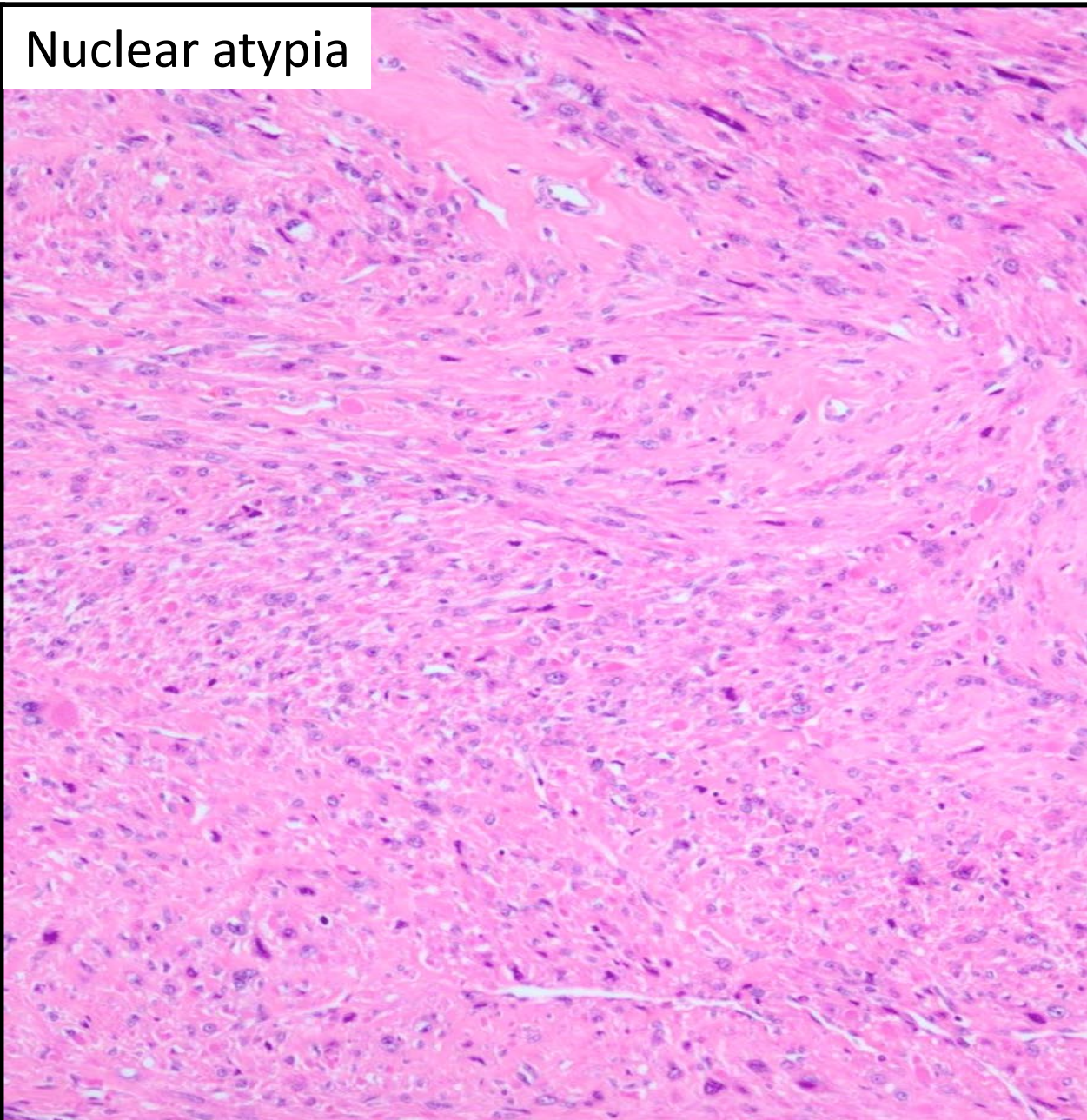
Edema with Cyst Formation



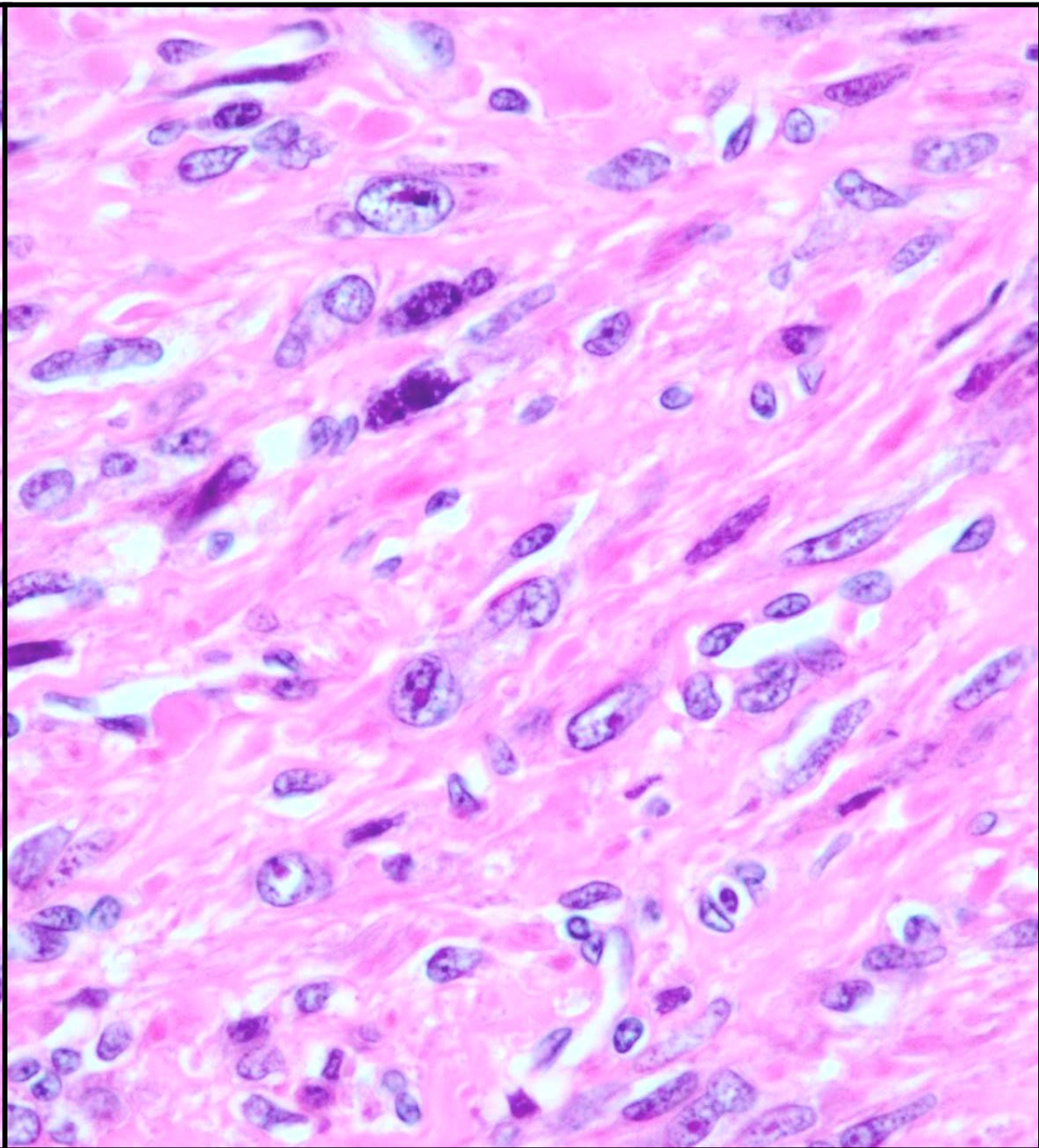
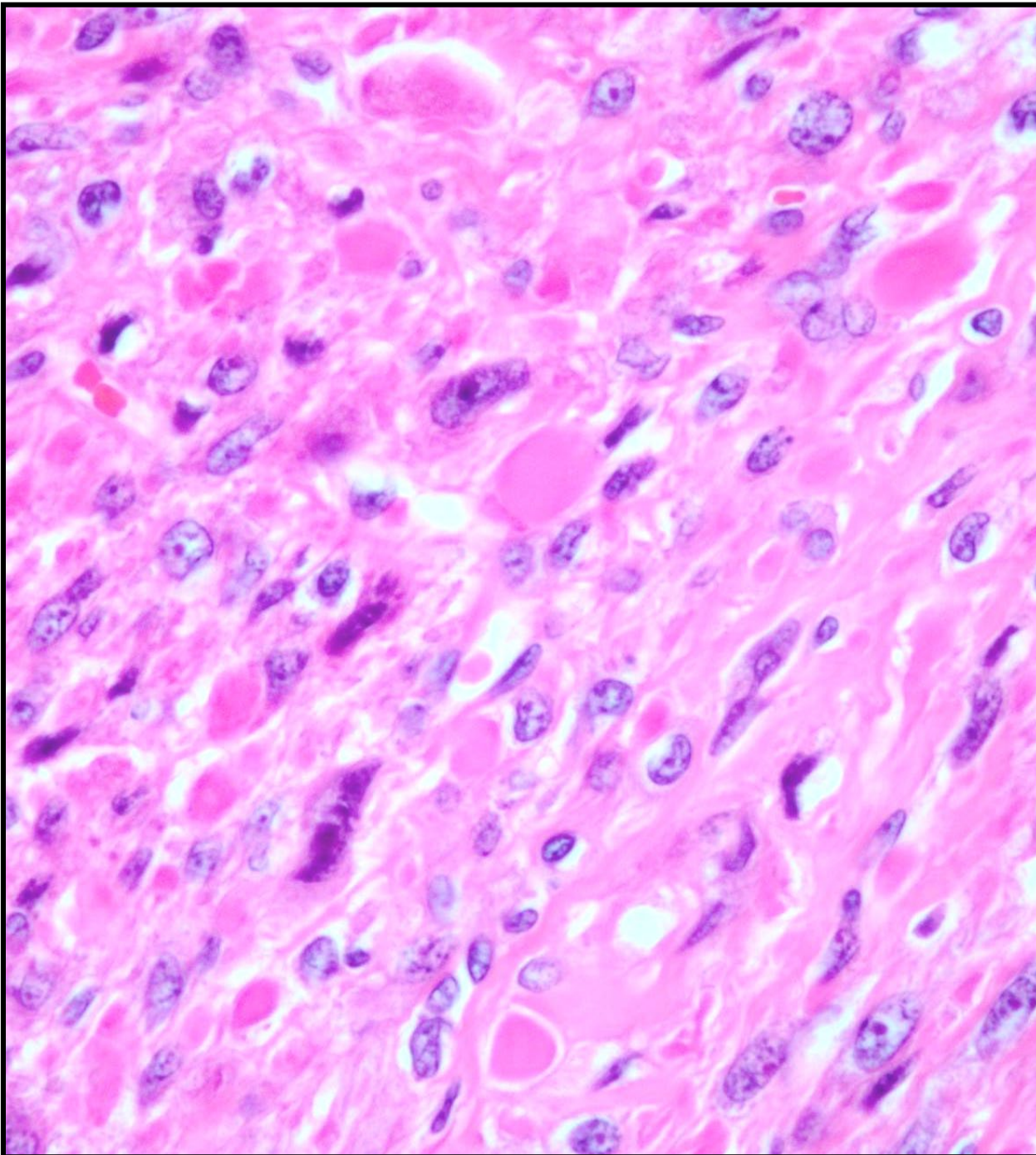
Staghorn vessels

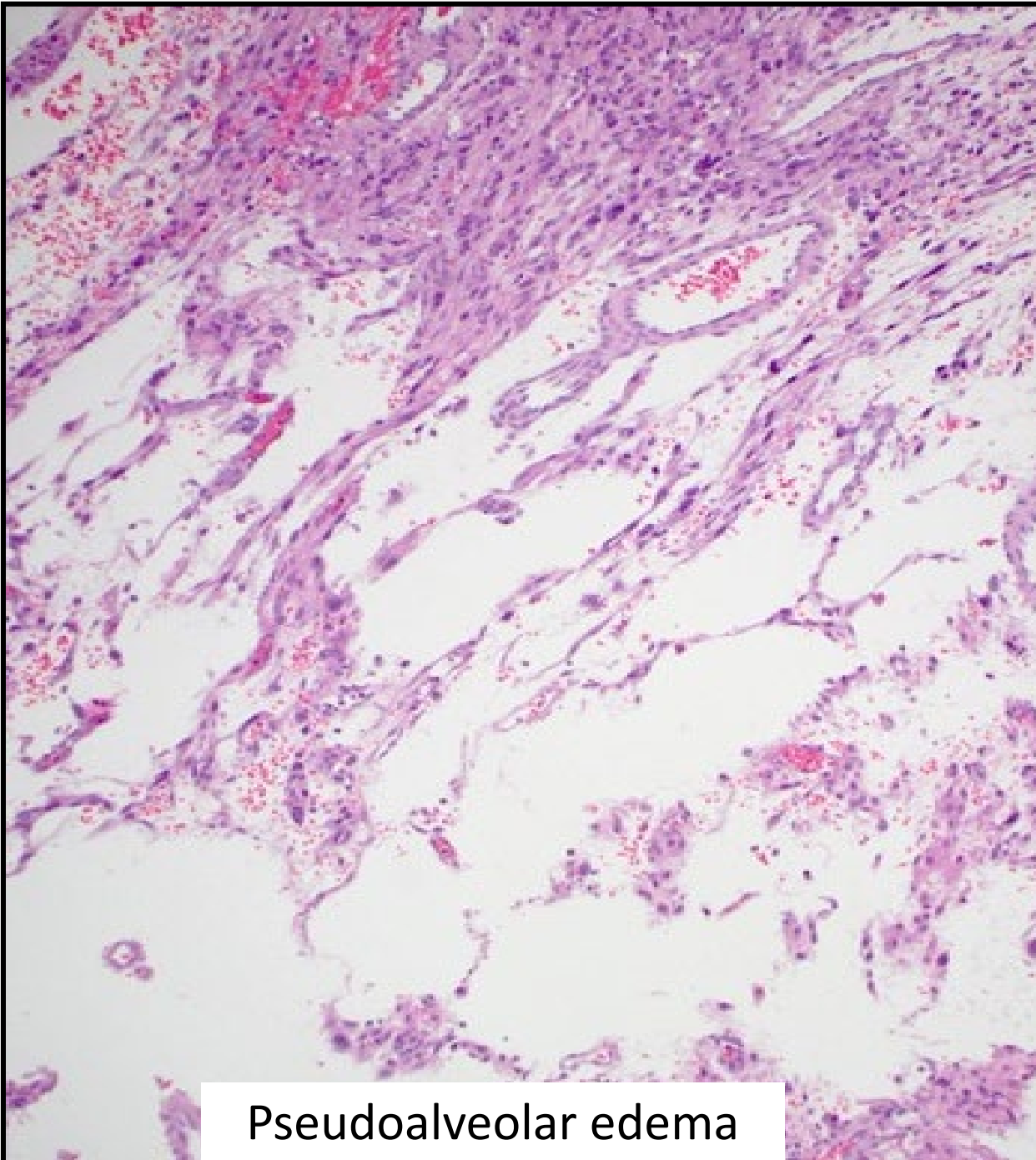


Nuclear atypia

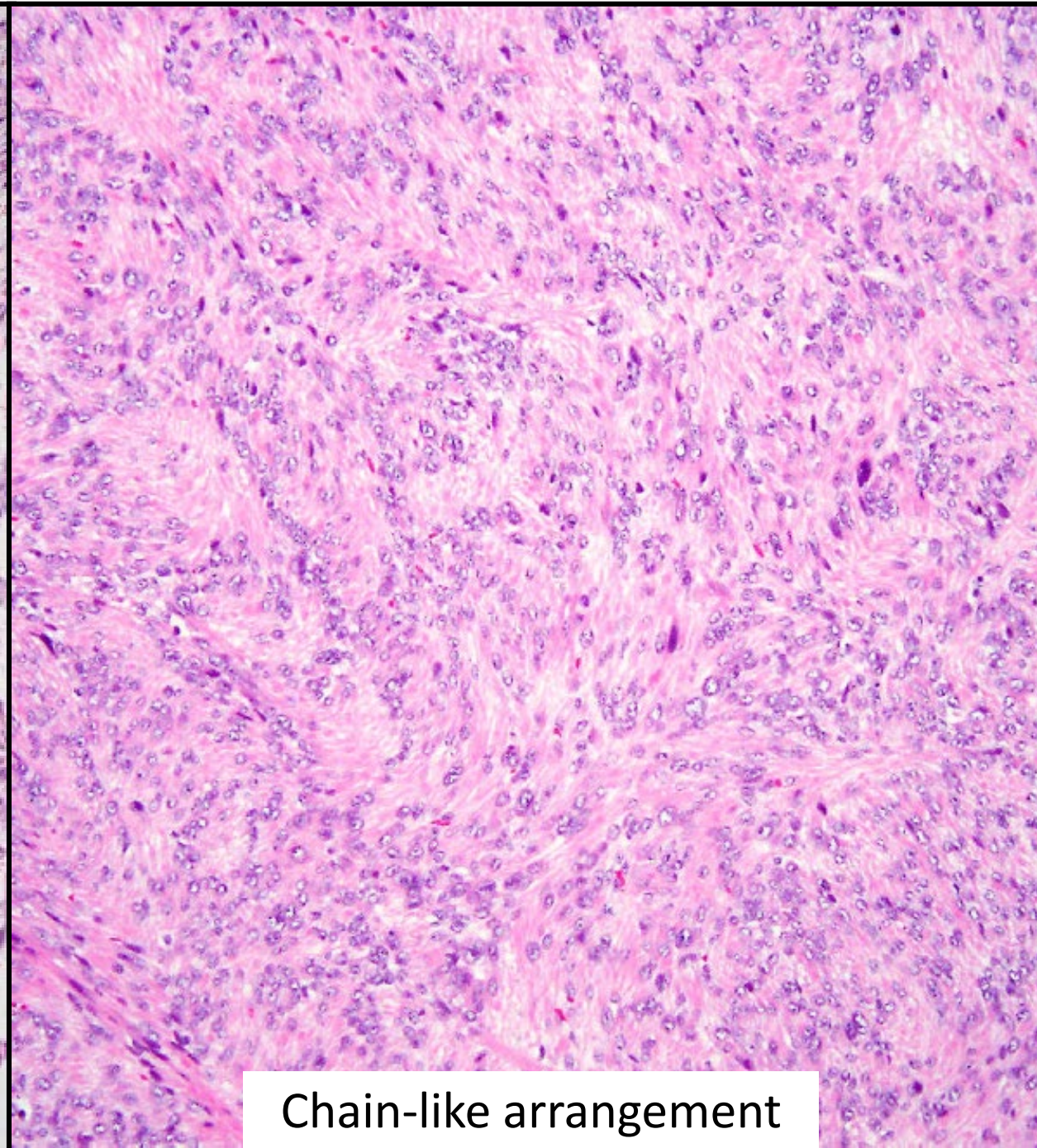


LM with features suggestive of FH deficiency

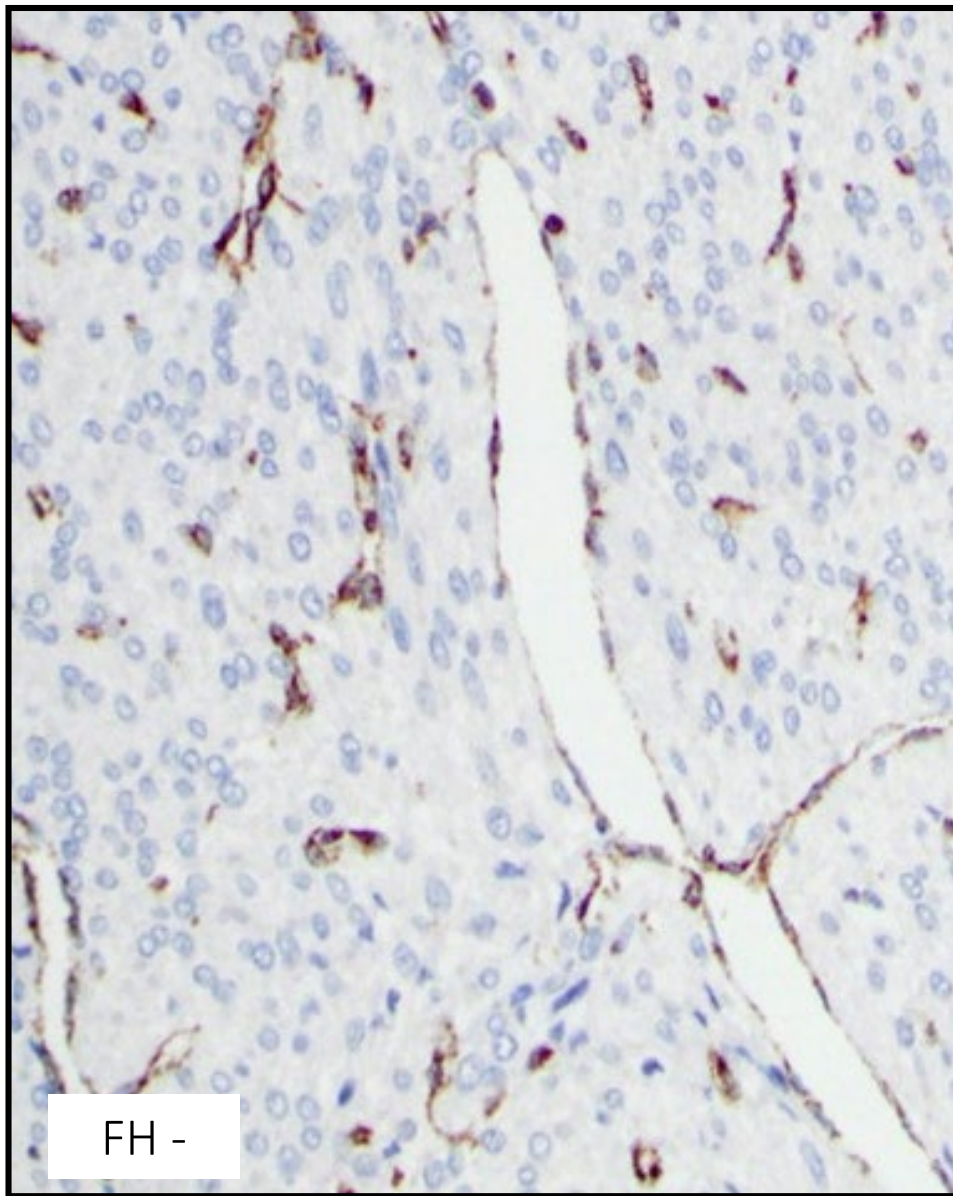




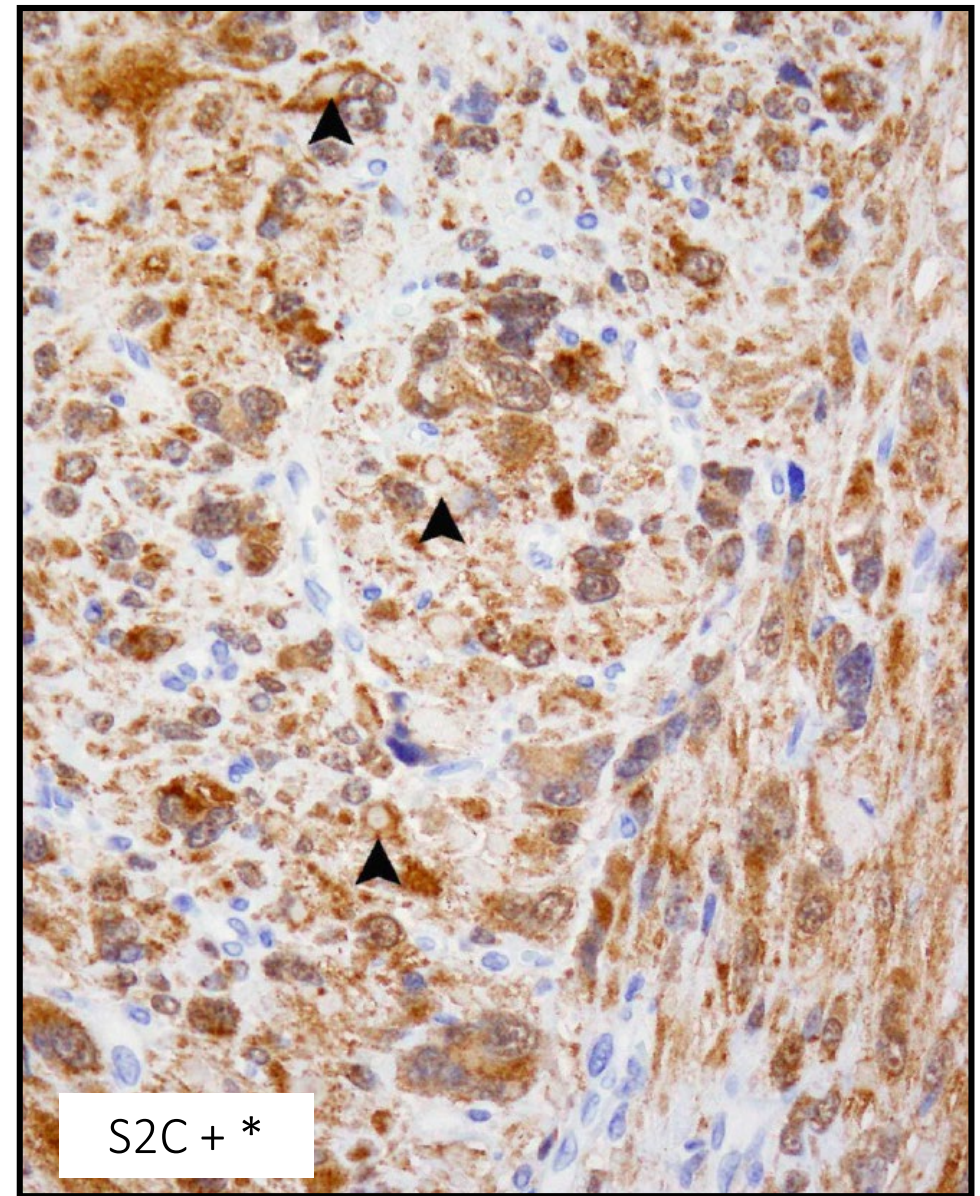
Pseudoalveolar edema



Chain-like arrangement



FH can be + due to a missense mutation that produces a nonfunctional, but immunoreactive protein



*S-(2-succino) cysteine is not commercially available

Reyes C, et al. 2014

Hereditary Leiomyomatosis and Renal Cell Carcinoma (HLRCC) Syndrome

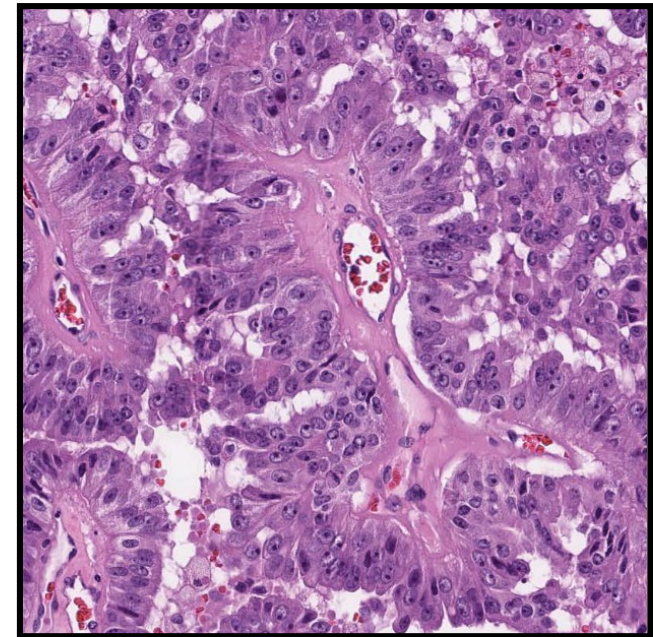
Secondary to germline mutation of the fumarate hydratase (FH) gene



98%, uterine leiomyomas



76%, single or multiple
skin leiomyomata



10-15%, FH deficient RCC,
an aggressive tumor

Leiomyoma with Features Suggestive of FH Deficiency

Due to somatic or germline mutations

Sensitivity and specificity remain controversial

No formal guidelines have been provided for genetic counseling



ORIGINAL ARTICLE

Prospective Detection of Germline Mutation of *Fumarate Hydratase* in Women With Uterine Smooth Muscle Tumors Using Pathology-based Screening to Trigger Genetic Counseling for Hereditary Leiomyomatosis Renal Cell Carcinoma Syndrome

A 5-Year Single Institutional Experience

Joseph T. Rabban, MD, MPH, Emily Chan, MD, PhD,* Julie Mak, MS, LCGC,† Charles Zaloudek, MD,* and Karuna Garg, MD**

(Am J Surg Pathol 2019;43:639–655)

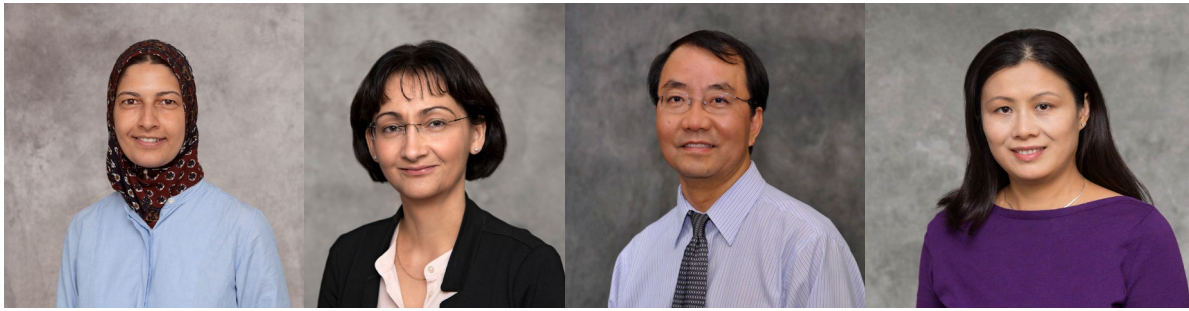
30 pts with FH deficient ULMs/2,060 pts with ULMs (1.4%)



10 pts underwent FH genetic testing

6 pts with FH germline mutations:
pathogenic mutations, 5; variant of
unknown significance, 1

All pts with family Hx of ULMs
1 pt with cutaneous LMs



660 Fumarate Hydratase-Deficient Uterine Leiomyoma: A 5-Year Prospective Analysis of Morphology-Based Screening and Patient Outcomes at a Single Institution

Heba Abdelal¹, Natalia Buza², Pei Hui³, Minhua Wang²

¹Yale New Haven Hospital, Yale School of Medicine, New Haven, CT, ²Yale School of Medicine, New Haven, CT, ³Yale University School of Medicine, New Haven, CT

18 pts with FH deficient ULMs/2,240 pts with ULMs (0.8%)

FH loss in 14 tumors (78%)



Genetic counseling offered to 10 of these 14 pts

8 pts were offered germline testing, 6 pts had it done

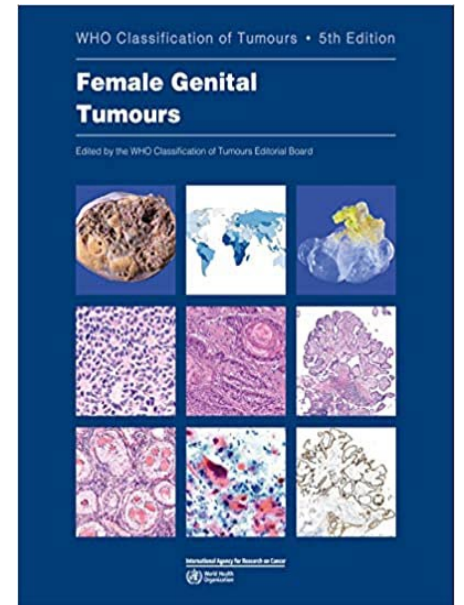
3 pts with FH germline mutations: pathogenic mutations, 2; variant of unknown significance, 1

Leiomyoma with Features Suggestive of FH Deficiency

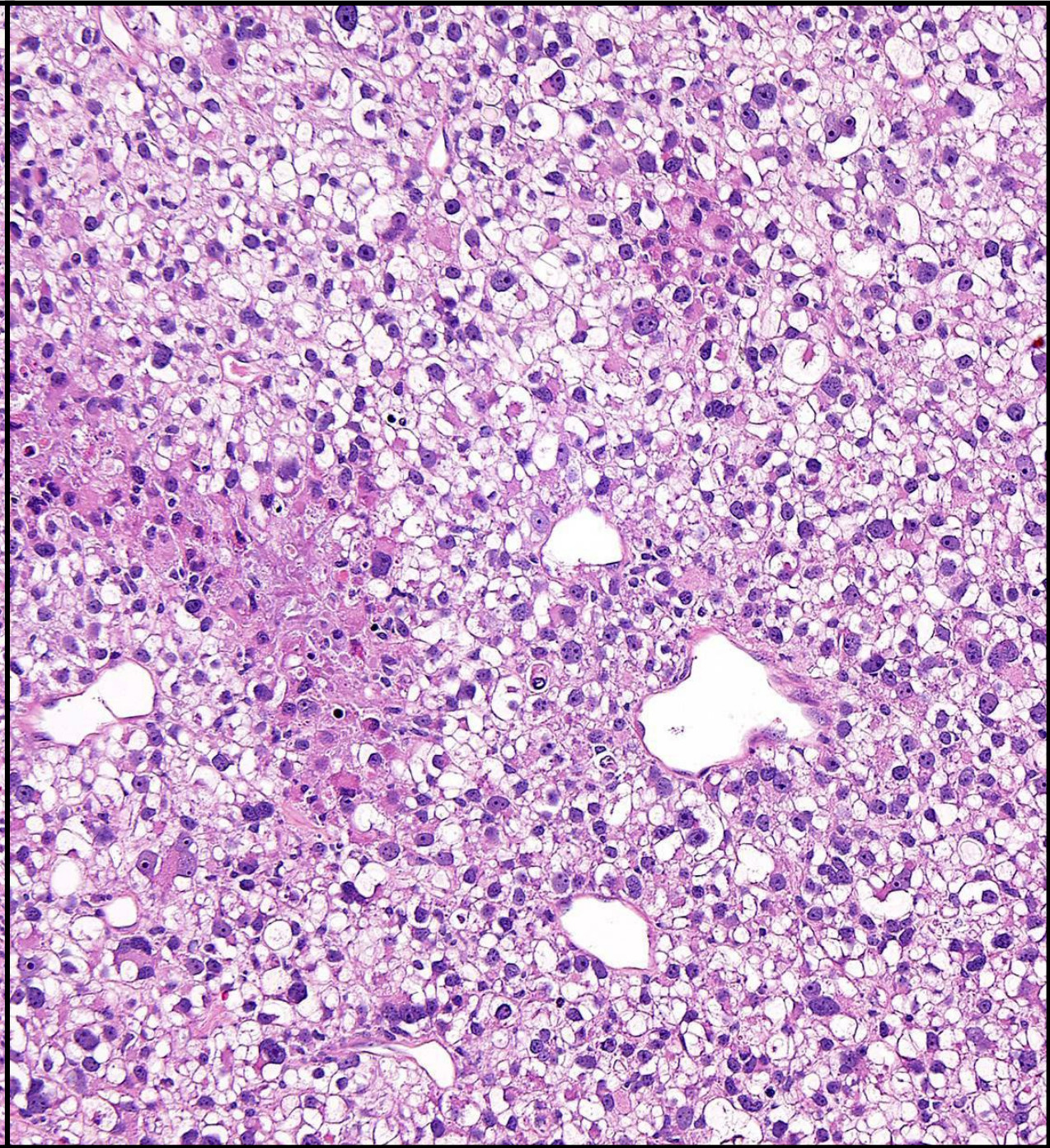
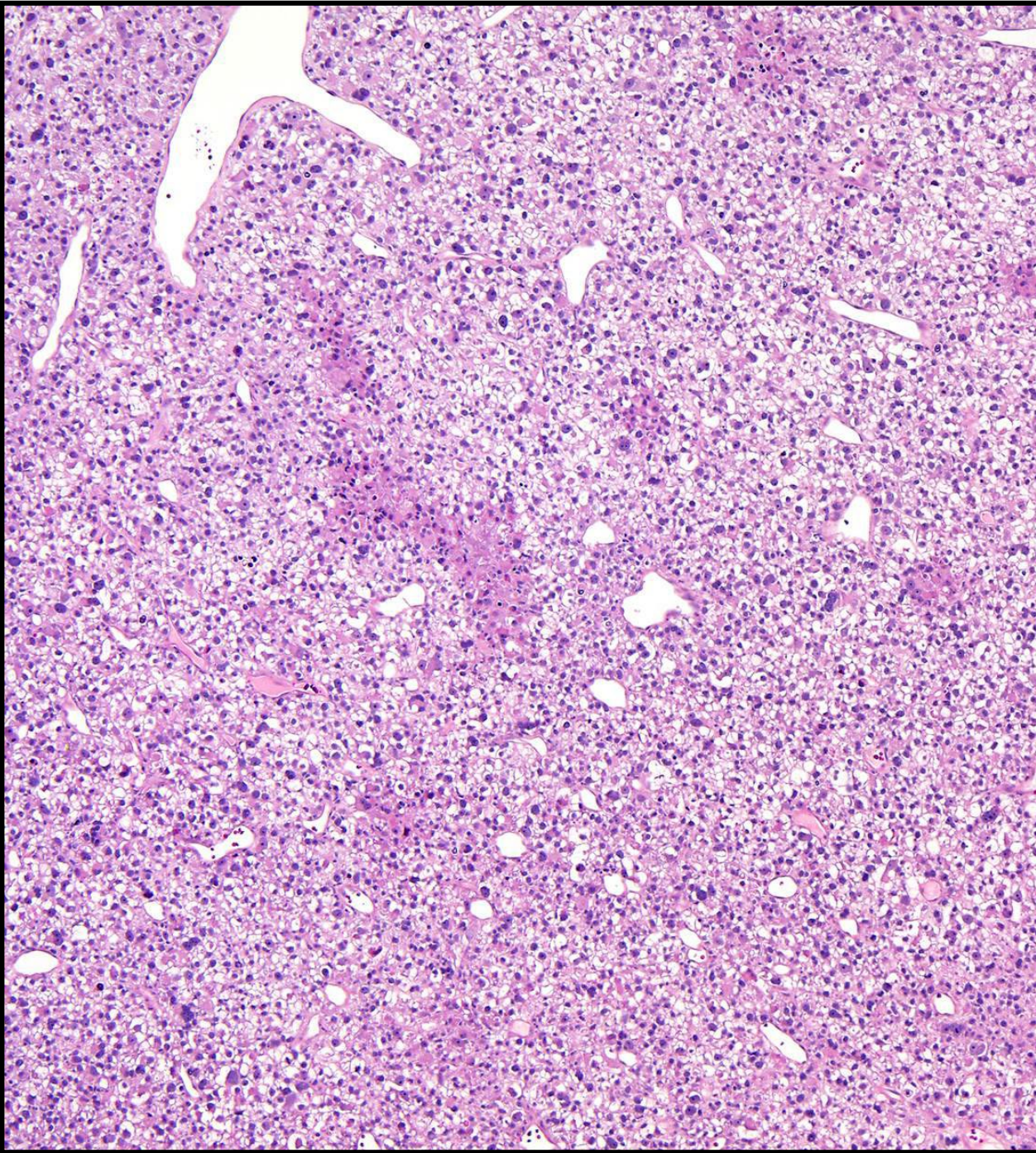
- Should not be called STUMP
- A comment should be included in the report
 - Features s/o FH deficiency can be due somatic or germline mutations
 - To determine clinically the need to proceed with germline testing
 - To double check personal and familial Hx
 - To exclude the presence of skin leiomyomas

PEComa

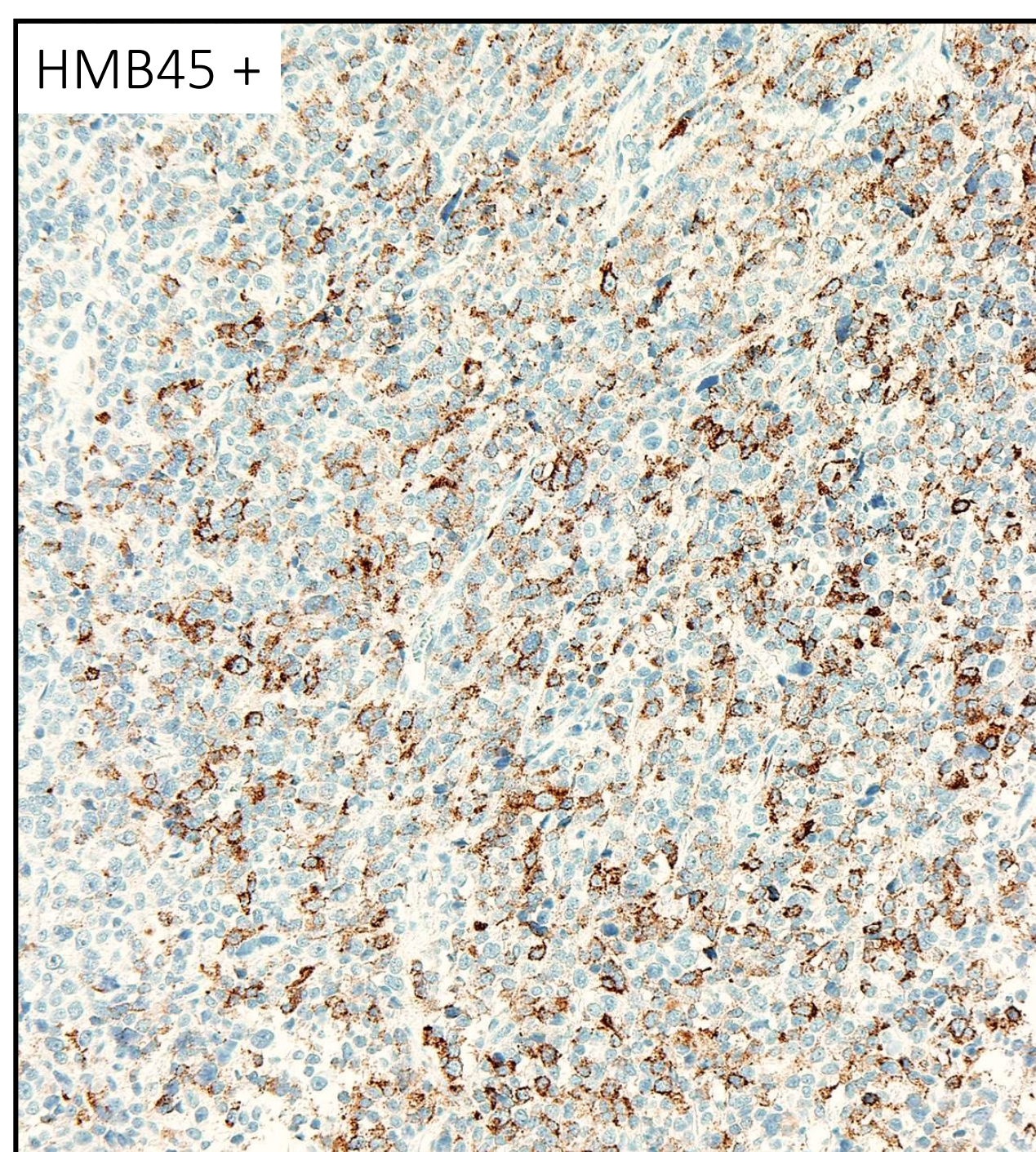
- Essential Dx Criteria:
 - Cells with clear to eosinophilic granular cytoplasm; thin-walled vessels surrounding nests of cells; expression of HMB45 or melan-A as well as at least one myoid marker
- Desirable Dx Criteria:
 - Confirmation of TFE-3 rearrangement or fusion in TFE3-rearranged tumors



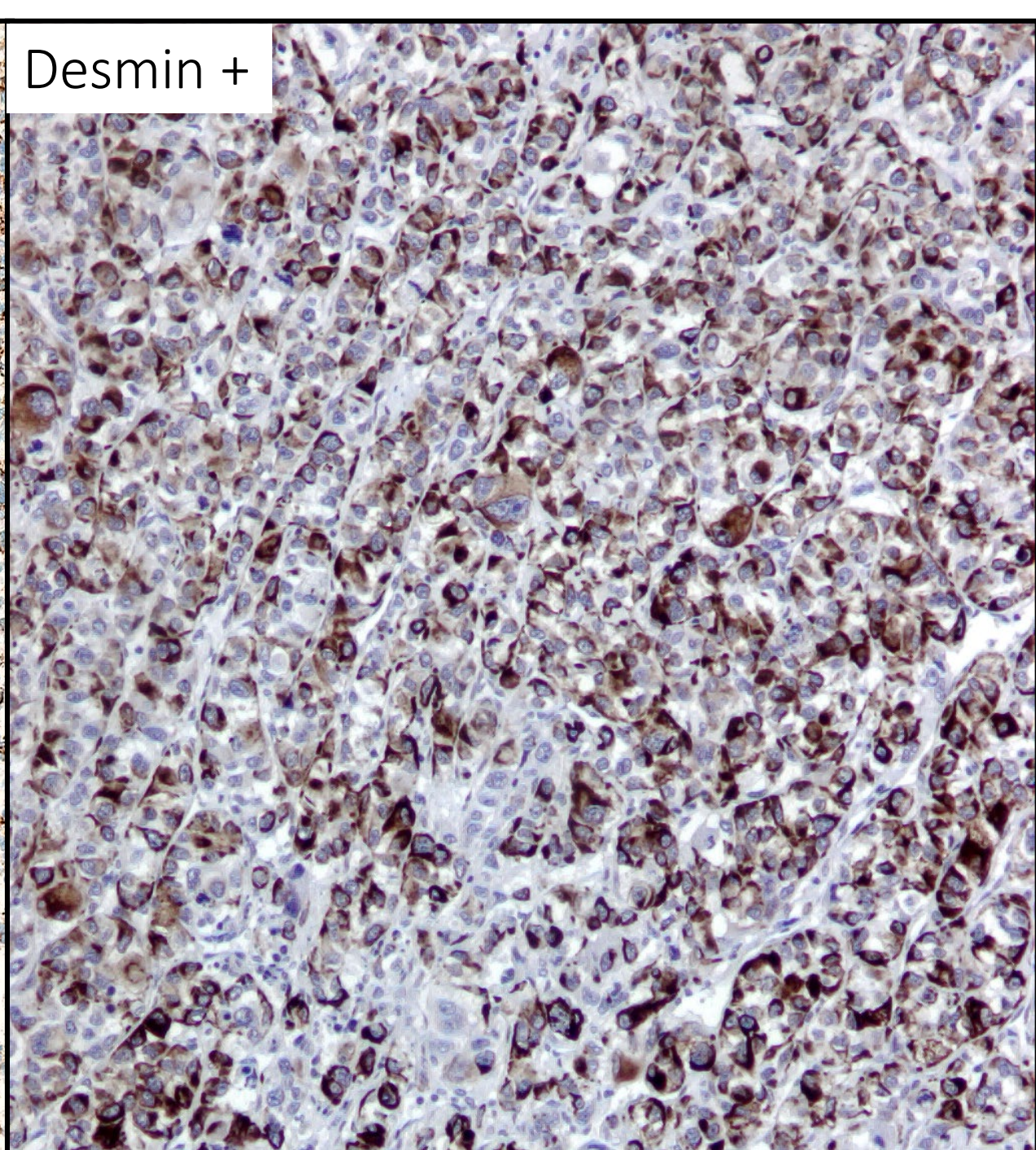
2020



HMB45 +

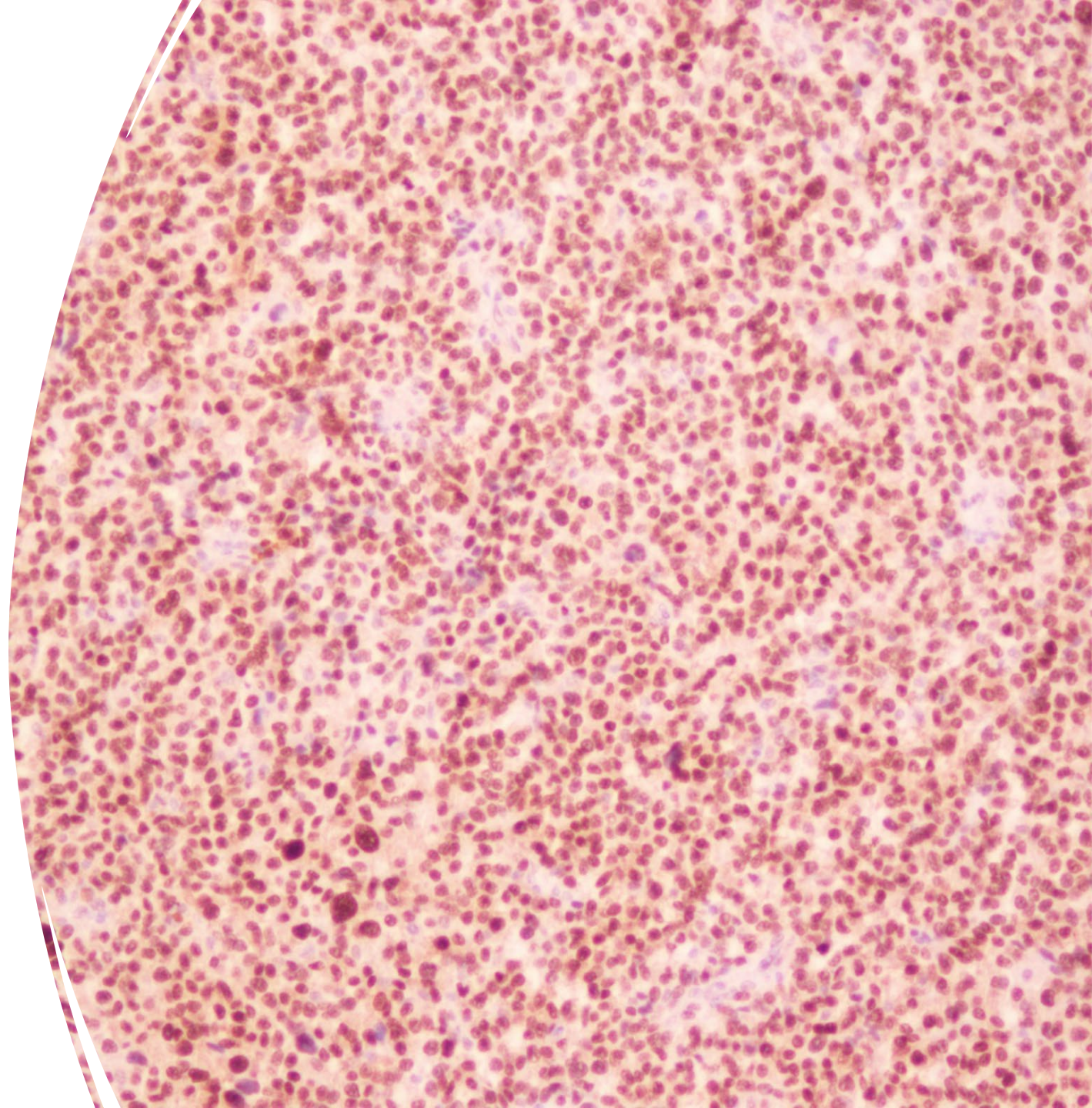


Desmin +

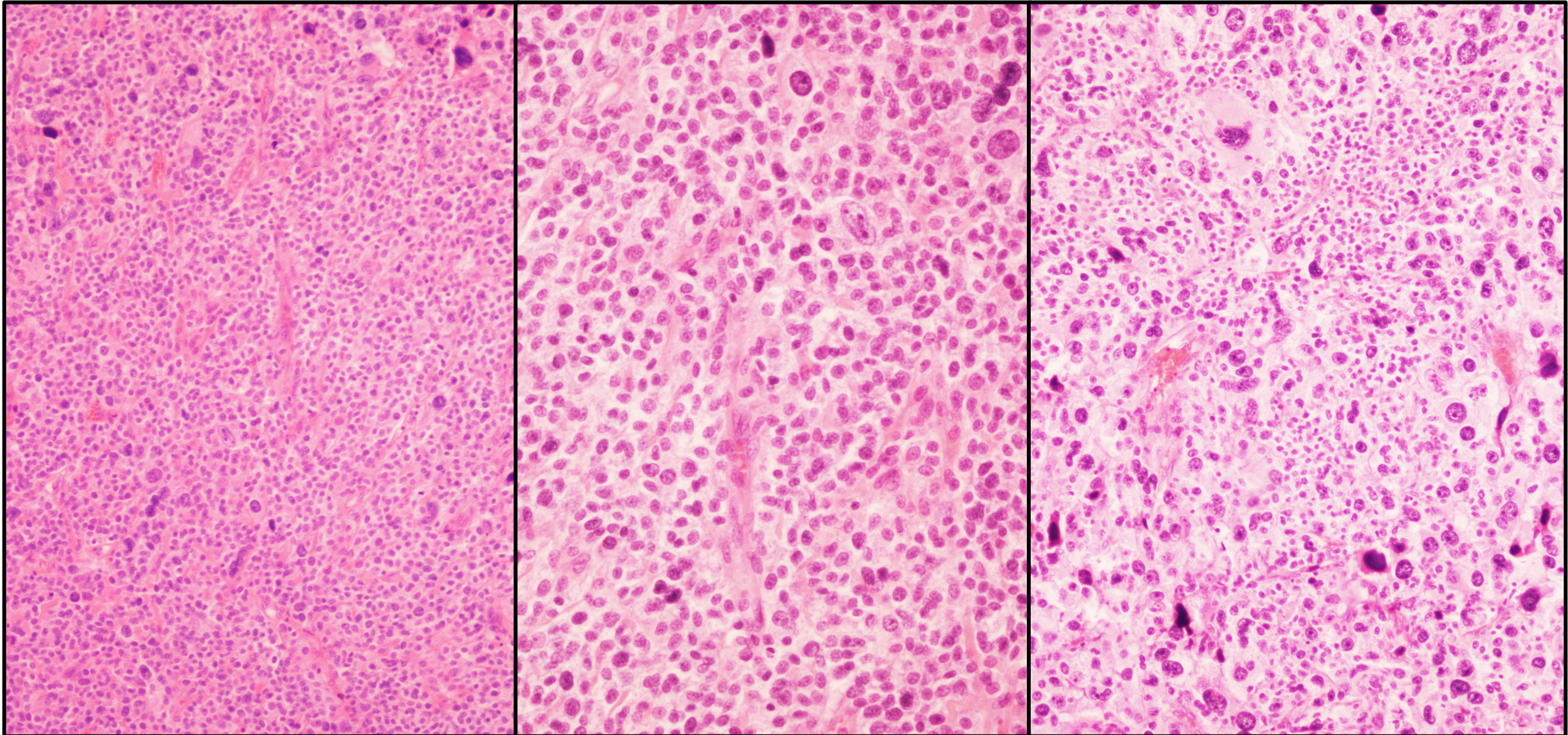


IHC for TFE-3 can be +

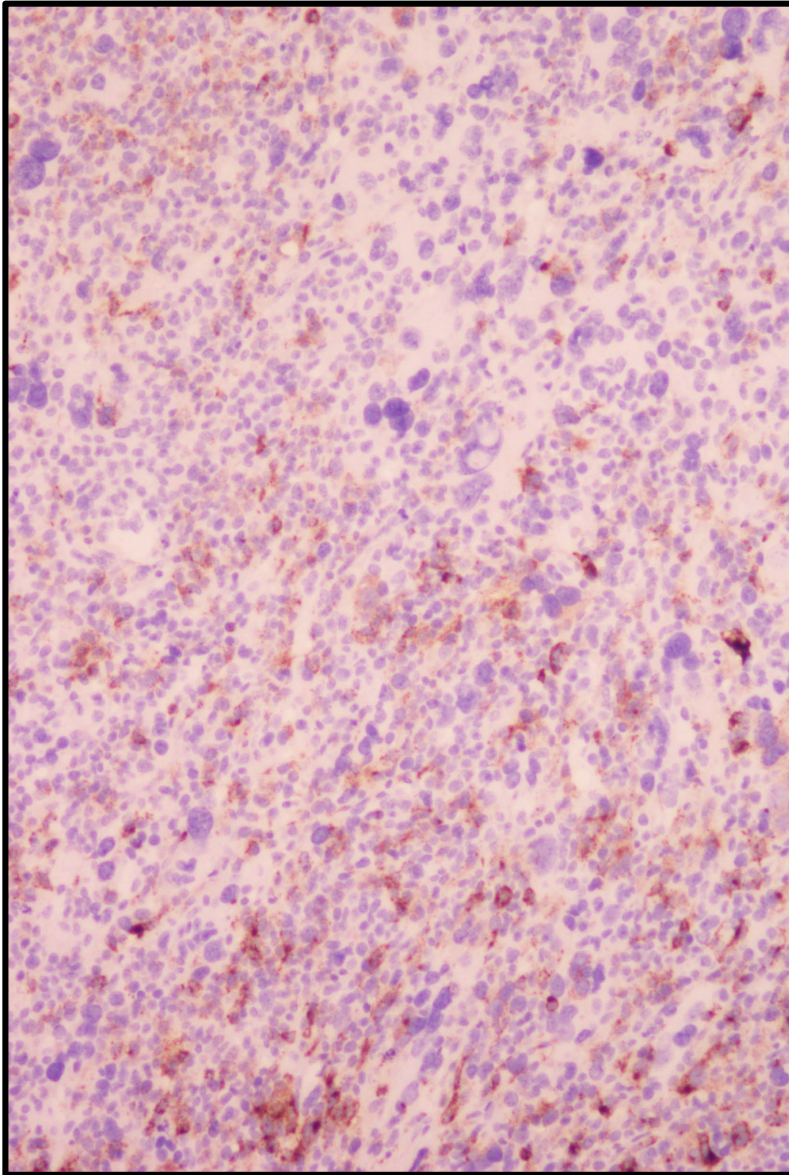
- This finding does not correlate with TFE3 rearrangement
- A positive IHC result → FISH analysis or reverse transcription PCR
- Targeted therapy with mTOR inhibitors can be used in cases of malignant PEComa
 - TFE3-rearranged malignant PEComa will not benefit from this tx



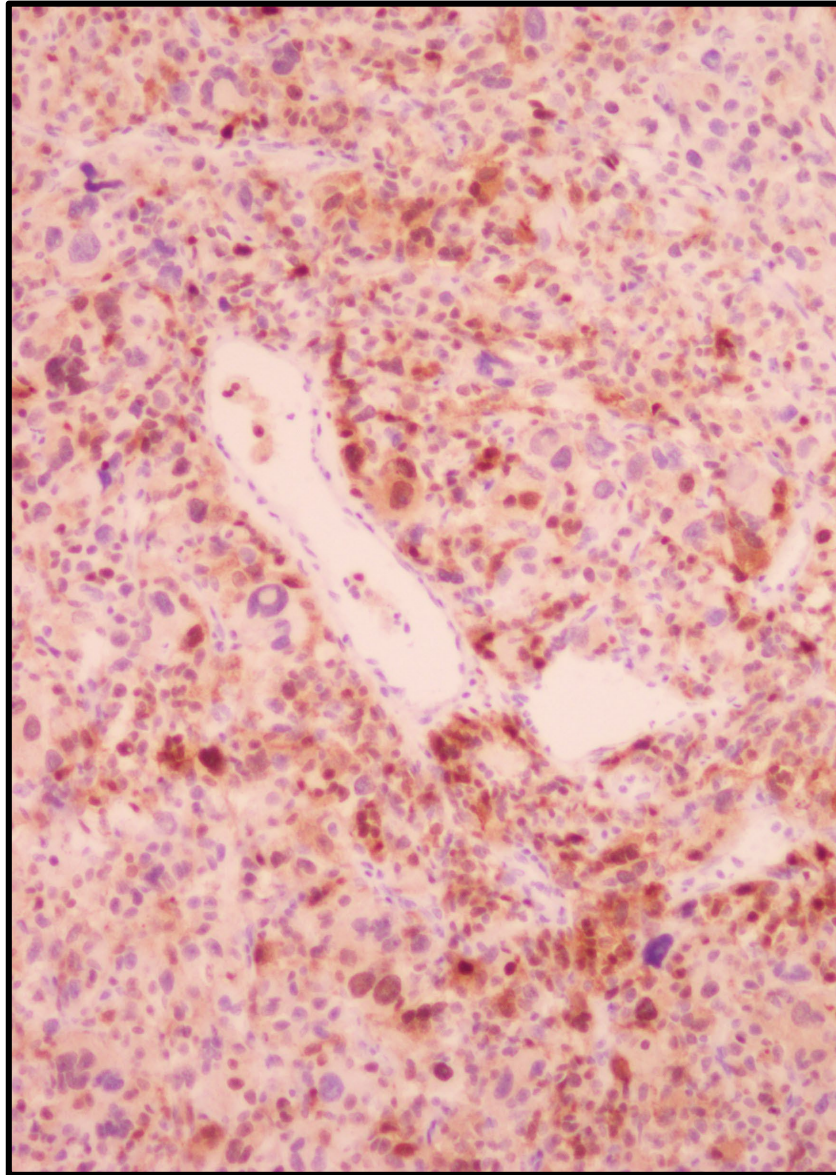
PEComa or NOT PEComa, that's the question!



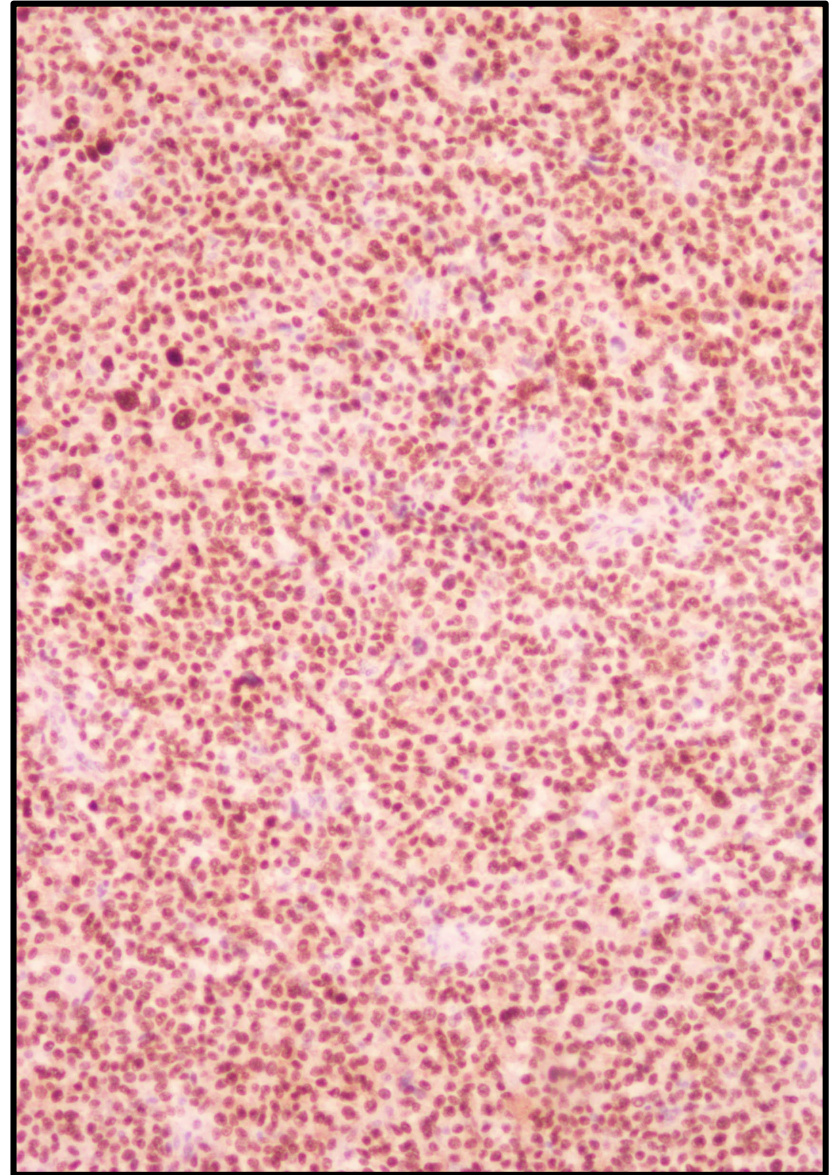
HMB-45 +P

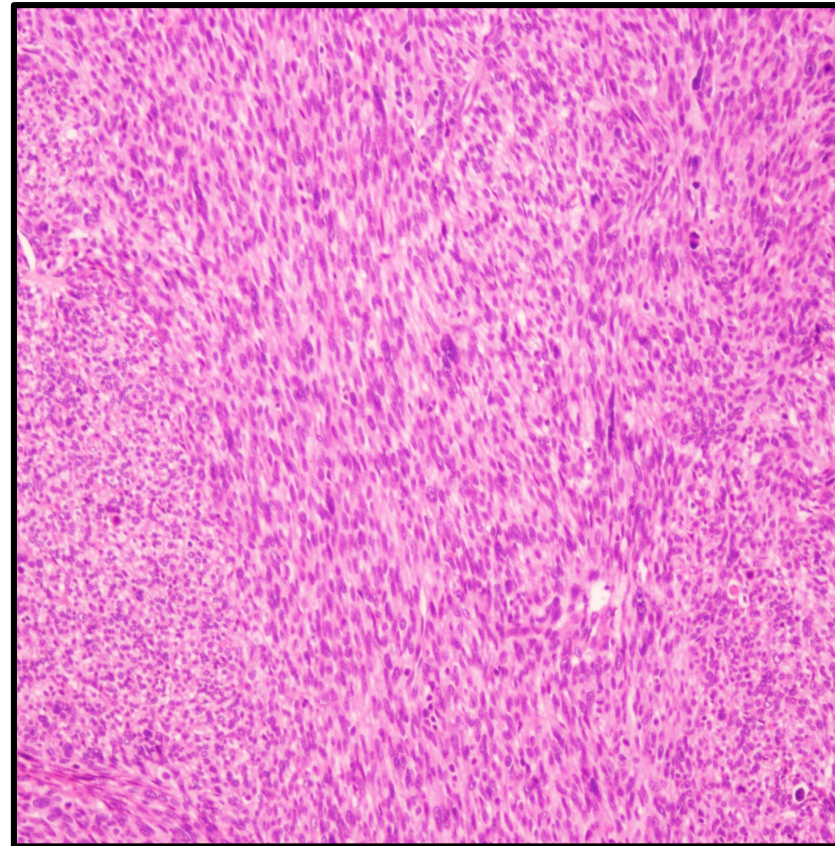
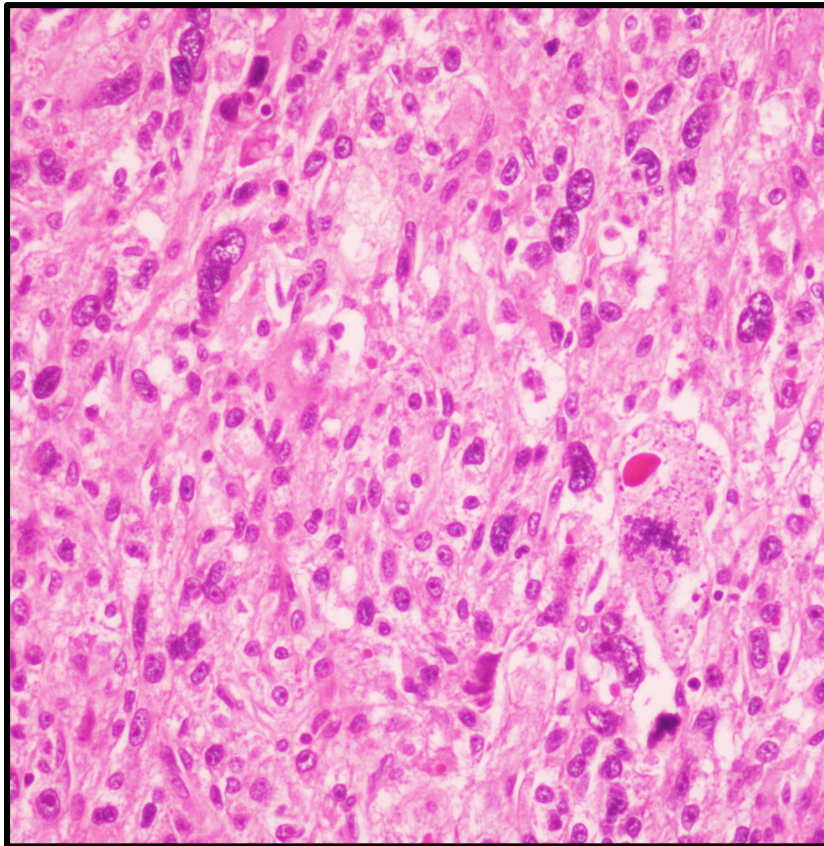
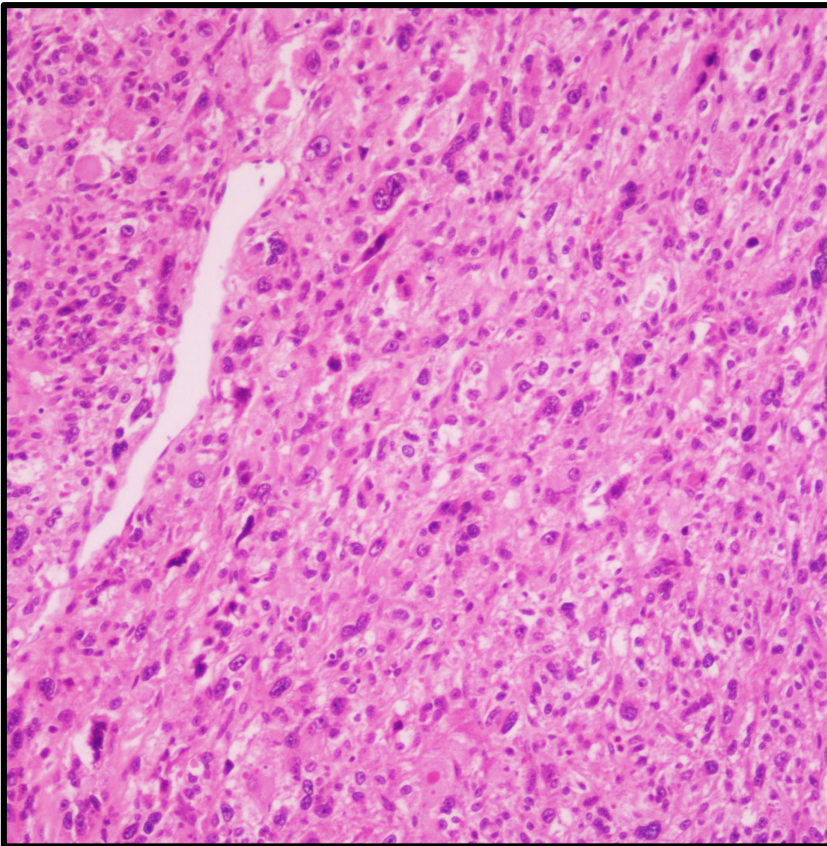


MITF +P

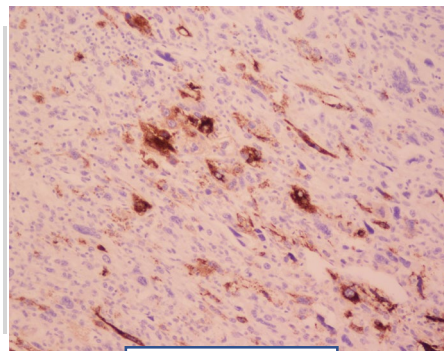


TFE-3 +

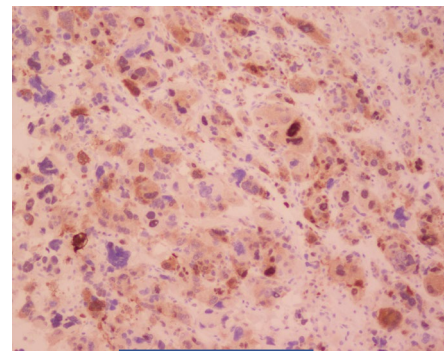




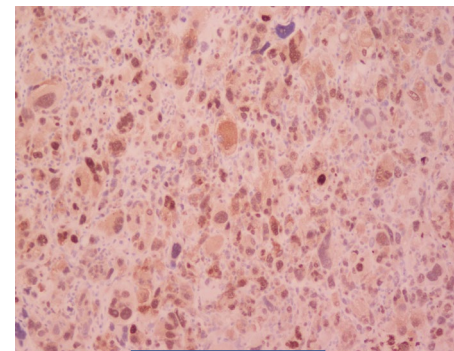
High grade
mesenchymal tumor
with myomelanocytic
differentiation



HMB-45



MITF



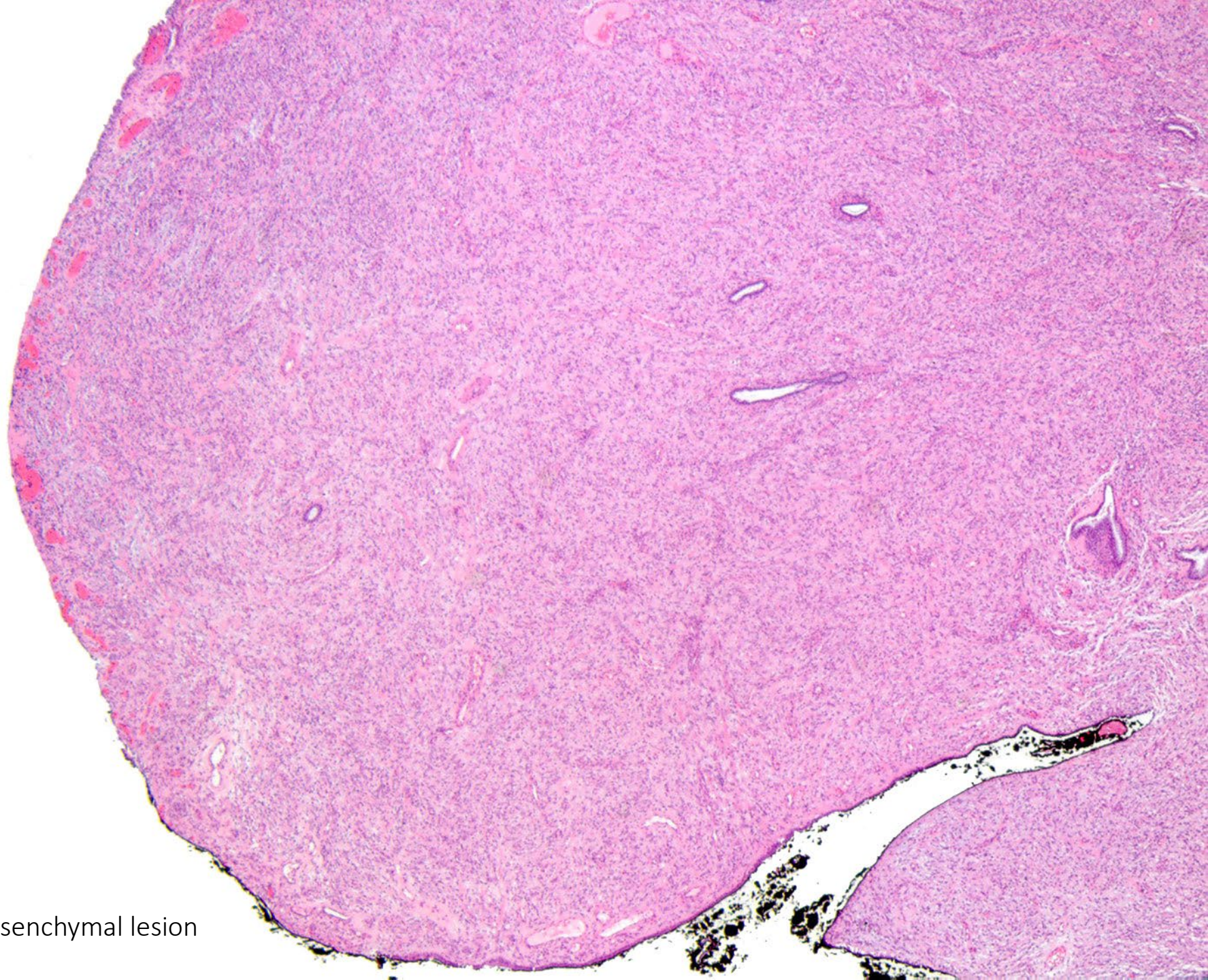
TFE-3

PEComa

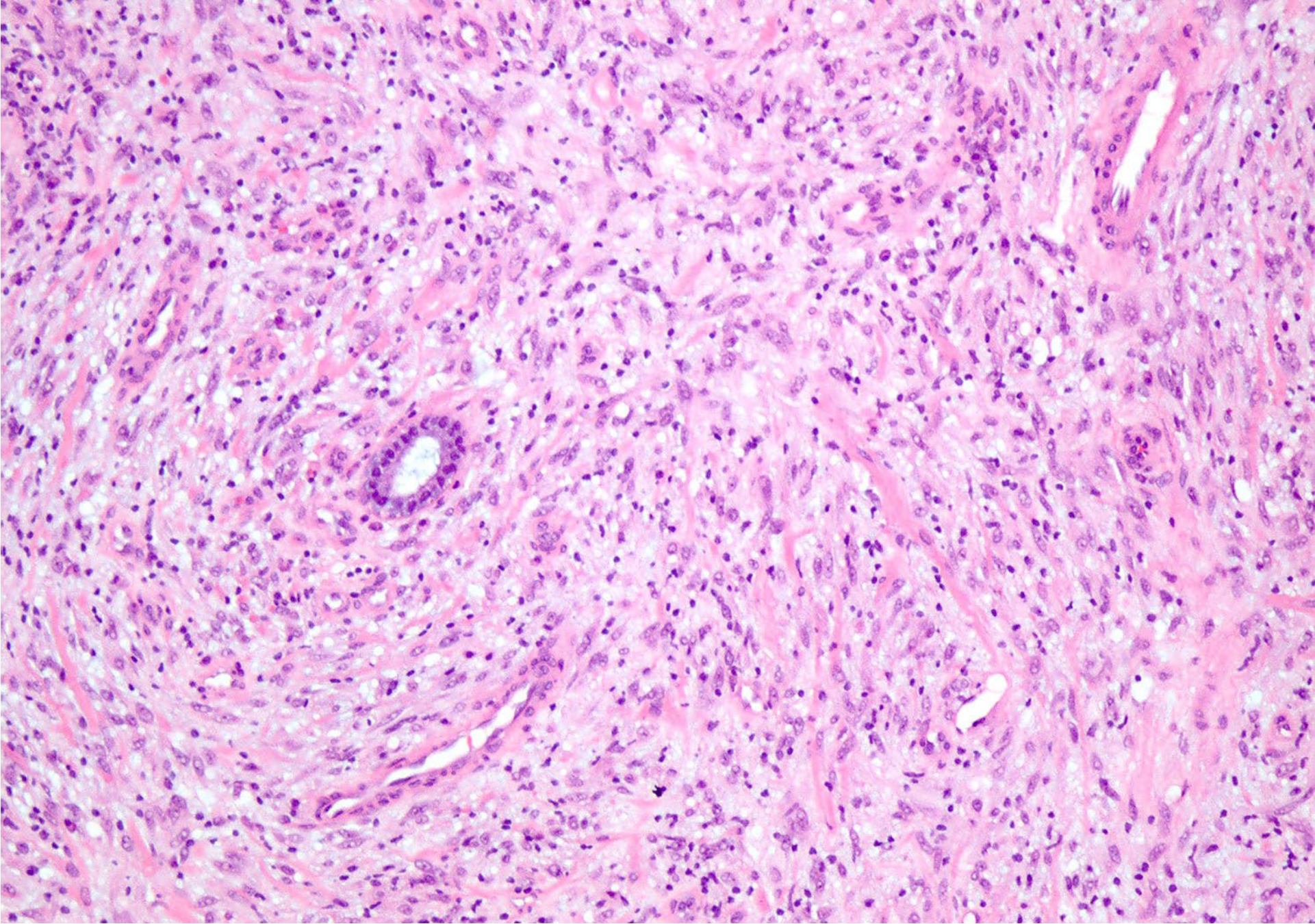
- NGS
 - TSC1 or TSC2 alterations
 - TFE3 rearrangement
- Gynecologic-specific criteria to predict behavior
 - Benign/uncertain malignant potential
 - <4 features (≥ 5 cm, high grade atypia, mitoses $>1/50$ HPFs, necrosis, LV invasion)
 - Malignant
 - ≥ 4 features

A difficult case a few years ago...

- A 30 year-old woman was found to have an abnormal Pap smear during a routine check-up visit
- Pap: LSIL, cannot rule out HSIL
- HRHPV, +
- LEEP

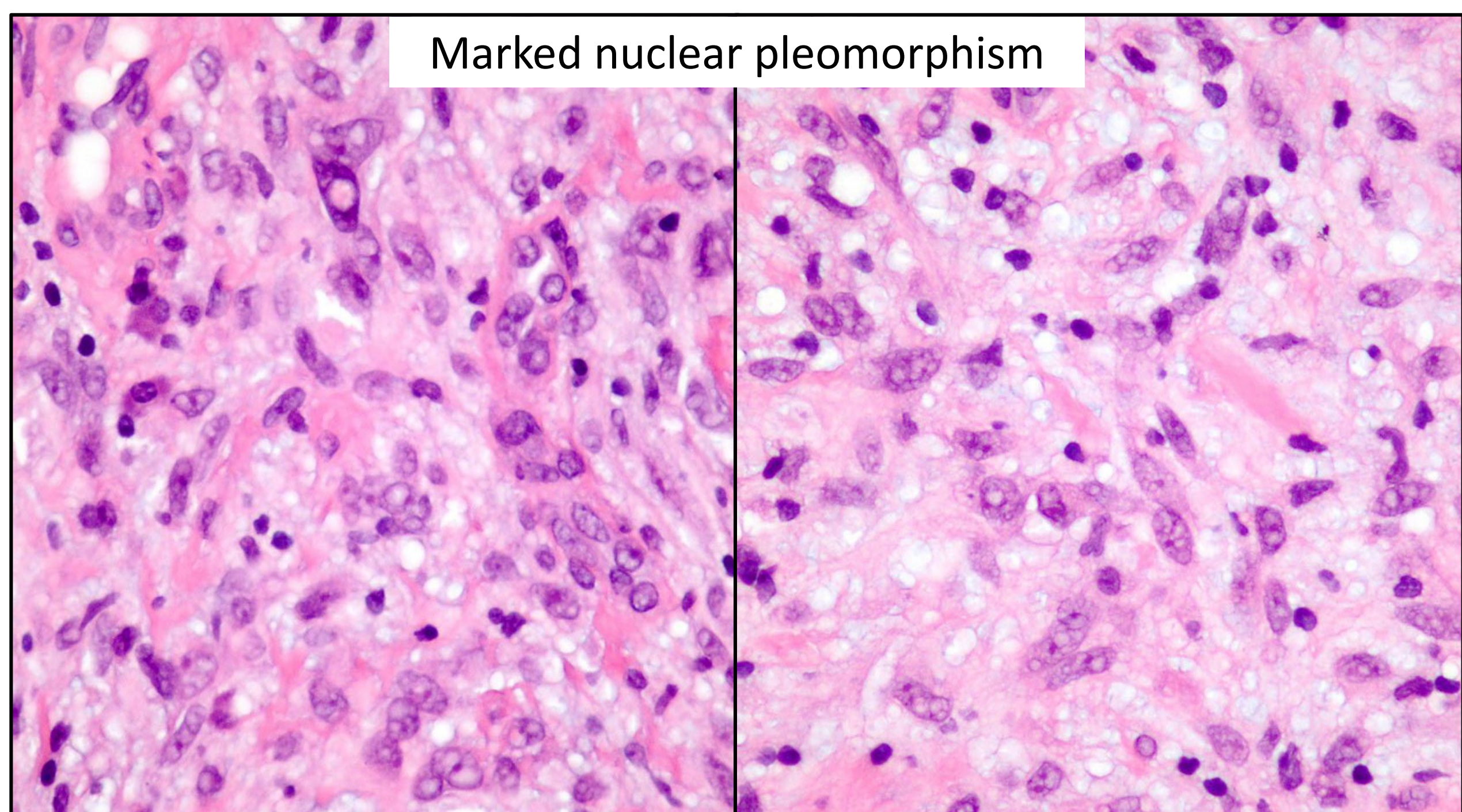


Polypoid mesenchymal lesion

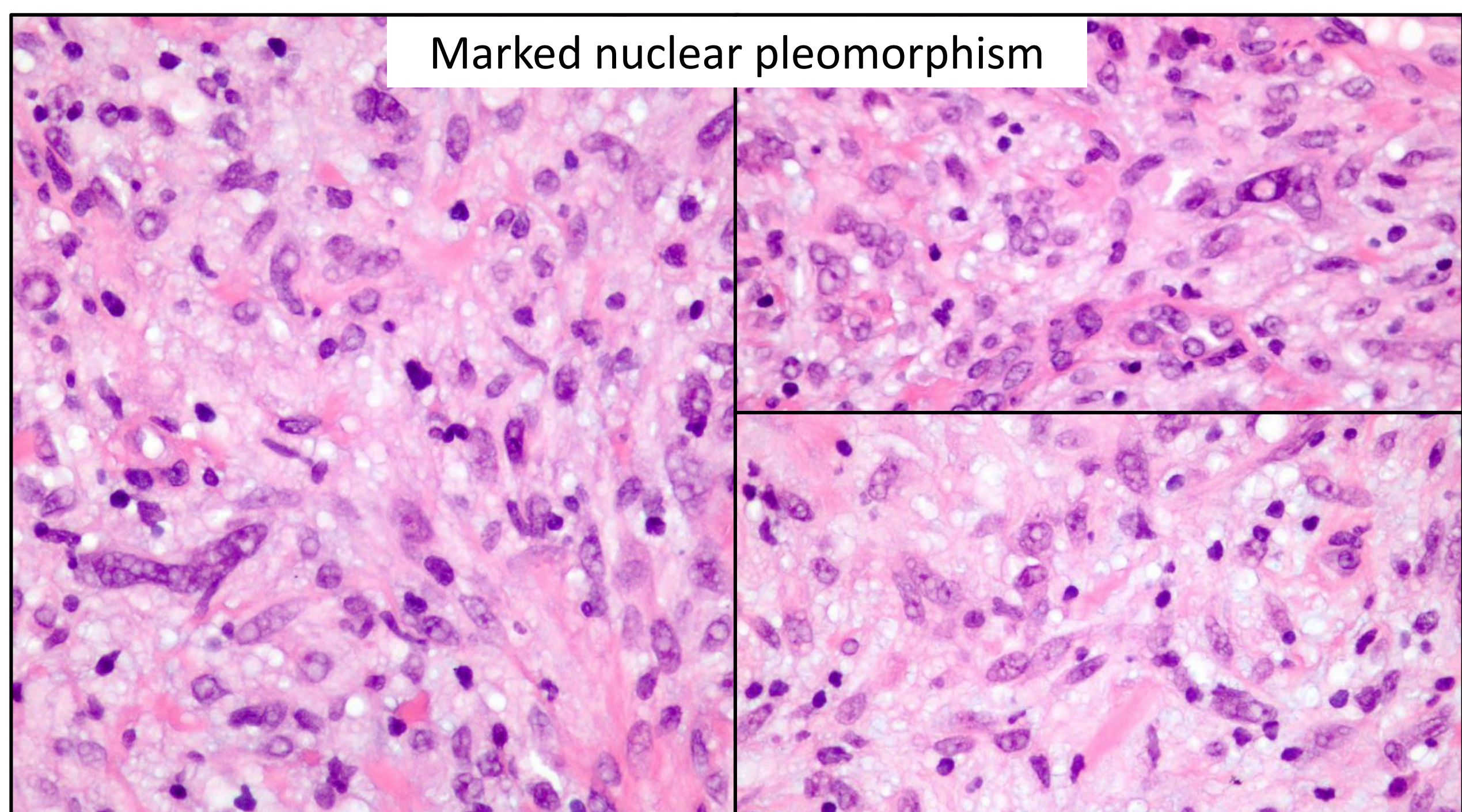


Proliferation of mesenchymal cells intermixed with inflammatory cells

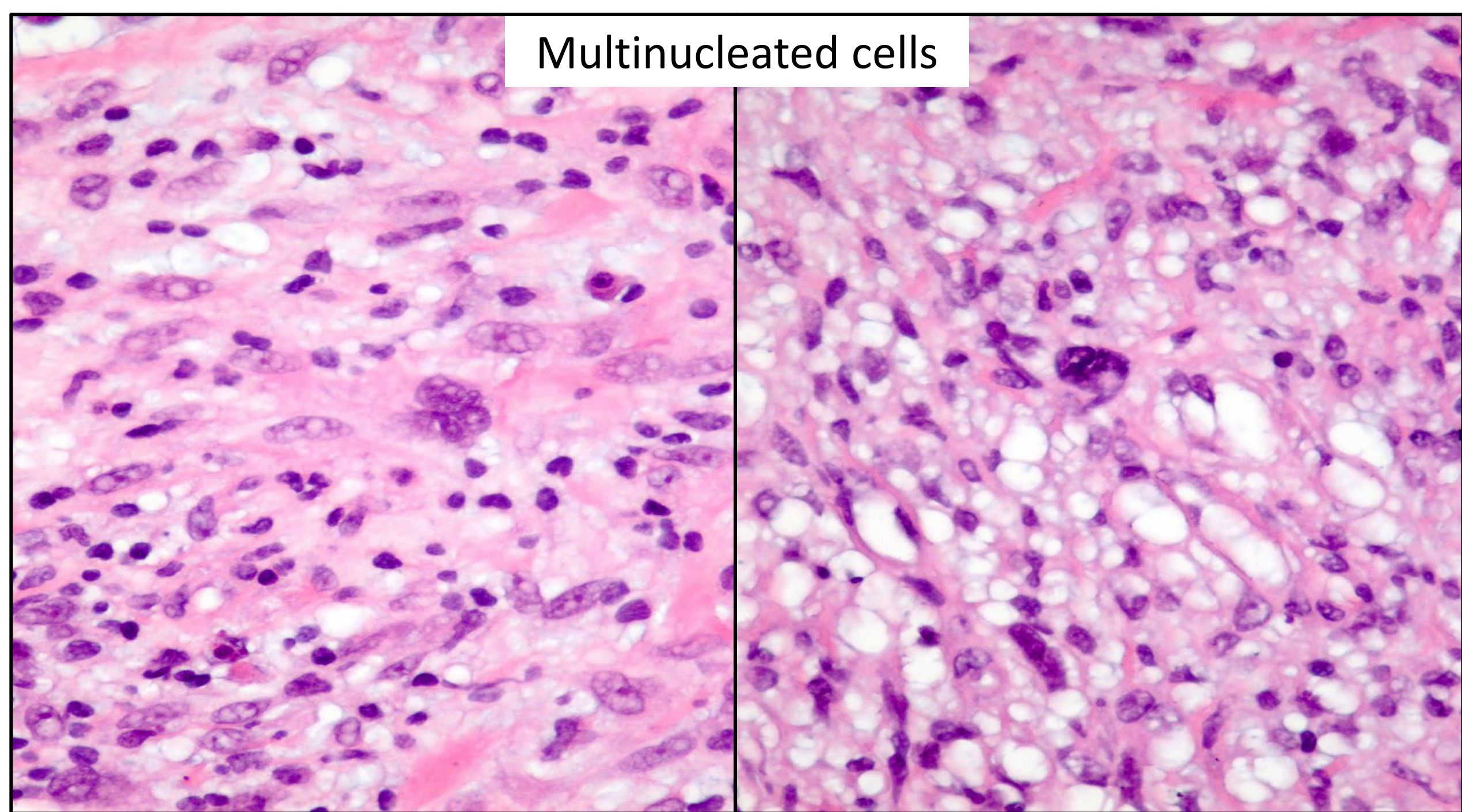
Marked nuclear pleomorphism



Marked nuclear pleomorphism



Multinucleated cells

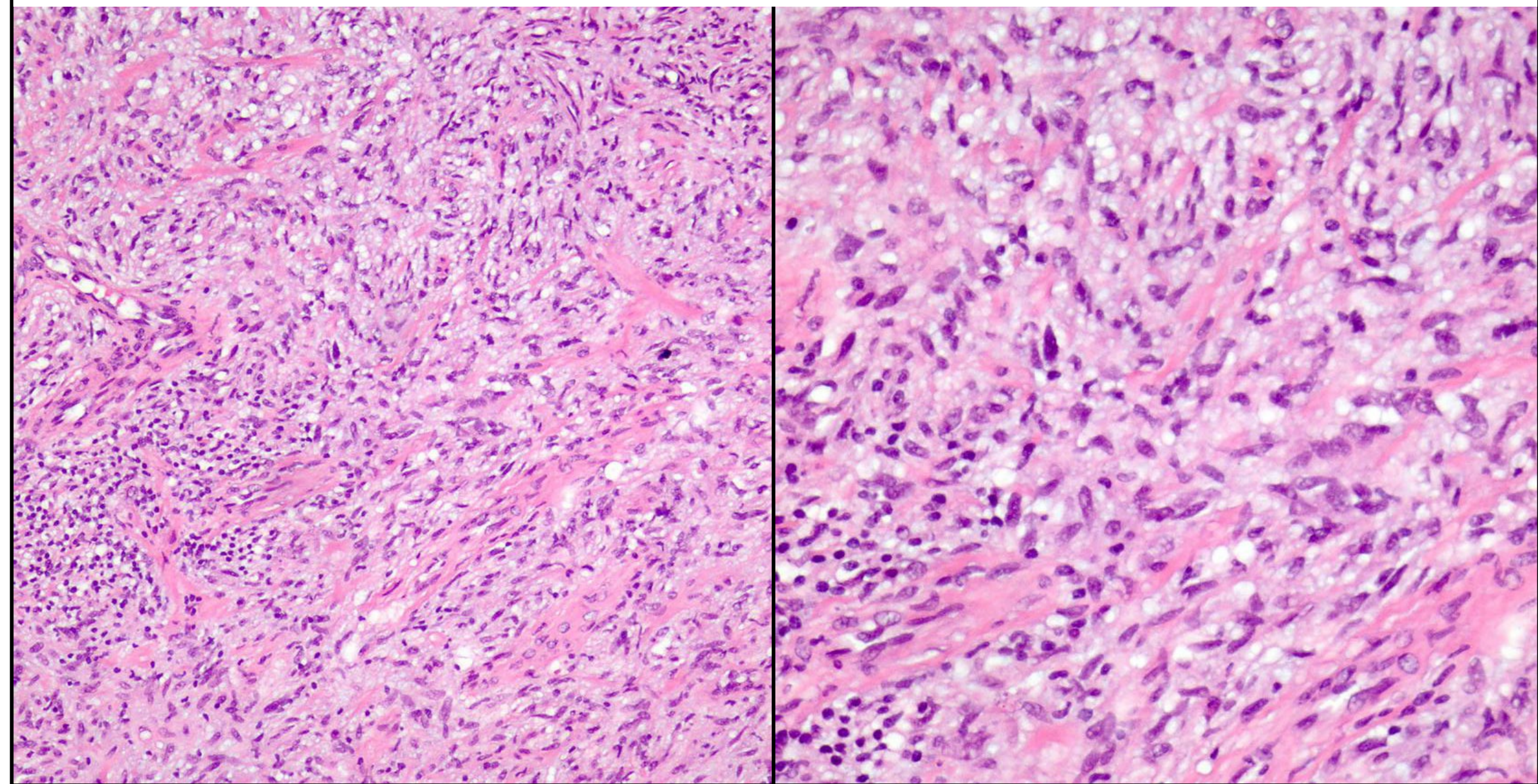


Pockets of inflammatory cells

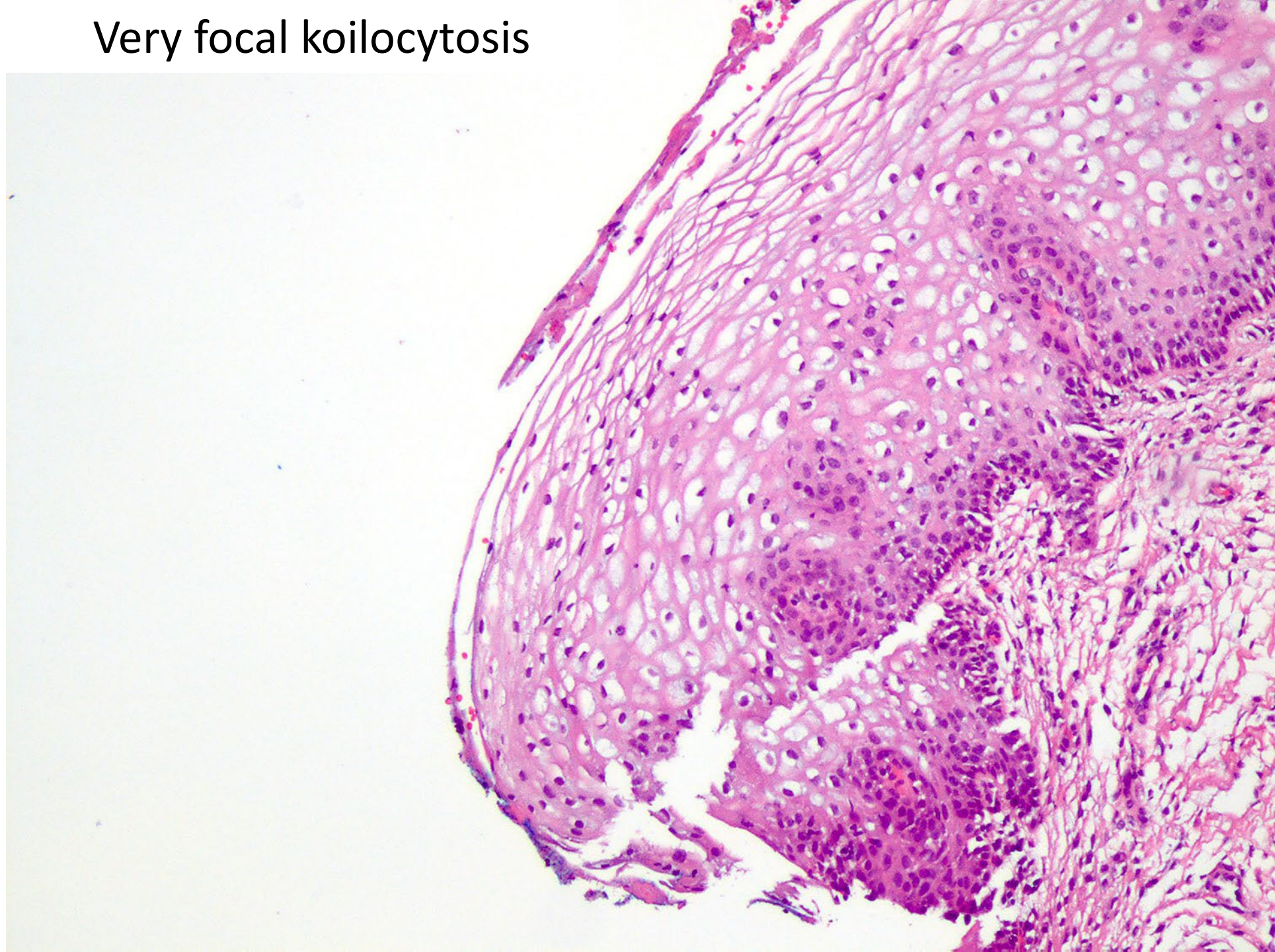
MI: 2 mitoses per 10 HPFs



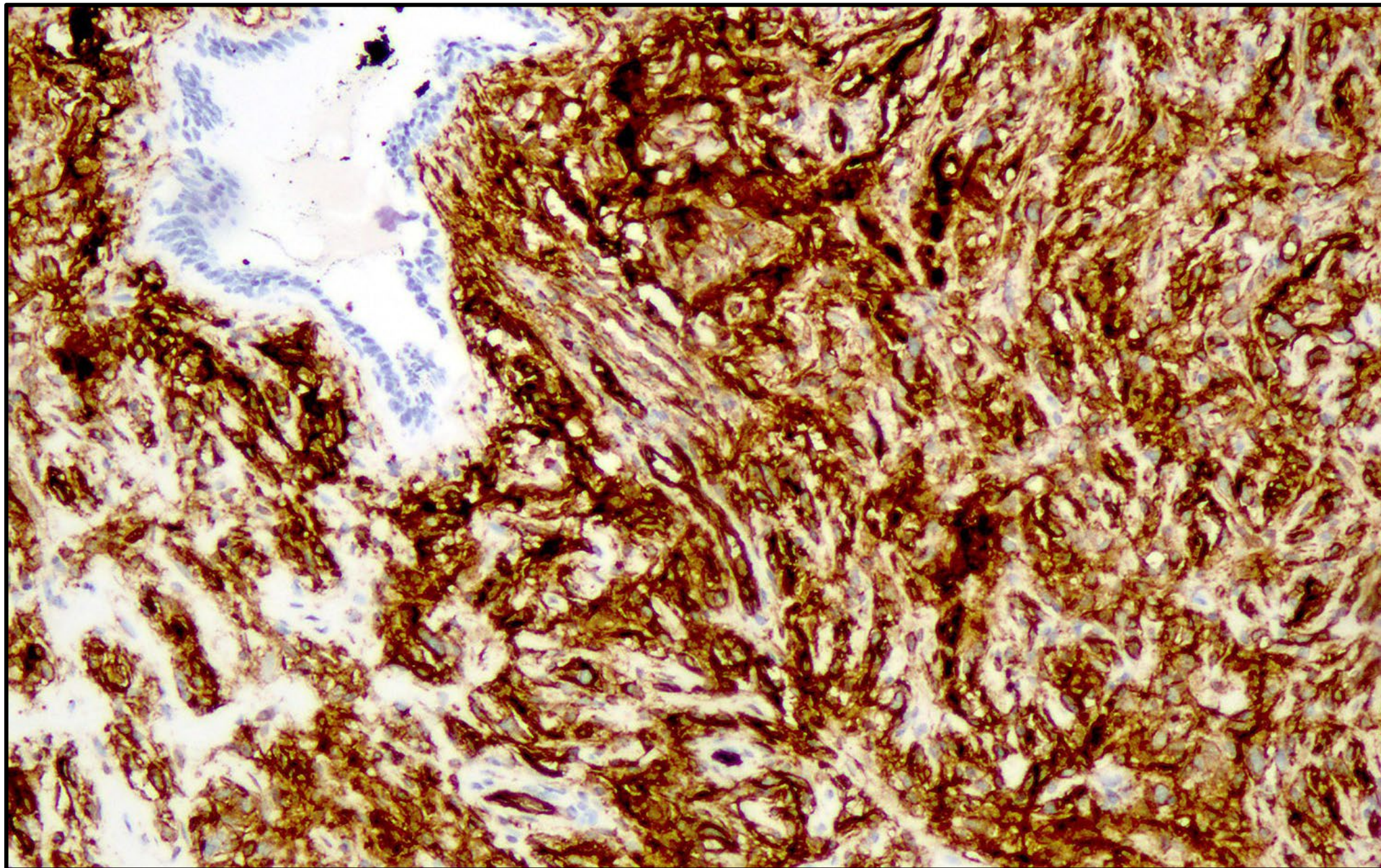
Skinny spindle cells and plump cells with mild to moderate pleomorphism



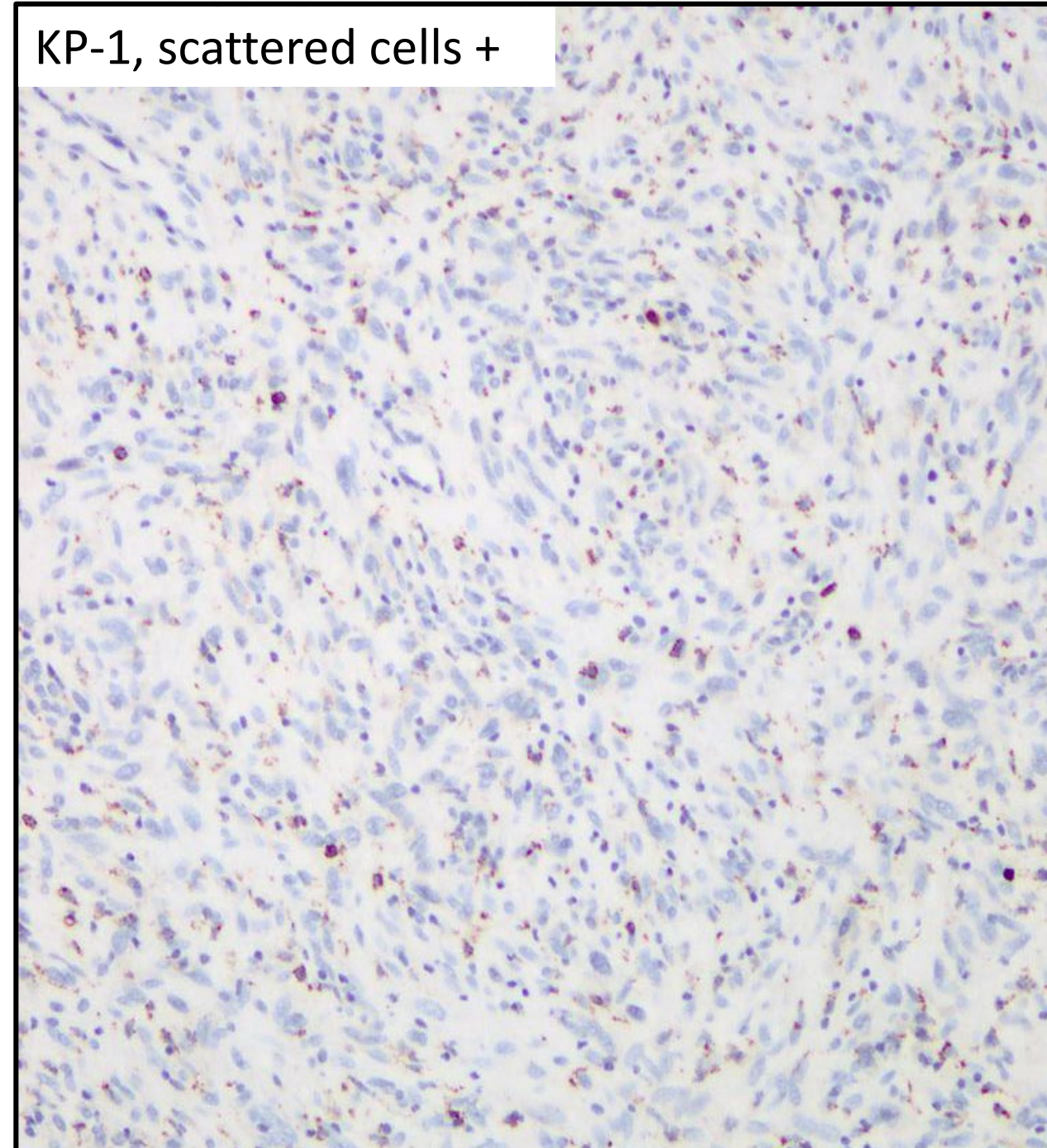
Very focal koilocytosis



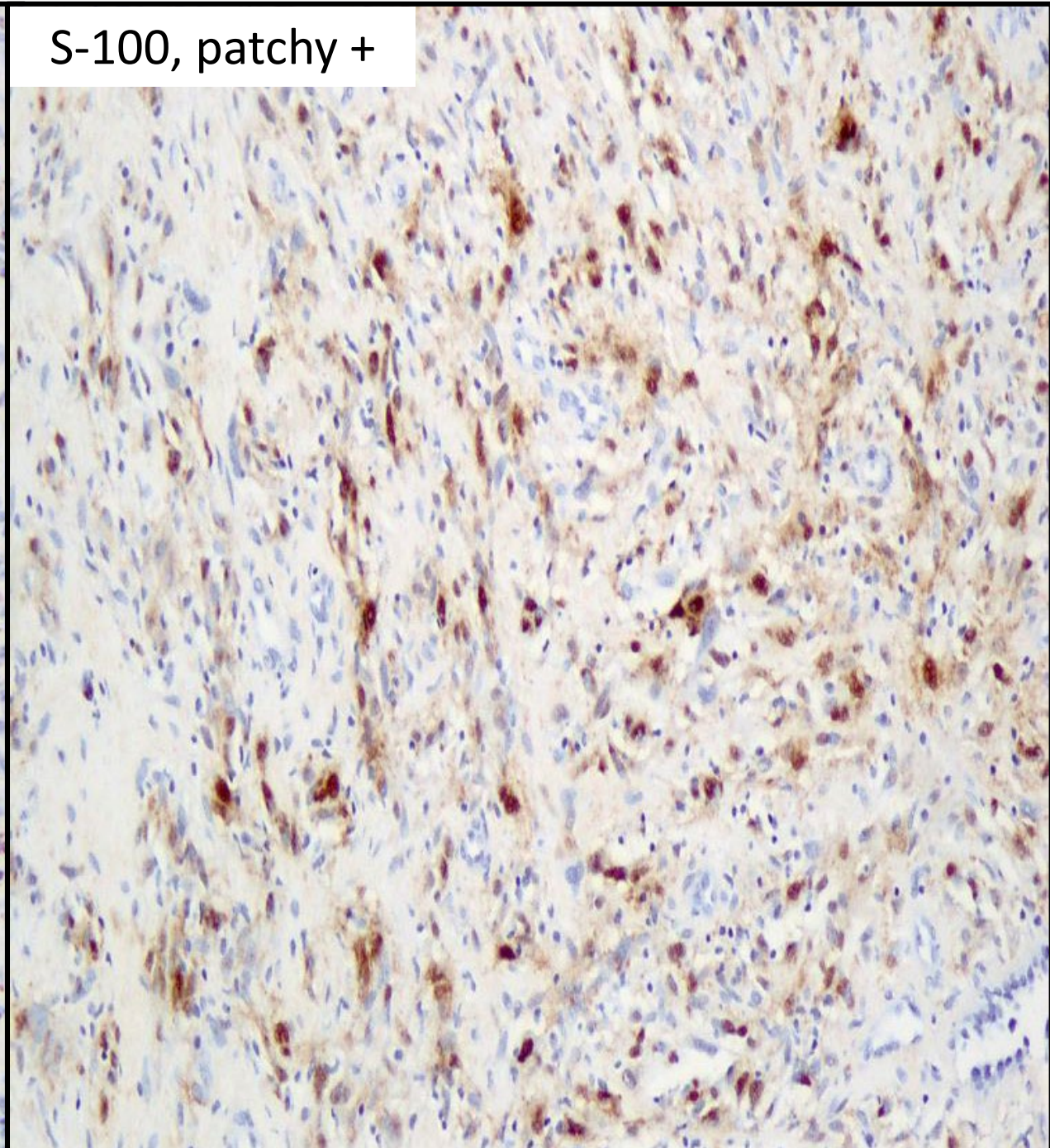
CD34, +



KP-1, scattered cells +

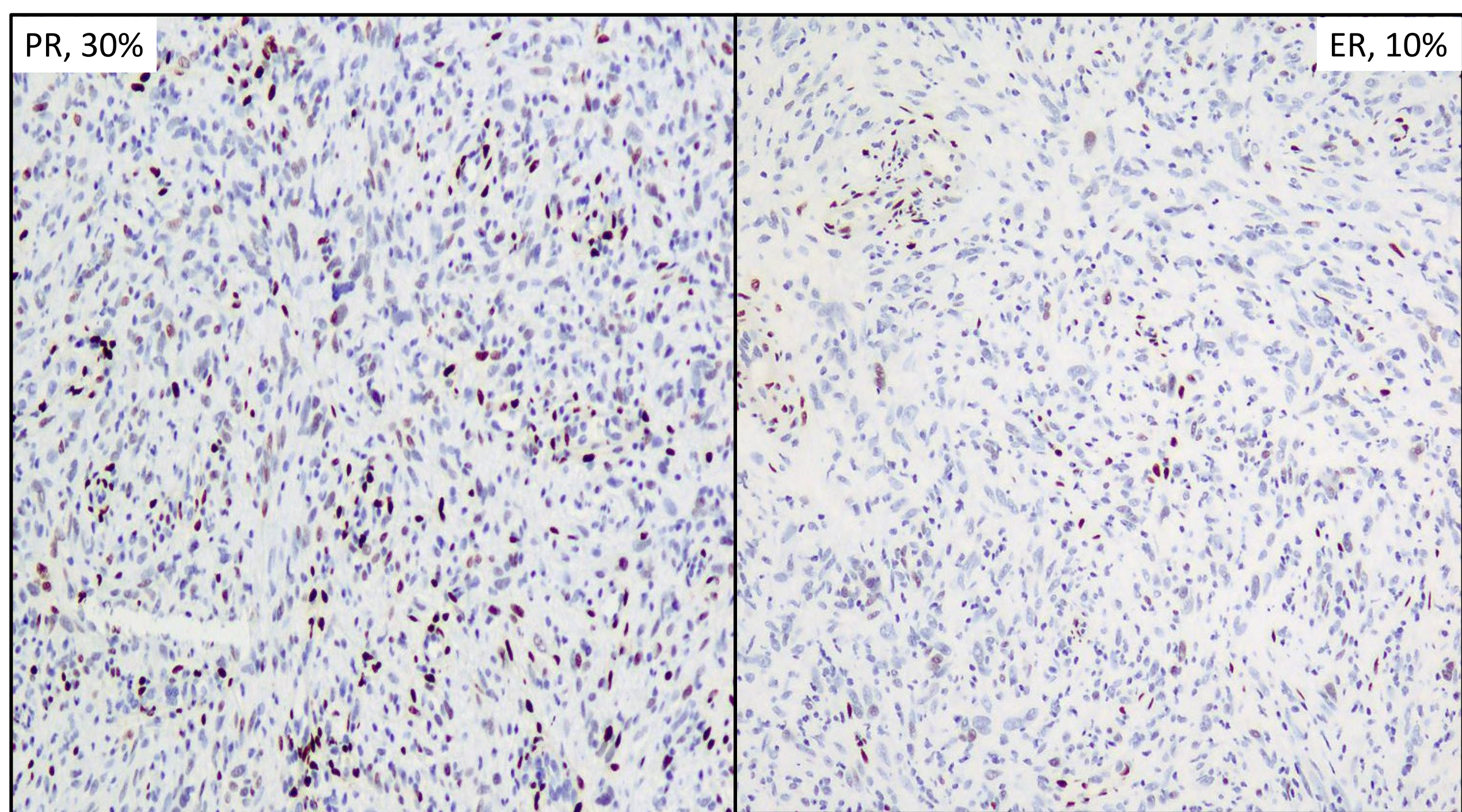


S-100, patchy +

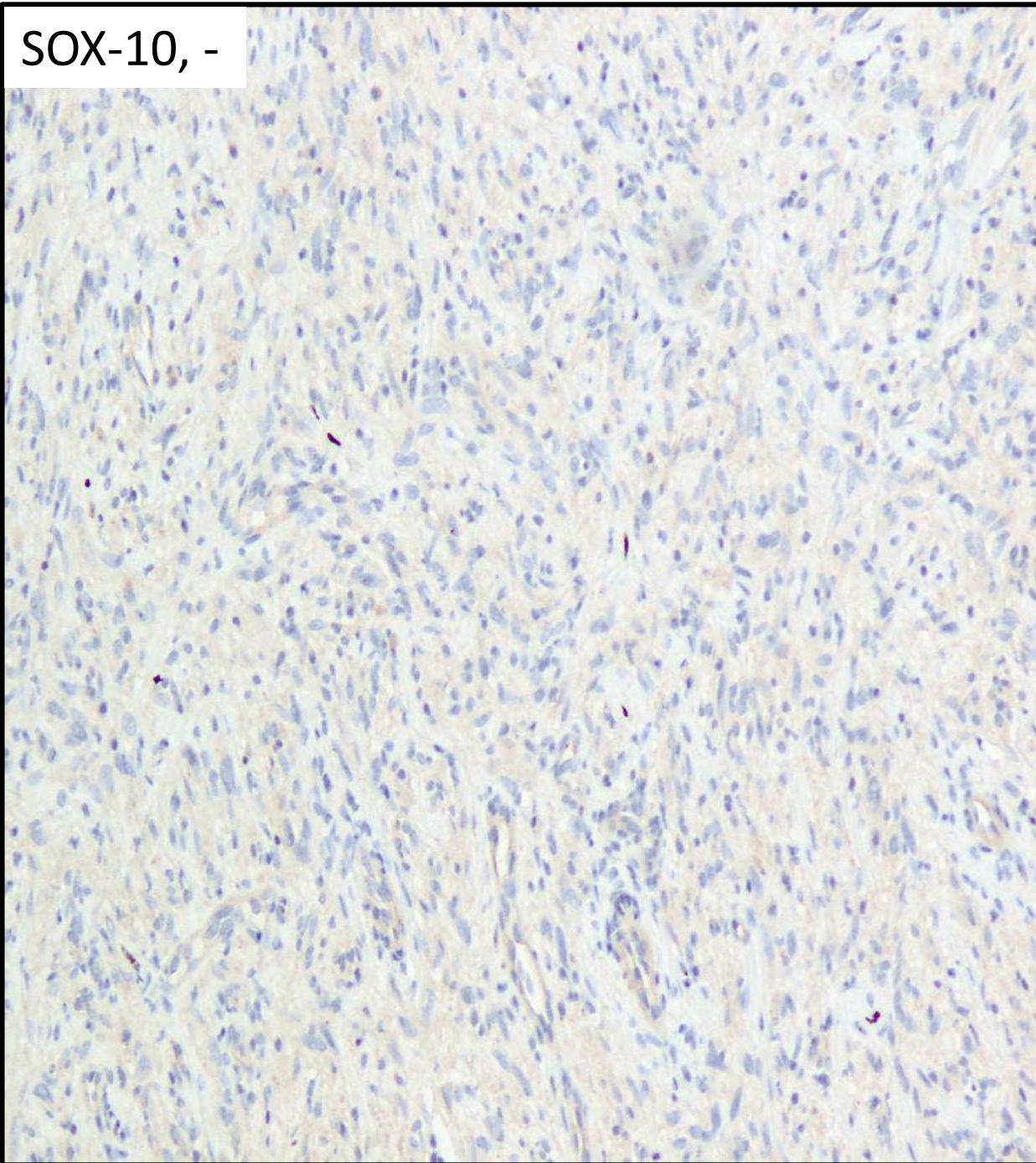


PR, 30%

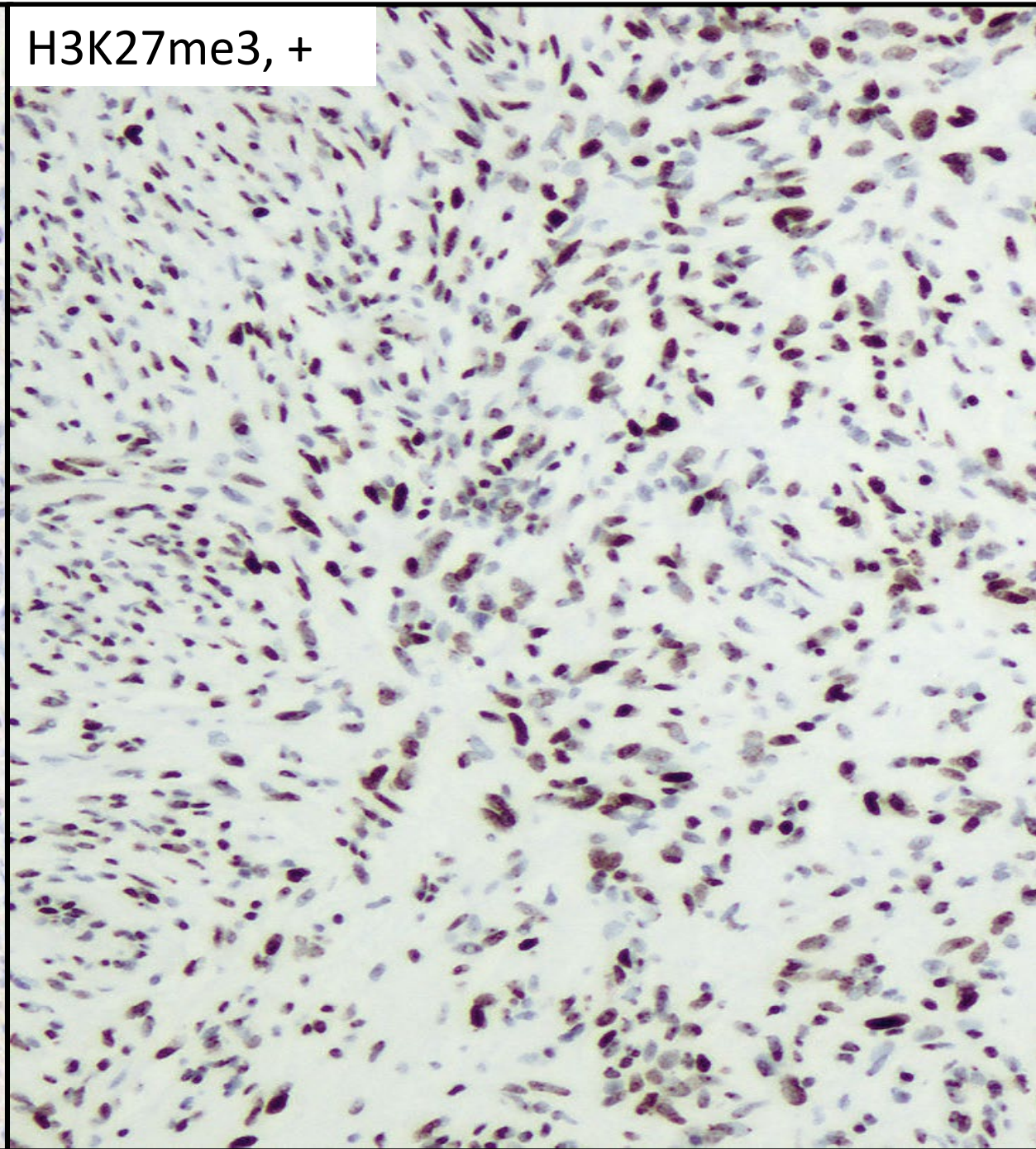
ER, 10%



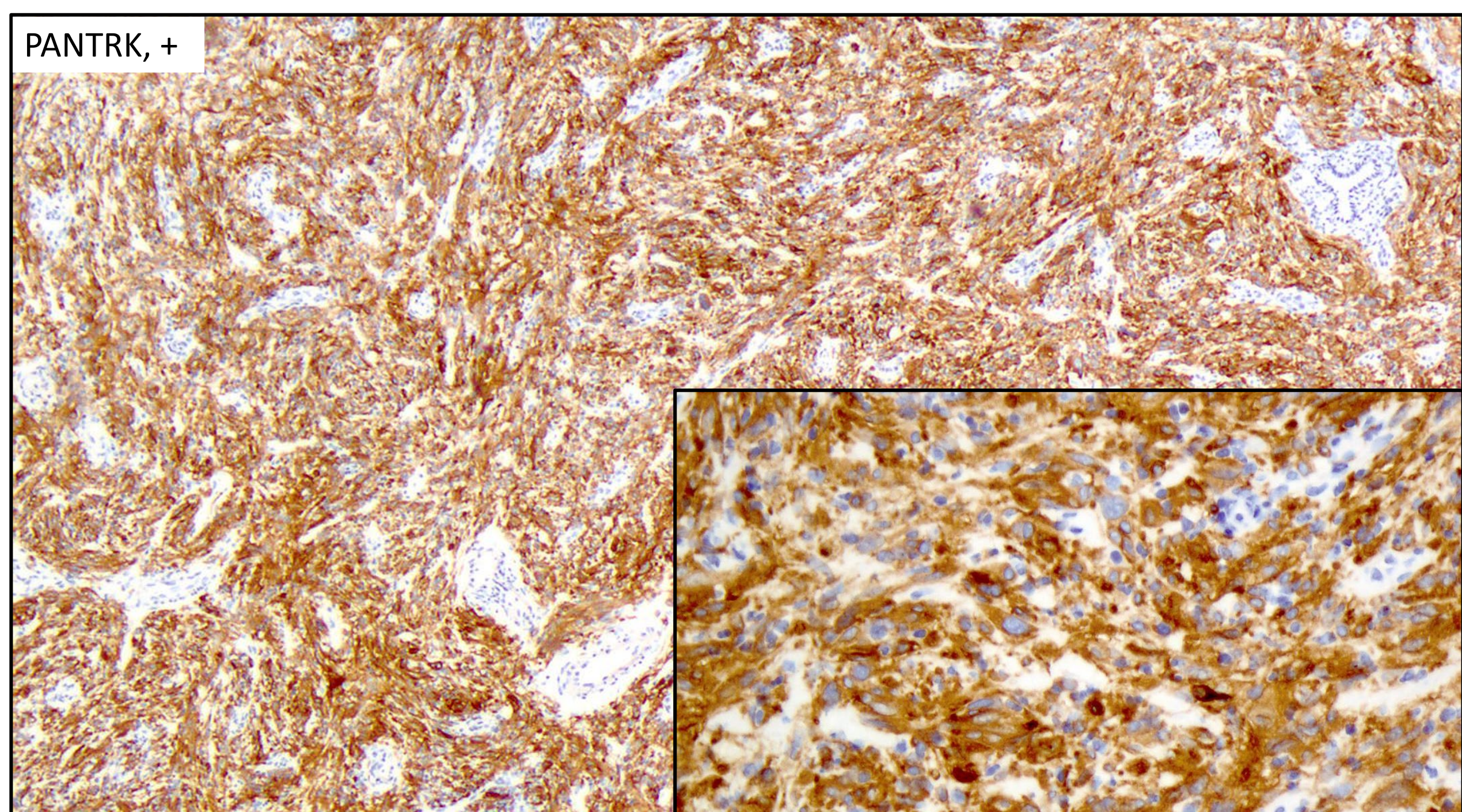
SOX-10, -



H3K27me3, +



PANTRK, +



Uterine Sarcoma with NTRK Fusion

Targeted next-generation RNA sequencing → TPM3/NTRK1 fusion

Targeted RT-PCR and Sanger sequencing → fusion transcripts
confirmed

NTRK Fusions Define a Novel Uterine Sarcoma Subtype With Features of Fibrosarcoma

Sarah Chiang, MD, Paolo Cotzia, MD,* David M. Hyman, MD,† Alexander Drilon, MD,‡
William D. Tap, MD,§ Lei Zhang, MD,* Jaclyn F. Hechtman, MD,* Denise Frosina, BS,*
Achim A. Jungbluth, MD, PhD,* Rajmohan Murali, MBBS, MD, FRCPA,* Kay J. Park, MD,*
Robert A. Soslow, MD,* Esther Oliva, MD,||¶ A. John Iafrate, MD, PhD,||¶ Ryma Benayed, PhD,*
Marc Ladanyi, MD,* and Cristina R. Antonescu, MD**



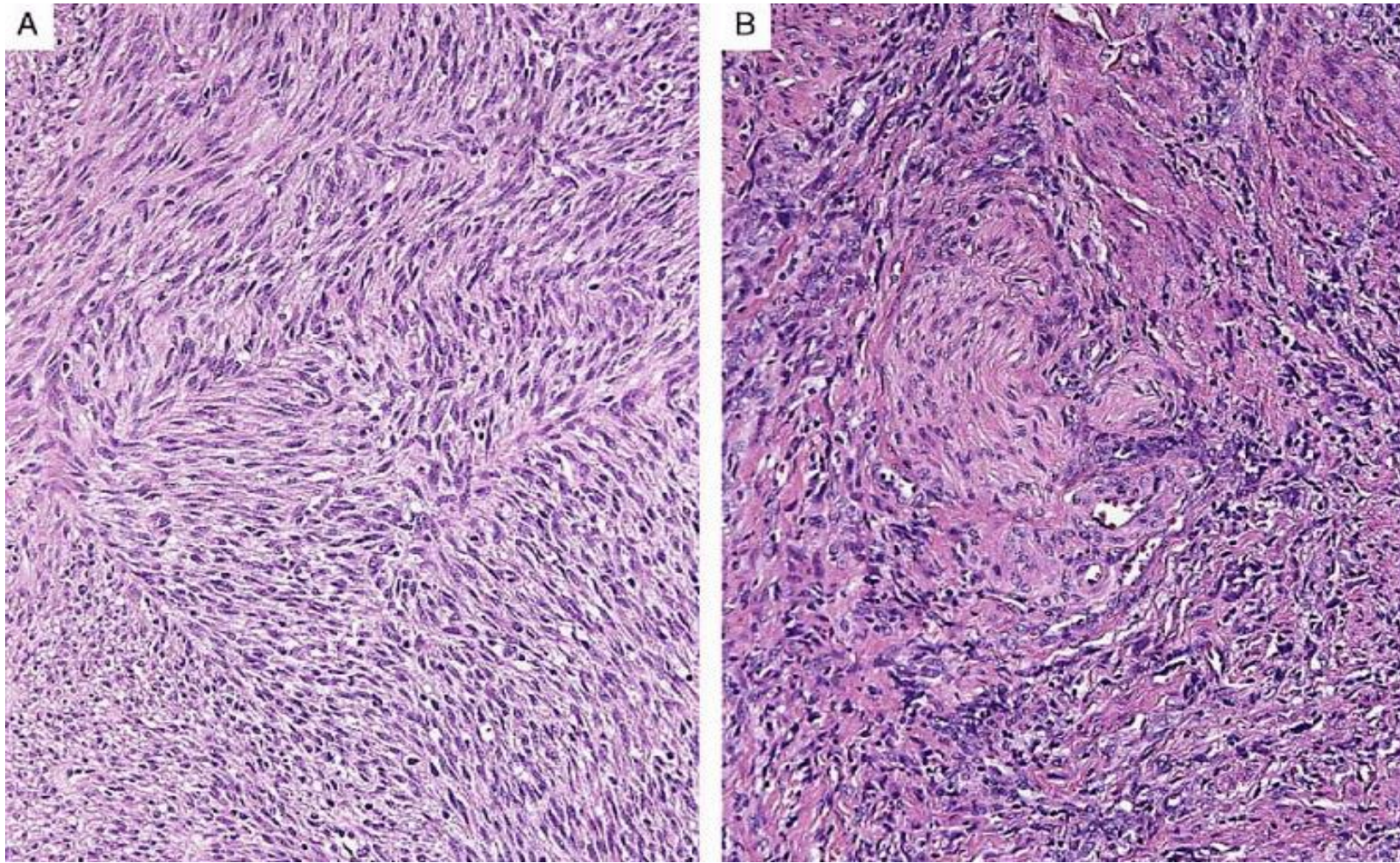
(Am J Surg Pathol 2018;42:791–798)

- Uterine Sarcomas with NTRK Fusion (4 cases)
 - TPM3-NTRK1, 1
 - LMNA-NTRK1, 1
 - TPR-NTRK1, 1
 - RBPMS-NTRK3, 1
- Tumors that can be treated with TRK inhibitors

Endocervical Fibroblastic Malignant Peripheral Nerve Sheath Tumor (Neurofibrosarcoma): Report of a Novel Entity Possibly Related to Endocervical CD34 Fibrocytes

*Anne M. Mills, MD, Jason R. Karamchandani, MD, Hannes Vogel, MD,
and Teri A. Longacre, MD*

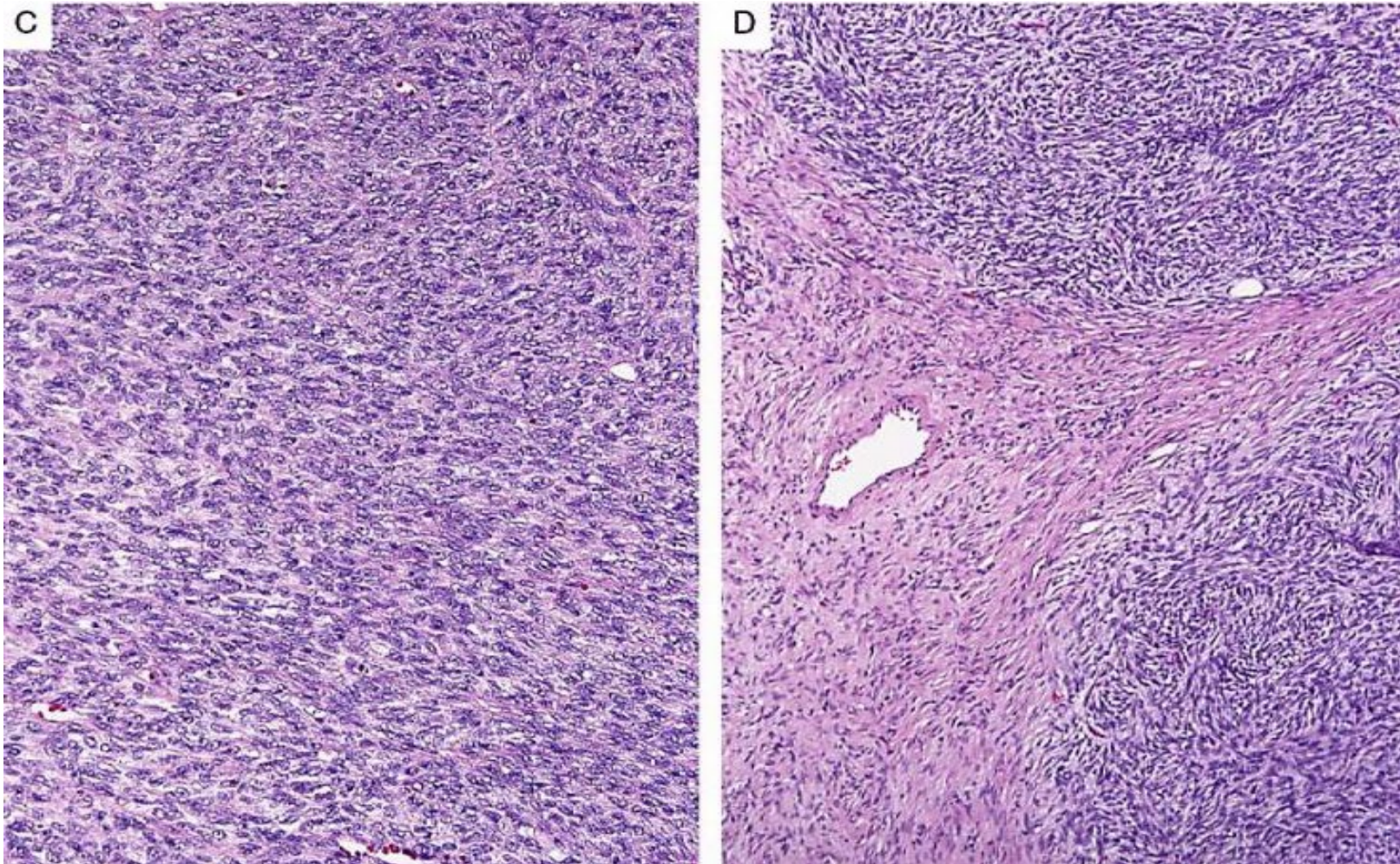
(Am J Surg Pathol 2011;35:404–412)

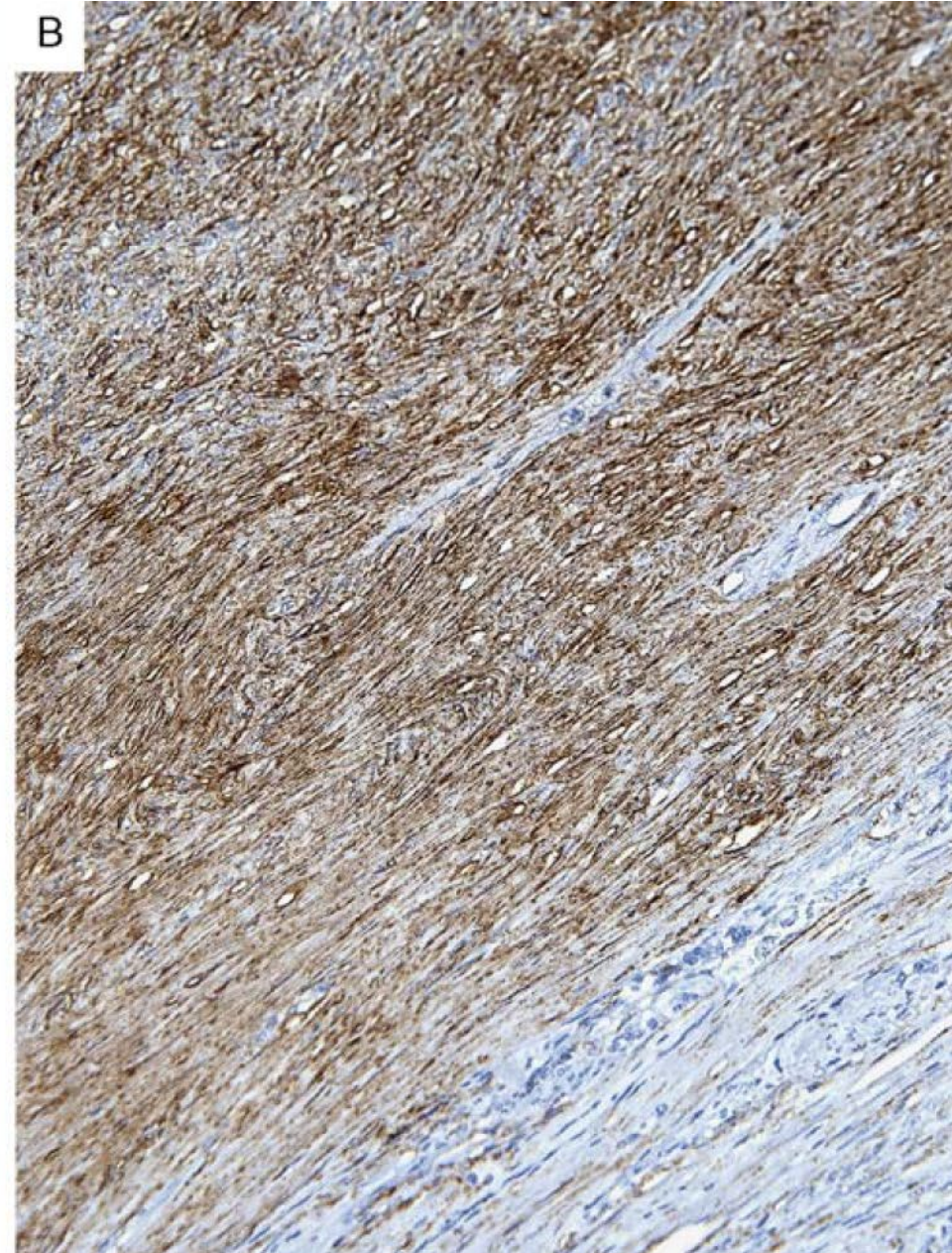
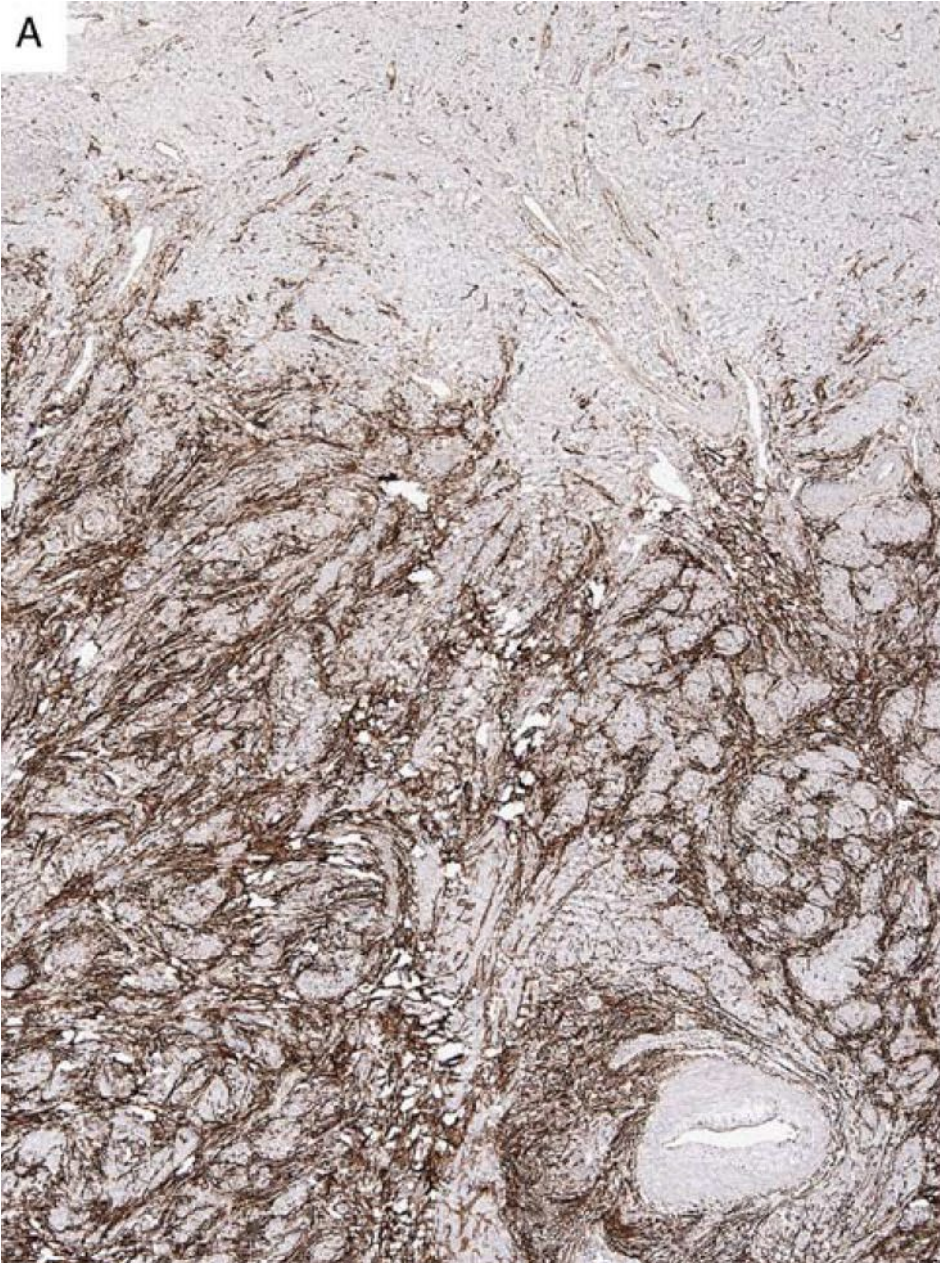


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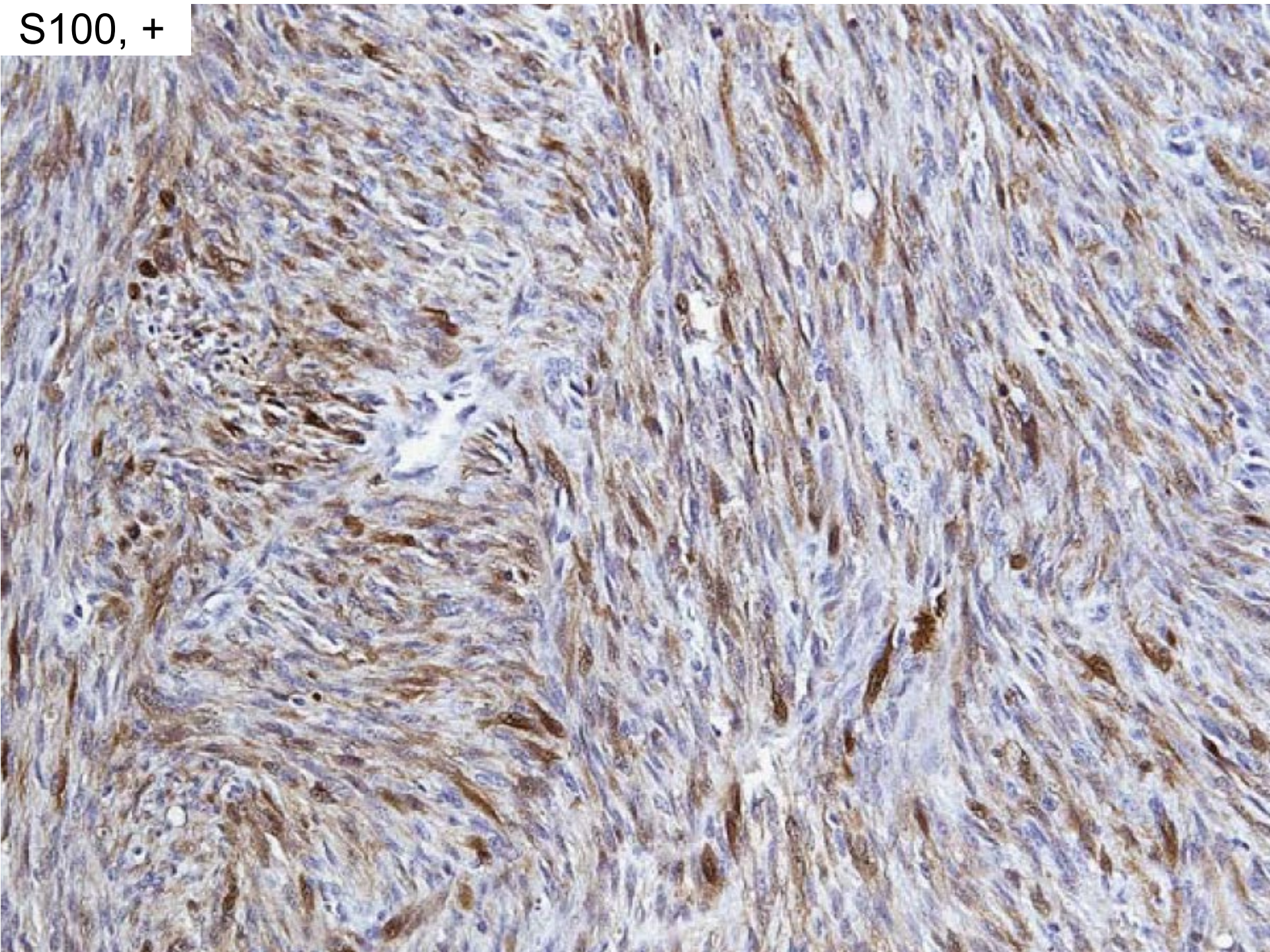
(Am J Surg Pathol 2011;35:404–412)





CD34, +

S100, +



ARTICLE



Uterine and vaginal sarcomas resembling fibrosarcoma: a clinicopathological and molecular analysis of 13 cases showing common *NTRK*-rearrangements and the description of a *COL1A1-PDGFB* fusion novel to uterine neoplasms

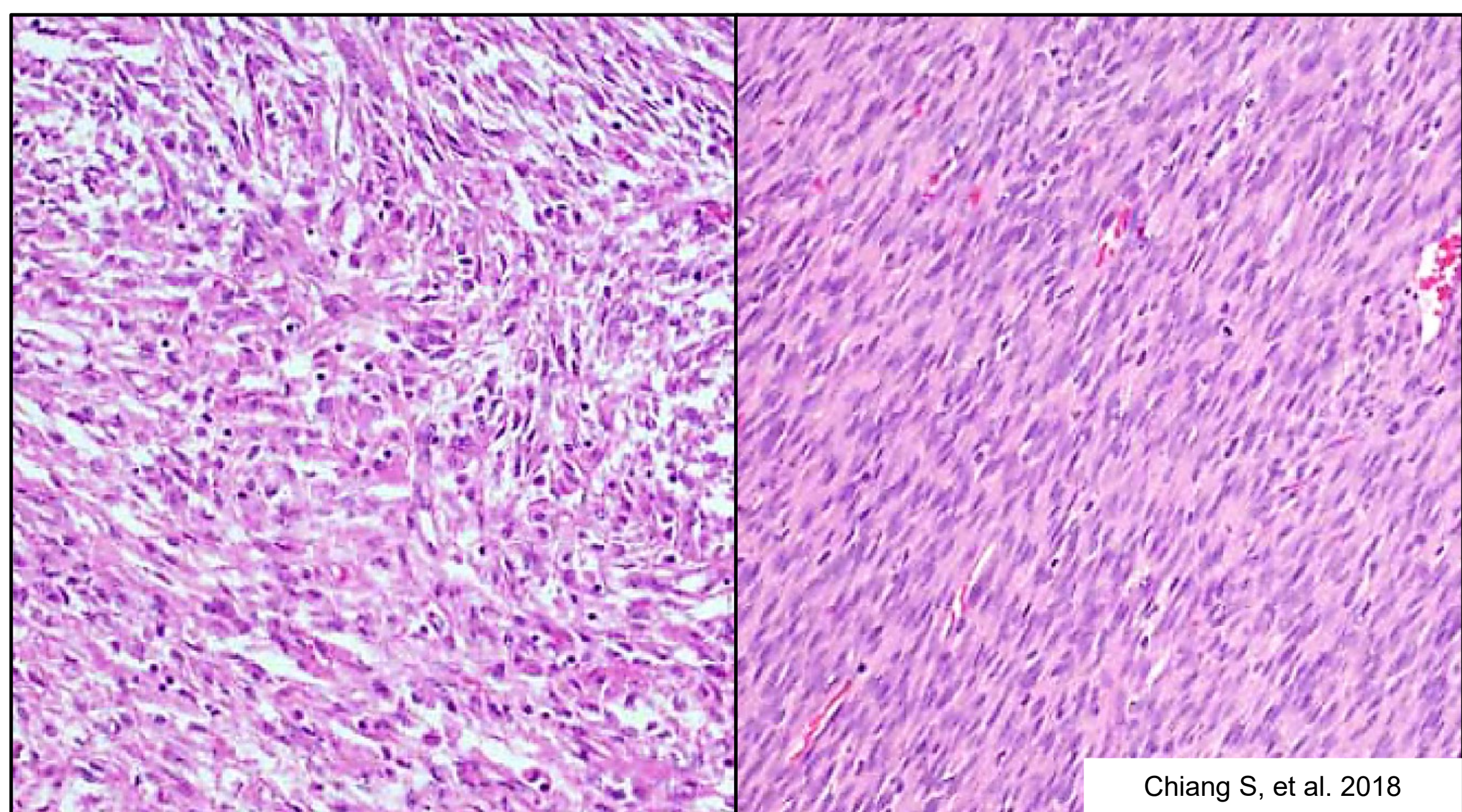
Sabrina Croce^{1,2} · Isabelle Hostein¹ · Teri A. Longacre³ · Anne M. Mills⁴ · Gaëlle Pérot¹ · Mojgan Devouassoux-Shisheboran⁵ · Valérie Velasco¹ · Anne Floquet⁶ · Frédéric Guyon⁷ · Camille Chakiba⁶ · Denis Querleu⁷ · Emmanuel Khalifa¹ · Laetitia Mayeur¹ · Flora Rebier¹ · Sophie Leguellec⁸ · Isabelle Soubeyran¹ · W. Glenn McCluggage⁹

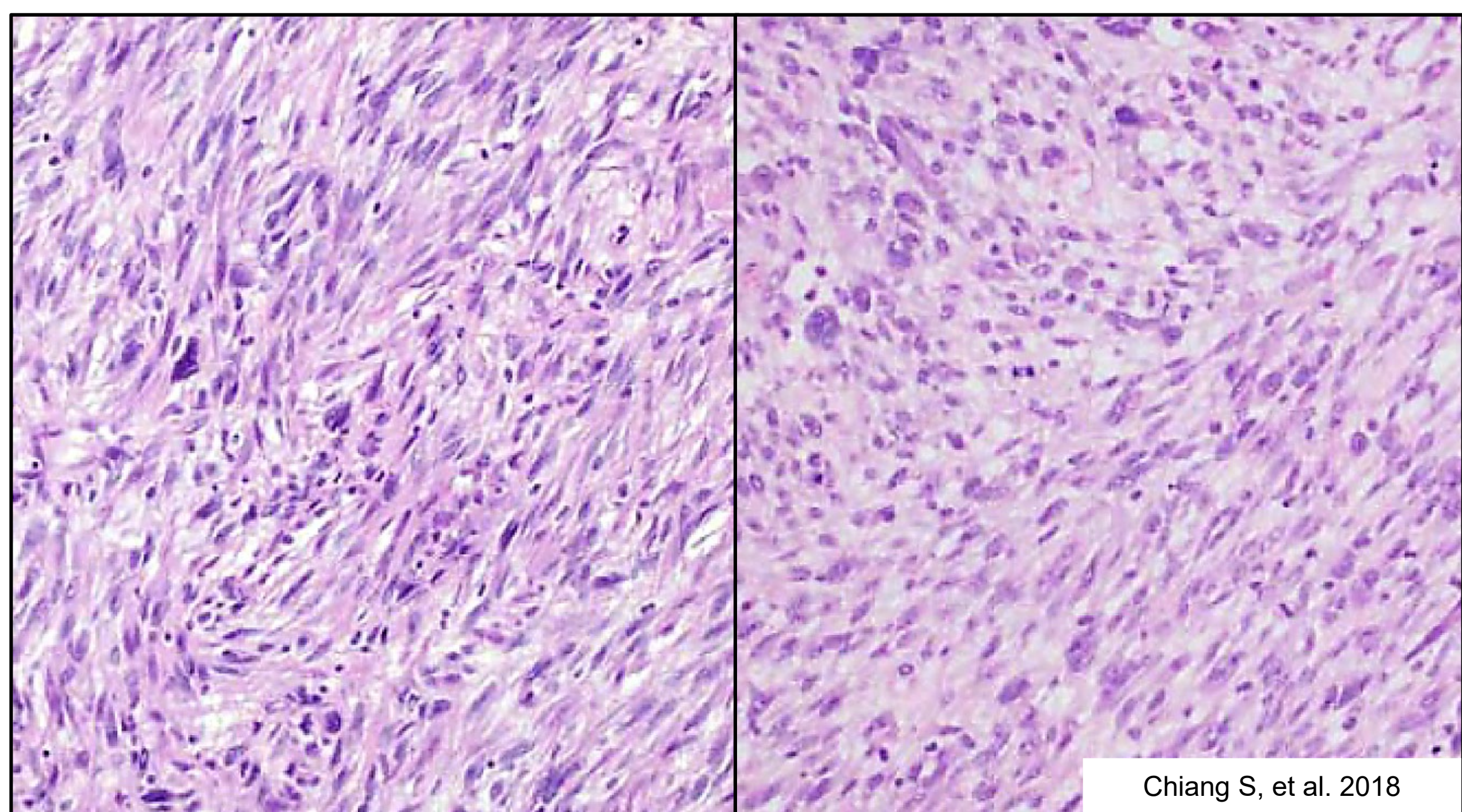
Received: 19 September 2018 / Revised: 2 November 2018 / Accepted: 2 November 2018
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- 7 cases with *NTRK* fusion
 - TPM3-*NTRK1* (6)
 - EMLA-*NTRK3* (1)
- 3 cases with *COL1A1-PDGFB* fusion
- 3 cases with no rearrangement
 - All S-100 + (diffuse, 2; focal, 1)
 - Loss of H3K27me3 (2)

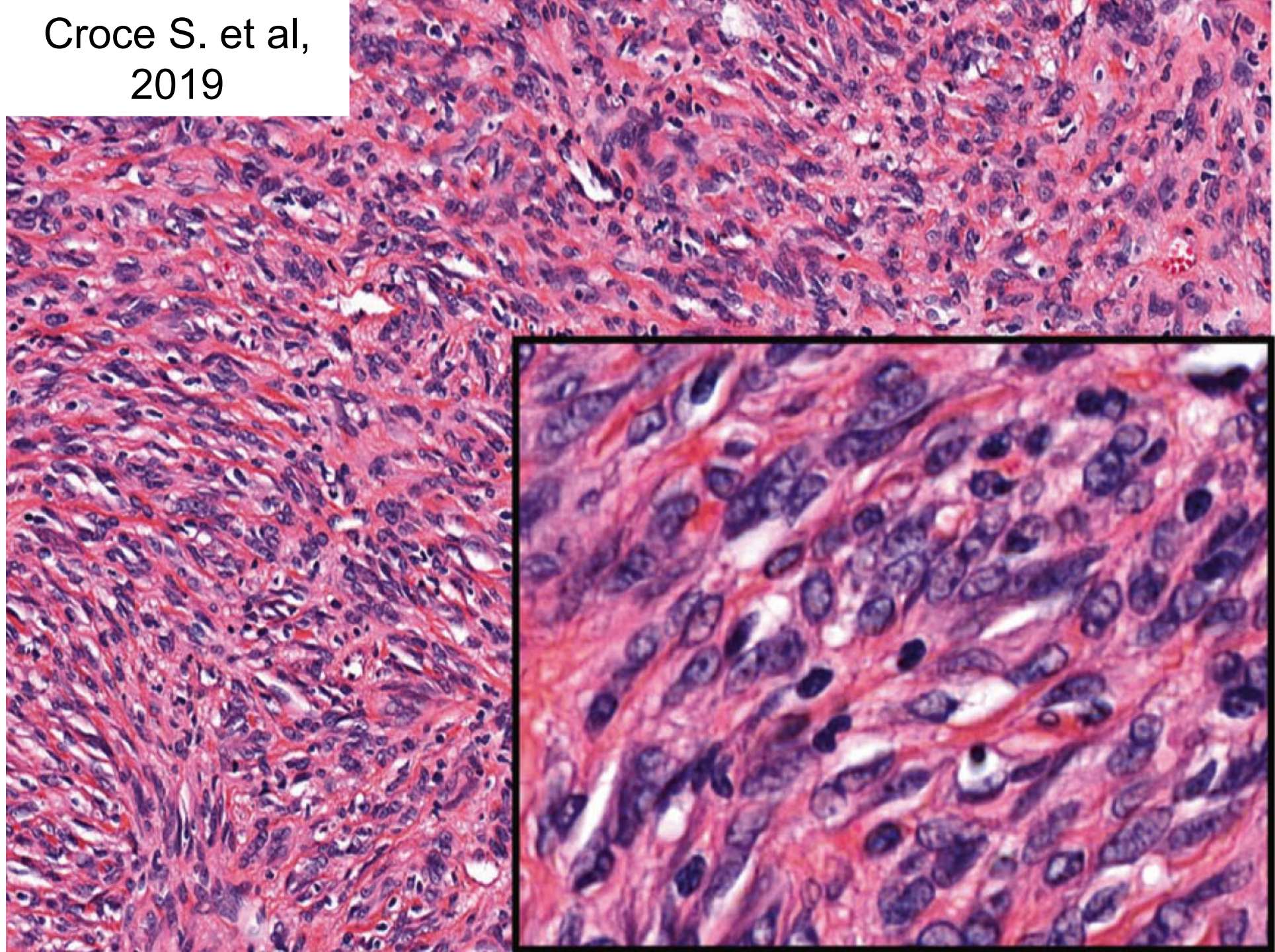
Uterine Sarcomas with NTRK Fusion

- Pattern
 - Diffuse patternless or fascicles
- Cells
 - Spindle cells with or without inflammatory cells
- Degree of atypia
 - Variable
- MI
 - 1 to 50 per 10 HPFs
- Necrosis
 - Variable

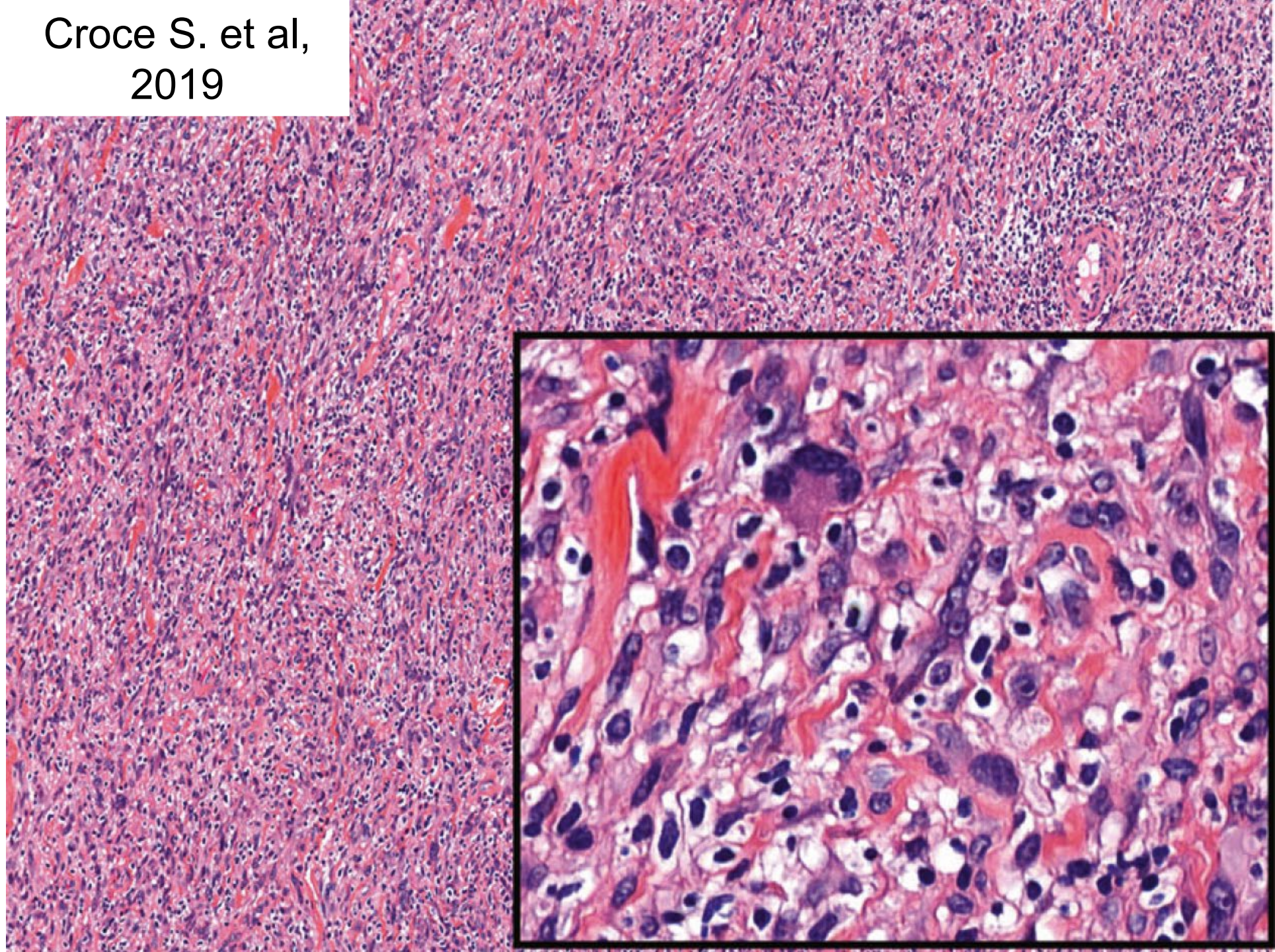




Croce S. et al,
2019



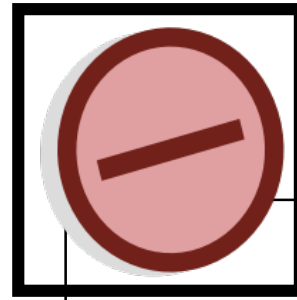
Croce S. et al,
2019



Uterine Sarcomas with NTRK Fusion IHC



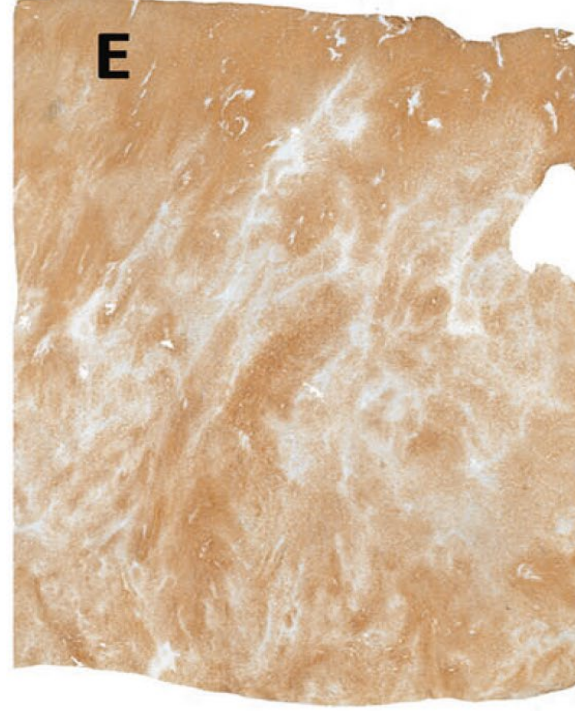
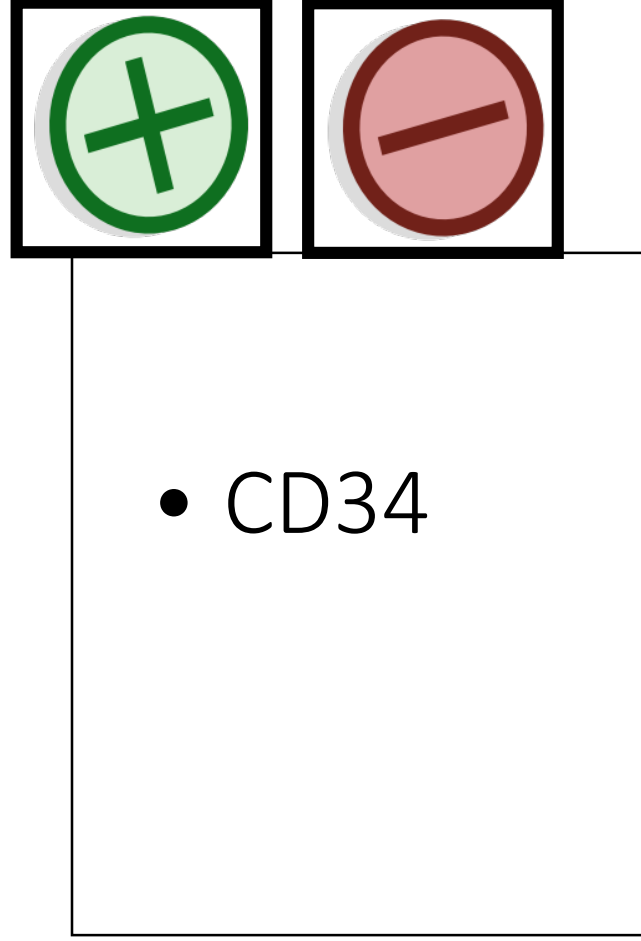
- Pan-TRK
- SMA (F)
- S-100 (F/ D)



- Desmin
- SOX-10
- ER (can be focally +)
- PR (can be focally +)

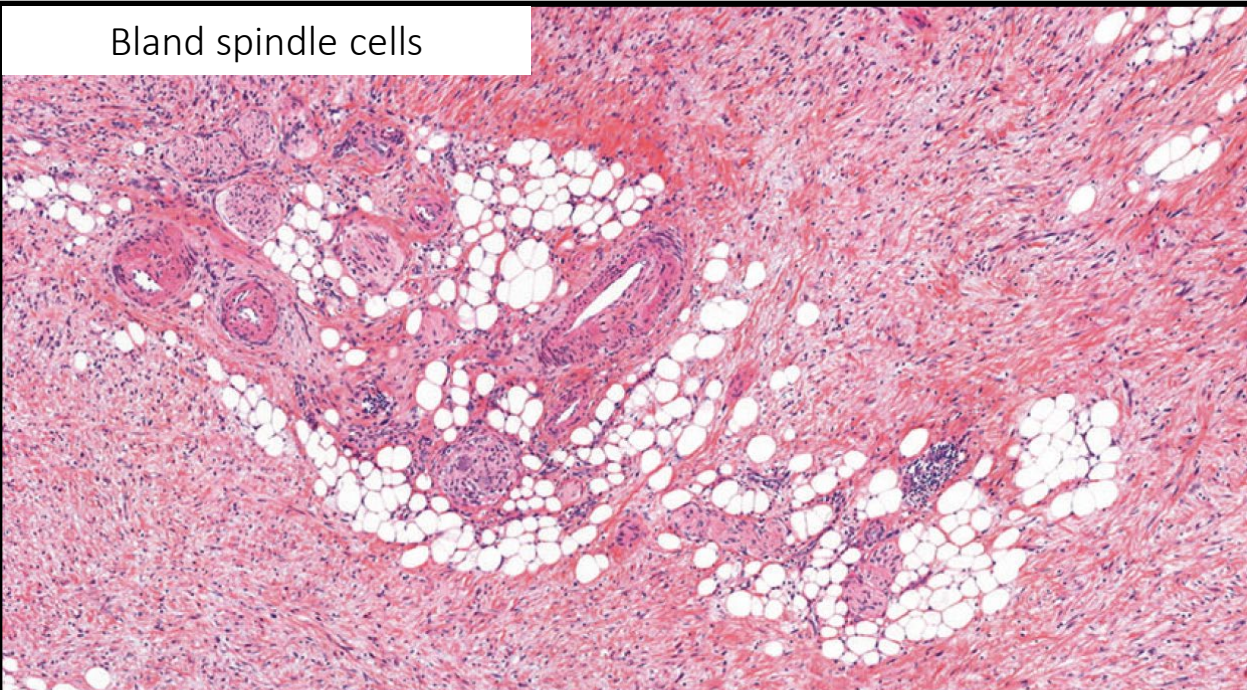
H3K27me3 retention of nuclear expression

Uterine Sarcomas with NTRK Fusion IHC

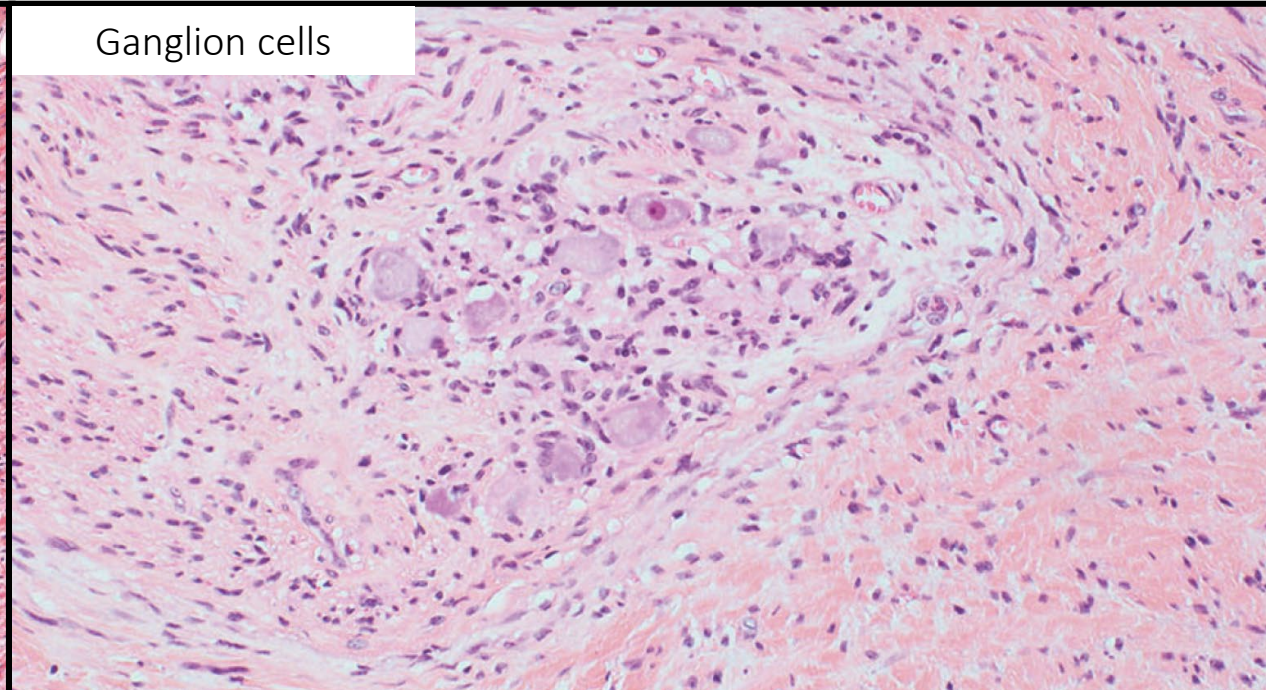


Croce S, et al. 2019

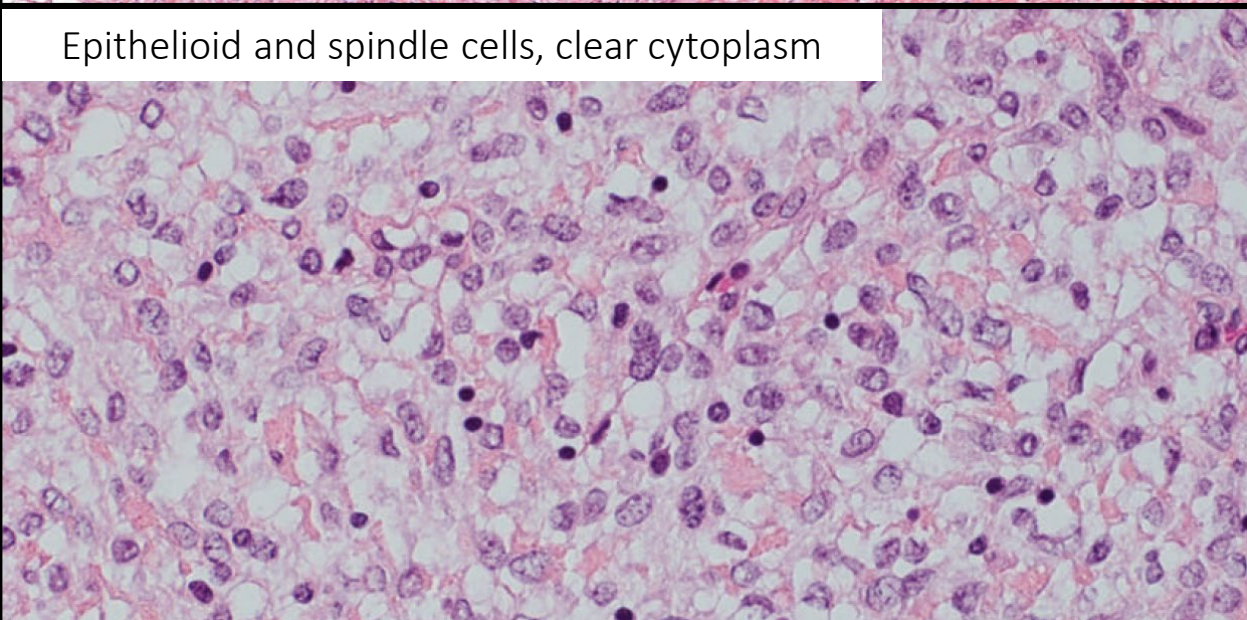
Bland spindle cells



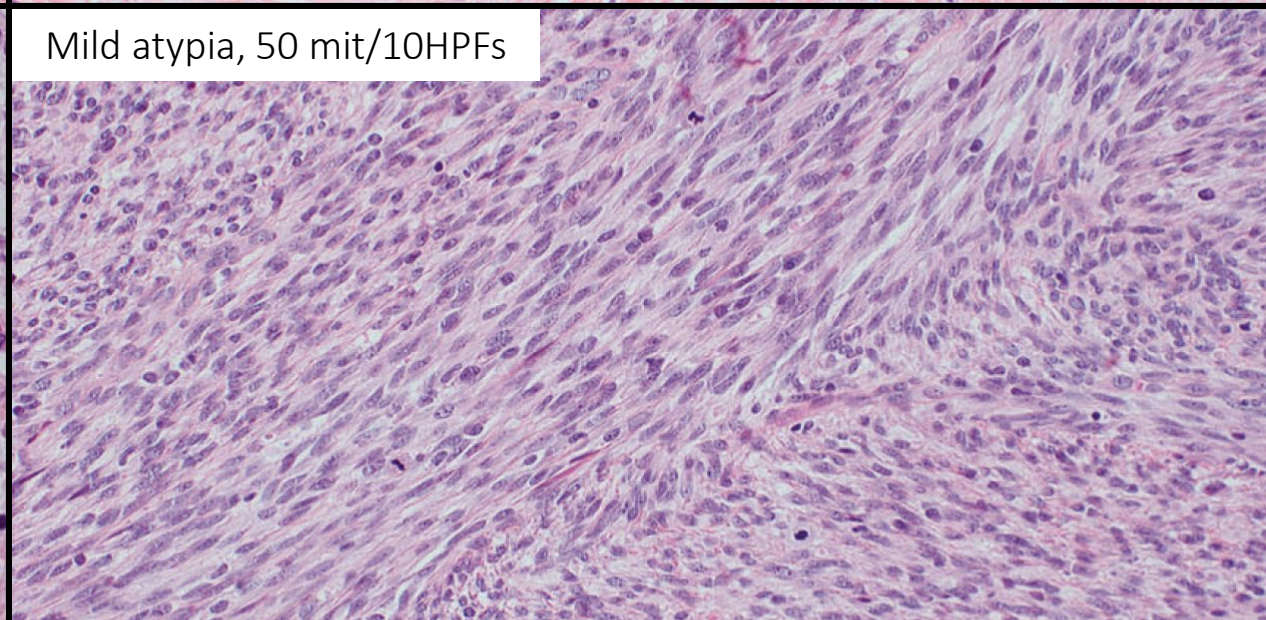
Ganglion cells



Epithelioid and spindle cells, clear cytoplasm



Mild atypia, 50 mit/10HPFs



“MPNS” based on S-100 +, and loss of H3K27me3 in 2/3 cases. Croce S, et al. 2019

Uterine Sarcomas with NTRK Fusion

- MSK study, 4 pts
 - 2 NED at 2 mos and 11 mos, respectively
 - 1 DOD at 78 mos (Surg + Chemo)
 - 1 AWD at 7 mos (Surg +Chemo)
 - Lung mt at presentation
- Collaborative study (France/Northern Ireland/USA), 6 pts with F/U
 - 2 AWD
 - 4 NED

Uterine Sarcomas with NTRK Fusion

- First generation NTRK inhibitors
 - High response rates (>75%) regardless of tumor histology
 - Advanced-stage NTRK fusion positive tumors eventually become refractory to TRK inhibition
- Second generation NTRK
 - Currently tested under clinical trials

