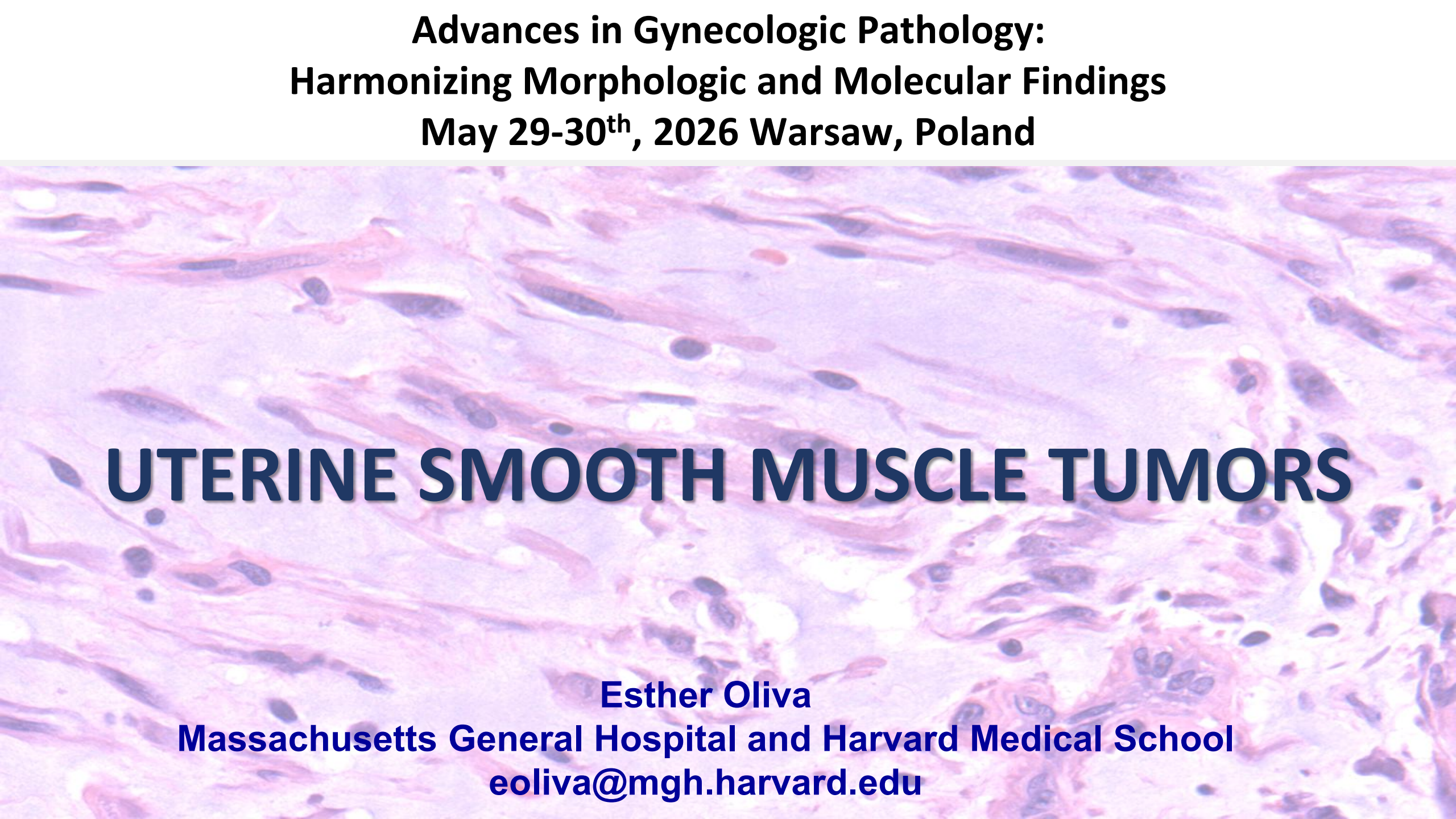


**Advances in Gynecologic Pathology:
Harmonizing Morphologic and Molecular Findings
May 29-30th, 2026 Warsaw, Poland**



UTERINE SMOOTH MUSCLE TUMORS

**Esther Oliva
Massachusetts General Hospital and Harvard Medical School
eoliva@mgh.harvard.edu**

CASE

Clinical History

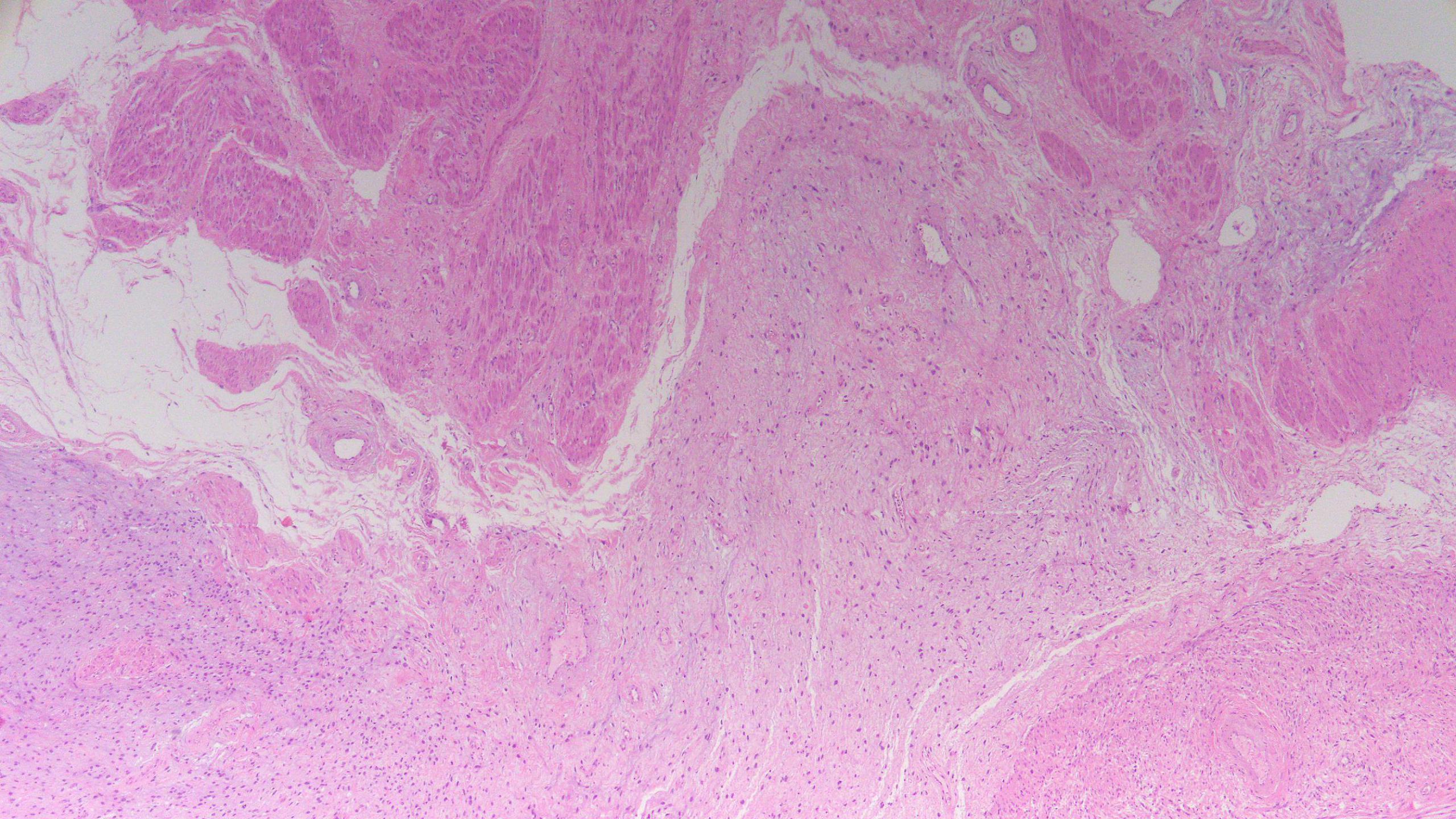
88 year old female with a 6-month history of pelvic pain and altered bowel habits

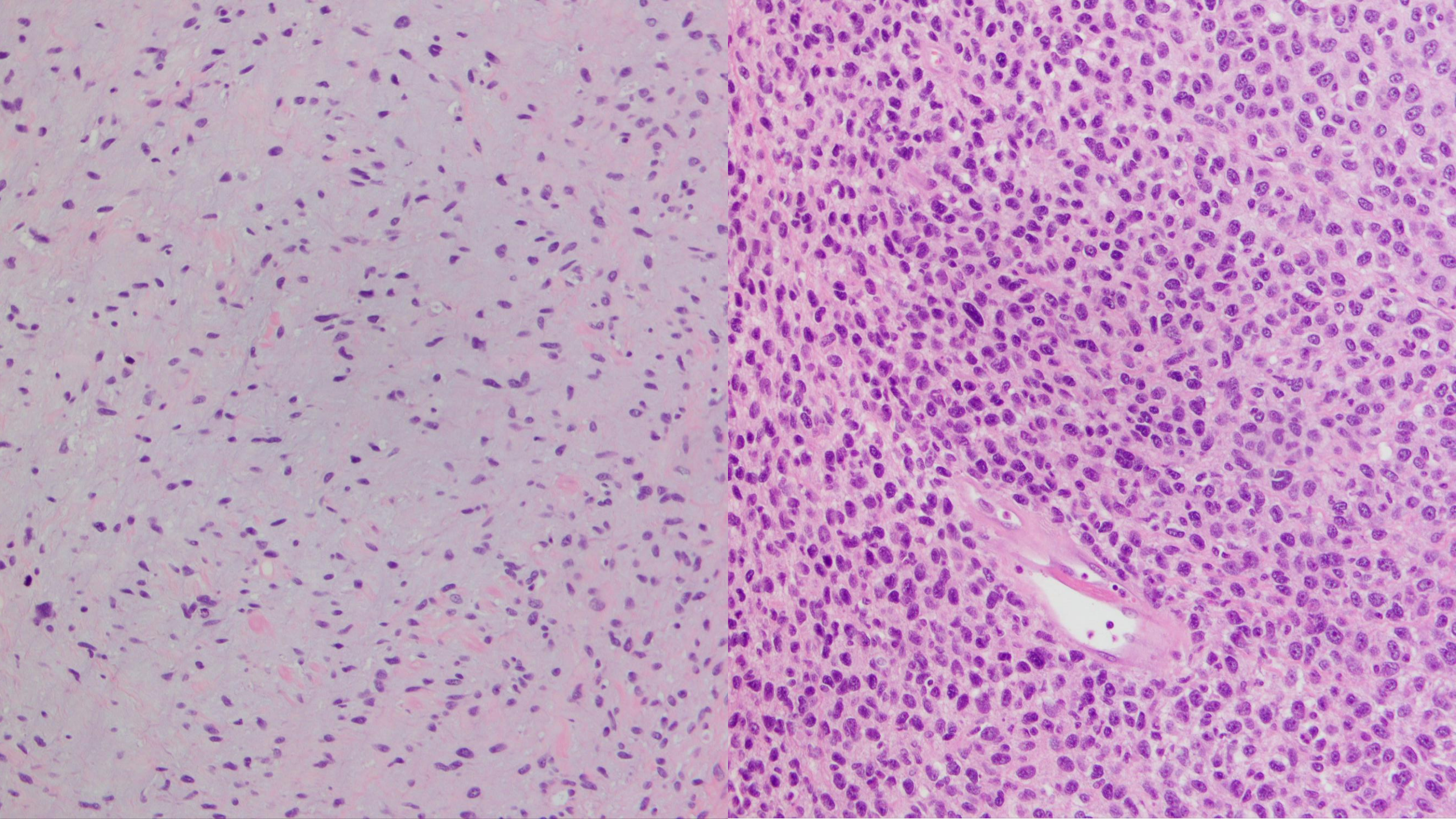
Abdominal CT demonstrated a 12.2 cm mass arising from posterior uterus- degenerated subserosal fibroid?

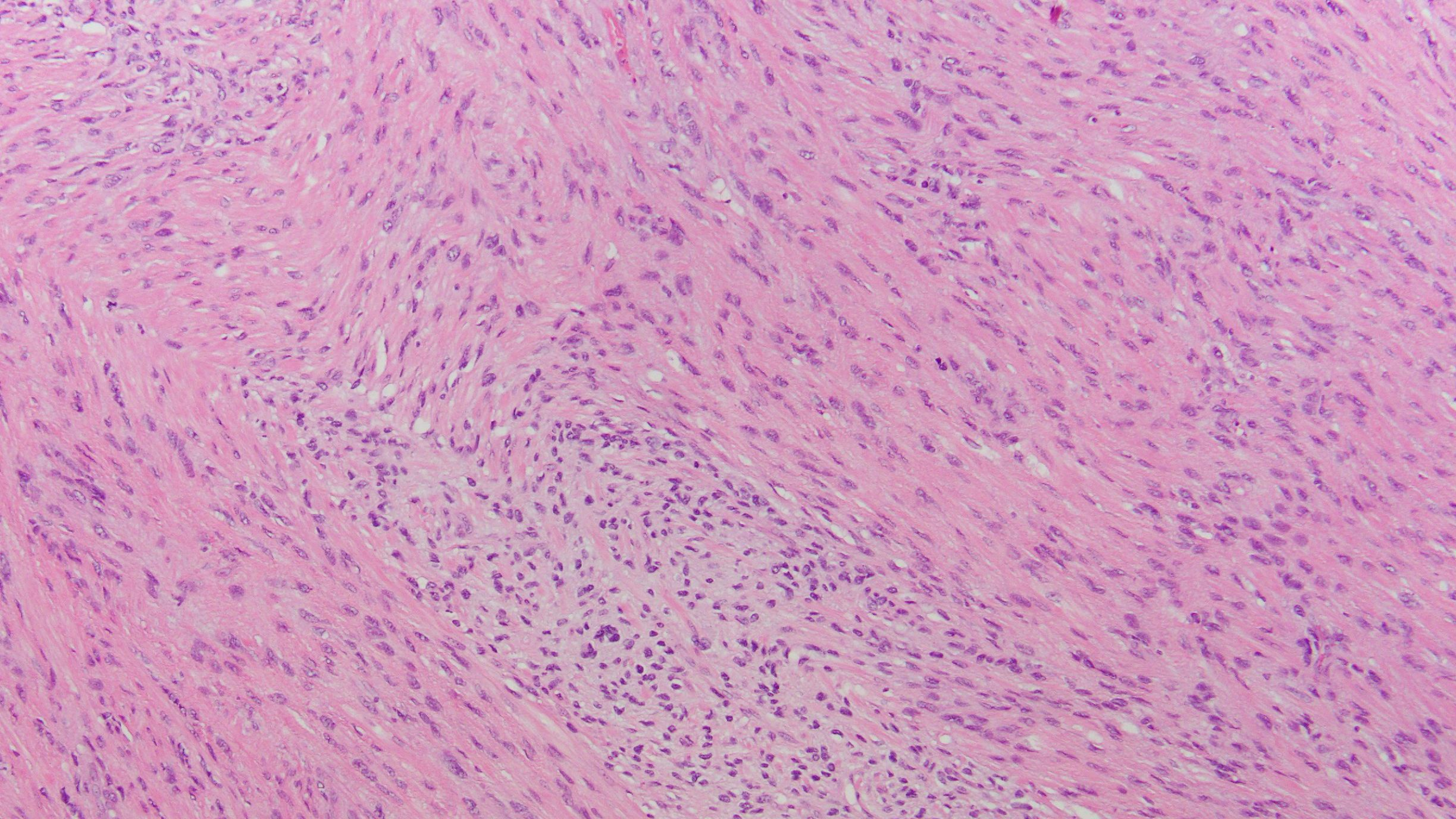
She underwent radical hysterectomy, bilateral salpingo-oophorectomy and excision of a rectal nodule

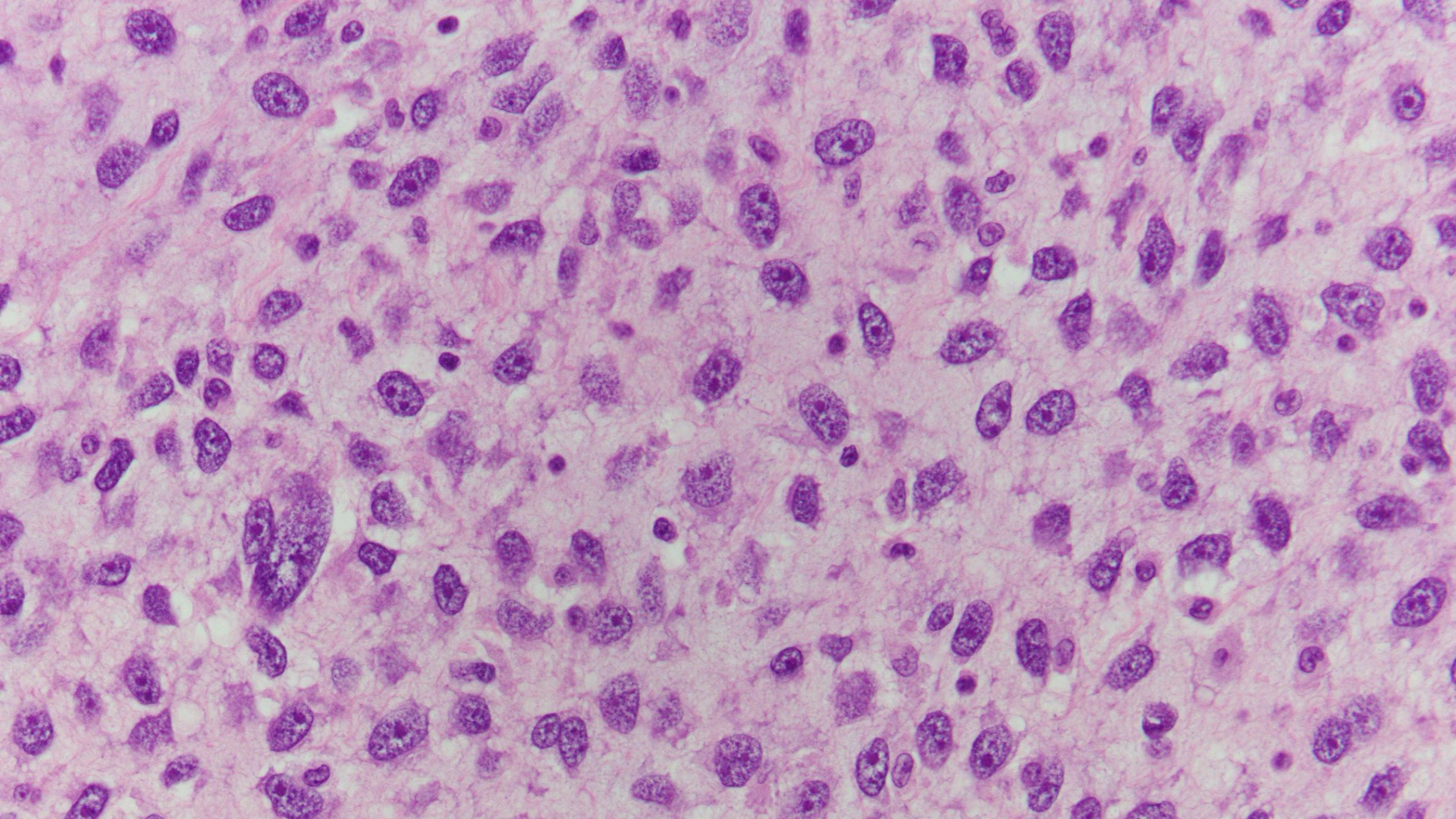
+ RADIATION













Note: Sections show an infiltrating myxoid tumor with extensive mitoses and focal necrosis. Immunohistochemical studies show that tumor cells are positive for desmin (patchy, strong), CD10 (diffuse, strong), PLAG1 (diffuse, strong), BCOR (patchy, weak, MDM2 (diffuse, moderate) and CylinD1 (patchy, moderate) and are negative for SMA, S100, caldesmon, ALK1 and ROS. H3K27M immunostain shows retained expression.

**Molecular studies were performed
with no PLAG1 Rearrangement**

.....BUT.....

- Gli1 amplification**
- MDM2 amplification**
- CDK4 amplification**

DIAGNOSIS:

UTERINE GLI1 AMPLIFIED SARCOMA

Argani P, et al.
GLI1 Gene Alterations in Neoplasms
of the Genitourinary and Gynecologic Tract
Am J Surg Pathol 2022, PMID: 34907995

GLI1 GENE ALTERATIONS

- Glioma-associated homologue-1 (GLI1): gene located on chromosome 12q13.3-14.1, encoding a zinc-finger transcription factor in the Kruppel family, a downstream effector of the Sonic hedgehog (SHH) signaling pathway
- First found to be amplified in a range of malignancies, including carcinomas (e.g., esophageal, hepatocellular, gastric, breast, and pancreas) and melanomas
- GLI1 alterations (amplification or fusion events) described in a diverse and expanding group of unrelated mesenchymal tumors

GLI1 RELATED NEOPLASMS

Pericytic phenotype and myoid differentiation
with *β-actin*, *MALAT1*, and *PTCH1*, *APOD*, *DERA* partners

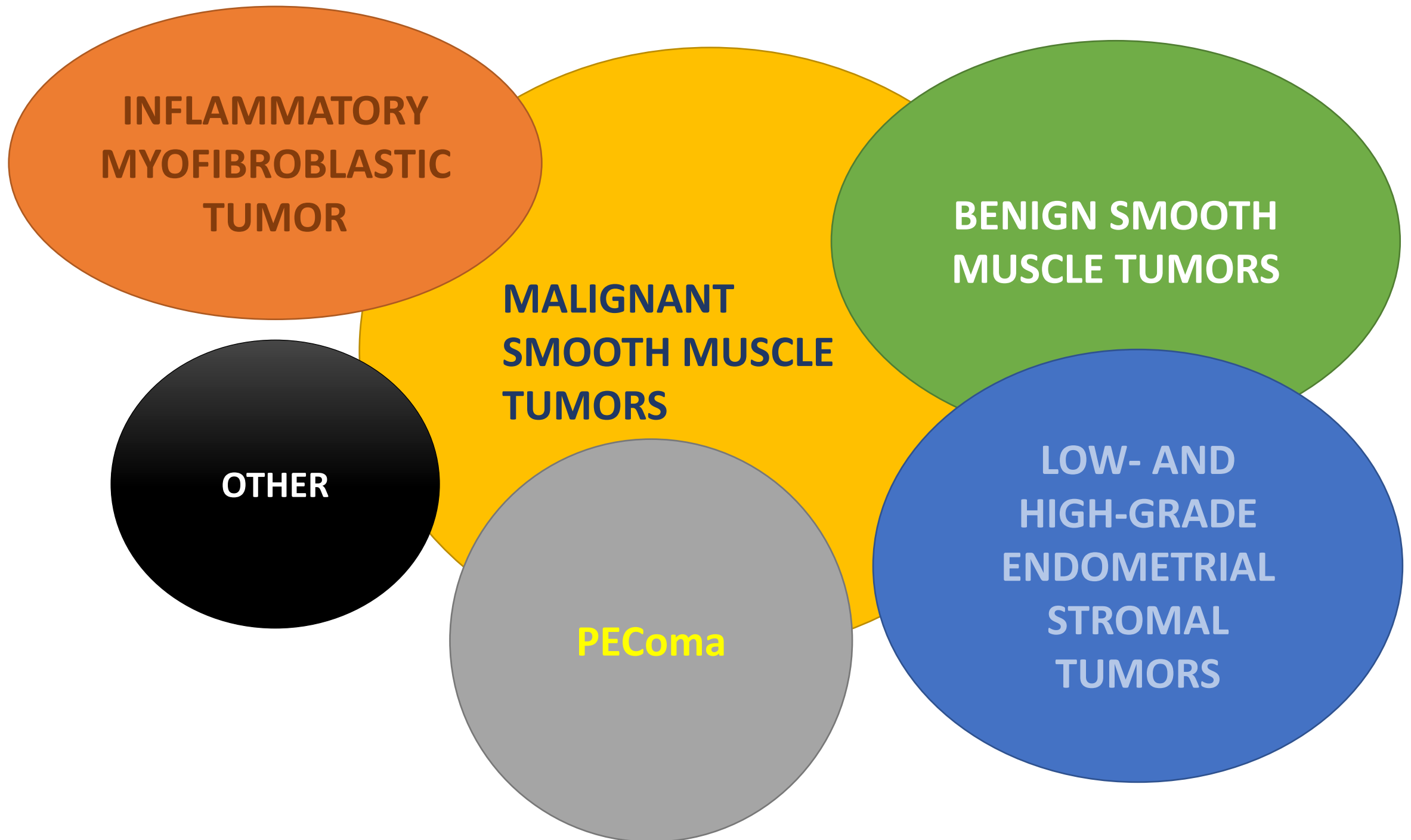
- Pericytoma with t(7;12) (typically tongue, stomach and soft tissue)
- Plexiform fibromyxoma
- Gastroblastoma
- Malignant epithelioid neoplasms with GLI1 gene rearrangements/
amplifications
- GLI1 fused, rearranged, or amplified genitourinary and gynecologic
neoplasms
- Common coamplification of nearby genes, such as CDK4, MDM2,
HMGA2, and STAT6

Stomach

GLI1-altered mesenchymal tumor: a clinicopathologic and molecular analysis of ten additional cases of an emerging entity

Liu J, qt al. Virchows Arch. 2022;480:1087-1099

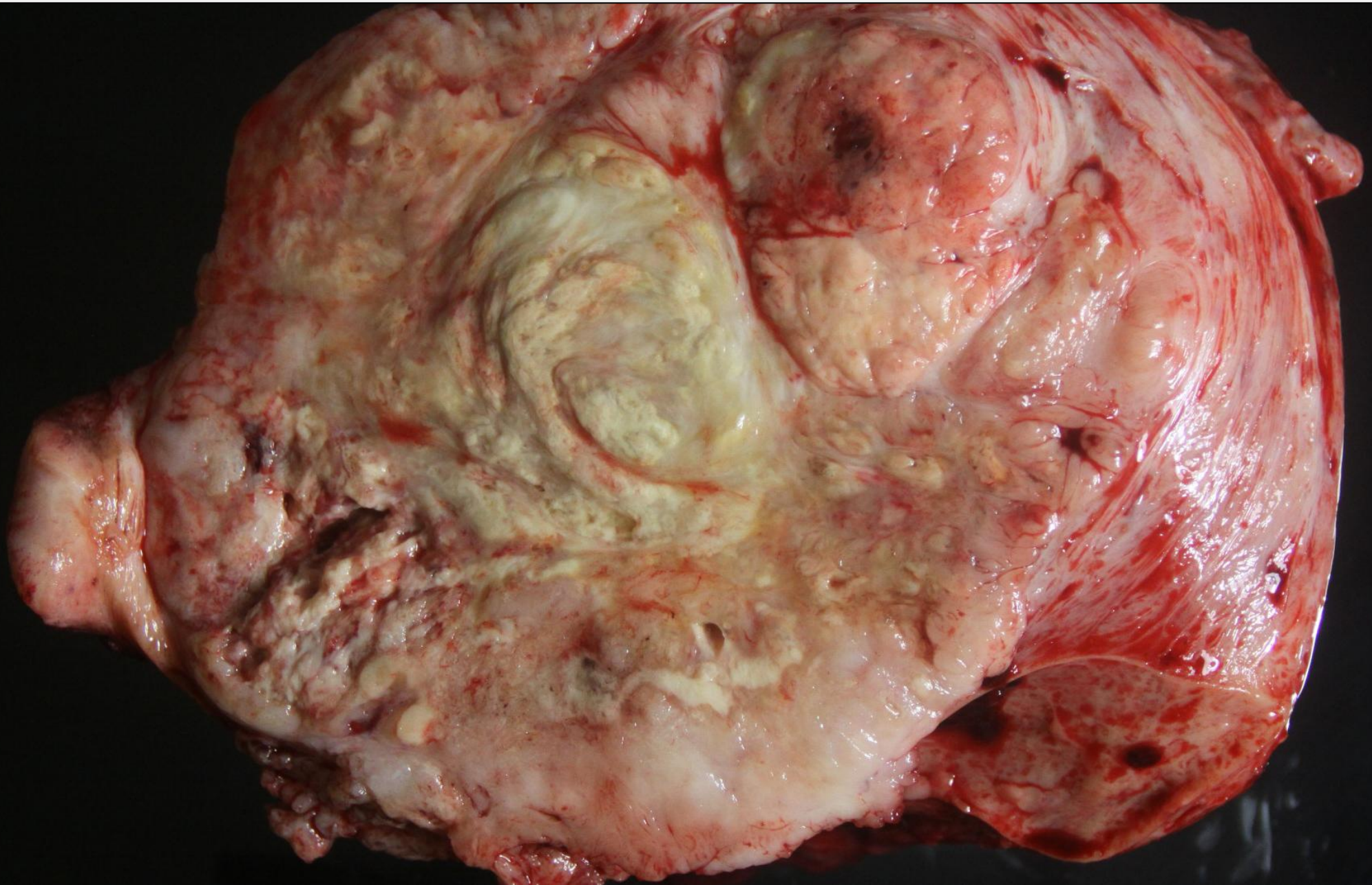
- Wide age range; 7M:3F (but overall, in literature equal gender distribution)
- Oral cavity>>> stomach, cervix (also described in ovary) elbow, groin, and thigh
- Infiltrative and multinodular growth
- 9 round to epithelioid cells: 1 spindled cells
- Rich capillary network
- Diffuse CD56 and variable S100 (+) (some actin, CD10, AE1/3-Cam5.2), SOX10 (-)
- GLI1 fusions>>> amplifications (the latter associated with MDM2 and CDK4 positivity)
- Relatively short follow-up; recurrences in 2 patients, low malignant potential



SMOOTH MUSCLE TUMORS

- Benign or malignant or STUMP?
- Cell type?
- What is in the differential diagnosis?

LEIOMYOSARCOMA

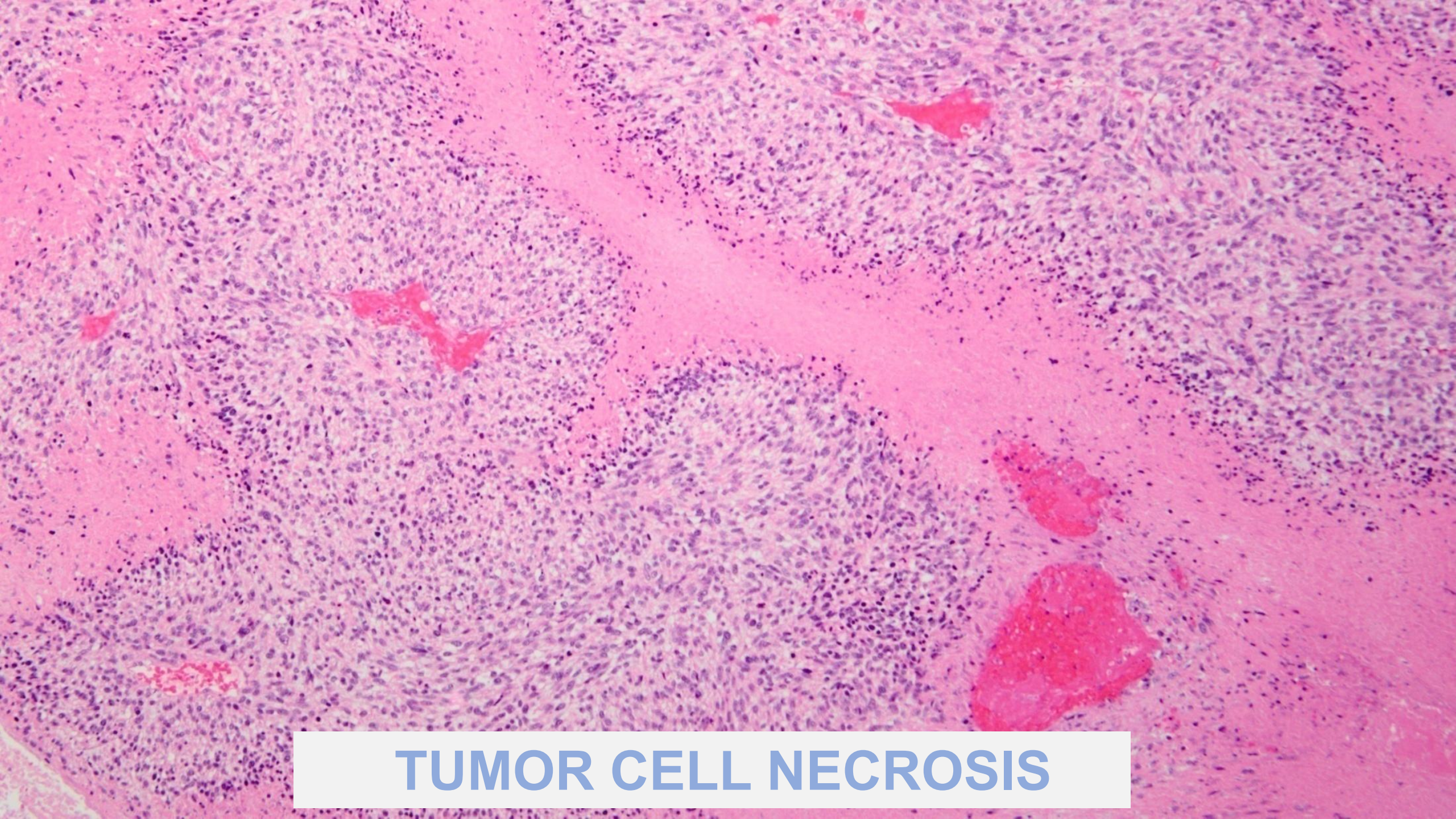


SPINDLE LEIOMYOSARCOMA

Bell et al, Am J Surg Pathol 1994;18:535

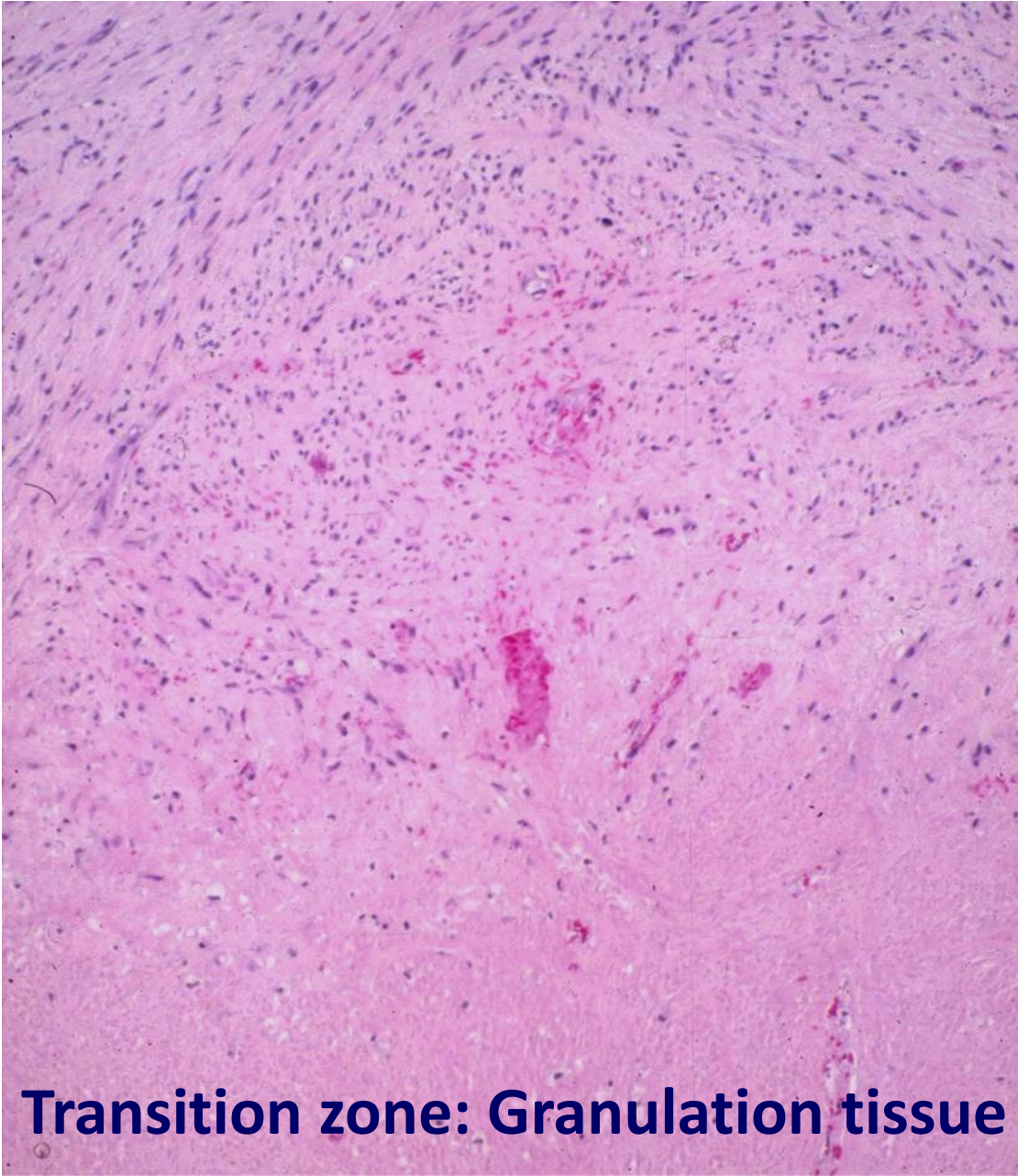
- **Tumor cell necrosis**
- **Diffuse moderate to marked atypia**
- **High mitotic rate (>10 MFs/10HPFs)**

*** any two of these criteria diagnostic**

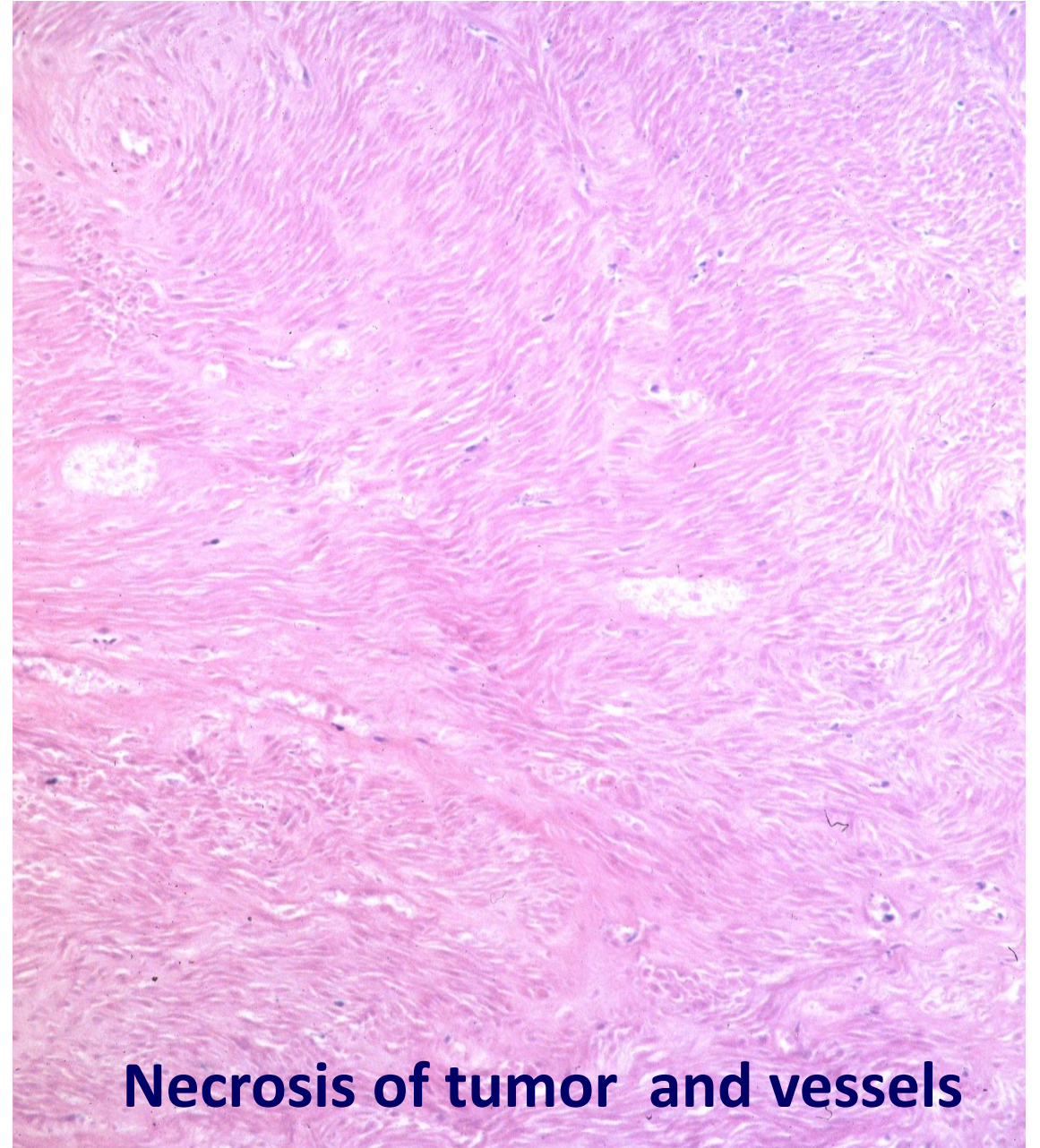


TUMOR CELL NECROSIS

INFARCT-TYPE NECROSIS

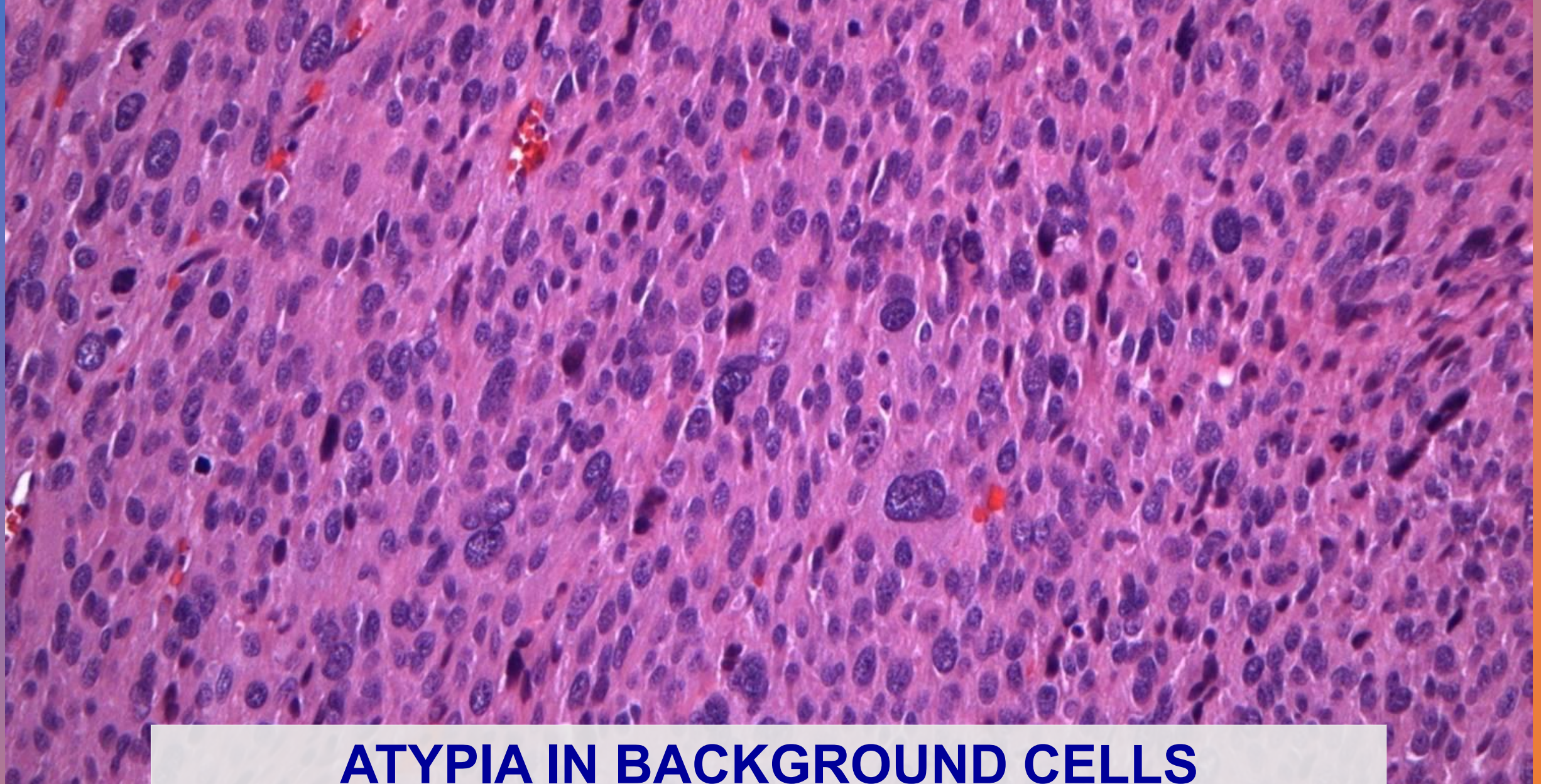


Transition zone: Granulation tissue

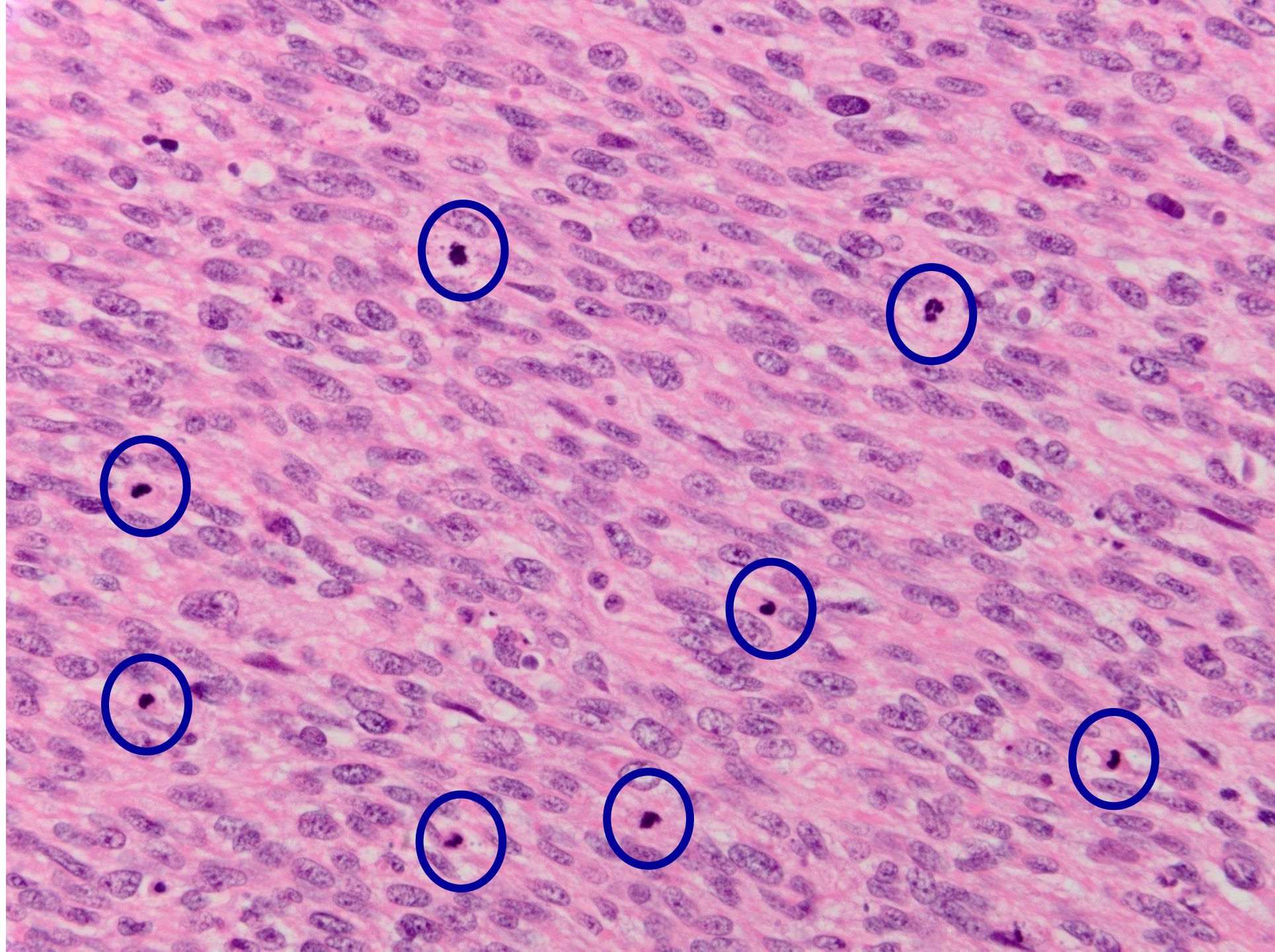


Necrosis of tumor and vessels

LEIOMYOSARCOMA



ATYPIA IN BACKGROUND CELLS



LEIOMYOSARCOMA GRADING

Low vs High grade

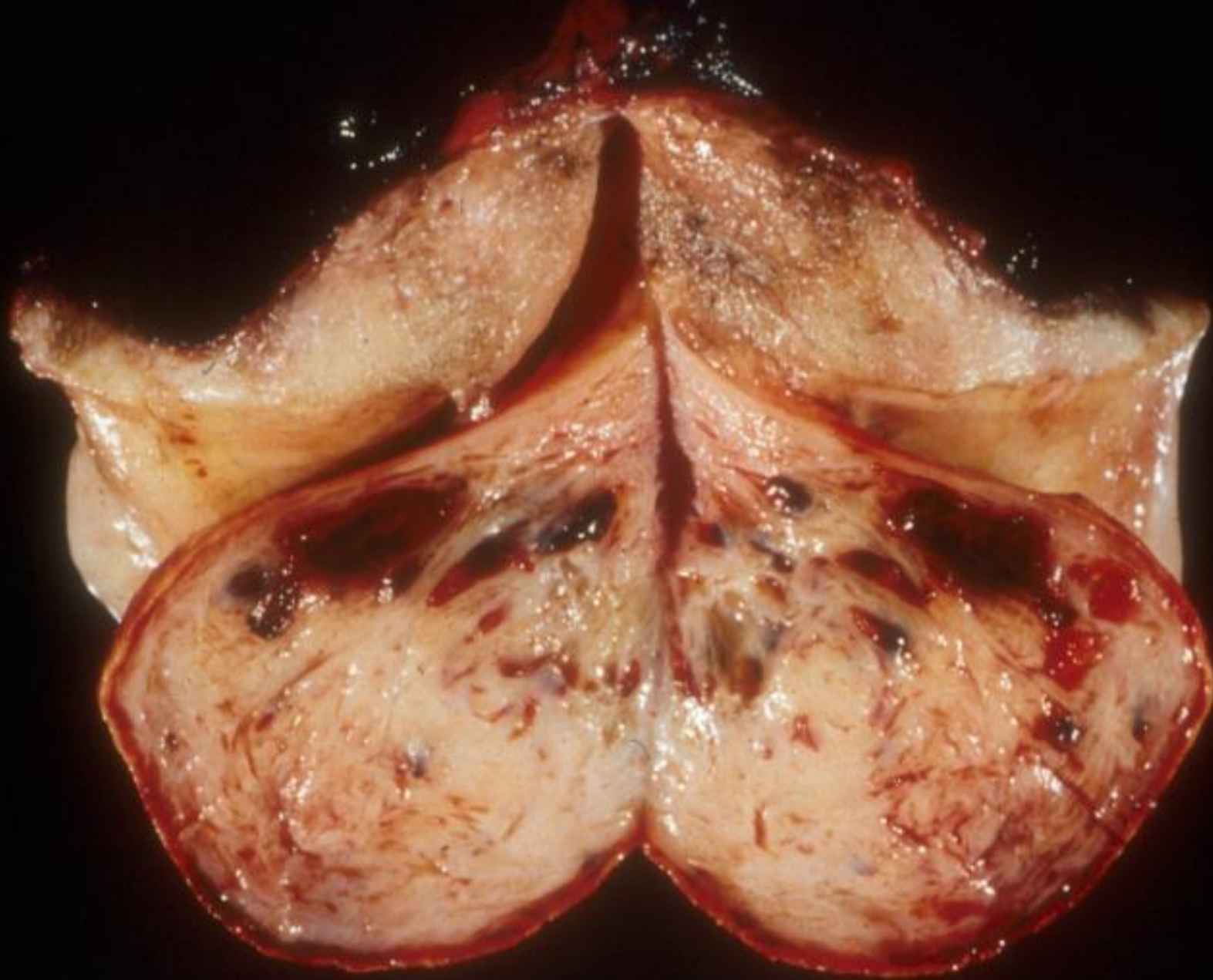
**Based on current (Stanford) criteria
all leiomyosarcomas are high-grade**

.....**Low-grade leiomyosarcomas exist,
but criteria not well defined**

SPINDLE LEIOMYOSARCOMA

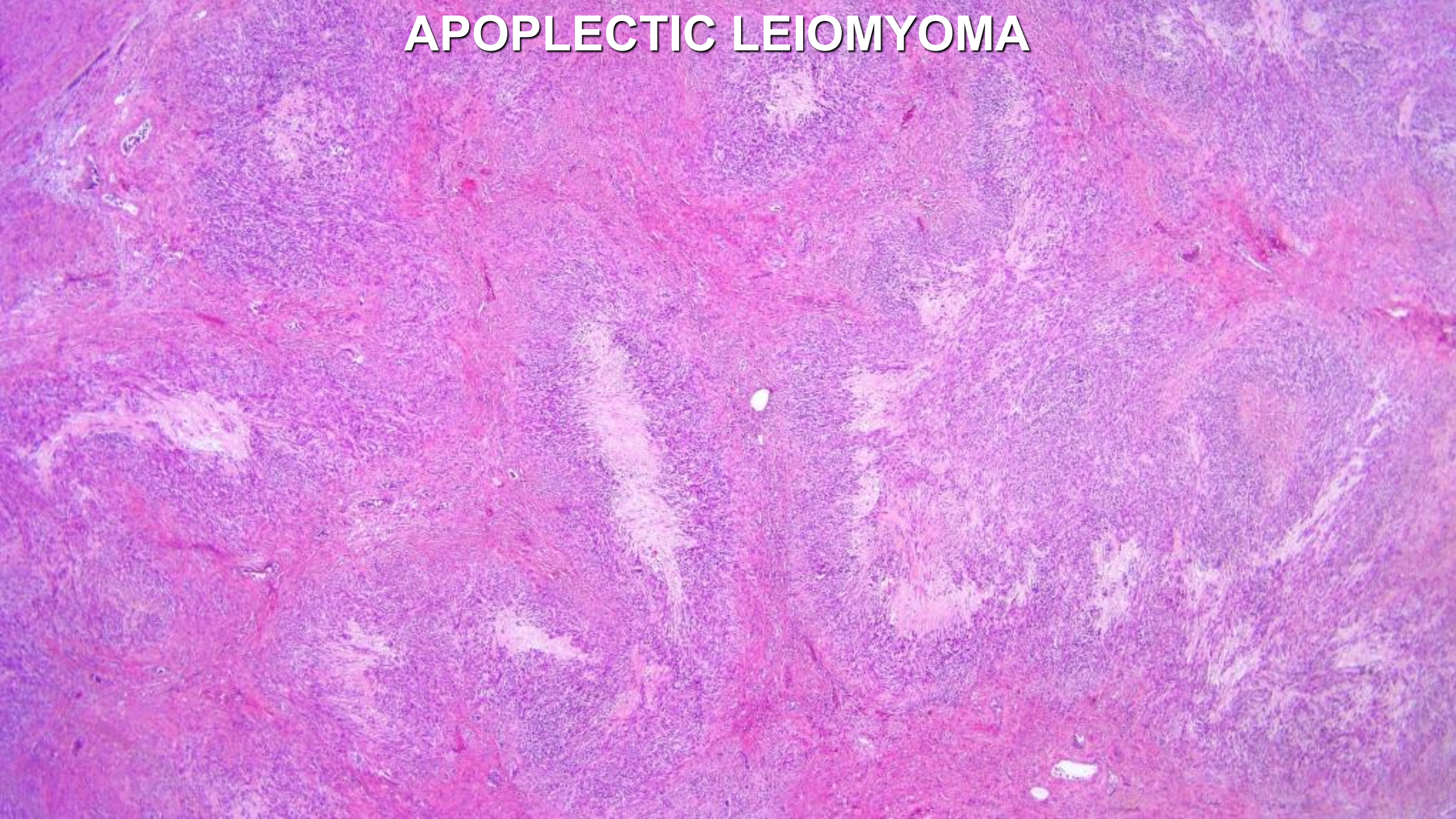
Differential Diagnosis

- **Apoplectic leiomyoma**
- **Leiomyoma with bizarre nuclei**
- **Mitotically active leiomyoma**
- **Highly cellular leiomyoma**
- **Rhabdomyosarcoma**
- **Undifferentiated uterine sarcoma
(Diagnosis of exclusion)**

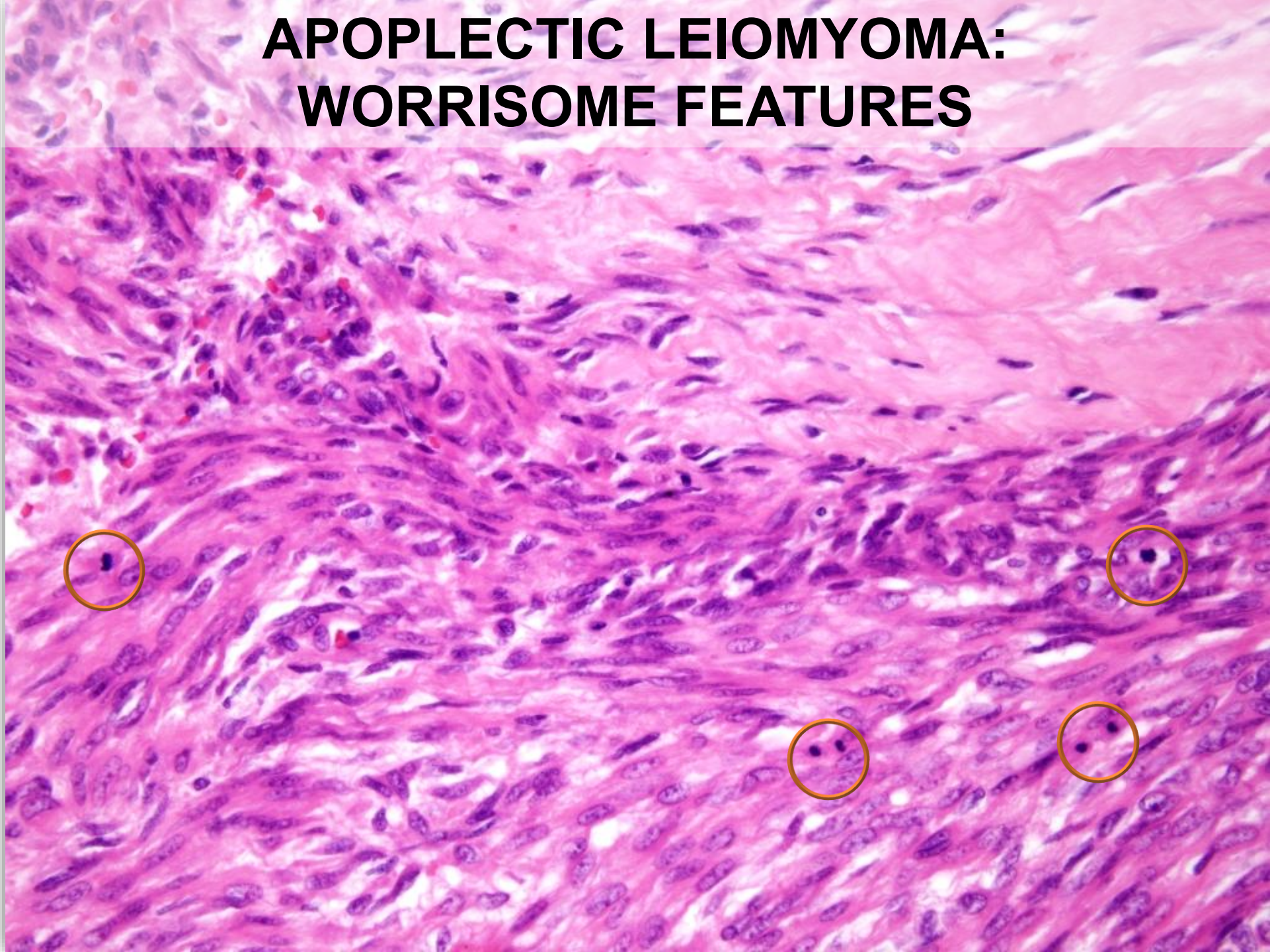


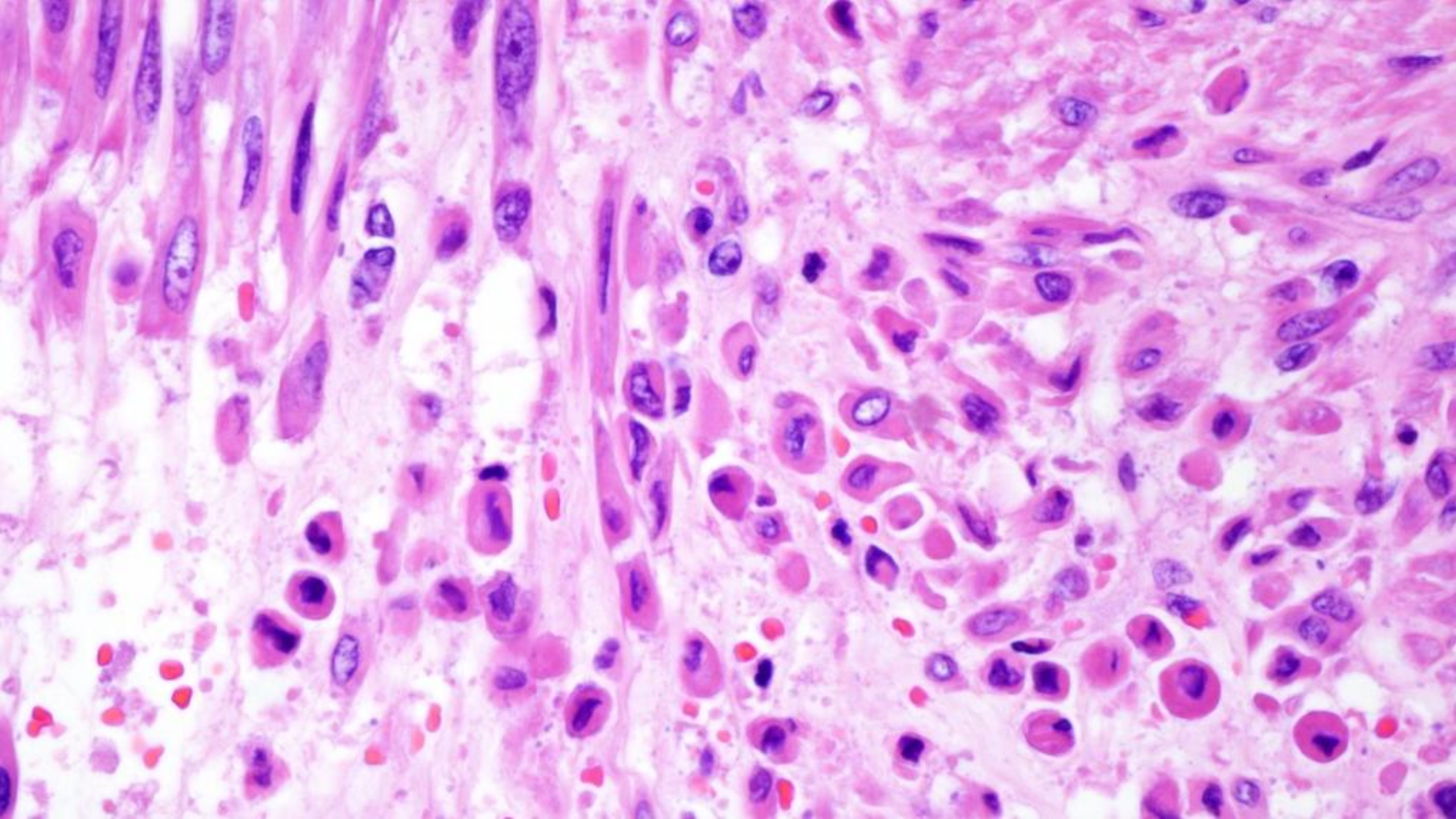
Apoplectic Leiomyoma

APOPLECTIC LEIOMYOMA

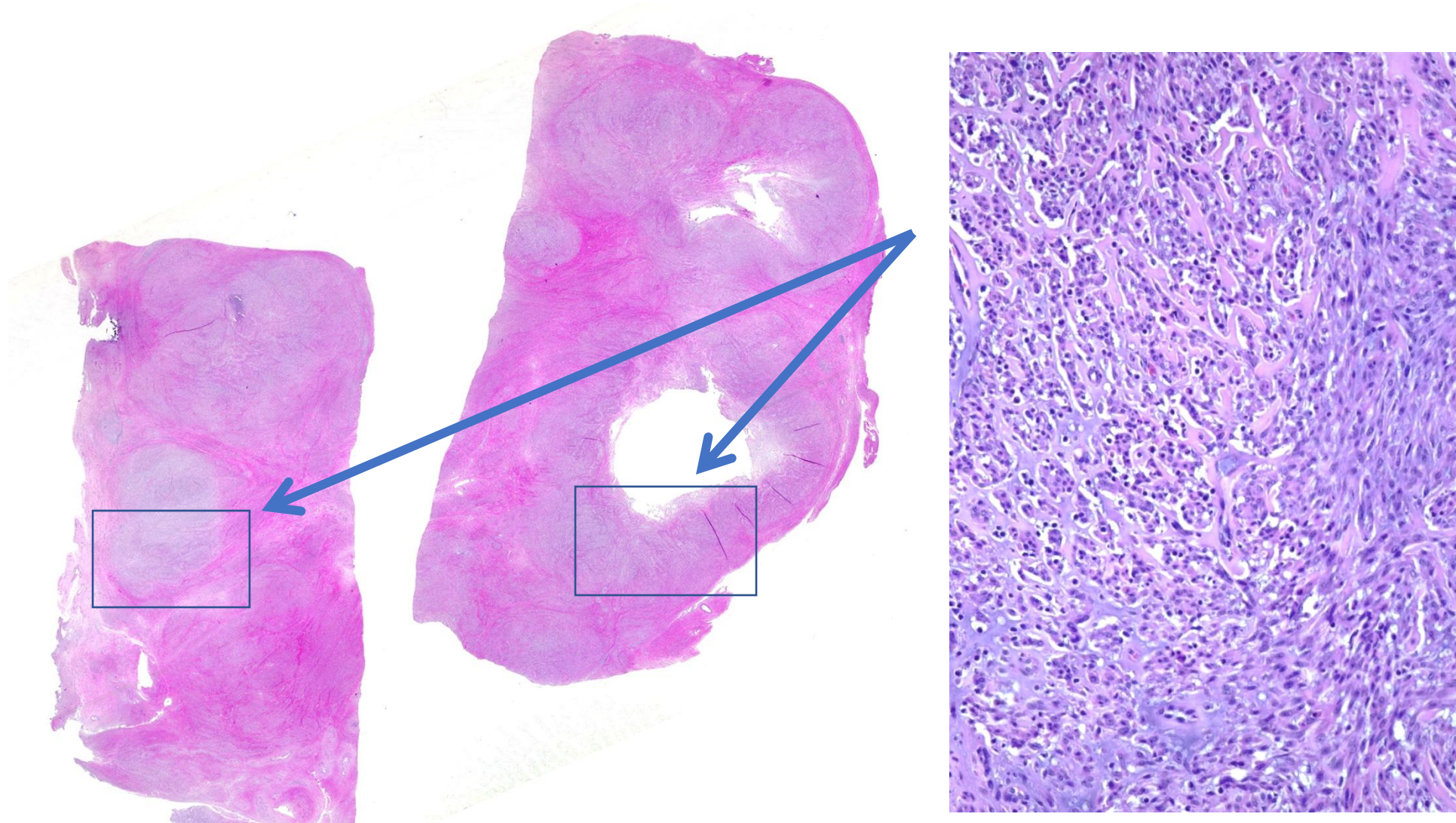


APOPLECTIC LEIOMYOMA: WORRISOME FEATURES



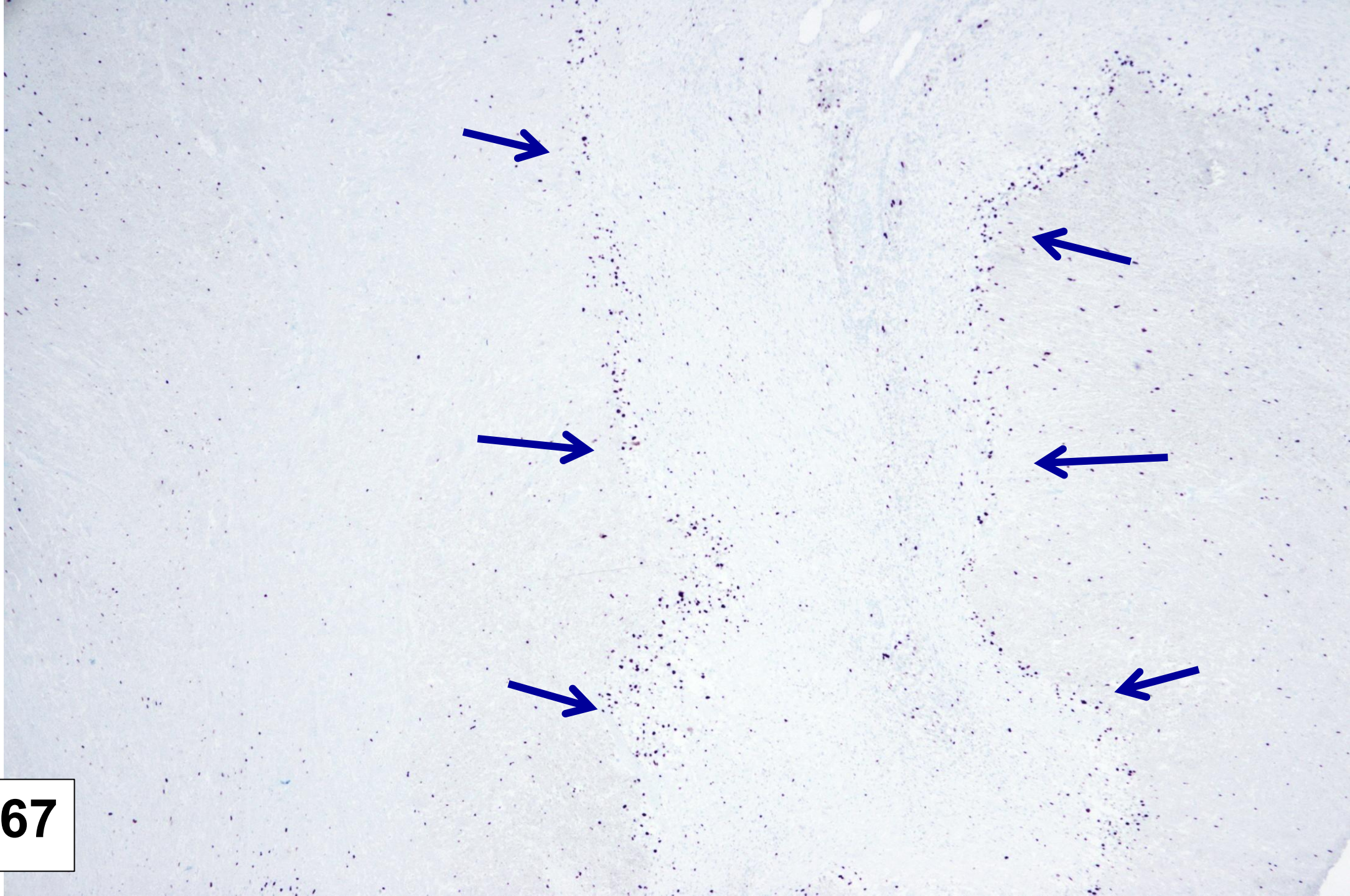


LEIOMYOMA with APOPLECTIC CHANGE

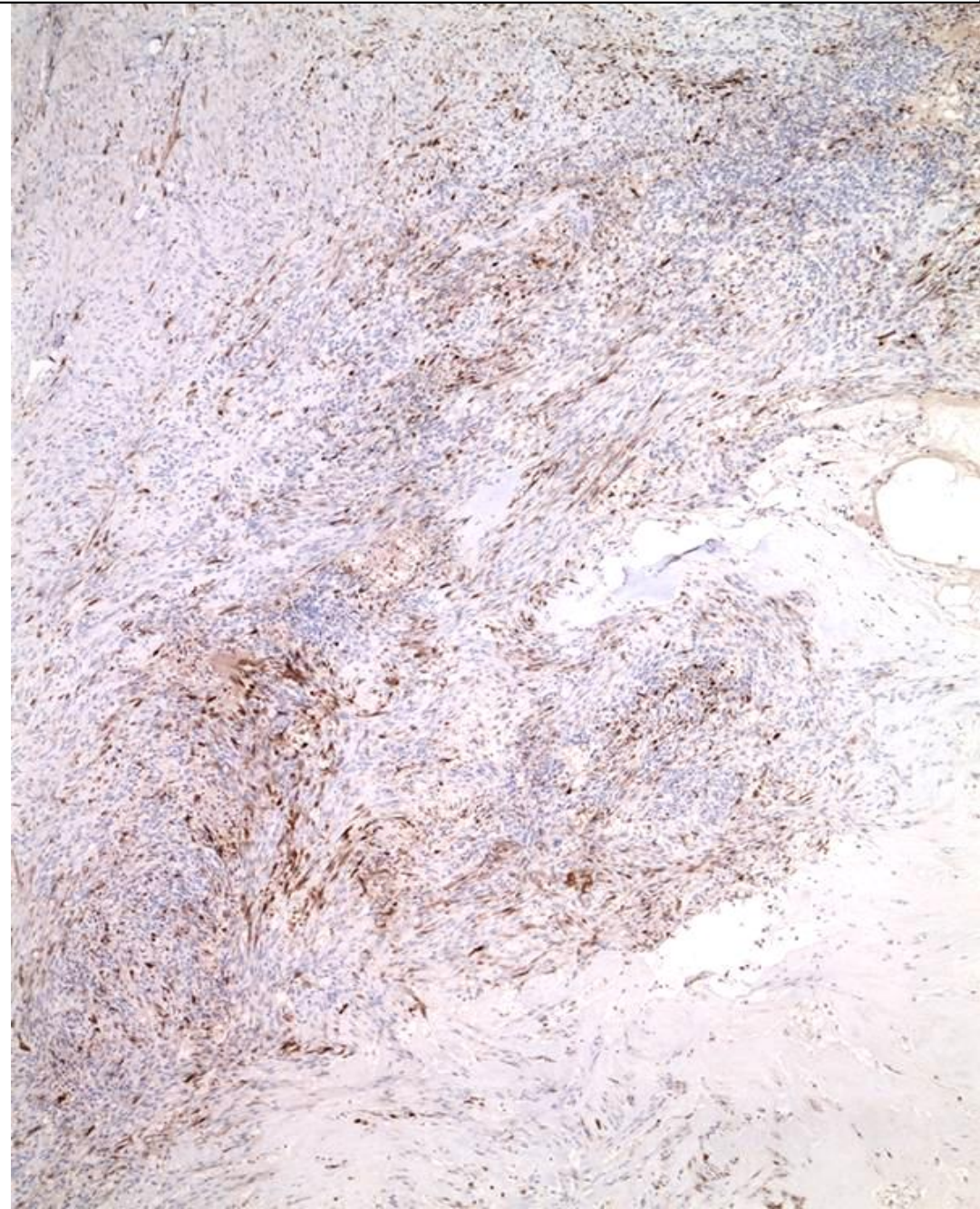
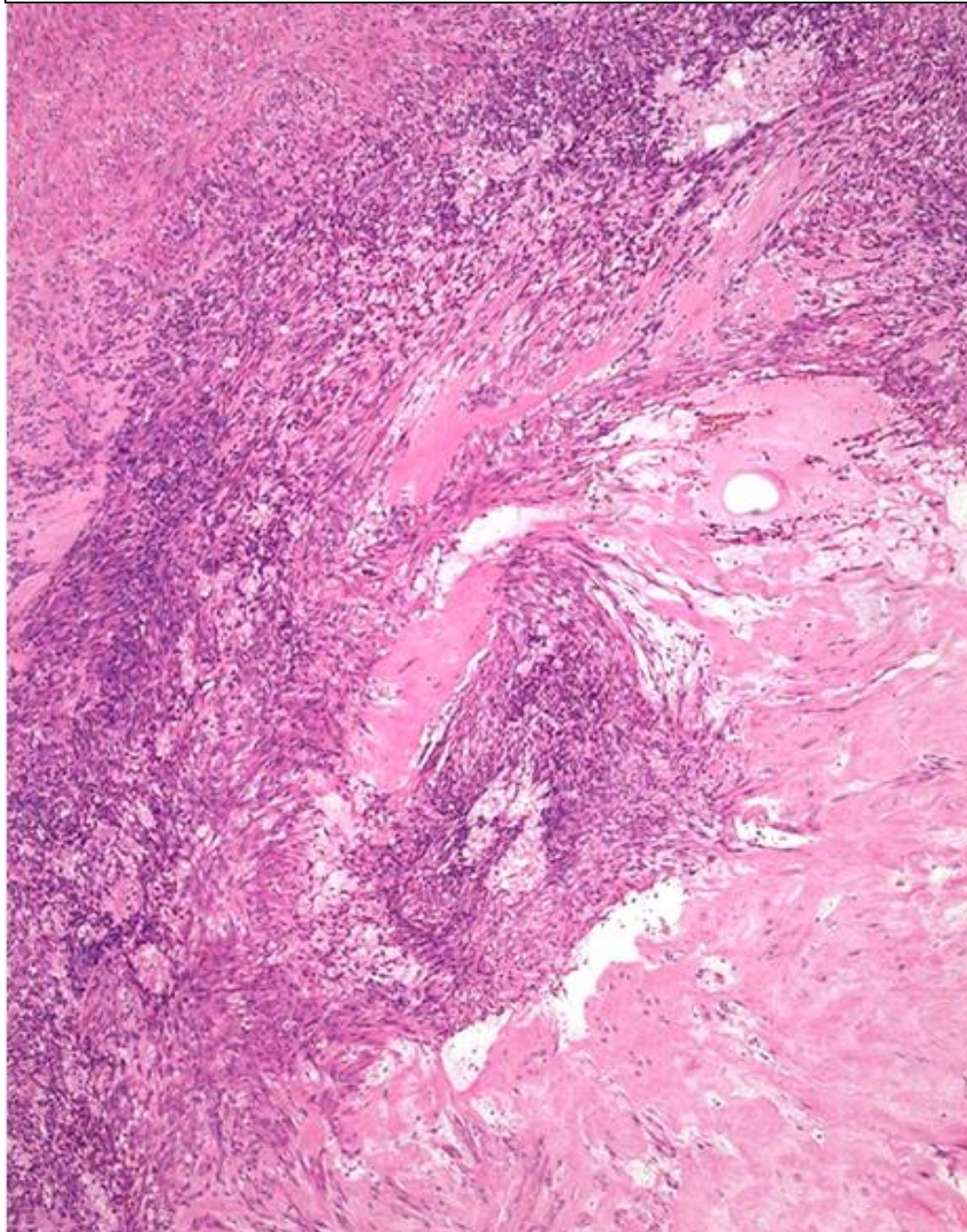


Evaluate tumor away from areas of infarction

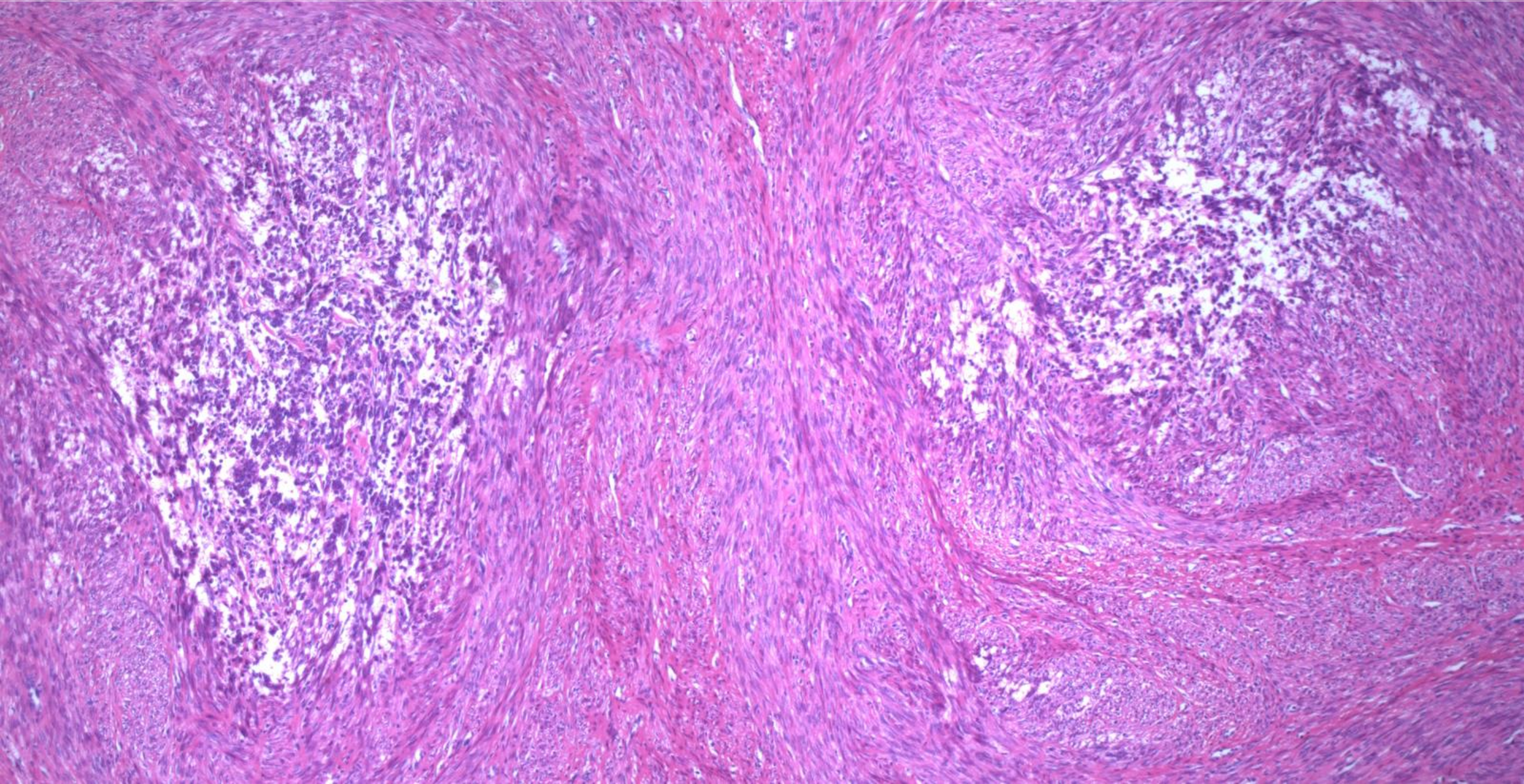
Ki67

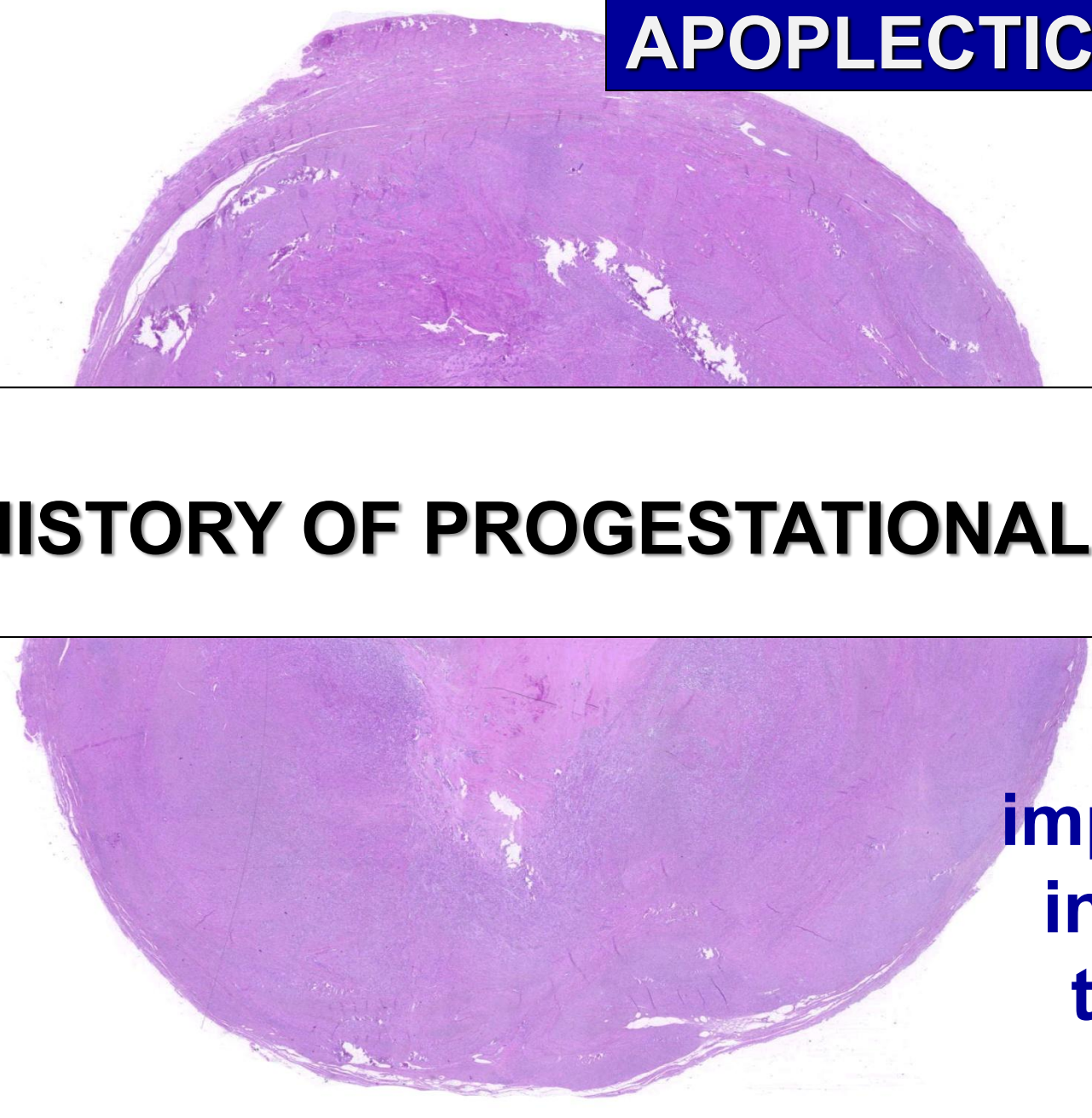


APOPLECTIC LEIOMYOMA: p16 POSITIVE



APOPLECTIC LEIOMYOMA: CLUES





APOPLECTIC LEIOMYOMA

HISTORY OF PROGESTATIONAL THERAPY

**“Zonation”
important feature
in recognizing
the tumor as
BENIGN**

MITOTICALLY ACTIVE LEIOMYOMA

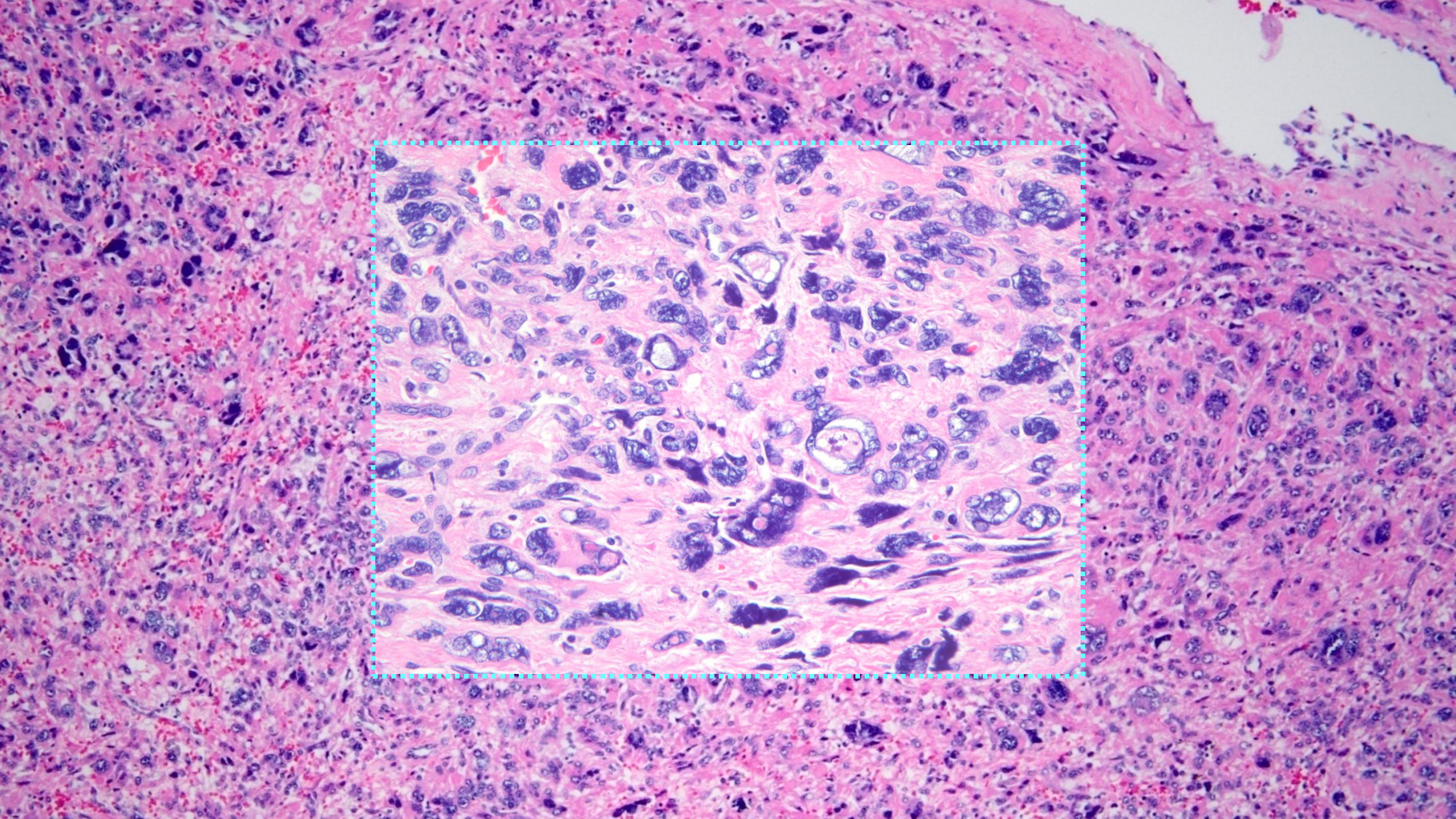


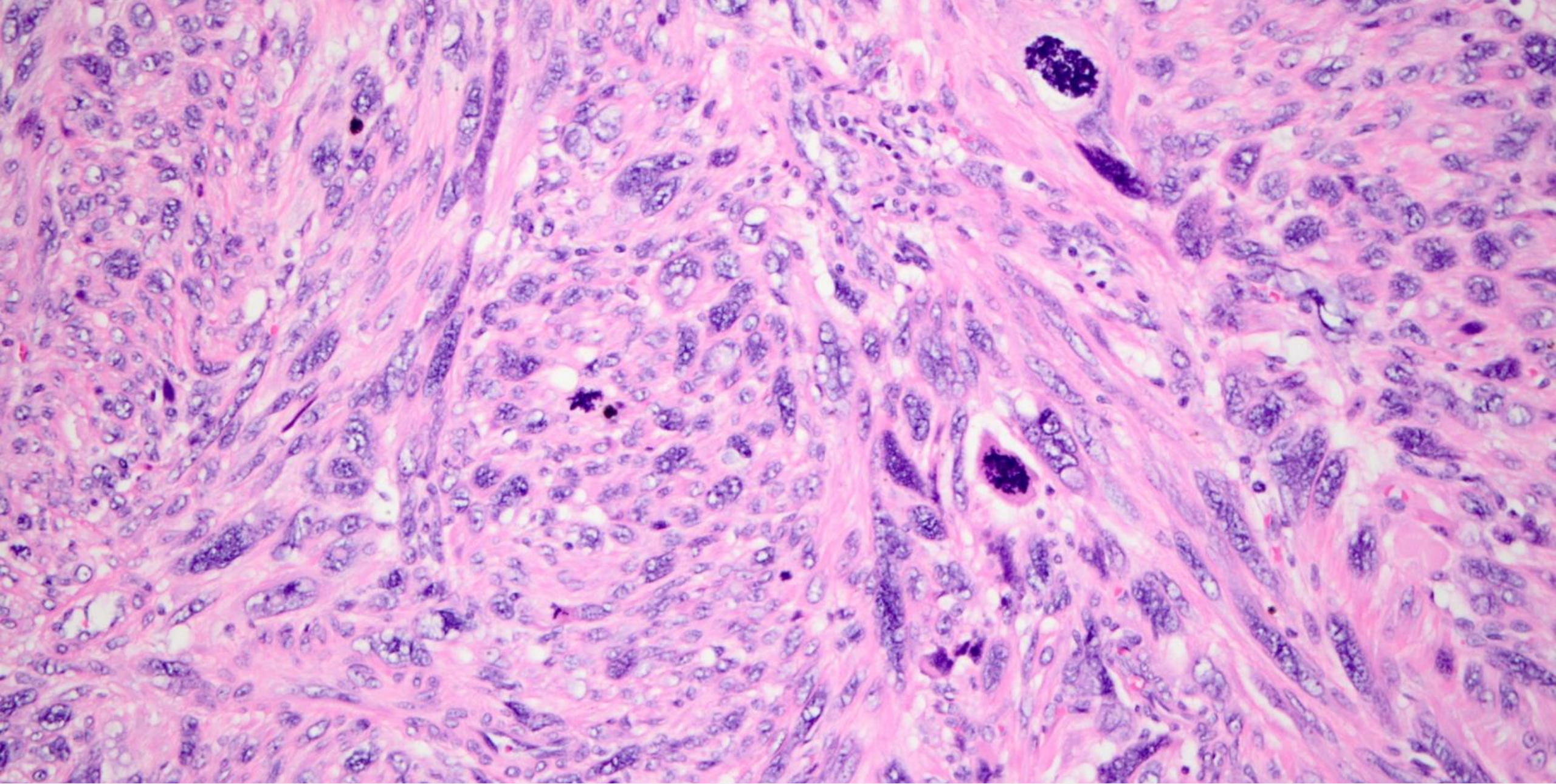
NO CYTOLOGIC ATYPIA !

Leiomyomas with Bizarre Nuclei (synonym: symplastic)

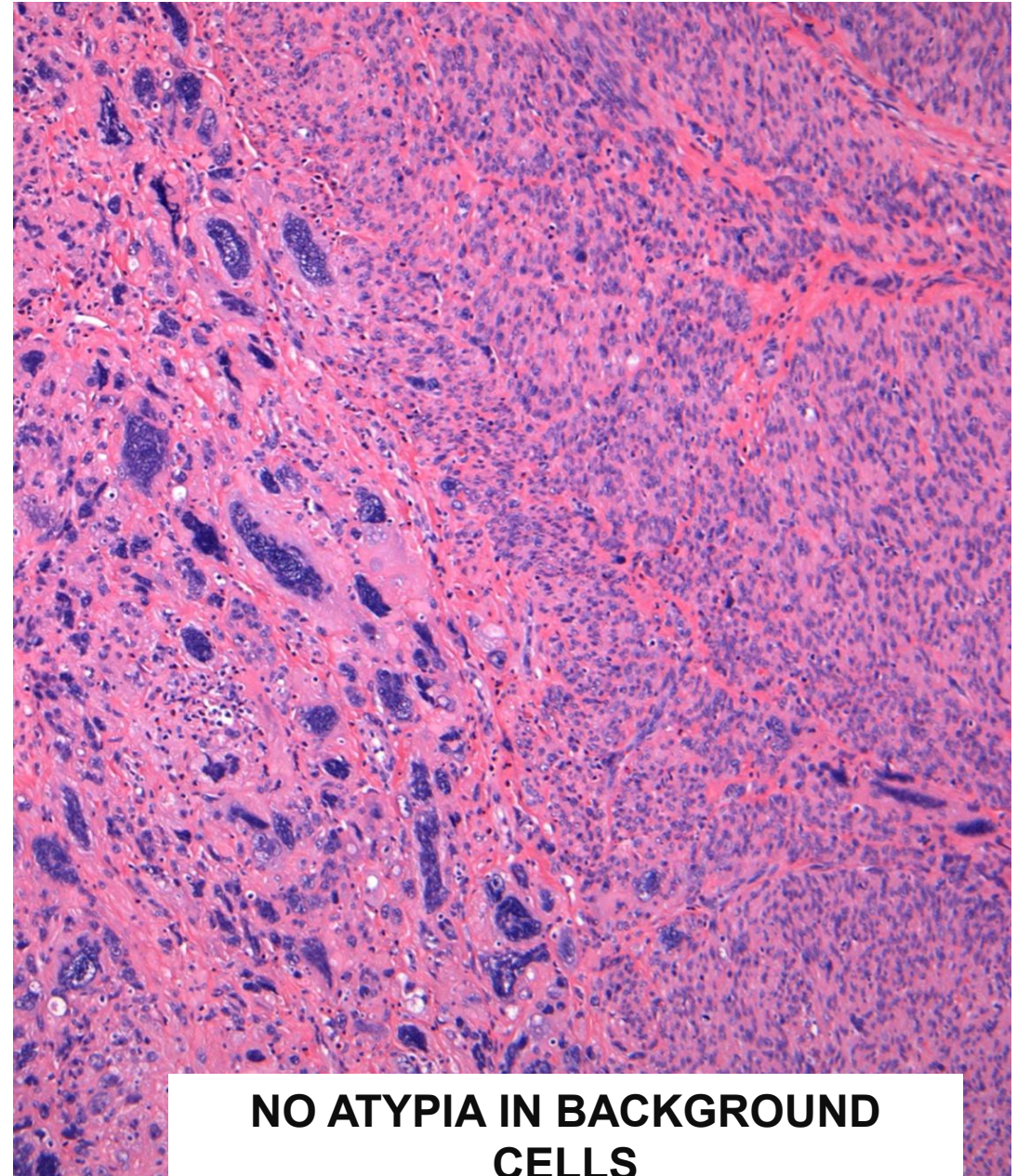
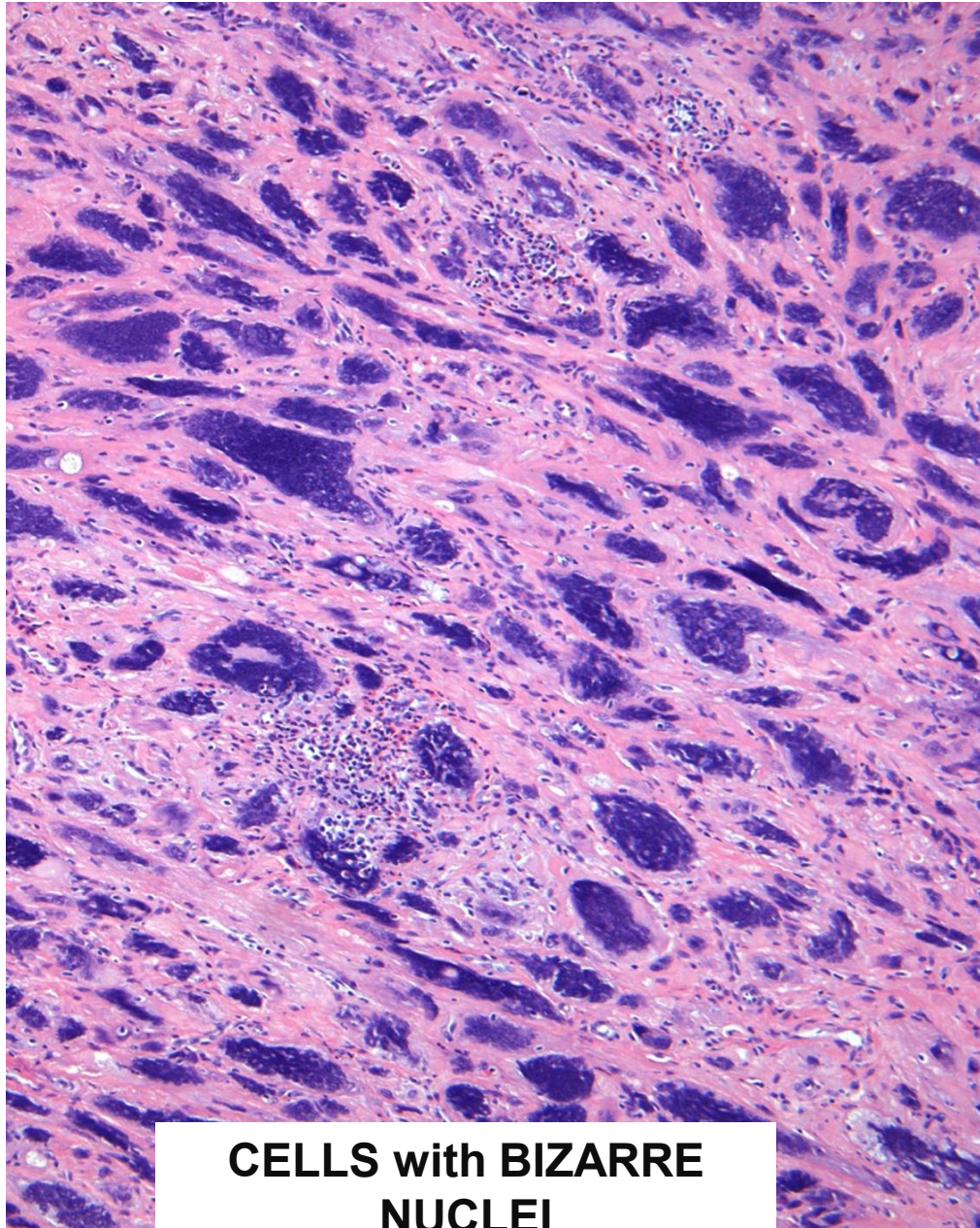
CONCERNING FEATURES :

- Bizarre mono or multinucleated cells with nuclear pseudoinclusions
- Diffuse distribution or high density of cells
- Karyorrhectic nuclei and coarse chromatin
- Prominent nucleoli
- Mitotic counts focally up to 7/10HPFs
(average 1-2)



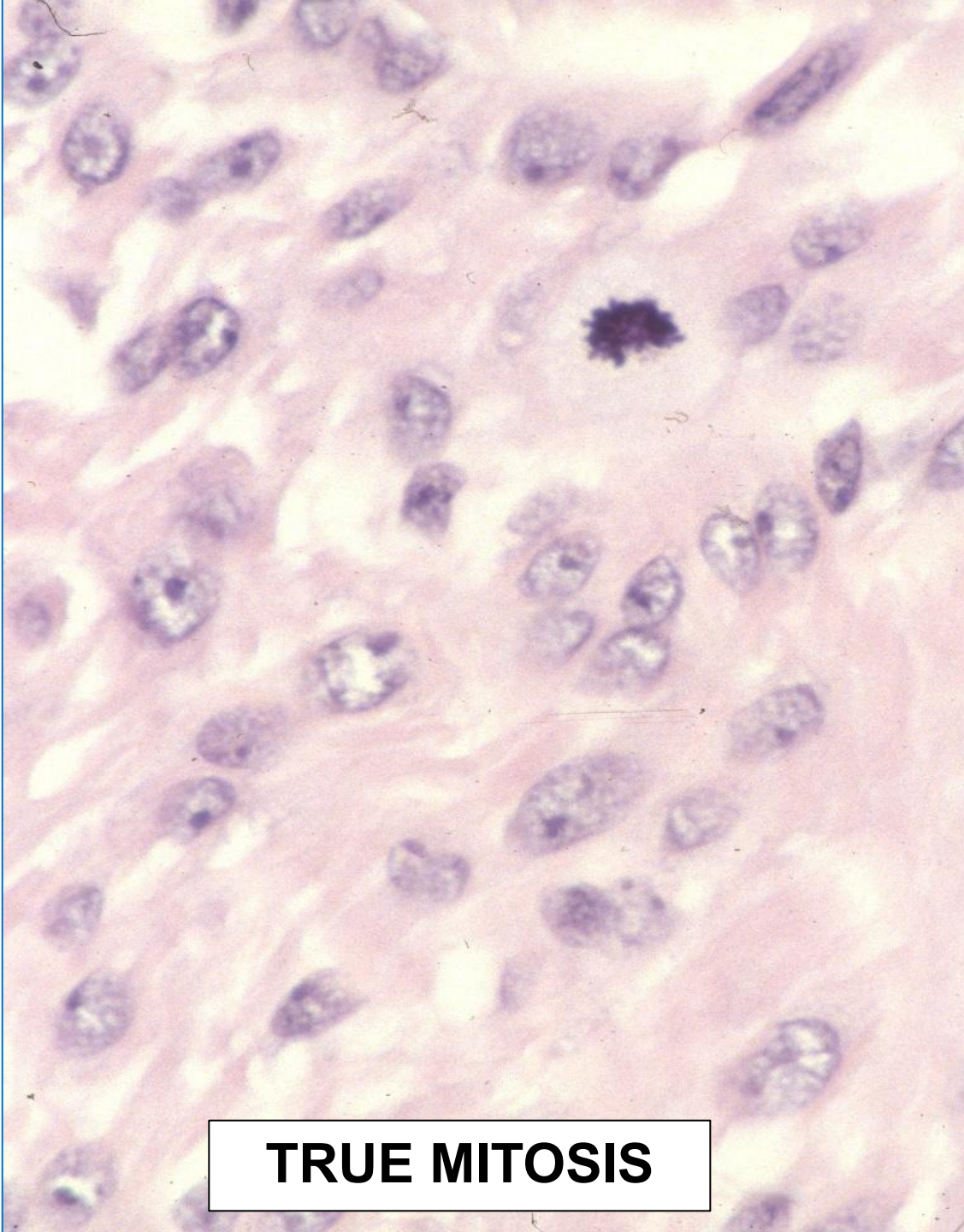


Karyorrhectic nuclei often counted as atypical mitoses

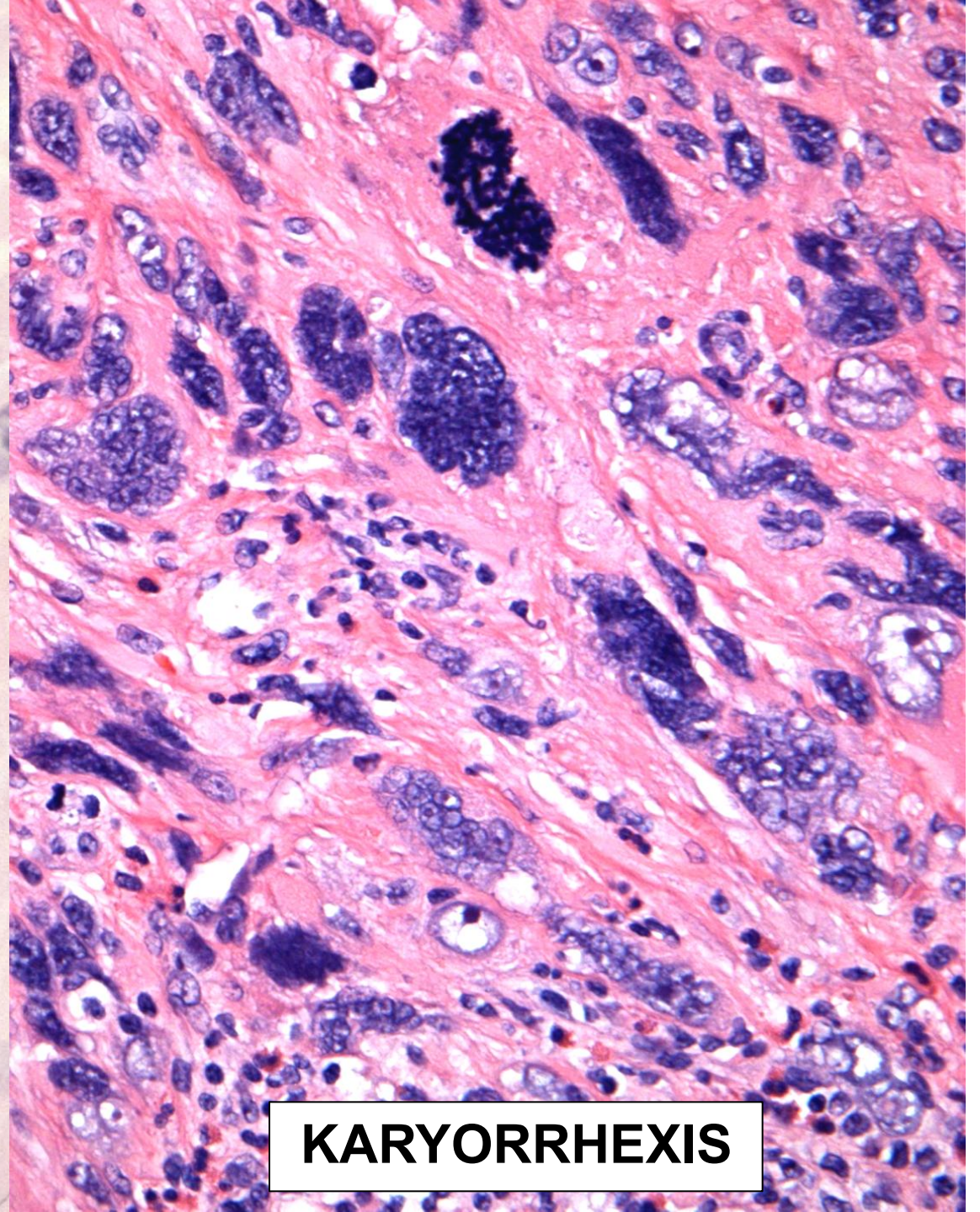


Leiomyoma with Bizarre Nuclei vs Leiomyosarcoma

	<u>LMBN</u>	<u>LMS</u>
Mitotic count	<10	>10
Tumor cell necrosis	-	+
DNA ploidy	Diploid	Aneuploid
MIB-1	Low	High
ER/PR	+	+ (~50%)
p53	-/+	+
p16	+/-	+
<i>MED12 mutations</i>	Uncommon	Rare



TRUE MITOSIS



KARYORRHEXIS

Leiomyoma with Bizarre Nuclei vs Leiomyosarcoma

- **Ki-67 is very often performed but is infrequently helpful as results show extensive overlap between leiomyoma with bizarre nuclei and leiomyosarcoma**
- **Ki-67 typically overestimates mitotic index**

Mills AM, et al, Am J Surg Pathol 2013

Predictors of adverse outcome in uterine smooth muscle tumours of uncertain malignant potential (STUMP): a clinicopathological analysis of 22 cases with a proposal for the inclusion of additional histological parameters

Mamta Gupta,^{1,2} Anna L Laury,³ Marisa R Nucci^{2,4} & Bradley J Quade^{2,4} 

¹Department of Pathology, Beth Israel Deaconess Medical Center, ²Harvard Medical School, Boston, MA, ³Department of Pathology, Cedars-Sinai, Los Angeles, CA, and ⁴Division of Women's and Perinatal Pathology, Department of Pathology, Brigham and Women's Hospital, Boston, MA, USA

If adverse outcome, features included:

- moderate–severe nuclear atypia (7)
- Infiltrative or irregular margins (5)
- vascular intrusion (3)
- atypical mitoses (2)
- epithelioid features (1)

Necrosis not particularly associated with adverse outcomes

Evaluation of criteria to distinguish uterine smooth muscle tumors of uncertain malignant potential (STUMP) from mimics and improved prediction of patient outcome: A multi-institutional study of 51 cases

Philip P. Ip¹, Zehra Ordulu², Diana Lim³, Robert A. Soslow⁴, Robert H. Young², Liwei Jia⁴, Sarah Chiang⁴, Esther Oliva²

DepDepartments of Pathology: University of Hong Kong, Hong Kong.

Department of Pathology, National University Hospital, Singapore, Department of Pathology, Memorial Sloan Kettering Cancer Center, New York.

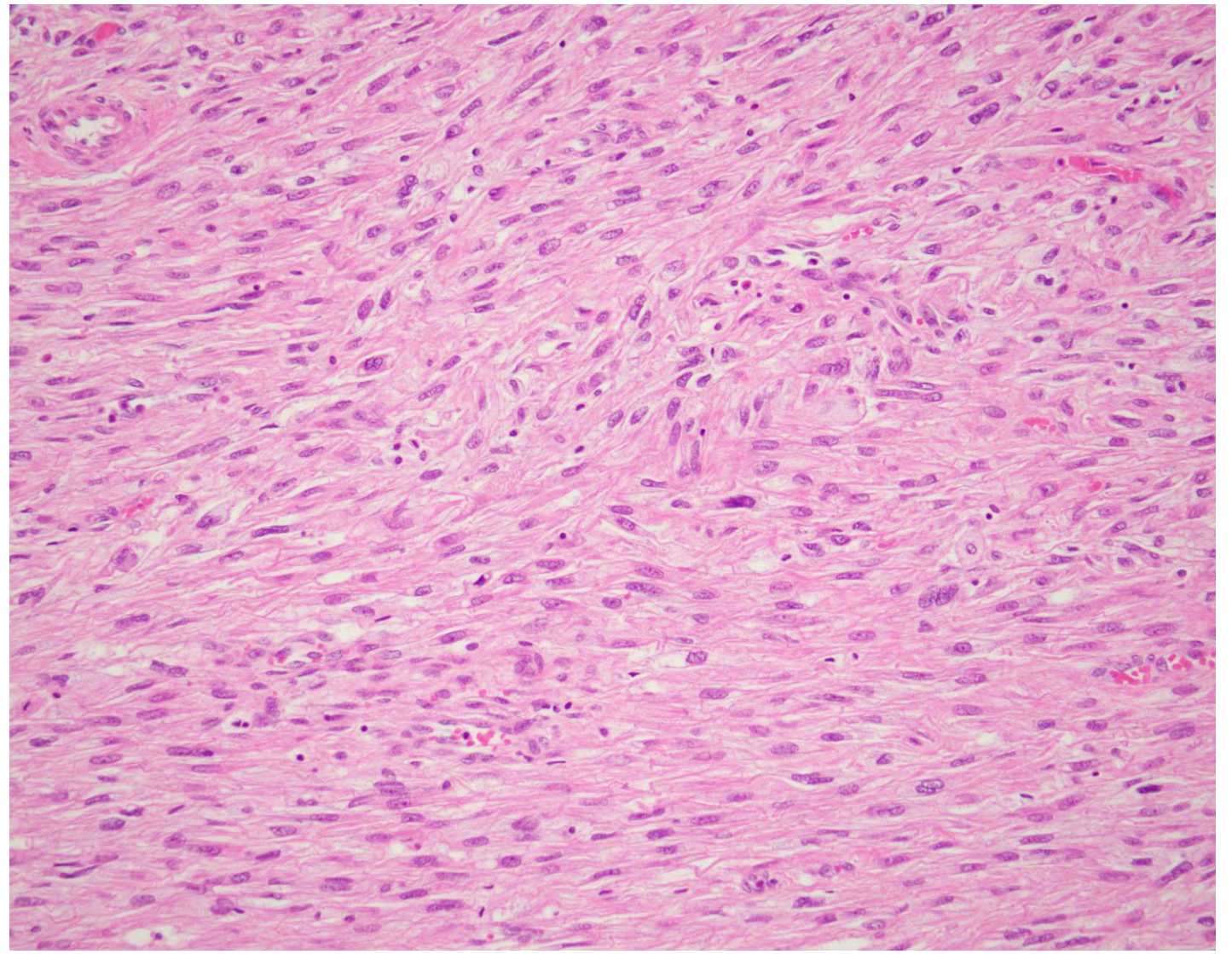
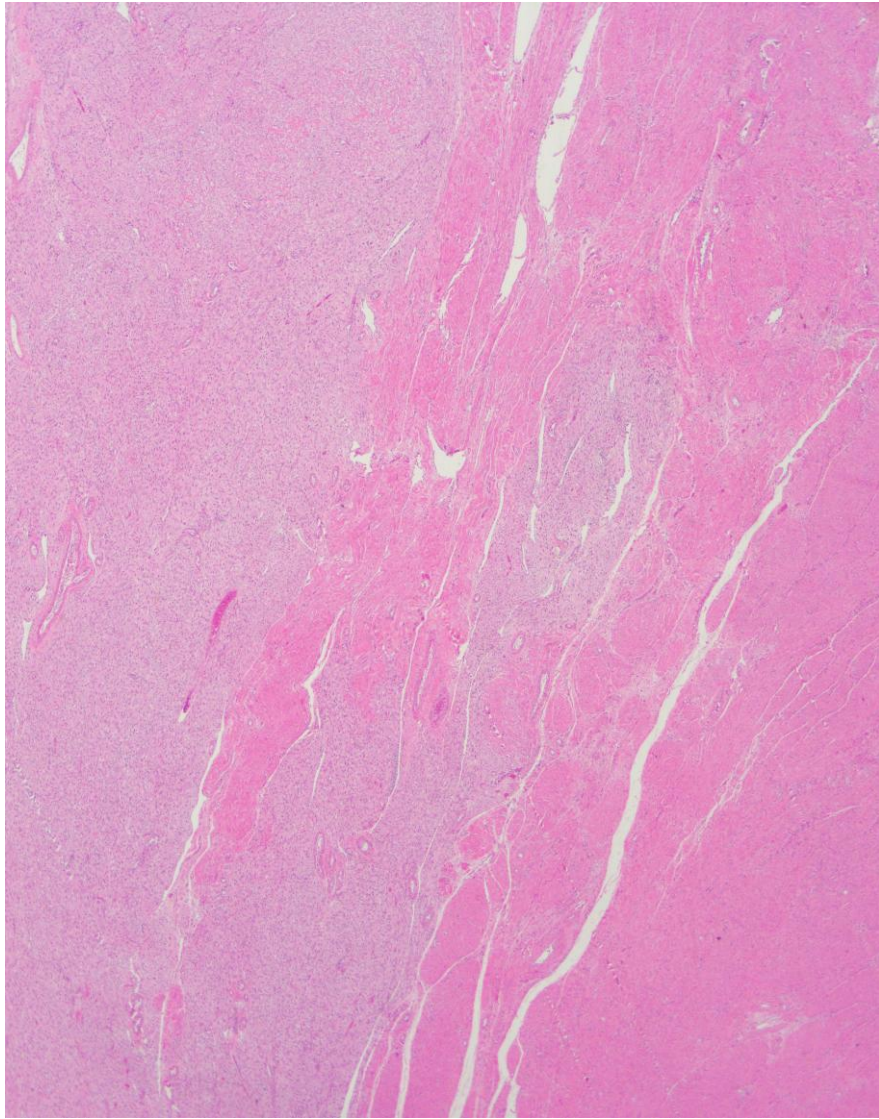
Massachusetts General Hospital, Harvard Medical School, Boston. USCAP 2019

- Diagnostic criteria vary among pathologists. After consensus review by a panel of experienced gynecologic pathologists, original diagnosis changed in 49% cases to leiomyoma variants, high-grade leiomyosarcoma, others
- Combination of histologic features such as nuclear atypia, mitoses, tumor cell necrosis, infiltrative margins, vascular space intrusion/invasion, and focal myxoid or epithelioid differentiation present in tumors with +/- recurrences
- Prominent long sweeping fascicles significantly present in tumors followed by recurrence

STUMP-WHO (5th EDITION)

Guidelines for spindle cell tumors

- 1- Focal/multifocal/diffuse atypia with 7-9 mitoses/10HPFs without TCN
 - 12-17% of these tumors have recurred but also some even with < mitoses
- 2- If TCN but no other worrisome features (~28%)
 - These tumors have also recurred
- 3- Tumors with >15 mitoses/10HPFs without cytologic atypia or TCN
 - None has recurred
- 4- If diffuse atypia and uncertain mitotic count (often due to karyorrhexis)



Diagnosed as STUMP with posterior omental metastases

Smooth Muscle Tumor of Uncertain Malignant Potential “STUMP”

**DO NOT USE FOR
LEIOMYOMA VARIANTS!**

LMS

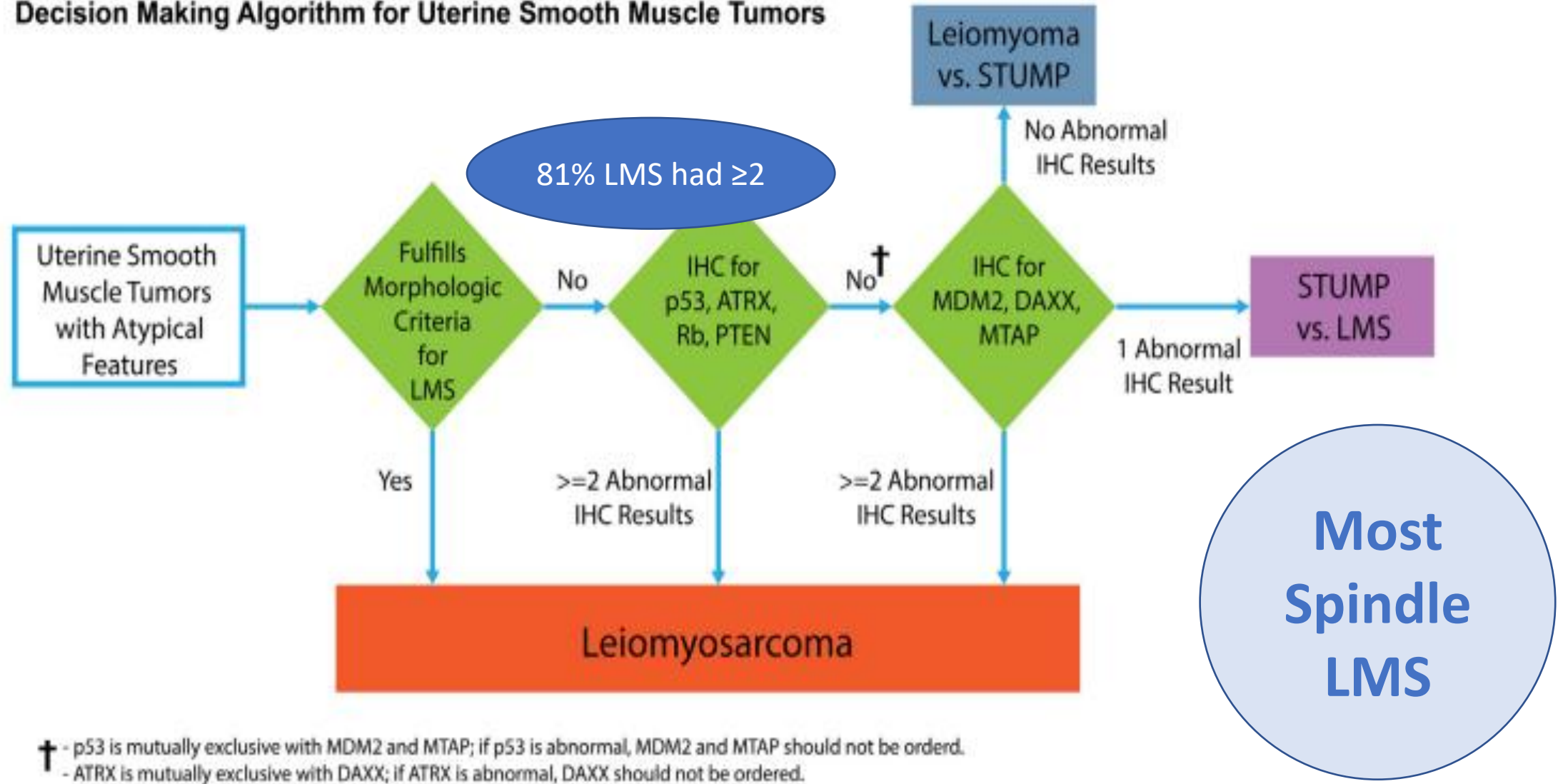
```
graph TD; LMS[LMS] --> Mutations[TP53 (40%), (ATRX) (26%), MED12 (21%); BRCA2 (rare) mutations]; LMS --> Rearrangements[HMGA2 rearrangements]; LMS --> Chromosomes(> 60% complex numerical and structural chromosomal aberrations including losses on 10q, 11q, 13q, 22q, 6q, and 2p, and gains on Xp, 1q, 5p, 8q, and 17p 264,418-427);
```

***TP53 (40%), (ATRX) (26%),
MED12 (21%); BRCA2 (rare)
mutations***

HMGA2 rearrangements

**> 60% complex
numerical and structural
chromosomal
aberrations including
losses on 10q, 11q, 13q,
22q, 6q, and 2p, and
gains on Xp, 1q, 5p, 8q,
and 17p 264,418-427**

Decision Making Algorithm for Uterine Smooth Muscle Tumors

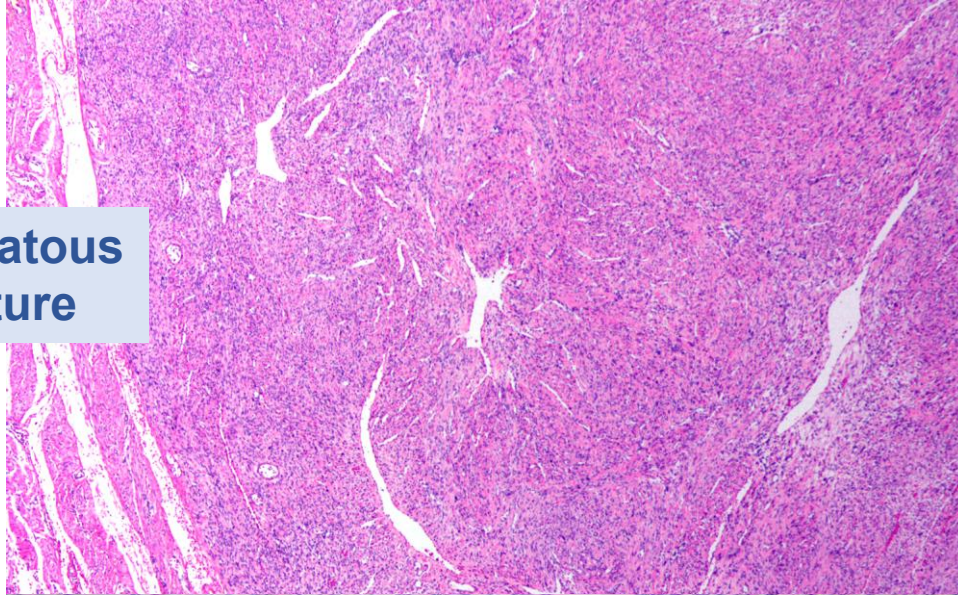


94% (157/167) showed at least one genomic abnormality involving TP53, RB1, ATRX, PTEN, CDKN2A or MDM2 with 80% showing alterations in two genes

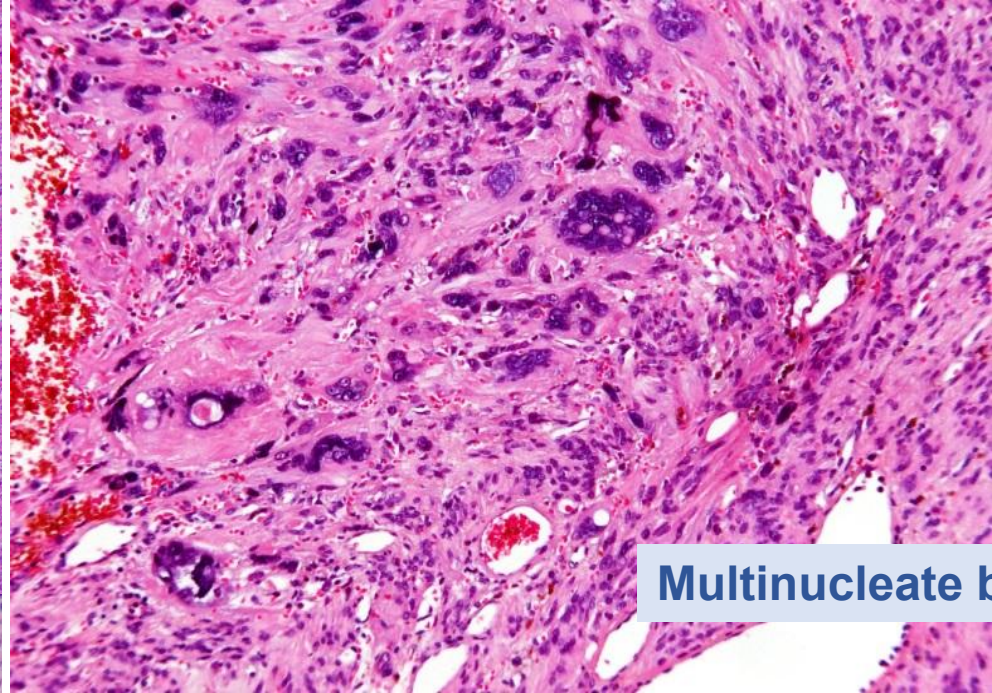
HEREDITARY LEIOMYOMATOSIS AND RENAL CELL CARCINOMA SYNDROME

- **Autosomal dominant**
 - **Multiple pilar leiomyomas of skin**
 - **Uterine leiomyomas (early onset)**
 - **Papillary renal cell carcinoma, high-grade**
-
- **Most patients develop leiomyomas**
 - **Only 15-20% develop renal cell carcinoma**

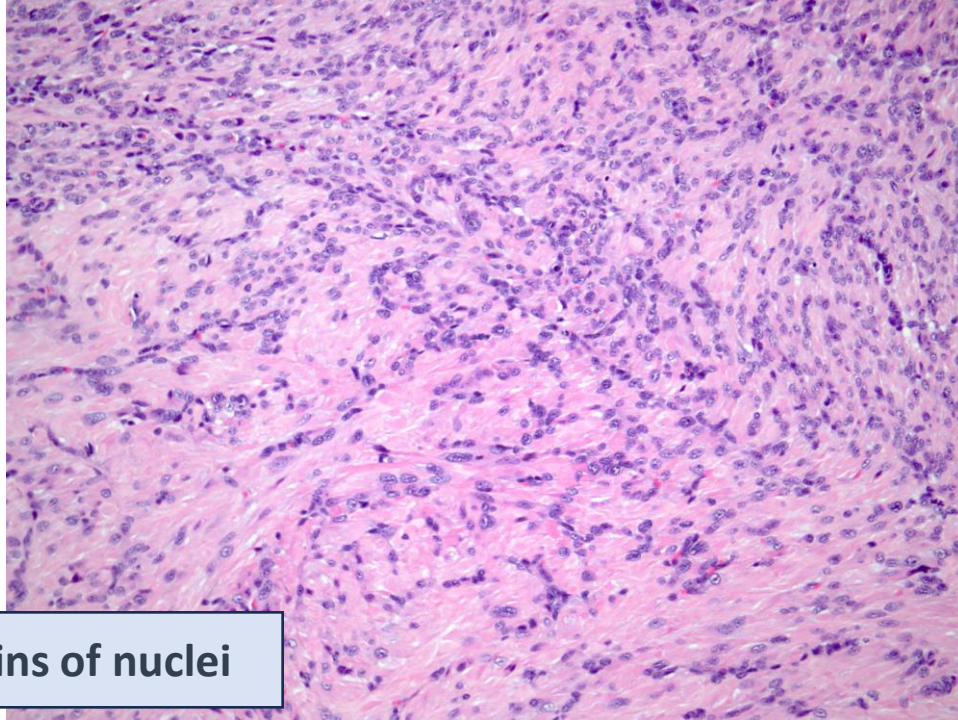
LEIOMYOMATOSIS-RENAL CELL CARCINOMA SYNDROME



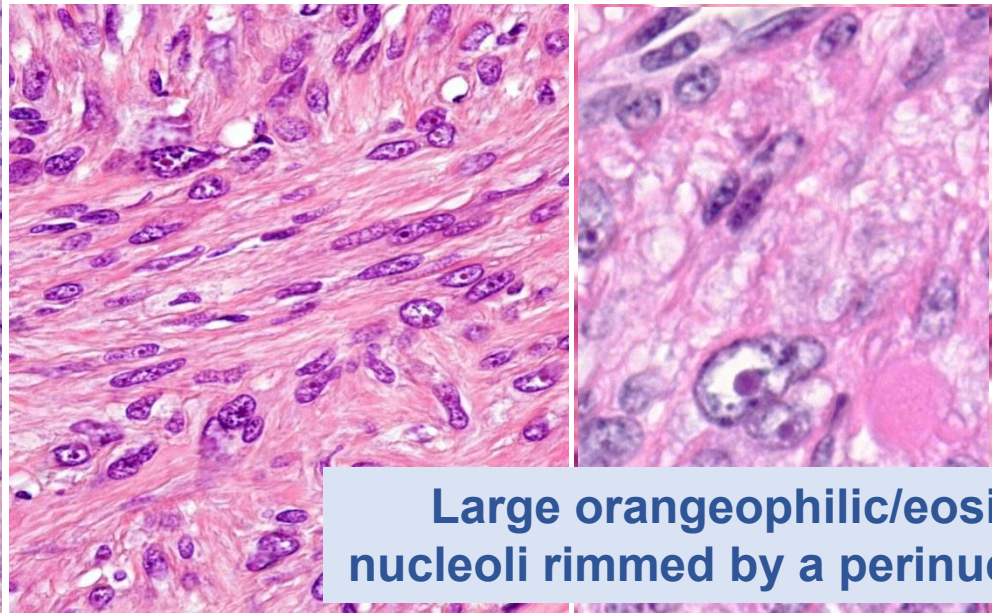
Pericytomatous
vasculature



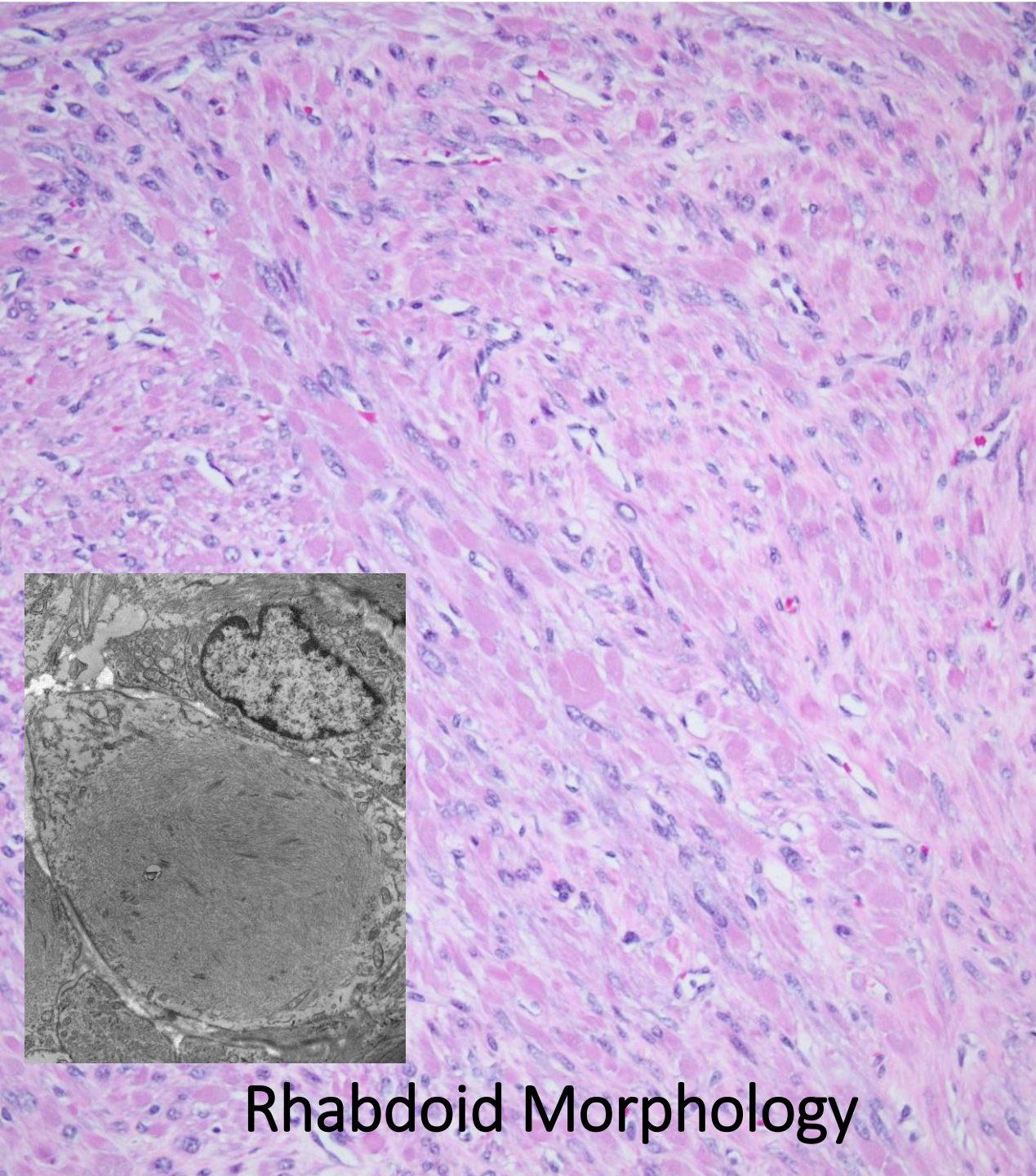
Multinucleate bizarre cells



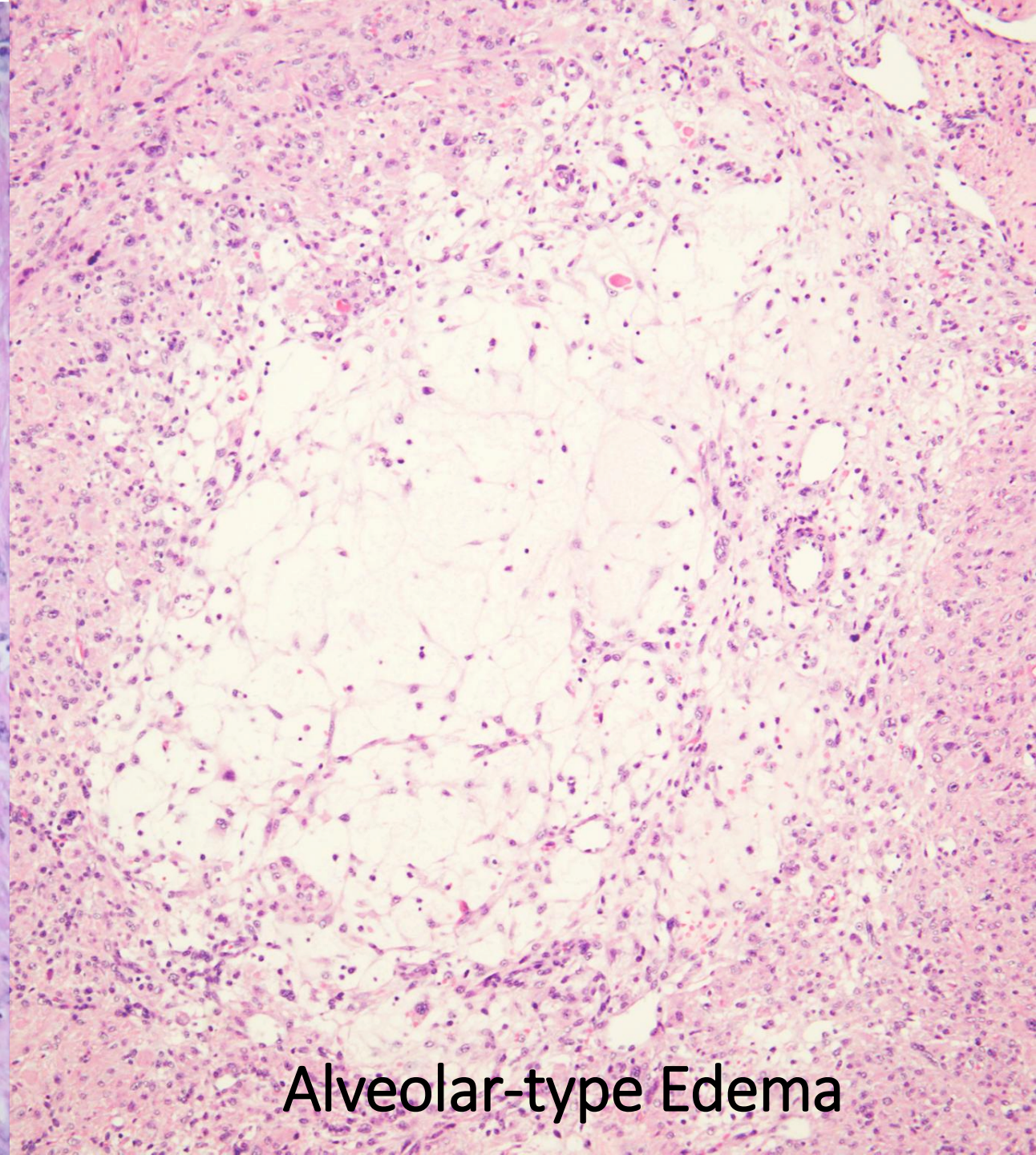
Small chains of nuclei



Large orangeophilic/eosinophilic
nucleoli rimmed by a perinucleolar halo

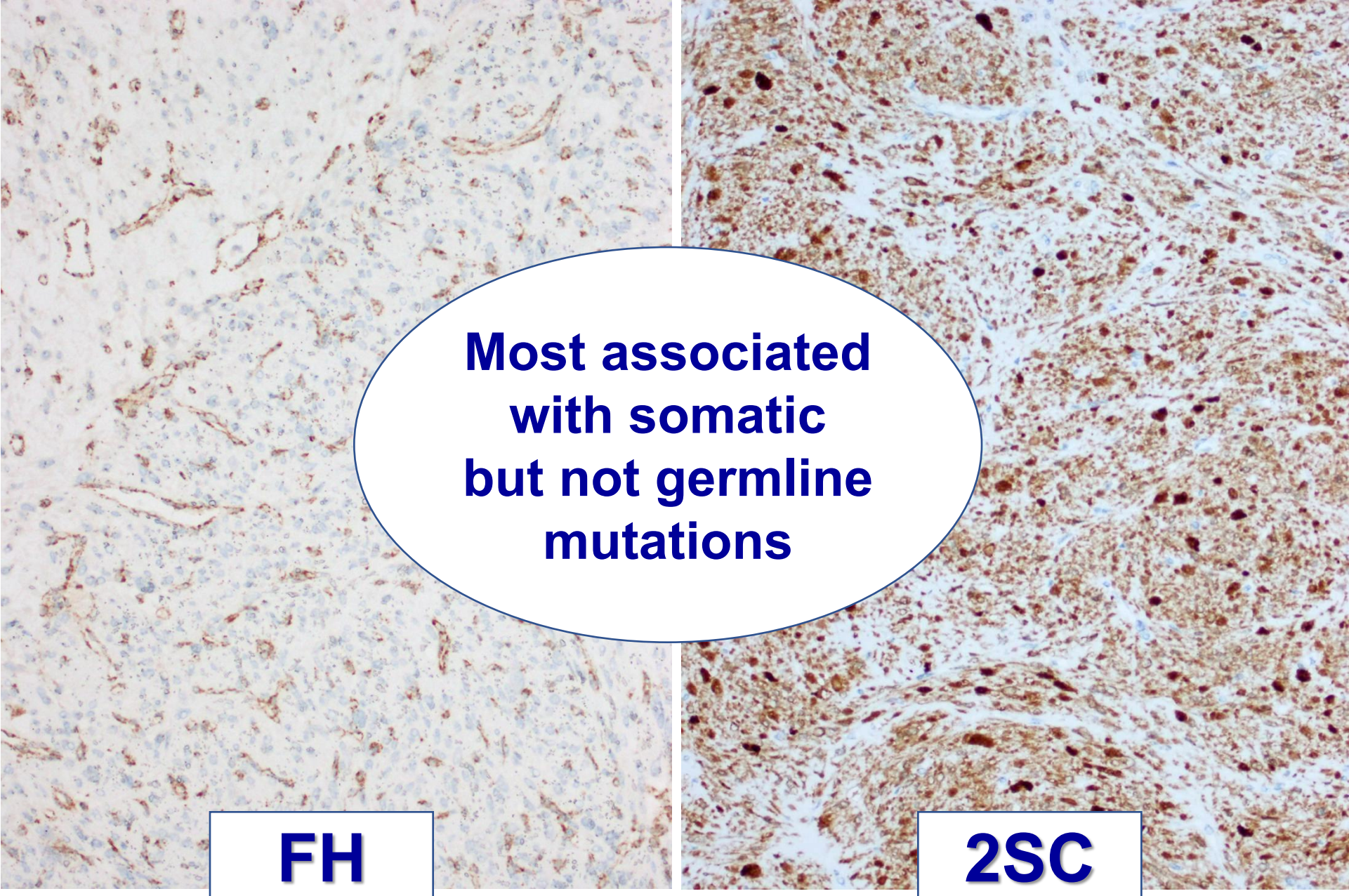


Rhabdoid Morphology

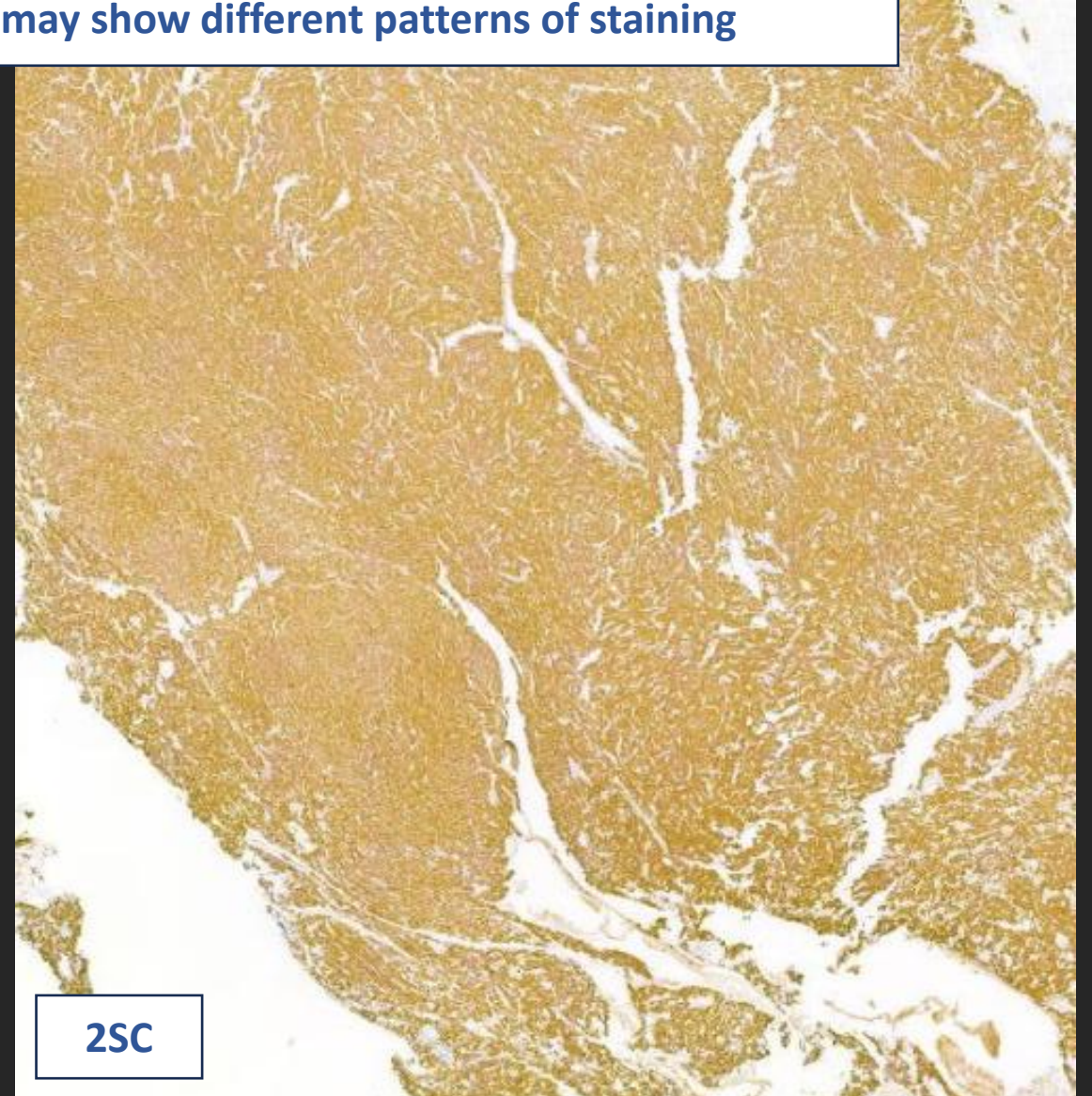
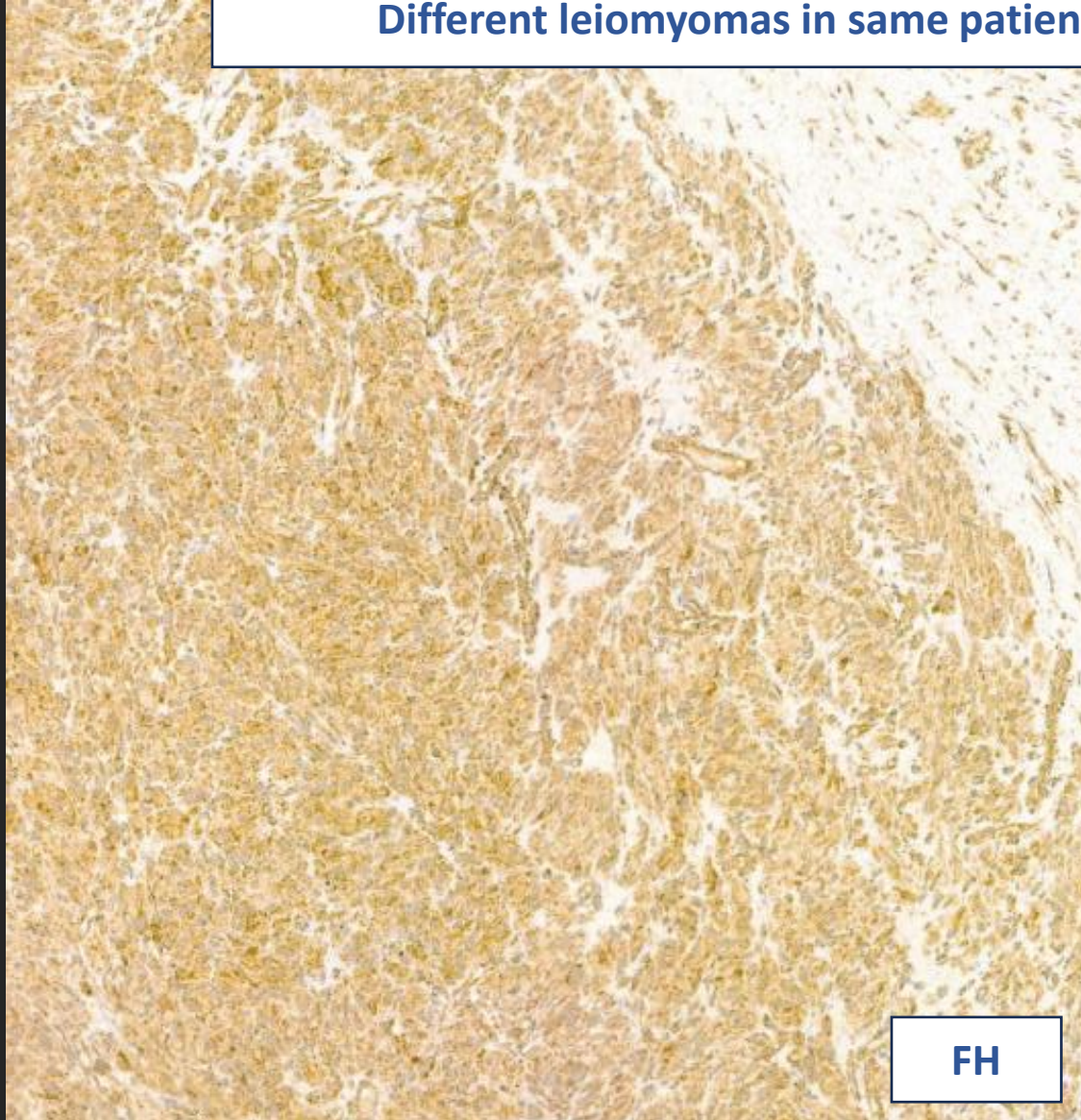


Alveolar-type Edema

LEIOMYOMA WITH BIZARRE NUCLEI



Aberrant preserved expression of FH more common in germline mutations
Different leiomyomas in same patient may show different patterns of staining



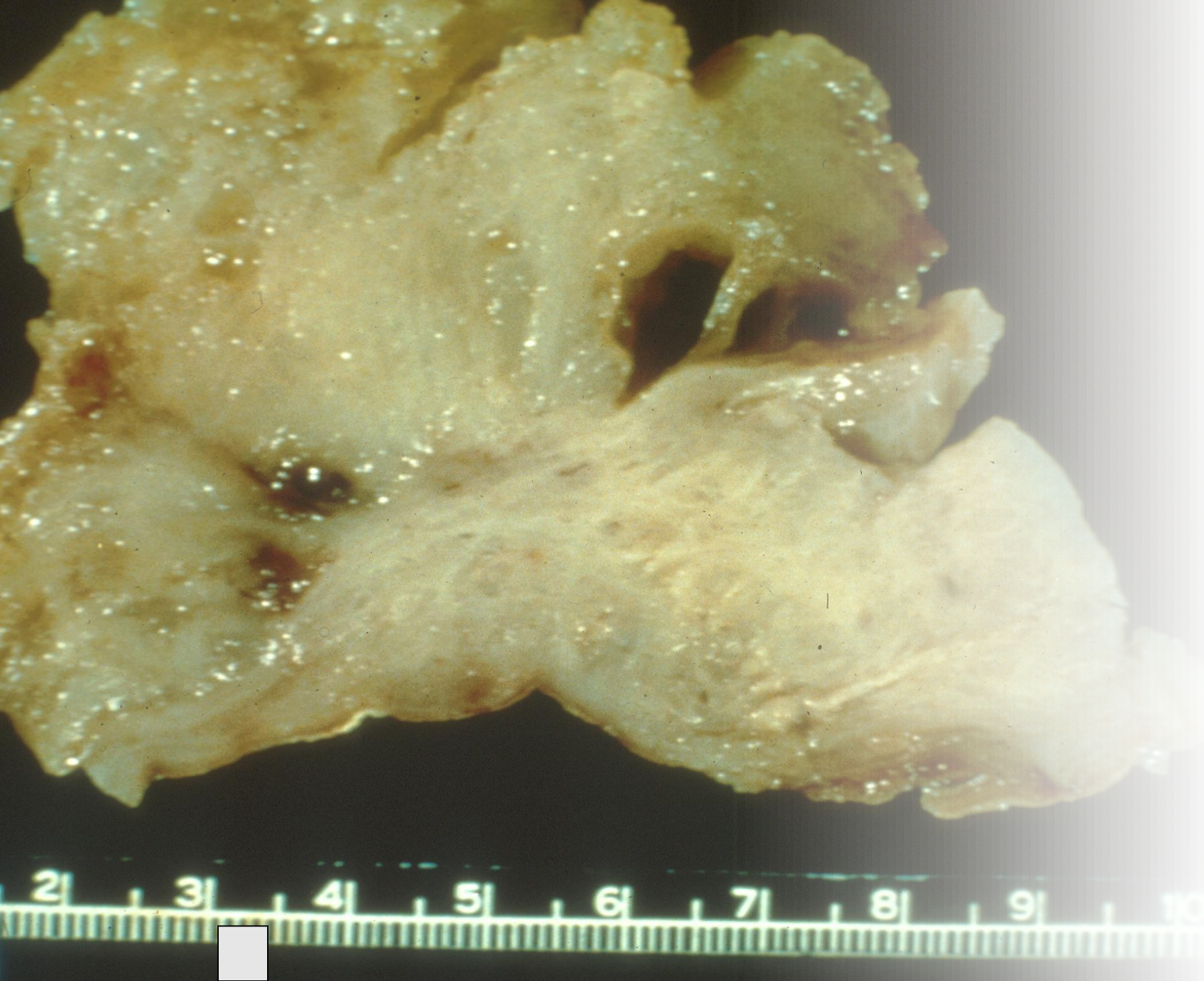
Prospective Detection of Germline Mutation of *Fumarate Hydratase* in Women With Uterine Smooth Muscle Tumors Using Pathology-based Screening to Trigger Genetic Counseling for Hereditary Leiomyomatosis Renal Cell Carcinoma Syndrome

A 5-Year Single Institutional Experience

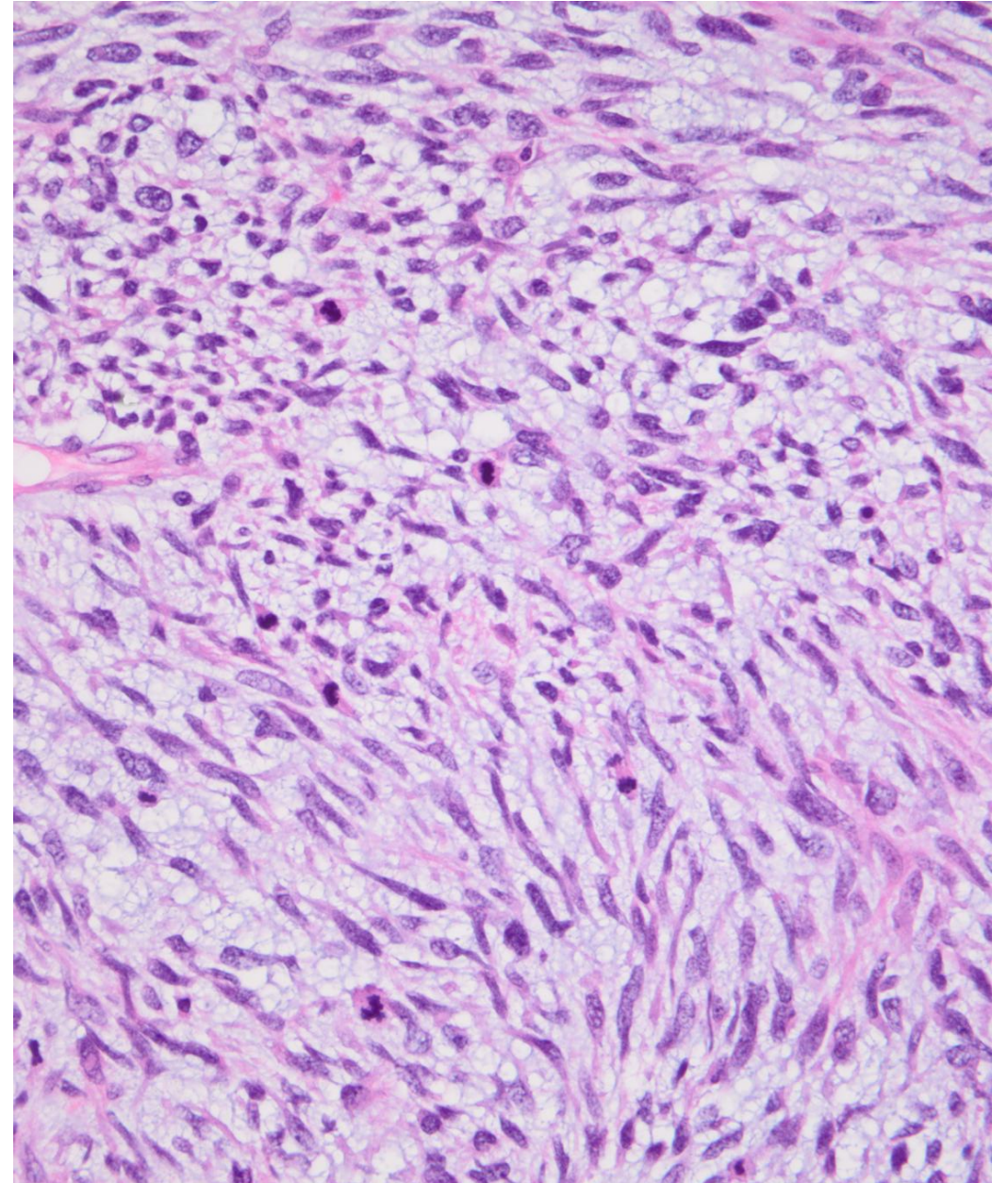
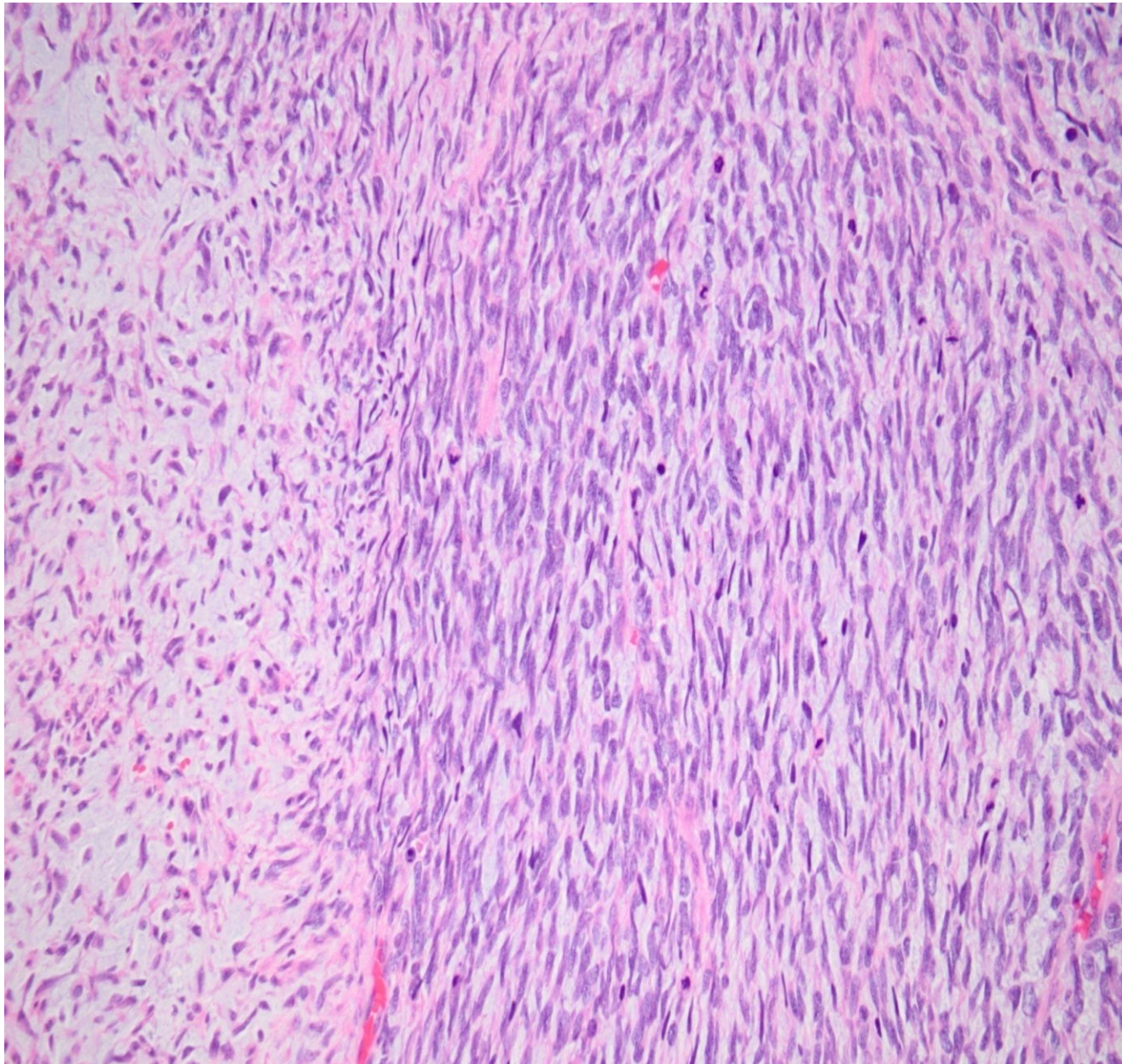
- U-SMT from 2060 women evaluated for FH-d morphology (staghorn vessels, macronucleoli surrounded by clear halo, eosinophilic globules) in a 5-year period and noted in 30 (1.4%)
- 10/30 elected FH genetic testing and 6/10 had a germline mutation
- Abnormal FH expression was not very reliable to trigger genetic counseling with no difference in incidence of pathogenic FH germline mutation between FH-d morphology U-SMT with abnormal vs normal FH expression
- Morphologic screening confirmed genetic diagnosis of HLRCC syndrome in 0.24% of all women (24-40 years) with any type of U-SMT (BN and conventional); thus, morphology-based screening with genetic counseling referral can result in diagnosis of HLRCC syndrome in unselected women with U-SMT

BLURB:

Although these features may be seen in leiomyomas that are part of Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC) Syndrome, in most cases tumors are sporadic. Genetic consultation and additional testing may be indicated if clinical suspicion is high.



MYXOID
LEIOMYOSARCOMA

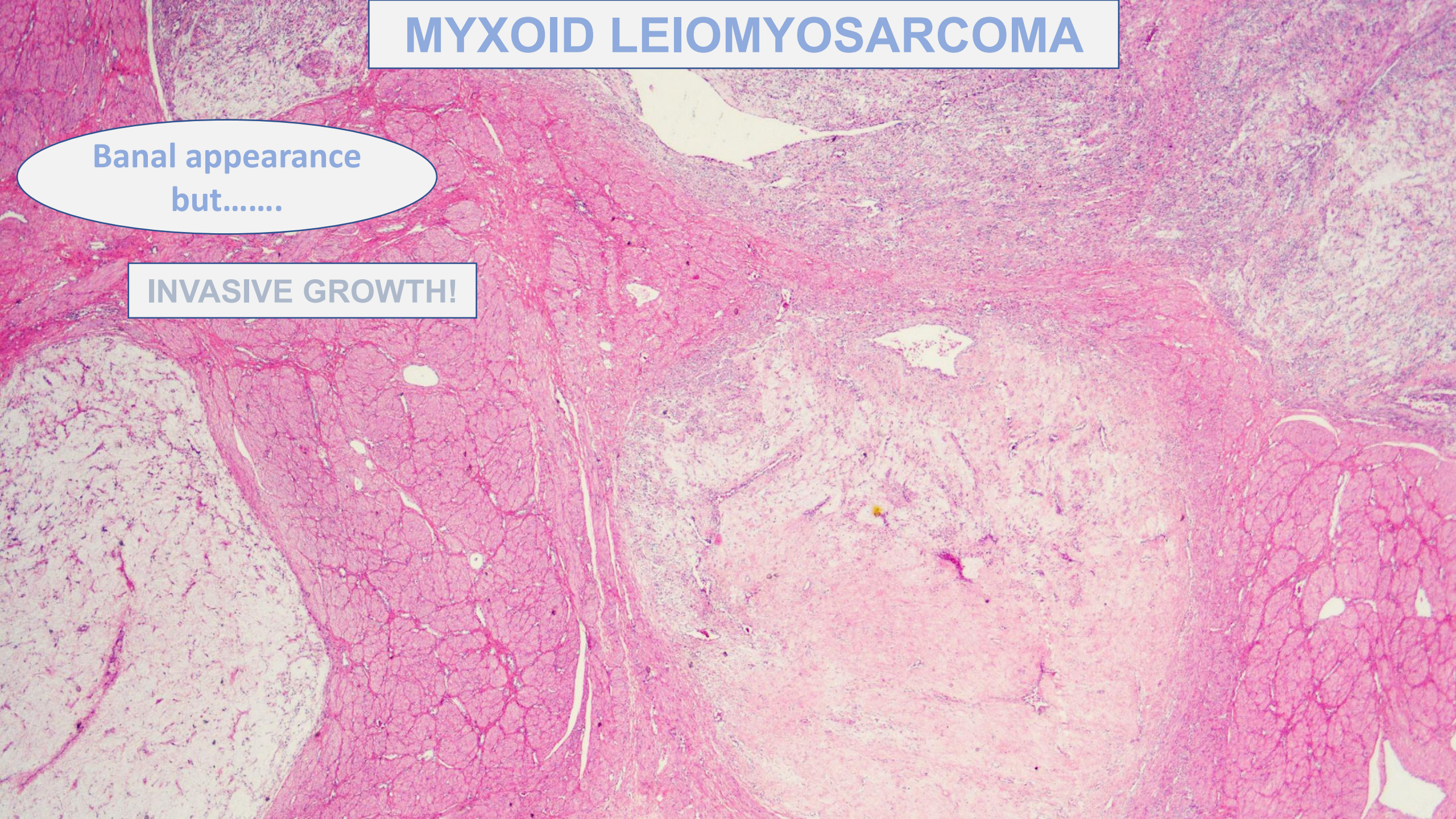


Threshold to diagnose myxoid LMS ranges from >30 to $>60\%$

MYXOID LEIOMYOSARCOMA

Banal appearance
but.....

INVASIVE GROWTH!



Myxoid Smooth Muscle Tumors

Atkins K et al., Modern Pathol 132A, 2001

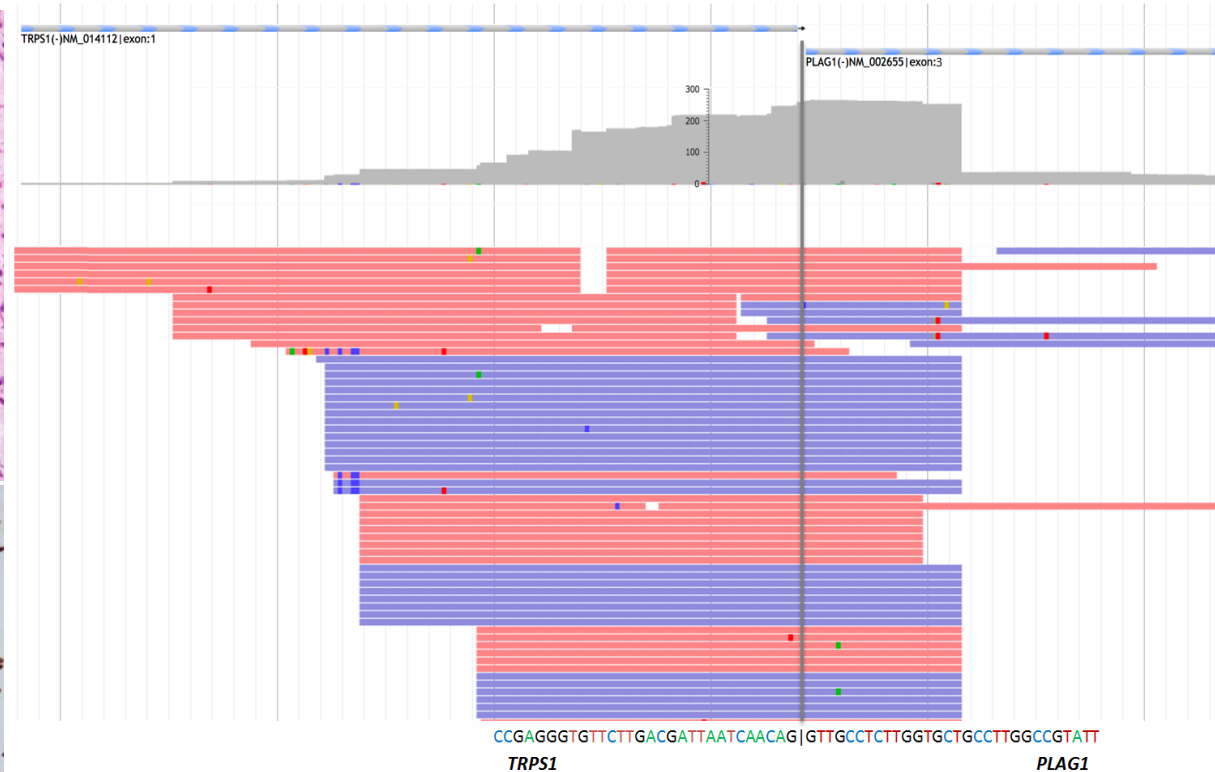
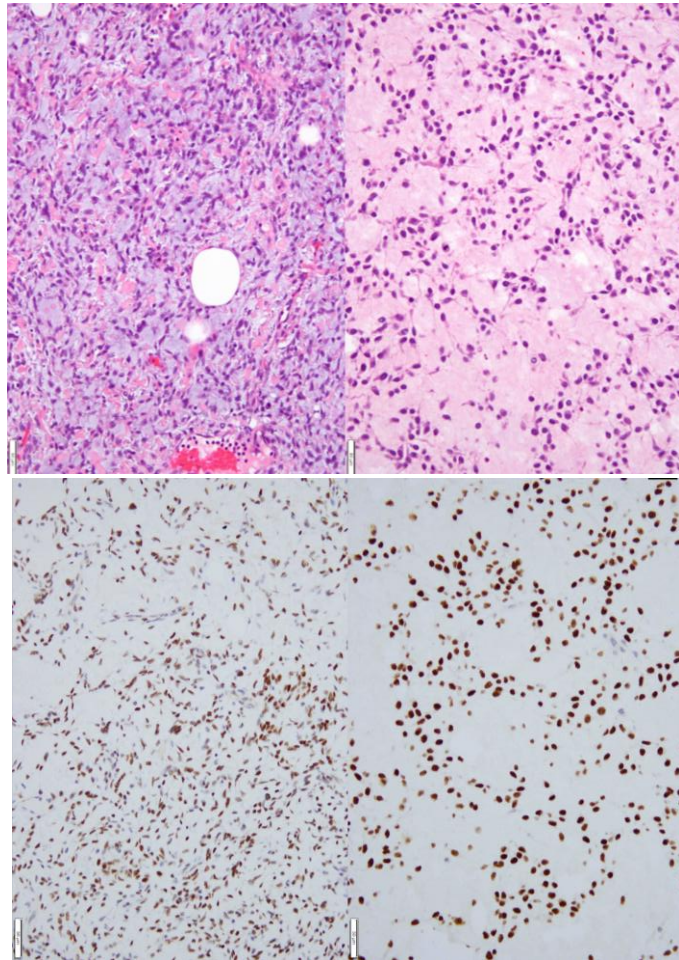
- Presence of tumor cell necrosis or severe cytologic atypia warrant the diagnosis of malignancy
- In the absence of tumor cell necrosis or severe cytologic atypia, **a mitotic index of >2/10HPFs** is indicative of malignant behavior

Parra-Herran C et al, Am J Surg Pathol 2016;40:285

Goh R et al, Modern Pathol 2016, 29, suppl2, 285A

Tumors with < 2mitoses/10 HPFs may also be associated with an aggressive behavior

Novel PLAG1 Gene Rearrangement Distinguishes a Subset of Uterine Myxoid Leiomyosarcomas From Other Uterine Myxoid Mesenchymal Tumors



TRPS1-PLAG1 fusion > RAD51B-PLAG1 fusion (NGS/FISH)

Arias Stella JA et al, Am J Surg Pathol 2019; 43:382-388

No distinctive morphologic features

PLAG1-Rearranged Uterine Sarcomas: A Study of 11 Cases Showing a Wide Phenotypical Spectrum Not Limited to Myxoid Leiomyosarcoma-Like Morphology

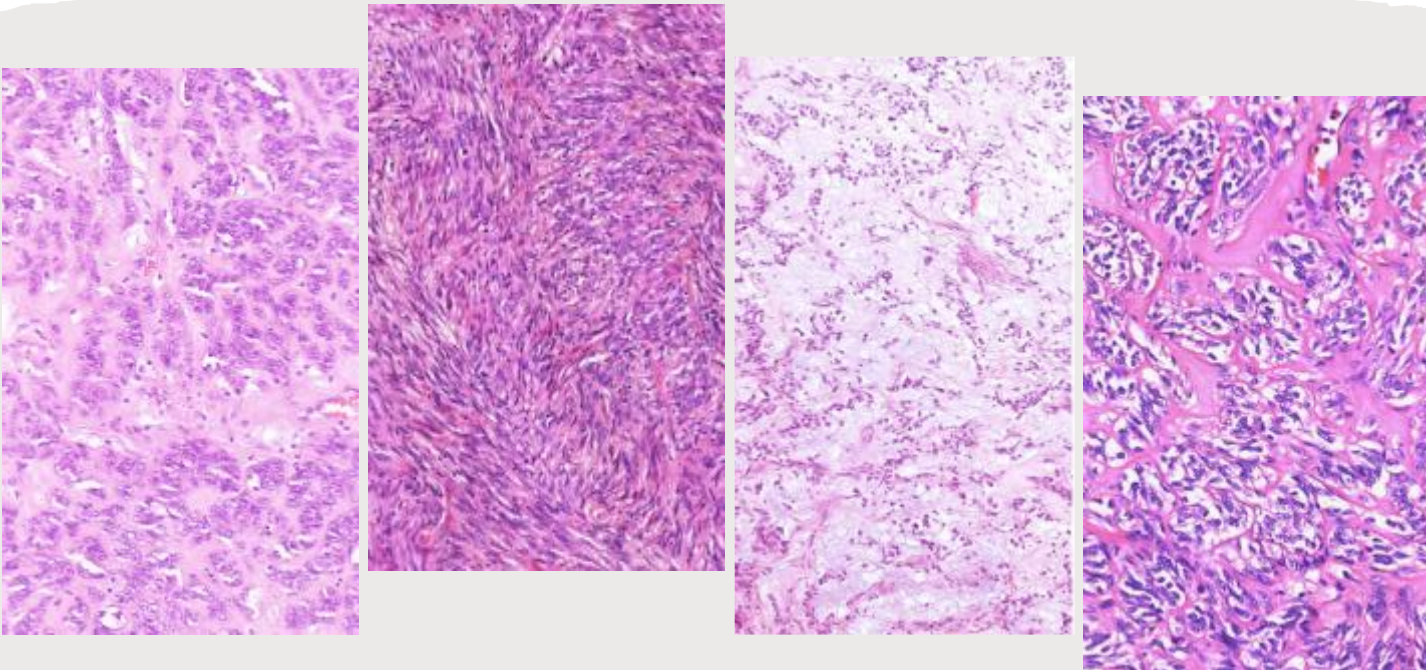
Michael Michal^{a,b,*}, Abbas Agaimy^c, Sabrina Croce^d, Gunhild Mechttersheimer^e, John M. Gross^f, Deyin Xing^f, Debra A. Bell^g, Sounak Gupta^g, Elaheh Mosaieby^{a,b}, Petr Martínek^a, Natálie Klubíčková^{a,b}, Květoslava Michalová^{a,b}, Jiří Bouda^h, Jindřich Fínekⁱ, Tahyna Hernandez^j, Michal Michal^{a,b}, J. Kenneth Schoolmeester^k, Ondrej Ondič^{a,b}

Modern Pathol 2024

Most tumors - nondescript NOS-spindle or less commonly epithelioid cell sarcomas-

Unusual features:

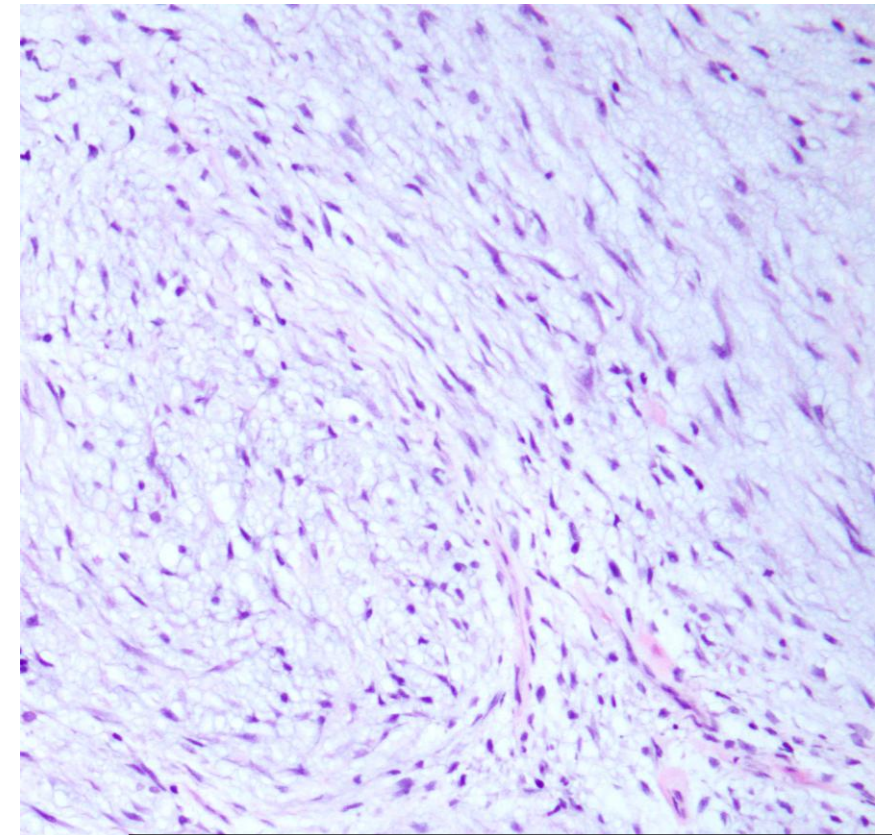
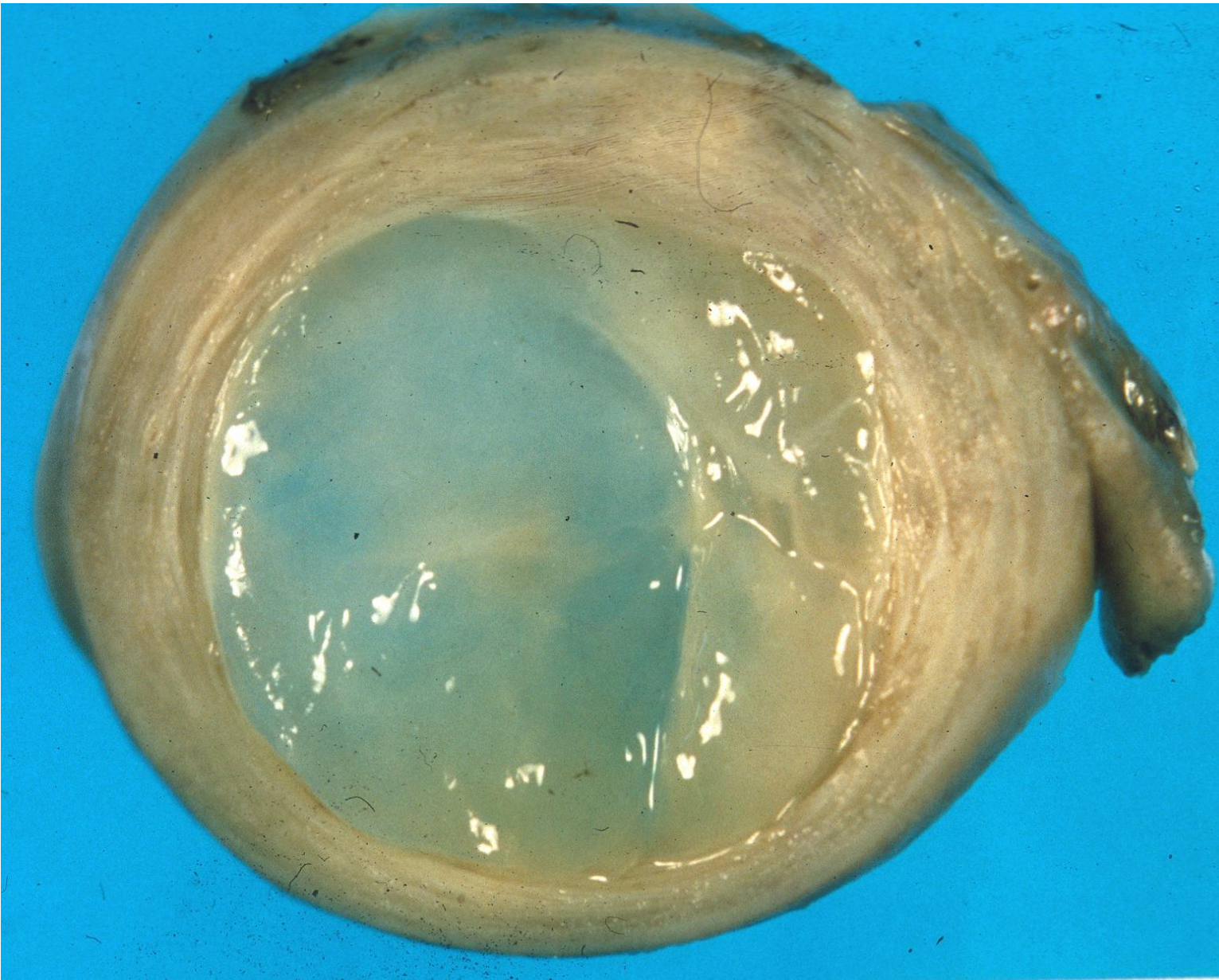
- Hyalinized stroma
- Adipocytic differentiation mimicking myxoid liposarcoma
- Osteosarcomatous differentiation
- Undifferentiated pleomorphic



UTERINE MYXOID LESIONS

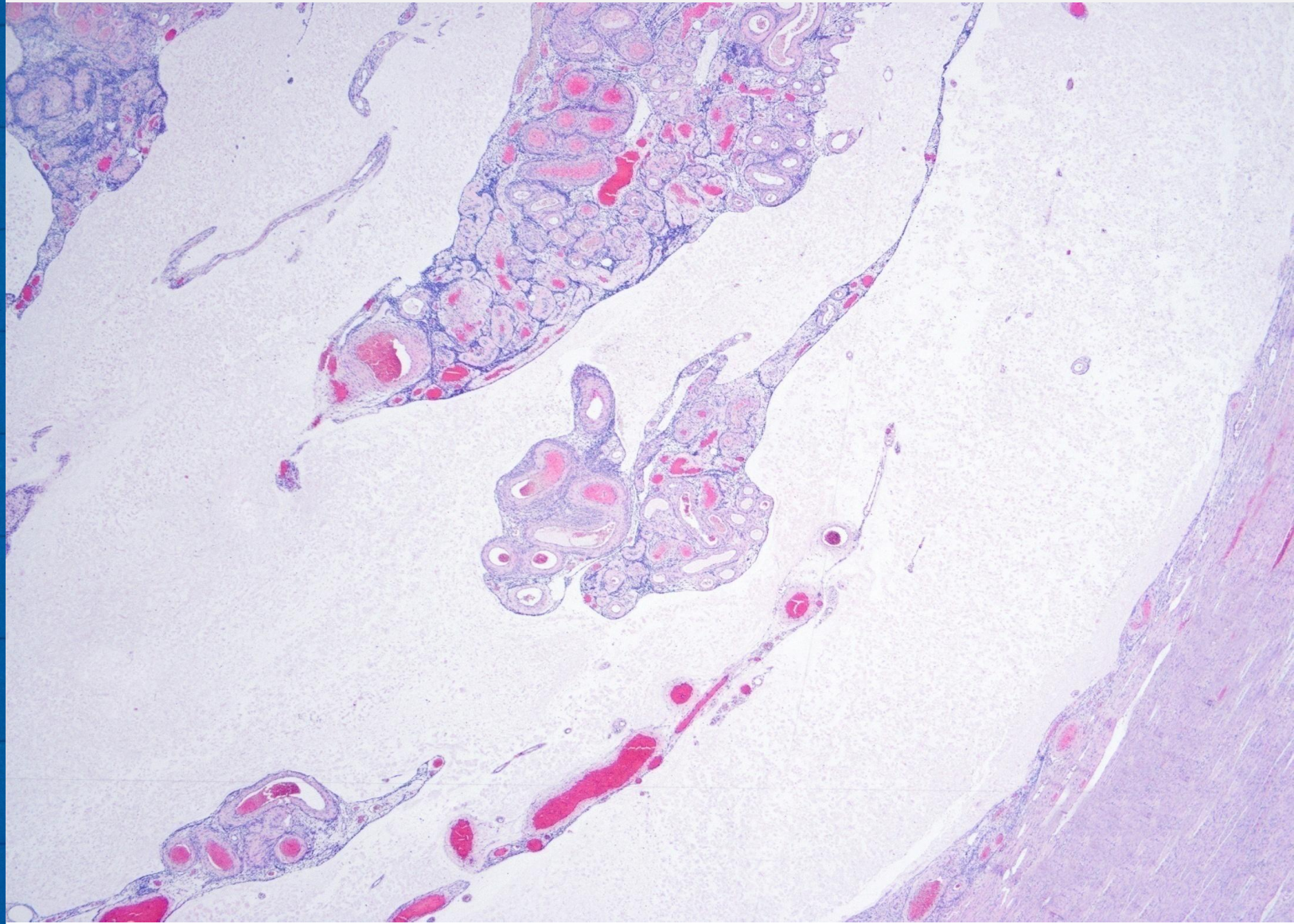
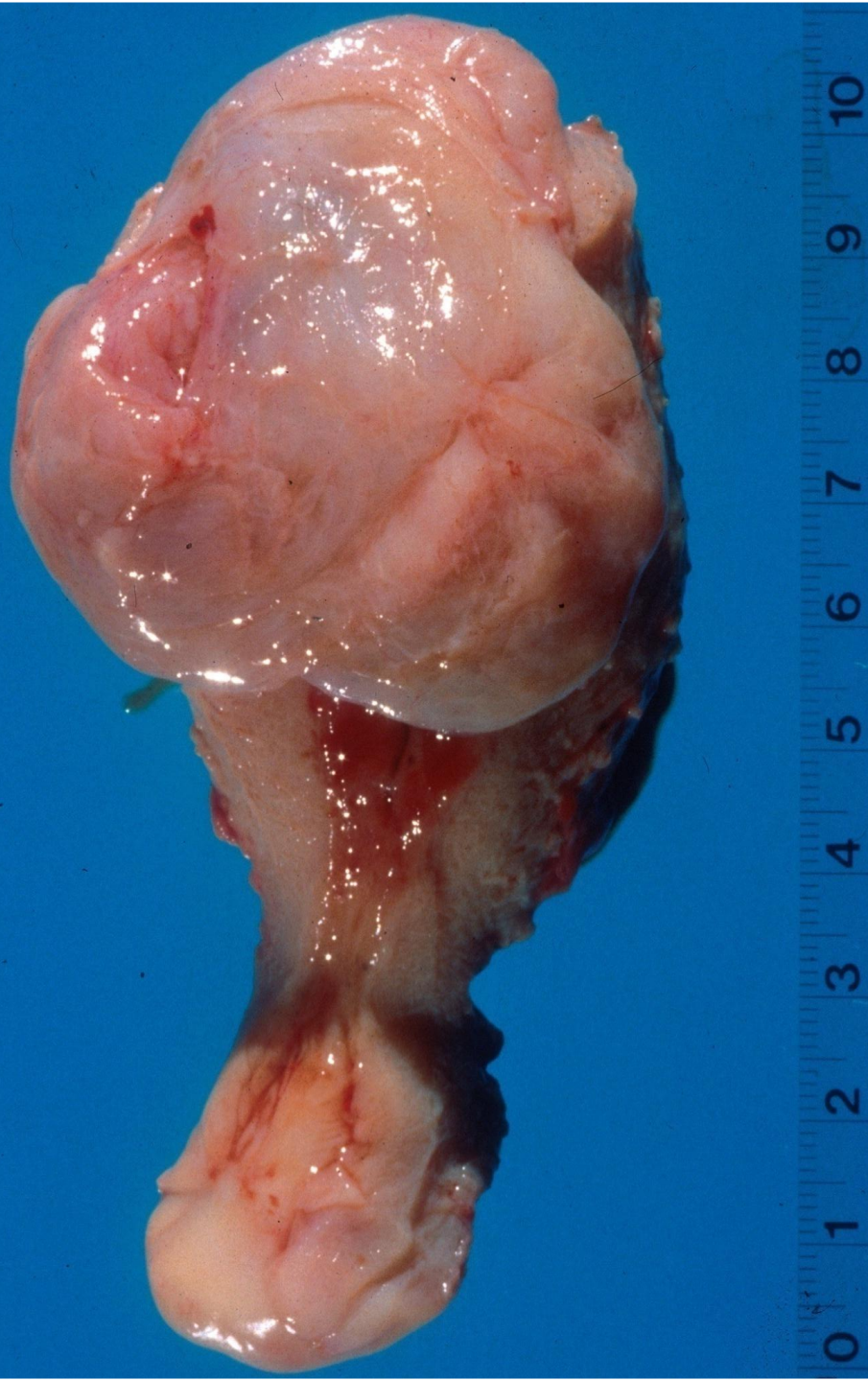
- Myxoid change in leiomyoma (conventional, in pregnancy, or apoplectic)
- Myxoid smooth muscle tumors
 - Benign (rare)
 - Malignant (uncommon)
- Inflammatory myofibroblastic tumor
- Endometrial stromal tumors
 - Low-grade fibromyxoid (uncommon)
 - BCOR high-grade (rare)
- Other: PLAG1 rearranged uterine sarcomas, Embryonal rhabdomyosarcoma, liposarcoma, solitary fibrous tumor, NTRK sarcomas, fibroblastic sarcomas with features of malignant nerve sheath tumor, sarcomas with GLI1 gene alterations....
- Myxoidosis or myxoid change in uterine wall

MYXOID LEIOMYOMA <5 cm



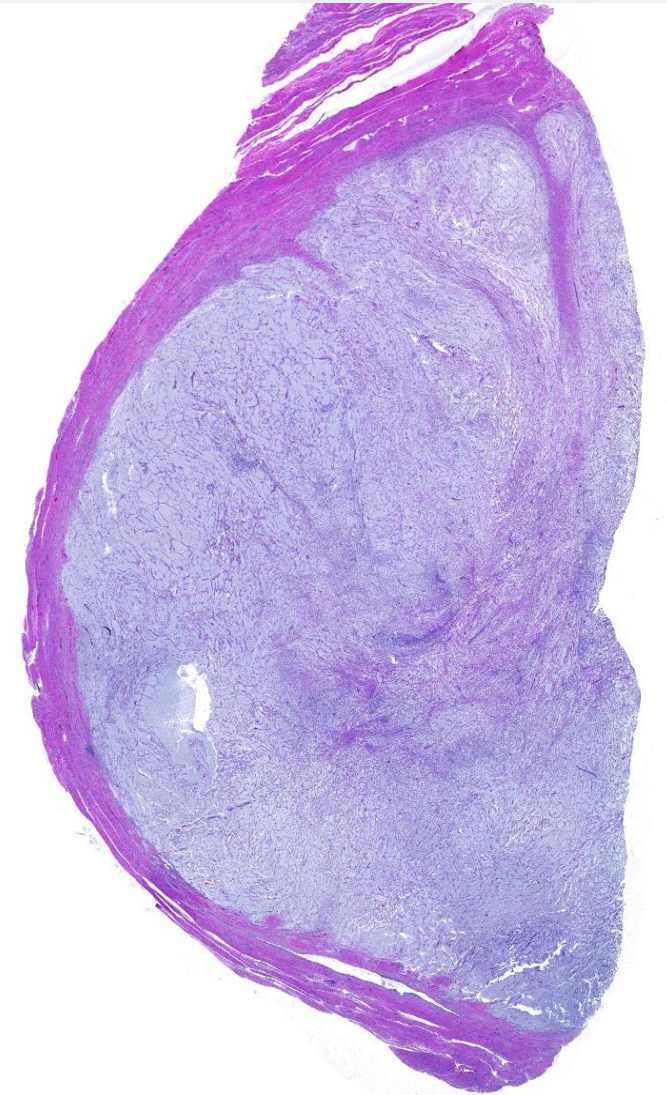
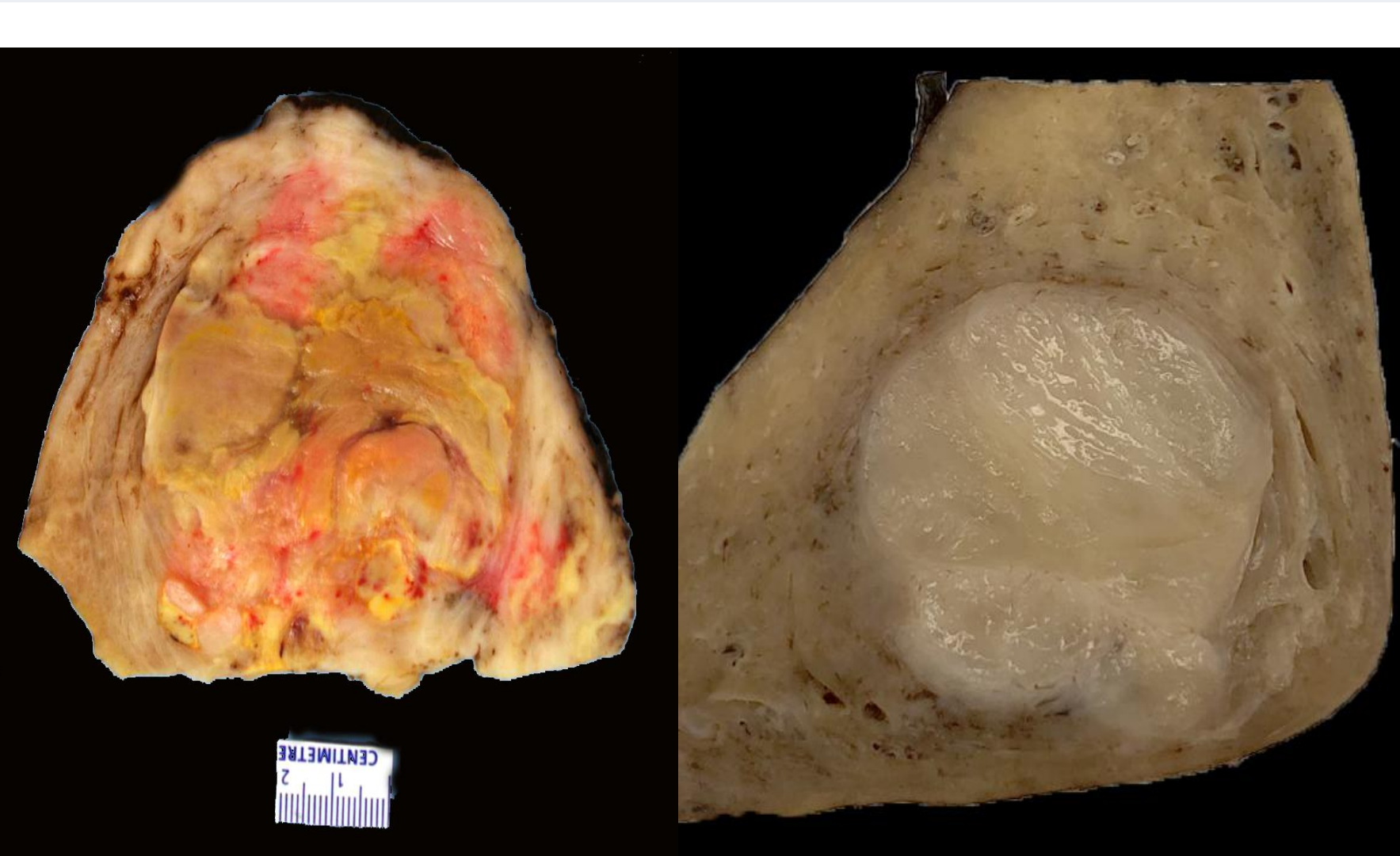
WELL- CIRCUMSCRIBED
NO CYTOLOGIC ATYPIA
NO MITOSES

LEIOMYOMA WITH HYDROPIK CHANGE



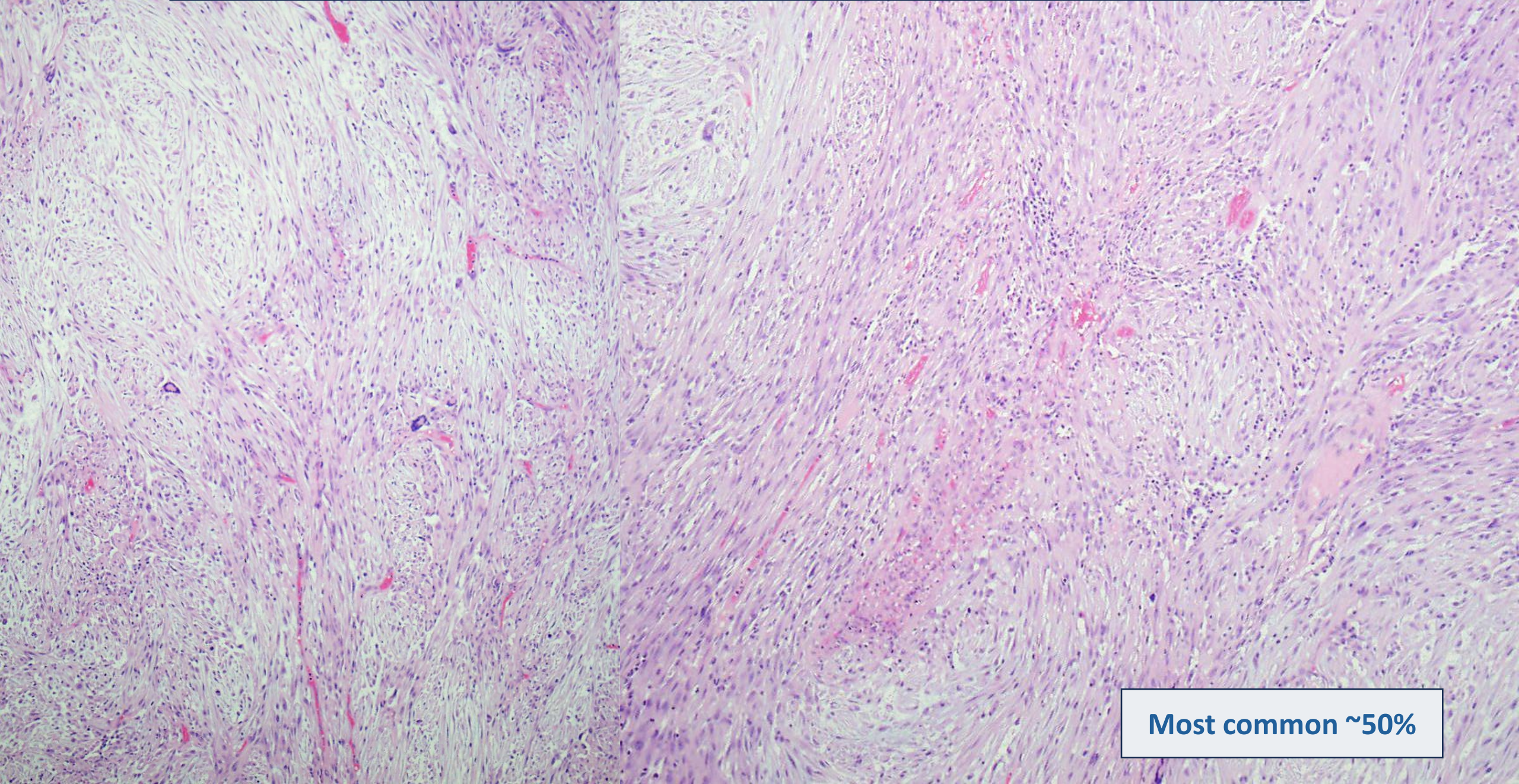
**WATERY FLUID=EDEMA:
ALCIAN BLUE NEGATIVE**

INFLAMMATORY MYOFIBROBLASTIC TUMOR

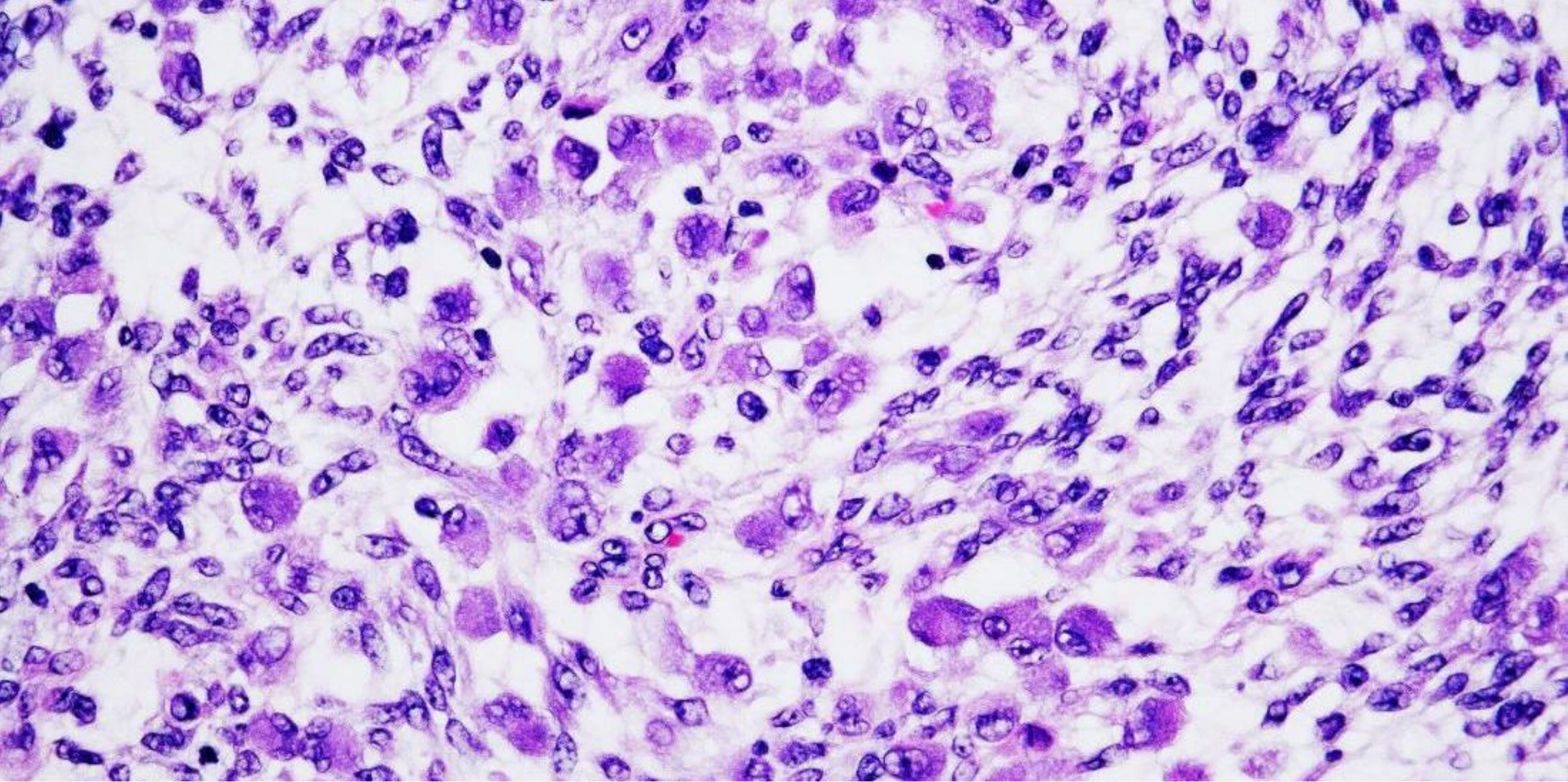


May be strikingly myxoid

MYXOID PATTERN – MAY MIMIC OTHER MYXOID MESENCHYMAL TUMORS

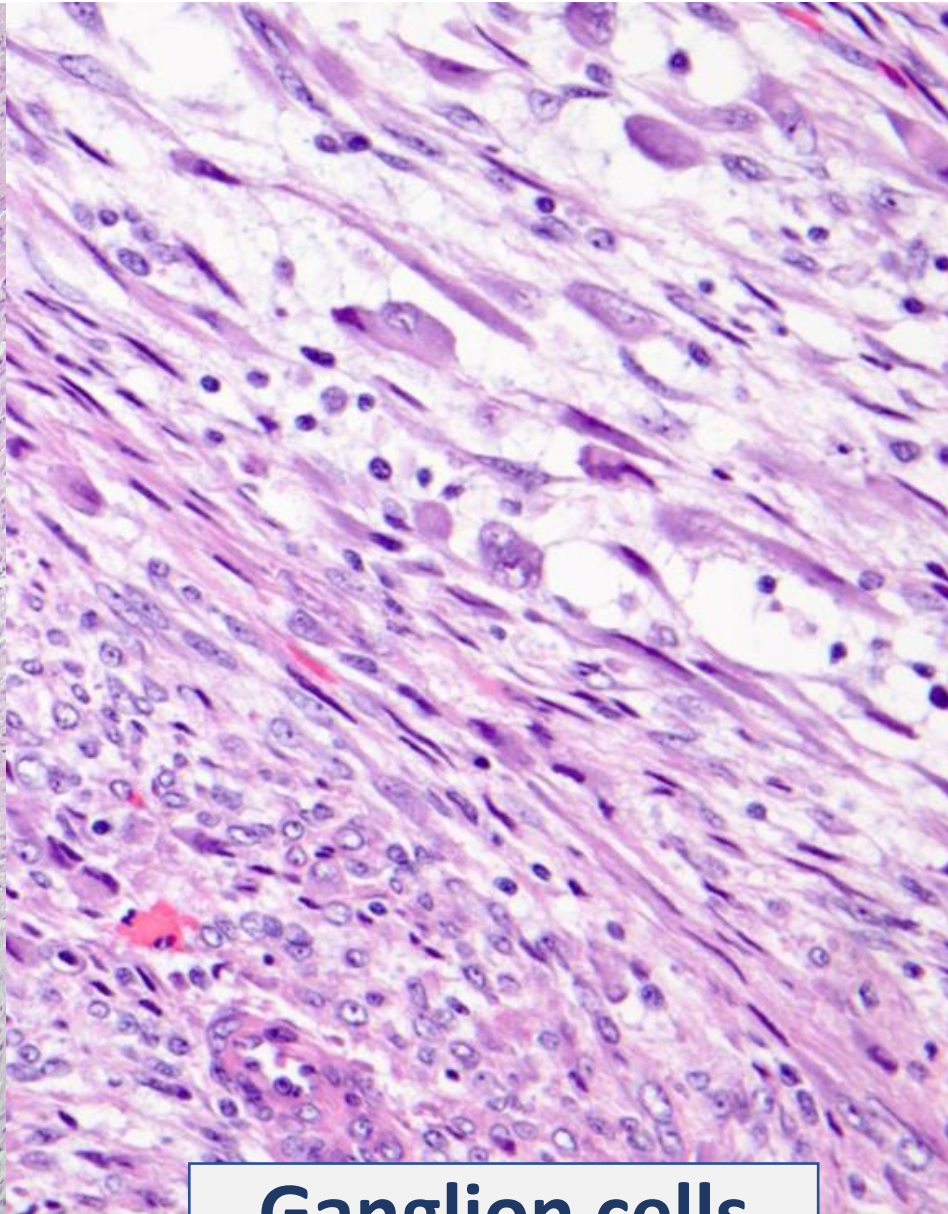
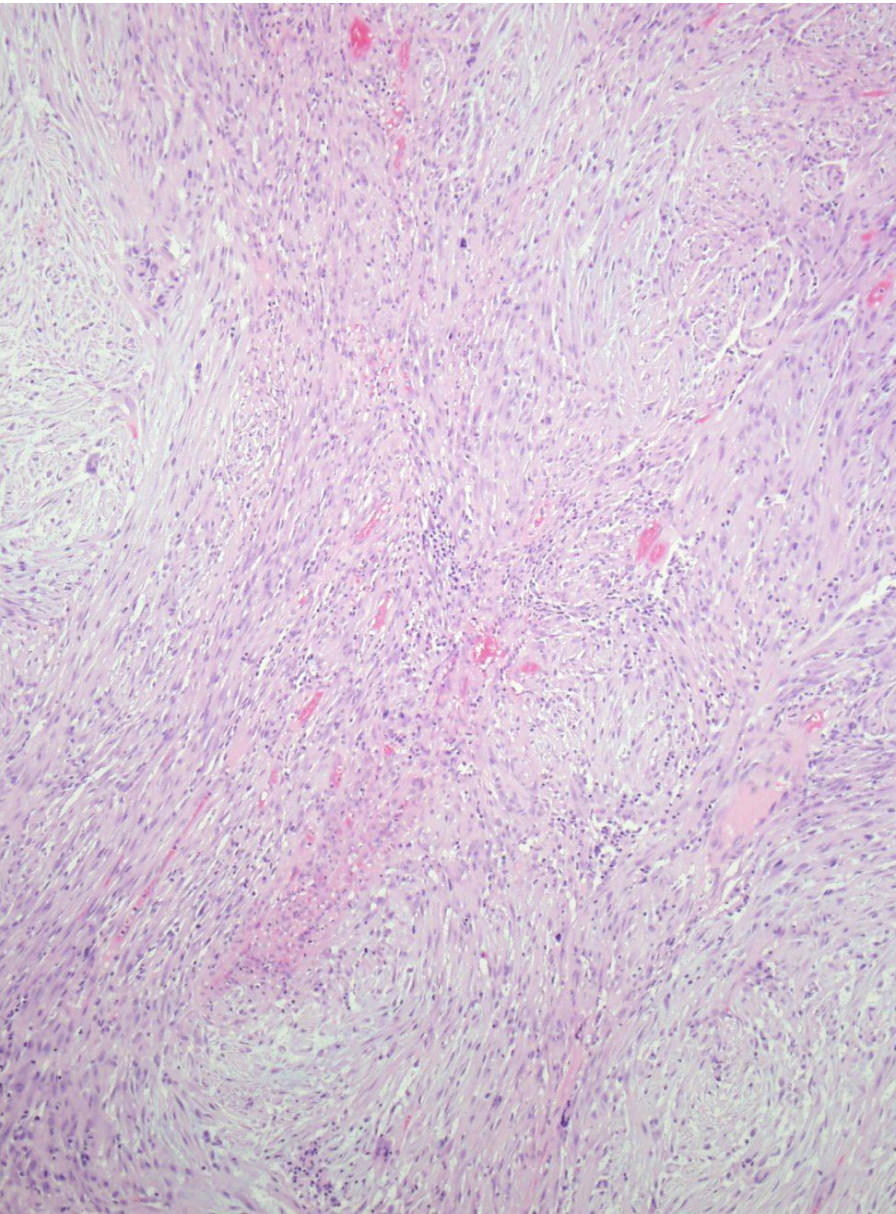


Most common ~50%

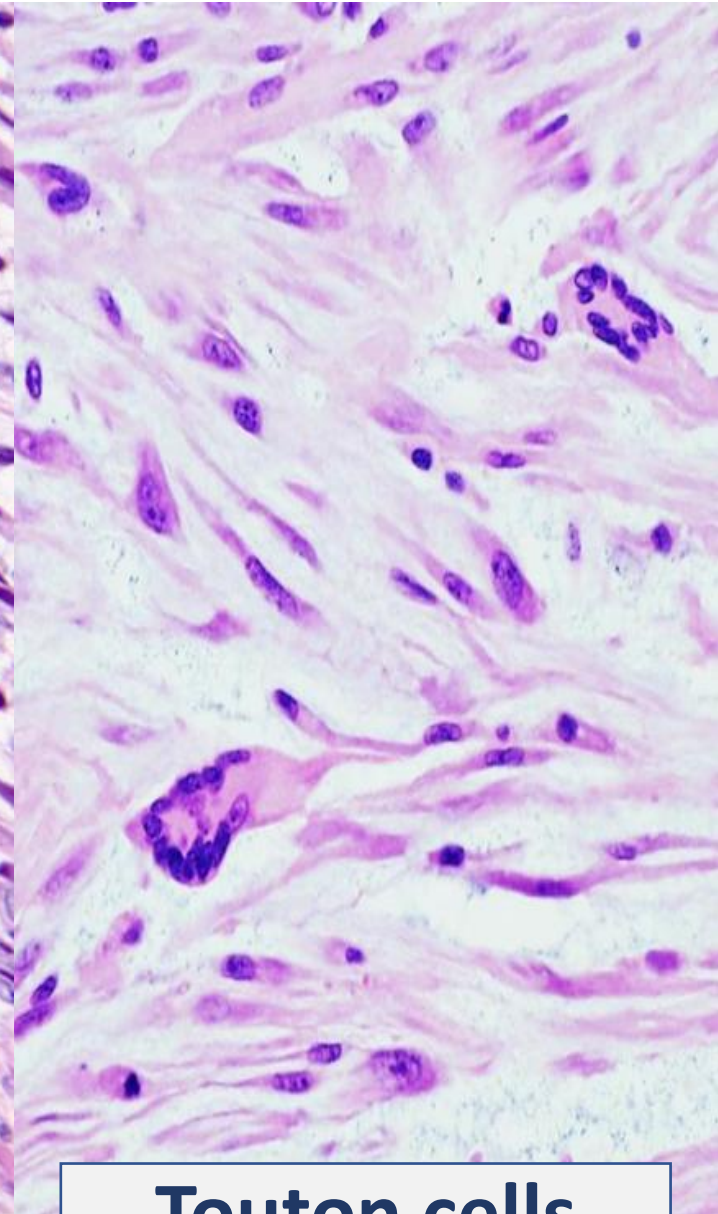


GANGLION-LIKE CELLS

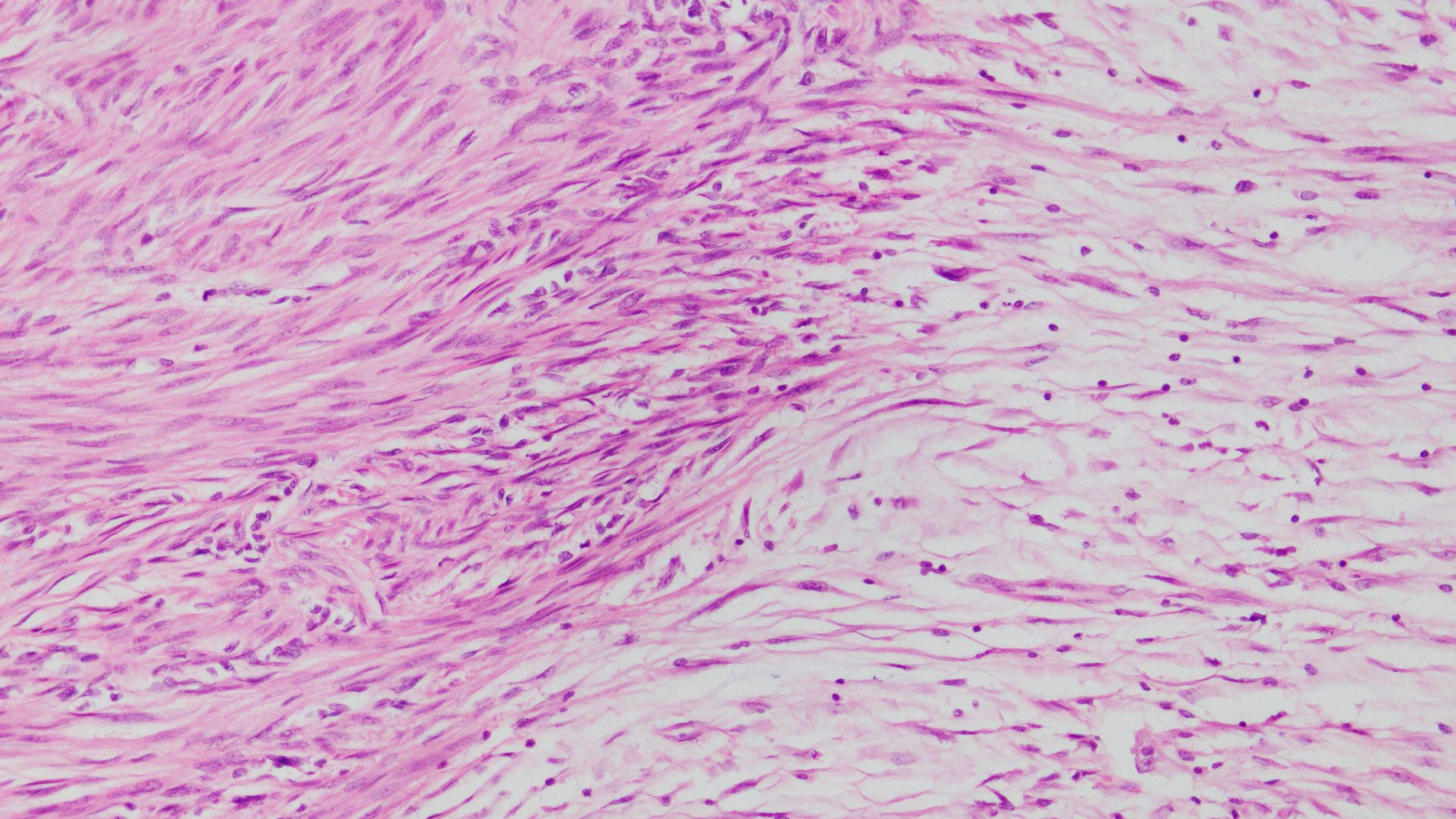
INFLAMMATORY MYOFIBROBLASTIC TUMOR



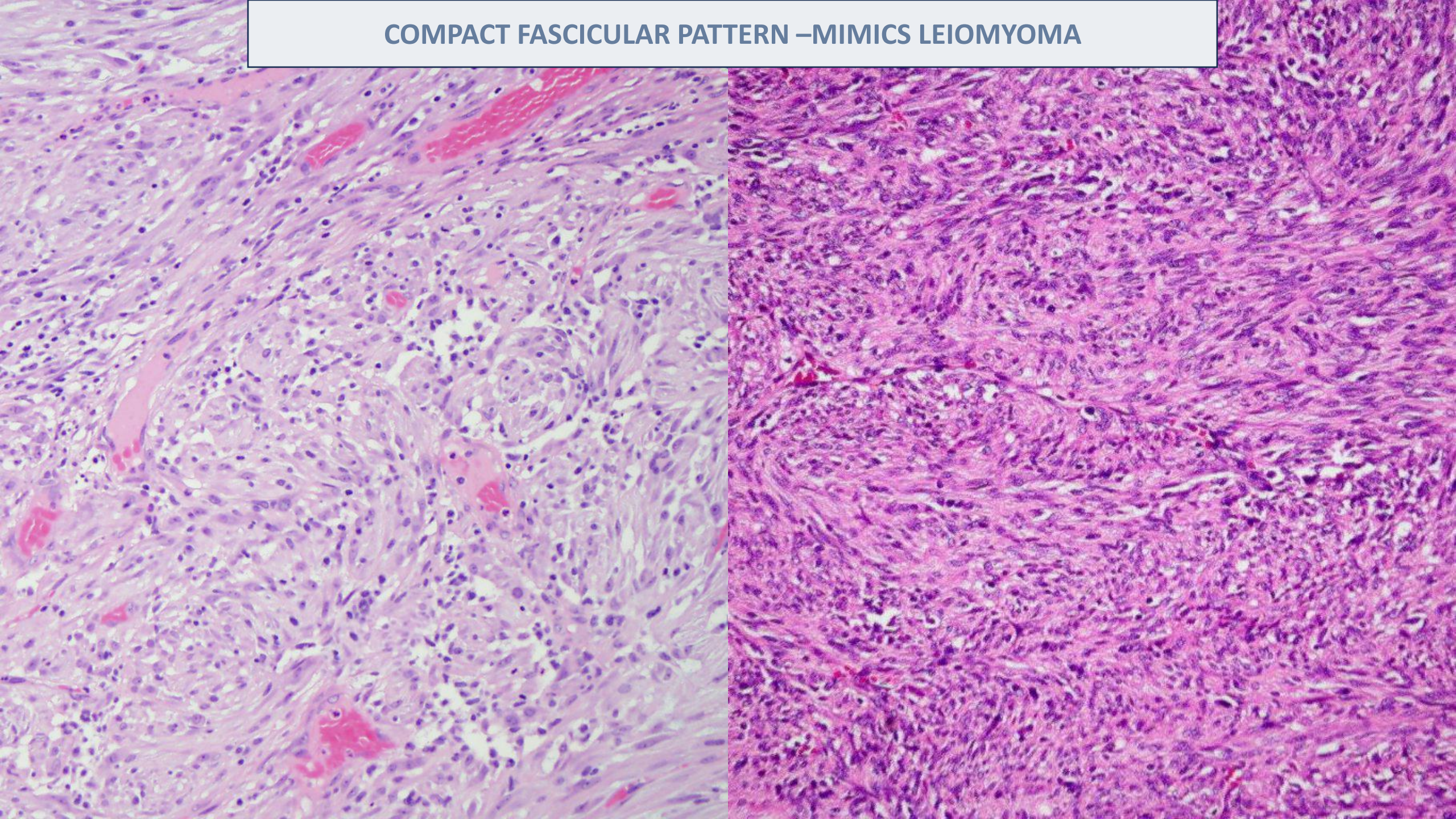
Ganglion cells



Touton cells



COMPACT FASCICULAR PATTERN –MIMICS LEIOMYOMA

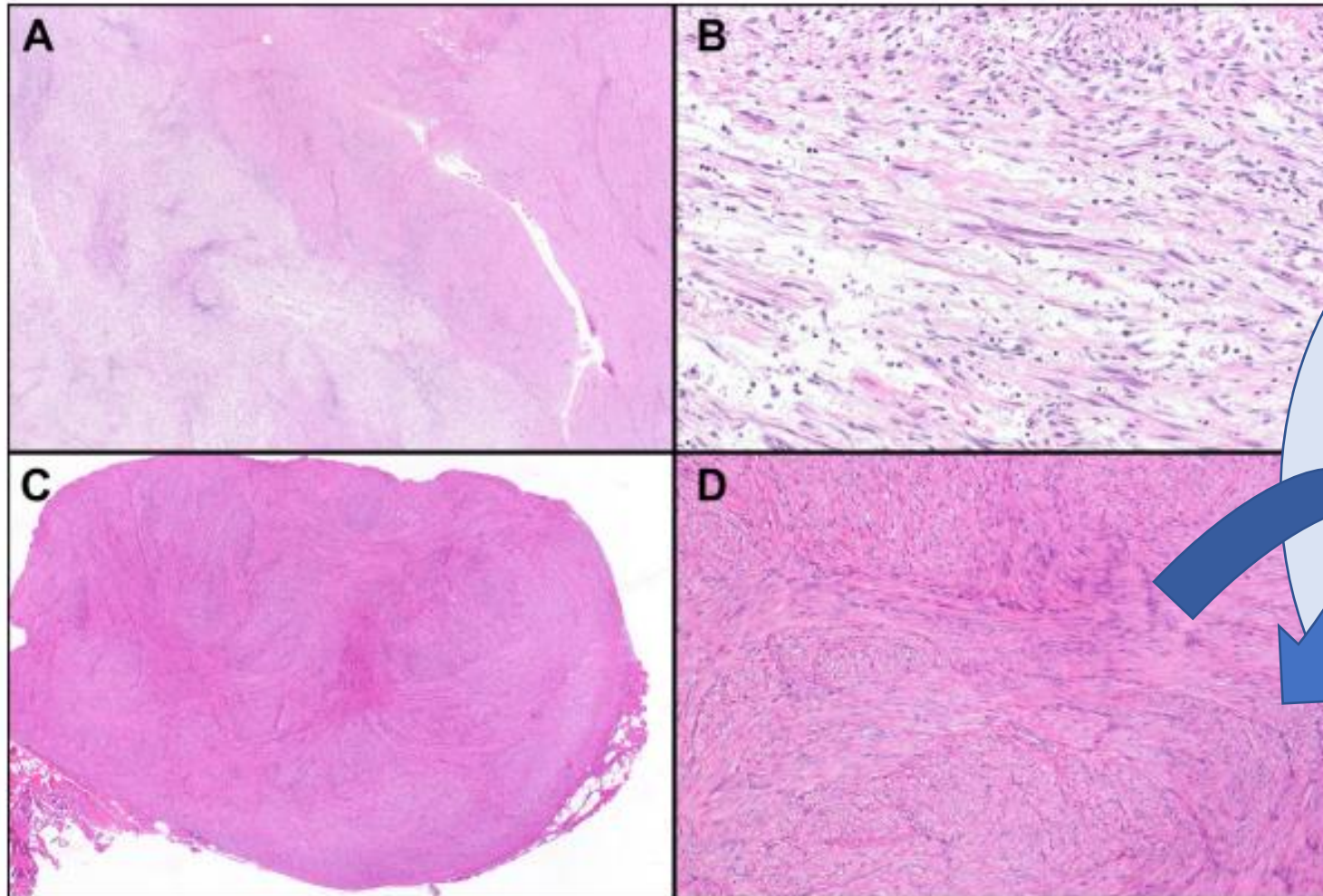


Leiomyoma-like Morphology in Metastatic Uterine Inflammatory Myofibroblastic Tumors

Kyle M. Devins^{a,*}, Wesley Samore^a, G. Petur Nielsen^a, Vikram Deshpande^b, Esther Oliva^a

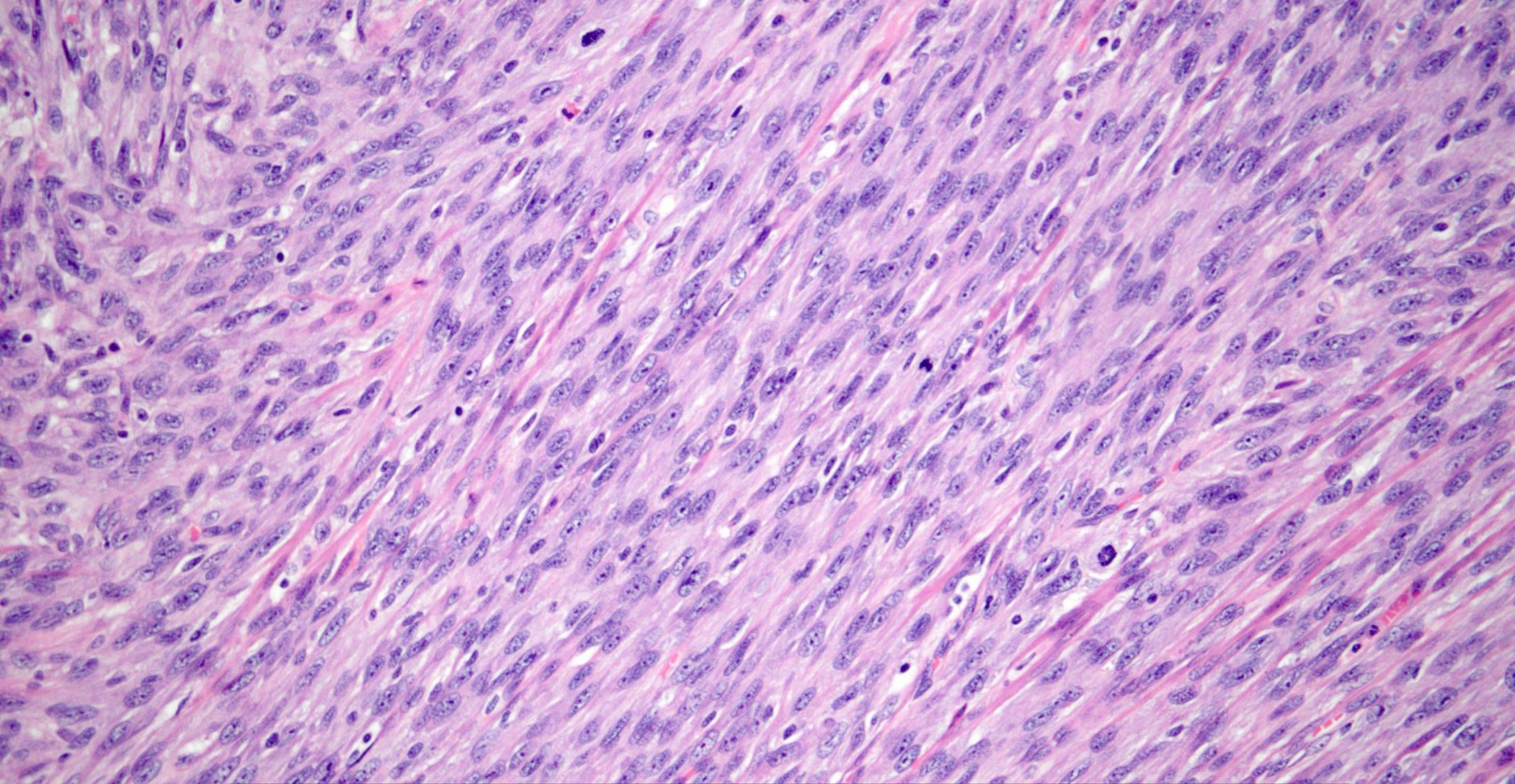
Modern Pathol 2023

Also reported in primary tumors

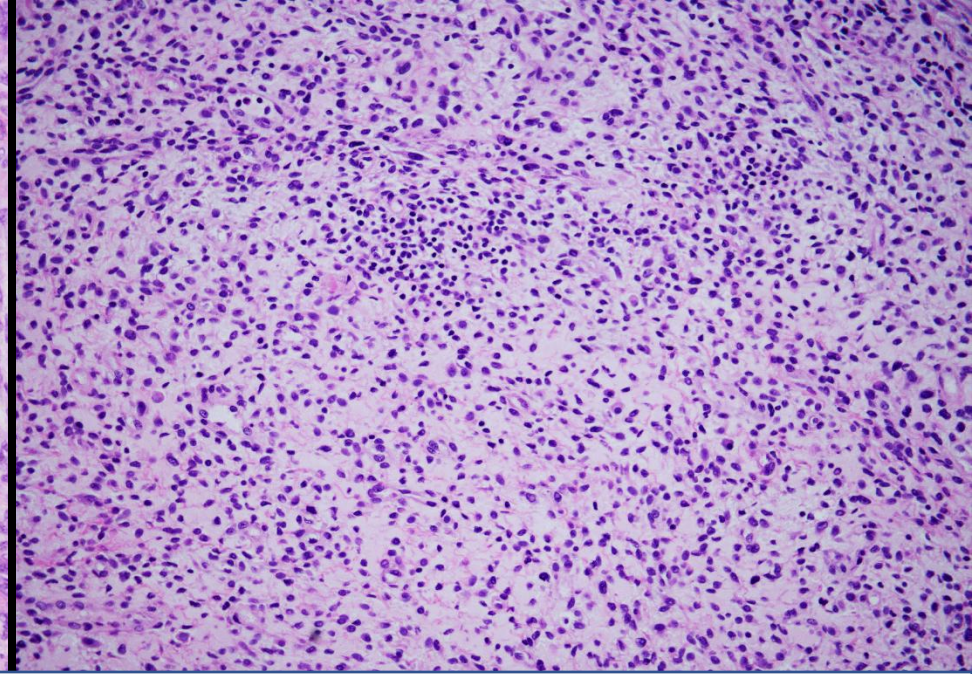
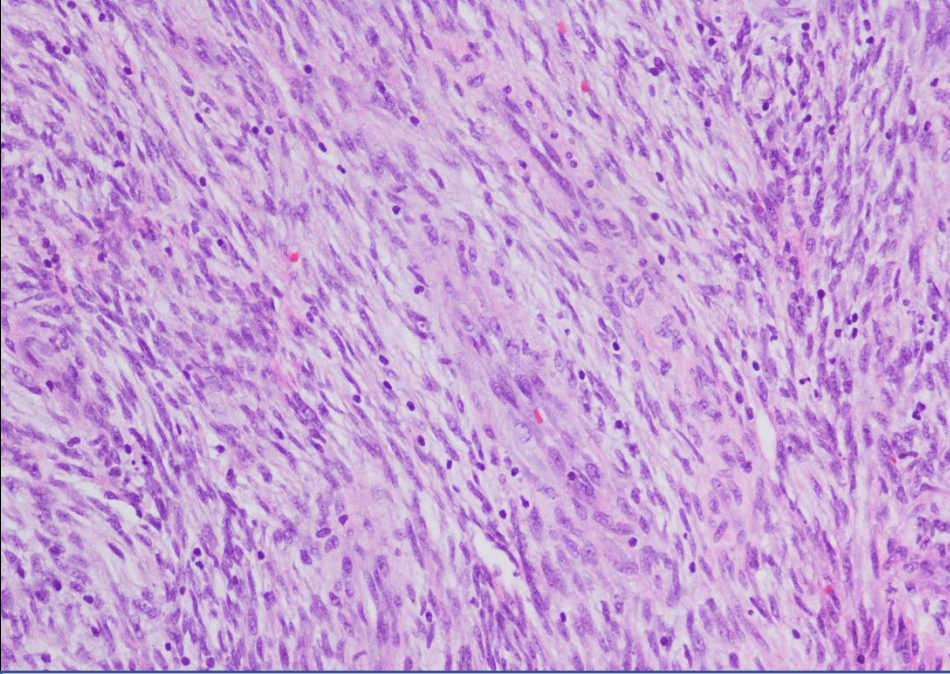


**Recurrence-
leiomyoma-like**

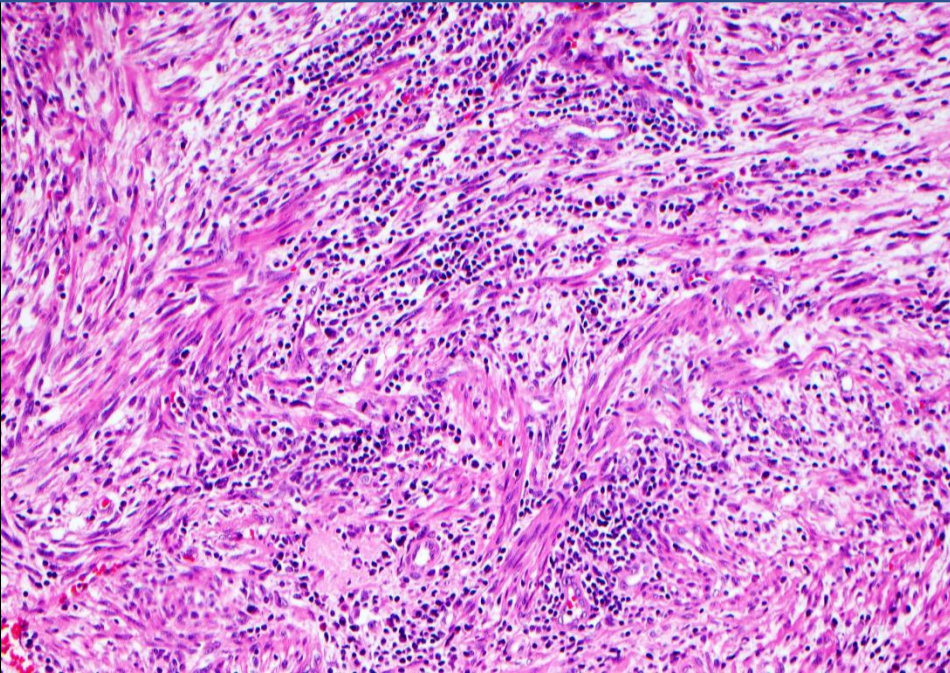
**ASK FOR PRIOR
HISTORY AND
REVIEW SLIDES IF
POSSIBLE**



Cytologic atypia and mitoses mimics Leiomyosarcoma



INFLAMMATORY INFILTRATE

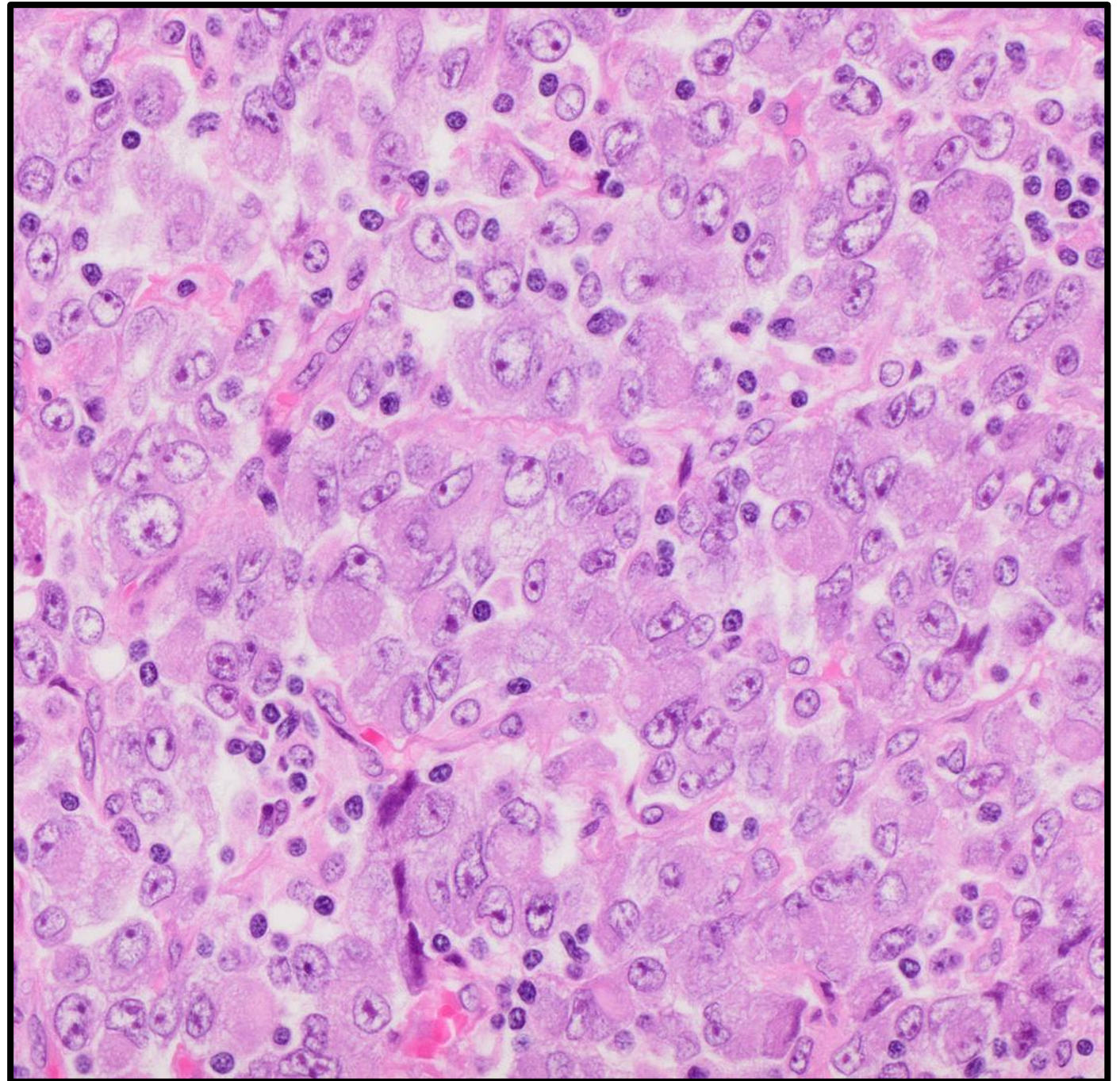


Location

- **Compact-Predominant: 46%**
- **Equally Distributed: 31%**
- **Myxoid-Predominant: 23%**

Epithelioid Inflammatory Myofibroblastic Sarcoma

- **Always malignant**
- **Rarely reported in uterus and ovary**



Inflammatory Myofibroblastic Tumor of the Uterus: An immunohistochemical Study of 23 Cases

Bennett JA et al, Am J Surg Pathol 2020

Transgelin

22/23 (96%)

(more sensitive than other smooth muscle markers in ddx)

IFITM1

19/23 (83%)

(more specific than CD10 in dx of ESTs)

BCOR

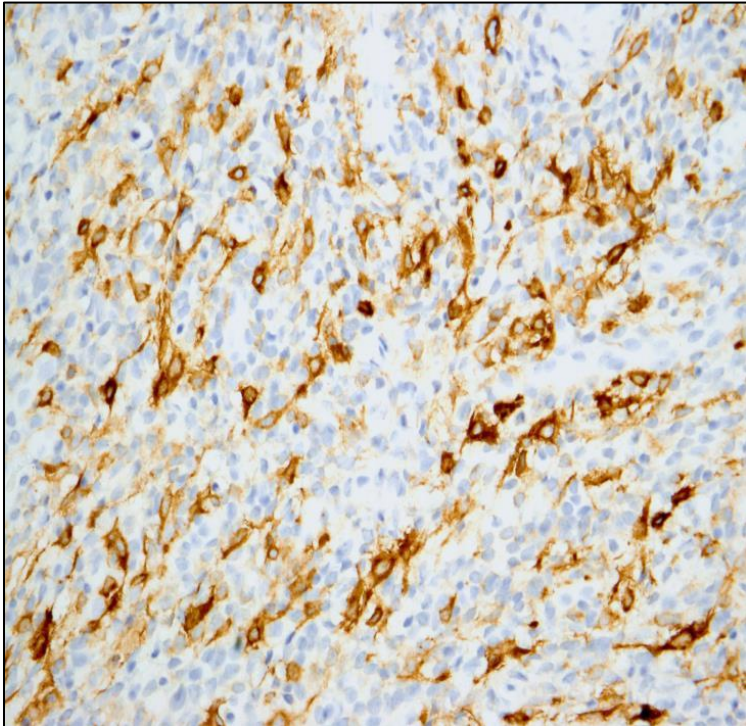
8/20 (40%)

p53 wild type

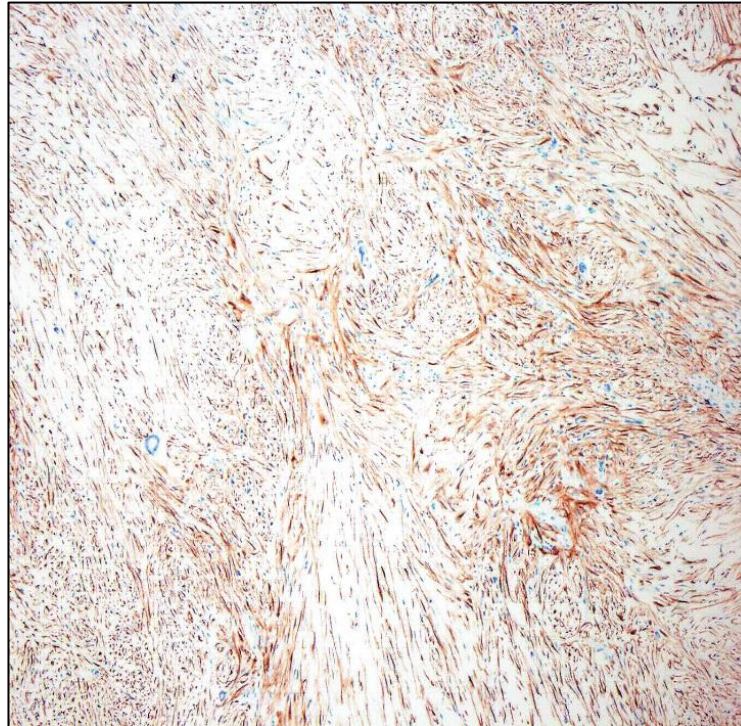
23/23 (100%) (with exceptions)

ALK POSITIVITY

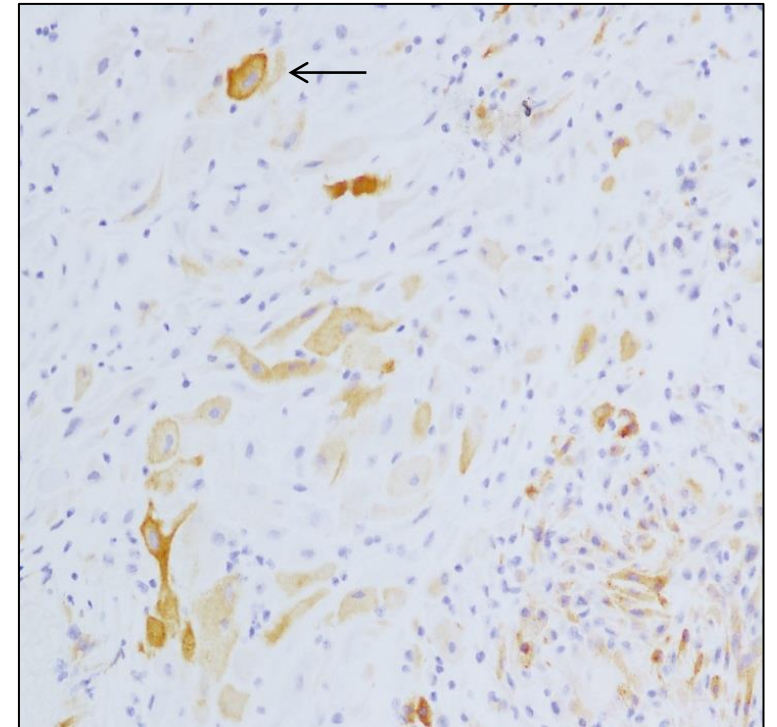
PATTERNS OF EXPRESSION



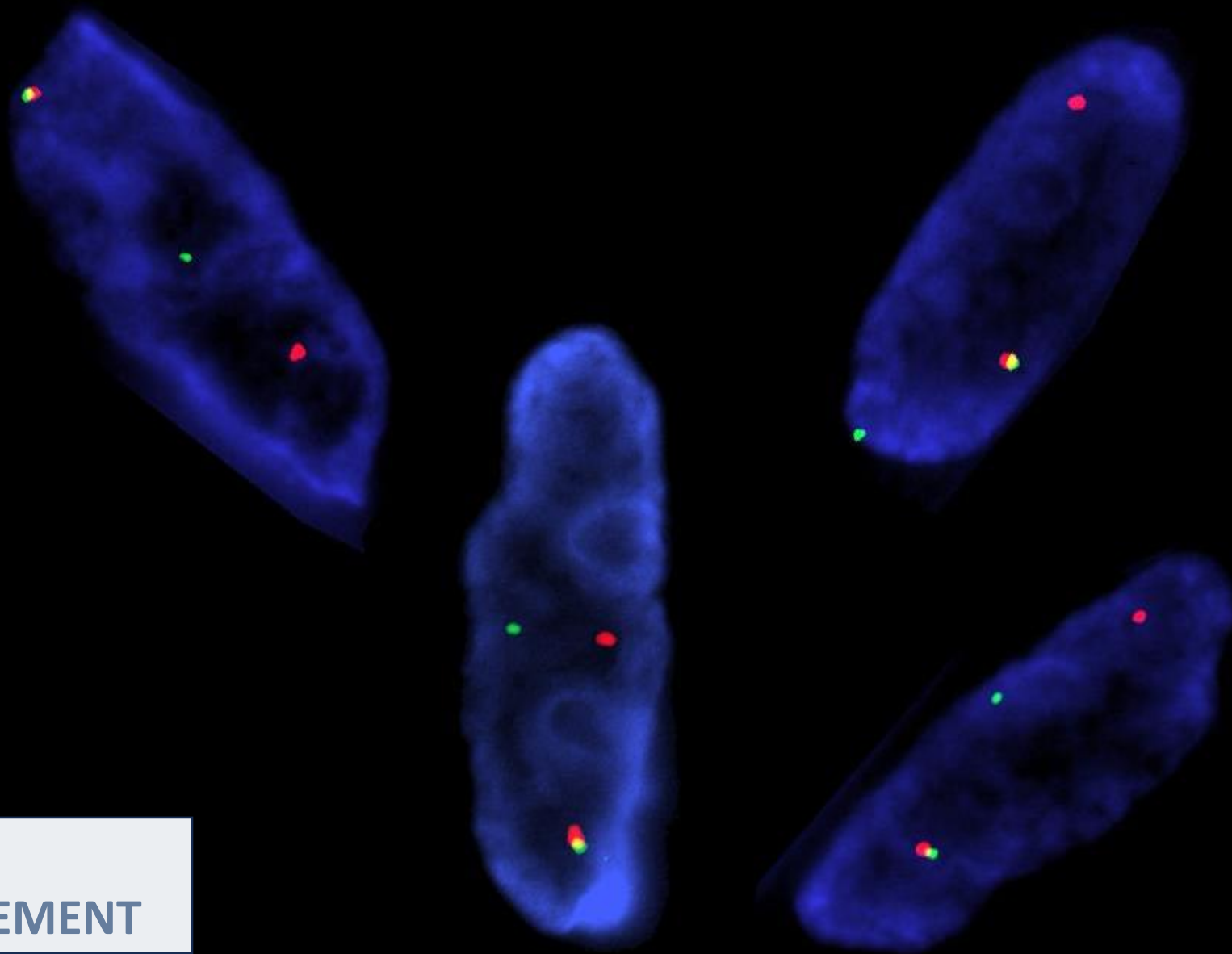
**Cytoplasmic with
perinuclear
accentuation**



Cytoplasmic



**Cytoplasmic with
distinct staining of
membrane**



ALK
REARRANGEMENT

New Proposed Risk Stratification Score

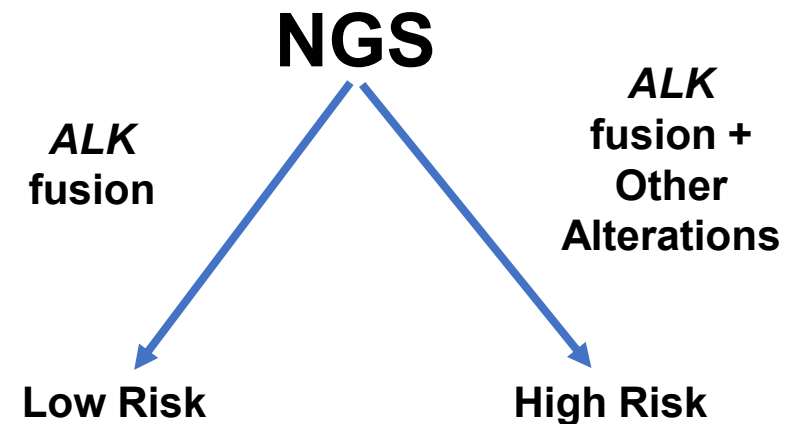
Age > 45 years

Size $\geq$ 5 cm

Mitoses $\geq$ 4/10
HPFs

Infiltrative Border

Outcome (n=52)	Low Risk (0 Points)	Intermediate Risk (1-2 Points)	High Risk ($\geq$ 3 Points)
Benign (n=30)	11	19	0
Aggressive (n=22)	0	4	18



Ladwig et al. Am J Surg Pathol 2023

Abnormal p16 in Malignant IMTs

Case	1	2	3	4*	5	6*	7	8#	9	10	11	12	13	14	15	16	17	18#
Behavior	E	E																
p16																		
MTAP																		
Copy Number																		

Malignant	E EIMS	Benign	S Subclonal
< 1%	1-90%	> 90%	S Subclonal
Lost	Retained	Not Tested	S Subclonal
Unstable	Stable	Not Tested	

CDKN2A																		
CDKN2B																		
TERT																		
RICTOR																		
PTEN																		
PNKP																		
IKZF1																		
MTAP																		
CDKN1A																		
ATM																		
SF1																		

Deletion	Amplification	Frameshift	Nonsense	Promoter Mutation	Not Tested
----------	---------------	------------	----------	-------------------	------------

Abnormal p16 expression in most malignant IMTs:

<1%: Usually associated with *CDKN2A* (+/- *CDKN2B*) deletion

>90%: Often with *TERT* promoter mutations

*Recurrence tested #Tested by comparative genomic hybridization

Uterine Inflammatory Myofibroblastic Tumors:

p16 as a Surrogate for *CDKN2A* Deletion and Predictor of Aggressive Behavior

Devins KM et al, Am J Surg Pathol 2024

- Independent utility of p16 to identify tumors with potential aggressive behavior
- p16 may be particularly useful in tumors with incomplete clinicopathologic information for risk stratification and for further stratifying intermediate-risk tumors in settings where NGS is unavailable or cost-prohibitive

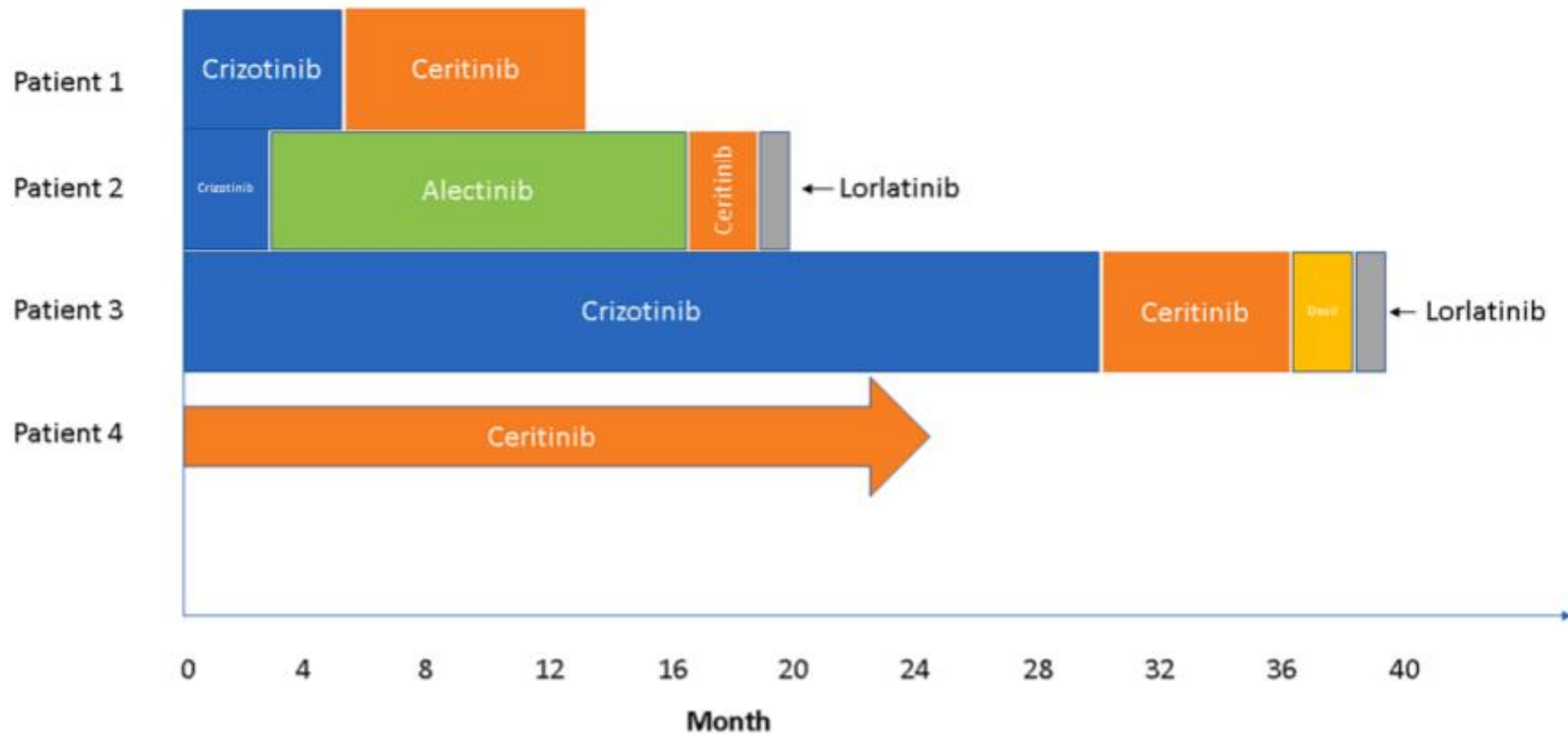
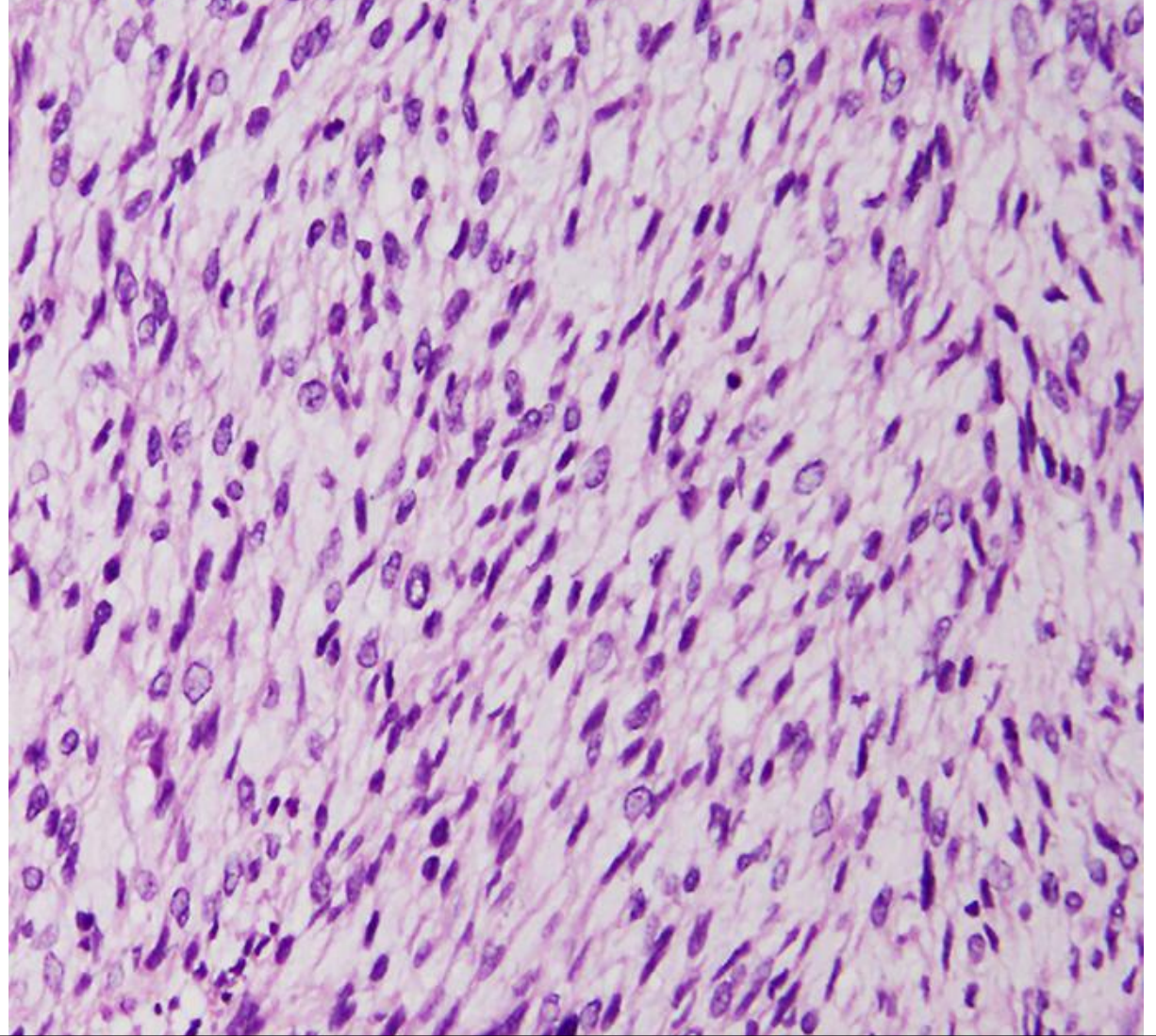
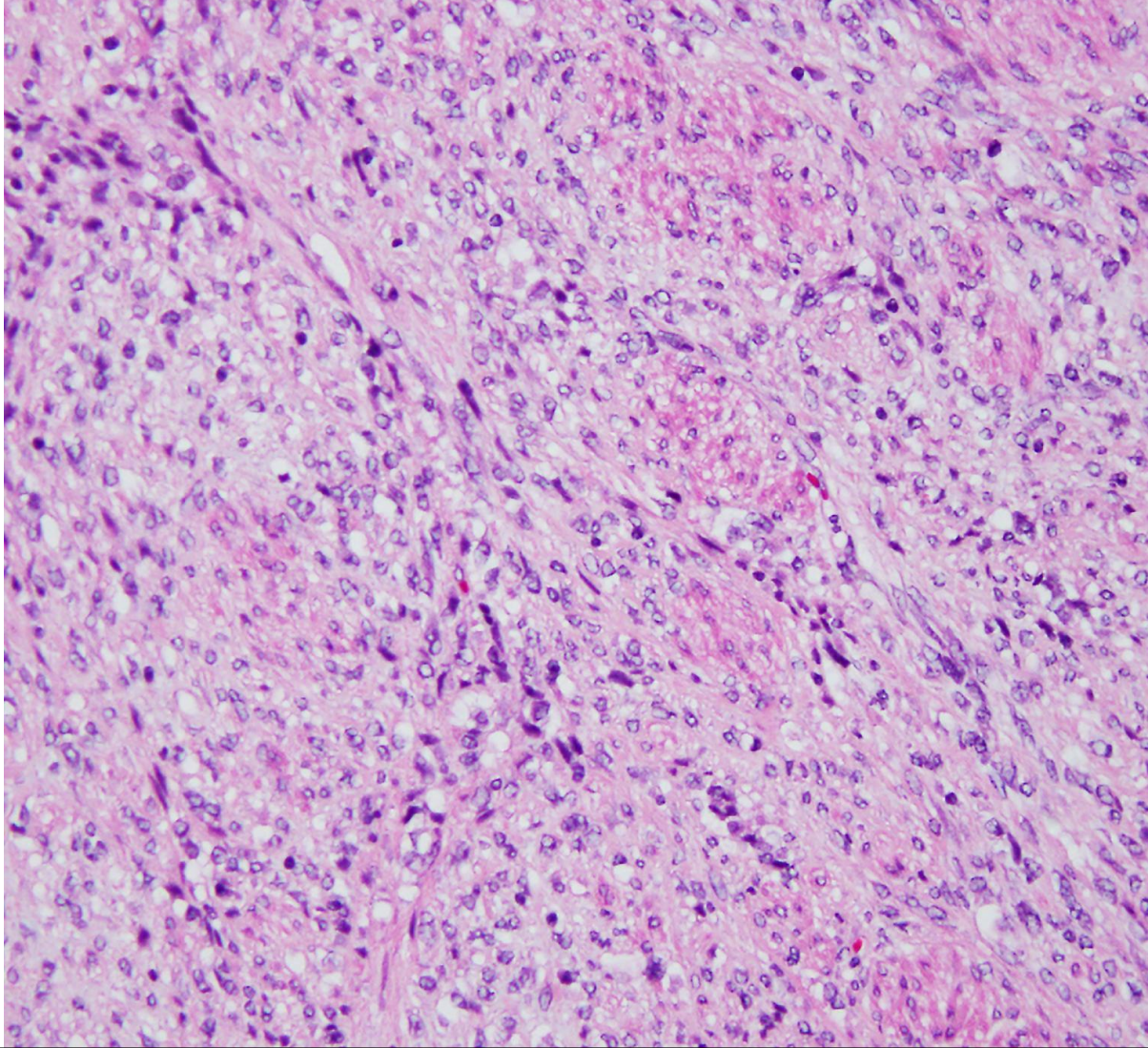


Fig. 2. Response to *ALK* inhibitors in uterine mesenchymal tumors harboring *ALK* fusions.

KEEP IN MIND:

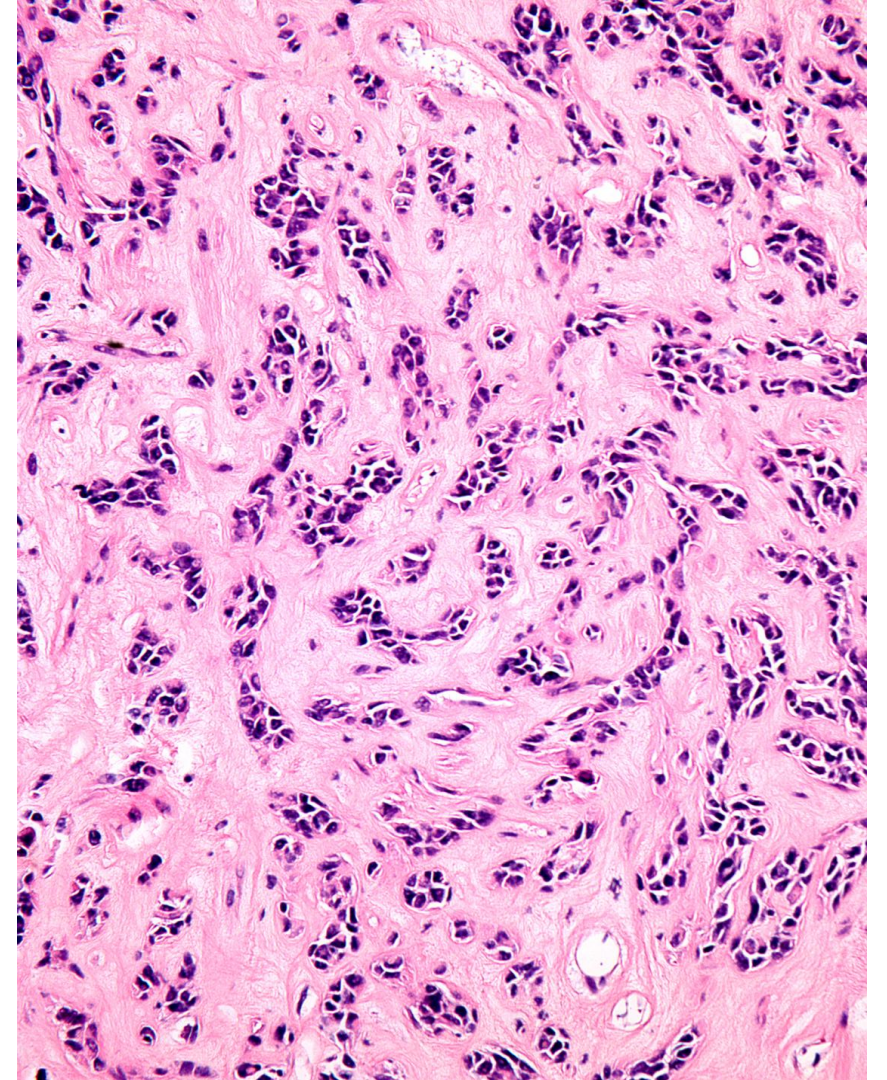
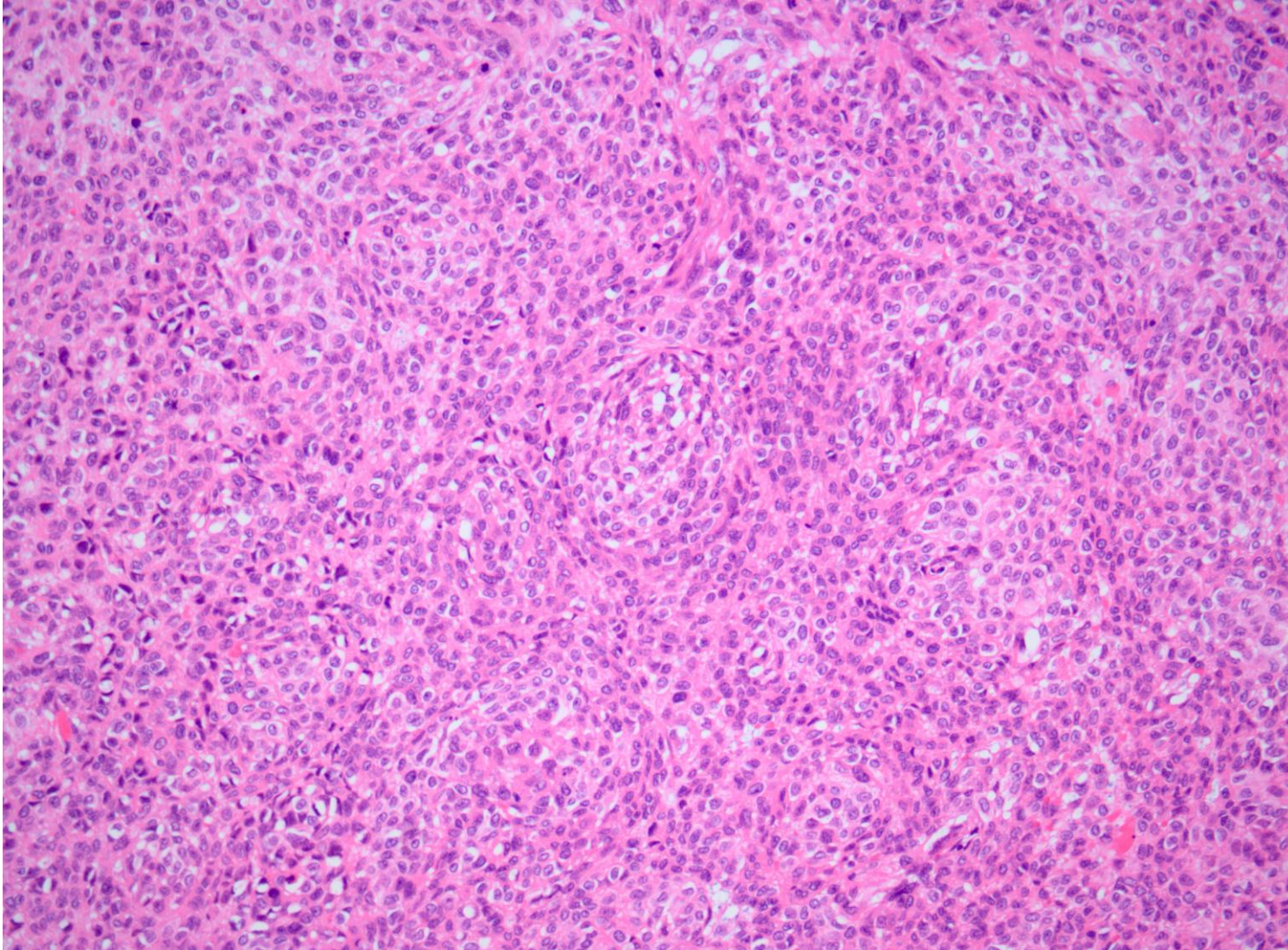
- Broad differential diagnosis of myxoid uterine neoplasms
- The finding of inflammatory infiltrate and/or ganglion-like cells should raise possibility of IMT. ALK/ROS stains and/or FISH should be performed, as smooth muscle markers are positive in SMTs and IMTs and criteria for malignancy differ between these two tumor types
- ALK immunostain is highly sensitive and specific for detection of ALK rearrangements
- If small well circumscribed tumor with no mitoses: no prognostic or therapeutic implications if the diagnosis of IMT is missed. However, important to recognize IMTs when malignant even with smooth muscle-like morphology applying specific algorithm as may be treated with ALK inhibitors
- In recurrence setting, important to check prior history of hysterectomy for leiomyomas and if possible review slides, to exclude possibility of IMT for treatment purposes

BCOR-ZC3H7B HIGH-GRADE ENDOMETRIAL STROMAL SARCOMA



**CLOSELY MIMICS MYXOID LEIOMYOSARCOMA,
up to 25% misdiagnosed as such in different series**

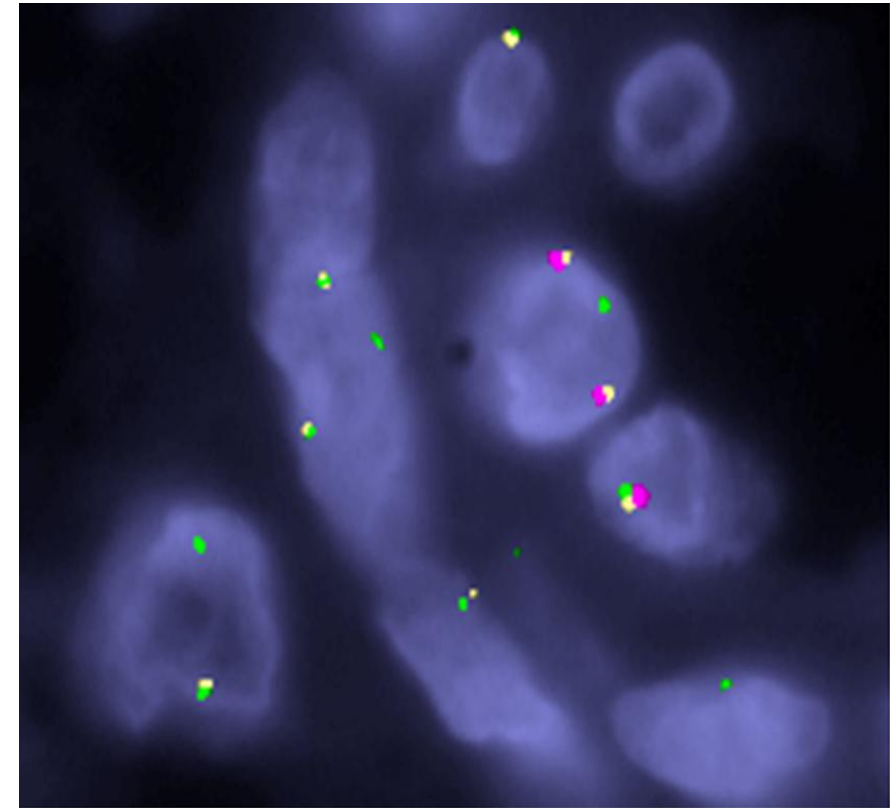
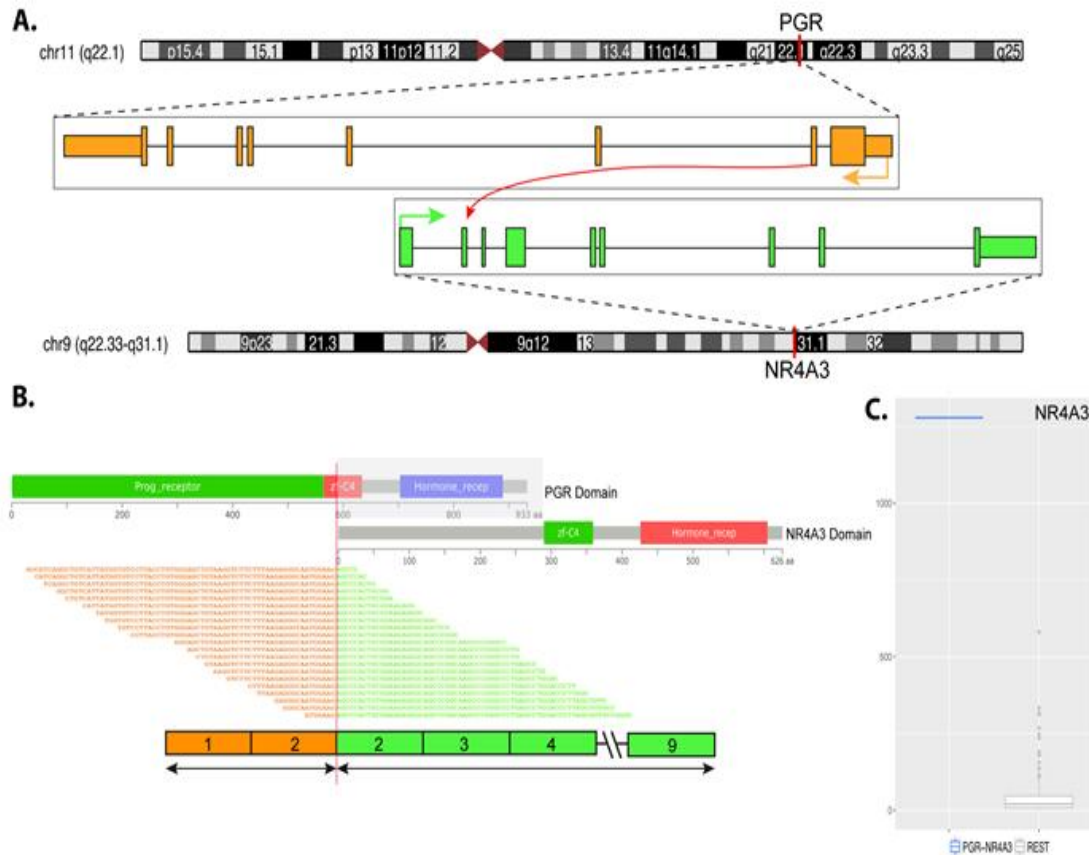
EPITHELIOID LEIOMYOSARCOMA



EPITHELIOID SMOOTH MUSCLE TS

- No widely accepted criteria for predicting behavior as rare
- **Epithelioid Leiomyosarcoma:**
 - ≥ 4 MFs/10HPFs & grade 2 or 3 nuclei
 - or
 - Tumor cell necrosis
- **Epithelioid Smooth Muscle Tumor, probably benign:**
 - ≤ 2 MFs/10HPFs, no tumor cell necrosis
and at most mild nuclear atypia

EPITHELIOID LEIOMYOSARCOMA (*PGR fusion* subset), with *t(9,11)*



PGR-NR4A3 fusion ----projected fusion protein including the progesterone receptor domain of PGR

PGR mutations rare; seen in 2% of EC and 0.2% of high-grade serous carcinomas

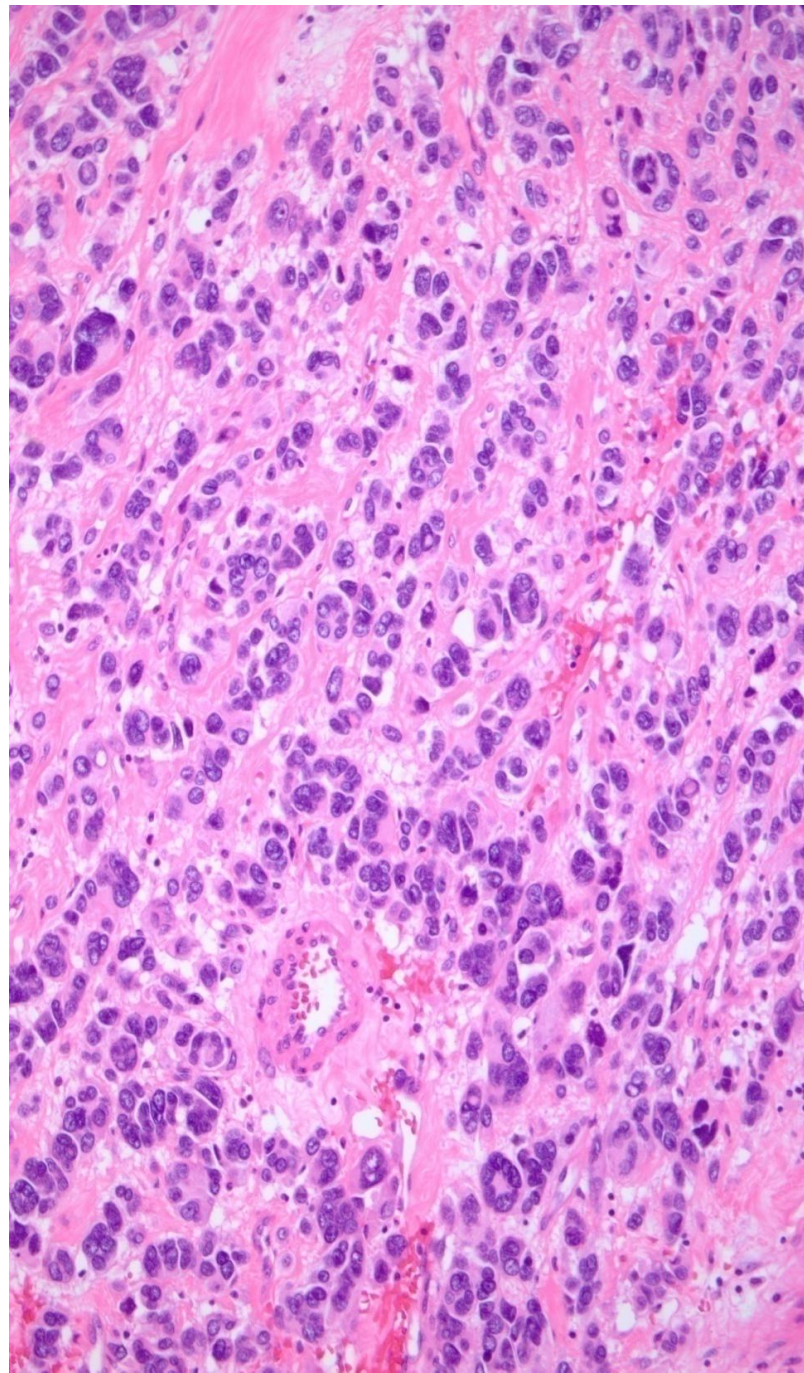
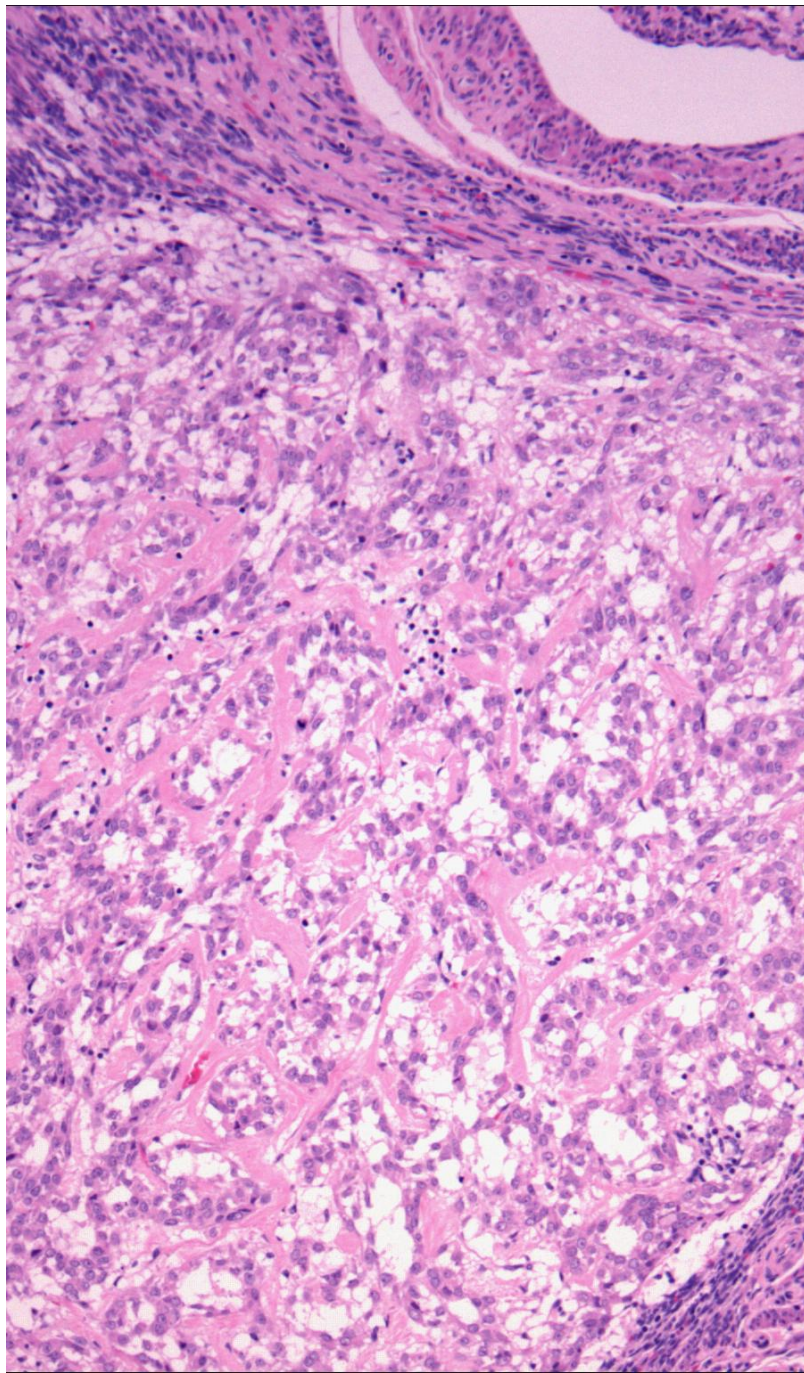
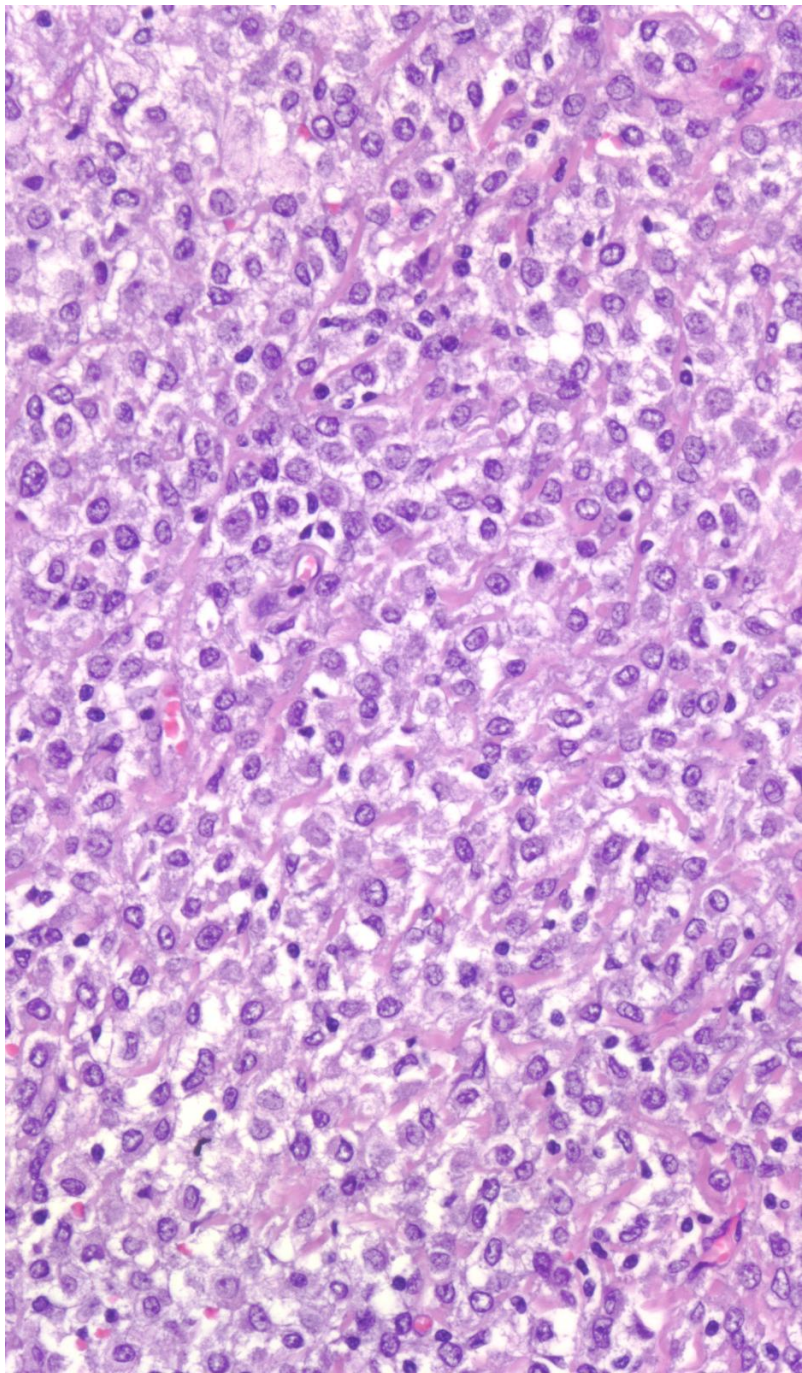
EPITHELIOID LEIOMYOSARCOMA

Differential Diagnosis:

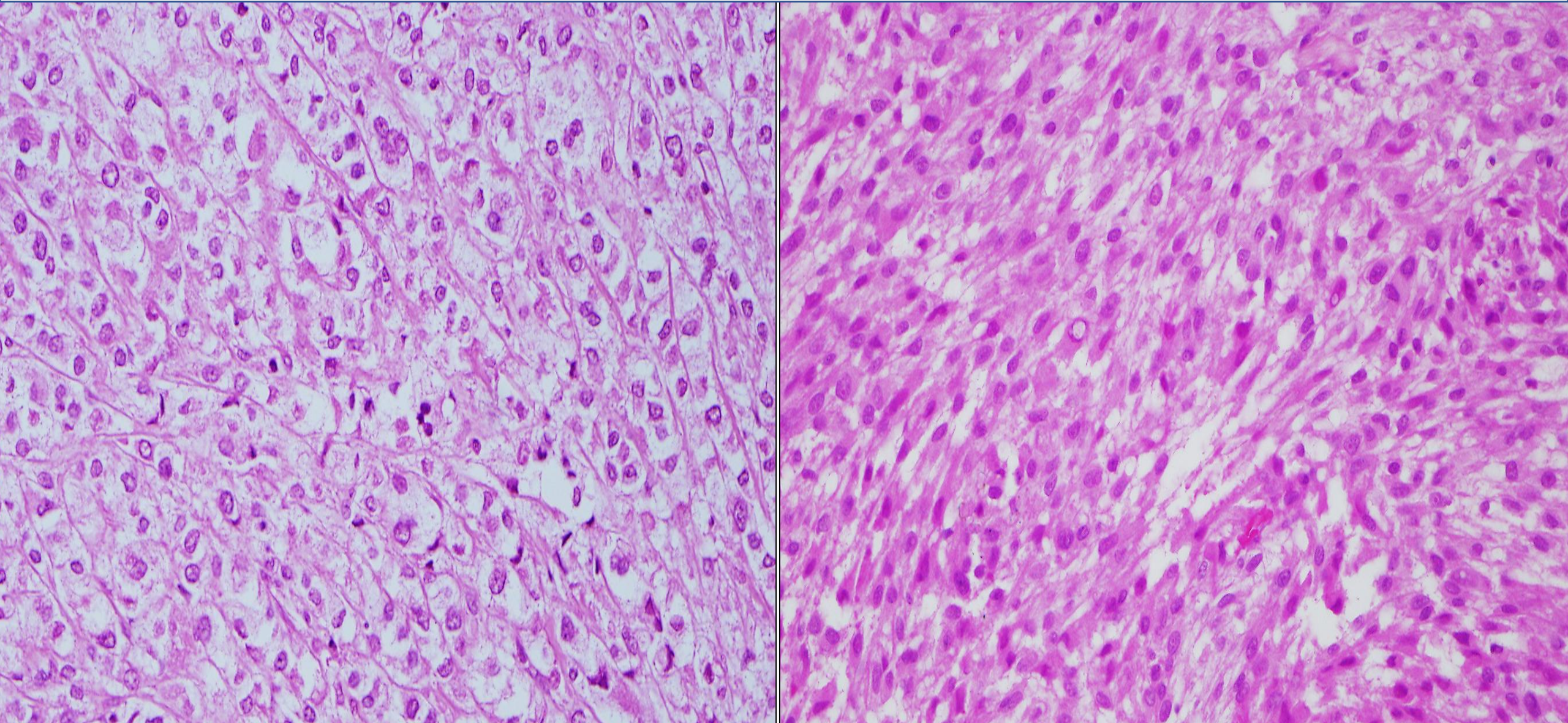
- **Poorly differentiated carcinoma**
- **PEComa**
- **UTROSCT**
- **Epithelioid endometrial stromal sarcoma**
- **Intermediate-type trophoblastic tumors**
- **Melanoma**
- **Other (rhabdomyosarcoma, angiosarcoma, alveolar soft part sarcoma, GIST)**
- **SMARCA4 deficient uterine sarcoma**
- **Metastases**

PERIVASCULAR EPITHELIOID CELL TUMOR (PEComa)

- **Mesenchymal tumor composed of perivascular epithelioid cells (PECs) that express melanocytic and smooth muscle markers**
- **Uterine corpus > cervix > vagina > ovary > broad ligament**
- **Wide age range and clinical presentation non-specific**
- **Most sporadic but ~10% associated with tuberous sclerosis**
- **Potential treatment with mTOR inhibitors**



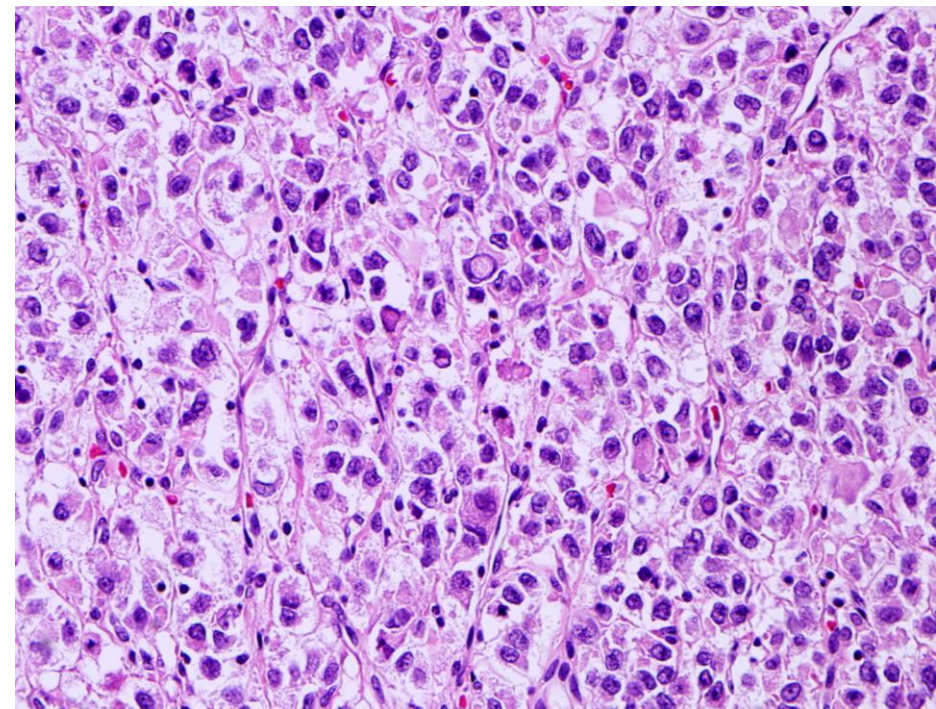
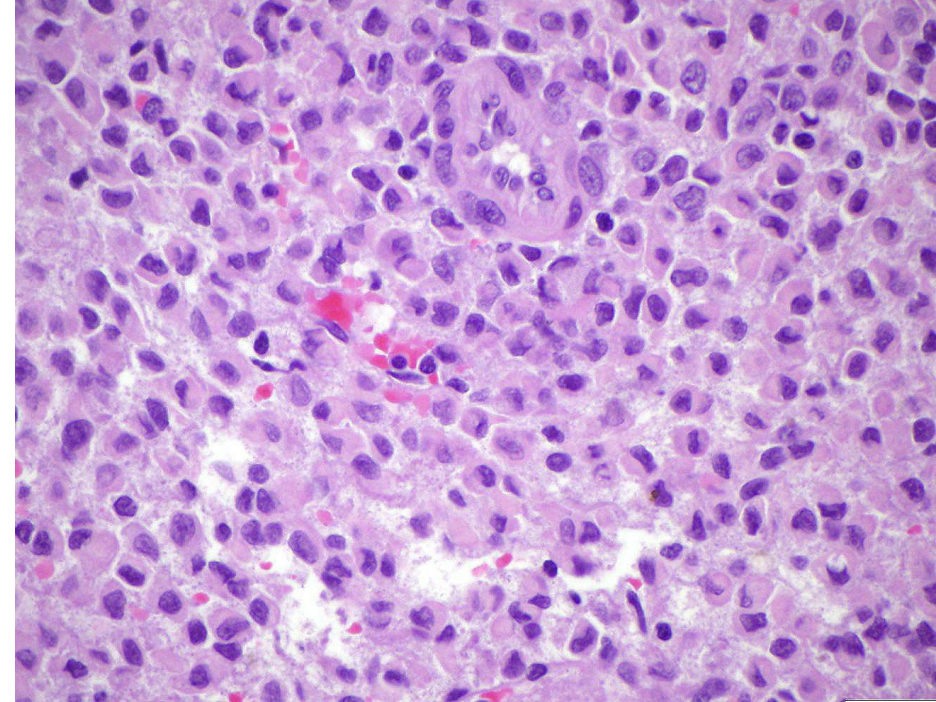
PECOMA

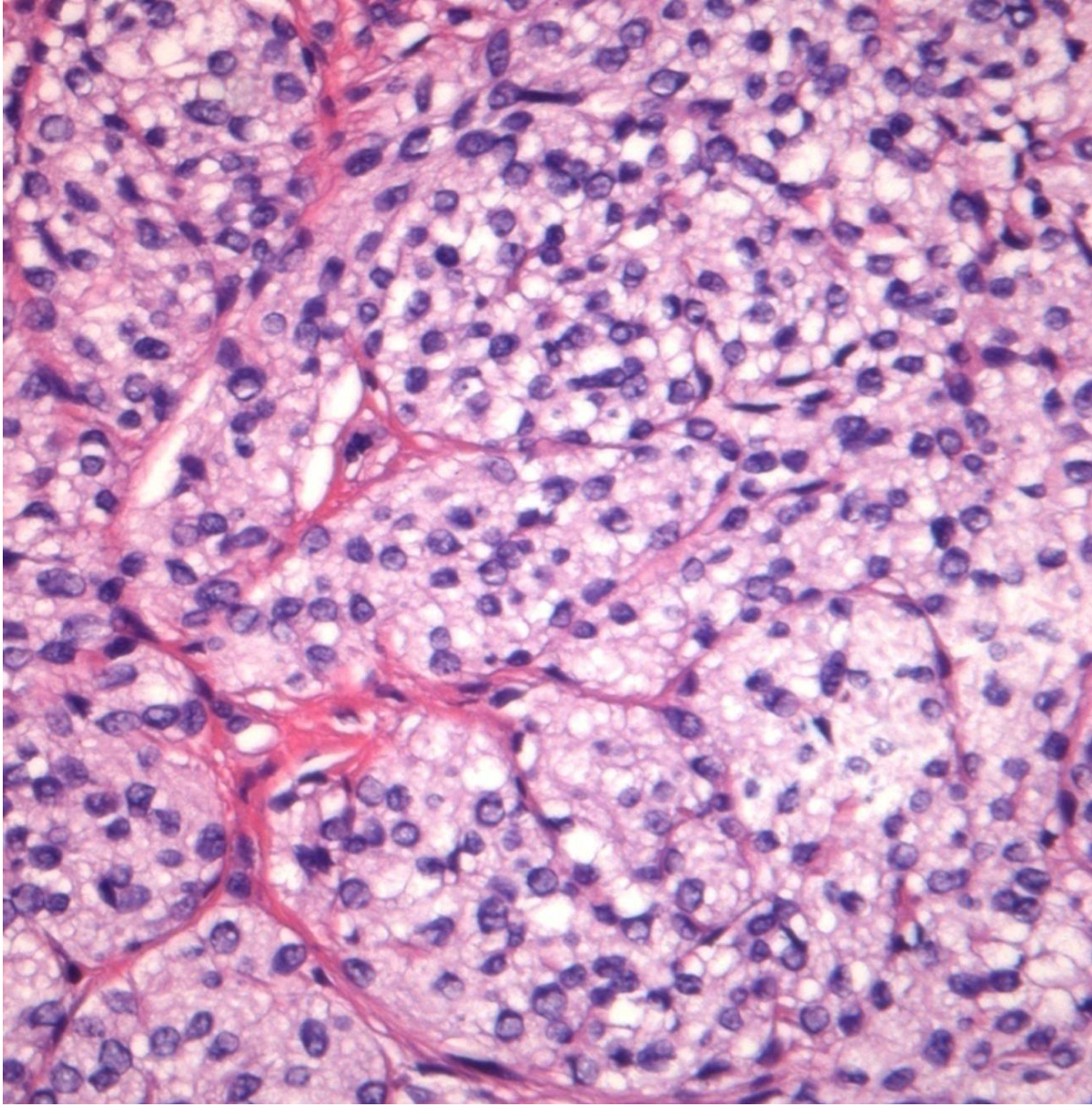
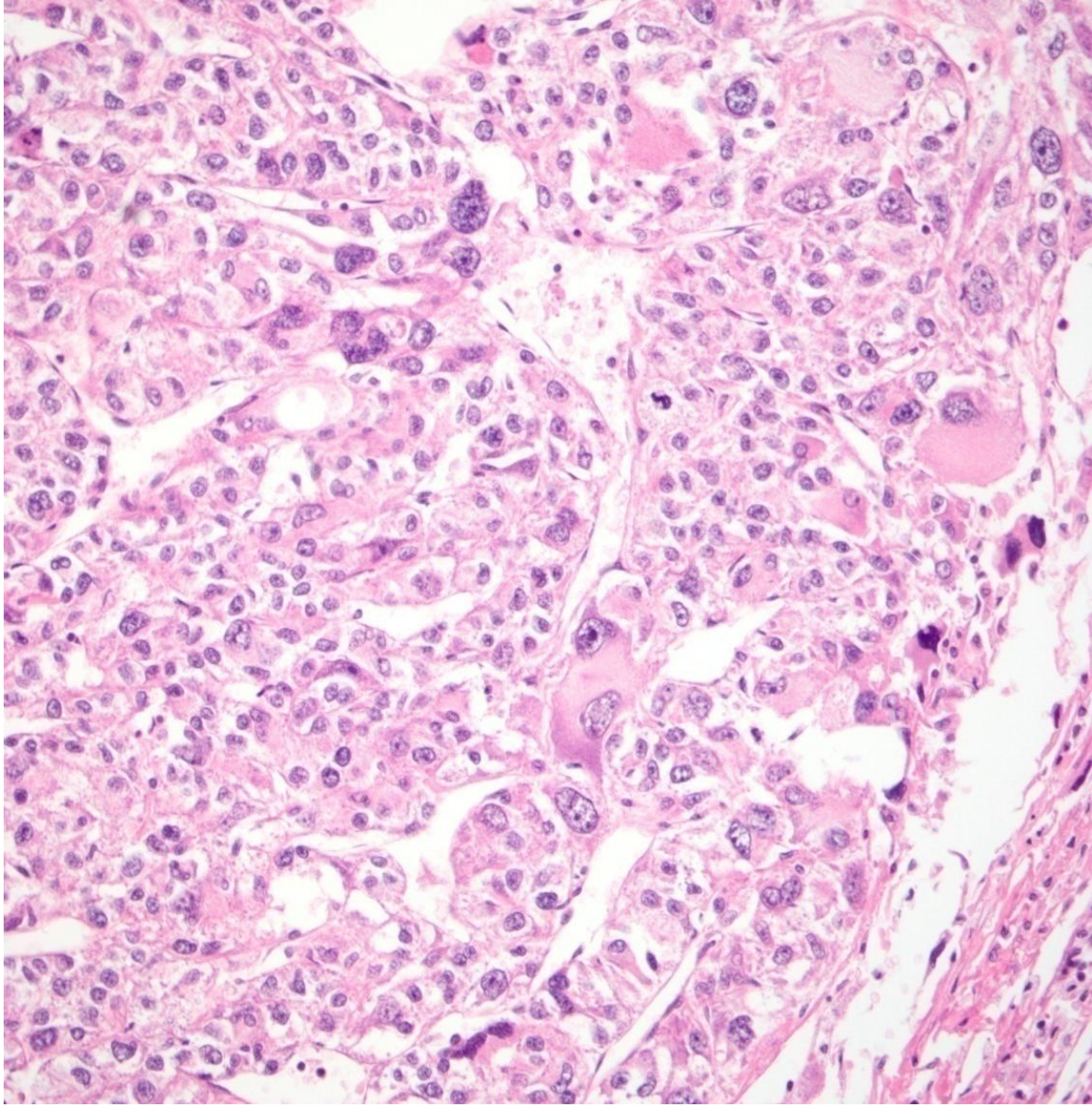


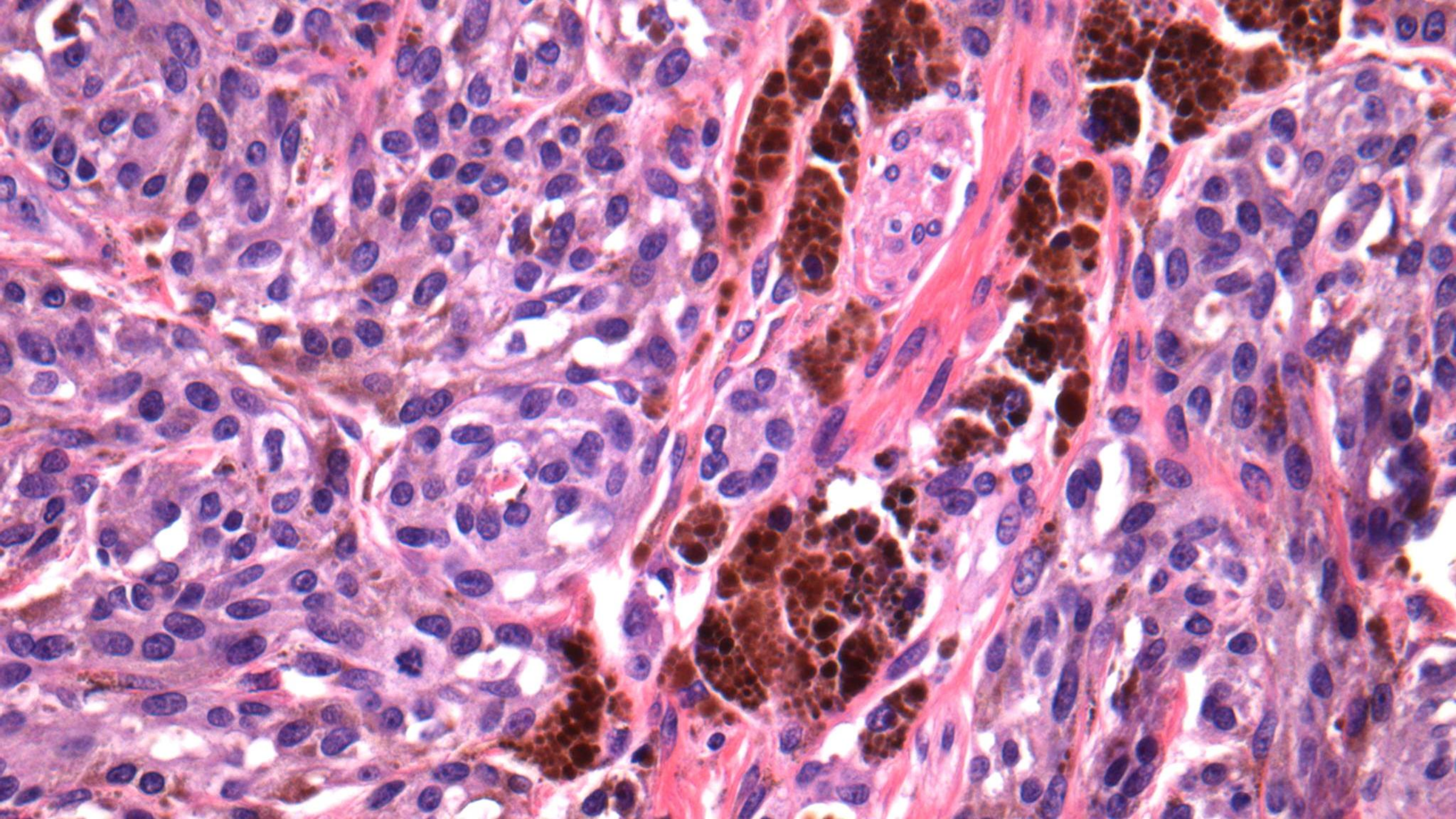
Epithelioid >>> Spindle

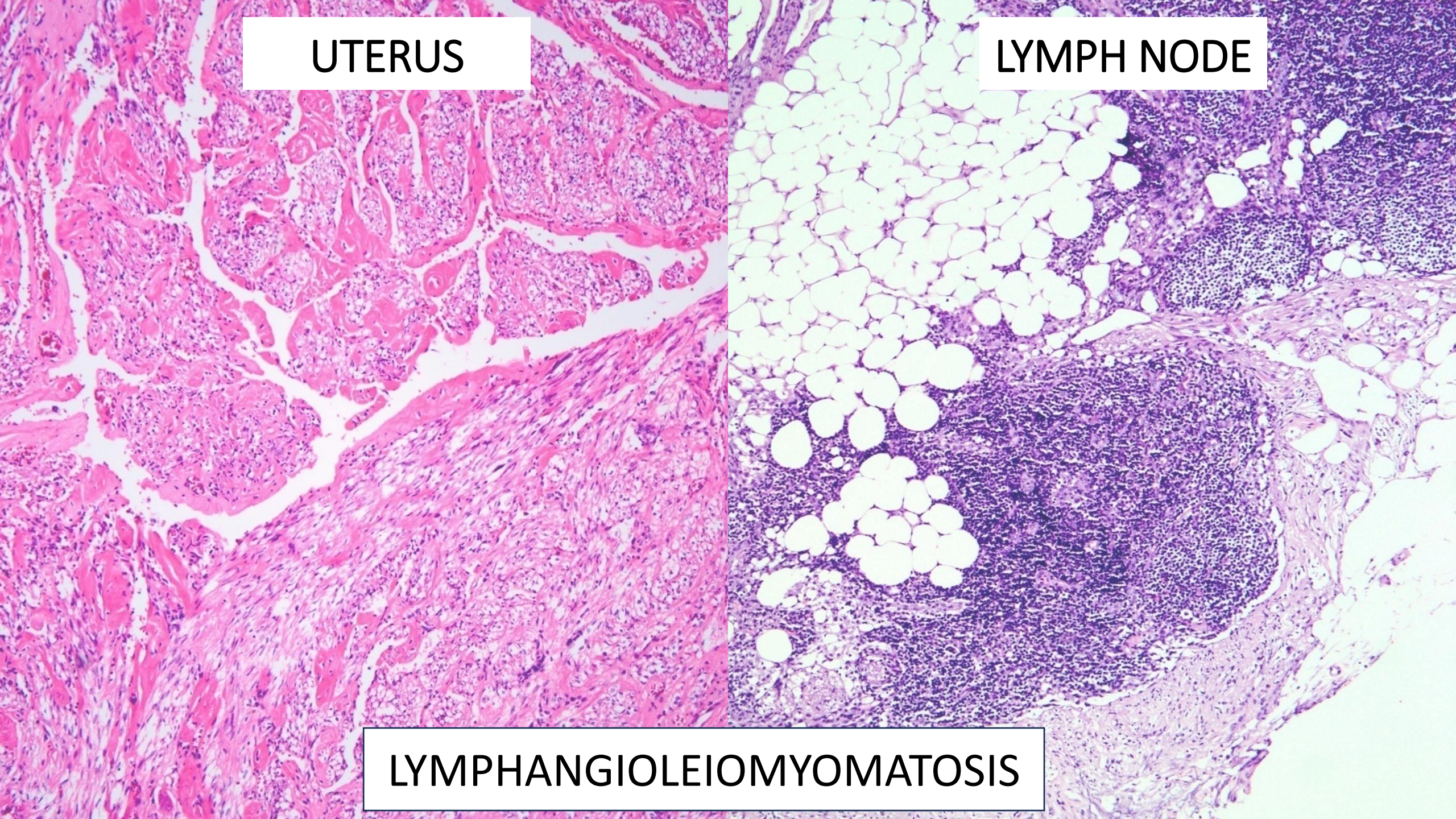


PEComa: CYTOLOGY









UTERUS

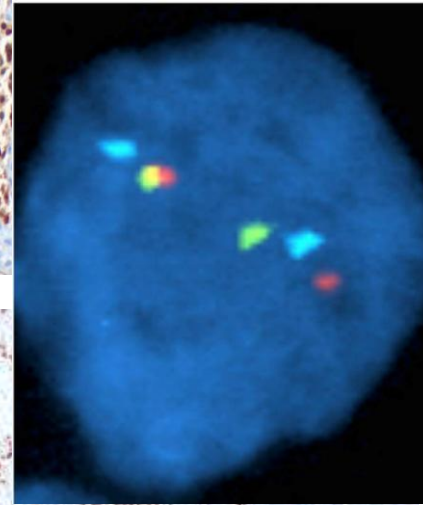
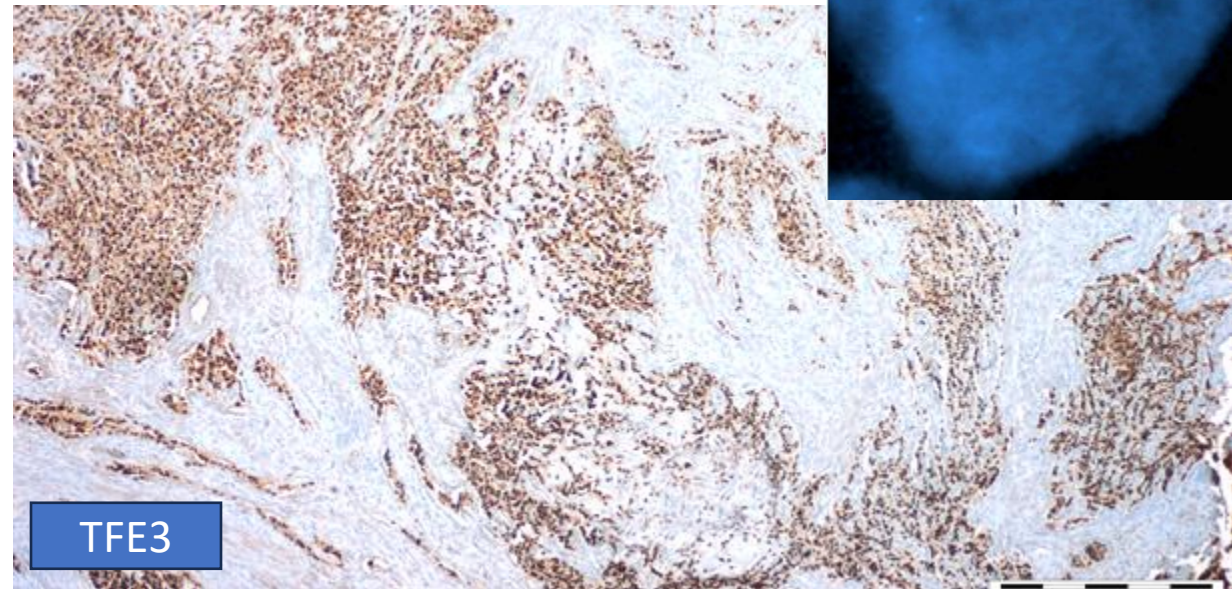
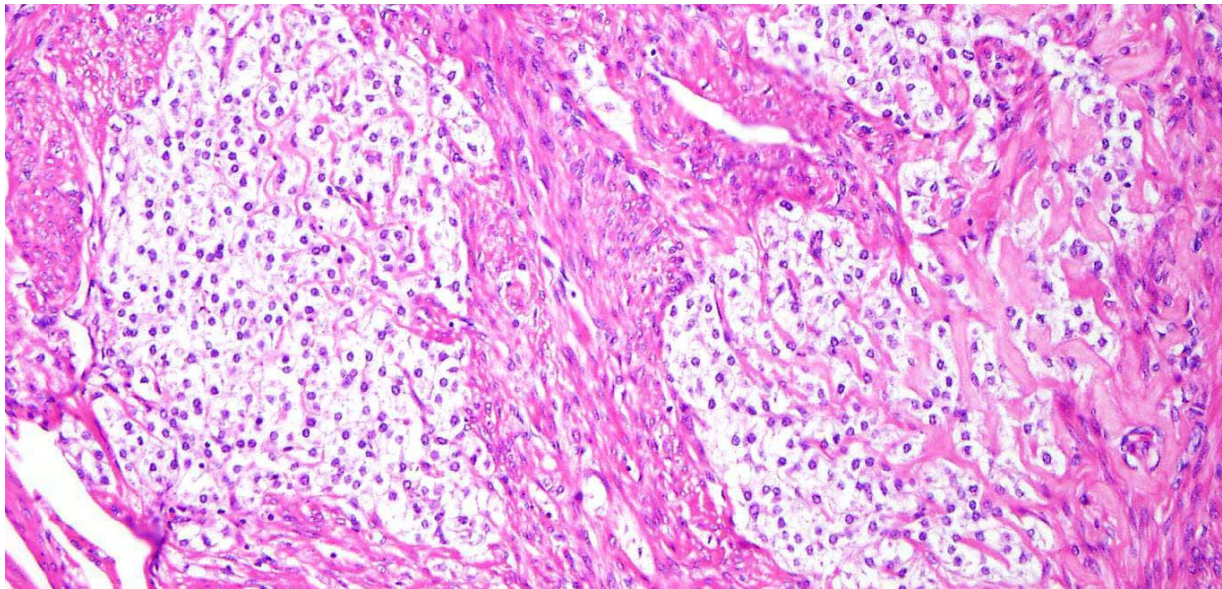
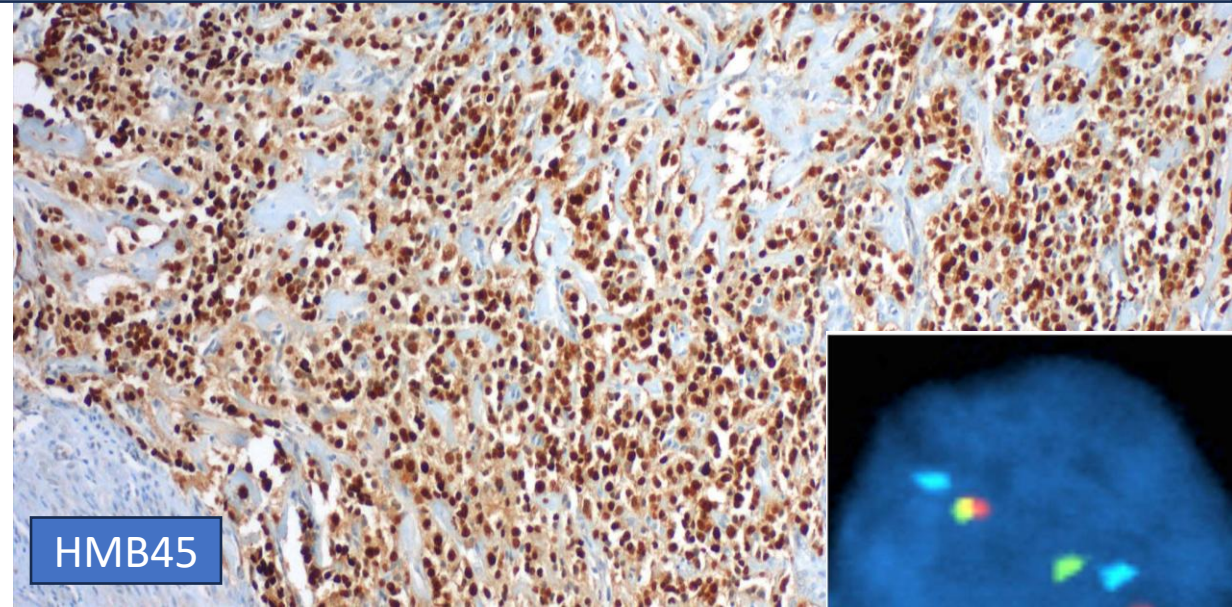
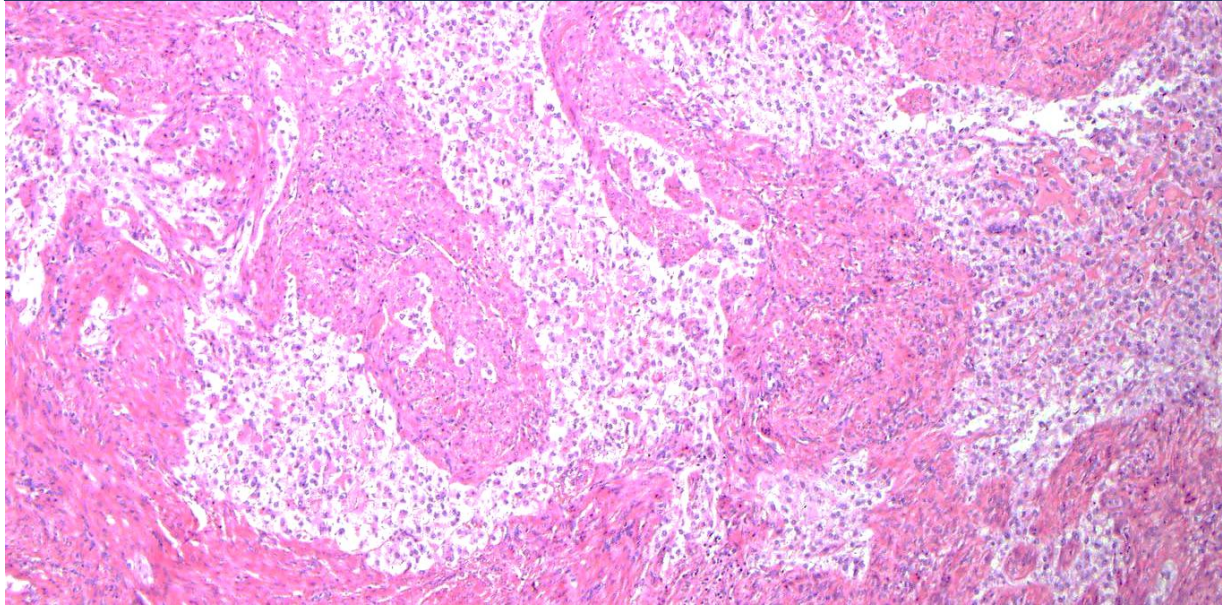
This histological image shows a section of tissue with two main components. On the left, the uterine tissue is visible, characterized by its pinkish-red color and complex, folded structure. On the right, a lymph node is present, showing a dense cluster of small, dark-staining cells. A large, pale, circular area within the lymph node represents a lymphangioma, which is a benign tumor of the lymphatic system. The lymphangioma is composed of dilated lymphatic spaces filled with clear fluid, surrounded by a thin layer of endothelial cells. The overall appearance is that of a benign, non-invasive growth within the lymph node.

LYMPH NODE

LYMPHANGIOLEIOMYOMATOSIS

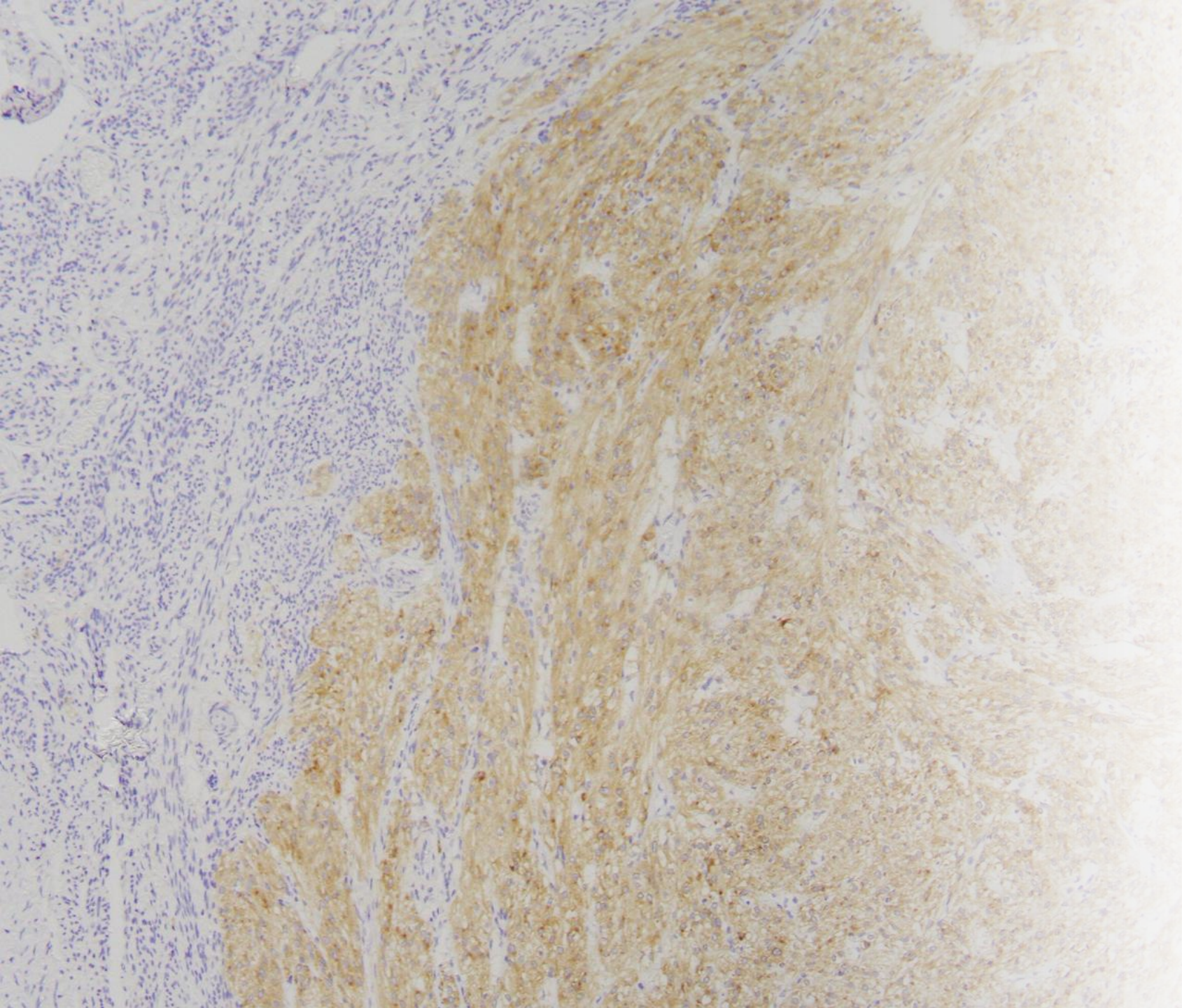
***TFE3*-REARRANGED PEComa**

Young patients; Smooth muscle markers minimally +; NO *TSC* GENE MUTATIONS; no Tuberous Sclerosis



- **HMB45**: Variably expressed in 99% of PEComas
- **Melan-A**: Often focal and less extensive than HMB45
- **MiTF**: Not very reliable marker and non-specific
- **Smooth muscle markers**: Always positive at least for one
 - Smooth muscle actin (~90%) > desmin > caldesmon
 - More often positive in spindle areas
- **Cathepsin K**: Often strongly and diffusely positive
- **PNL2**: Variable cytoplasmic positivity
- **TFE3**: Positive in only tumors with fusion
- **ER/PR**: May be positive
- **AE1/3, s100, and CD10**: Rarely positive
- **PAX8**: Negative

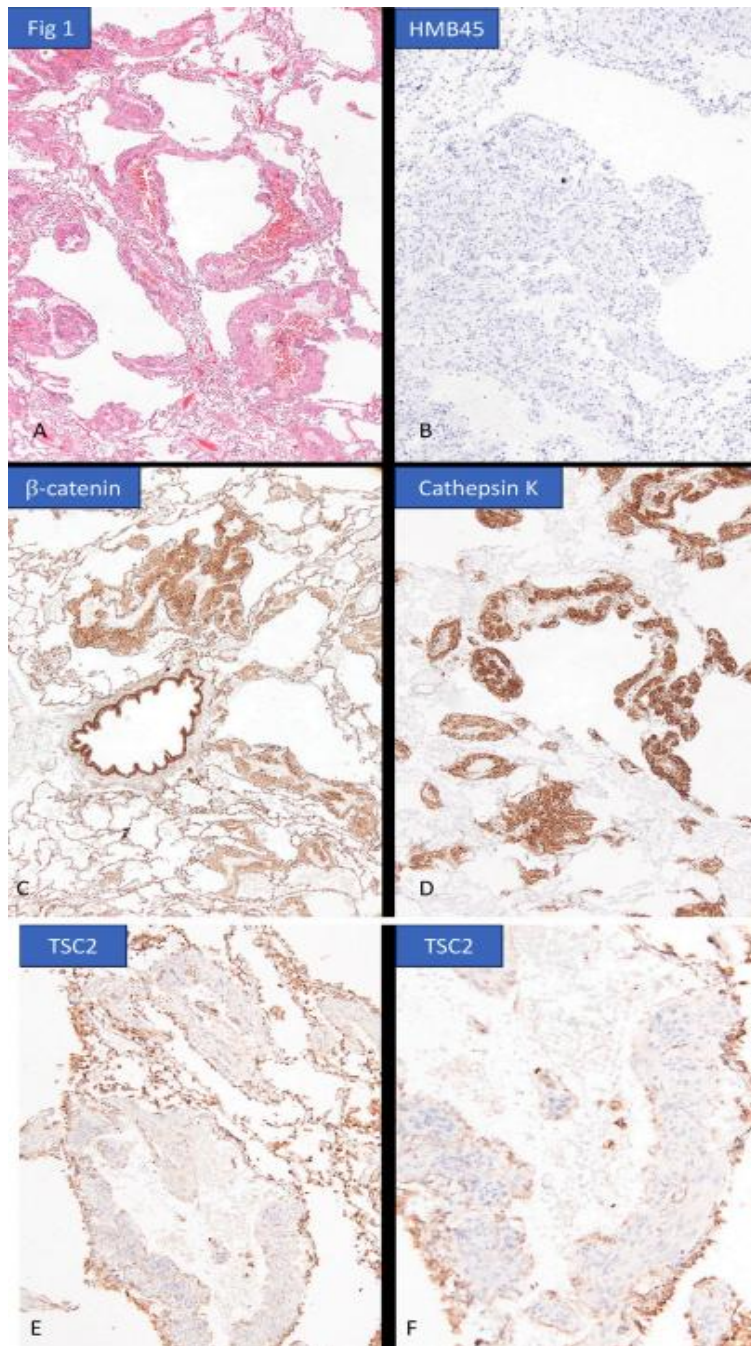
TSC1/2
alterations
common



GPNMB

(Glycoprotein
nonmetastatic
melanoma protein B)

- Closely regulated by TSC/mTOR-TFE pathway and cytoplasmic positivity correlated with TSC/mTOR-TFE pathway alteration
- Experience in GYN tumors in DDX very limited



TSC2, cathepsin K, and β -catenin as immunohistochemical markers for lymphangioleiomyomatosis^{☆,☆☆}

Abdullah Alfayez, Eric Belanger, Simon Cheung, Andrew Churg^{*,}

Human Pathol 2024

Genetic validation of a TSC2 immunohistochemistry assay in TSC/mTOR-pathway altered renal tumors

Amir Akbari^{a,b,*}, Clarence Rachel Villanueva^a, Ondrej Hes^c, Sean R. Williamson^d, Shivani Kandukuri^b, Shivani Sharma^e, Aggarwal Aditi^e, Kristyna Pivovarcikova^c, Pedram Argani^a, Sambit K. Mohanty^f, Kaushal Asrani^a, Tamara L. Lotan^{a,g,h}

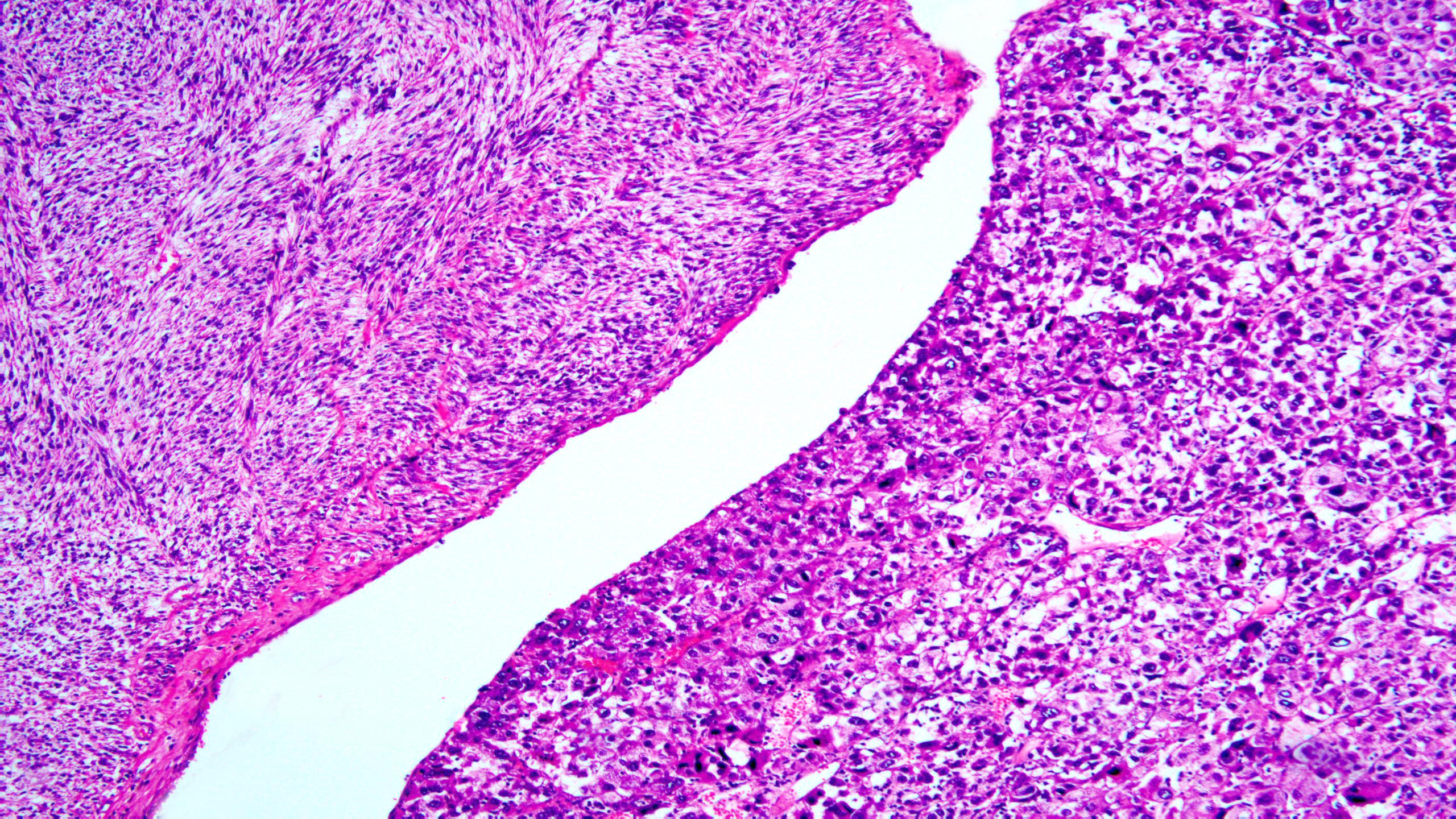
Human Pathol 2024

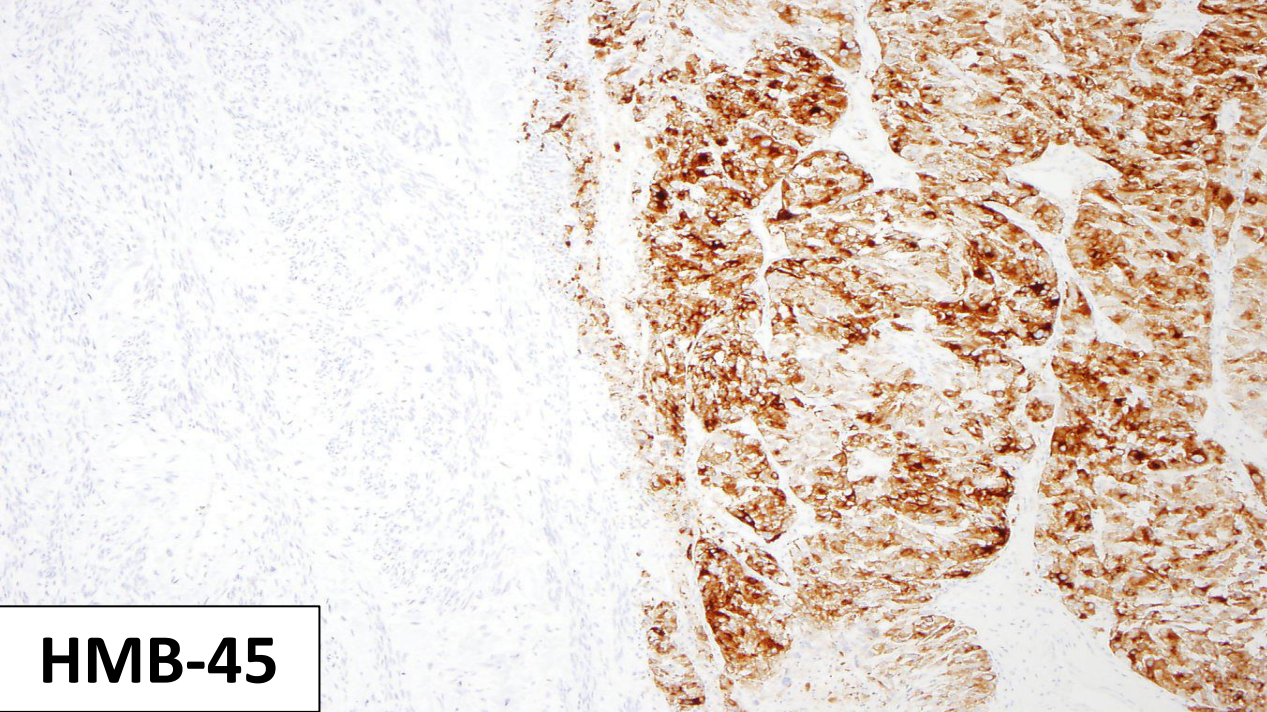
...Experience not know in
gynecologic tumors

	WHO 2013	WHO 2020
Benign		< 3 features: ≥ 5 cm, high-grade atypia, >1 mitoses/50 HPFs, necrosis, LVI
Uncertain malignant behavior	Nuclear pleomorphism /multinucleated giant cells or >5 cm	
Malignant	≥ 2 features: >5 cm, infiltration, high-grade atypia, >1 mitoses/50 HPFs, necrosis, vascular invasion	≥ 3 features

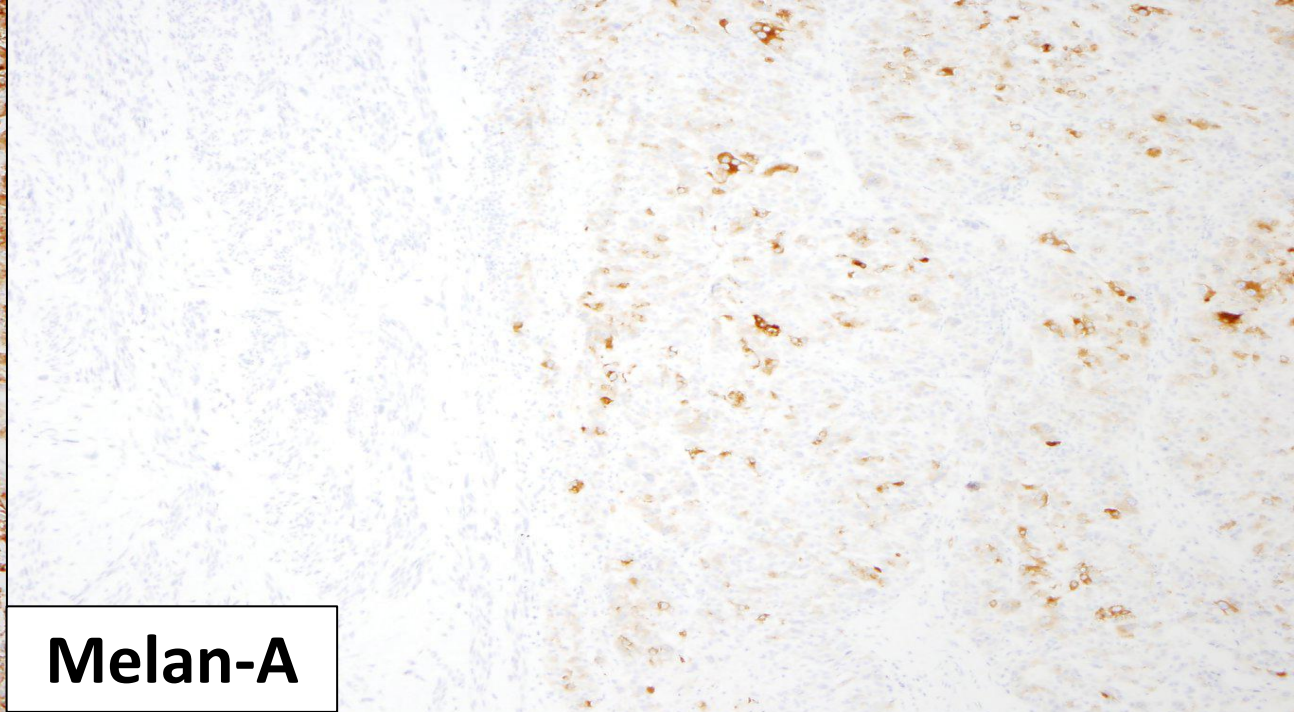
Malignant PEComas Often Harbor *TP53* and/or *ATRX* Mutations

	3	4	9 ^a	12	16	24	
<i>TSC1</i>							NS
<i>TSC2</i>							DEL
<i>ATRX</i>							FS
<i>TP53</i>							SP
							MS
							R

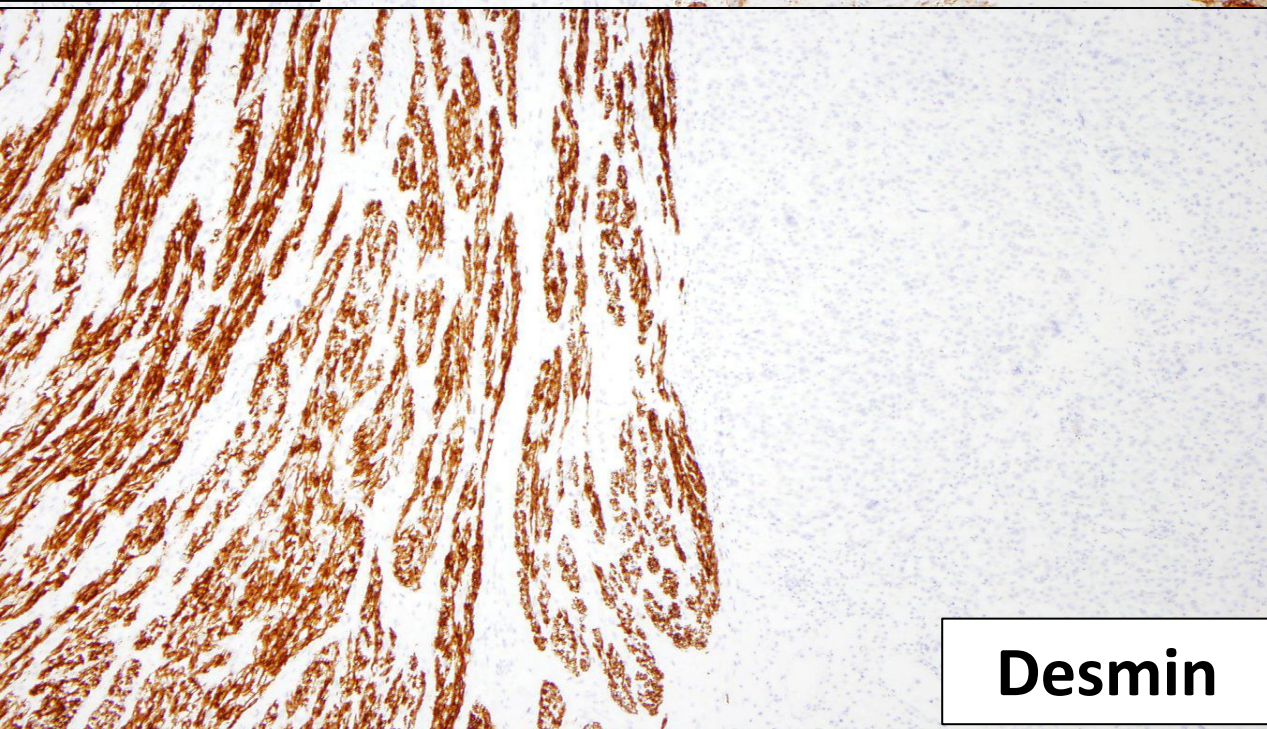




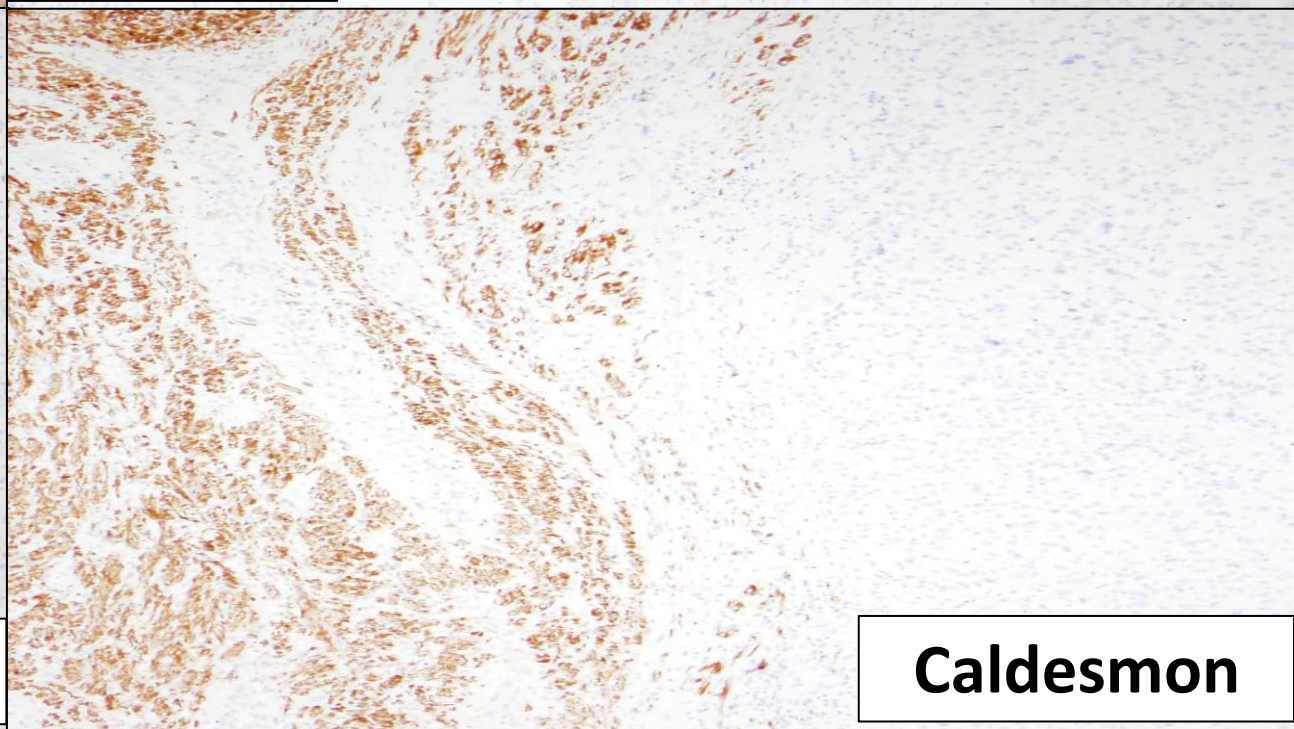
HMB-45



Melan-A



Desmin



Caldesmon

**Mesenchymal
Neoplasm with
Myomelanocytic
Differentiation**

```
graph LR; A[Mesenchymal Neoplasm with Myomelanocytic Differentiation] --> B[TSC Alteration]; A --> C[TFE3 Fusion]; A --> D[No TSC, TFE3, or LMS alterations and >50% HMB-45]; A --> E[No TSC, TFE3, or LMS alterations and <50% HMB-45]; B --> F[Classic PEComa]; C --> G[TFE3 Translocation-Associated PEComa]; D --> H[Favor PEComa]; E --> I[Descriptive Diagnosis];
```

***TSC* Alteration**

Classic PEComa

***TFE3* Fusion**

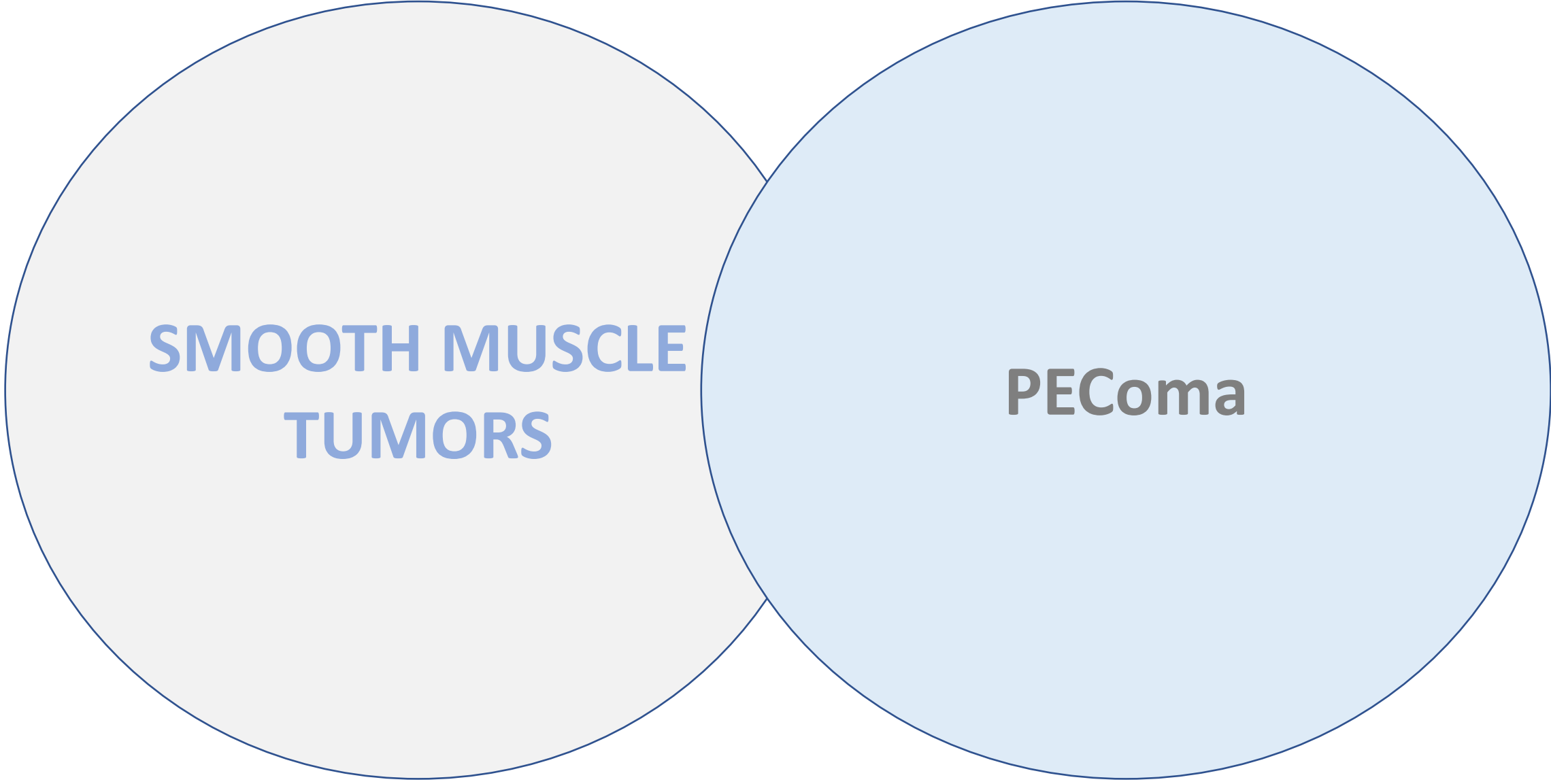
***TFE3* Translocation-
Associated PEComa**

**No *TSC*, *TFE3*, or
LMS alterations
and >50% HMB-45**

Favor PEComa

**No *TSC*, *TFE3*, or
LMS alterations
and <50% HMB-45**

**Descriptive
Diagnosis**



A Venn diagram consisting of two overlapping circles. The left circle is light gray and contains the text 'SMOOTH MUSCLE TUMORS' in blue. The right circle is light blue and contains the text 'PEComa' in dark gray. The circles overlap in the center, but no text is present in the intersection.

**SMOOTH MUSCLE
TUMORS**

PEComa

A Clinicopathologic and Molecular Characterization of Uterine Sarcomas Classified as Malignant PEComa

*William J. Anderson, MBChB, Fei Dong, MD, Christopher D.M. Fletcher, MD,
Michelle S. Hirsch, MD, PhD, and Marisa R. Nucci, MD*

- 15 patients
- Mutually exclusive variants in TSC1 (27%) and TSC2 (20%)
- Recurrent alterations also identified in TP53 (53%), RB1 (30%), ATRX (33%), and BRCA2 (13%)
- Important role of targeted sequencing in tumors with focal melanocytic marker expression

CONCLUSIONS

- Integration of gross, morphologic, immunohistochemical features key
- Panel of antibodies, but not a single stain should be used as the latter may lead to the incorrect diagnosis
- Overlapping morphologic features and immunohistochemical staining patterns exists within different tumors
- If unusual (morphology or immunohistochemical profile), molecular testing may be helpful
- Establishing correct diagnosis important as at least some mesenchymal tumors may be treated with specific targeted therapy

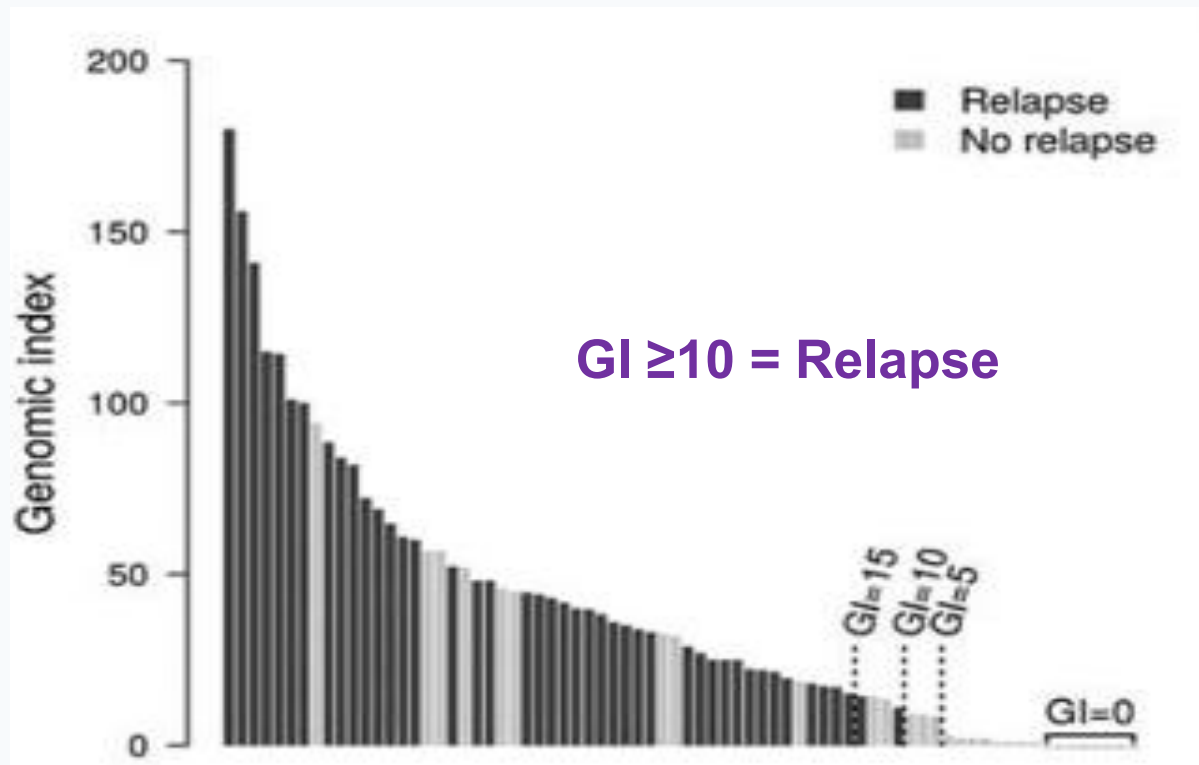
Uterine Leiomyoma

CNV: Stable genome

Uterine Leiomyosarcoma

CNV: Genome instability
(Genomic Scar/HRD)

Smooth Muscle Tumors of Uncertain Malignant Potential (STUMP)



- There is a gradient of **genomic complexity** that correlates with **outcome**
- STUMPs with **genomic index ≥ 10** are reclassified as **“molecular leiomyosarcoma”**