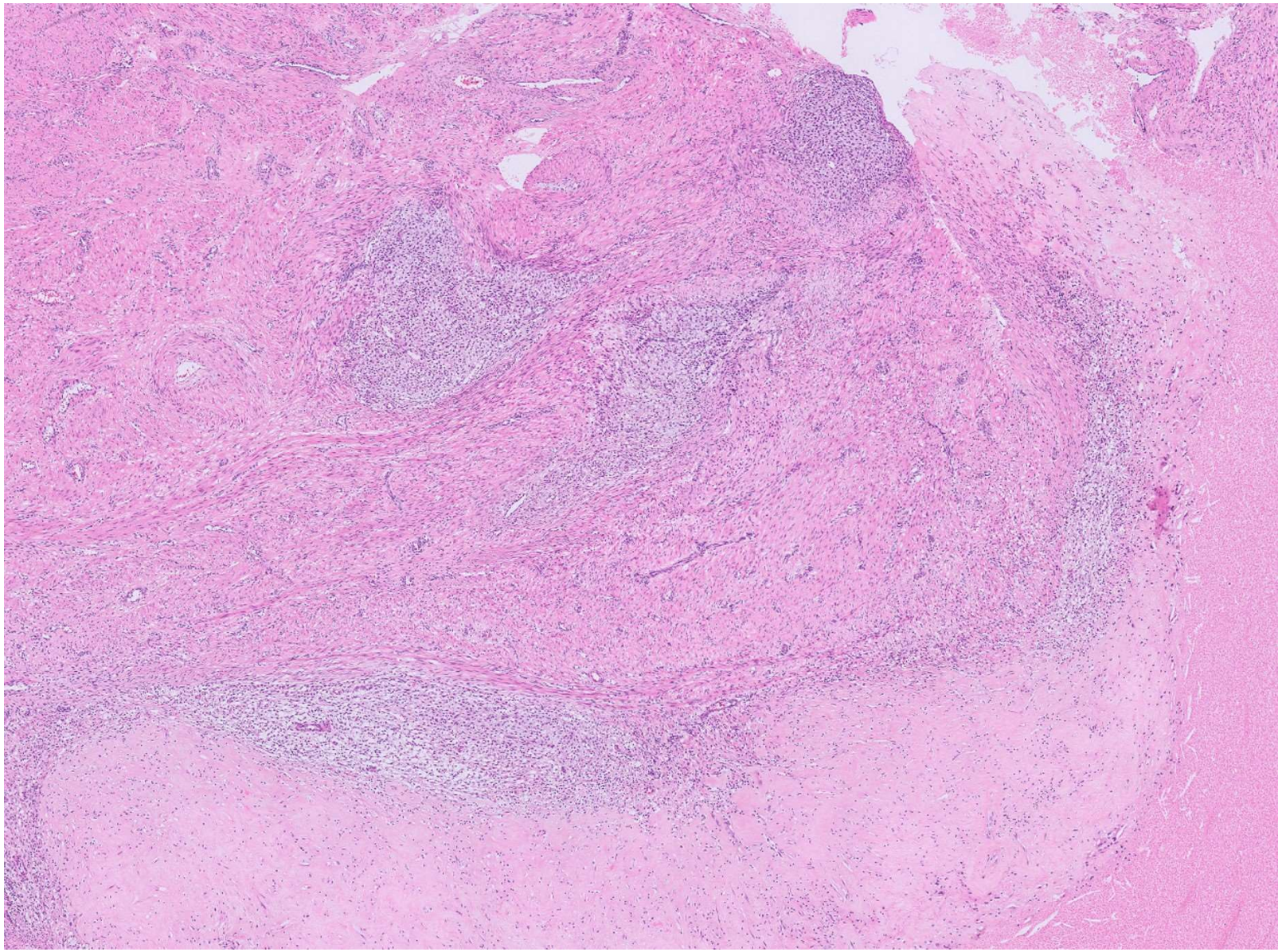
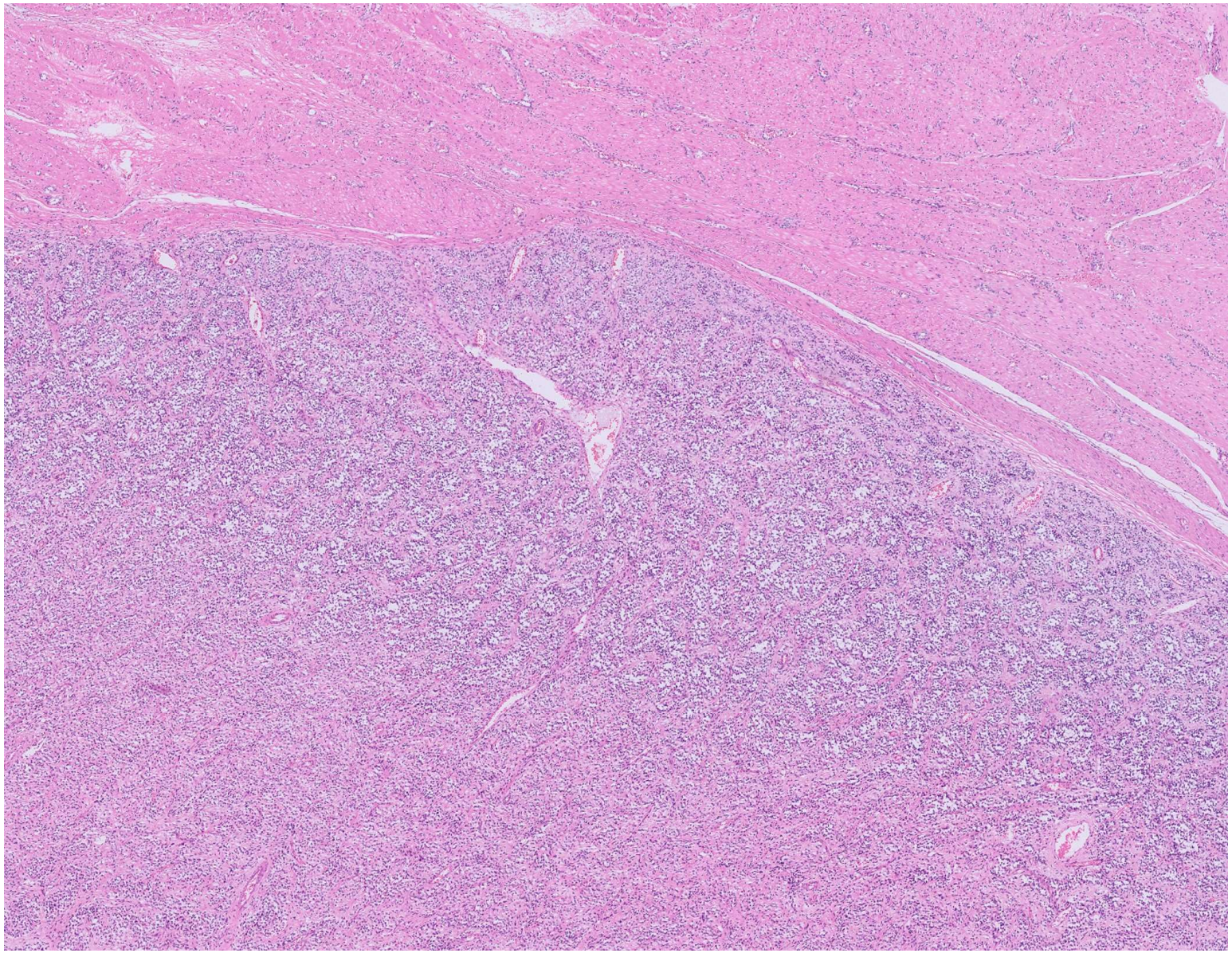
Mesenchymal tumors of the uterine myometrium: Let's see what's interesting

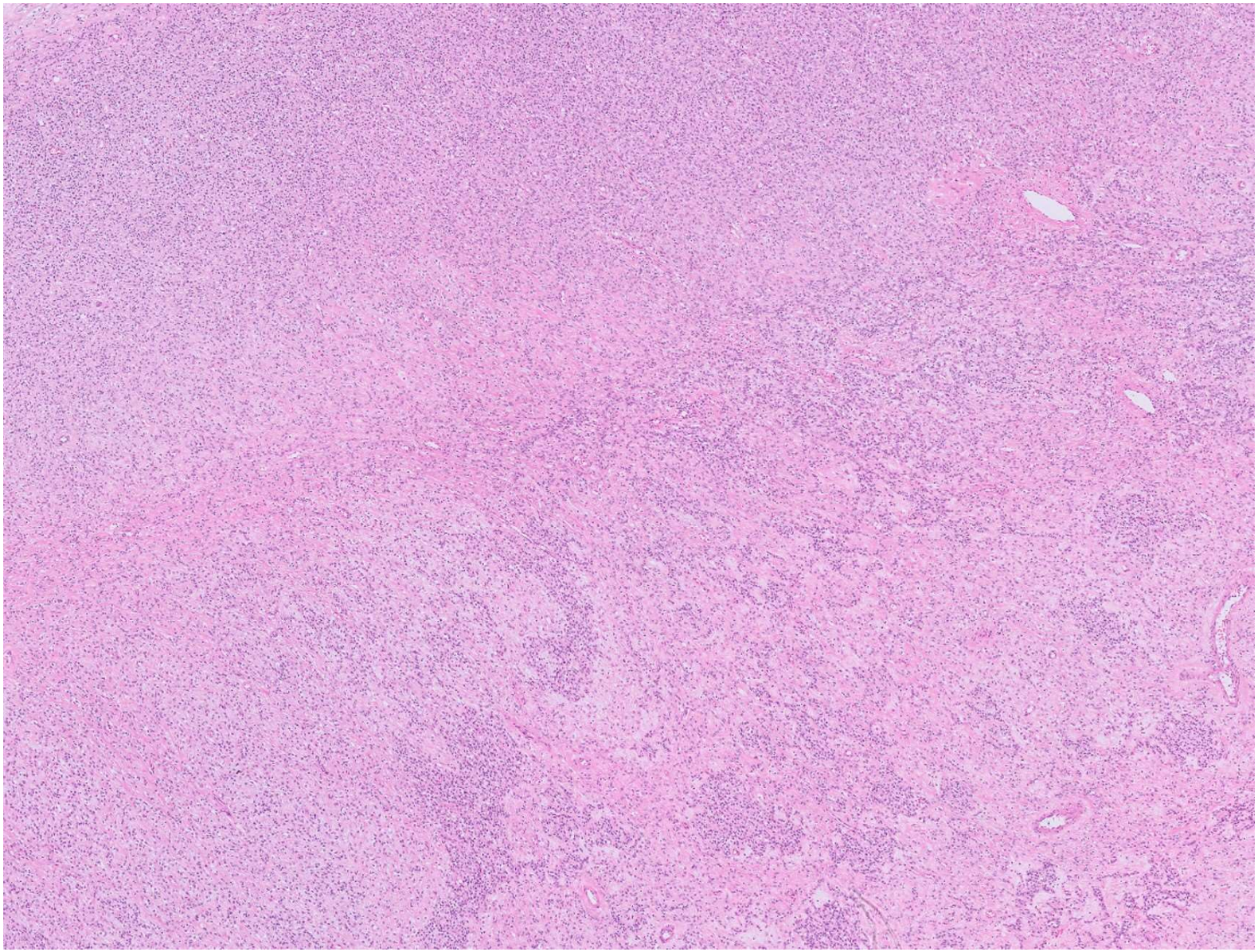
Eunah Shin, MD, PhD
Yongin Severance Hospital
Yonsei University

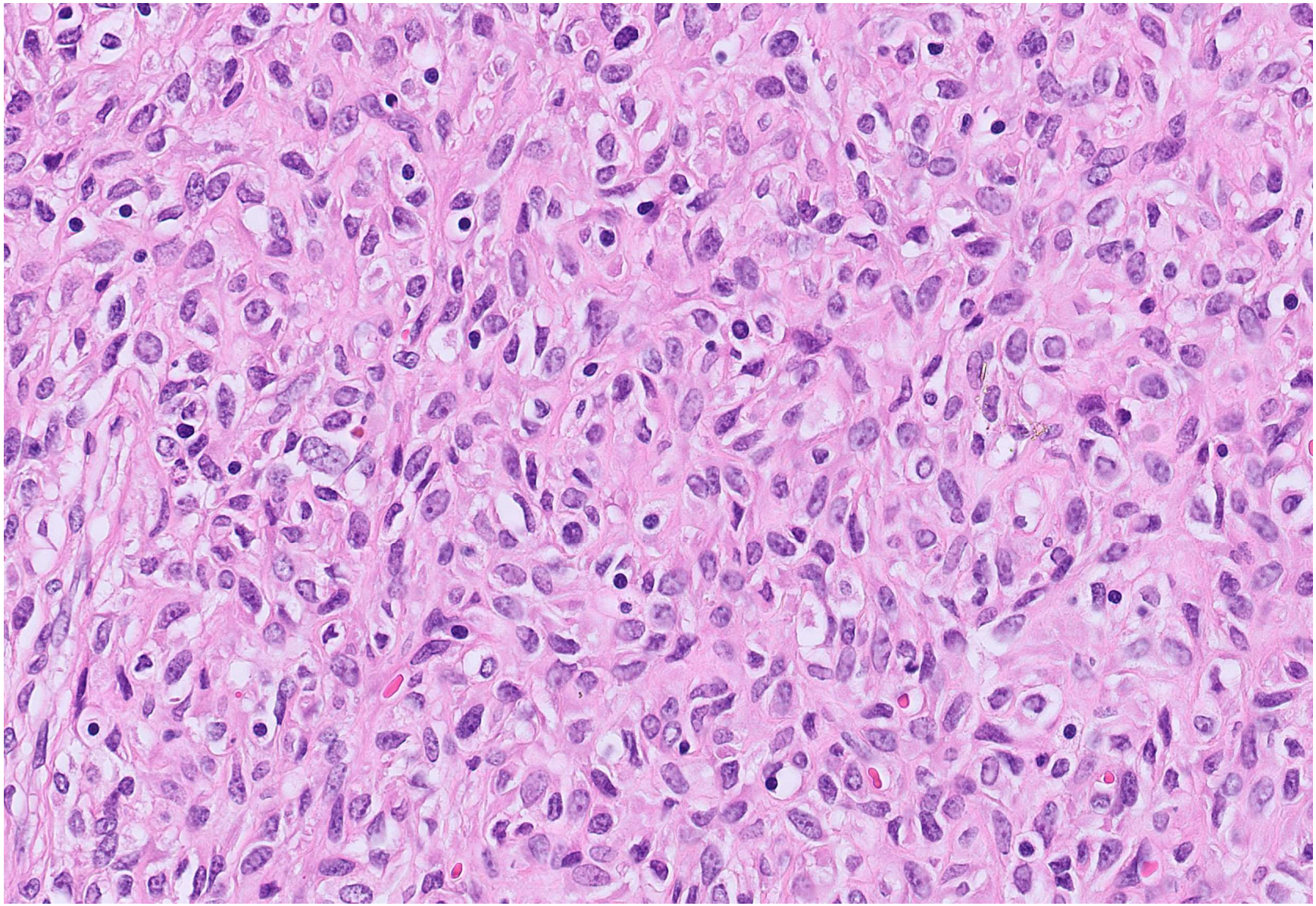
Case 1.

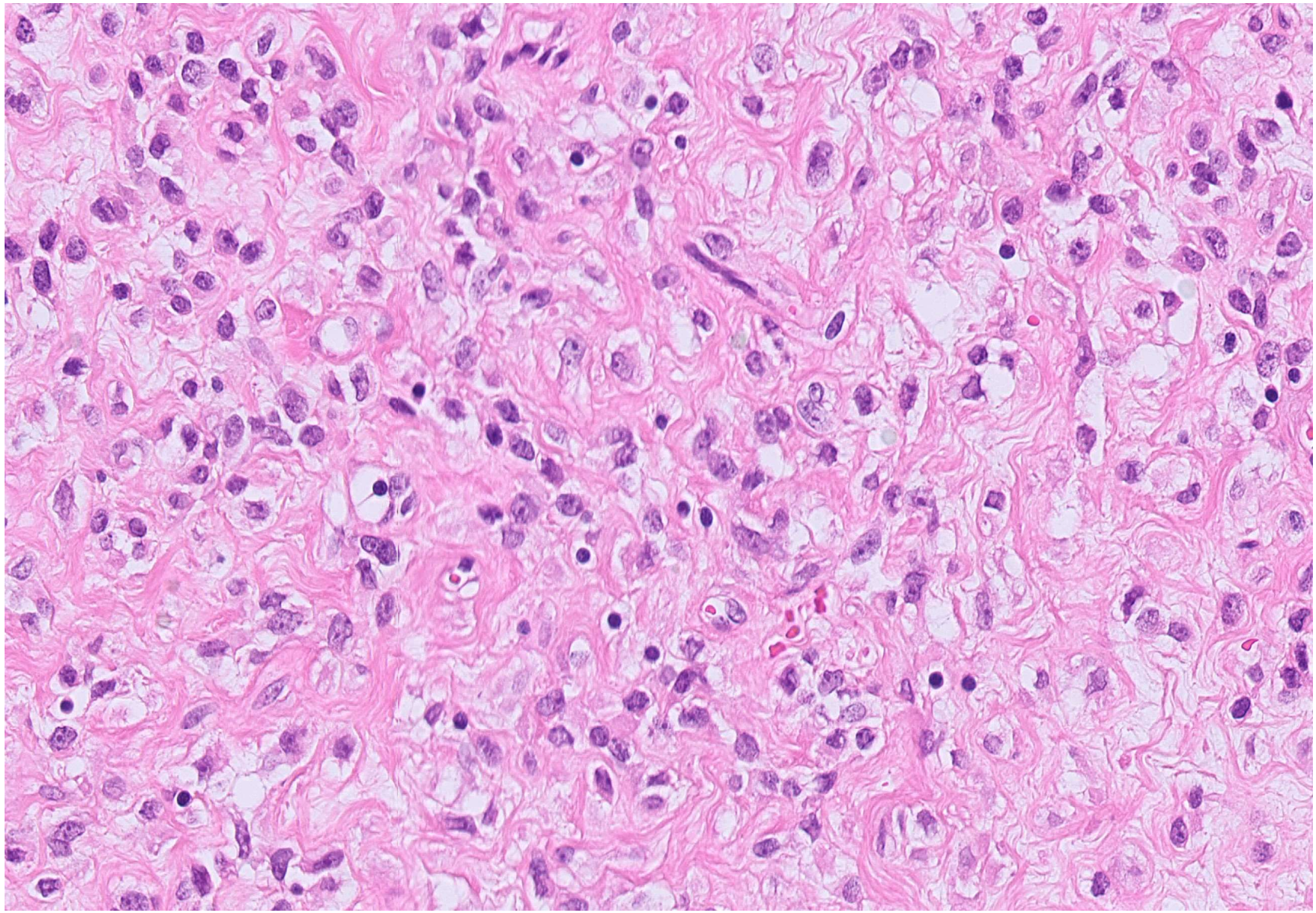
- 33/F
- Referred for myomectomy
- Ultrasonogram: 7cm sized intramural nodule with degenerative change

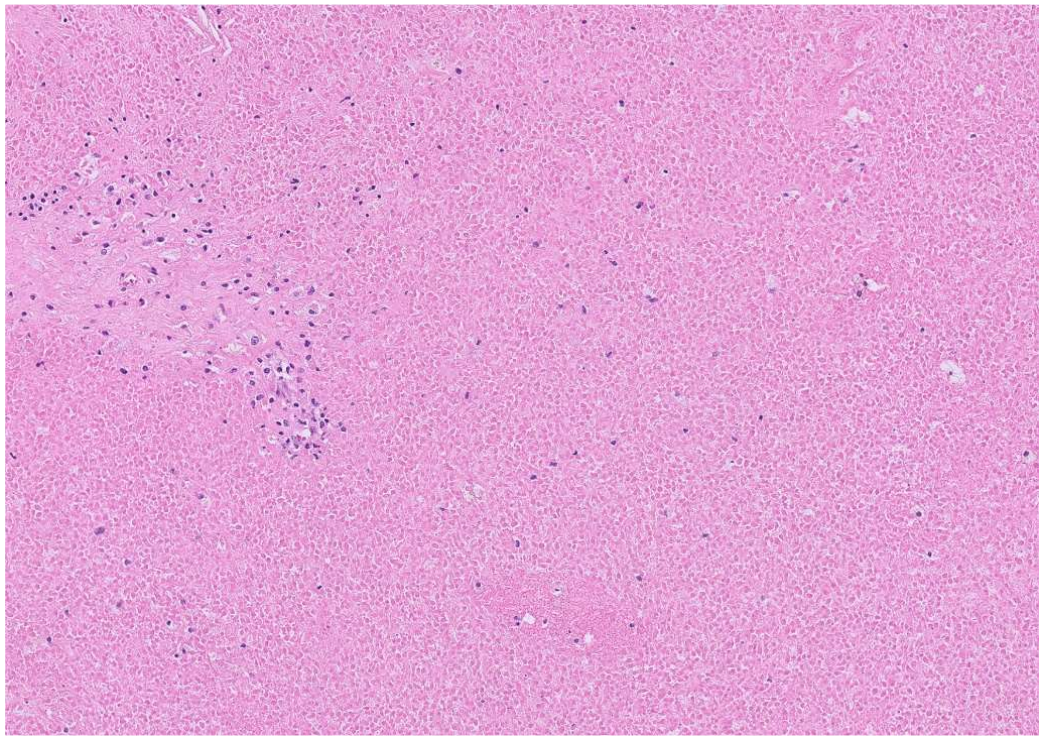


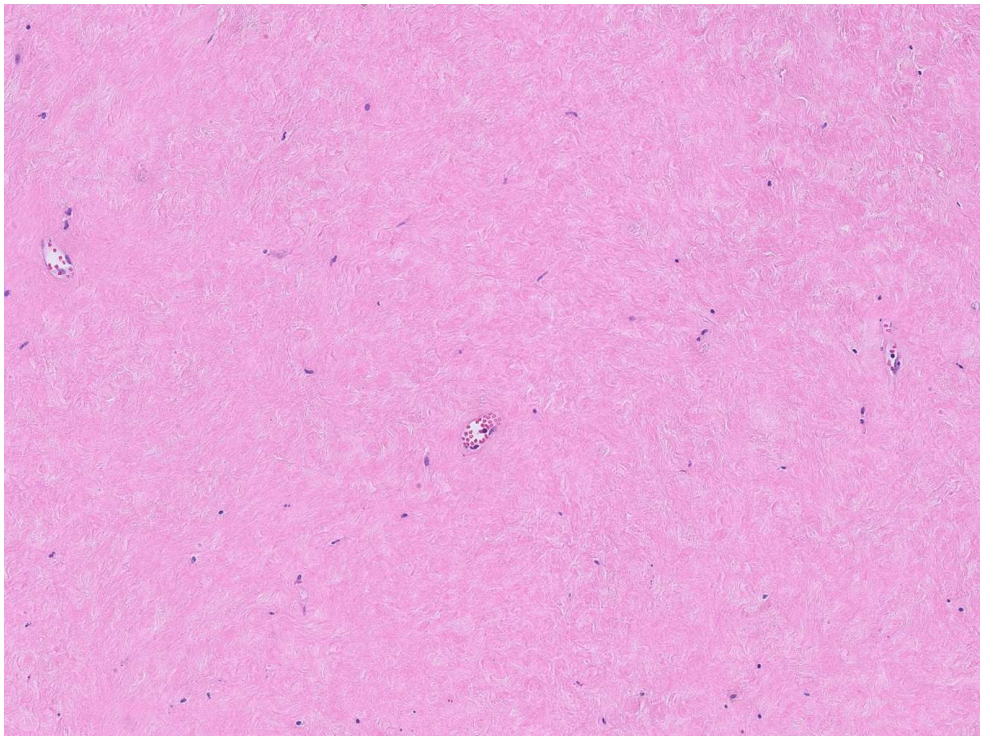


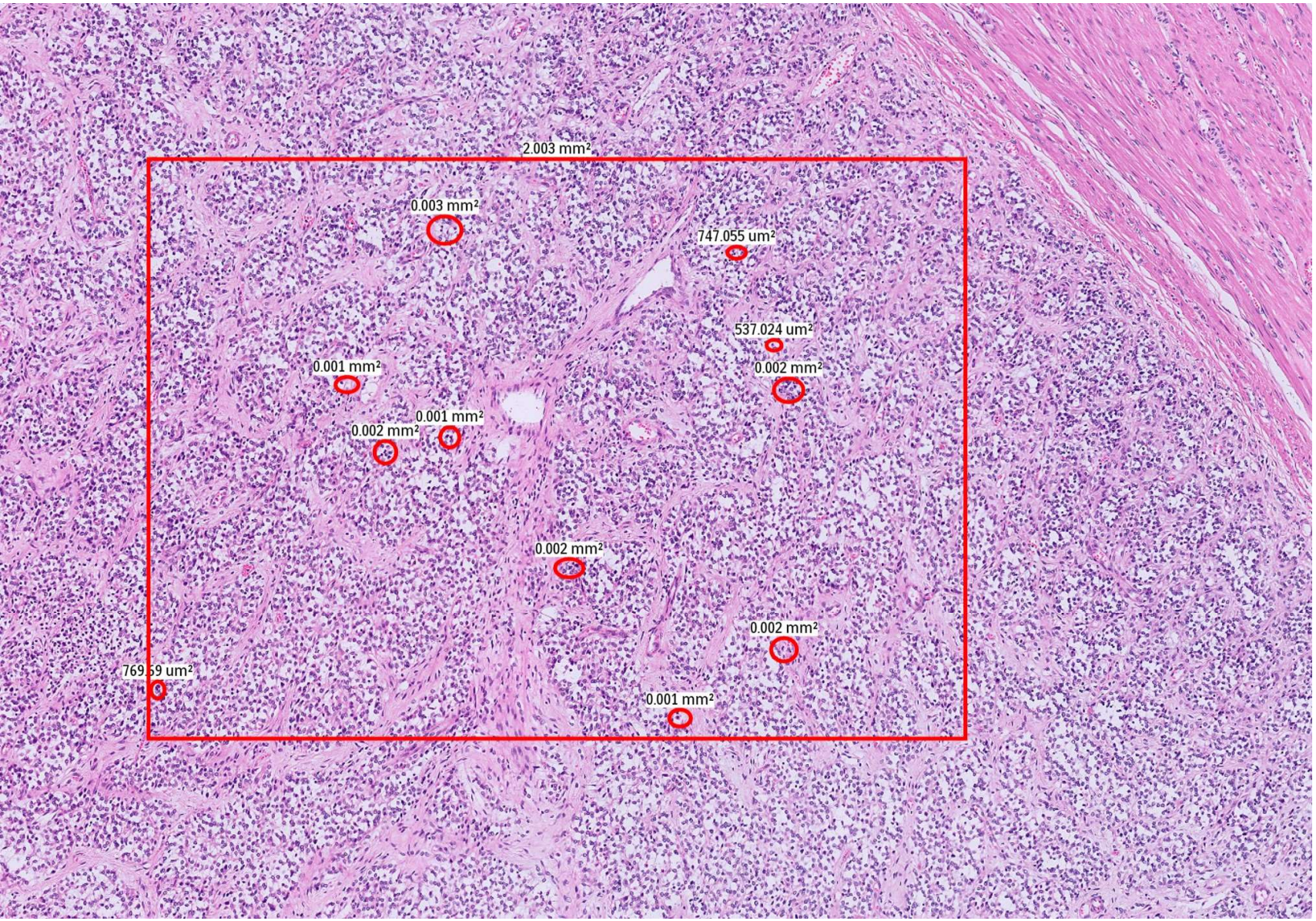








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0.003 mm²
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537.024 um²
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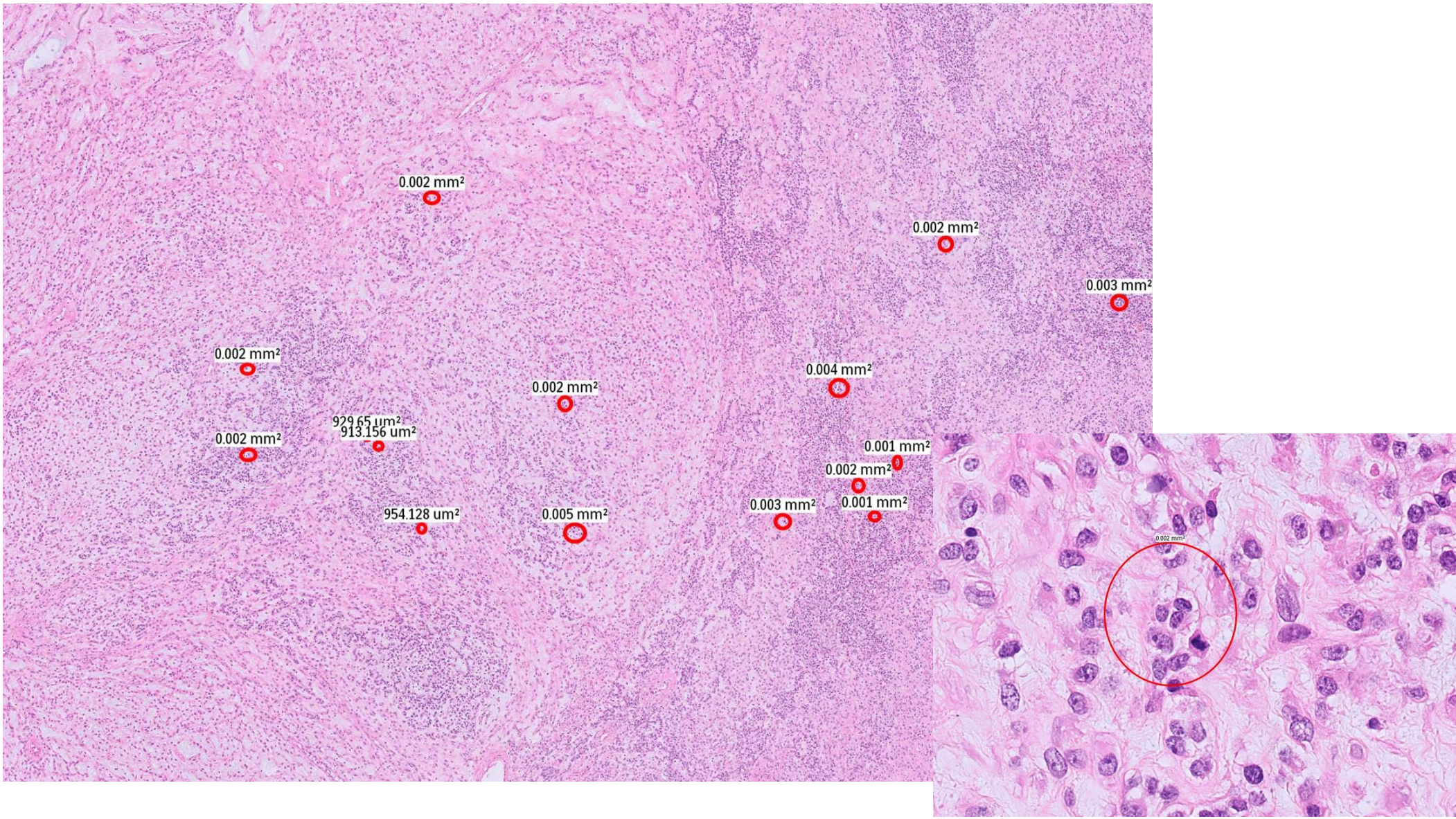
769.59 um²
0.001 mm²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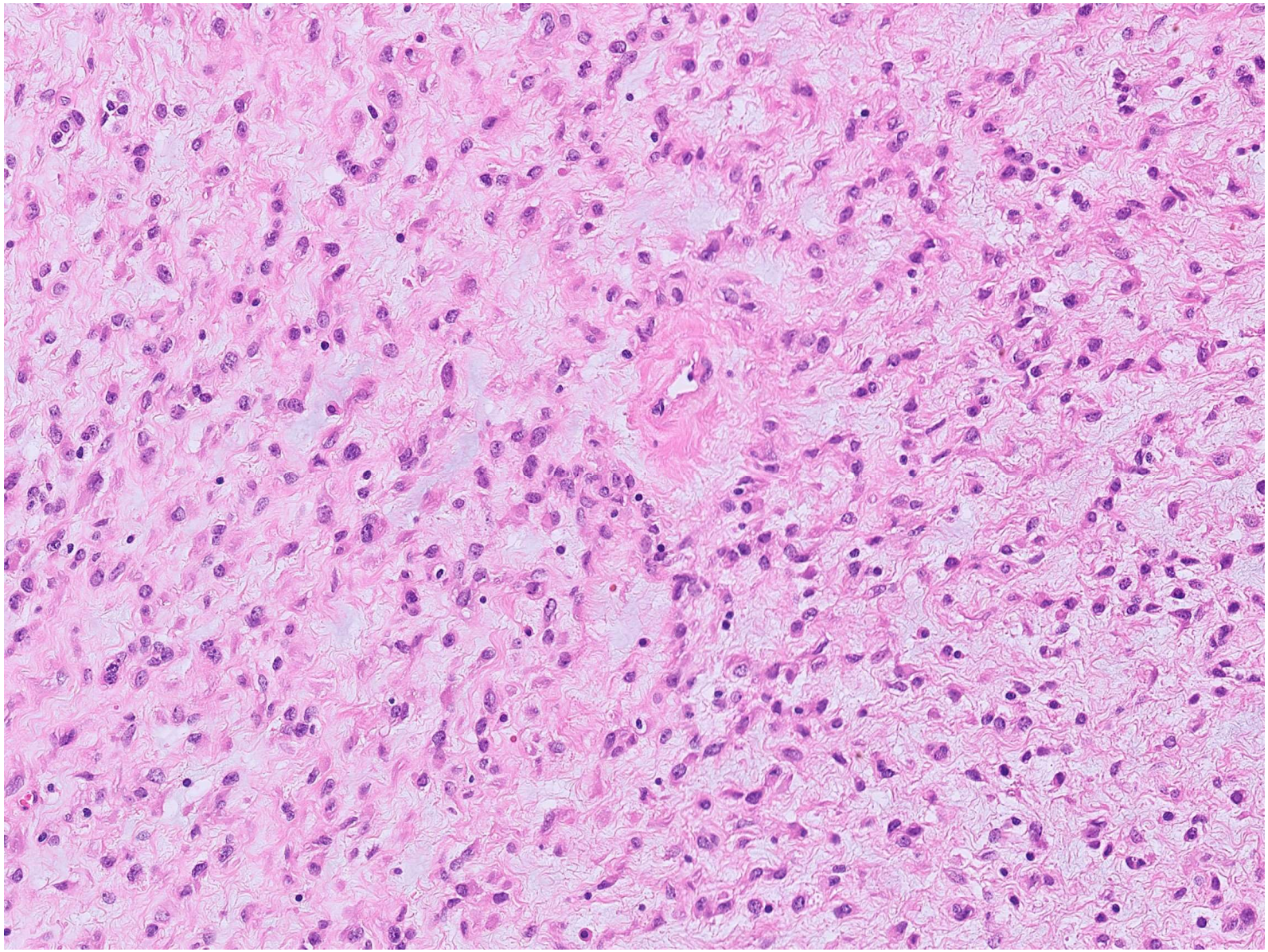
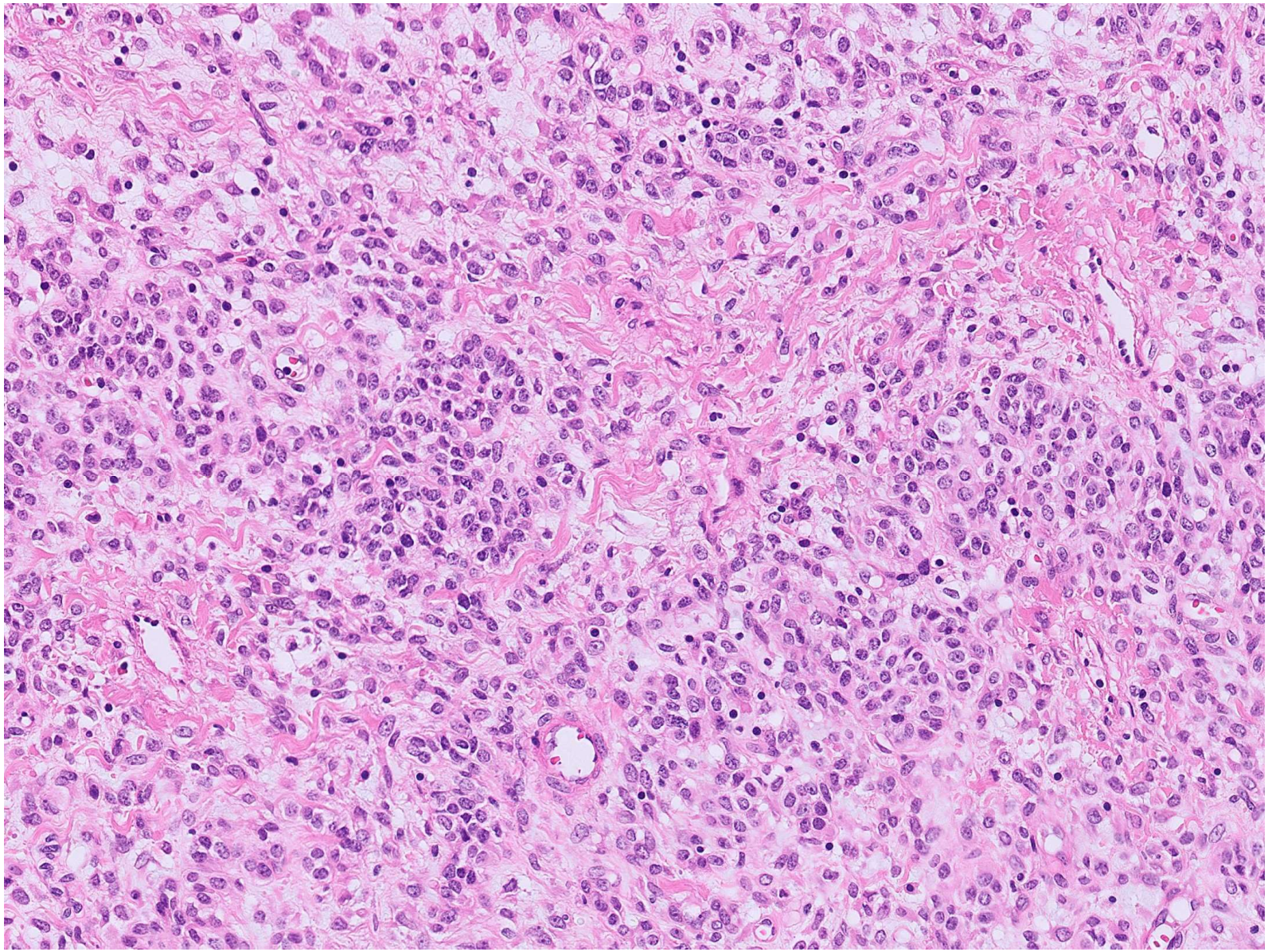
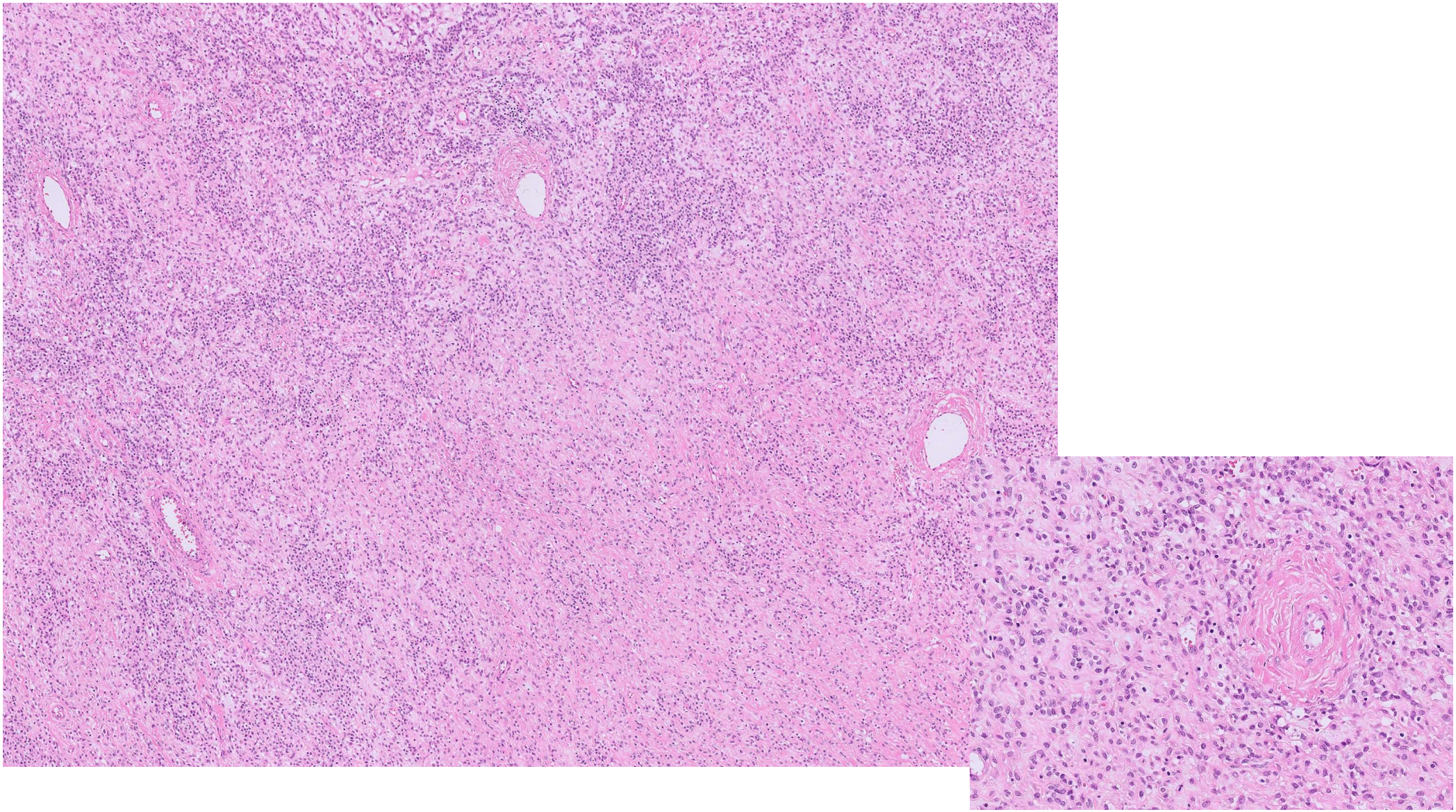
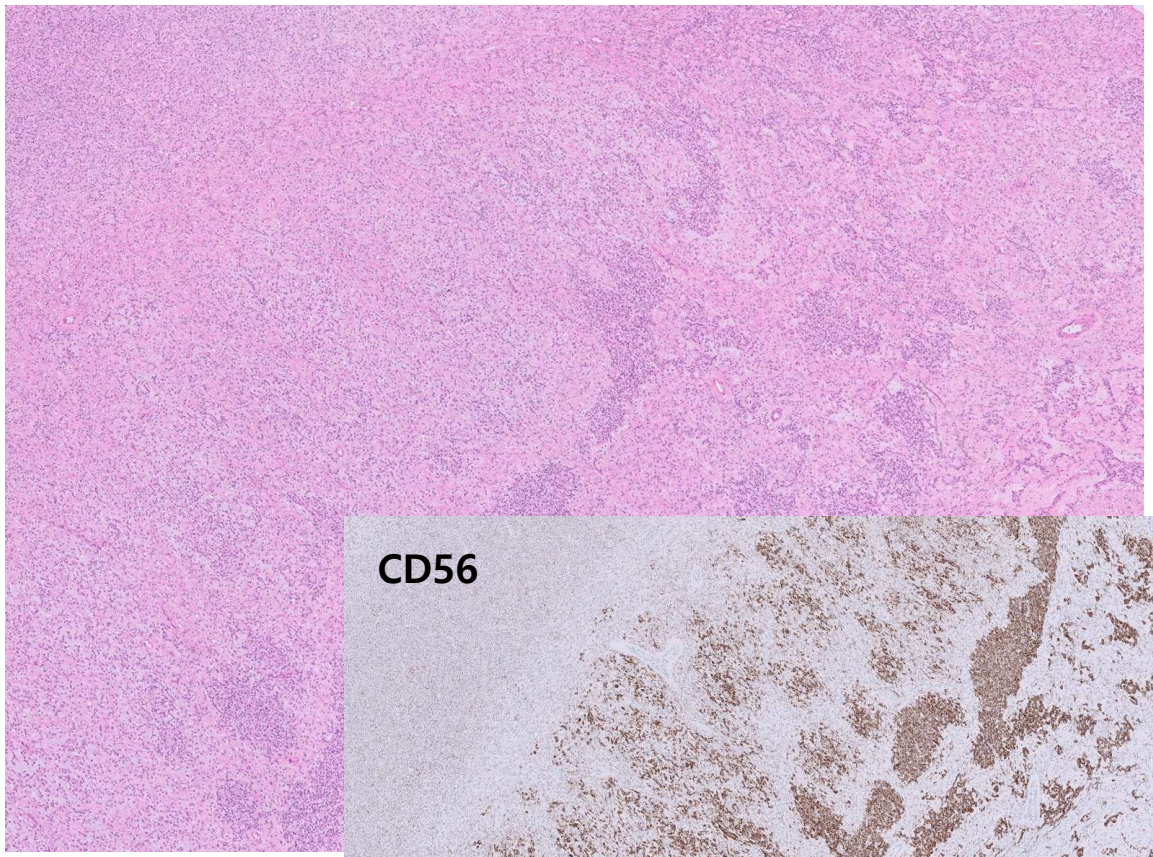
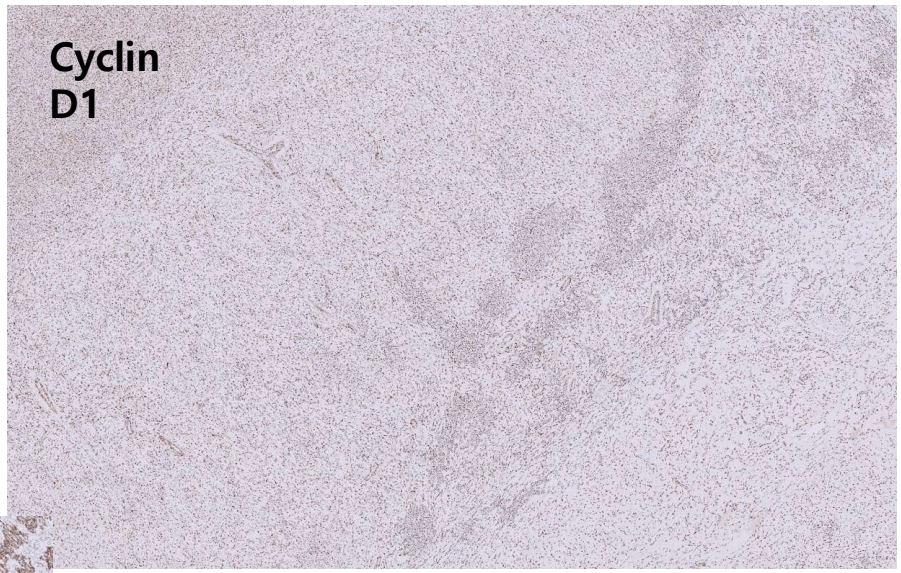
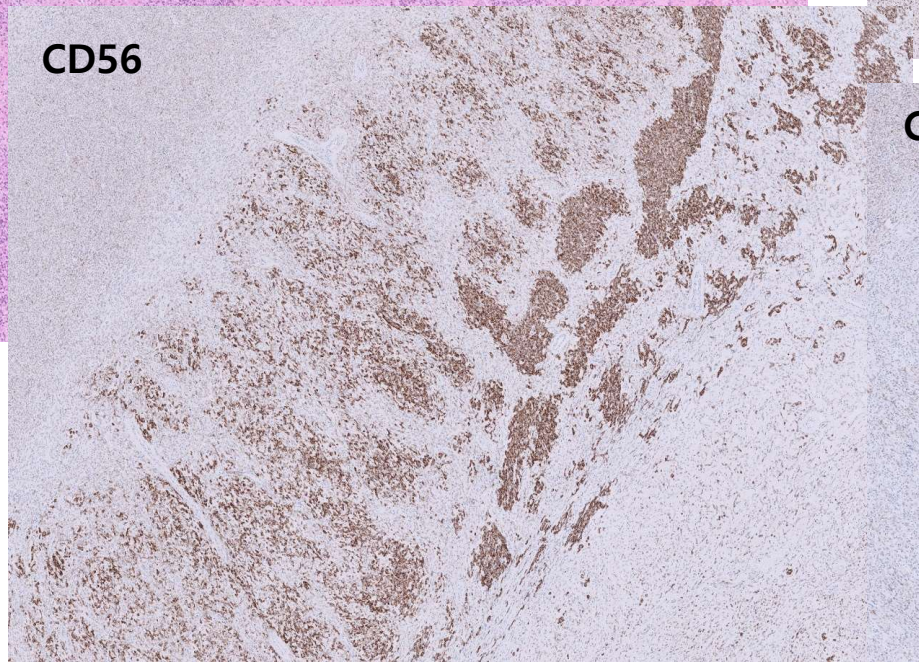









Cyclin
D1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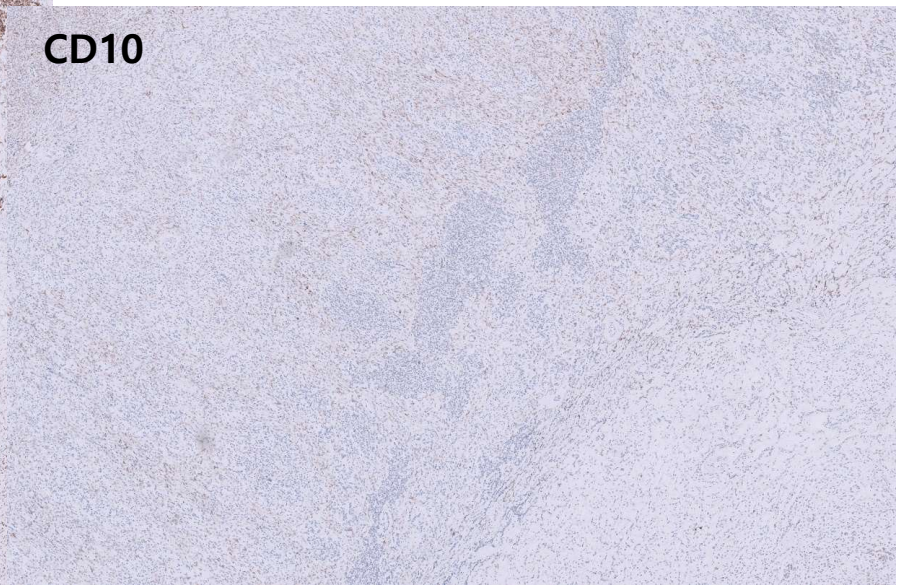
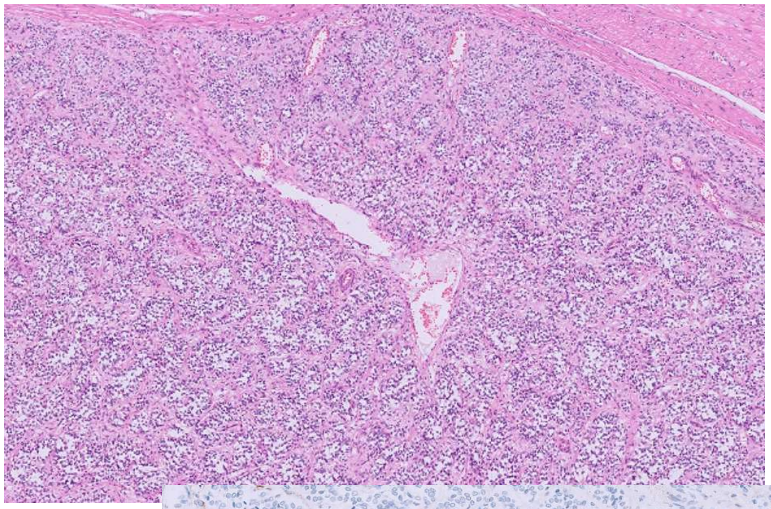
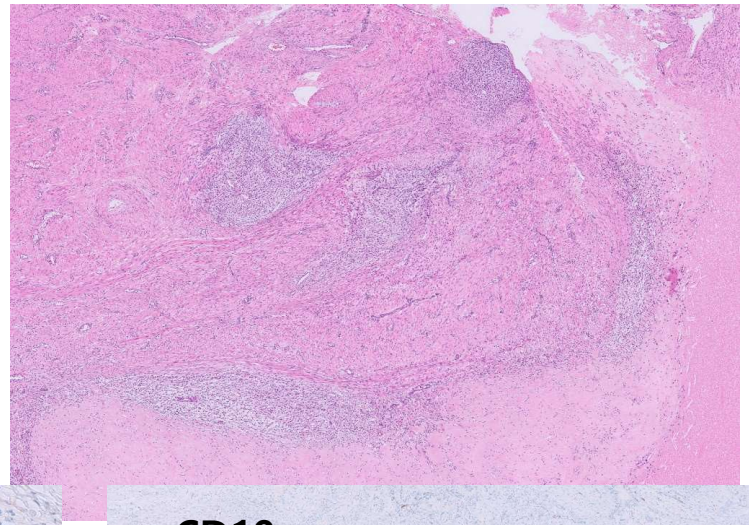
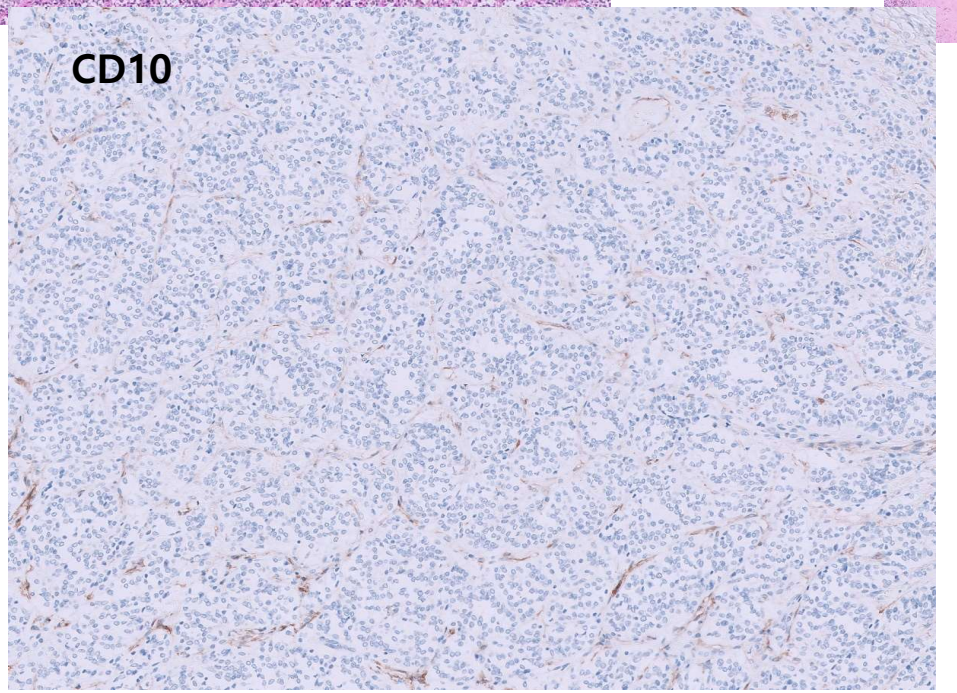

CD10



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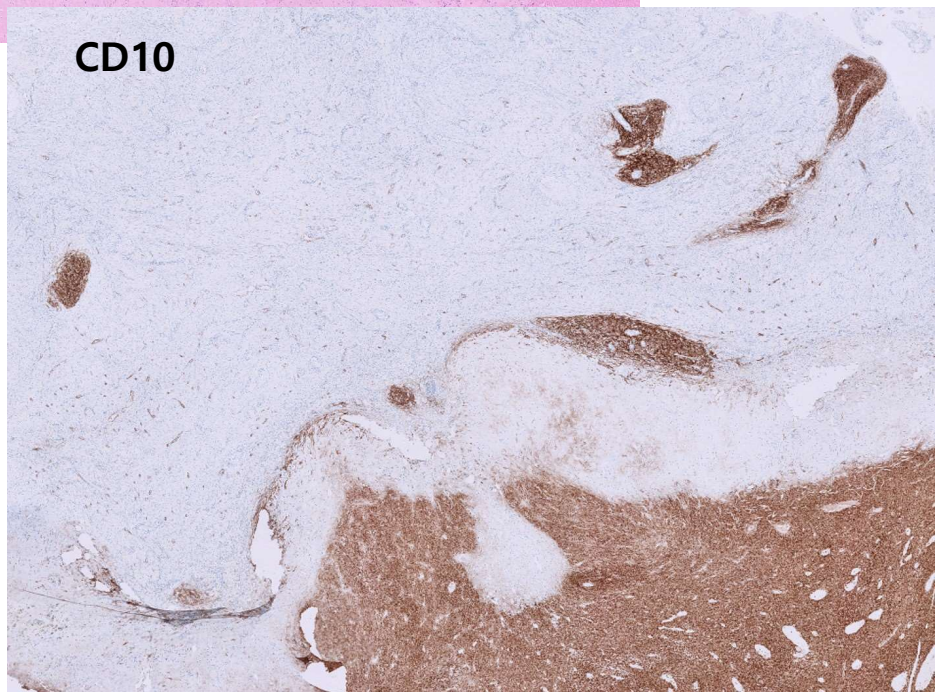
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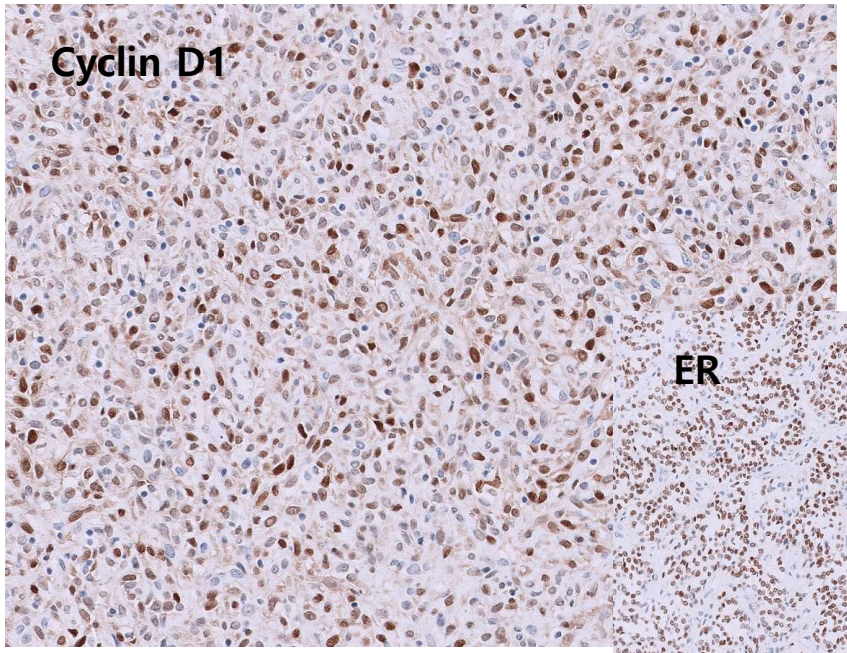
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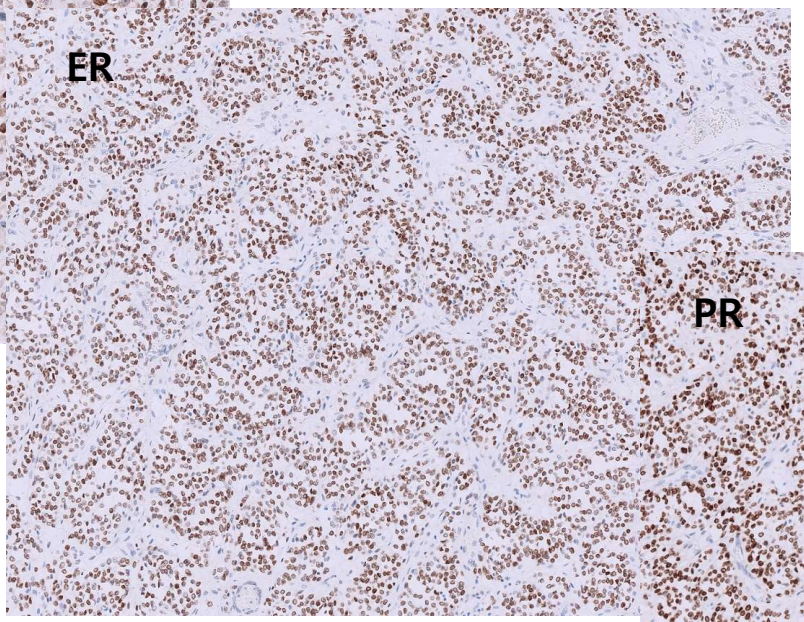
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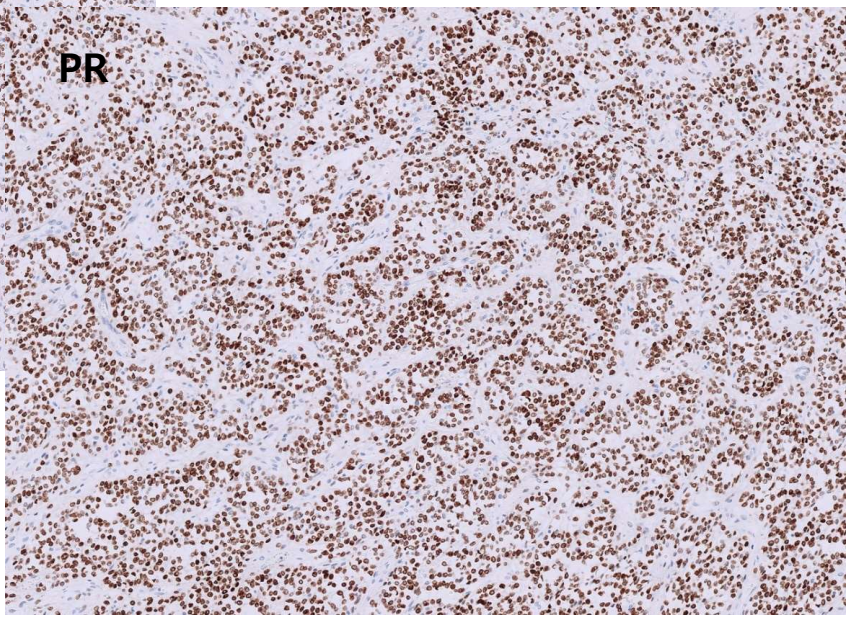
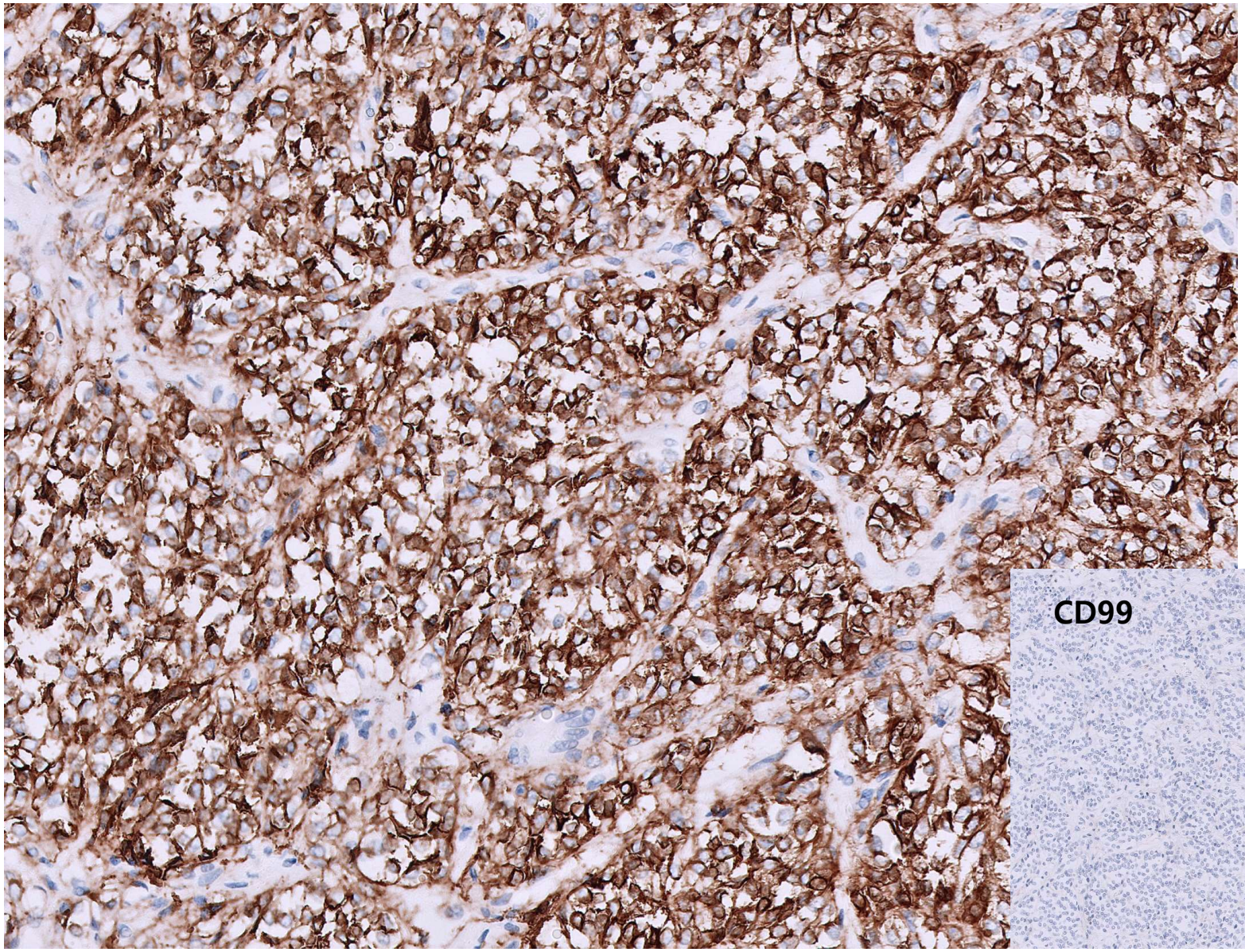
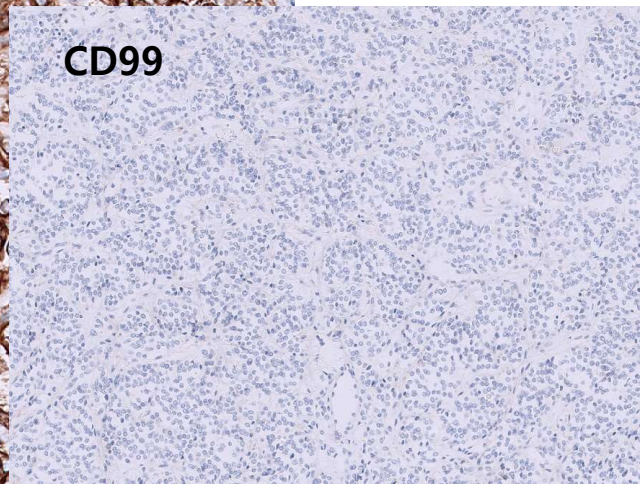
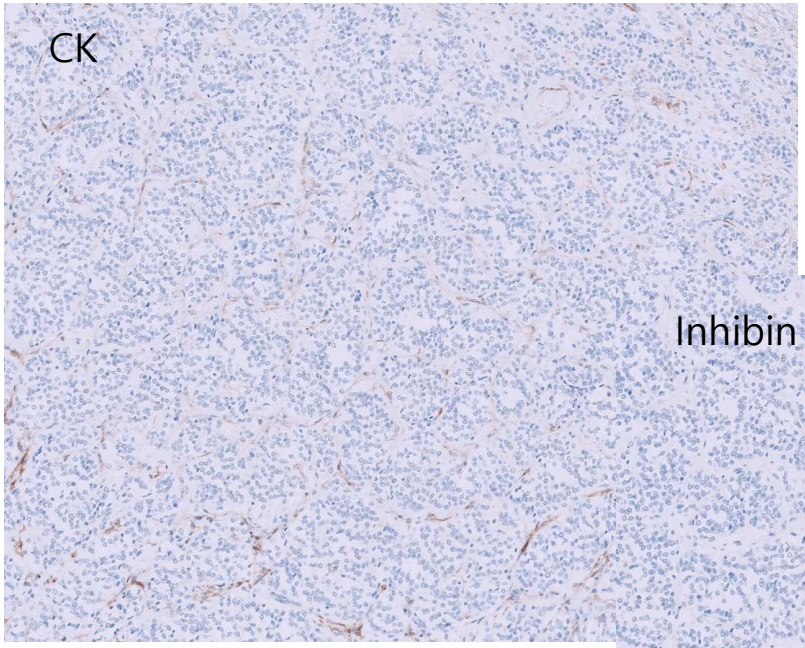

PR

CD56



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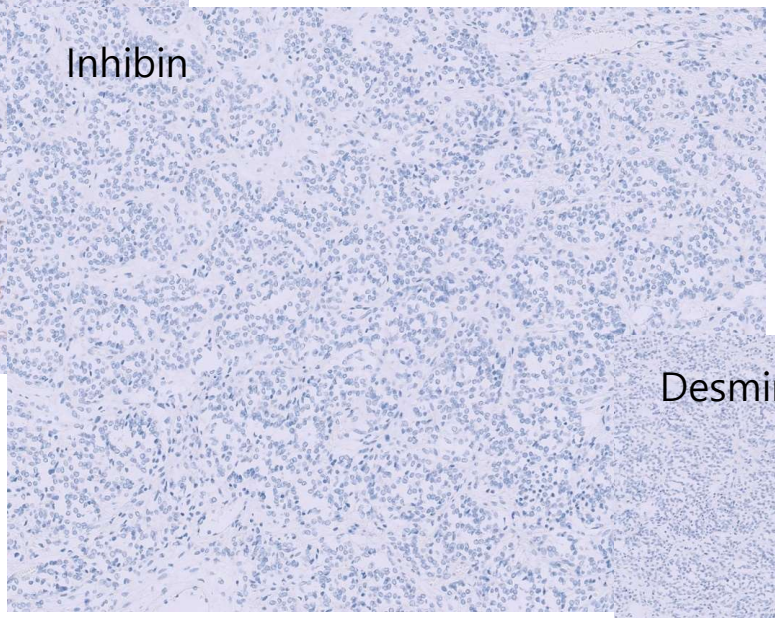
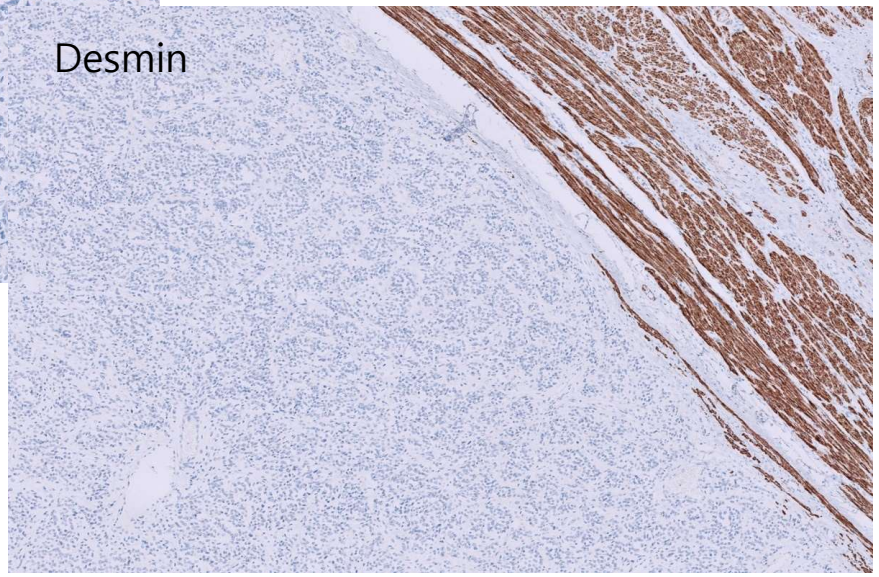
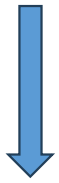

Inhibin


Desmin

Summary of the histologic features

- Tongue-like permeation of the myometrium
- Mild to moderate atypia (proliferative phase endometrial stromal cells)
- Brisk mitotic activity
- Hyaline plaques
- Necrosis



LGESS

- Expansile pattern of invasion
- Brisk mitotic activity
- Necrosis
- Monomorphic high grade round or spindle cells
- Myxoid stroma

HGESS

Histology of LGESS

- **Essential: proliferative-phase endometrial stromal-type tumor cells permeating the myometrium, with or without lymphovascular invasion**

- **Tongue-like infiltration**
- **Intravascular tumor plugs**
- **Uniform, oval to fusiform nuclei with no or minimal atypia**
- **Scant cytoplasm**
- **Delicate arteriolar network**
- **Whorling around the vessels**
- **Low to brisk mitosis**
- **Hyaline plaques, foamy histiocytes, cystic change, necrosis**
- **Diffuse and strong expression of CD10, ER, PR, and focal cyclin D1 positivity**

- **Atypical features:**

Smooth muscle differentiation

Fibromyxoid/fibrous change

Sex cord-like differentiation

Immunoprofile of the tumor

Positive

- ER
- PR

- CD10
- CyclinD1
- CD56

Negative

- CK
- Calretinin
- Inhibin-alpha
- Desmin
- HMB45
- C-kit
- DOG1
- CD99

Differential diagnoses

Low grade endometrial stromal sarcoma (LGESS)

High grade endometrial stromal sarcoma (HGESS)

Undifferentiated uterine sarcoma (UUS)

Perivascular epithelioid cell tumor (PEComa)

Epithelioid gastrointestinal stromal tumor (GIST)

Epithelioid leiomyosarcoma

Uterine tumor resembling ovarian sex-cord tumor (UTROSCT)

Diagnostic work-up

• Calretinin • Inhibin-alpha UTROSCT	• Desmin Epithelioid leiomyosarcoma	• HMB45 PEComa	• C-kit • DOG1 GIST

Diagnostic work-up

Diagnostic work-up

- **Histology**

- **Immunohistochemistry**

CD10+

ER+
PR+
C-kit –
CD99 –

CD10–
Cyclin D1+
CD56+

ER+
PR+

Final diagnosis

ENDOMETRIAL STROMAL SARCOMA, HIGH GRADE,
with areas of low grade endometrial stromal sarcoma

- **Expansile and permeative myometrial invasion**
- **Mitosis: 12/2mm2 (10 HPFs)**
- **Necrosis: Present, extensive**
- **Vascular invasion: Not identified**

Genetic fusions in LGESS

- *JAZF1-SUZ12*
- *JAZF1-PHF1*
- *EPC1-PHF1*
- *MEAF6-PHF1*
- (two thirds)

(Less common)

- *MBTD1-EZHIP*
- *BRD8-PHF1* (also in high grade)
- *EPC2-PHF1*
- *EPC1-SUZ12*

Genetic fusions in HGESS

- *YWHAE-NUTM2A/B*
- *ZC3H7B-BCOR*
- *BCOR* ITD (internal tandem duplication)

(Rare)

- *EPC1-BCOR*
- *JAZF1-BCORL1*
- *BRD8-PHF1*

Molecular identification of ESS

- ***YWHAE-NUTM2A/B***

- May be associated with fibromyxoid or conventional LGESS
- High grade component positive for cyclinD1, BCOR, c-kit, CD56, CD99
- Negative for DOG1

- ***ZC3H7B-BCOR***

- Positive for cyclin D1, BCOR(50%), CD10, ER, PR (variable)
- Negative for desmin (may be focal positive for SMA and pan-TRK; unrelated to NTRK rearrangement)

- ***BCOR* ITD**

- Less positive for CD10, diffusely positive for cyclinD1 and BCOR
- Negative for ER and PR
- May be positive for desmin but negative for SMA
- May be associated with fibromyxoid or conventional LGESS
- High grade component positive for cyclinD1, BCOR, c-kit, CD56, CD99
- Negative for DOG1

Immunophenotype of ESS

2020 WHO Classification

Tumor type	CD10	ER	PR	CyclinD1	Desmin
LGESS	+ (D)	+ (D)	+ (D)	-/+ (F)	+ (F/D)
YWHAE-NUTM2A/B Low grade component	+ (D)	+ (D)	+ (D)	-/+ (F)	-
YWHAE-NUTM2A/B High grade component	-	-	-	+ (D)	-
ZC3H7B-BCOR HGESS	+ (D)	-/+ (F)	-/+ (F)	+ (D)	-
BCOR ITD HGESS	+ (F/D)	-	-	+ (D)	-/+ (F)

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Recurrent *KAT6B/A::KANSL1* Fusions Characterize a Potentially Aggressive Uterine Sarcoma Morphologically Overlapping with Low-grade Endometrial Stromal Sarcoma

Abbas Agaimy, MD[1], **Blaise A. Clarke, MD**[2], **David L. Kolin, MD**[3], **Cheng-Han Lee, MD**[4], **Jen-Chieh Lee, MD, PhD**[5], **W Glenn McCluggage, FRCPath**[6], **Patrik Pöschke, MD**[7], **Robert Stoehr, PhD**[1], **David Swanson, BSc**[8], **Gulisa Turashvili, MD**[8,9], **Matthias W. Beckmann, MD**[7], **Arndt Hartmann, MD**[1], **Cristina R. Antonescu, MD**[10], **Brendan C. Dickson, MD, MSc**[8,9]

[1]Institute of Pathology, Erlangen University Hospital, Comprehensive Cancer Center, European Metropolitan Area Erlangen-Nuremberg (CCC ER-EMN), Friedrich Alexander University of Erlangen-Nuremberg, Erlangen, Germany

[2]University Health Network, Toronto, ON, Canada

[3]Brigham and Woman's Hospital, Boston, MA, USA

[4]BC Cancer Agency, Vancouver, BC, Canada

[5]Department and Graduate Institute of Pathology, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan

[6]Department of Pathology, Belfast Health & Social Care Trust, Belfast, United Kingdom

[7]Department of Gynecology and Obstetrics, Erlangen University Hospital, Comprehensive Cancer Center, European Metropolitan Area Erlangen-Nuremberg (CCC ER-EMN), Friedrich Alexander University of Erlangen-Nuremberg, Erlangen, Germany

[8]Department of Pathology & Laboratory Medicine, Mount Sinai Hospital, Toronto, ON, Canada

[9]Department of Pathobiology and Laboratory Medicine, University of Toronto, Toronto, ON, Canada

- **13 KAT6B/A::KANSL1 fusion positive uterine stromal neoplasm**

- **Original diagnoses mostly LGESS with atypical features (limited CD10 expression, sex cord-like features, pericytic vasculature, and frequent myxoid changes)**

- **Variable histological overlap with LGESS:**

Well circumscribed, lacking permeative and angioinvasive growth typical of LGESS

Diffuse sheets with prominent spiral-type arterioles

Frequent pericytoma-like vascular pattern

Variable myxoid stromal changes

Variable mitotic activity (1 ~ >20 / 10HPFs)

Table 2:

Gross and microscopic findings in *KAT6B/A::KANSL1* fusion positive uterine sarcomas

No	Tumor location	Peripheral border	Predominant histology	Sex cord-like features	Myxoid change	Hyaline collagen deposits	Eosinophilic myoid cells	Necrosis	Mitoses/10 hpf
1	Myometrial	Well-circumscribed	LG-ESS-like	Present	Present	Absent	Absent	Present	22
2	Endometrial	Not assessable (curettage)	LG-ESS-like	Absent	Absent	Absent	Absent	Absent	1
3	Myometrial	Well-circumscribed	LG-ESS-like	Present	Present	Present	Absent	Absent	12
4	Myometrial	Infiltrative	LG-ESS	Absent	Present	Present	Present	Absent	3
5	(A) Myometrium (B) Broad ligament	(A) Well-circumscribed (B) Not assessable (disrupted)	(A) LG-ESS-like (B) Biphasic undifferentiated	(A) Absent (B) Absent	(A) Absent (B) Present	(A) Present (B) Present	(A) Present (B) Present	(A) Present (B) Present	(A) 2 (B) >20
6	Myometrial	Well-circumscribed	LG-ESS-like	Absent	Present	Absent	Present	Present	1
7	Intracavitary, protruding through cervical canal, extending to outer 1/3 of myometrium	Well-circumscribed	LG-ESS-like	Present	Present	Present	Absent	Present	3
8	Myometrial	Well-circumscribed (radiologically)	LG-ESS-like	Absent	Absent	Present	Present	Absent	2
9	Myometrial	Infiltrative	Undifferentiated spindle-epithelioid cells	Absent	Present	Absent	Absent	Present	>20
10	Myometrial	Well-circumscribed, focal myometrial entrapment	Fibromyxoid variant of LG-ESS-like	Present	Present	Present	Present	Present	3
11	Myometrial	Well-circumscribed	LG-ESS-like	Present	Present	Present	Present	Present	8
12	Myometrial	Well-circumscribed	Sex cord-like	Present	Absent	Present	Present	Present	16
13	Myometrial with exophytic polypoid component	Infiltrative with myometrial vascular involvement	LG-ESS-like	Absent	Absent	Absent	Absent	Present (extensive)	2

LG-ESS=low-grade endometrial stromal sarcoma; N/A=not available.

Table 3:

Immunohistochemical findings in *KAT6B/A::KANSL1* fusion positive uterine sarcomas

No	Desmin	SMA	h-CD	CD10	CyclinD1	ER	PR	Calretinin	Inhibin	CK	WT1
1	-	+	-	-	-	++	+++	-	-	-	-
2	-	++	-	+++	+++	+++	+++	-	-	-	-
3	-	+	-	+++	-	++	+++	-	-	-	-
4	-	-	-	+++	-	N/A	N/A	N/A	N/A	N/A	N/A
5	++	N/A	N/A	+++	N/A	N/A	N/A	++	+	++	+++
6	-	++	-	+	-	+++	+++	N/A	N/A	-	N/A
7	N/A	N/A	N/A	+++	++	+++	+++	++	-	++	+
8	+	+++	+	+++	+	+++	+++	N/A	N/A	++	+++
9	-	+	-	+	++	-	-	N/A	N/A	N/A	N/A
10	-	++	+	+	-	-	-	N/A	N/A	N/A	N/A
11	+++	+	N/A	+	N/A	+++	+++	+	-	-	N/A
12	-	-	-	+	-	-	-	-	N/A	+	N/A
13	+	+	-	+++	+	+++	+++	-	-	+	+++

+=<25%, ++=25–50%, +++=>50%, h-CD: h-caldesmon, N/A: not available

Key points

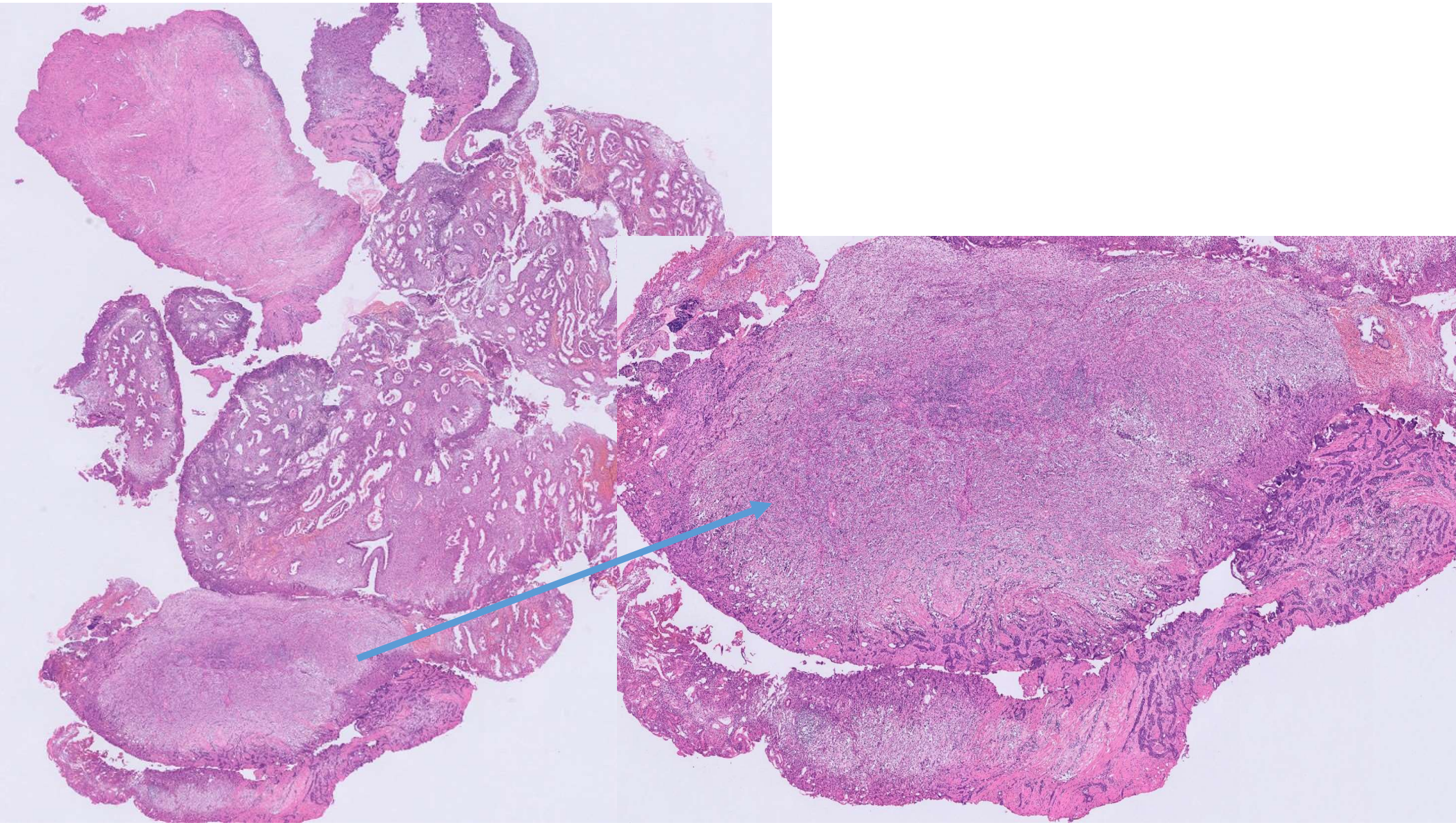
- **Endometrial stromal neoplasm (2020 WHO Classification)**
  - **Endometrial stromal nodule**
  - **Low grade endometrial stromal sarcoma**
  - **High grade endometrial stromal sarcoma**
  - **Undifferentiated uterine sarcoma**

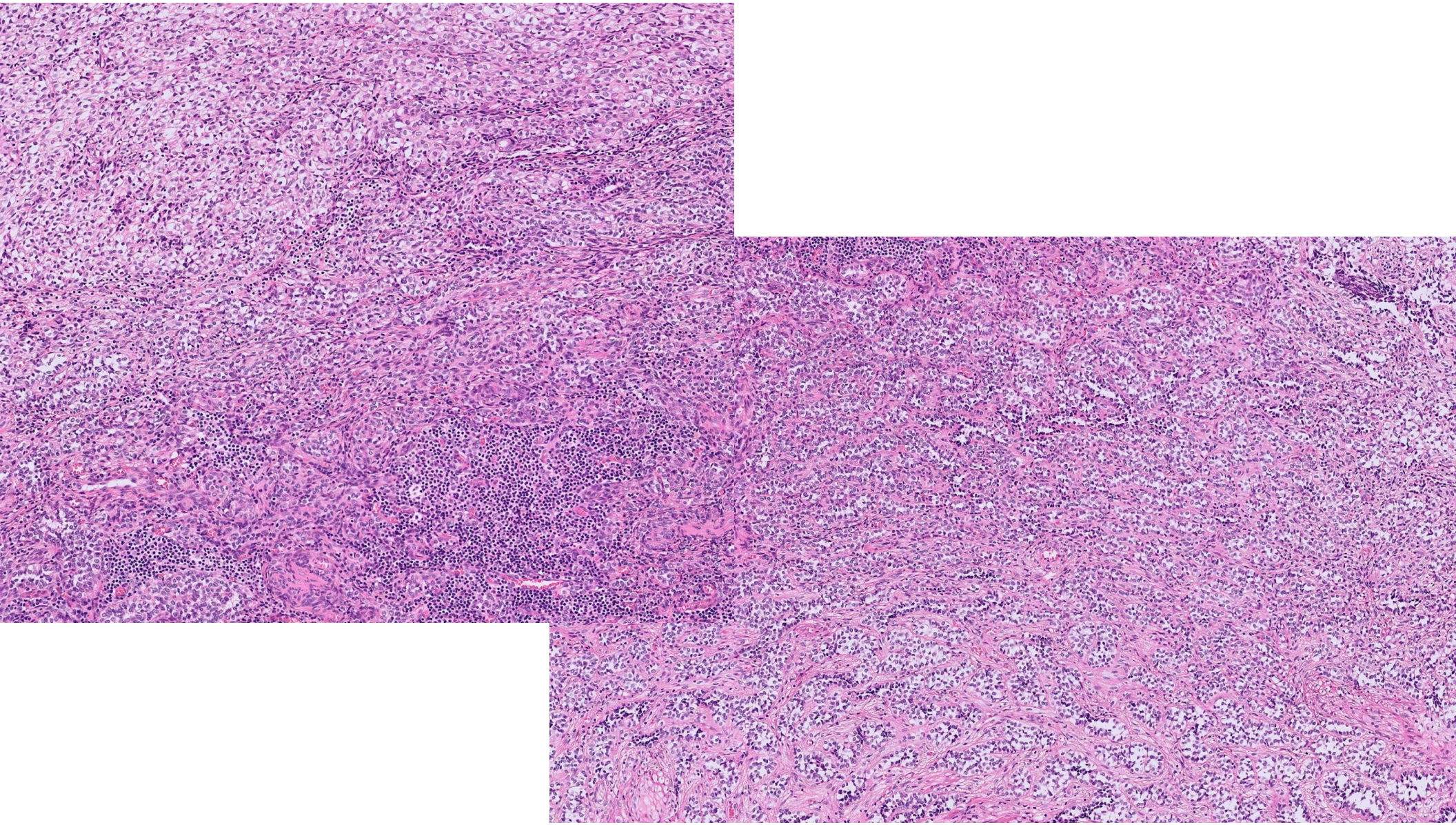
- **Usually LGESS and HGESS show classic histologic features and immunohistochemical profile of each**

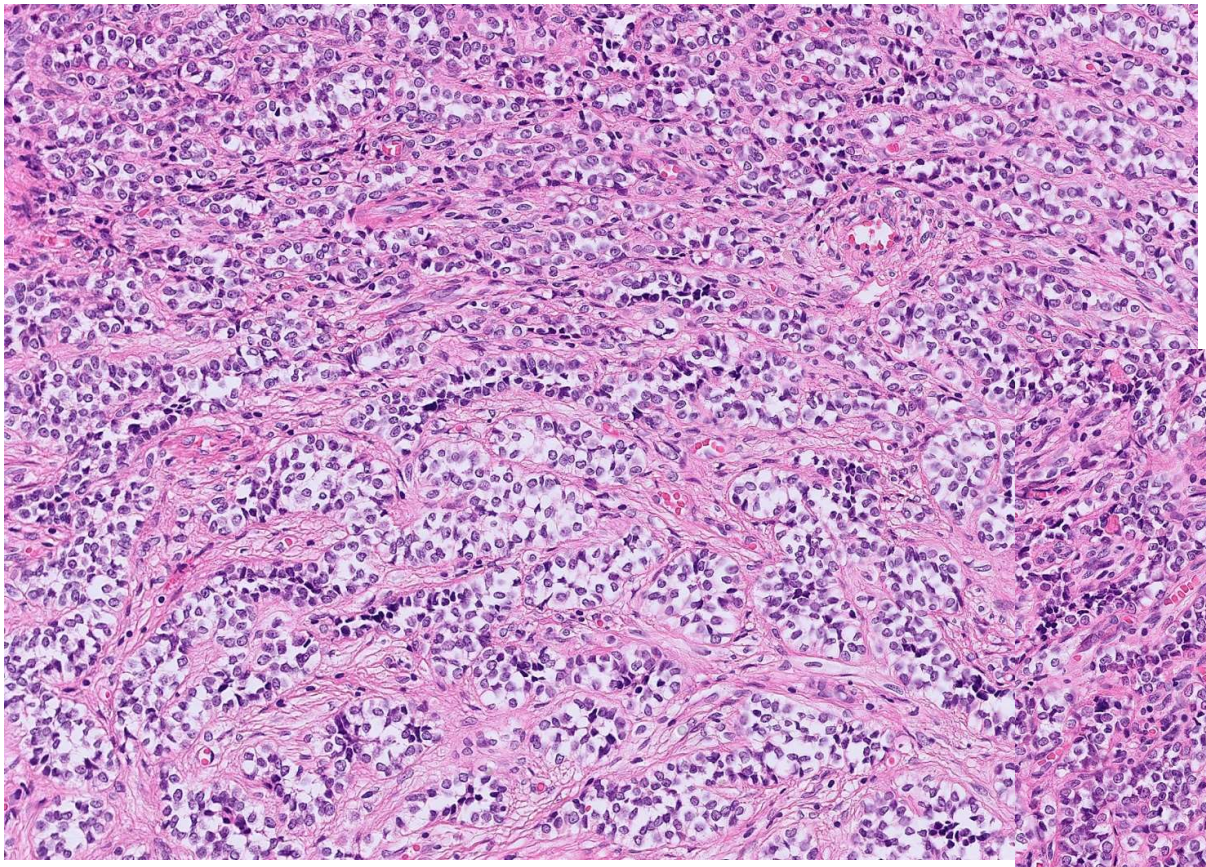
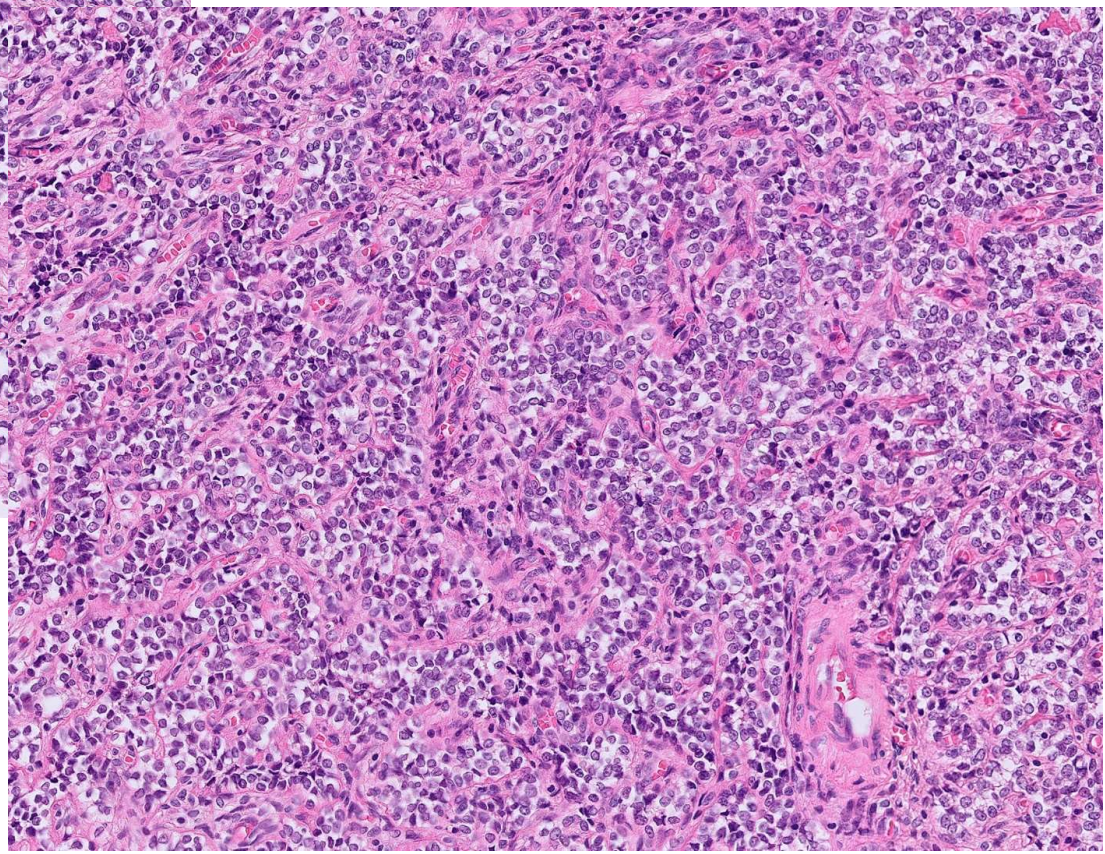
- **In cases showing overlapping features, molecular subtyping can render accurate diagnosis: It helps to be aware of histologic and immunohistochemical features of each molecular subtypes**

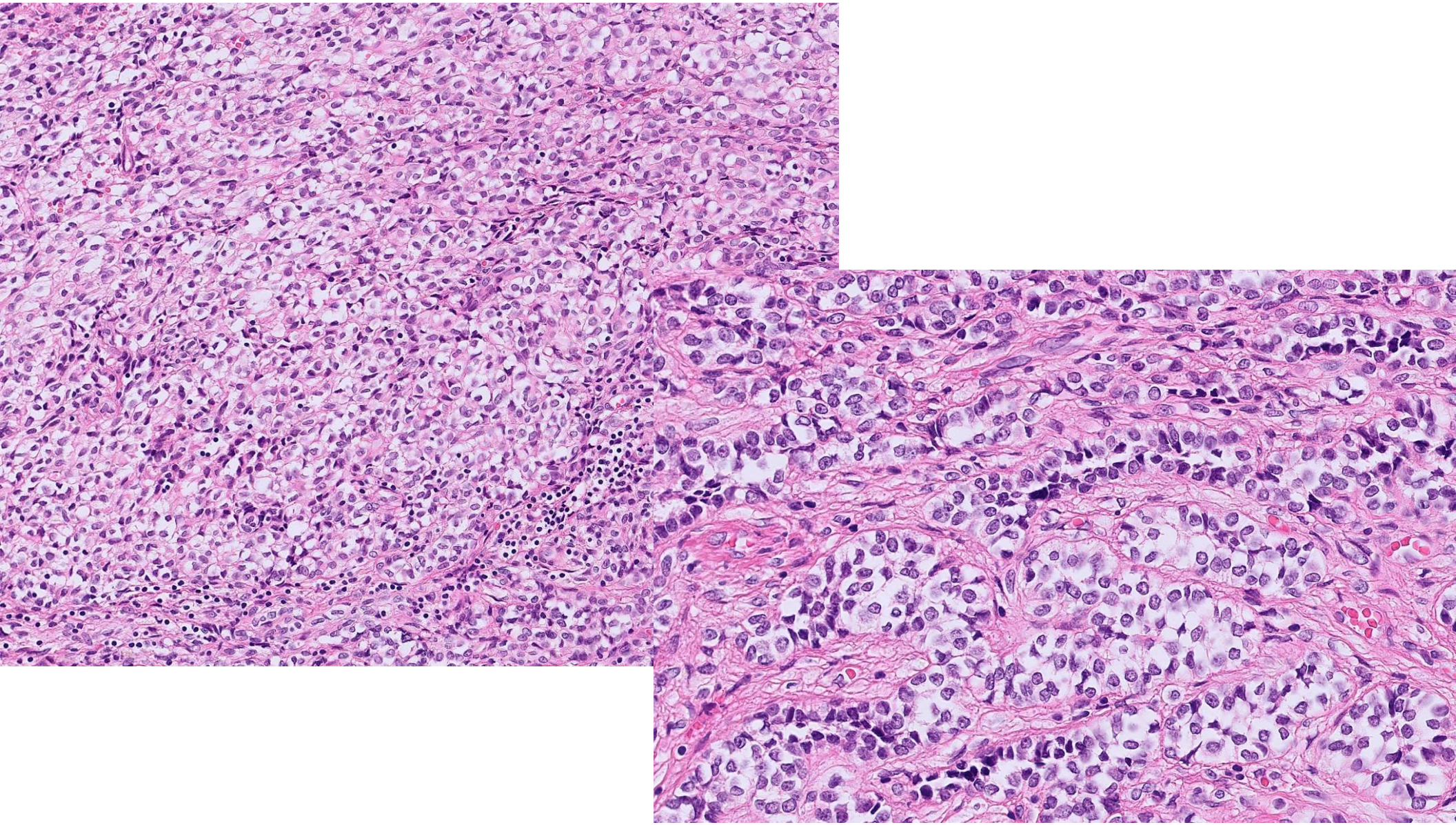
Case 2.

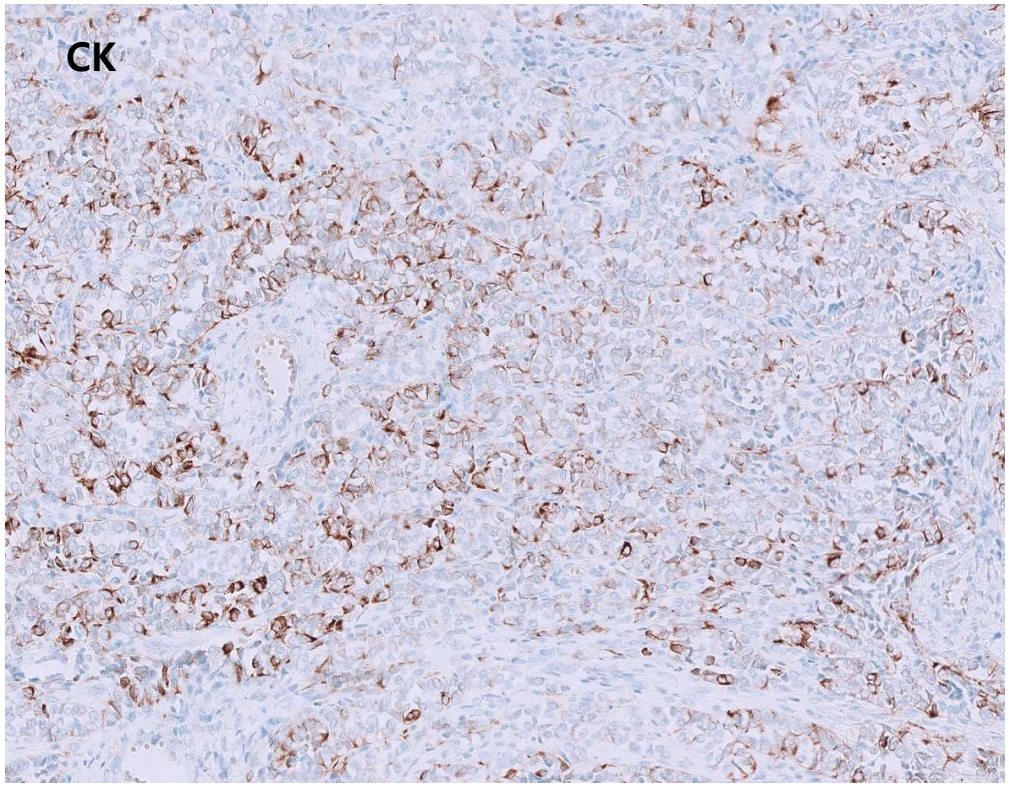
- **47/F**
- **Referred for endocervical polypectomy**
- **Ultrasonography: endometrium 1.27cm, homogeneous echogenicity**

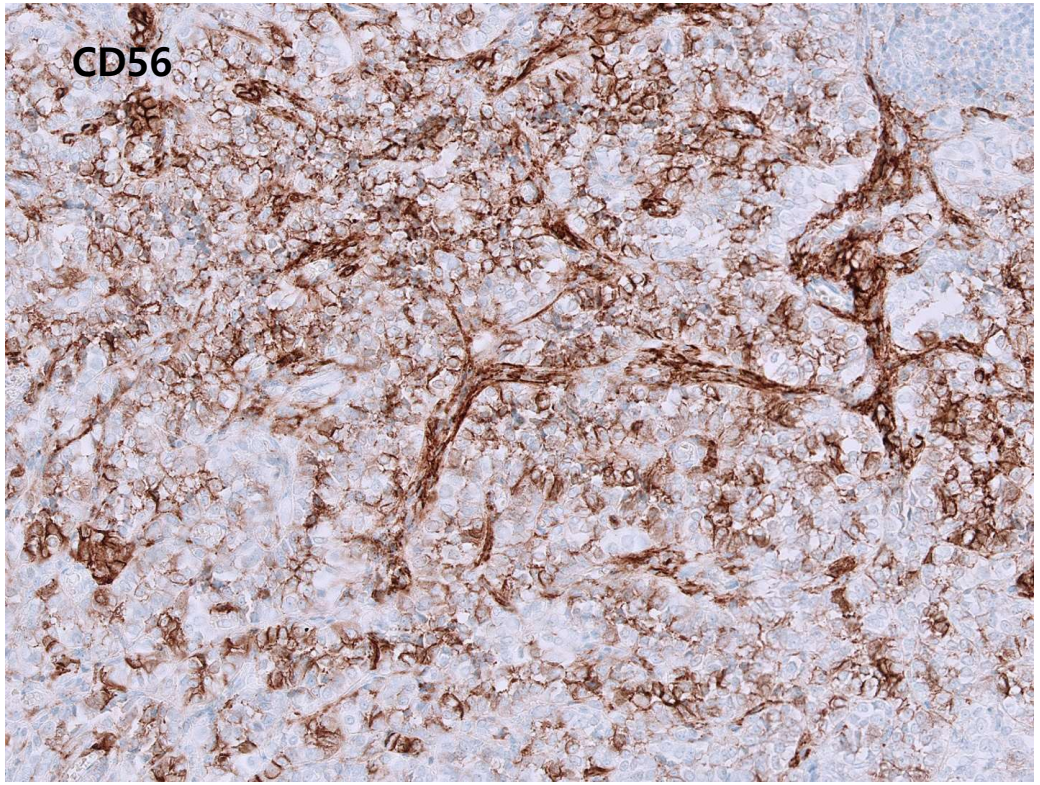







CK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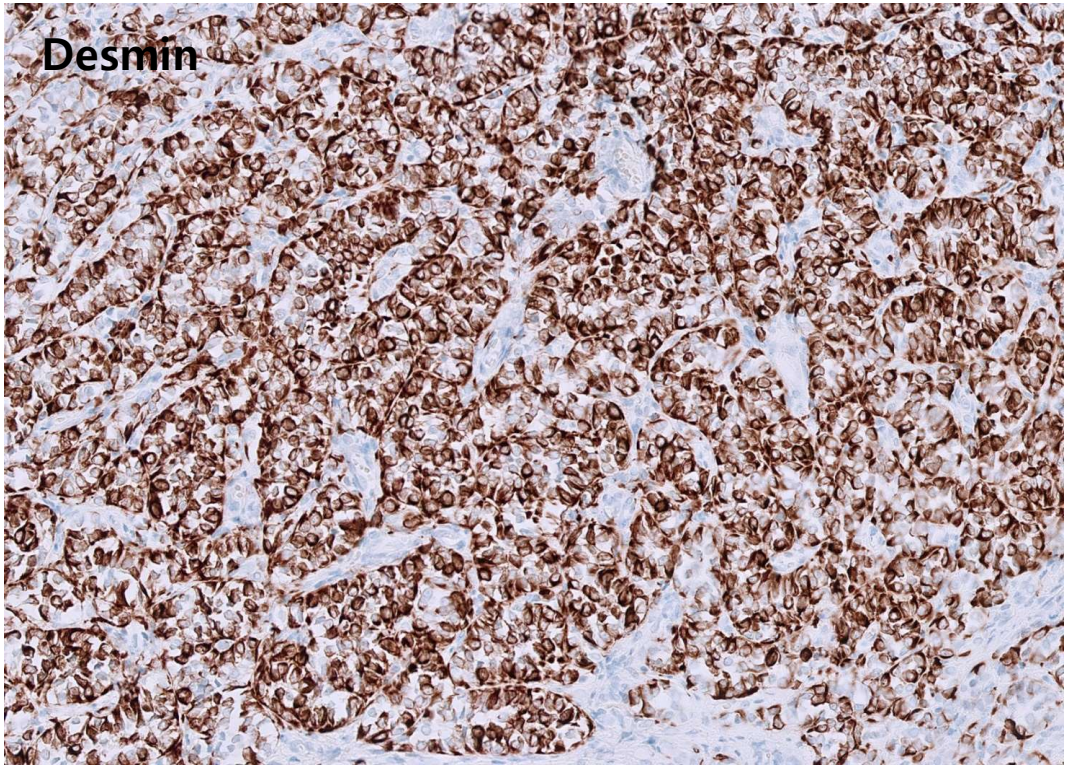
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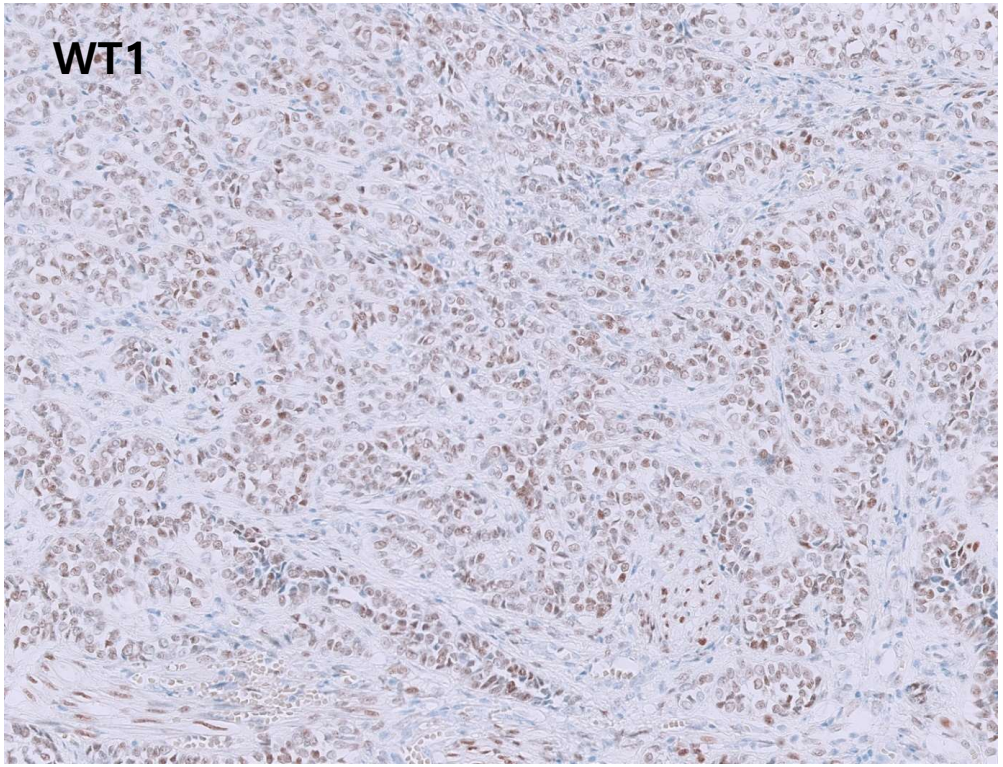
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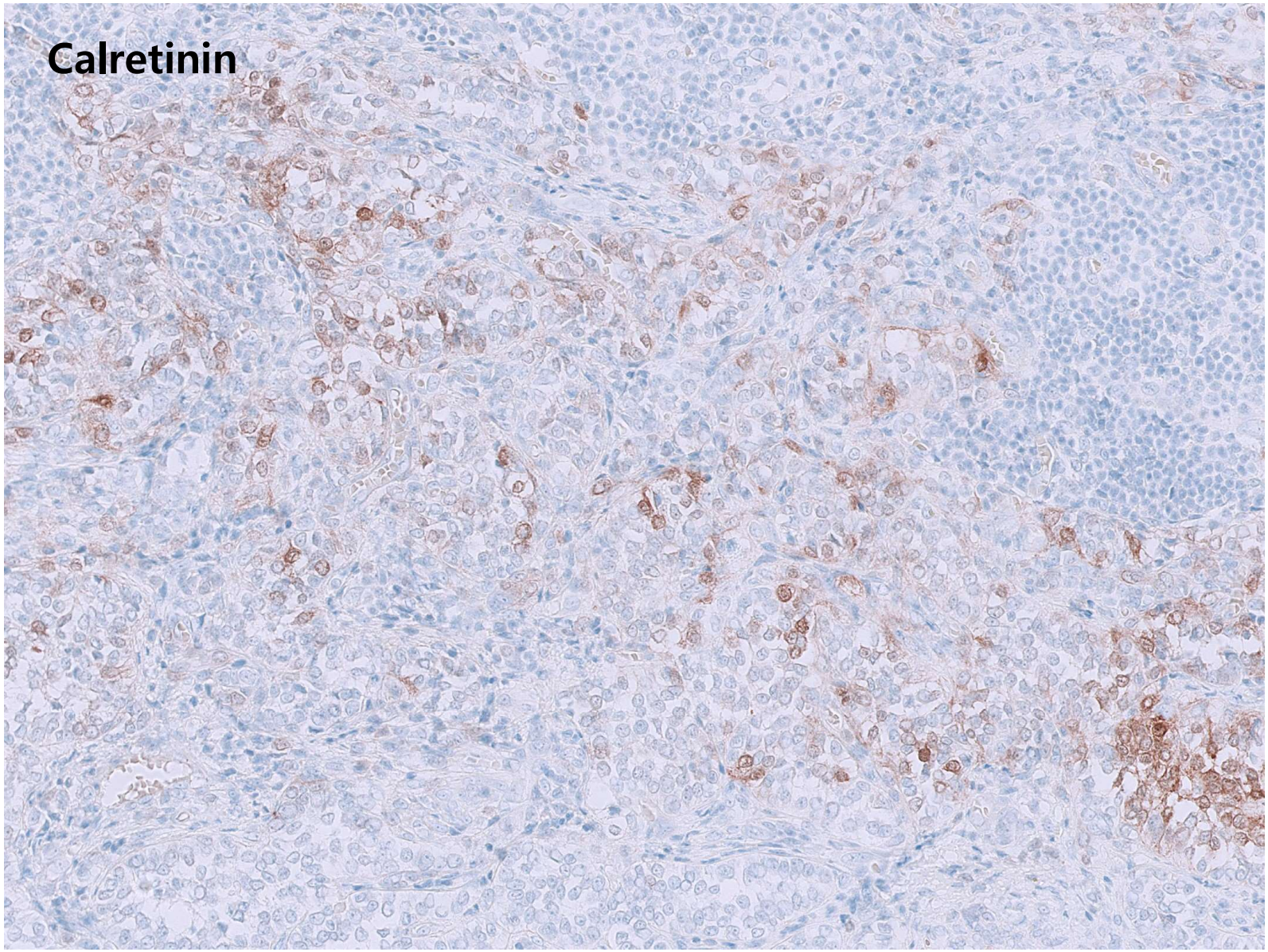
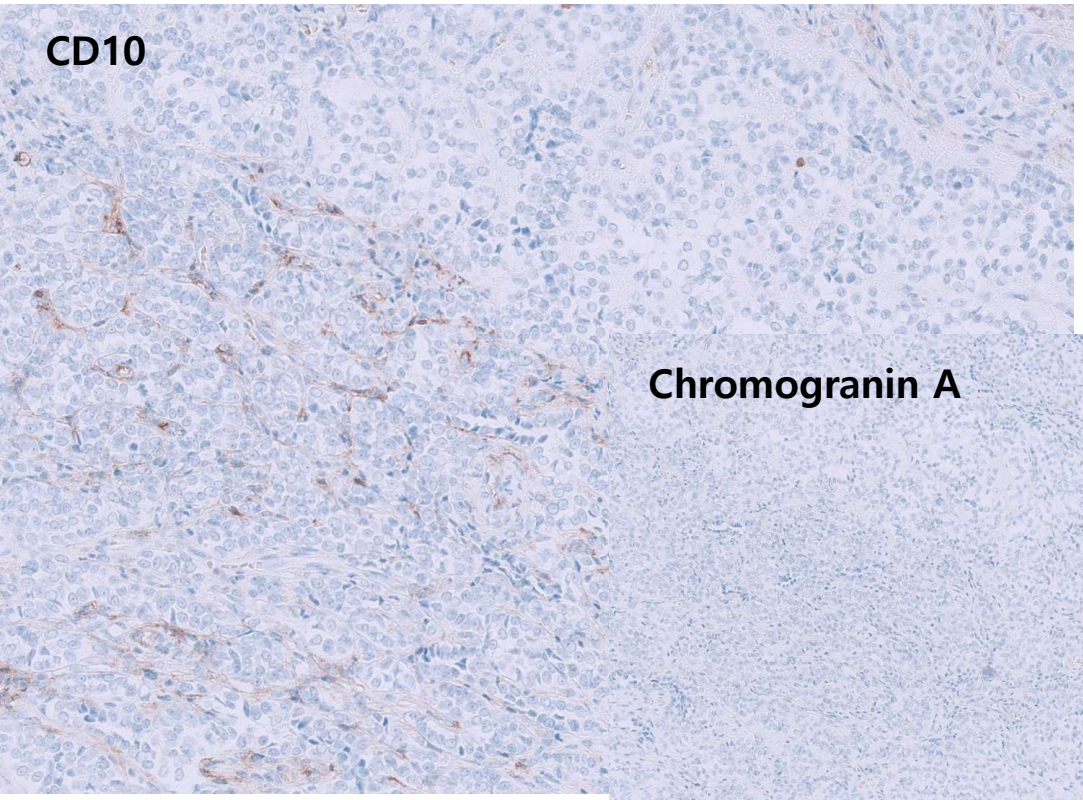
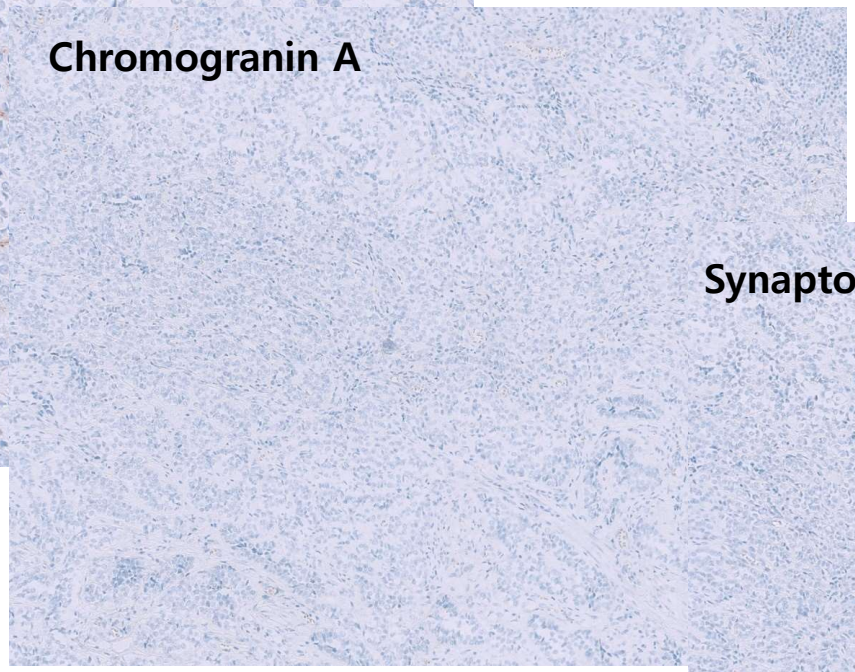
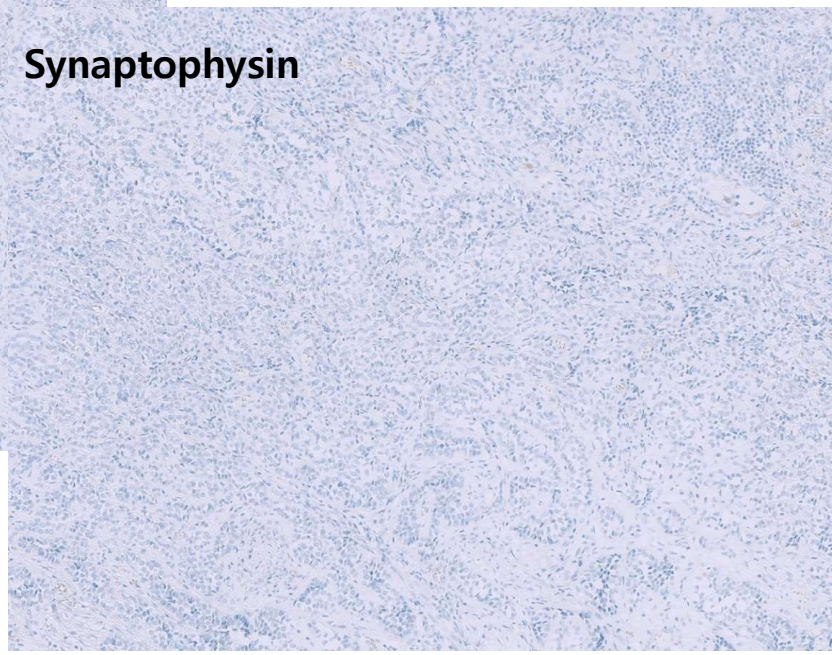

Calretinin


CD10


Chromogranin A


Synaptophysin

Immunoprofile of the tumor

Positive

- CD56
- Desmin
- WT1

- CK(AE1/3)
- Calretinin

Negative

- Synaptophysin
- Inhibin-alpha
- Chromogranin A
- CD10

Differential diagnosis

- **CD10 –**

Endometrial stromal neoplasm:

- **LGESS with sex cord-like differentiation**
- **HGESS with YWHAE and BCOR mutations**

- **CK +**

Leiomyoma

- **Desmin +**

Epithelial neoplasm:

- **Adenosarcoma with sex cord-like differentiation**
- **Corded and hyalinised or sertoliform endometrioid adenocarcinoma.**

Final diagnosis

Uterine tumor resembling ovarian sex cord tumor (UTROSCT)

UTROSCT

- Uterine neoplasm with morphological patterns that resemble those seen in ovarian sex cord tumors without recognizable endometrial stroma

- <1% of uterine mesenchymal tumors
- Middle aged women

- Hypothesized to arise from pluripotent mesenchymal, endometrial stromal, or displaced ovarian sex cord cells

- Pathogenesis uncertain

Immunoprofile of UTROSCT

Sex-cord markers

- Inhibin
- Calretinin
- WT1
- CD56
- CD99
- SF1
- FOXL2
- Melan A

Epithelial markers

- CK
- EMA

ER/PR

CD10

Smooth muscle markers

- Actin
- Desmin
- h-caldesmon

Molecular alteration of UTROSCT

- *ESR1* or *GREB1*
- *NCOA1*
- *NCOA2*
- *NCOA3*
- *CTNNB1*
- *NR4A3*
- *SS18*

- No *JAZF1-SUZ12*

(LGESS)

- No *FOXL2 alterations*

(Adult granulosa cell tumor)

- No *DICER1 alterations ZC3H7B-BCOR*
- (Sertoli-Leydig cell tumor)

Histopathology

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REVIEW

Uterine mesenchymal tumours: recent advances

Amir Momeni-Boroujeni & Sarah Chiang
Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY, USA

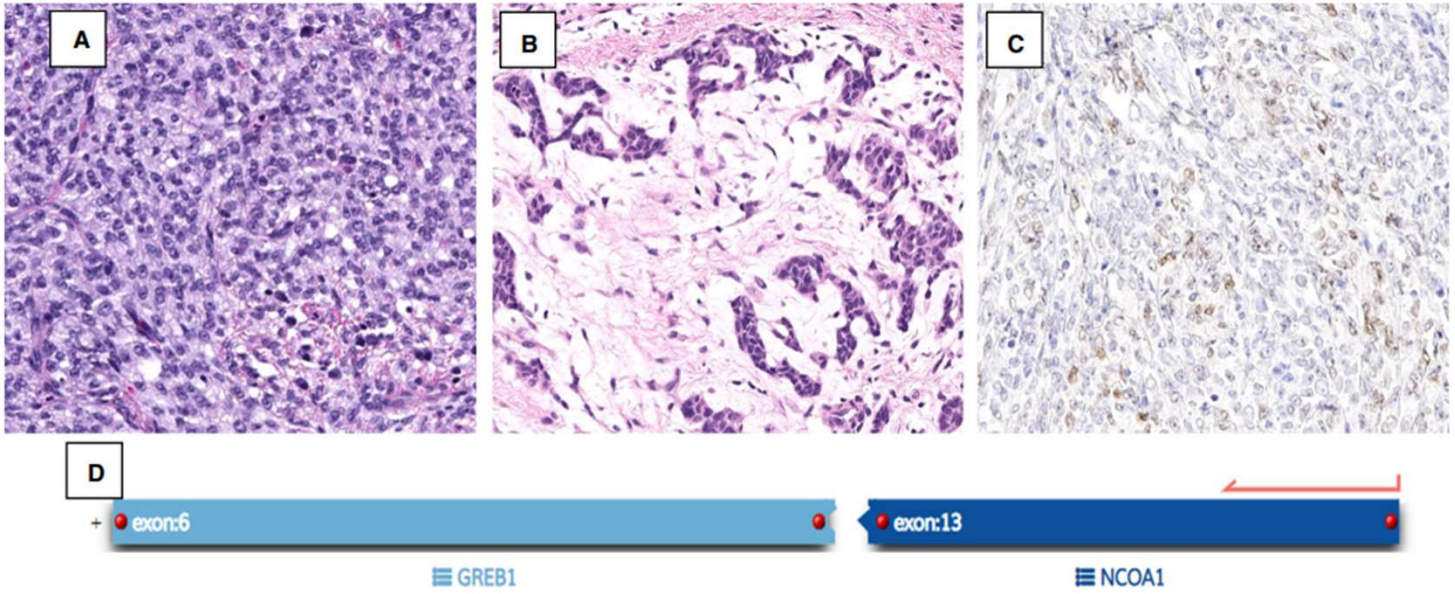


Figure 5. Uterine tumour resembling ovarian sex cord tumour (UTROSCT) with *GREB1–NCOA1* fusion. **A**, Epithelioid cells form sheets and (**B**) foci of trabecular and corded growth patterns. **C**, Nuclear FOXL2 staining of variable intensity can be observed. **D**, Fusion of *GREB1* exon 6 and *NCOA1* exon 13 is detected by targeted RNA sequencing.

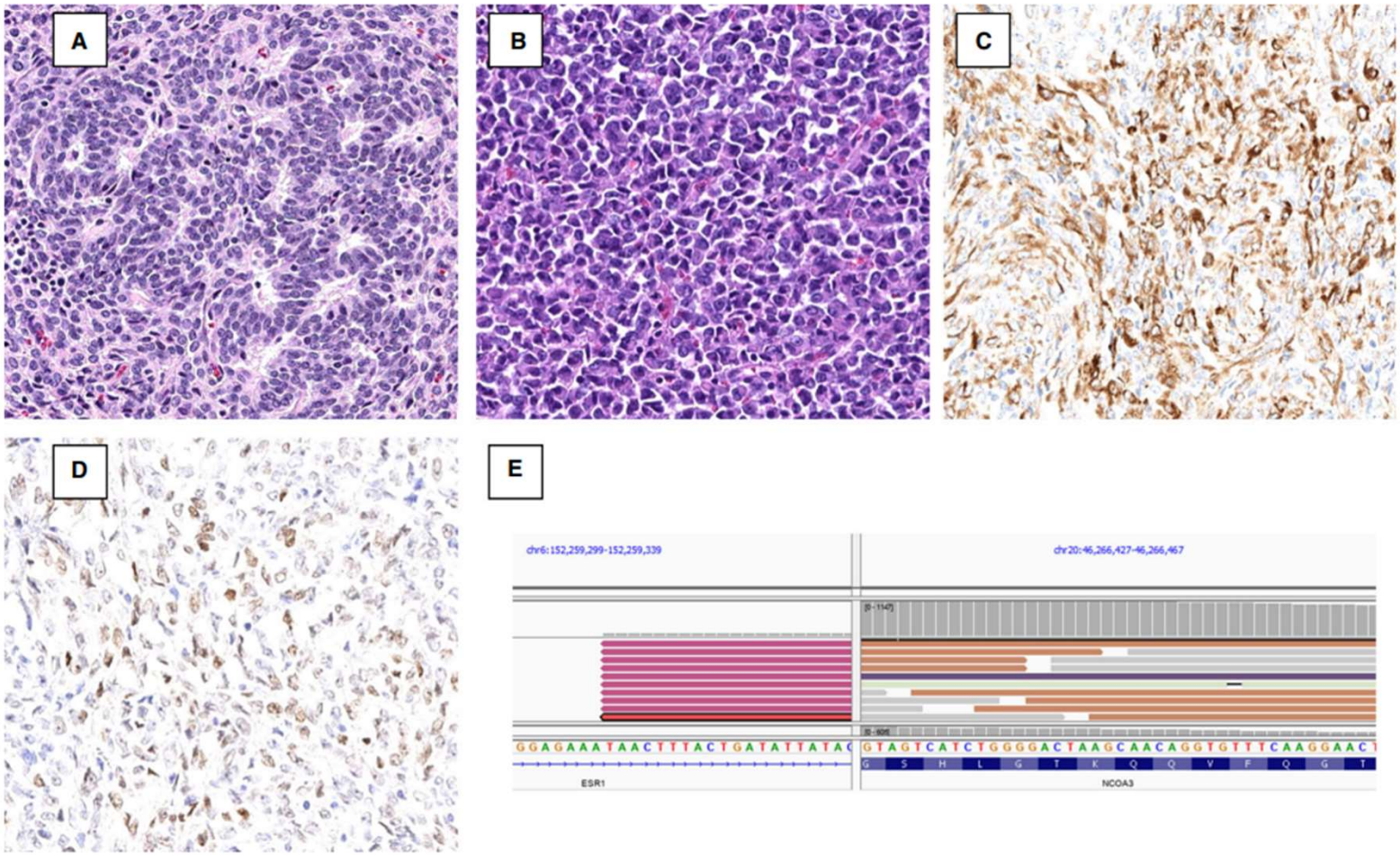


Figure 6. Uterine tumour resembling ovarian sex cord tumour (UTROSCT) with *ESR1–NCOA1* fusion. **A**, Granulosa-like foci is seen in a background of (**B**) epithelioid cells in sheets. **C**, AE1/AE3 and (**D**) FOXL2 expression contributes to a polyphenotypical profile. **E**, Targeted DNA sequencing confirms an *ESR1–NCOA1* fusion.

Molecular alteration of UTROSCT

- ***GREB1***

- *GREB1* fusion-positive UTROSCT are polyphenotypical.
- Positive for ER, PR, CD56 and CD99
- Variably express smooth muscle, epithelial, sex cord, and neuroendocrine markers
- May be positive for CD10, WT1, melan A, c-KIT and b-catenin.
- Negative for h-caldesmon, HMB45, S100, myogenin and SALL4 expression.
- Cyclin D1 expression in < 50% of tumour cells is infrequent and BCOR staining is absent

- ***ESR1***

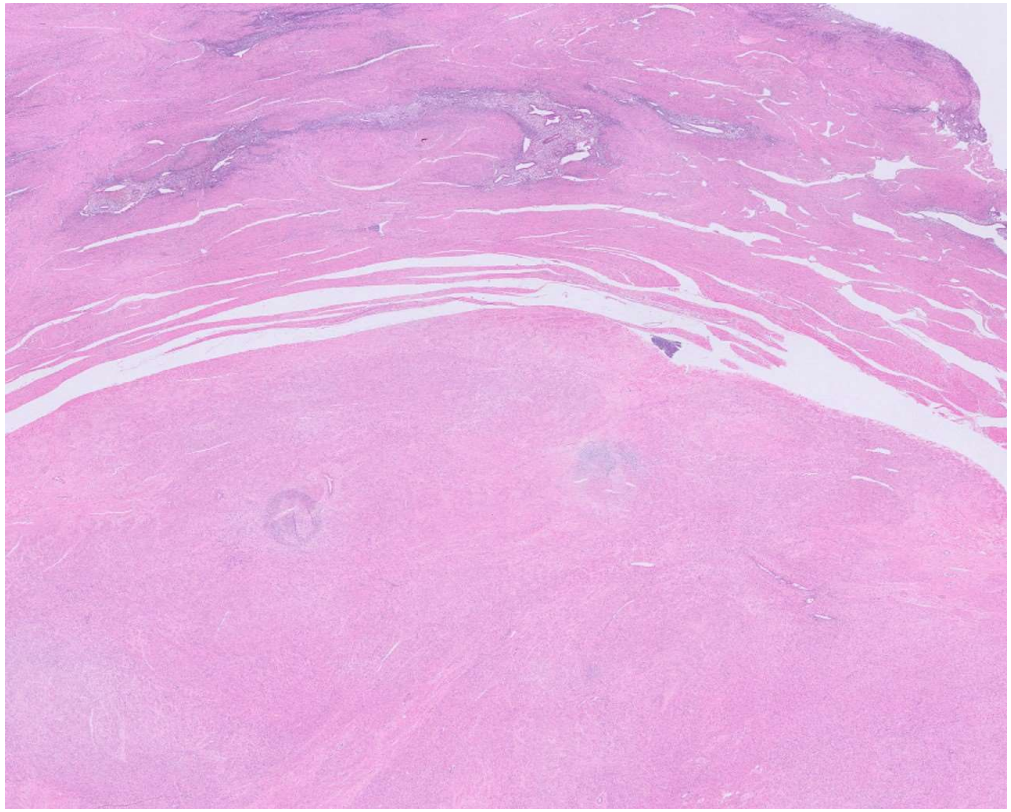
- Exhibit unequivocal sex-cord elements such as Sertoli- and granulosa-like epithelioid cells with small vesicular nuclei
- Mitotic figures rare
- Necrosis absent
- Positive for calretinin, inhibin, WT1, CD56, CD99, AE1/AE3 and, less commonly, melan-A.

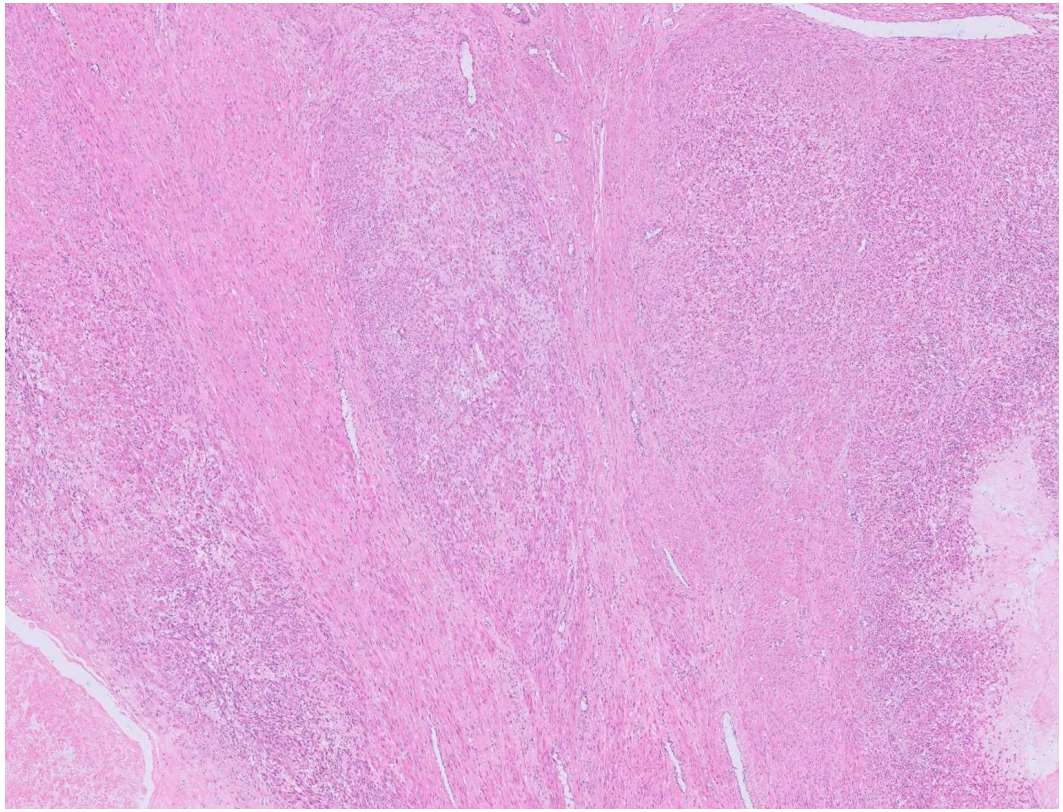
Malignant UTROSCT

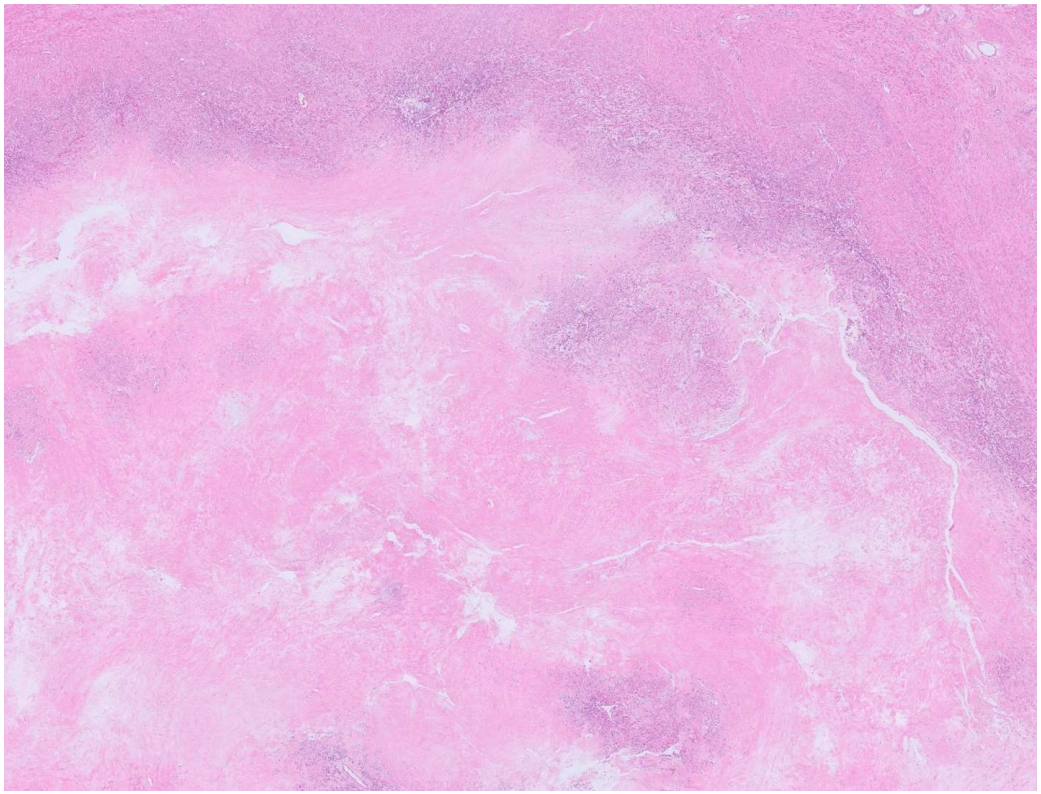
- Approximately 24% of UTROSCT
- Necrosis and a mitotic index of ≥2/10 HPF (≥1/ mm2)
- May include GREB1 fusion-positive tumors
- Clinical behavior is difficult to predict, given the considerable morphological and immunohistochemical overlap among UTROSCT regardless of fusion status.

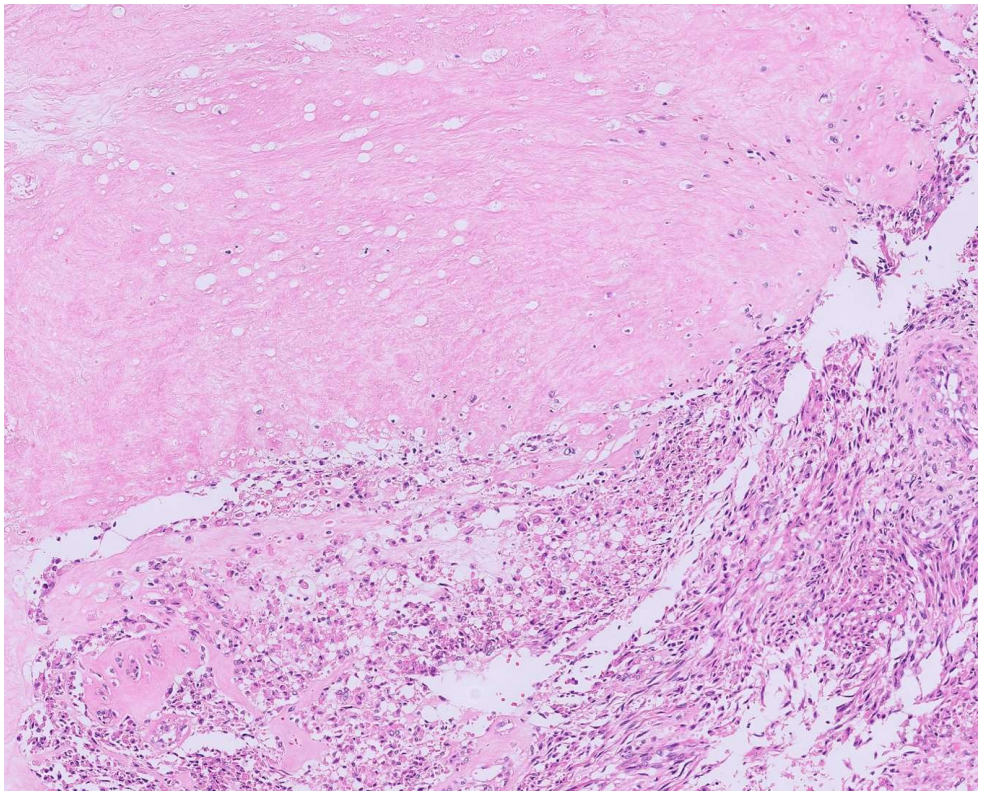
Case 3.

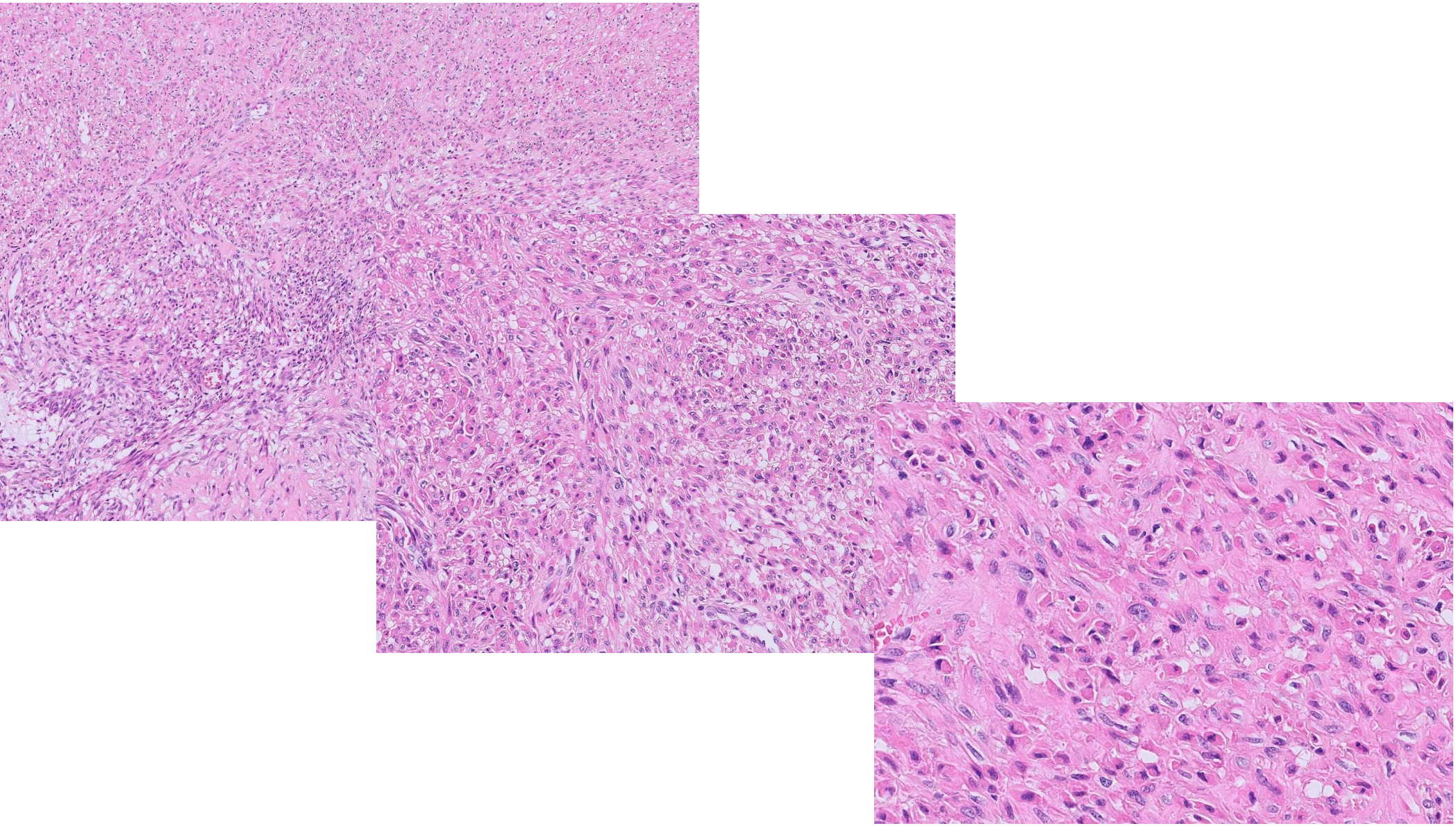
- 49/F
- Referred for total laparoscopic hysterectomy for removal of leiomyomas

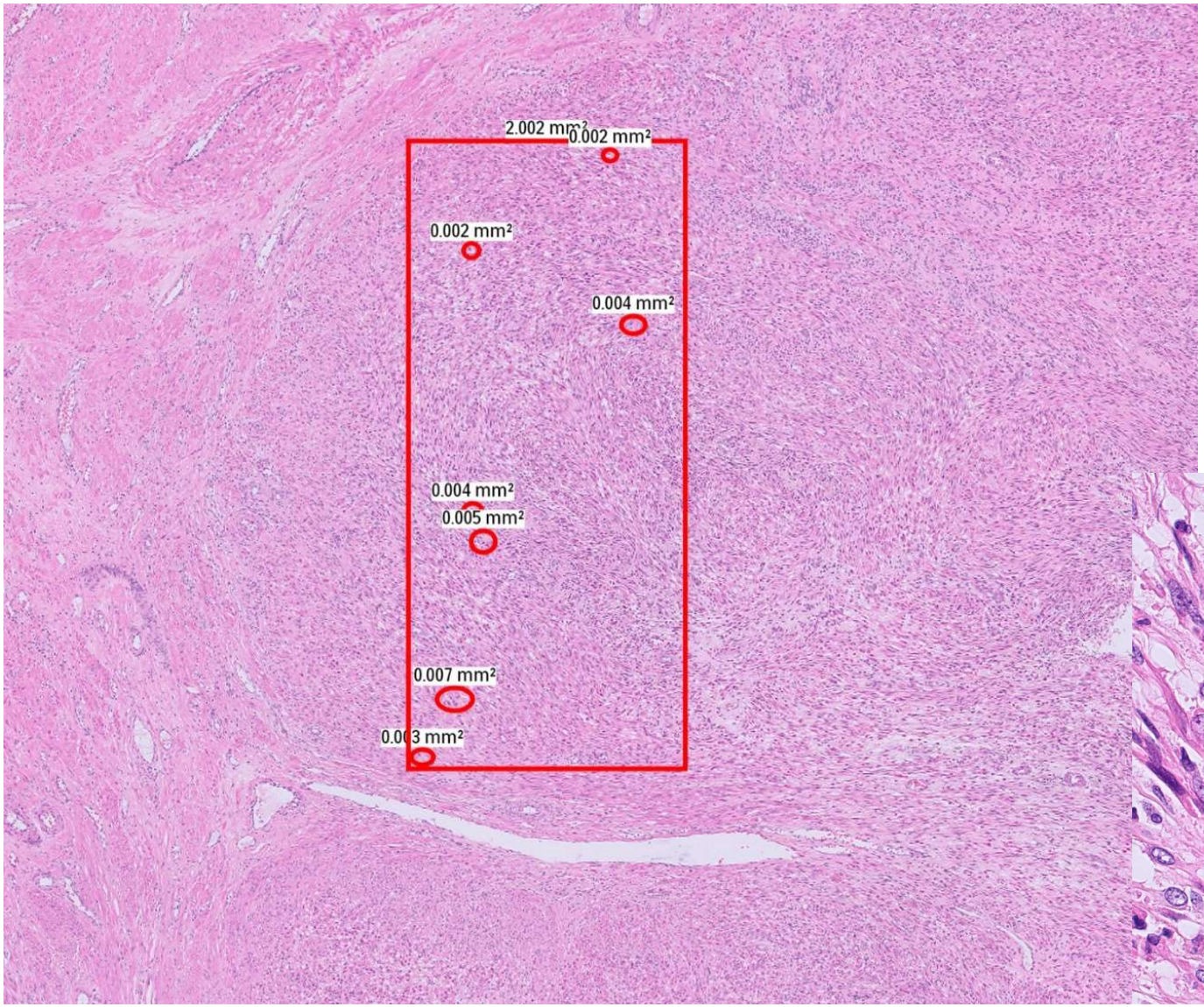


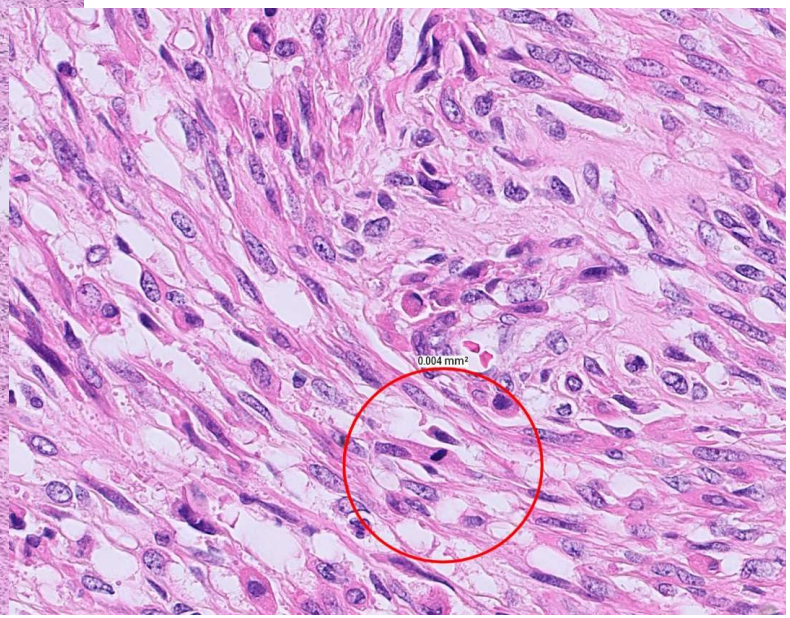


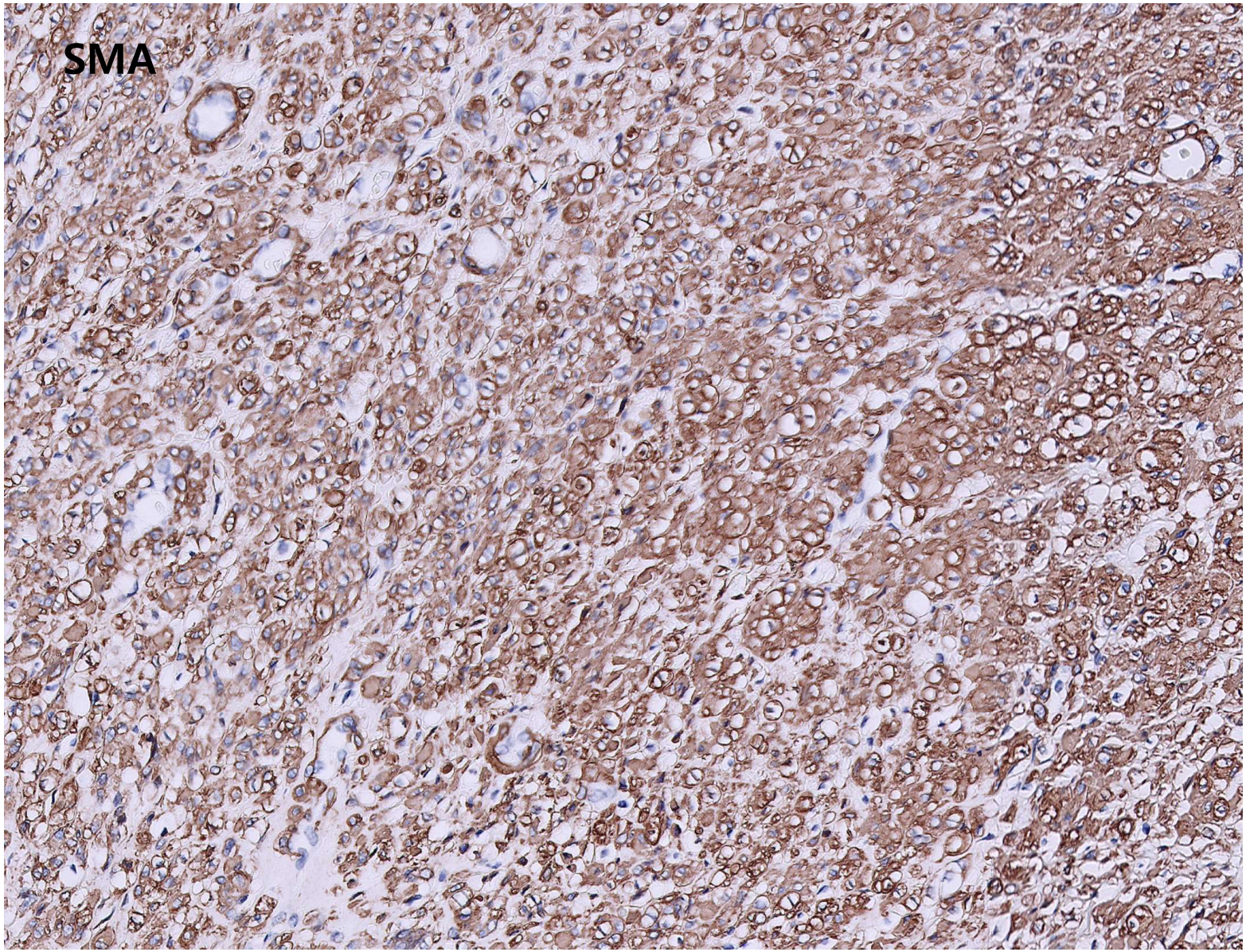


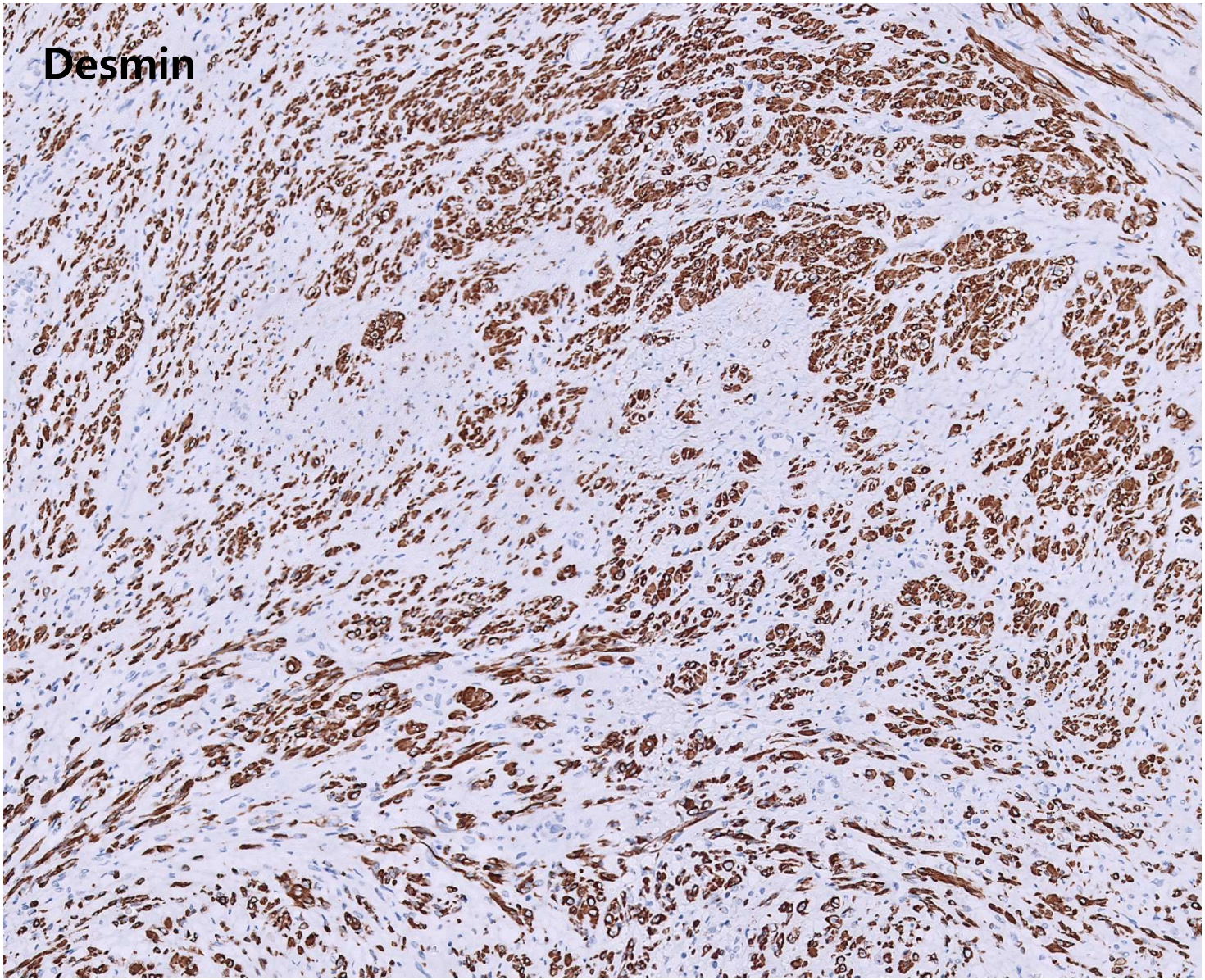


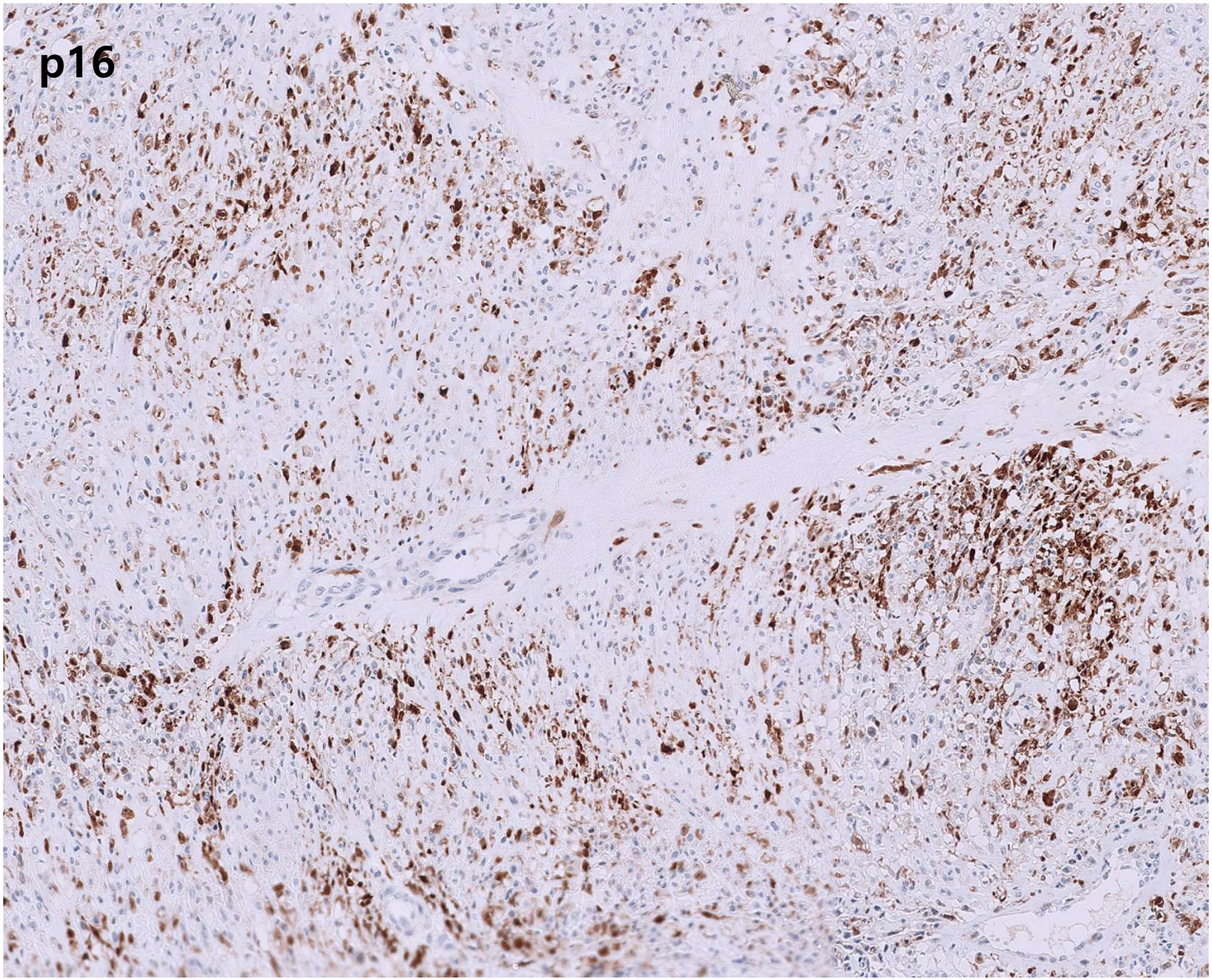



2.002 mm²
0.002 mm²
0.002 mm²
0.004 mm²
0.004 mm²
0.005 mm²
0.007 mm²


0.004 mm²


SMA


Desmin


p16

Diagnostic work-up

Leiomyoma VS. **Leiomyosarcoma**

Assessment of
- **Cytologic atypia**
- **Tumor cell necrosis**
- **Mitoses**

Diagnostic work-up: Essential criteria

Conventional

: 2 or more

- Marked atypia
- Tumor cell necrosis
- $\geq$ 4 mitoses / mm^2

Epithelioid

: 1 or more

- Moderate to severe atypia
- Tumor cell necrosis
- $\geq$ 1.6 mitoses / mm^2

Myxoid

: 1 or more

- Moderate to severe atypia
- Tumor cell necrosis
- $\geq$ 0.4 mitoses / mm^2
- Infiltrative borders / irregular margins

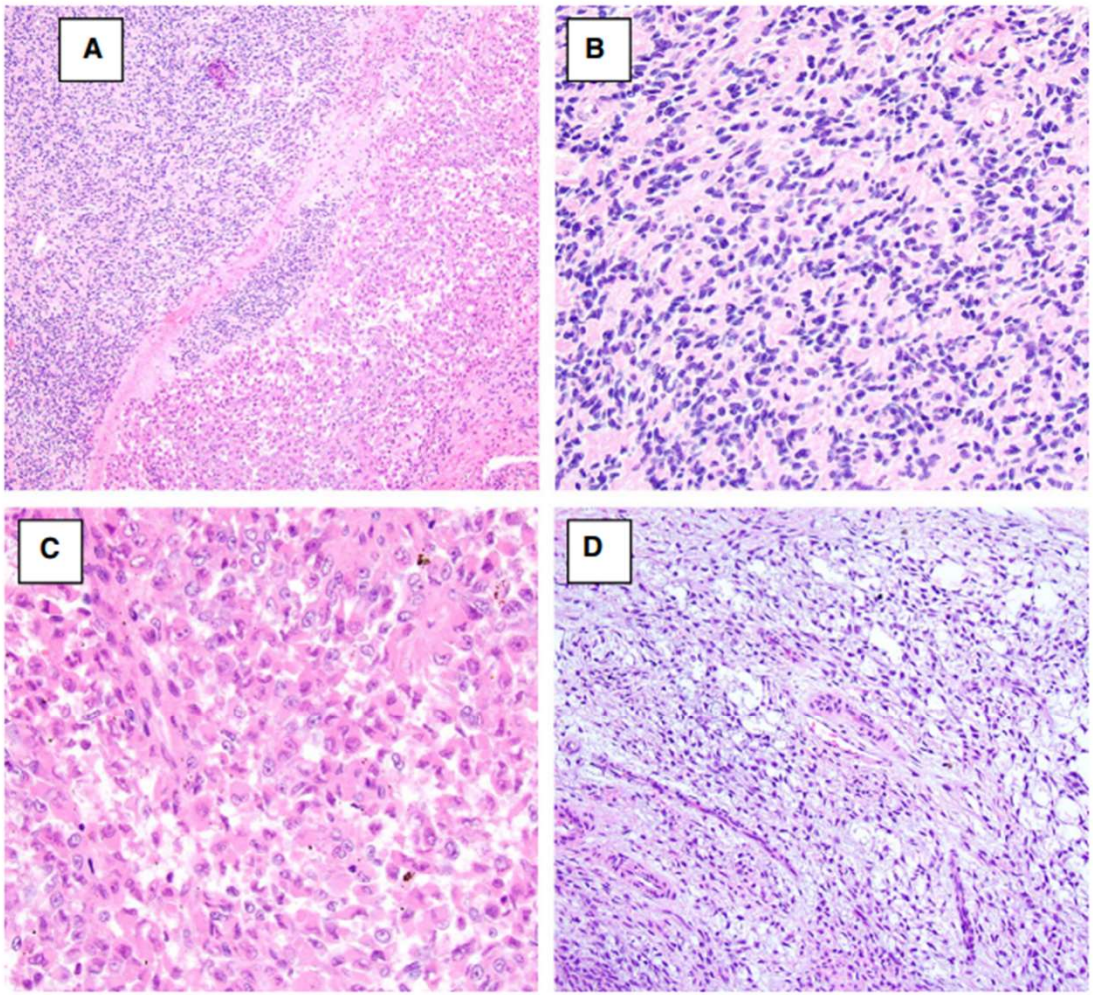
Final diagnosis

LEIOMYOSARCOMA, EPITHELIOID TYPE, with hyalinization

- ◇ Size of the tumor: 3.5cm
- ◇ Mitoses: 5/10HPF (2.4mm2)
- ◇ Cytologic atypia: Moderate
- ◇ Tumor cell necrosis: Not identified
- ◇ Vascular invasion: Not identified
- ◇ Additional finding: Adenomyosis

Epithelioid leiomyosarcoma

- Predominant epithelioid appearance (>50%)
- Round or polygonal cells with eosinophilic or clear cytoplasm
- Rhabdoid or signet-ring cell like
- May occasionally be extensively hyalinized
- Expression of muscle markers can be weak or patchy if poorly differentiated



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REVIEW

Uterine mesenchymal tumours: recent advances

Amir Momeni-Boroujeni & Sarah Chiang
Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Progesterone receptor gene (*PGR*) rearrangement in epithelioid leiomyosarcoma

Figure 7. Epithelioid leiomyosarcoma (LMS) with *NR4A3–PGR* fusion. **A**, Tumours are biphasic and consist of (**B**) a bland spindle cell proliferation associated with (**C**) plump epithelioid and rhabdoid cells with abundant eosinophilic cytoplasm and large vesicular nuclei. **D**, Myxoid matrix may be present.

Targeting the Molecular and Immunologic Features of Leiomyosarcoma

by **Brandon M. Cope** [1,†], **Raymond S. Traweek** [2,†], **Rossana Lazcano** [3], **Emily Z. Keung** [2,4], **Alexander J. Lazar** [3,5], **Christina L. Roland** [2] and **Elise F. Nassif** [6,*]

[1] Department of Surgery, Keesler Medical Center, Biloxi, MS 39534, USA

[2] Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA

[3] Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA

[4] Department of Genomic Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA

[5] UTHealth Houston Graduate School of Biomedical Sciences, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA

[6] Department of Sarcoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA

[*] Author to whom correspondence should be addressed.

[†] These authors contributed equally to this work.

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Table 2. Characterization of LMS as defined by three major molecular subtypes.

LMS Subtype	Prognosis	Mutational Burden	Cellular Lineage	Molecular Characteristics	Gene Expression	Immune Microenvironment
Well-differentiated ST-LMS	Better	Low	Vascular and digestive smooth muscle	*MYOCD* amplification and upregulated muscle-associated transcripts *TP53* mutations	Enriched: PDGFRA, LRRC15, IGF1R	Inflammatory NK cell signature
Dedifferentiated ST-LMS	Poor		Vascular smooth muscle	*DMD* deletion Reduced markers of muscle differentiation *PTEN* loss, overexpression of Akt pathway *RB1* and *TP53* mutations	Enriched: *ACTA1*, *SYNM*, *LMO1*	Higher immune infiltration overall, dominated by M2-Macrophages Higher leukocyte count overexpression
uLMS	Poor		Gynecologic (uterine, vaginal, fallopian tube) smooth muscle	*DMD* expression inhibition *PTEN* loss, overexpression of Akt pathway *TP53* mutations *RB1* fusion and loss of function	Enriched: ESR1, PGR, EMX2	M2 macrophage-dominant

PGR fusion positive

- Necrosis is rare
- lymphovascular invasion may be seen.
- Positive for desmin, ER and PR.
- H-caldesmon staining is rare.
- Negative for CD10, HMB45 and myogenin expression.
- **Demonstrate nuclear monomorphism compared to typical epithelioid LMS that often have marked nuclear pleomorphism.**
- PGR fusion-positive sarcomas appear to have indolent behaviour.