



The British Association of Gynaecological Pathologists

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**The British Association of
Gynaecological Pathologists**

Vulvo-Vaginal Update Course

Vulvovaginal Mesenchymal Lesions: Old Phenotypes, New Pitfalls

Aarti E. Sharma, MD

Brigham and Women's Hospital/Harvard Medical School

November 29, 2024



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Vulvo-Vaginal Update Course

Vulvovaginal Mesenchymal Lesions: Old Phenotypes, New Pitfalls

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I have no financial conflicts of interest to disclose

Anogenital Mesenchyme: Cellular Lineages

- Myofibroblastic/Fibroblastic
- Smooth Muscle
- Adipocytic
- Nerve Sheath
- Endothelial
- Uncertain Differentiation

Anogenital Mesenchyme: Impressions (‘Phenotypes’)

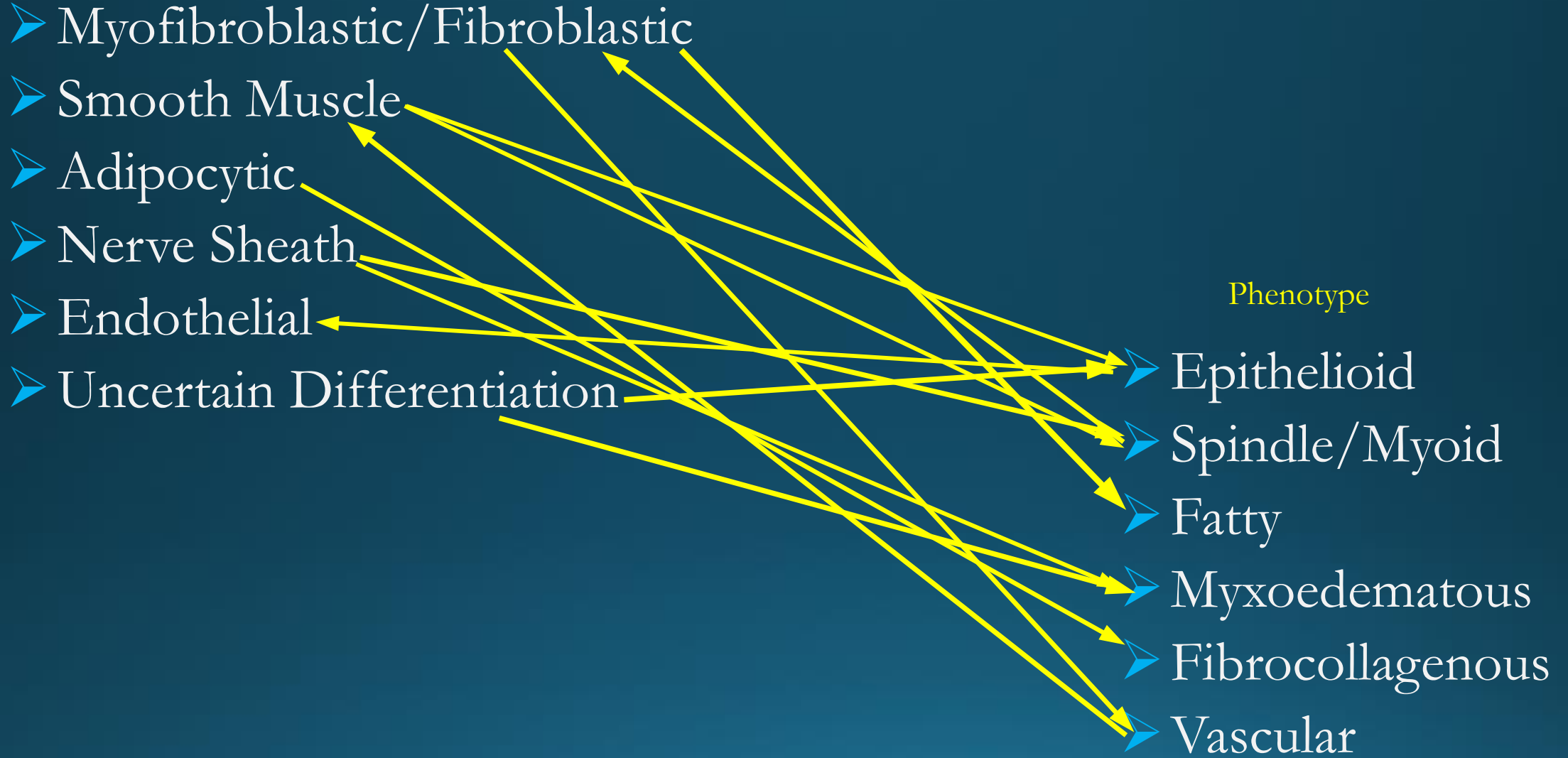
- Epithelioid
- Spindle/Myoid
- Fatty
- Myxoedematous
- Fibrocollagenous
- Vascular

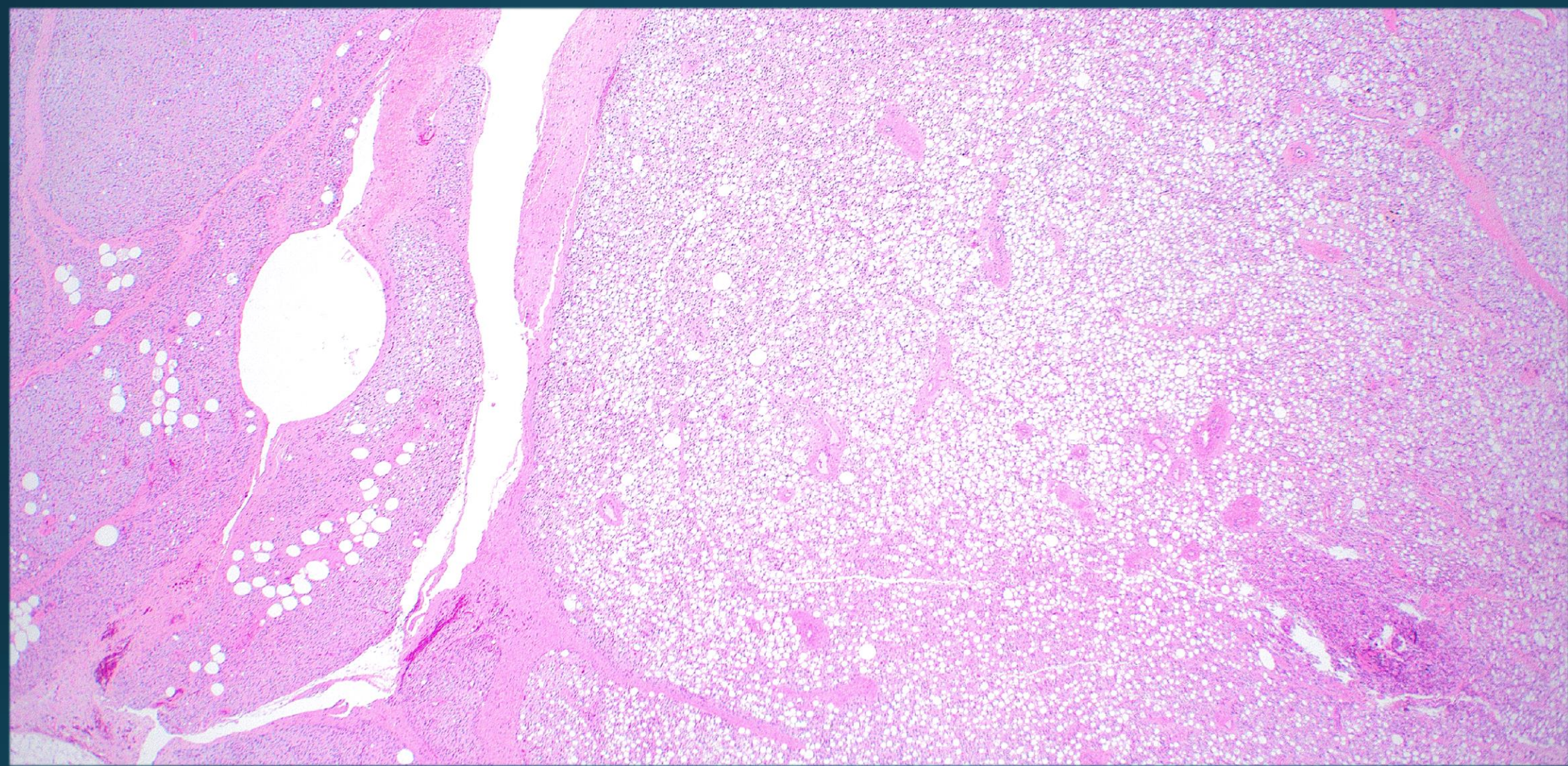
Lineage

- Myofibroblastic/Fibroblastic
- Smooth Muscle
- Adipocytic
- Nerve Sheath
- Endothelial
- Uncertain Differentiation

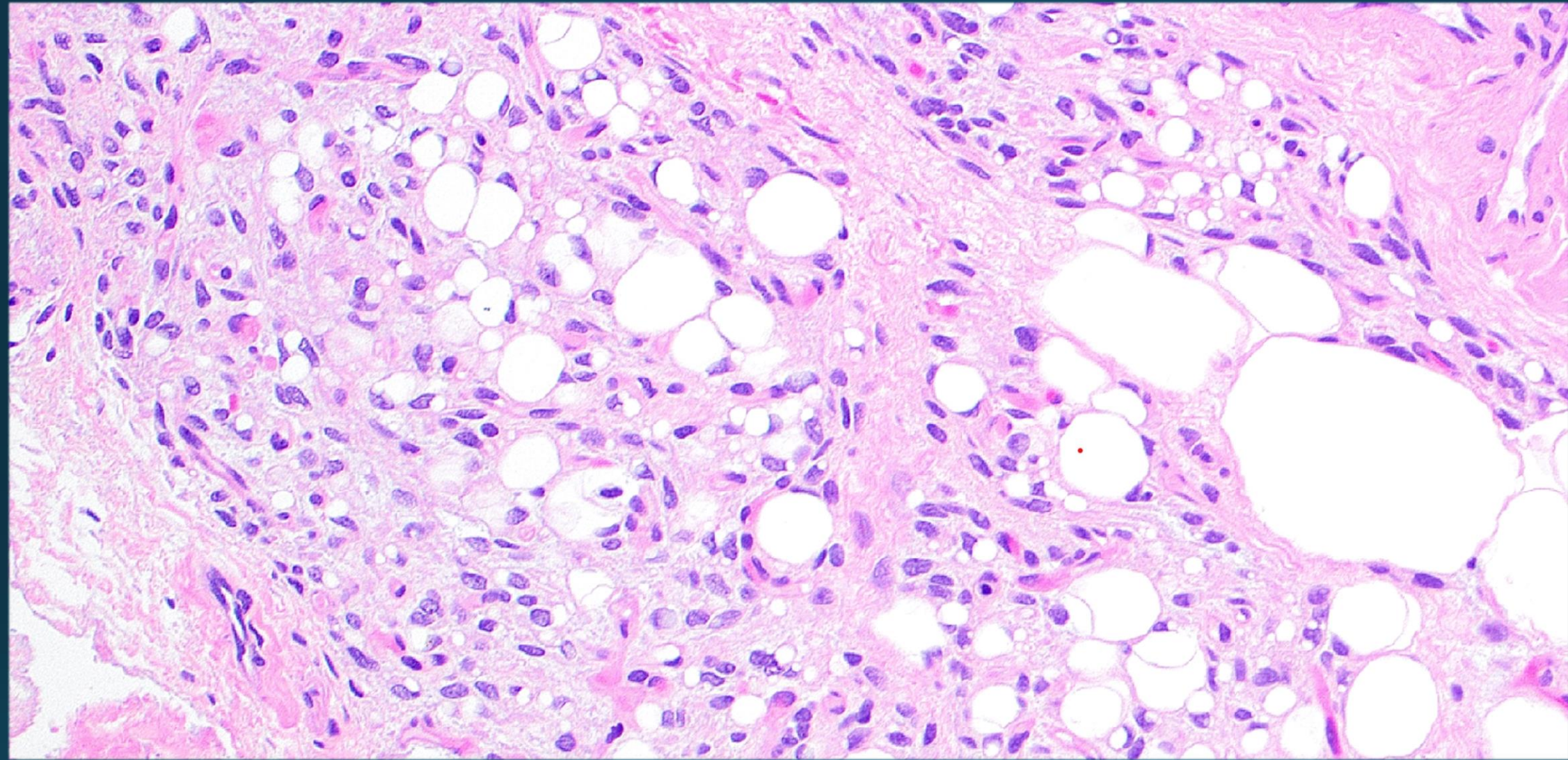
Phenotype

- Epithelioid
- Spindle/Myoid
- Fatty
- Myxoedematous
- Fibrocollagenous
- Vascular





35-year-old obese female,
13 cm perineal mass

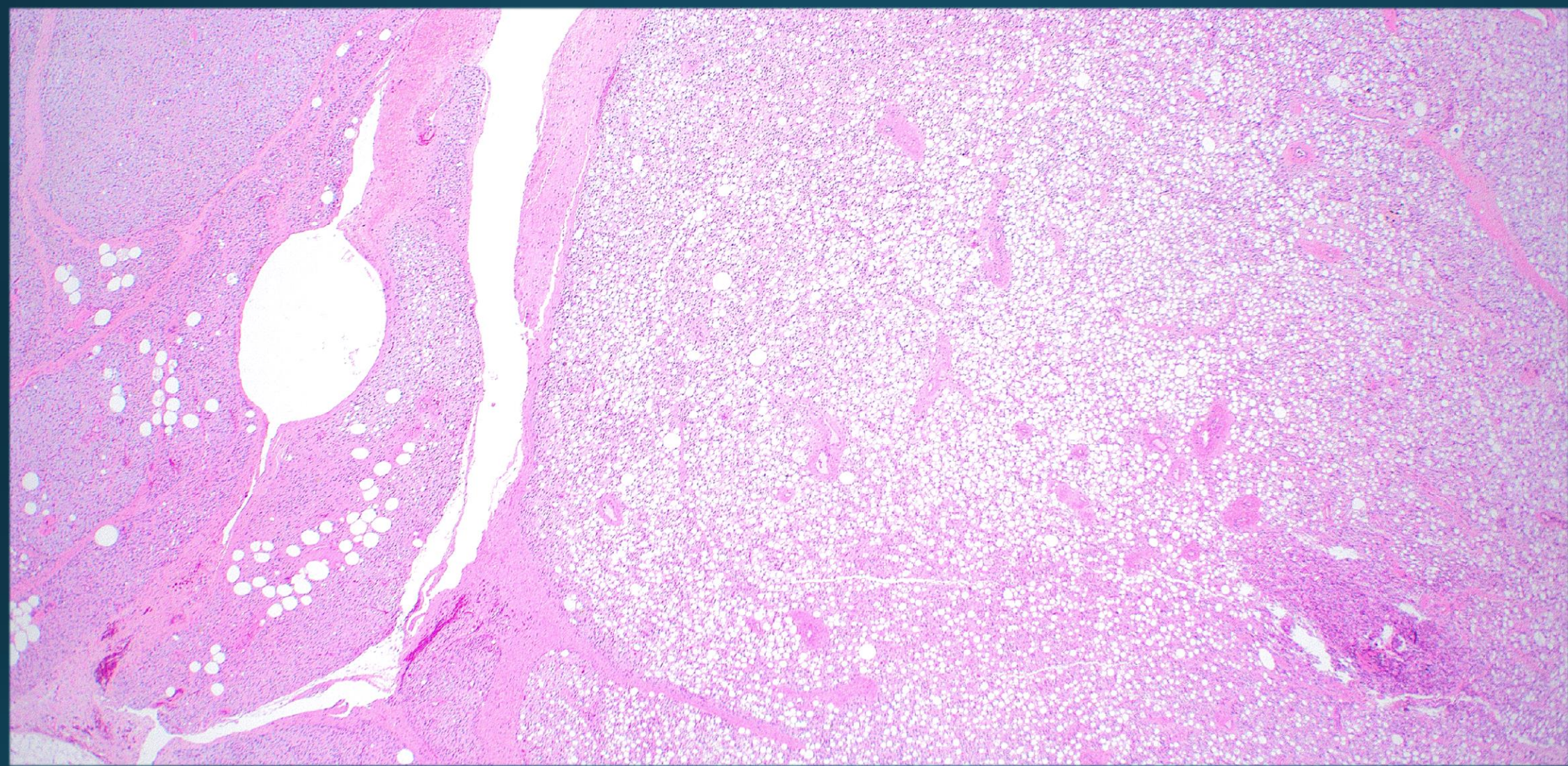


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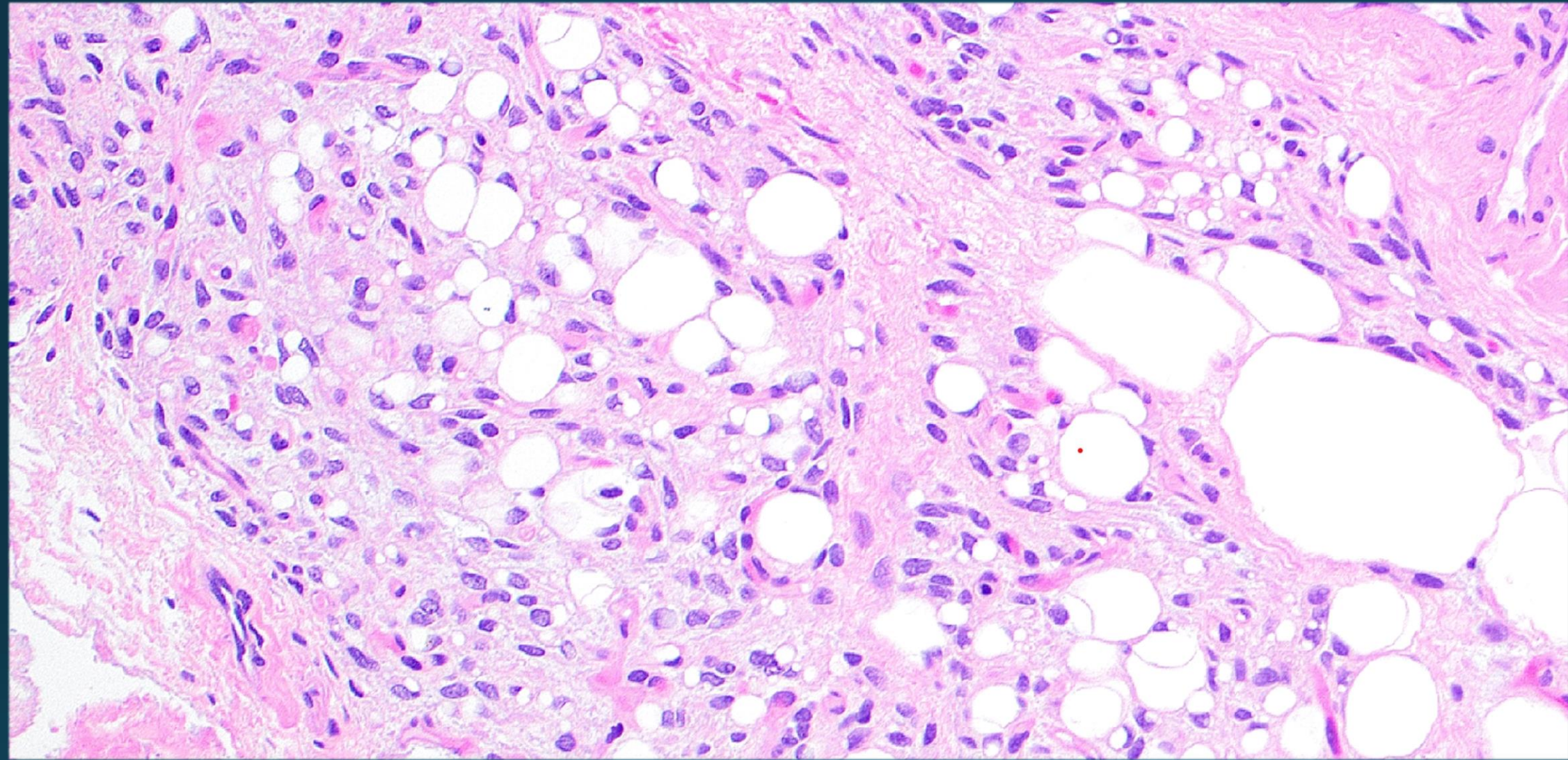
POLL

What is the lesional phenotype?

- ☐ Epithelioid
- ☐ Spindle/Myoid
- ☐ Fatty
- ☐ Myxoedematous
- ☐ Fibrocollagenous
- ☐ Vascular



35-year-old obese female,
13 cm perineal mass



35-year-old obese female,
13 cm perineal mass

‘PHENOTYPE’: **FATTY**

Differential Diagnosis

Lipoma/
Liposarcoma

Fat-predominant
RB1-deficient
neoplasms
(cellular angiofibroma,
mammary-type
myofibroblastoma)

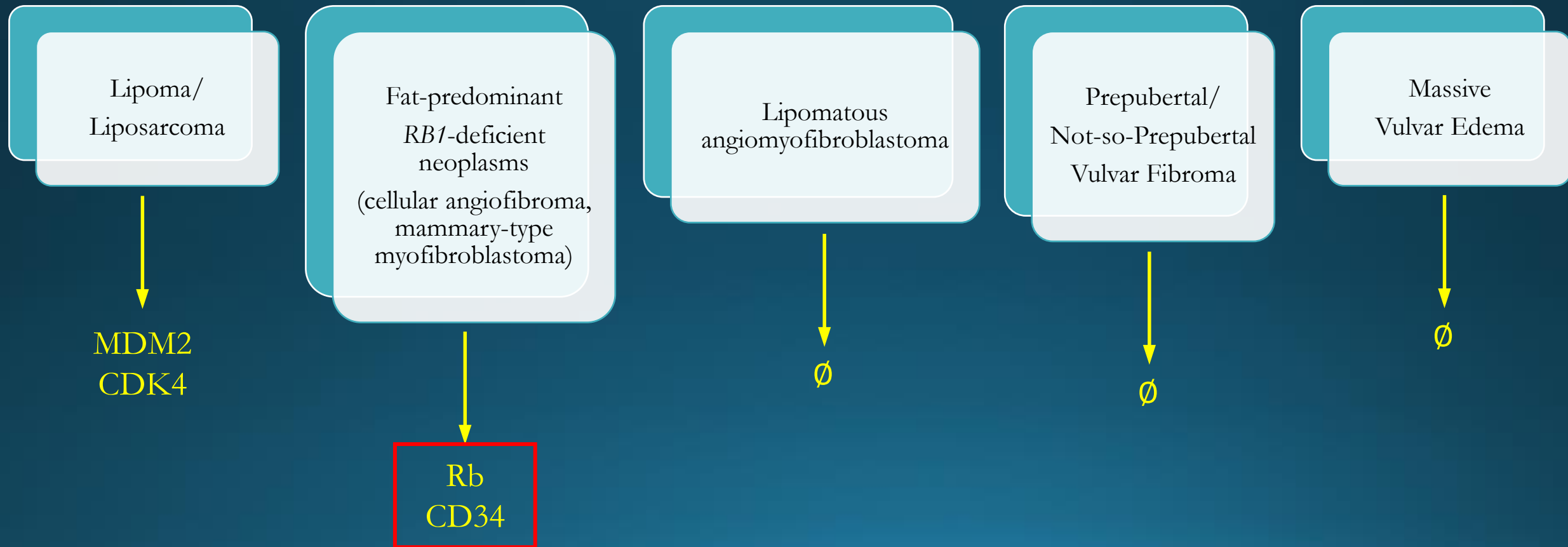
Lipomatous
angiomyofibroblastoma

Prepubertal/
Not-so-Prepubertal
Vulvar Fibroma

Massive
Vulvar Edema

'PHENOTYPE': **FATTY**

IHC Workup

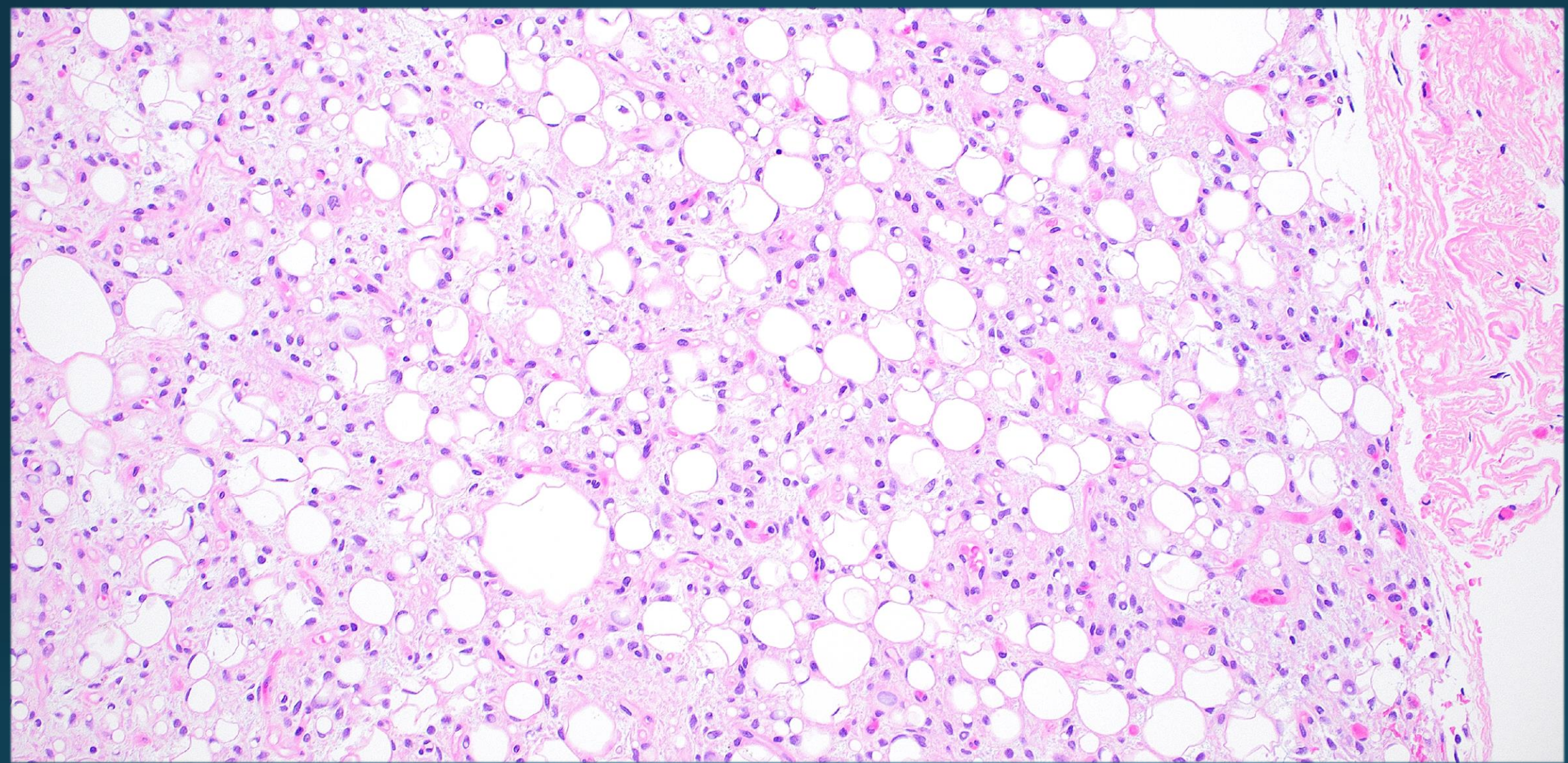


IHC PITFALLS: **Rb**

- Frequently challenging to interpret
 - Attributed to **single/monoallelic *RB1* deletion** (not double)
 - Consider **13q FISH**
- **Nonspecific** event – deletion/mutation in numerous **benign/malignant mesenchymal** lesions

IHC PITFALLS: **CD34**

- Marker of multiple lineages:
 - Fibroblasts
 - Endothelial cells
 - Cells of uncertain differentiation
 - Hematopoietic blasts
- May be **positive** in scars, angiomyxomas, nerve sheath tumors, epithelioid sarcoma
- Does **not** stain **epithelial** cells



13 cm perineal mass

All ancillary studies negative

Lipoblastoma-Like Tumor

Adipocytic/Fibroblastic lineage

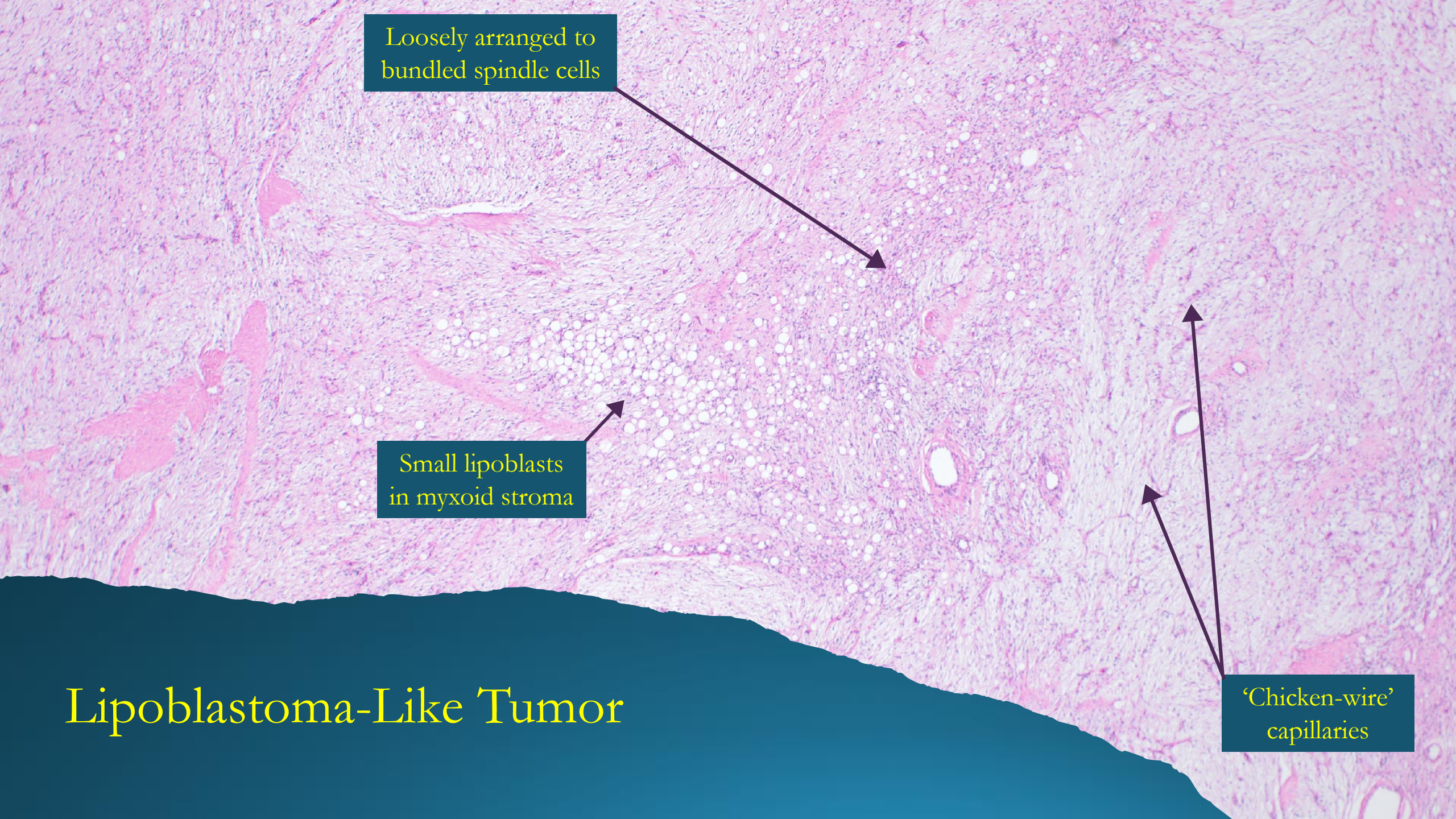
- Combination of features from:
 - **Myxoid liposarcoma**
 - **Lipoblastoma**
 - **Lipofibromatosis**
- Rb IHC may show falsely aberrant loss
- No reproducible alterations to date
 - *DDIT3*, *MDM2*, *CDK4*, *PLAG1*, *RB1* non-aberrant
- Indolent, but may **recur** or metastasize

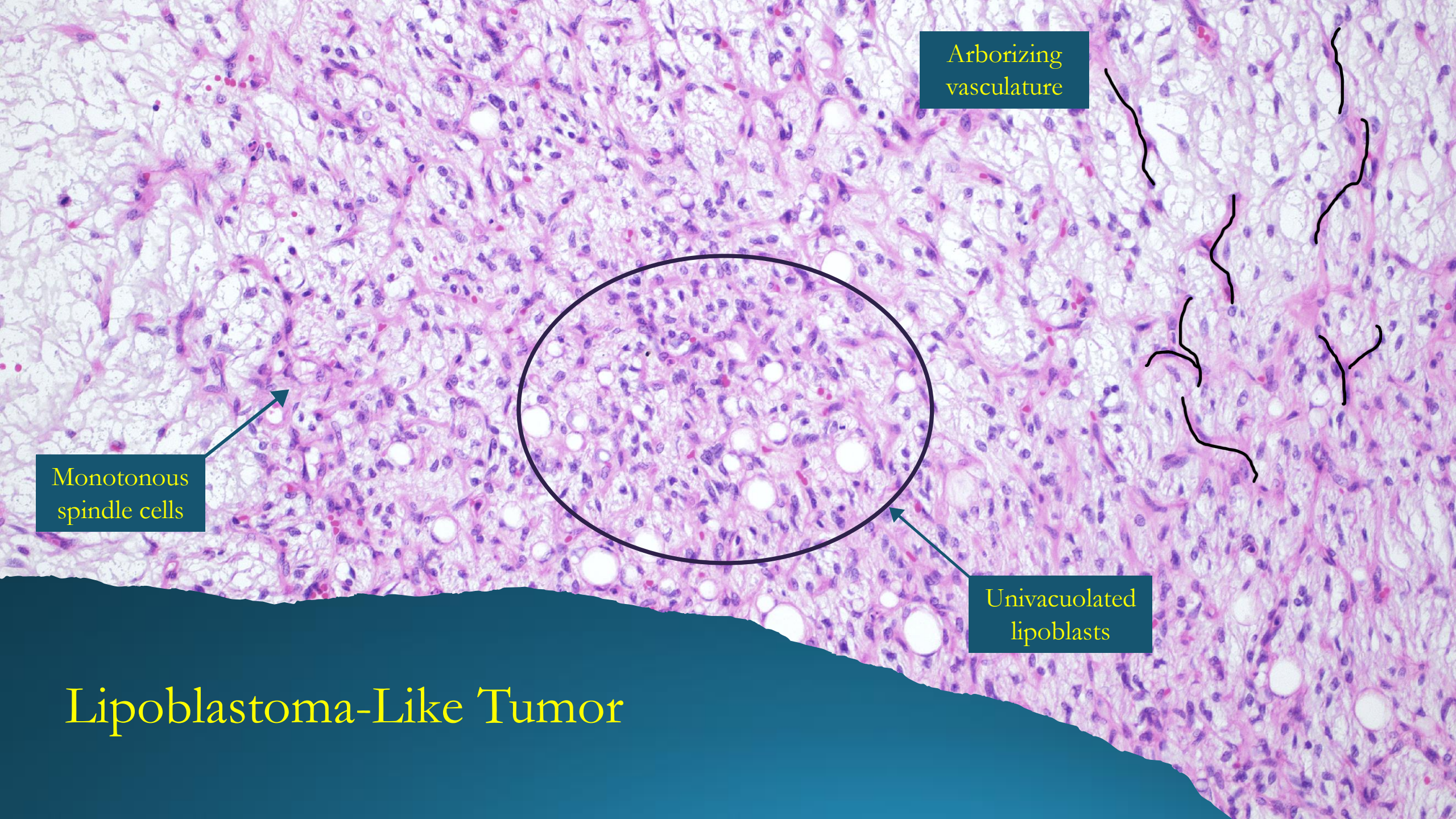
Loosely arranged to
bundled spindle cells

Small lipoblasts
in myxoid stroma

'Chicken-wire'
capillaries

Lipoblastoma-Like Tumor



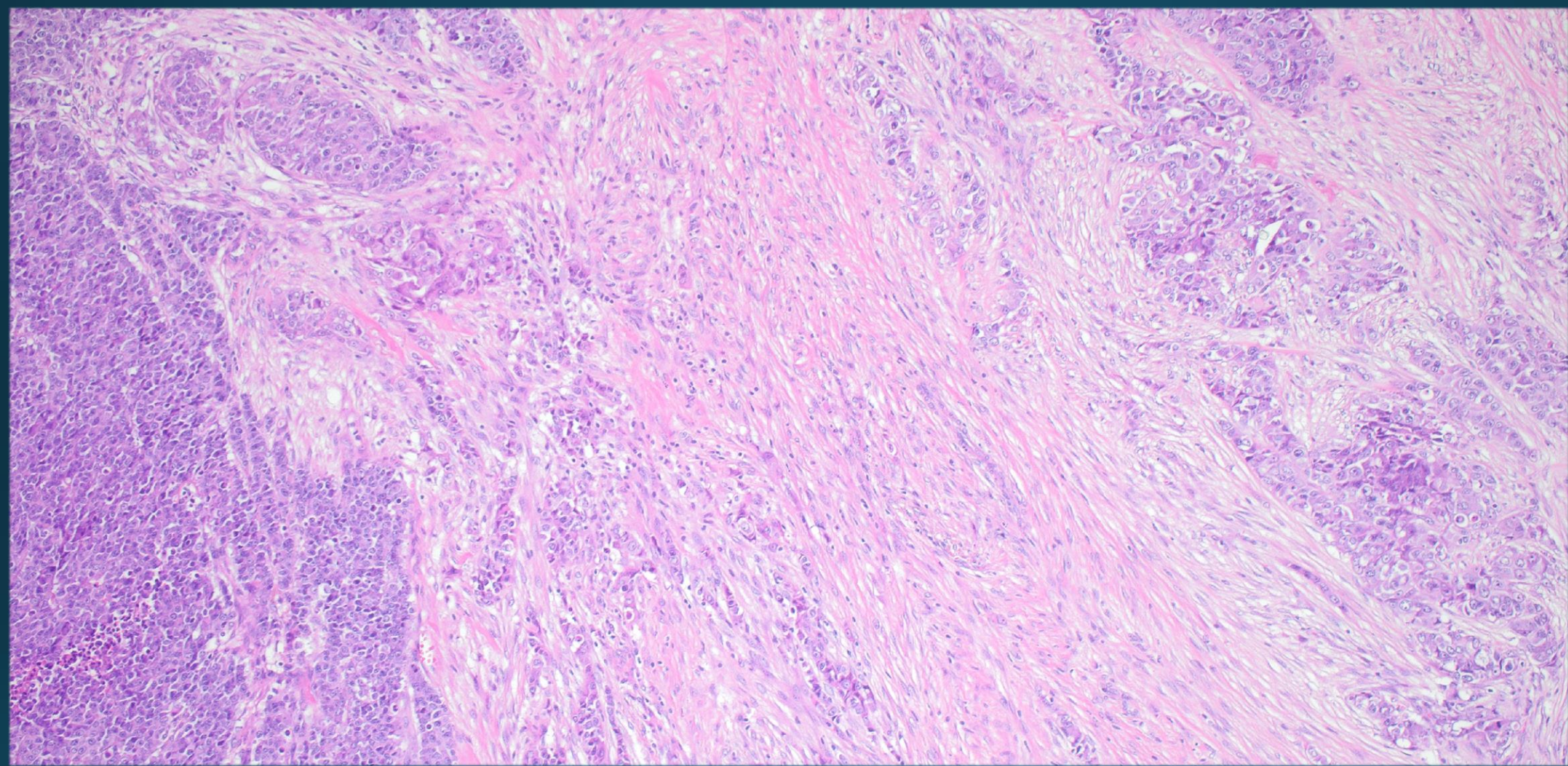


Arborizing
vasculature

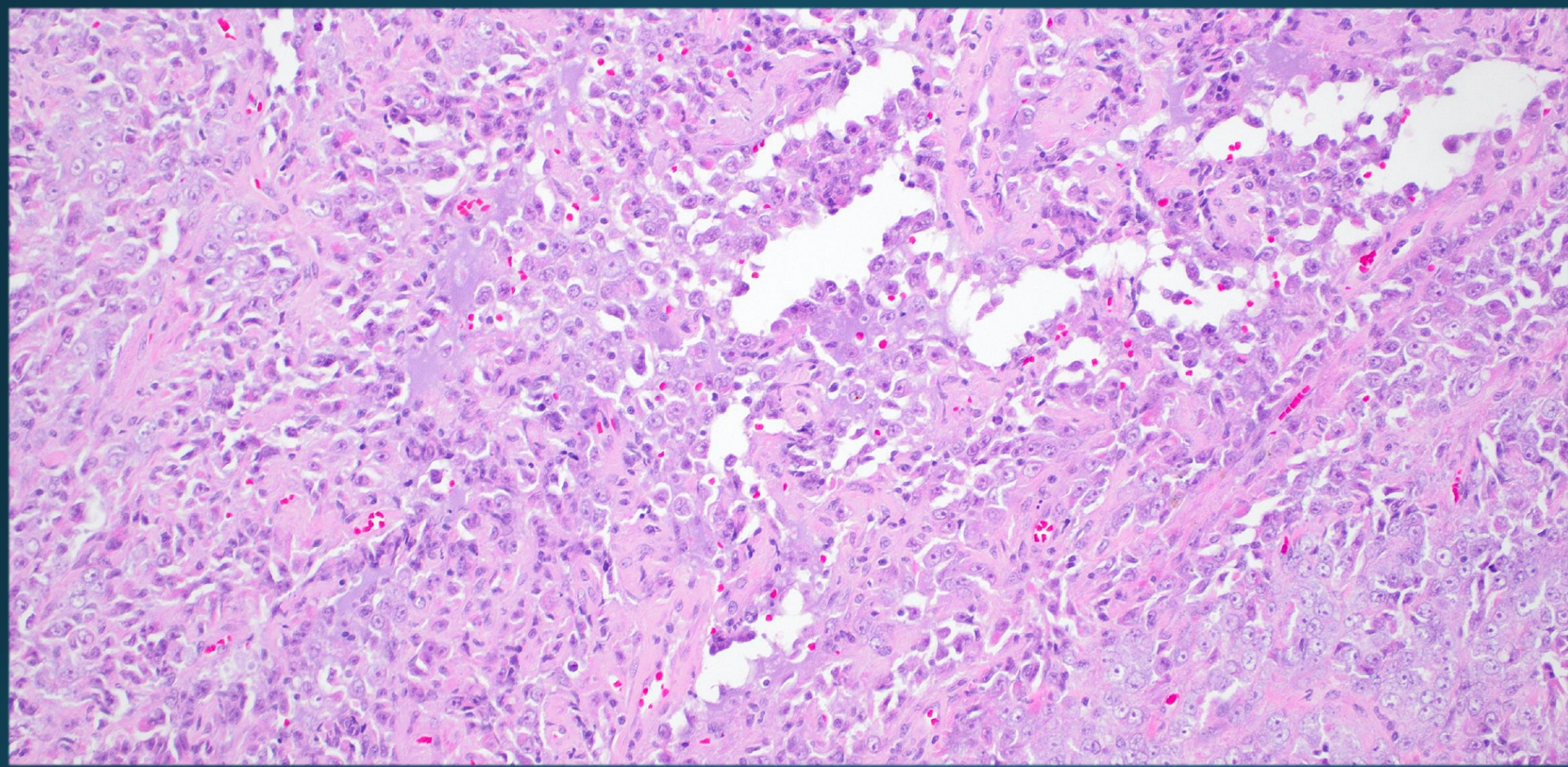
Monotonous
spindle cells

Univacuolated
lipoblasts

Lipoblastoma-Like Tumor



62-year-old female,
'Bartholin gland abscess'



62-year-old female,
'Bartholin gland abscess'

‘PHENOTYPE’: **EPITHELIOID**

Differential Diagnosis

Carcinoma

Melanoma

Epithelioid
smooth muscle
neoplasm

Epithelioid
angiosarcoma

Myoepithelial

'PHENOTYPE': **EPITHELIOID**

IHC Workup

Carcinoma

Melanoma

Epithelioid
smooth muscle
neoplasm

Epithelioid
angiosarcoma

Myoepithelial

Cytokeratins
EMA
p40, p16, p53

SOX10
S100

SMA
Desmin
H-caldesmon
HMGA2

CD31
ERG
~CD34

Cytokeratins
EMA
S100/SOX10/GFAP
p63/SMA/calponin

IHC PITFALLS: **KERATINS, EMA**

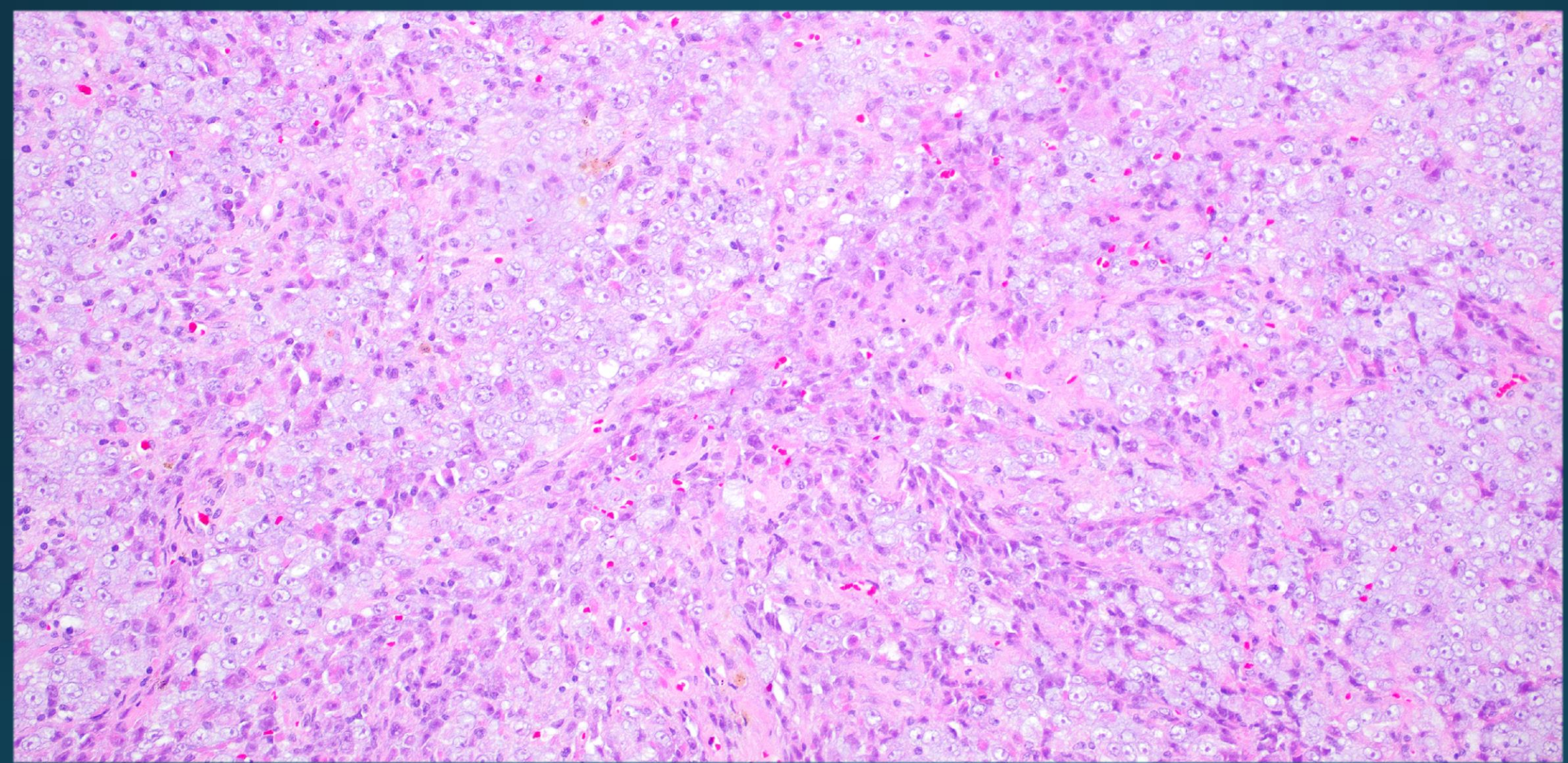
- May be **positive** in **mesenchyme** of any lineage
 - Especially **epithelioid variants** (~strong but usually **patchy**)
- May be completely **absent** in **poorly differentiated** or **sarcomatoid** carcinomas
 - p16, p53

IHC PITFALLS: p16

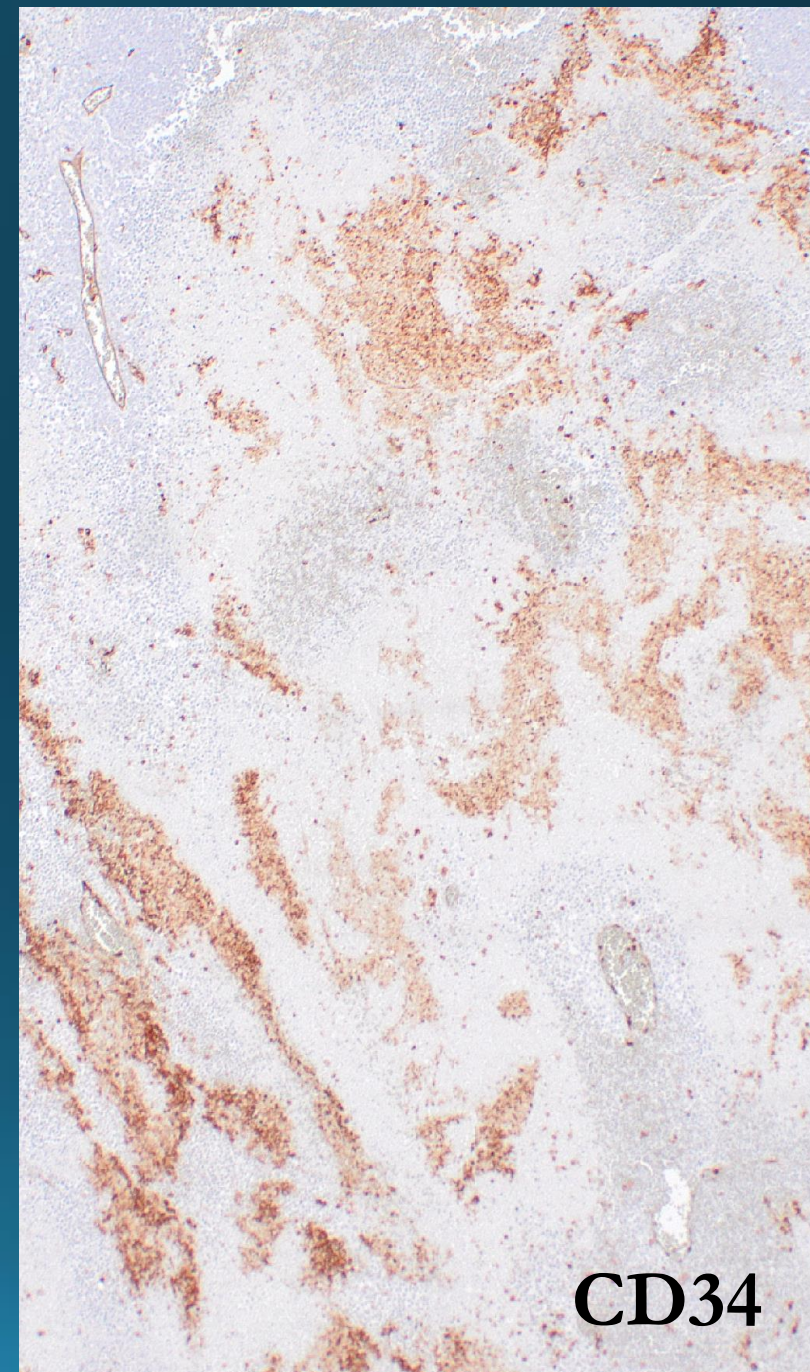
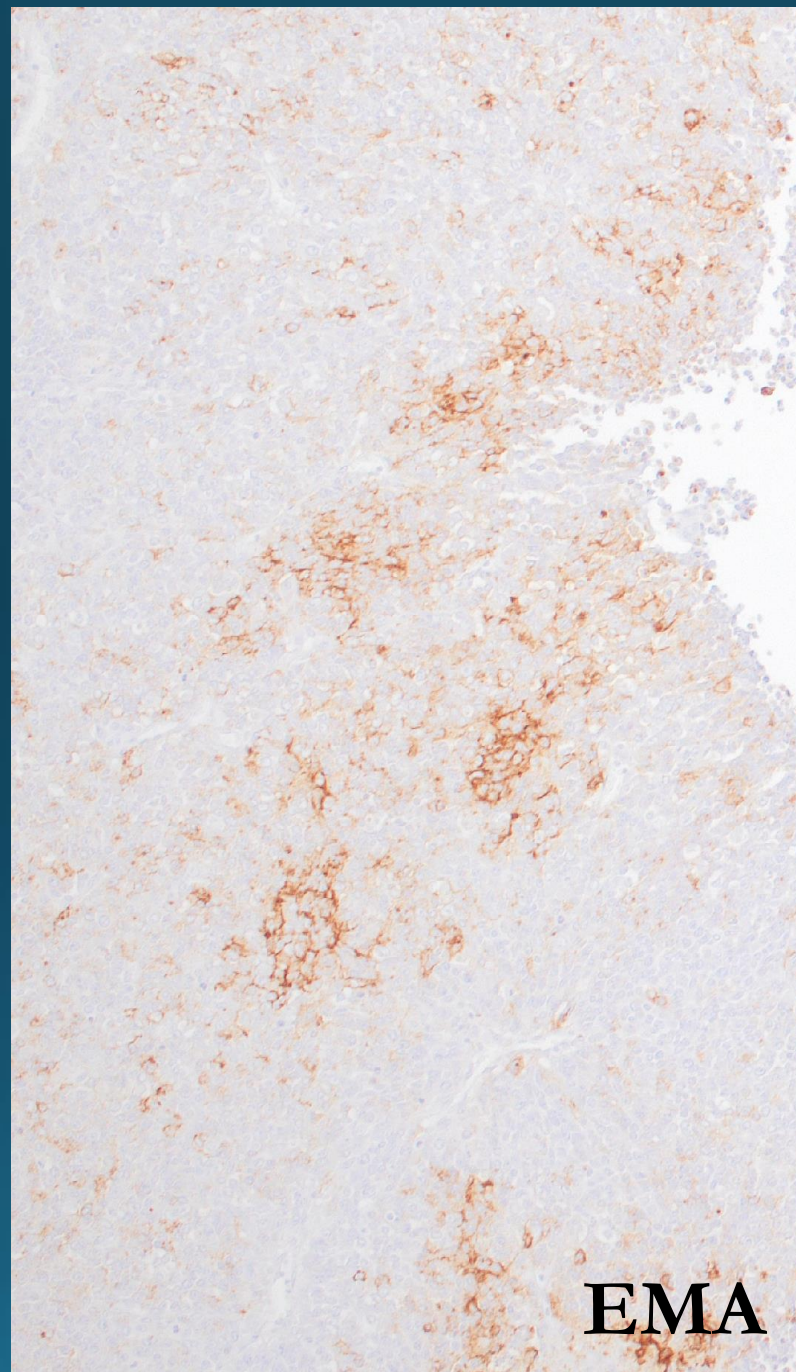
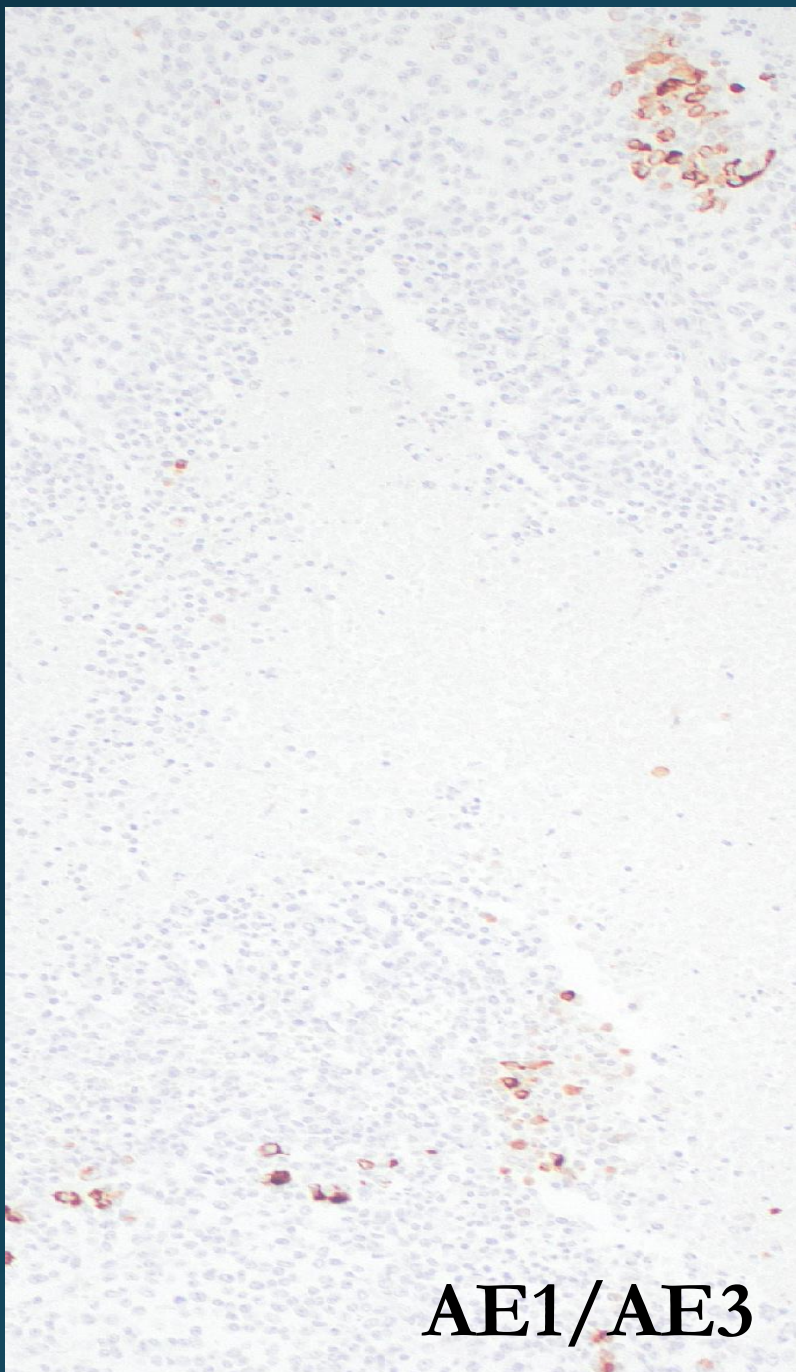
- May be **block-positive** in any high-grade mesenchymal neoplasm
 - Do not misinterpret as HPV-associated epithelial process
 - Regardless of association with upstream *TP53* alteration

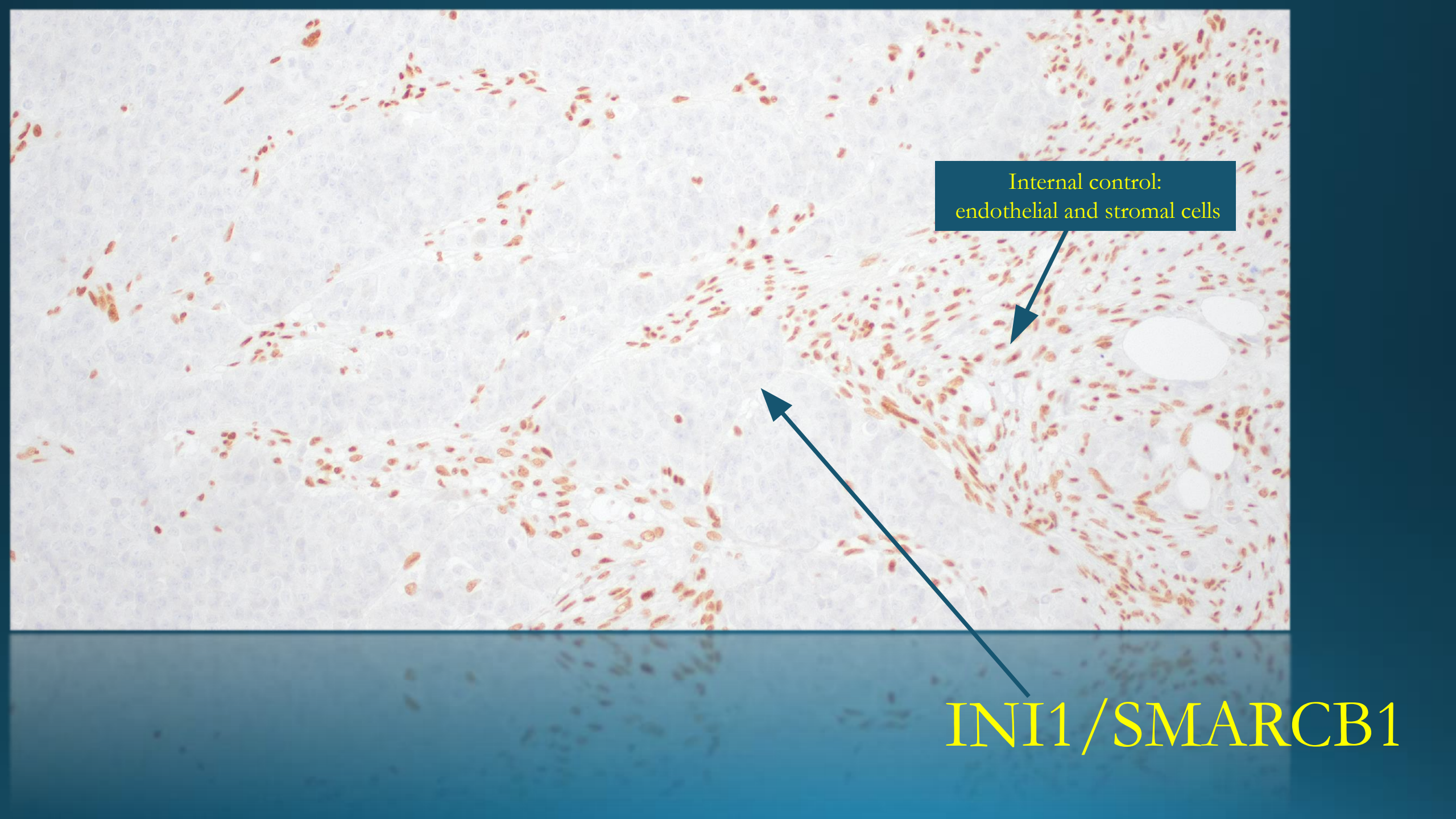
IHC PITFALLS: p53

- May be **mutant-pattern** in any high grade mesenchymal neoplasm
 - De novo or post-radiation *TP53* alterations
 - Do not misinterpret as serous carcinoma or HPV-independent squamous process



‘Bartholin gland abscess’





Internal control:
endothelial and stromal cells

INI1/SMARCB1

Proximal- Type Epithelioid Sarcoma

'Uncertain' lineage

- Infiltrative periphery
- Syncytial sheeted architecture
- Large, **uniformly atypical epithelioid** cells
- **Voluminous pink**, occasionally eccentric cytoplasm ('rhabdoid')
- **Vesicular nuclei** ('pallor'), prominent red nucleoli

Proximal- Type Epithelioid Sarcoma

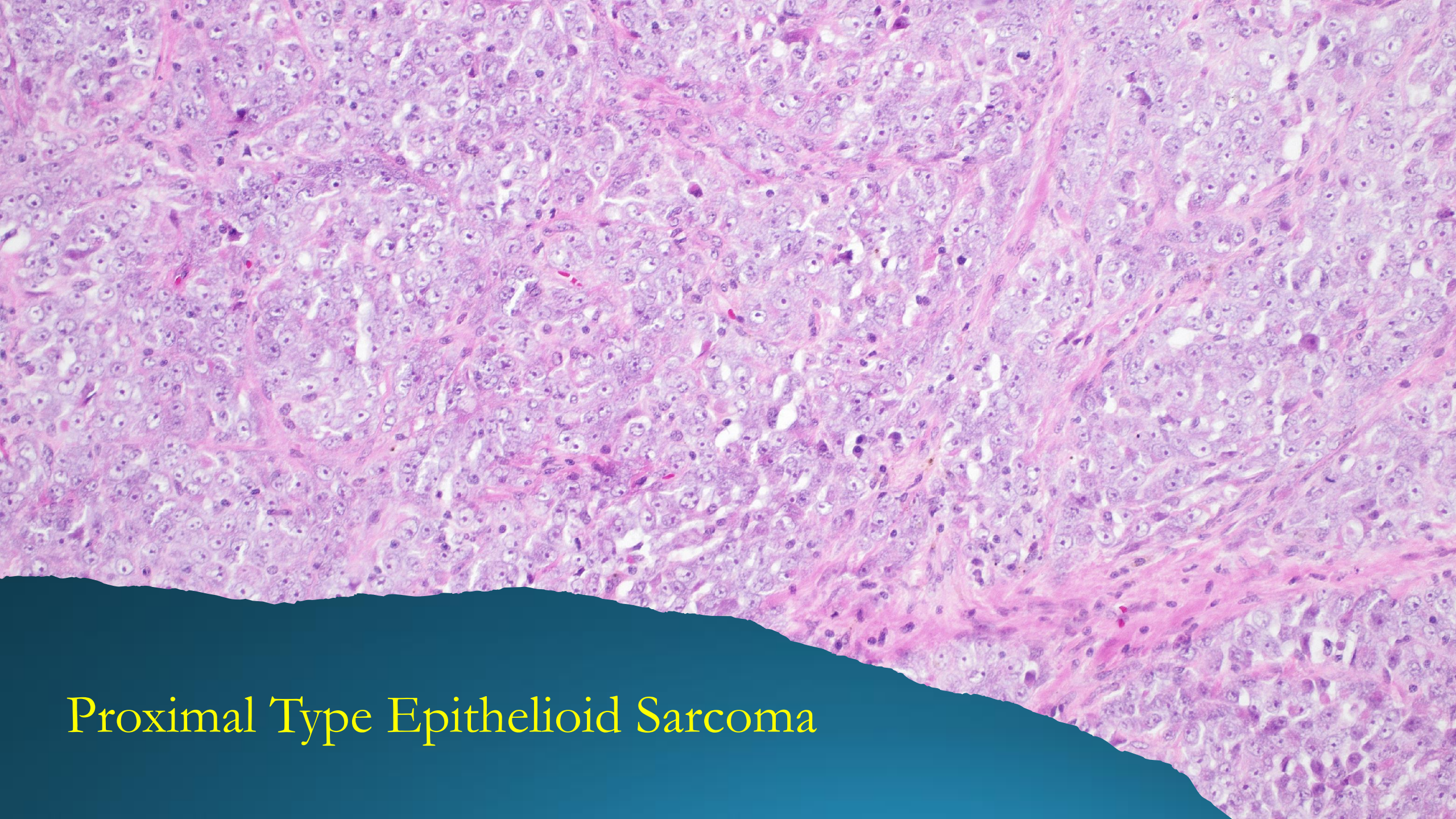
'Uncertain' lineage

- Keratin and/or EMA positivity **required**
- **CD34** may be **positive**
- Aberrant SMARCB1/INI1 loss

Proximal- Type Epithelioid Sarcoma

'Uncertain' lineage

- Highly aggressive
- **Nodal metastasis**



Proximal Type Epithelioid Sarcoma

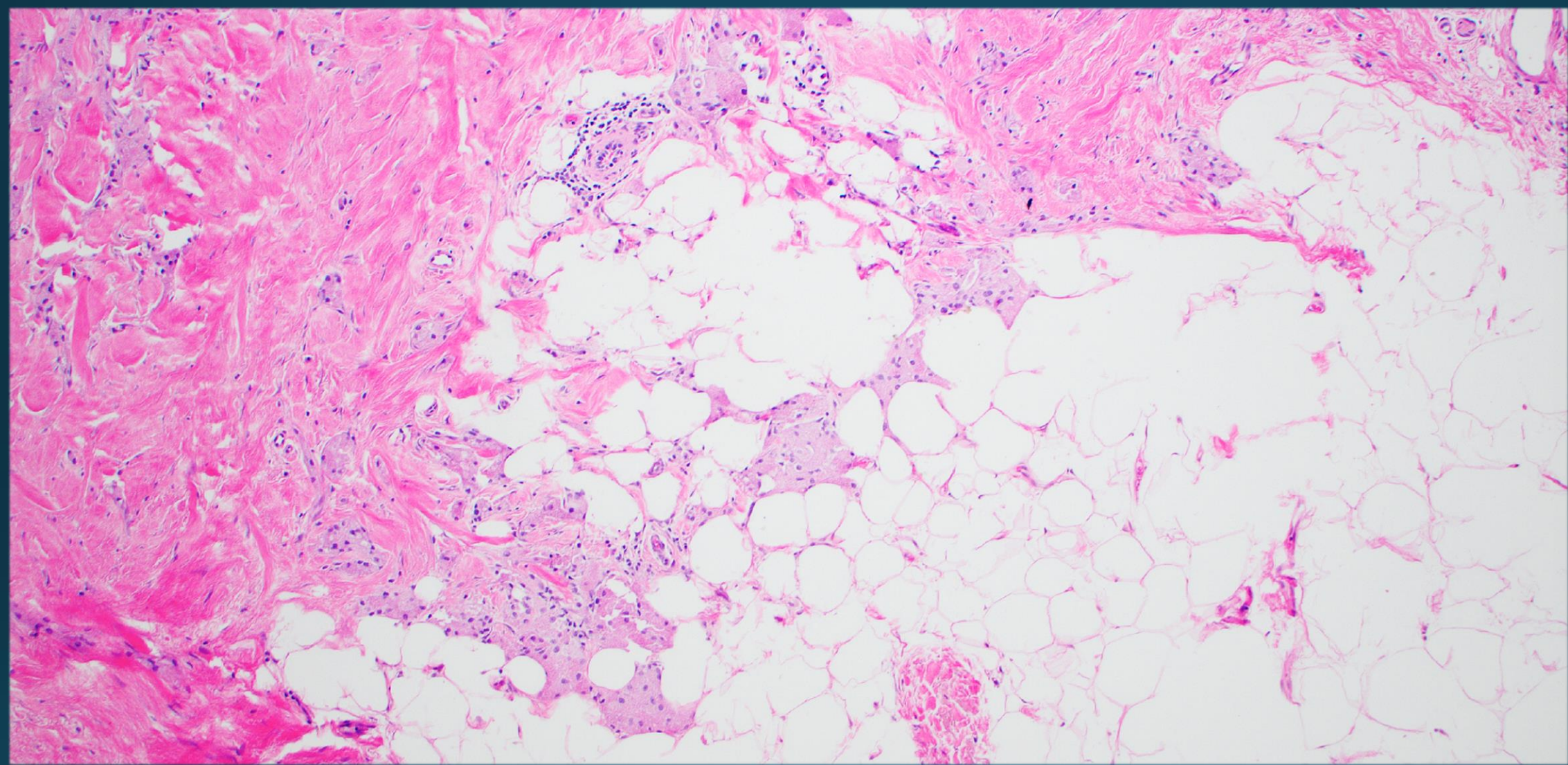


Open/vesicular
chromatin,
large nucleoli

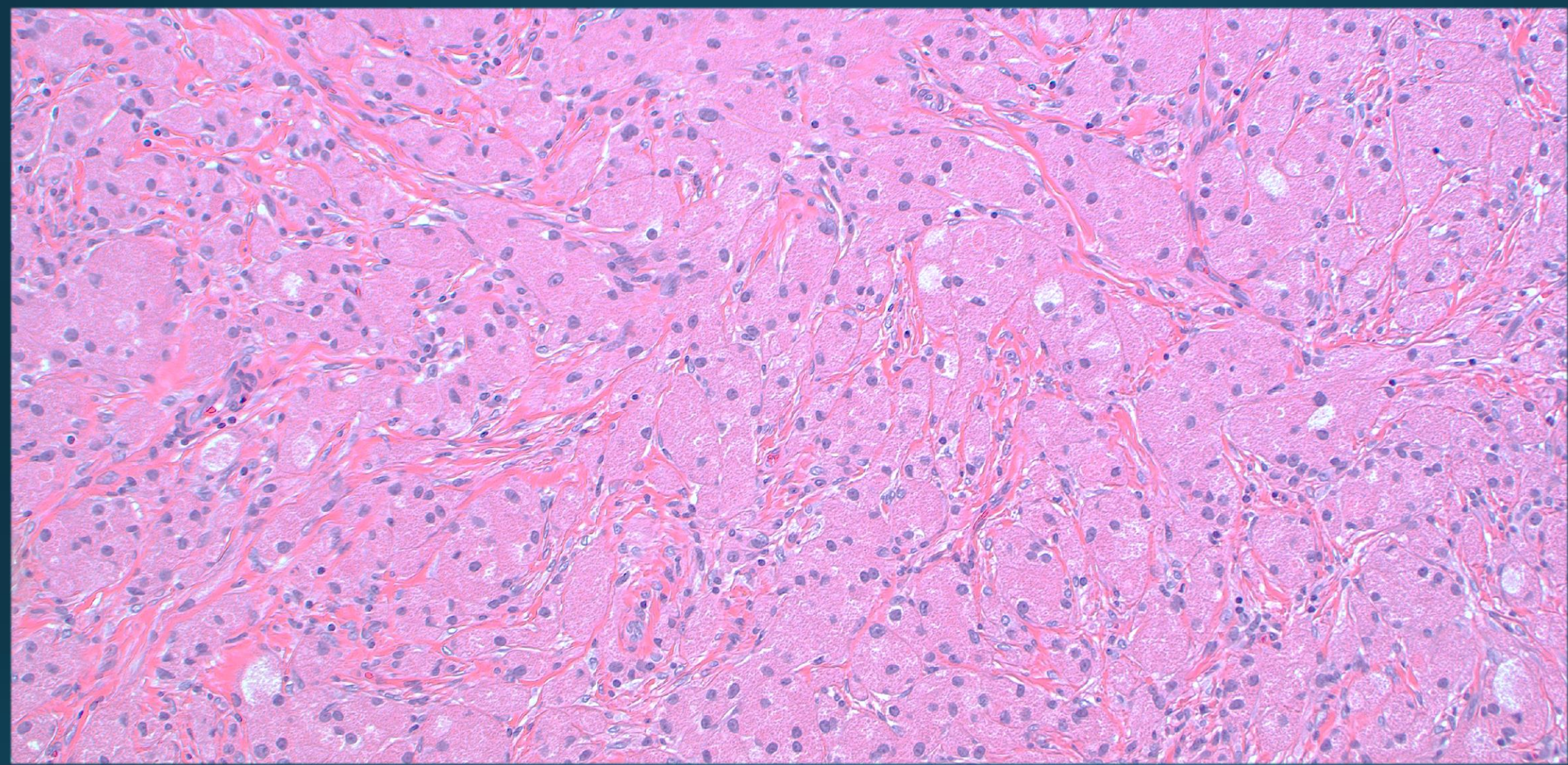
This histological slide shows a dense population of epithelioid cells. The cells have large, round to oval nuclei with a characteristic open or vesicular chromatin pattern. Many of these nuclei contain prominent, dark, eosinophilic nucleoli. The cytoplasm of the cells is abundant and appears pale pink, which is typical for this type of sarcoma. The cells are arranged in a disorganized, sheet-like pattern, with some areas showing more cellular cohesion than others. The overall architecture is consistent with a malignant neoplasm of epithelioid origin.

Voluminous
pale cytoplasm

Proximal Type Epithelioid Sarcoma



26-year-old female
1 cm pruritic labial lump

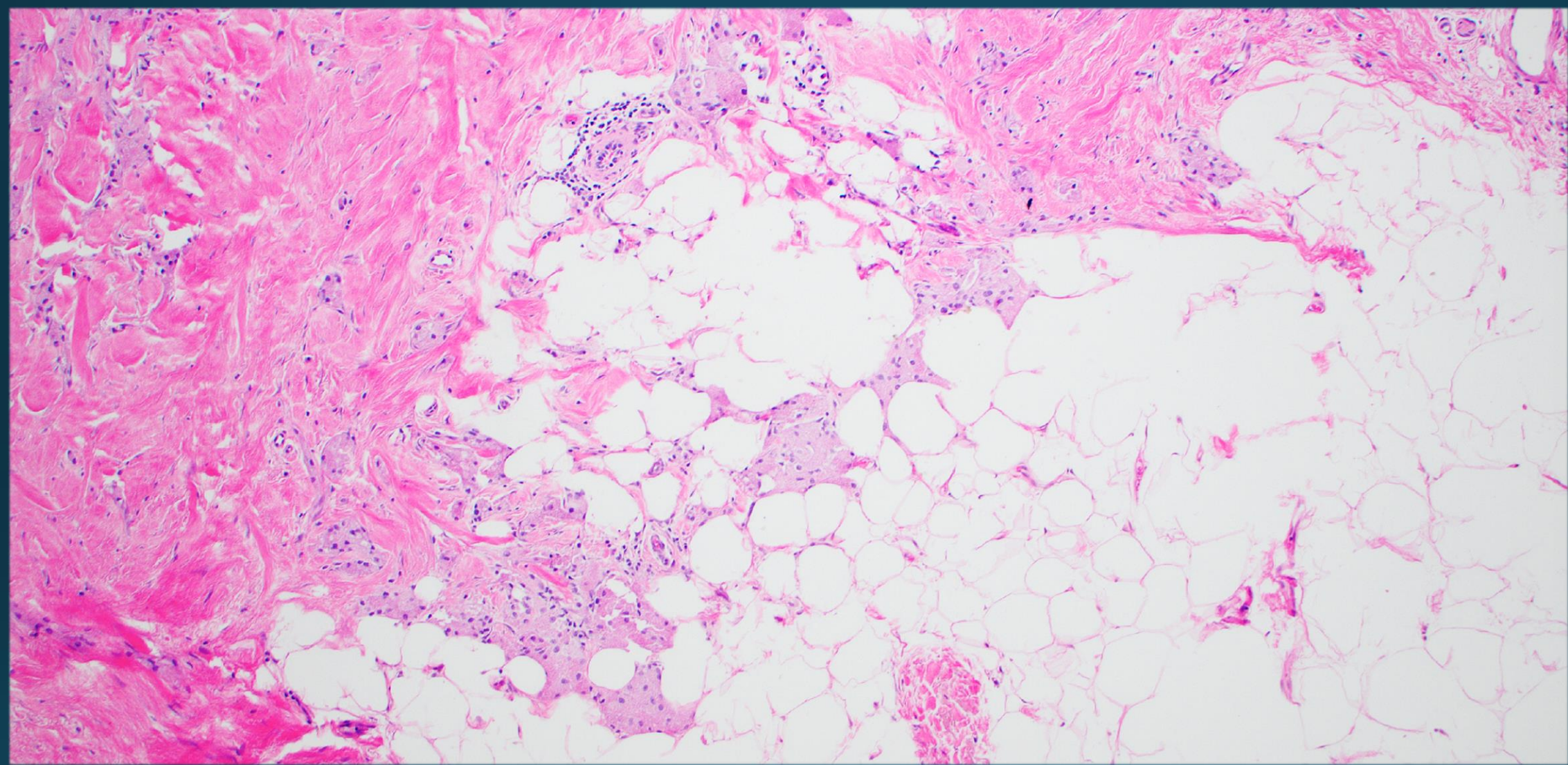


26-year-old female
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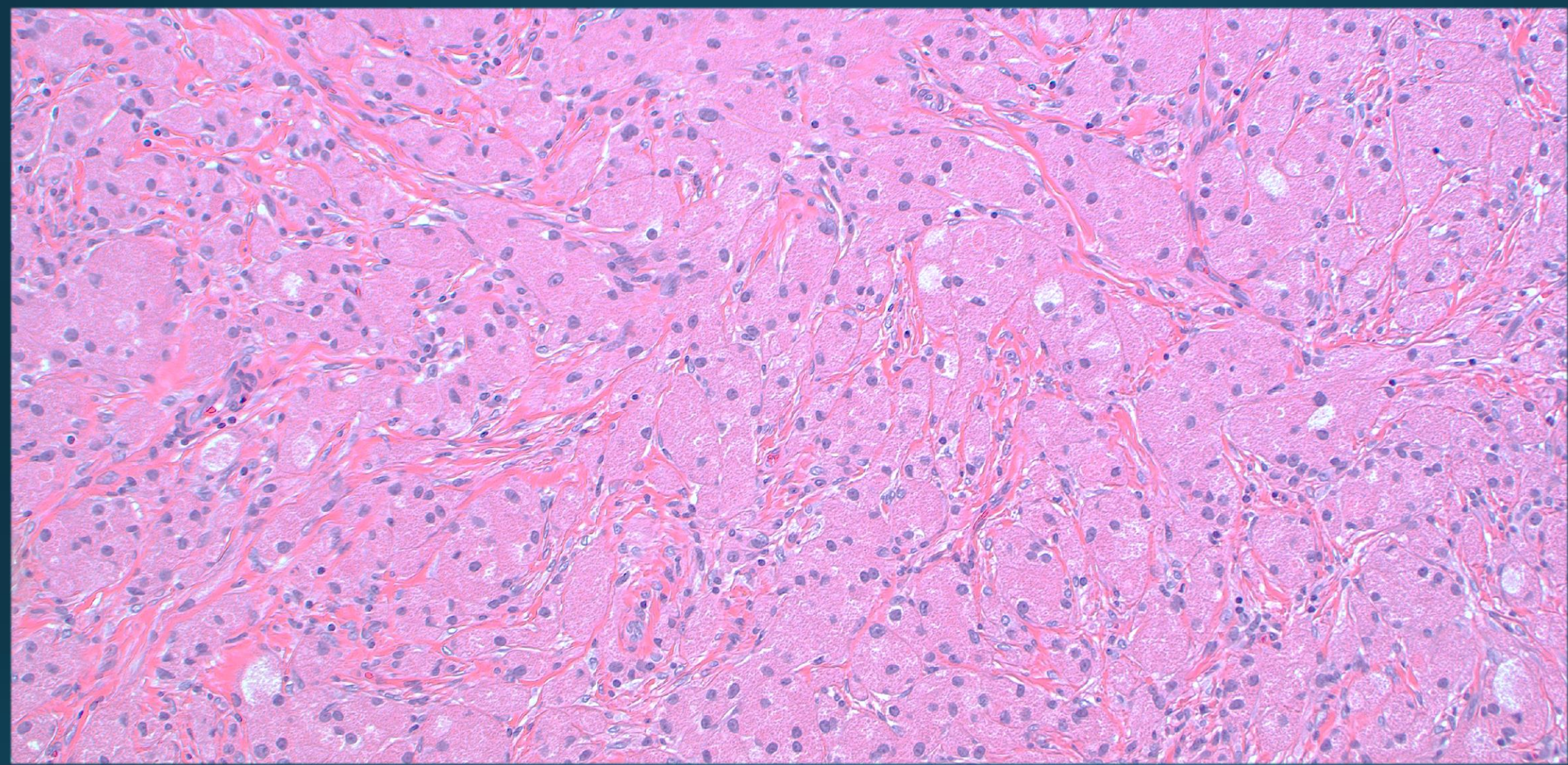
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What is the lesional phenotype?

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- ☐ Vascular



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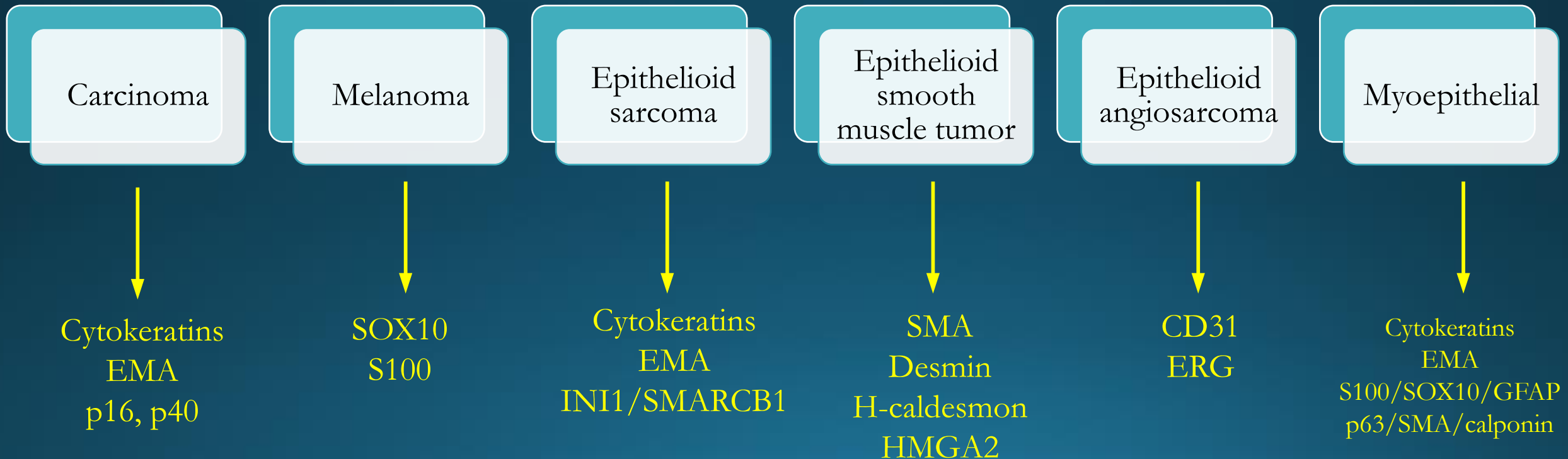


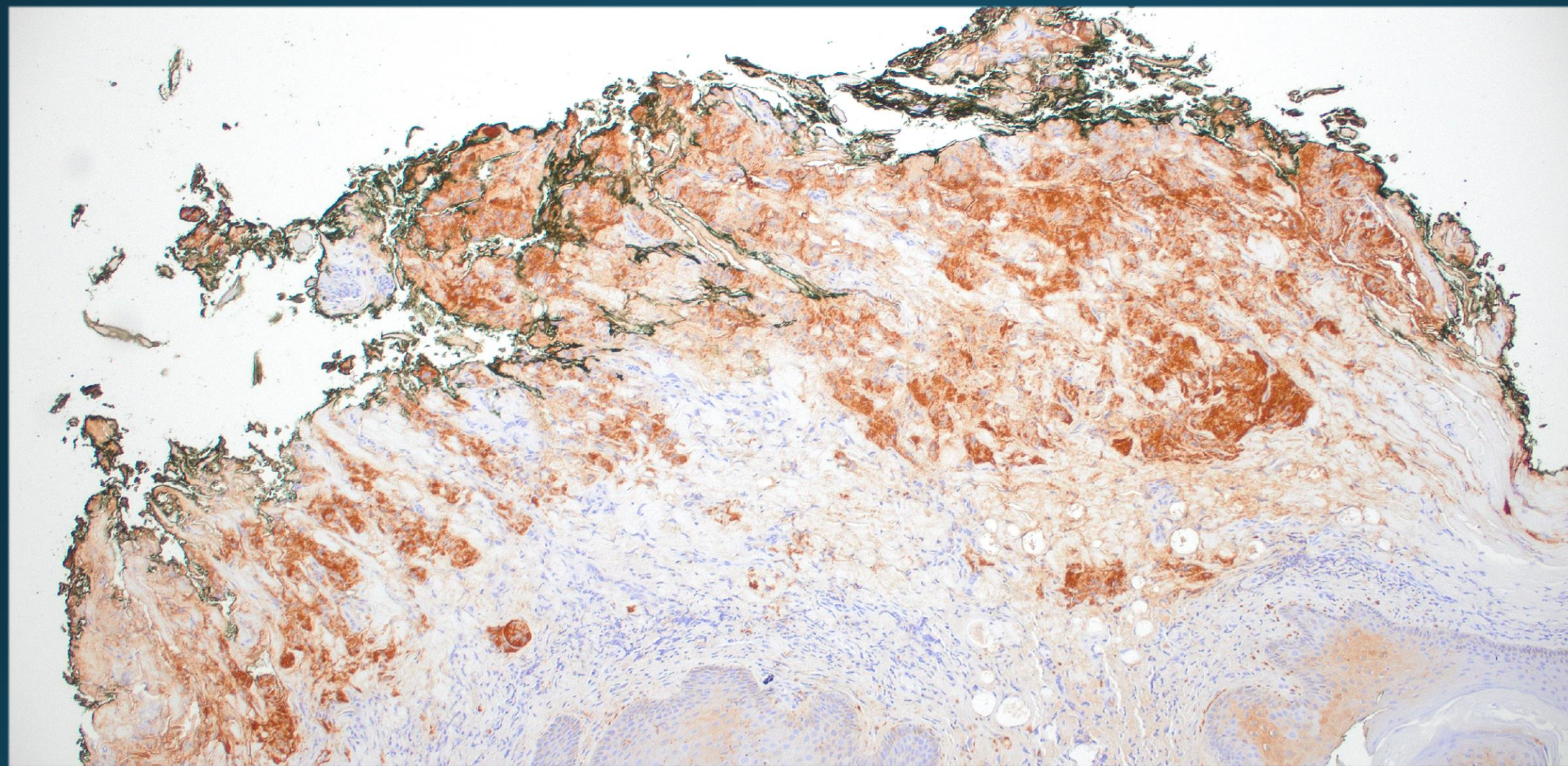
26-year-old female
1 cm pruritic labial lump

PHENOTYPE: **EPITHELIOID**

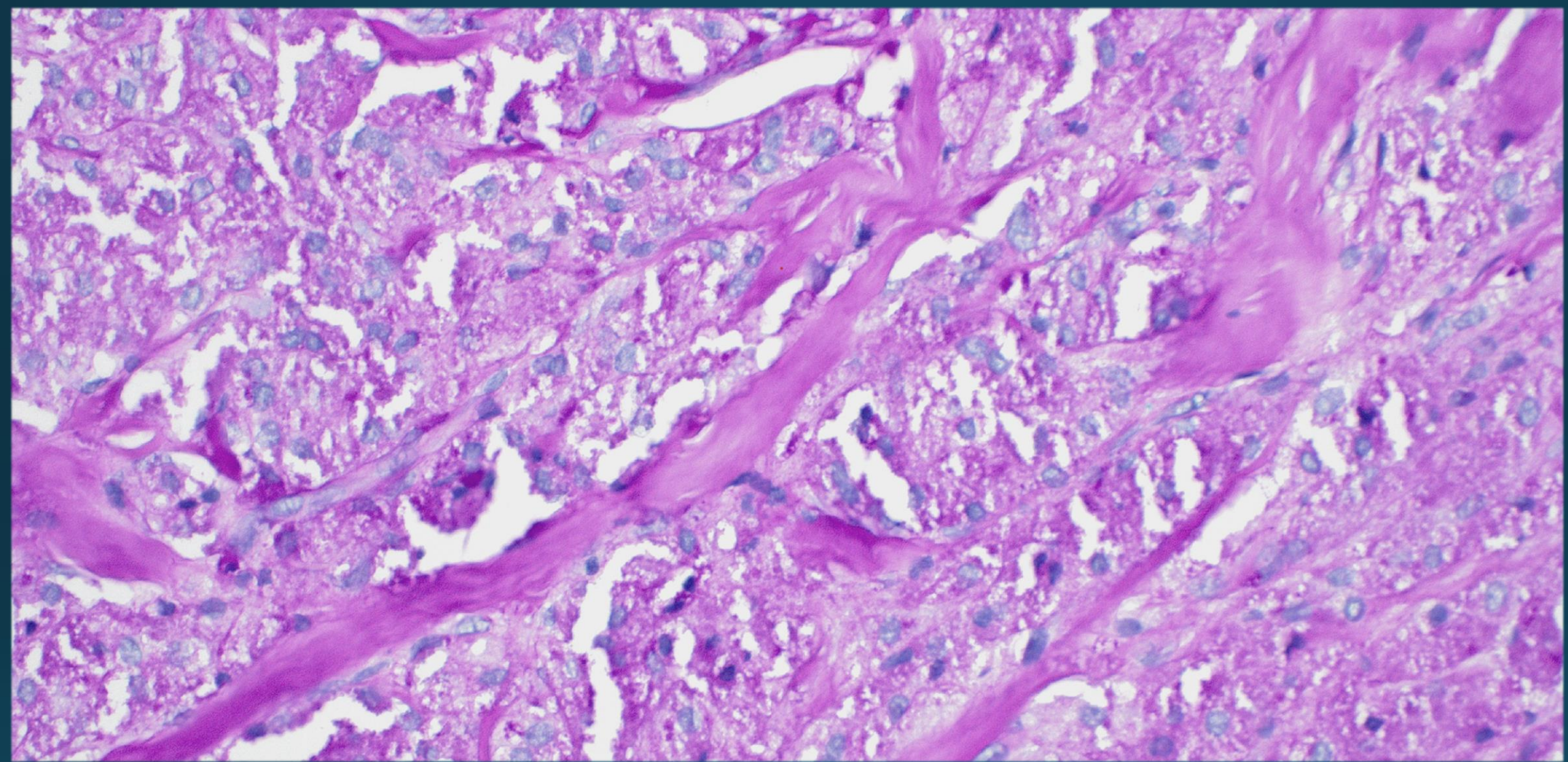
Differential Diagnosis

IHC Workup





S100



PAS

Vulvar Granular Cell Tumor

Nerve sheath lineage

- **Highly infiltrative** periphery without stromal response – margins often positive
- Syncytial nested to sheeted architecture
- **Polygonal/epithelioid** cells with bland small round nuclei
- Powdery **pink to amphophilic granular** cytoplasm
- **Pseudoepitheliomatous hyperplasia** **uncommon** in genital sites

Vulvar Granular Cell Tumor

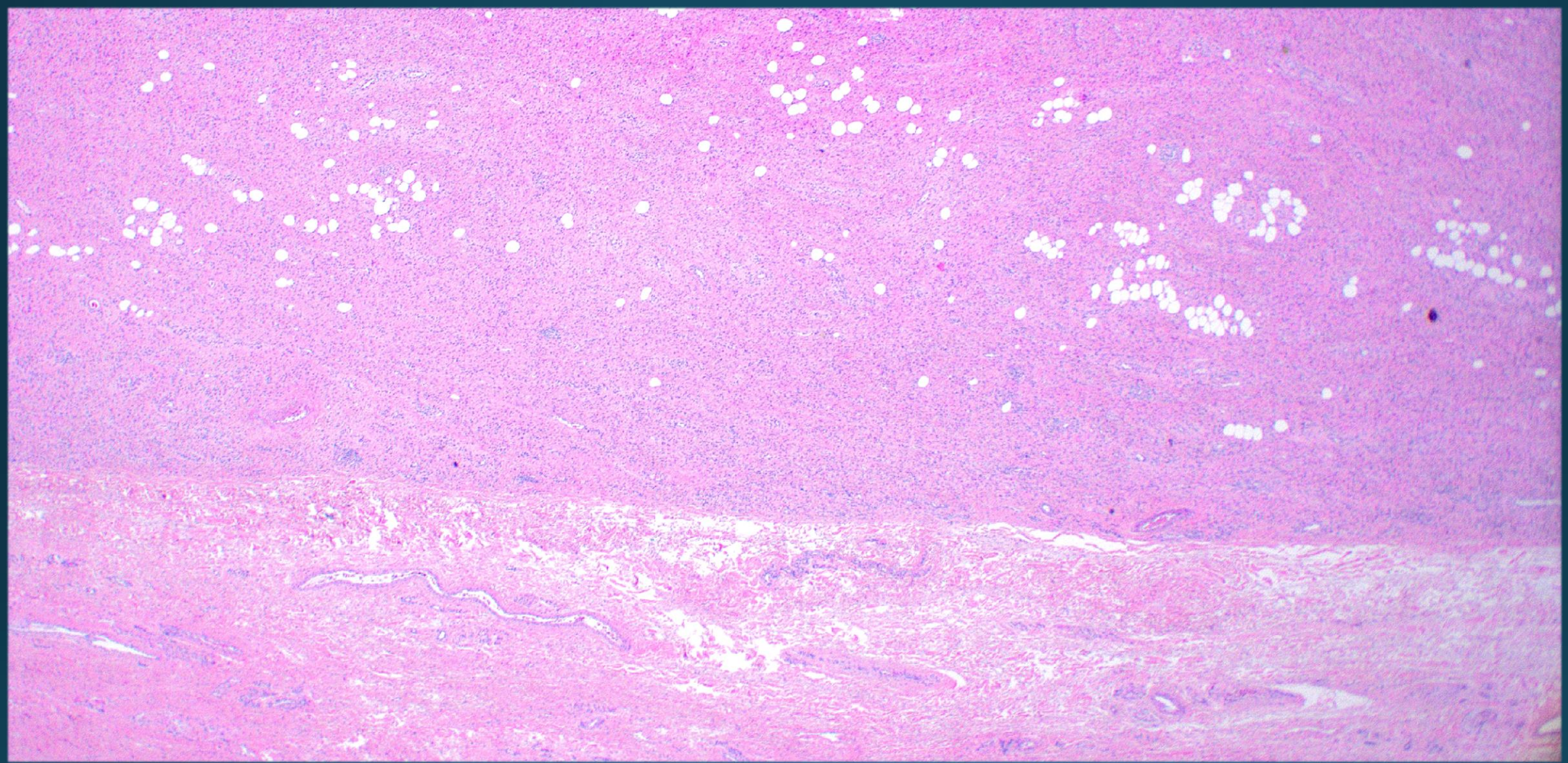
Nerve sheath lineage

- **S100, SOX10, PAS positive**
- HMB45 negative
- **Malignancy** (rare) per Fanburg-Smith criteria:
 - **≥3** of the following:
 - 2 mitoses per 10 HPFs
 - Necrosis
 - Cellular spindling
 - Nuclear vesiculation
 - Pleomorphism
 - Increased nuclear to cytoplasmic ratio

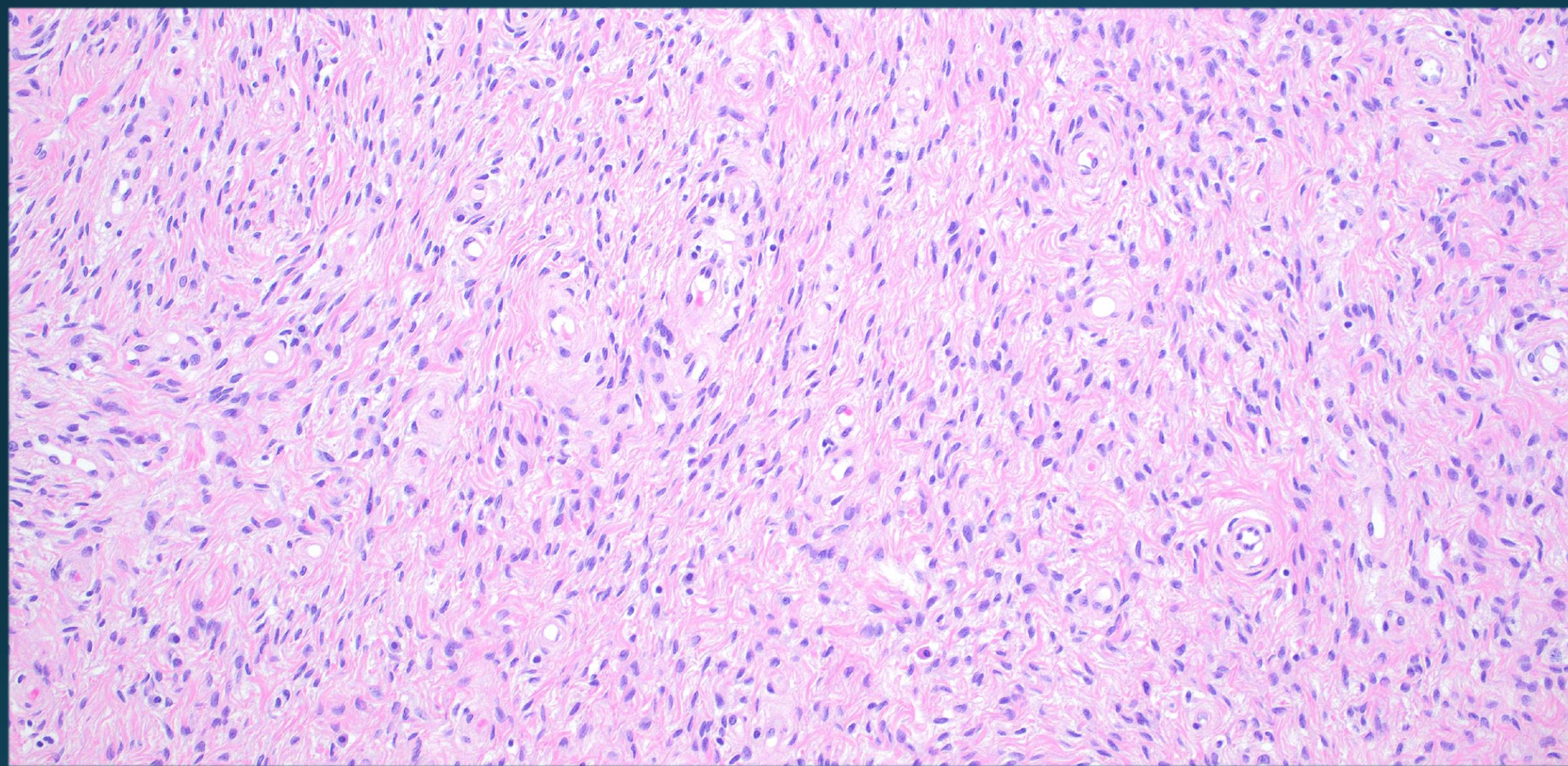
Vulvar Granular Cell Tumor

Nerve sheath lineage

- May be multifocal
- Benign but local recurrence in subset, independent of margin status
- Report margins: re-excision is convention if involved
 - Close surveillance appropriate if contraindicated



40-year-old female
3 cm subcutaneous vulvar mass



40-year-old female
3 cm subcutaneous vulvar mass

PHENOTYPE: **MYOID**

Differential Diagnosis

Leiomyoma/
Leiomyosarcoma

RB1-deficient neoplasms
(cellular angiofibroma,
mammary-type
myofibroblastoma)

Peripheral
nerve sheath tumor

Fasciitis/
Postoperative spindle
cell proliferations

PHENOTYPE: **MYOID**

IHC Workup

Leiomyoma/
Leiomyosarcoma

↓
SMA
Desmin
H-caldesmon
HMGA2

RB1-deficient neoplasms
(cellular angiofibroma,
mammary-type
myofibroblastoma)

↓
Rb
CD34

Peripheral nerve
sheath tumor

↓
SOX10
S100
EMA

Fasciitis/
Postoperative spindle
cell proliferations

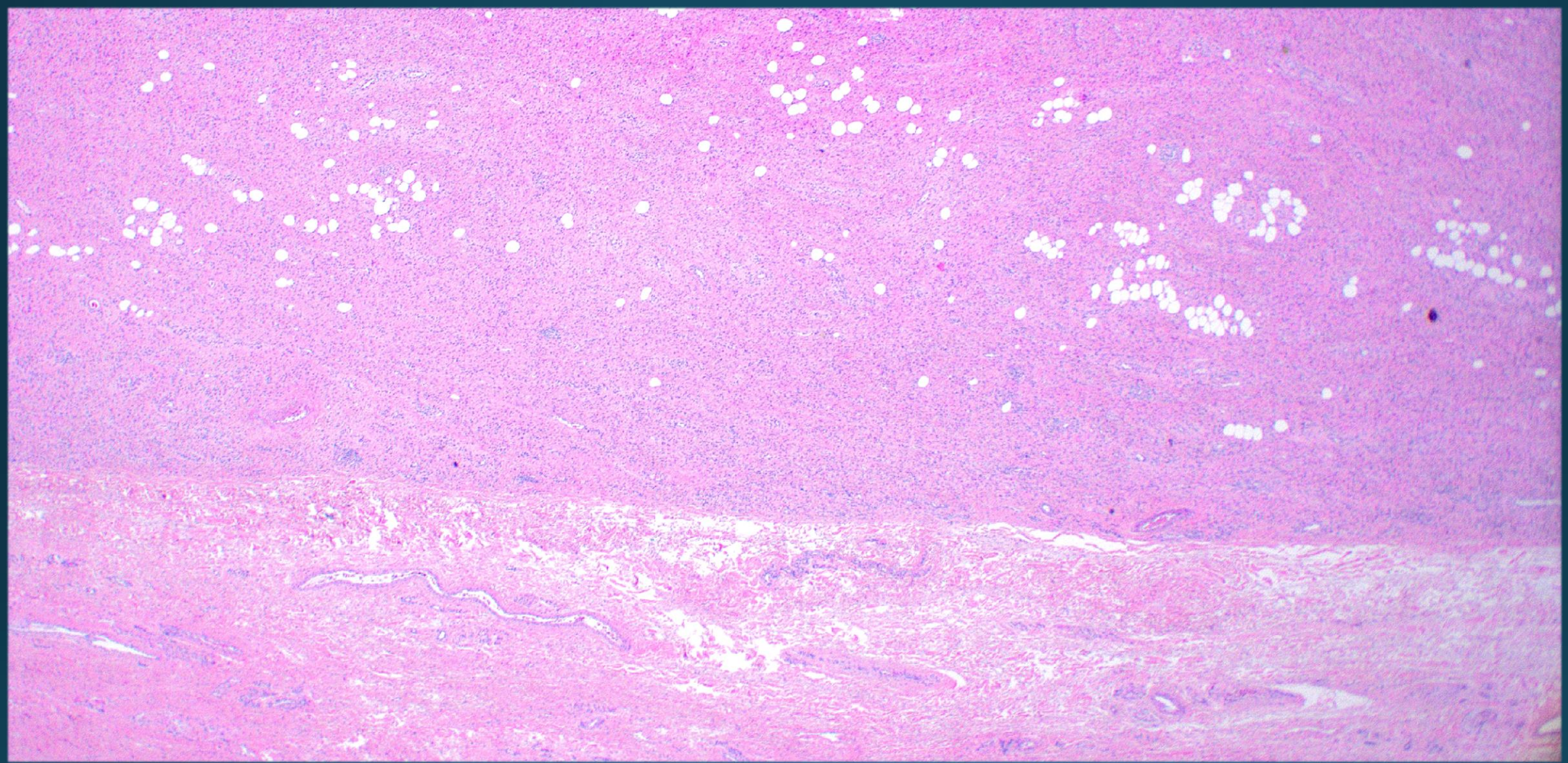
↓
Ø
(~SMA)
(~CD34)

IHC PITFALLS: CALDESMON

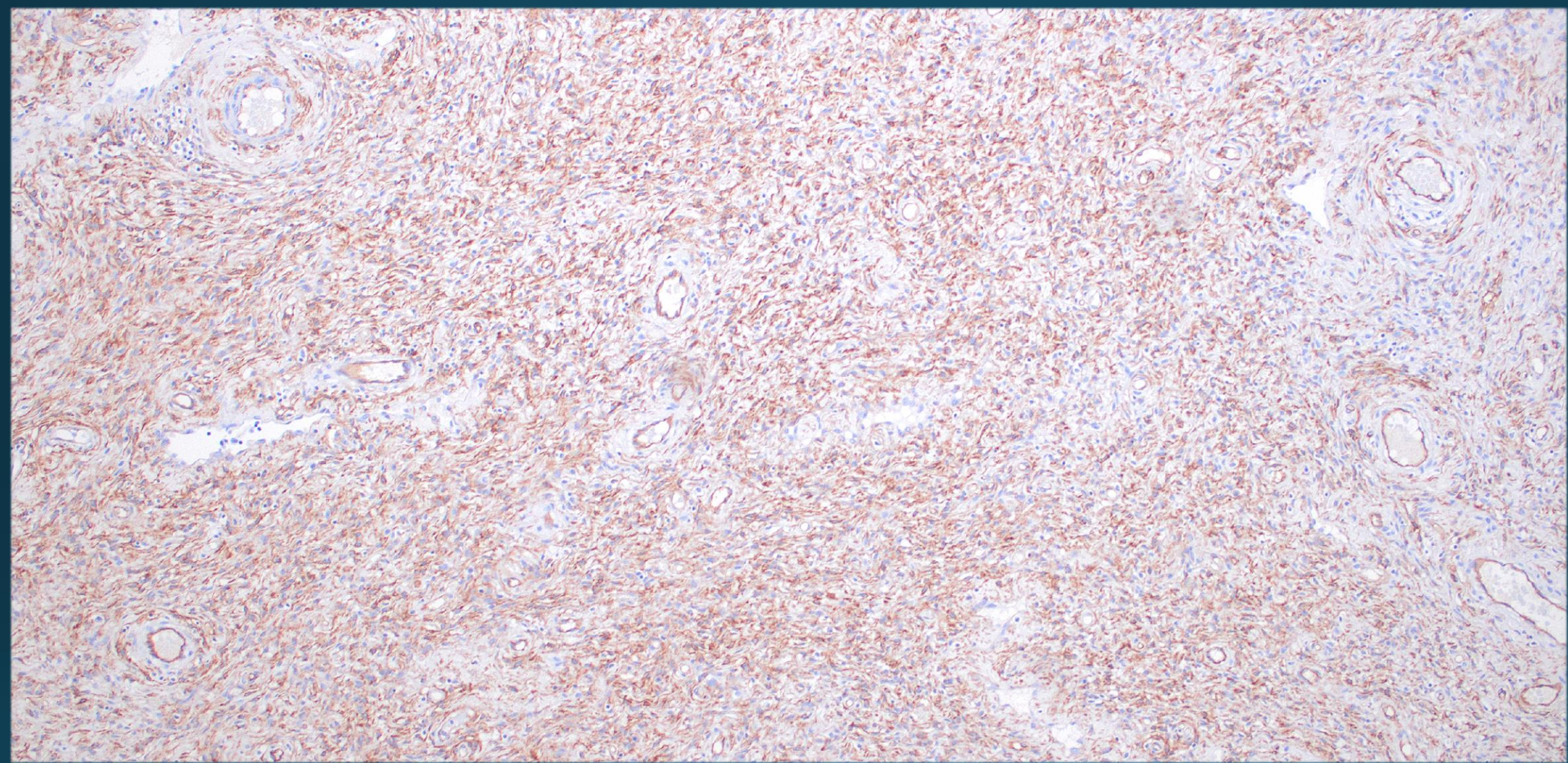
- All 'caldesmon' are **not the same**
 - H-caldesmon (**specific**) $\neq$ caldesmon (highly **nonspecific**)
- Mouse monoclonal **anti-H-caldesmon (Dako h-CD)**
- Check **internal negative controls**:
 - Epithelium
 - Endothelium
 - Inflammatory cells

IHC PITFALLS: HMGA2

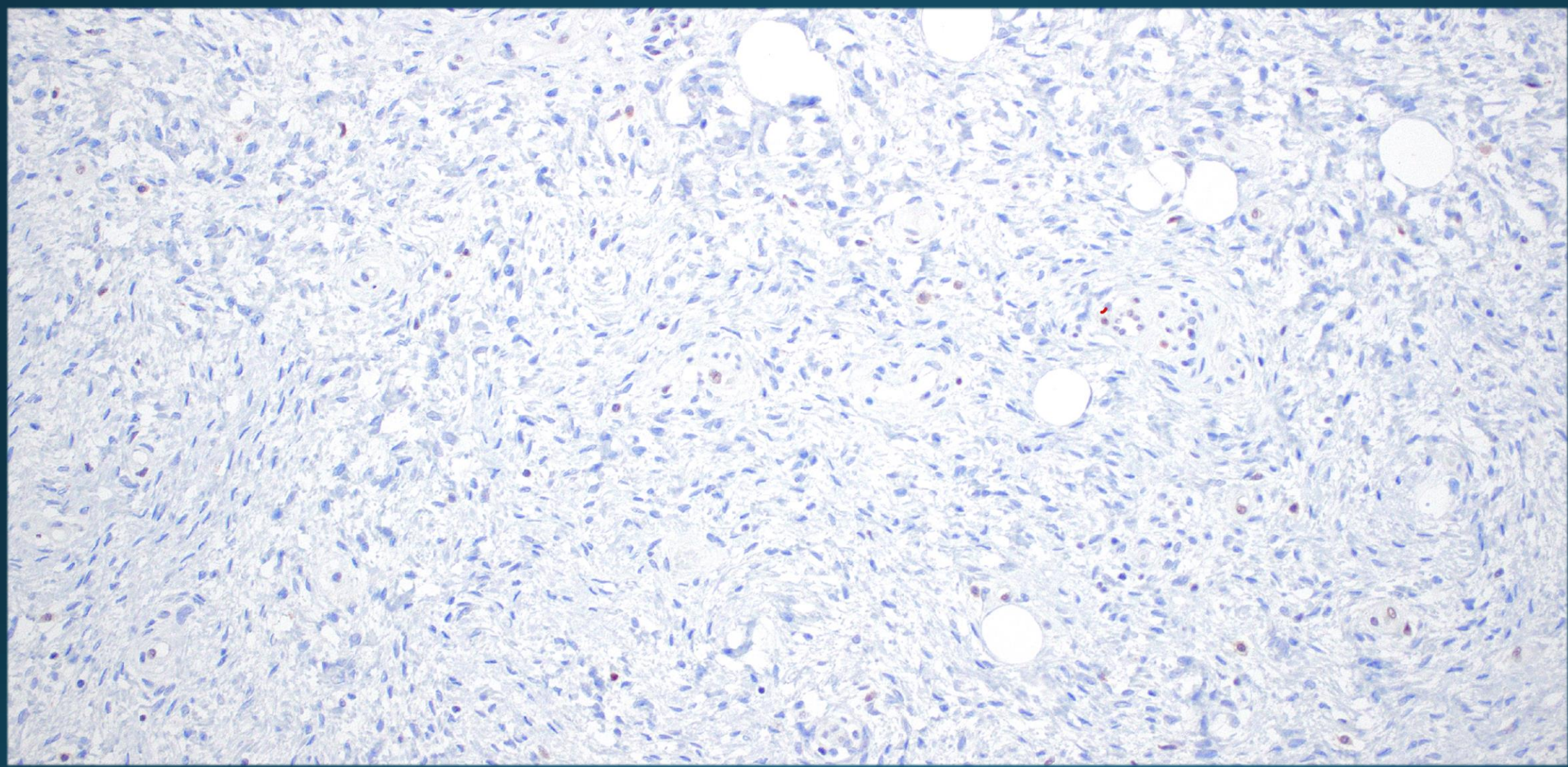
- IHC positivity $\neq$ underlying rearrangement
- Challenging to interpret
 - At margins or distant to margins (**aggressive angiomyxoma**)
 - Frequent nonspecific blush
- Rearrangement in **aggressive angiomyxomas**, **leiomyomas**, **lipomas** (among others)
 - Context essential for interpretation



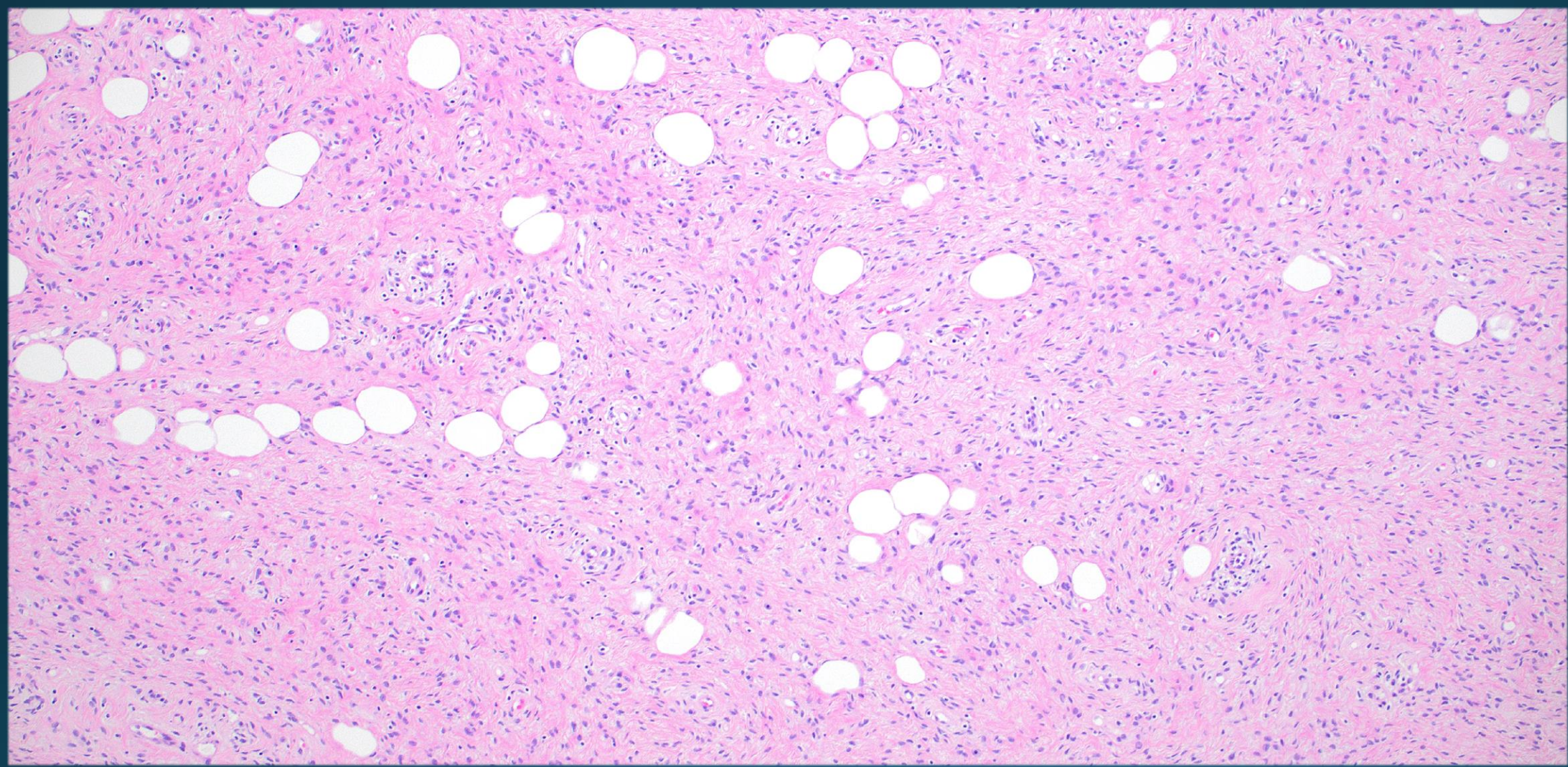
3 cm subcutaneous vulvar mass



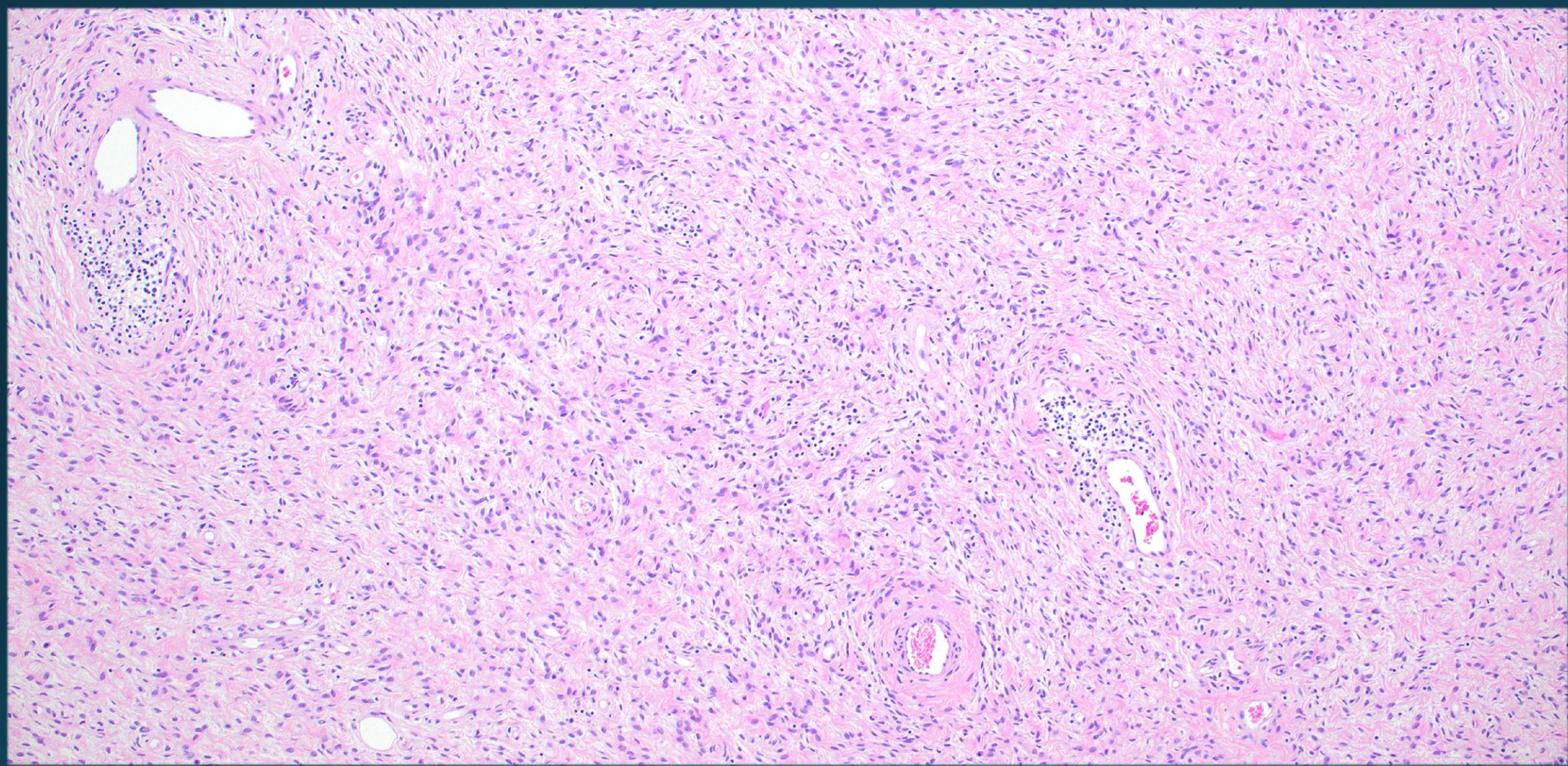
CD34



Rb



3 cm subcutaneous vulvar mass



3 cm subcutaneous vulvar mass

THANK YOU!