Pathology of EHE

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Epithelioid Hemangioendothelioma (EHE) Introduction

- Forms part of the spectrum of **epithelioid vascular tumors**
- **Originally** described as a tumor **of intermediate** (borderline) malignancy
- **Now classified as a malignant vascular neoplasm, albeit of lower grade than conventional angiosarcoma**
- The term “hemangioendothelioma” was coined to designate a vascular tumor with a biologic behavior intermediate between a hemangioma and an angiosarcoma
- **With the exception of EHE, all other types of hemangioendothelioma are considered tumors of intermediate grade**

Intermediate Vascular Tumors
Kaposiform hemangioendothelioma
Papillary intralymphatic angioendothelioma
Retiform hemangioendothelioma
Composite hemangioendothelioma
Pseudomyogenic hemangioendothelioma
Kaposi sarcoma
Malignant Vascular Tumors
Epithelioid hemangioendothelioma
Angiosarcoma
Epithelioid angiosarcoma
Spindle cell angiosarcoma

Hornick, Practical Soft Tissue Pathology, 2019
Enzinger, 7th edition 2020

Epithelioid Vascular Lesions

- **Epithelioid hemangioma, epithelioid hemangioendothelioma, epithelioid angiomatous nodule, epithelioid angiosarcoma**
- Plump **endothelial cells with abundant cytoplasm and occasional intracytoplasmic vacuoles**
- **Endothelial nature often not readily apparent**
- **Keratin** expression may occur
- **Differential diagnosis: epithelioid sarcoma, true epithelial tumors**

EHE

Clinical features

- Adults, slight female predominance; extremely uncommon in children
- **Skin, somatic soft tissue, lung, bone, liver; may arise at nearly any site**
- Histologic features identical, regardless of site, but clinical presentation and **prognosis dependent on anatomic location**
- **Cutaneous** EHE has an **excellent** prognosis
- **Lung or bone** EHE is **more aggressive** than soft counterpart
- **Multifocal lesions** are of **monoclonal origin** (i.e share identical gene fusion breakpoints) ⟶ **metastases**
- Overall metastatic rate 21%, mortality rate 17%

Hornick, Practical Soft Tissue Pathology, 2019
WHO, Classification of Tumours: Soft Tissue and Bone Tumours 2020

Clinical features of EHE by primary site

	Soft Tissue	Bone	Lung	Liver
Age at presentation	Wide range; mean 48 years	Peak in second decade	Wide range; mean 40 years	Wide range; mean 40–45 years
Sex	F = M	F = M	F > M (2–3:1)	F > M (1.5:1)
Solitary vs. multifocal	Solitary	60% multifocal	90% multifocal; 75% bilateral	85% multifocal
Metastatic rate	20%–30%	20%	20%–30%	35%–45%
Mortality rate	15%	20%	40%–45%	35%–45%

F, Female; *M*, male.

Hornick, Practical Soft Tissue Pathology, 2019

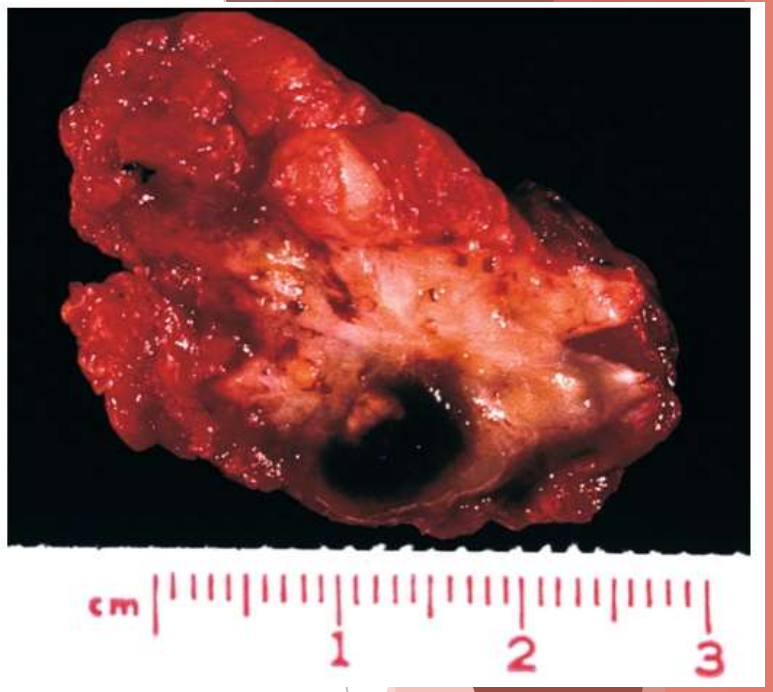
EHE - Pathologic features (I)

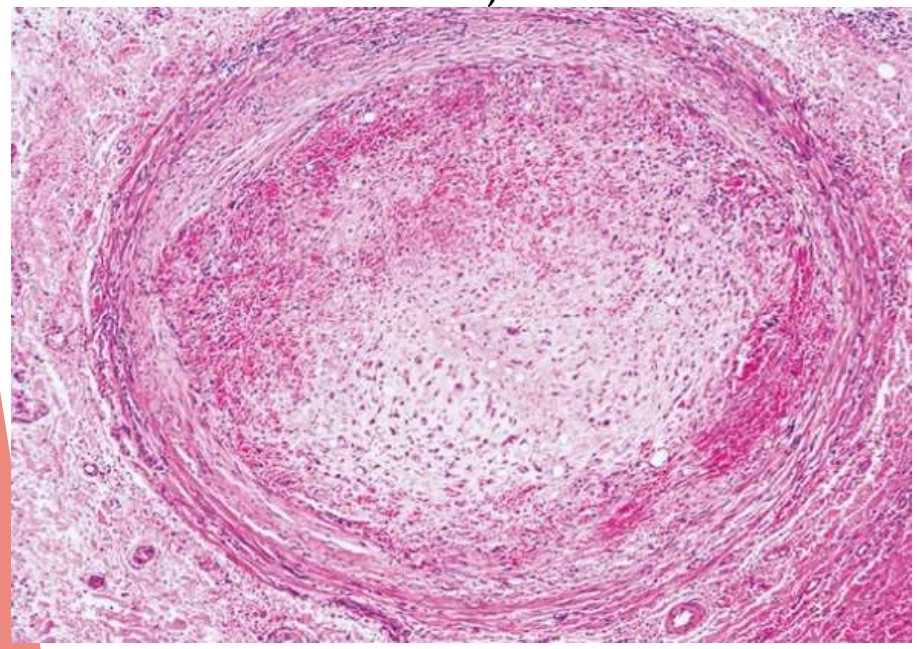
- **In 40-50% of cases origin from a small to medium - size vessel, usually a vein, often grossly** identifiable ⟶ **centrifugal growth of the tumor cells into the adjacent soft tissue**

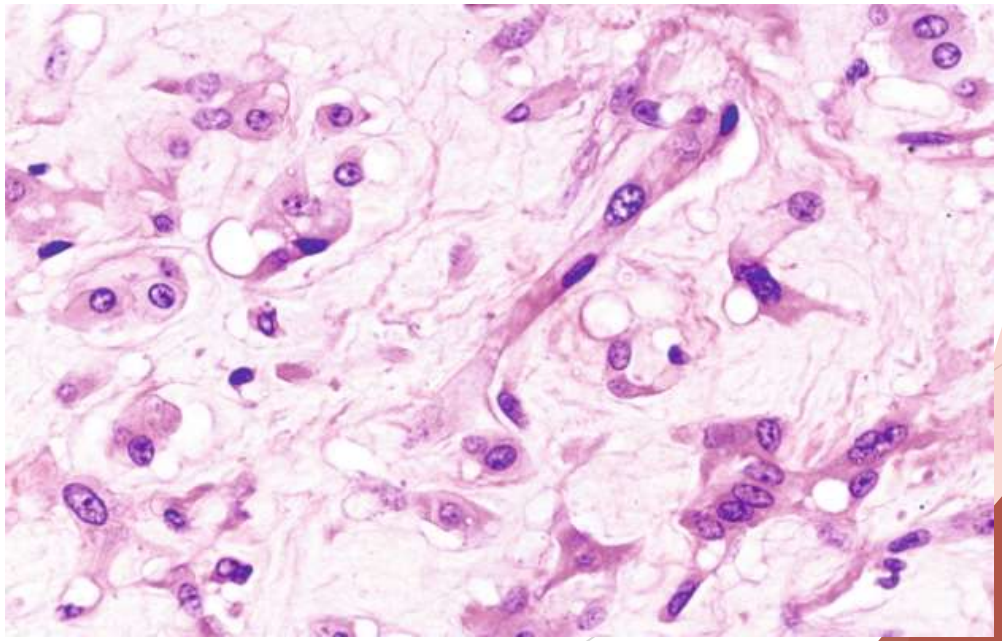
  ✓Not usually seen in cutaneous EHE

- **Primitive vascular differentiation in the form of intracytoplasmic lumina;** large distinct vascular channels rarely seen, usually in the peripheral portions of the tumor

  ✓Intracytoplasmic lumina contain erythrocytes, not mucin (d.d from adenoCa)



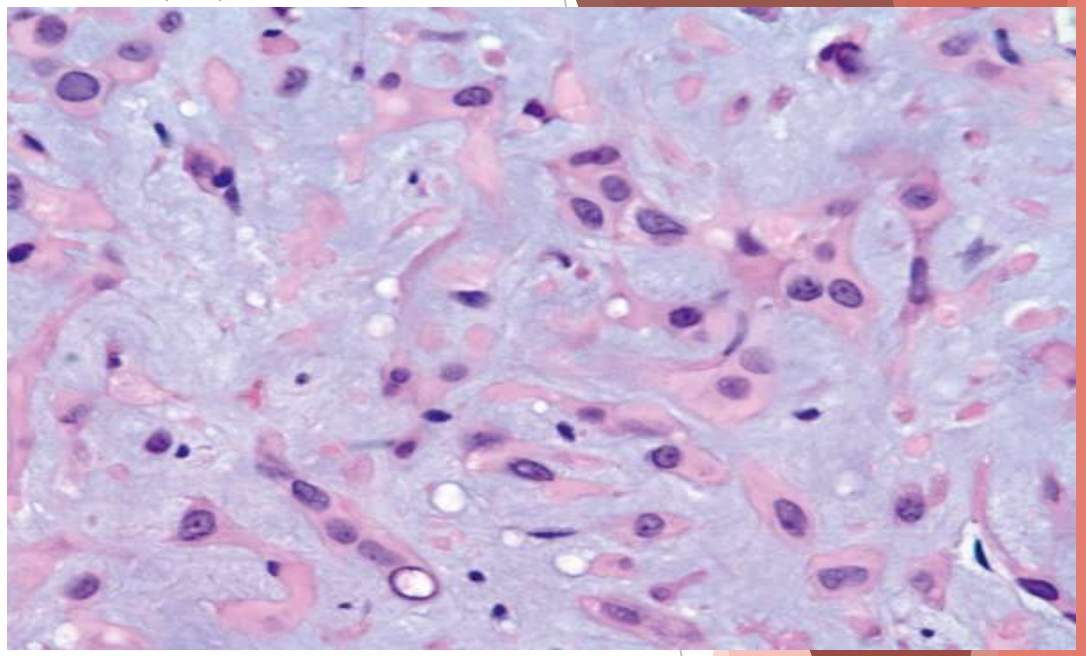


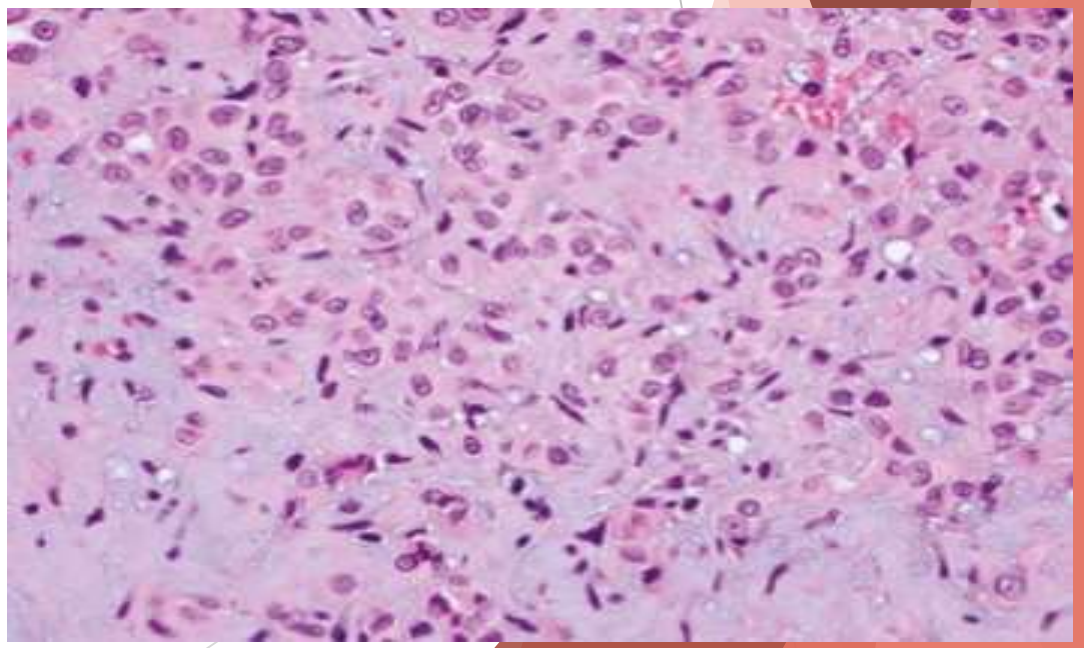


Hornick, Practical Soft Tissue Pathology, 2019
WHO Classification of Tumours: Soft Tissue and Bone Tumours 2020
Enzinger, 7th edition 2020

EHE - Pathologic features (II)

- **Epithelioid or slightly spindled neoplastic cells with eosinophilic cytoplasm and small nucleolus**
- **Anastomosing cords, strands or single cells, occasionally solid nests of neoplastic cells embedded in a myxohyaline stroma mimicking cartilage often with hemorrhage** (d.d from EMC)
- **Sparse inflammatory infiltrate** (d.d from epithelioid hemangioma)
- Subcutaneous and deep-seated tumors are diffusely infiltrative into adjacent fat or skeletal muscle
  - ✓Primary cutaneous tumors are small and circumscribed
- **Mitoses** are **very infrequent** (≤1/10 H.P.F)

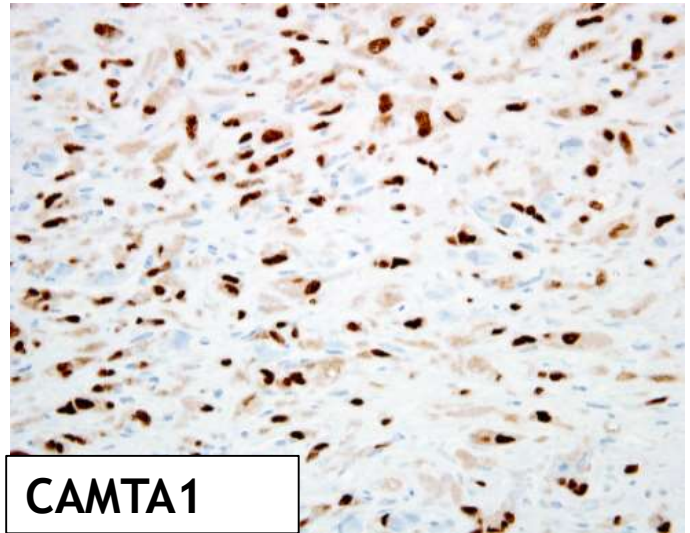




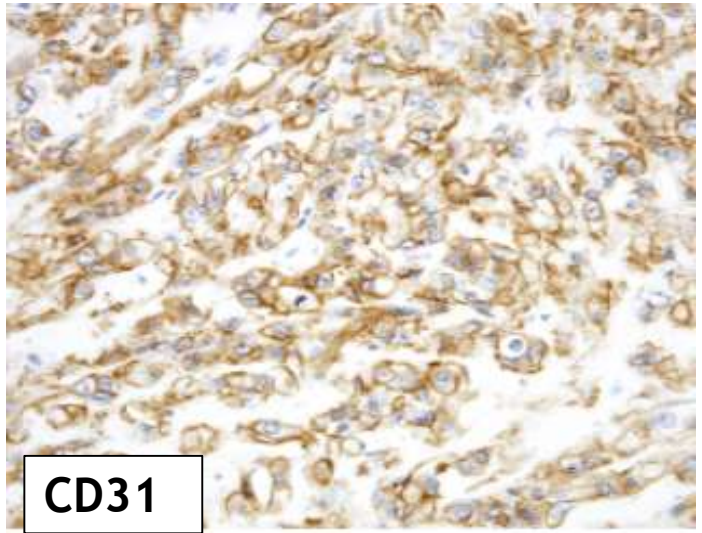
Hornick, Practical Soft Tissue Pathology, 2019
WHO Classification of Tumours: Soft Tissue and Bone Tumours 2020

EHE – immunophenotype and molecular genetics

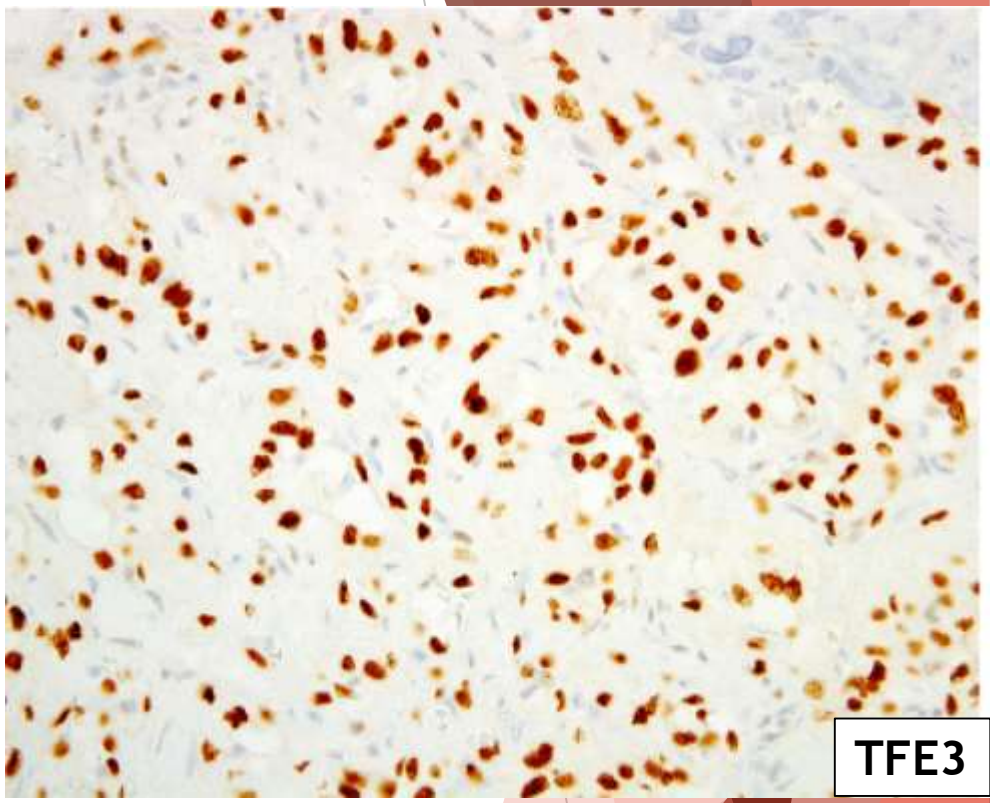
- **Endothelial markers:** CD31, CD34, Fli-1, ERG
  - ✓CD34 less often positive
- **Keratins** positive (may be diffusely expressed) in **25-50%** of cases
  - ✓EMA rarely expressed
- **D2-40 positive** in at least a **subset** of cases
- 50% of cases show actin positivity in the tumor cells
- **Diffuse nuclear reactivity for CAMTA-1 in WWTR1-CAMTA1 rearranged cases (85-90%)**
  - ✓**TFE3 may be also expressed in some CAMTA-1 rearranged**



CAMTA1



CD31



TFE3

- **Diffuse nuclear reactivity for TFE3 in YAP1-TFE3 rearranged cases (~10%)**

Hornick, Practical Soft Tissue Pathology, 2019
WHO Classification of Tumours: Soft Tissue and Bone Tumours 2020

Neoplasm	Genetic alteration (prevalence)	Immunohistochemical markers (sensitivity)
Epithelioid hemangioma	*WWTR1-FOSB*, *ZFP36-FOSB* (20% cellular subtype); *FOS-VIM*, *FOS-MBLNI*, *FOS-lincRNA*, *FOS-*(unknown) (50% cellular subtype)	FOSB: 75% conventional subtype; 100% ALHE subtype; 10% cellular subtype
Composite hemangioendothelioma	*PTBP1-MAML2* (rare) *EPC1-PHC2* (rare)	Synaptophysin (subset of aggressive cases; unknown sensitivity overall)
Pseudomyogenic hemangioendothelioma	*SERPINE1-FOSB* (? 55%) *ACTB-FOSB* (? 45%)	FOSB (nearly 100%)
Epithelioid hemangioendothelioma	*WWTR1-CAMTA1* (85%) *YAP1-TFE3* (5%)	CAMTA1 (85%) TFE3 (5%)

Papke Virch Arch 2020

YAP1/TAZ and the function of Hippo pathway

- **TAZ is the protein encoded by WWTR1**
- YAP1 and TAZ are highly homologous transcriptional coregulators that constitute the **end effectors of the Hippo pathway**, being expressed in the endothelial lineage
- The Hippo pathway constitutes a highly conserved tumor suppressive signal translocation pathway
- The main function of the Hippo pathway is to phosphorylate YAP and TAZ, this resulting in **cytoplasmic sequestration and degradation**
- **YAP/TAZ** function primarily as coactivators of gene transcription **promoting a pro-oncogenic transcriptional program** enhancing cell proliferation, survival and motility
- In a "Hippo-off" state, **YAP/TAZ** remain **unphosphorylated** and **are shuttled to the nucleus** where they promote the transcription of protumorigenic genes

Seavey, Gene Develop 2021
WHO Classification of Tumours: Soft Tissue and Bone Tumours 2020

YAP1 and TAZ Function

- **YAP1 and TAZ are major drivers of chemotherapy resistance, metastasis and cancer stem sell phenotypes in many cancers**

- **TAZ-CAMTA1 fusion** provides a C-terminal **nuclear localization signal** and results in a **constitutively activated TAZ-like protein**

- **In YAP1-TFE3 fused EHE**, the fusion protein acts as a transcription factor that uses the **transactivating domains and nuclear localization sequences of TFE3** and the TEAD DNA **binding site of YAP1** to elaborate a **YAP-like transcriptional program,** analogous to that in CAMTA1 rearranged EHE

Seavey, Gene Develop 2021
Dermawan. Mod Pathol 2021

Genes Dev. 2021 Apr 1;35(7-8):495-511. doi: 10.1101/gad.348221.120. Epub 2021 Mar 25.

WWTR1(TAZ)-CAMTA1 reprograms endothelial cells to drive epithelioid hemangioendothelioma

Jordan H Driskill [1 2], Yonggang Zheng [1], Bo-Kuan Wu [1], Li Wang [1], Jing Cai [1], Dinesh Rakheja [3 4 5 6], Michael Dellinger [7 8], Duojia Pan [1]

Genes Dev. 2021 Apr 1;35(7-8):512-527. doi: 10.1101/gad.348220.120. Epub 2021 Mar 25.

WWTR1(TAZ)- *CAMTA1* gene fusion is sufficient to dysregulate YAP/TAZ signaling and drive epithelioid hemangioendothelioma tumorigenesis

Caleb N Seavey [1 2 3], Ajaybabu V Pobbati [1], Andrea Hallett [1], Shuang Ma [1], Jordan P Reynolds [4], Ryan Kanai [5], John M Lamar [5], Brian P Rubin [1 4]

TAZ(WWTR1)-CAMTA1 is the key driver of EHE tumorigenesis

- **TAZ-CAMTA1 expression in endothelial cells is sufficient to drive the formation of vascular tumors with the distinctive features of EHE**, by initiationg an angiogenic and regenerative-like transcreptional program in endothelial cells
- Inhibition of TAZ-CAMTA1 results in the regression of these vascular tumors
- EHE is driven by dysregulation of the YAP/TAZ signaling mediated by TAZ-CAMTA1
- TAZ-CAMTA1 drives EHE formation with exquisite specificity in a mouse model

TAZ-CAMTA1 signaling potential therapeutic targets in EHE

- EHE possess an **endothelial progenitor phenotype**

Am J Transl Res. 2020 Aug 15;12(8):4561-4568. eCollection 2020.

Fluorescence *in situ* hybridization for *WWTR1–CAMTA1* has higher sensitivity and specificity for epithelioid hemangioendothelioma diagnosis

Panpan Yang [1], Shan Zhang [1], Chaowen Yu [2], Wentian Yan [1], Ningning Yang [1], Nan Li [1], Yuchen Huang [1], Hongchun Chen [1], Zhaogen Cai [1], Yan Zhao [1], Yanzi Qin [1], Xiaomeng Gong [1], Zhenzhong Feng [1]

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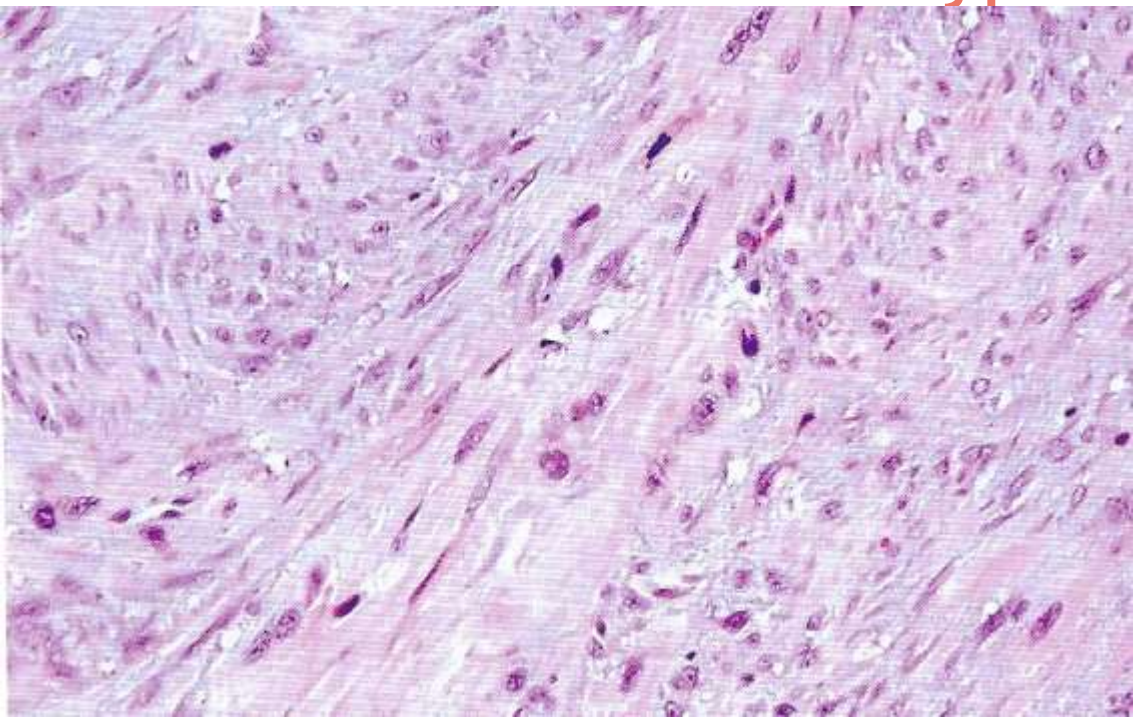
PMID: 32913529 PMCID: PMC7476104

Tumor Type	Total Cases	CAMTA1 Positive	CD31 Positive	CD34 Positive	FLI-1 Positive	ERG Positive
Epithelioid hemangioendothelioma	15	12	15	15	15	15
Epithelioid hemangioma	1	1	1	1	1	1
Epithelioid angiosarcoma	5	3	4	2	4	5
Epithelioid sarcoma	6	2	2	1	2	1
Pseudomyogenic hemangioendothelioma	2	0	1	0	2	2
Malignant melanoma	15	0	3	7	4	2
Malignant mesothelioma	8	0	2	2	0	0

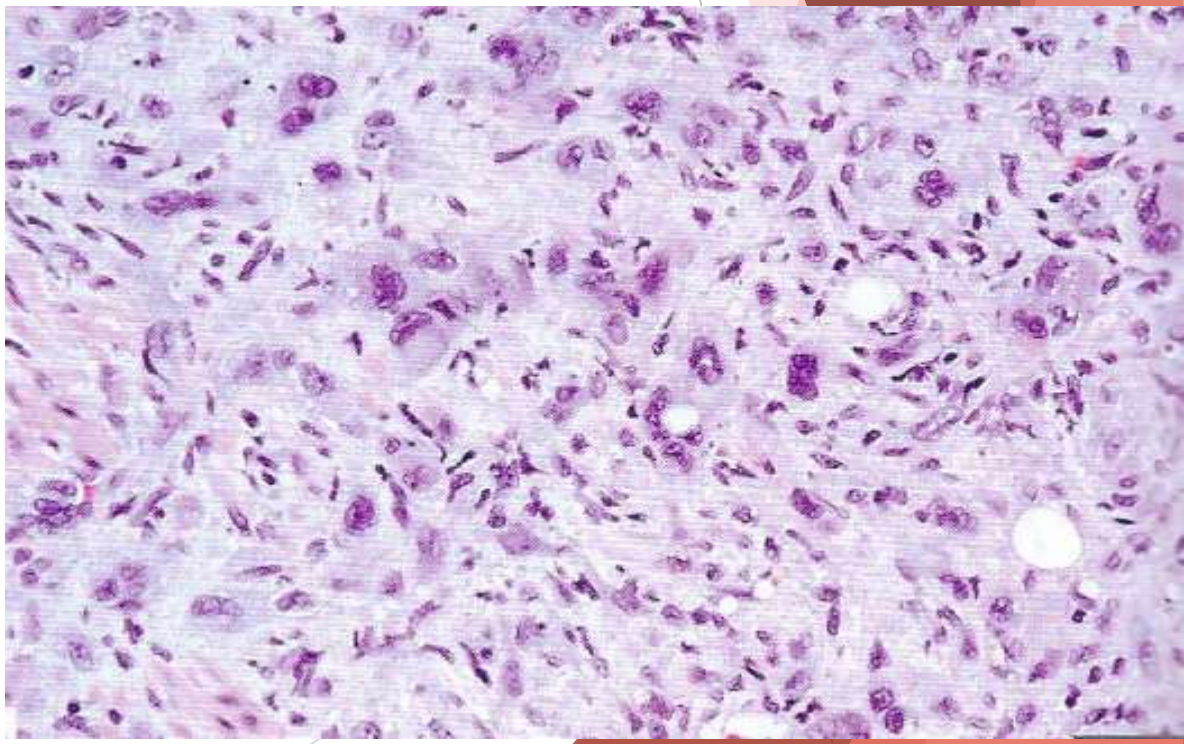
- 12/15 EHE positive for CAMTA1 expression (sensitivity 85.7%)
- **6/37 histologic mimics positive for CAMTA1 expression** (specificity 84%)
- **FISH for WWTR1-CAMTA1** fusion probe positive in 14/15 EHE but **in none of the histologic mimics** (sensitivity and specificity 100%)

EHE with atypical histological features



- Spindle-cell sarcomatous morphology
- **Seen in <10% of EHE**
- **Similarity with epithelioid angiosarcoma**
  - ✓Distinguished by the presence of the foci with EHE features
- **Size >3cm and mitotic rate (>3/50 H.P.F) associated with aggressive behavior**

- **Necrosis**
- **Nuclear pleomorphism with prominent nucleoli**
- **Increased mitotic activity (>3/50 H.P.F)**
- **Atypical histology requires at least 2 features**



Hornick, Practical Soft Tissue Pathology, 2019
WHO 2020, Classification of Vascular Tumors

EHE – Differential diagnosis (I)

- **Metastatic adenocarcinoma** → use of endothelial markers
- **High-grade myxoid liposarcoma** → use of endothelial markers
  [lobular architecture, presence of lipoblasts, S-100 frequently positive]
- **Extraskeletal myxoid chondrosarcoma** → use of endothelial markers
  [lobular architecture, monomorphous spindle cells arranged in a reticular pattern]

Hornick, Practical Soft Tissue Pathology, 2019

EHE – Differential diagnosis (II)

	Epithelioid Hemangioma	Epithelioid Angiomatous Nodule	Epithelioid Hemangioendothelioma[a]	Epithelioid Angiosarcoma
Architecture	Well-formed vessels predominate; focal cordlike or solid areas	Exophytic nodule; solid sheet of endothelial cells	Cords, strands, and single cells	Solid sheets, cleftlike spaces, and large, irregular vascular channels
Margins	Circumscribed	Circumscribed	Infiltrative	At least focally infiltrative
Cell shape	Cuboidal to hobnail	Plump, polygonal	Plump polygonal, oval, or stellate	Plump, polygonal
Cytoplasm	Eosinophilic to amphophilic	Eosinophilic to amphophilic	Pale pink, glassy	Eosinophilic to amphophilic
Intracytoplasmic vacuoles	Occasional	Occasional	Frequent	Variable
Inflammatory infiltrate	Prominent	Mild to moderate	Absent	Variable
Nuclear atypia	Absent to mild	Absent to mild	Mild to moderate	Moderate to severe
Mitotic figures	Rare	Variable	Rare/infrequent	Frequent

Hornick, Practical Soft Tissue Pathology, 2019

EHE – Differential diagnosis (III)

	EHE	ES-Like HE	ES
Cordlike growth pattern	+++	–	–
Coarse nodules often with central necrosis	+ (in malignant forms)	–	+++
Intracytoplasmic vacuoles	Common	Rare	Rare
Myxochondroid background	+++	–	–
Origin from vessel	>50%	No	No
Keratin	+/++	+++	+++
CD31	+++	++	–
CD34	+++	None so far	60%
Molecular genetics	t(7;16) fusion *WWTR1-CAMTA1*	t(7;19) (q22;q13) *SERPINE1-FOSB*	SMARCB1 (INI1) loss

EHE, Epithelioid hemangioendothelioma; ES-like HE, epithelioid sarcoma-like hemangioendothelioma (pseudomyogenic hemangioendothelioma; ES, epithelioid sarcoma)

Enzinger, 7th edition 2020

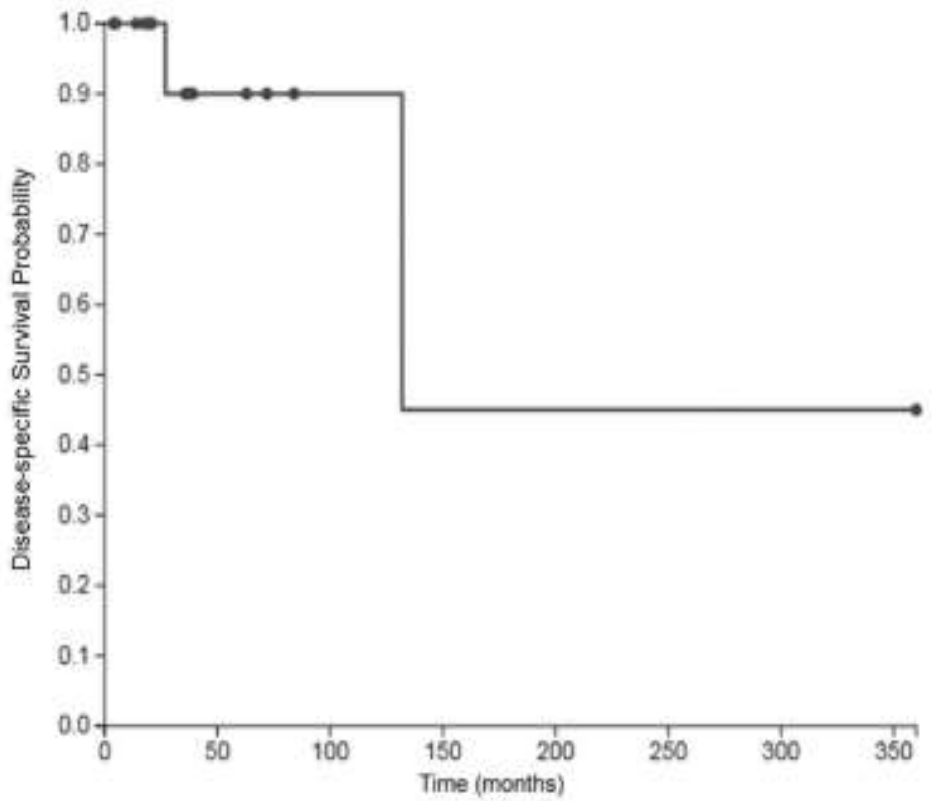
Mod Pathol. 2021 Dec;34(12):2211-2221. doi: 10.1038/s41379-021-00879-7. Epub 2021 Aug 11.

YAP1–TFE3–fused hemangioendothelioma: a multi-institutional clinicopathologic study of 24 genetically–confirmed cases

Josephine K Dermawan [1], Elizabeth M Azzato [1], Steven D Billings [1], Karen J Fritchie [1], Sebastien Aubert [2], Armita Bahrami [3], Marta Barisella [4], Daniel Baumhoer [5], Veronika Blum [6], Beata Bode [7], Scott W Aesif [1], Judith V M G Bovée [8], Brendan C Dickson [9], Mari van den Hout [10], David R Lucas [11], Holger Moch [12], Gabriel Oaxaca [1], Alberto Righi [13], Raf Sciot [14], Vaiyapuri Sumathi [15], Akihiko Yoshida [16], Brian P Rubin [17]

Affiliations + expand

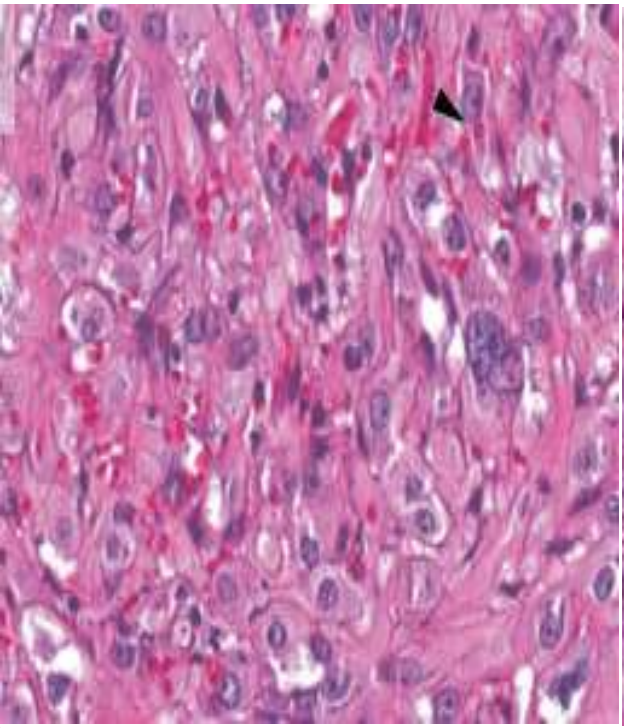
PMID: 34381186 DOI: 10.1038/s41379-021-00879-7

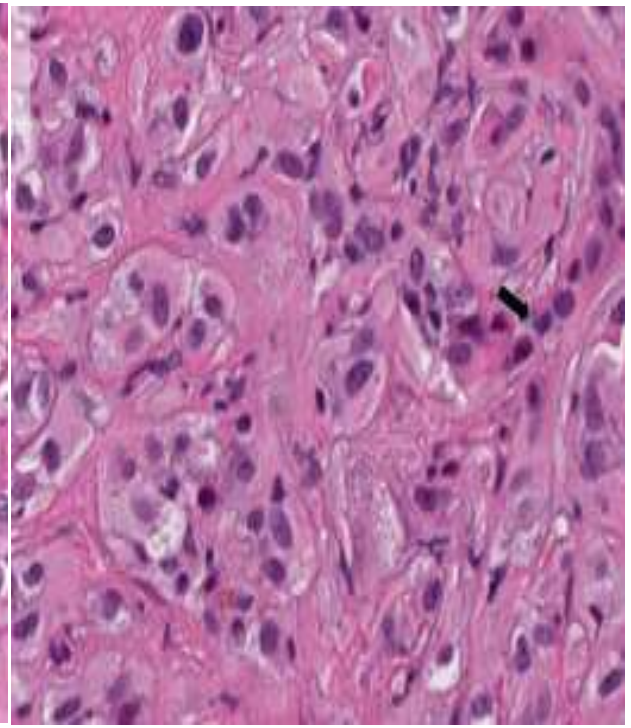


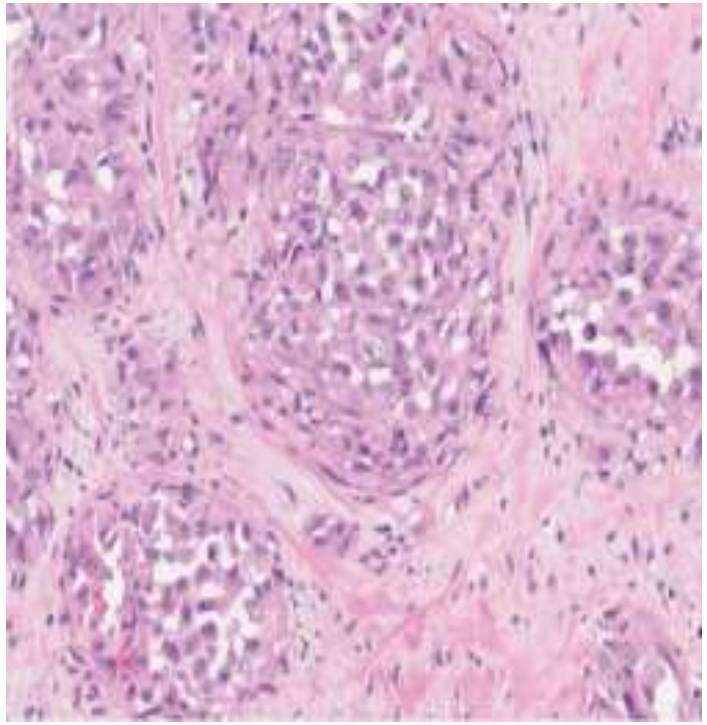
Survival outcome in patients with *YAP1-TFE3* hemangioendothelioma. 5-year (60 months) progression-free survival probability is 88%.

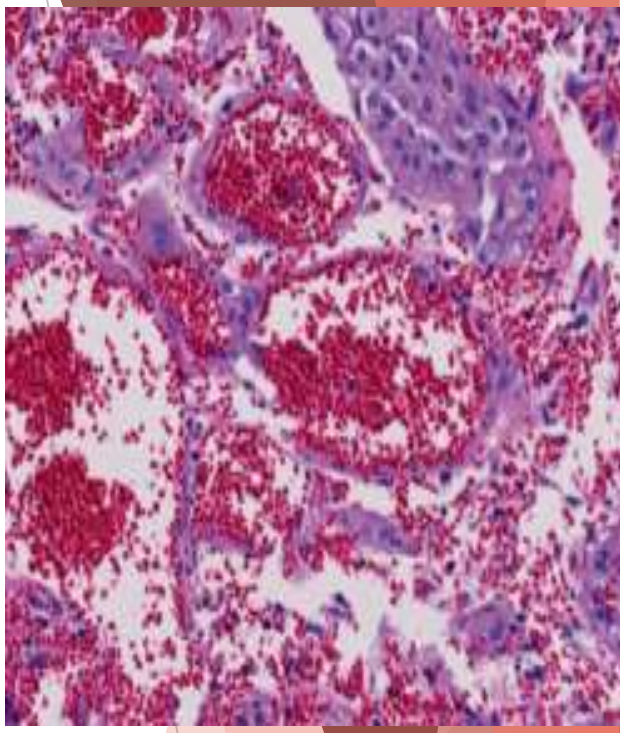
- **Female preponderance**; wide age range, often seen in young patients
- Most common in the **soft tissue(50%)**, followed by bone, lung and liver
- **Multifocal presentation in 2/3 of cases**
- **Despite multifocal and/or metastatic disease >47% of patients survived many years**
- 5 year PFS 88%, 35% of patients alive without disease
- **Proposed to be categorized as a distinct entity rather than a molecular variant of EHE**

Histological features of YAP1-TFE3 fused EHE (I)









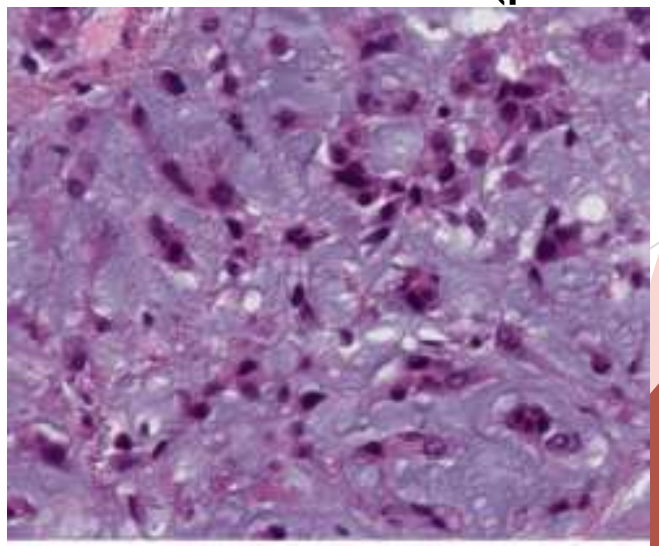
- **Solid sheets of coalescing nests**

✓Arrows → multinucleated cells

✓Arrowheads → lumina with intracytoplasmic red blood cells

Different patterns often coexisting within the same tumor

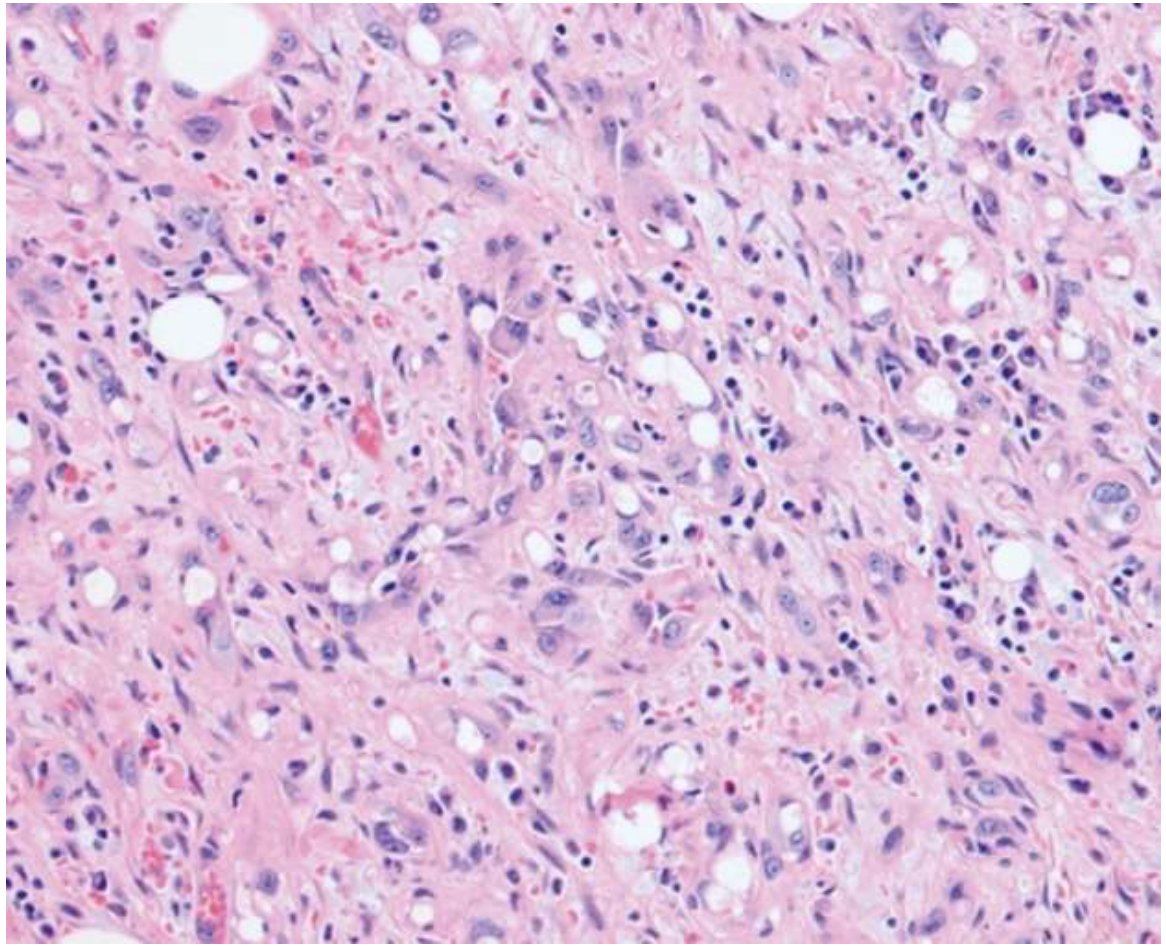
- **Pseudoalveolar and (pseudo)vasoformative pattern**



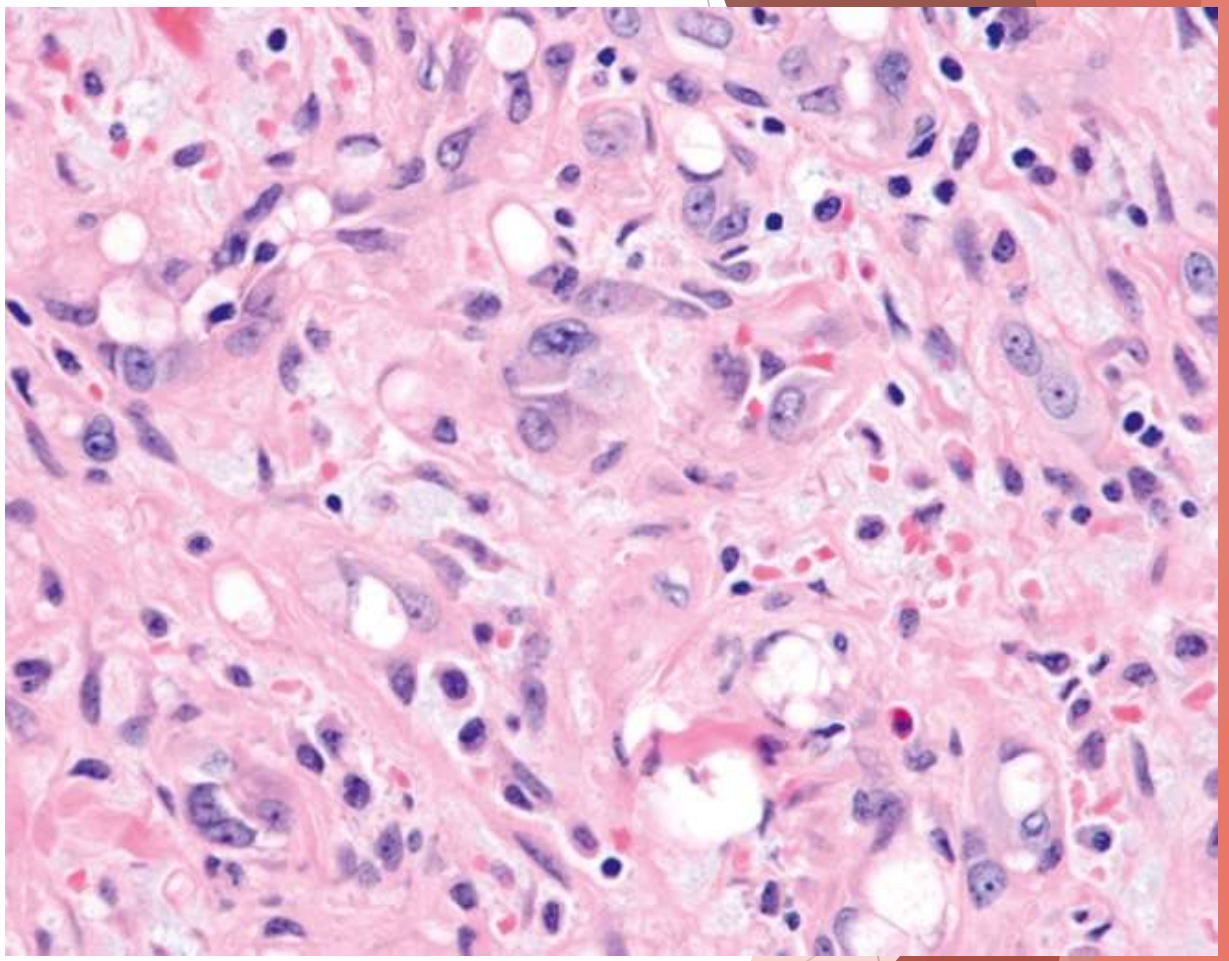
- **Typical (CAMTA1 rearranged) EHE appearance**

Dermawan, Mod Pathol 2021

Histological features of YAP1-TFE3 fused EHE (II)



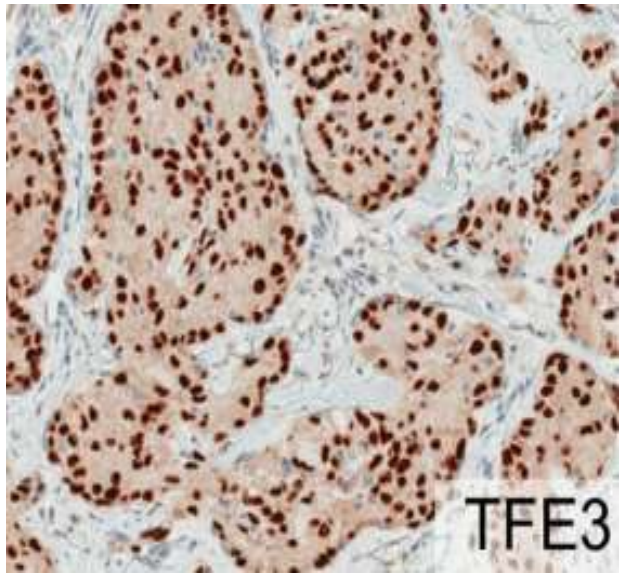
Multicellular vascular channels lined by epithelioid endothelial cells

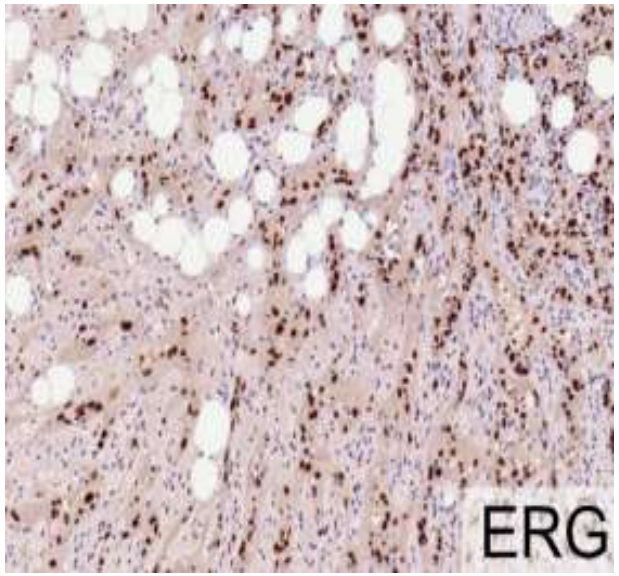


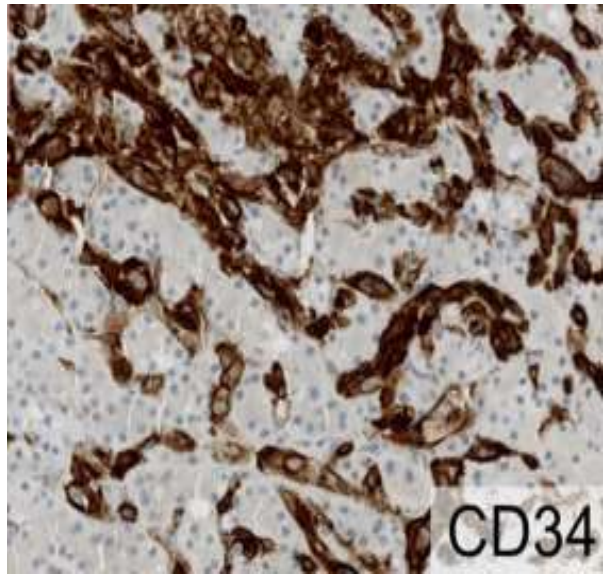
Endothelial cells displaying **cytoplasmic vacuoles**
Presence of **prominent inflammatory eosinophilic infiltrate** → **resemblence to epithelioid hemangioma**

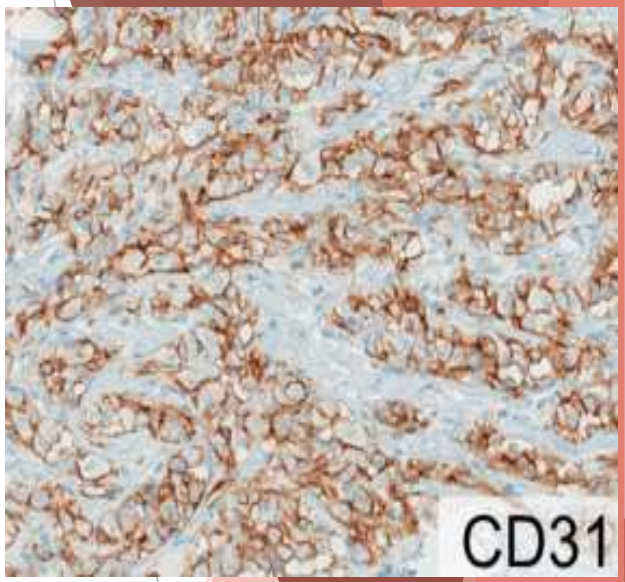
Dermawan, Mod Pathol 2021

IHC of YAP1-TFE3 fused EHE









- Initial screening panel: ERG, CD31, TFE3, CAMTA1
- **TFE3 also identified in a subset of CAMTA1 rearranged EHE ⟶ not recommended to be used in isolation**
- Loss of YAP1 C-terminus expression may be useful
- **TFE3 sensitive but not specific marker ⟶ confirmation with molecular analysis** of YAP1-TFE3 rearranged EHE histology

IHC Marker	# Positive Cases	# Negative Cases	% Positivity
ERG	22 (1 focal)	0	100
CD31	21 (1 focal)	0	100
CD34	15 (3 focal)	3	84
Cytokeratin AE1/AE3	3 (focal)	12	20
TFE3	19	0	100
CAMTA1	1	12	8
Other negative IHC markers (# cases)			
FOSB (4), SMA (3), desmin (6), S100 (9), SOX10 (3), HMB45 (6), CD68 (3)			

Dermawan, Mod Pathol 2021

Differential Diagnosis of YAP1-TFE3 fused EHE

Other neoplasms harboring TFE3 gene rearrangements

- **PEComa** (myomelanocytic phenotype – absence of vascular markers)
- **Xp11 translocation – associated renal cell carcinoma** (absence of vascular markers)
- **Alveolar soft part sarcoma** (absence of vascular markers, presence of ASPSCR1-TFE3 gene fusion)
- **Conventional (CAMTA1 rearranged) EHE** (CAMTA1 + 92% of cases)
- **Epithelioid angiosarcoma** (marked atypia, mitotic activity, necrosis)

Dermawan, Mod Pathol 2021

Am J Surg Pathol. 2021 May 1;45(5):616-626. doi: 10.1097/PAS.0000000000001660.

Clinicopathologic Characterization of Epithelioid Hemangioendothelioma in a Series of 62 Cases: A Proposal of Risk Stratification and Identification of a Synaptophysin–positive Aggressive Subset

Takahiro Shibayama [1], Naohiro Makise [2], Toru Motoi [3], Taisuke Mori [1], Nobuyoshi Hiraoka [1], Kan Yonemori [4 5], Shun-Ichi Watanabe [6], Minoru Esaki [7], Chigusa Morizane [8 5], Tomotake Okuma [9], Akira Kawai [10 5], Tetsuo Ushiku [2], Yasushi Yatabe [1], Akihiko Yoshida [1 5]

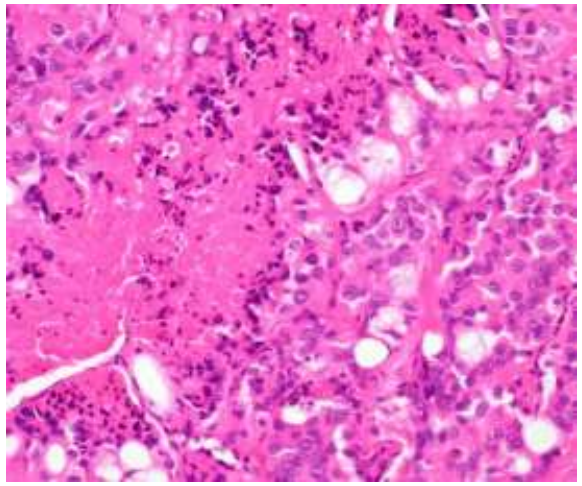
Affiliations + expand

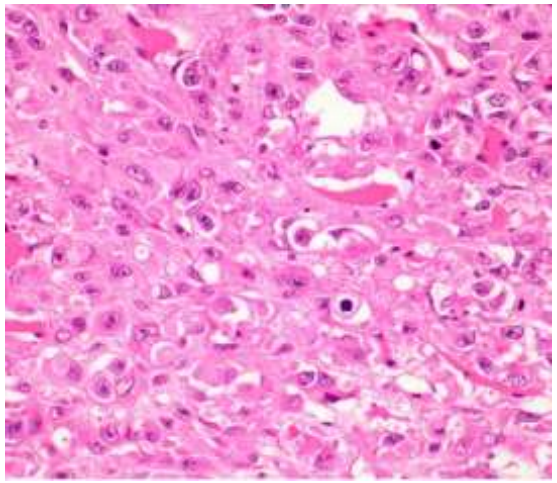
PMID: 33729740 DOI: 10.1097/PAS.0000000000001660

- 62 cases of EHE with CAMTa1/TFE3/WWTR1 alterations
  - ✓CAMTA1 subtype 59/62
  - ✓TFE3 subtype 2/62
  - ✓Variant WWTR1 (WWTR1- ACTL6A) subtype 1/62

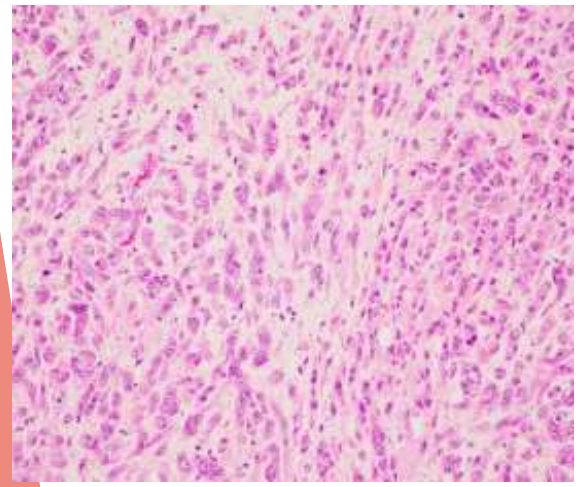
- **35.5%** (22/62) of cases **atypical histology: at least 2 of the following 3 features**
  - ✓**High mitotic activity (1/2 mm^2) [may be applied to needle biopsies]**
  - ✓**High nuclear grade (enlarged nuclei, prominent nucleolus)**
  - ✓**Coagulative necrosis**

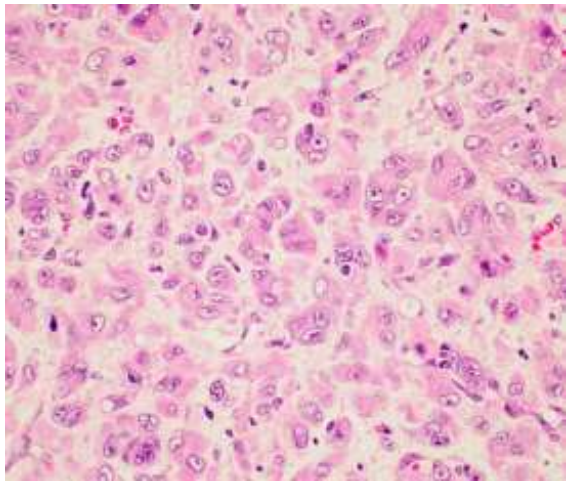
EHE with atypical histology



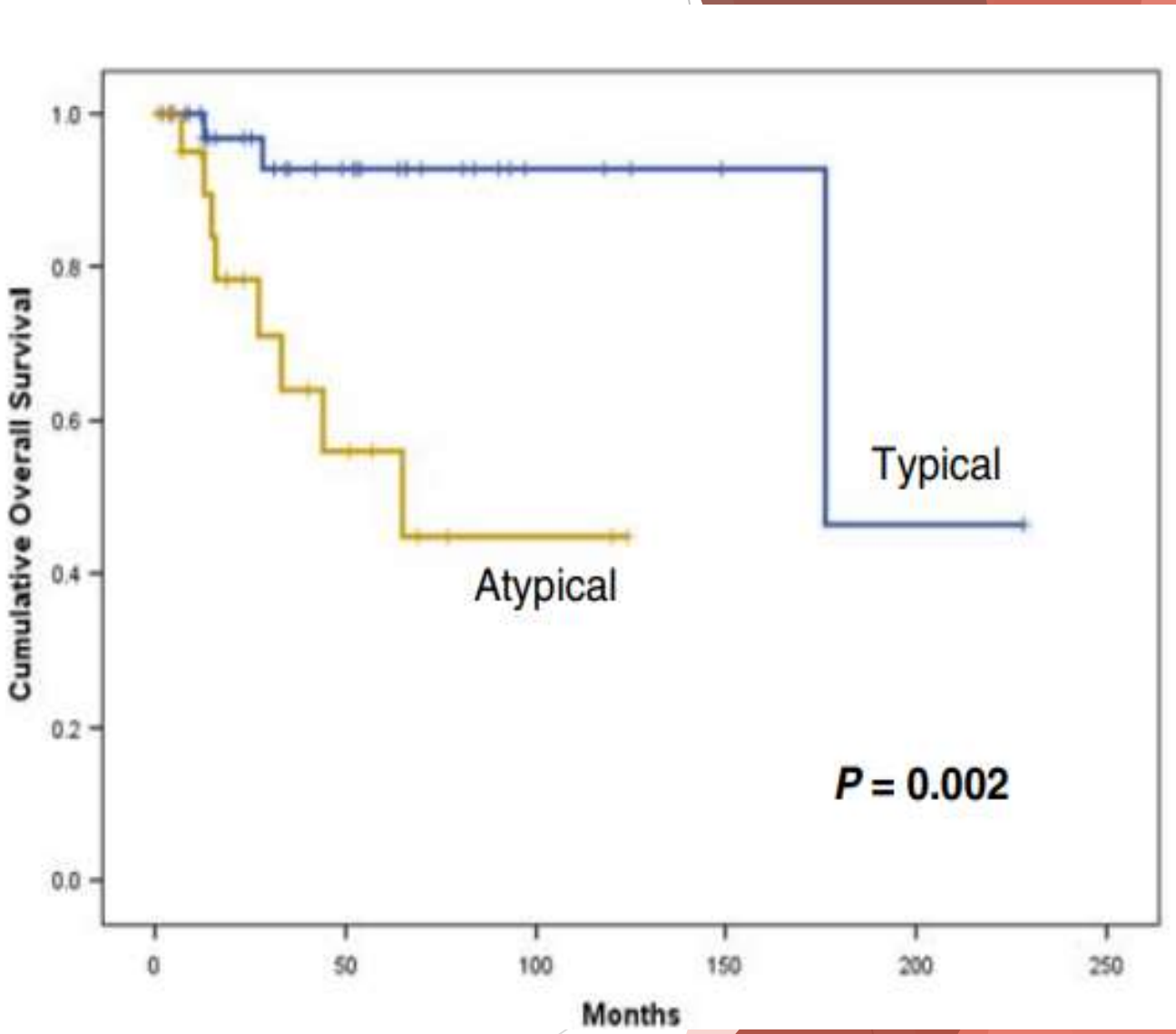


EHE of CAMTA1 subtype with atypical histology





EHE of variant WWT1 subtype with atypical histology – the tumor involved the heart



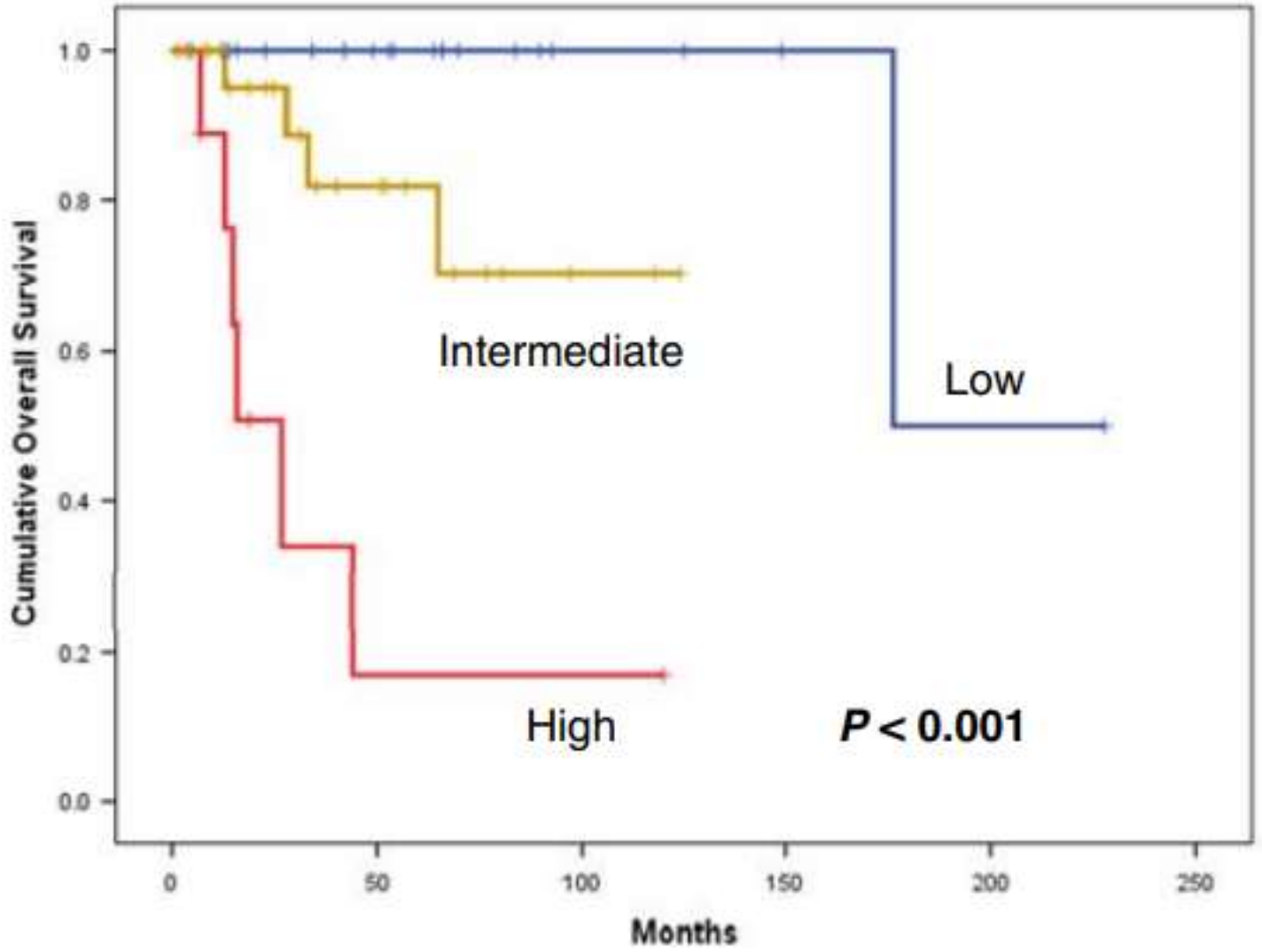
Shibayama, AJSP 2021

Clinicopathologic Characterization of Epithelioid Hemangioendothelioma in a Series of 62 Cases: A Proposal of Risk Stratification and Identification of a Synaptophysin-positive Aggressive Subset

A Proposed System for Risk Stratification of EHE

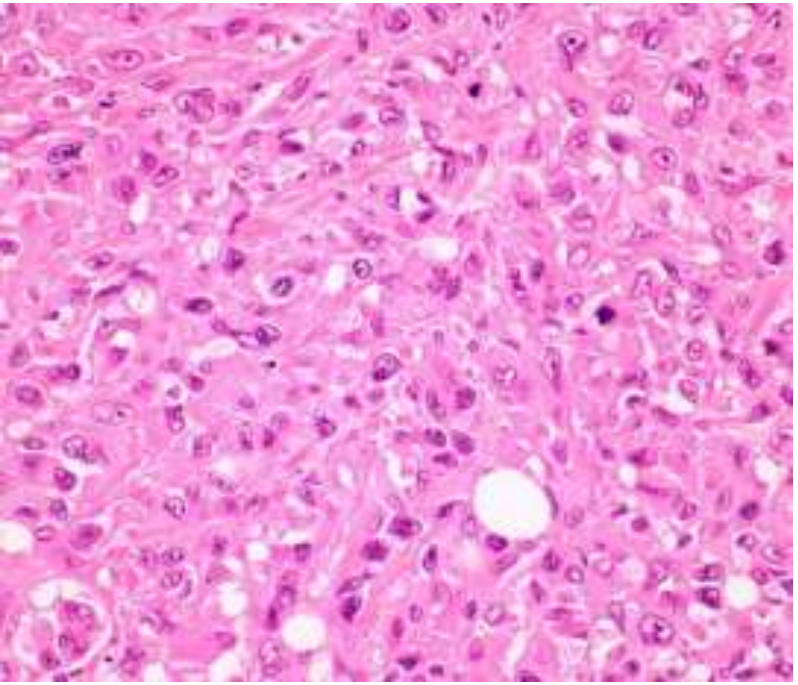
Risk Factors	Score
Tumor size (mm)	
≤ 30	0
> 30	1
Histology	
Typical	0
Atypical*	1
Risk category	**Total score**
Low	0
Intermediate	1
High	2

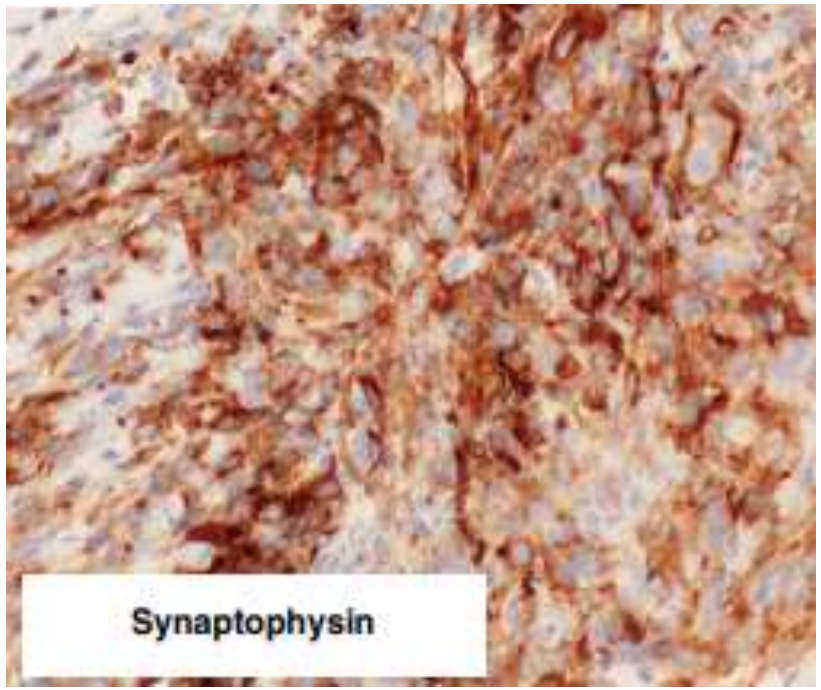
*Atypical histology is defined as having at least 2 of the following 3 findings: mitosis > 1/2 mm^2, high nuclear grade, and coagulative tumor necrosis. Any tumor histology that does not meet these criteria is considered typical.

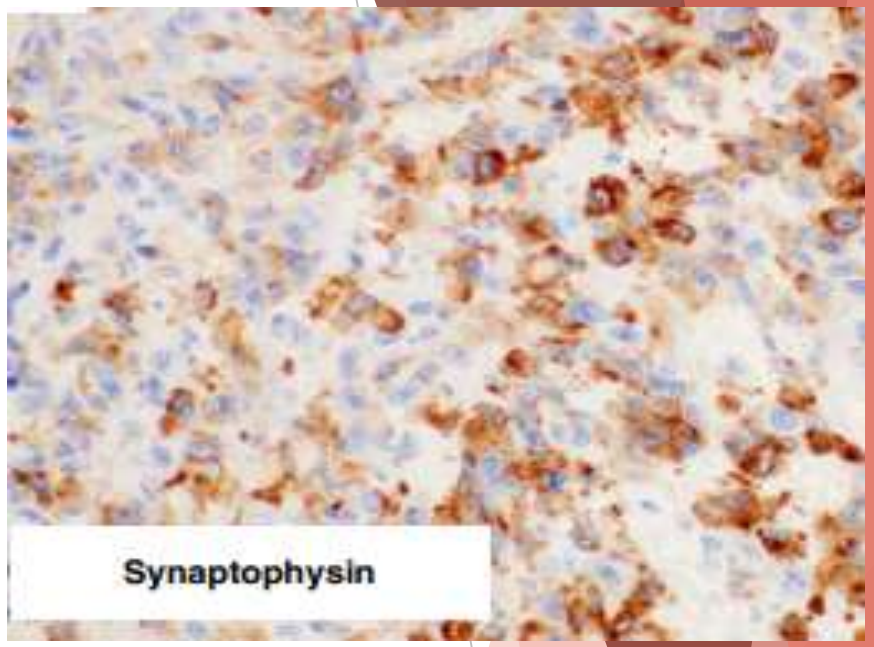


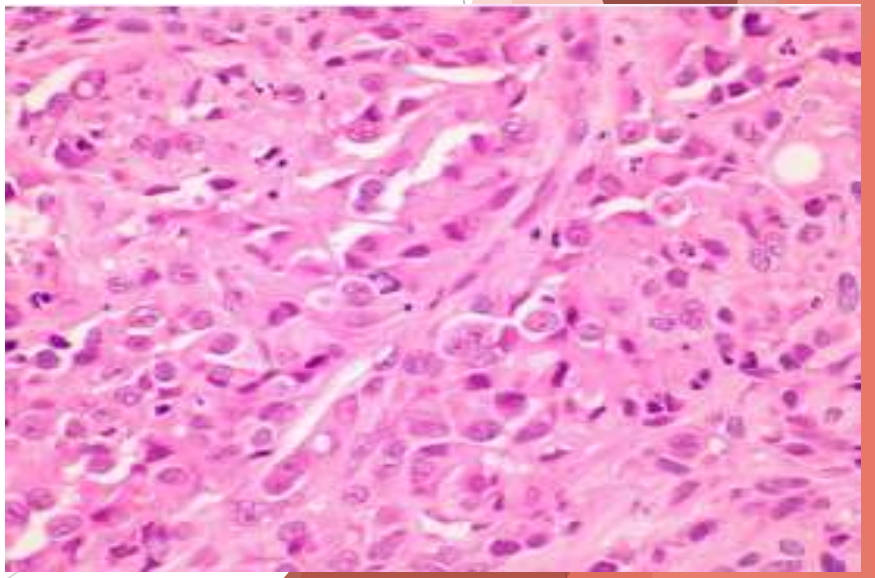
- **Large tumor size (>3cm) and histologic atypia the only parameters significantly associated with shorter survival (univariate and multivariative analysis)**

Synaptophysin expression in EHE





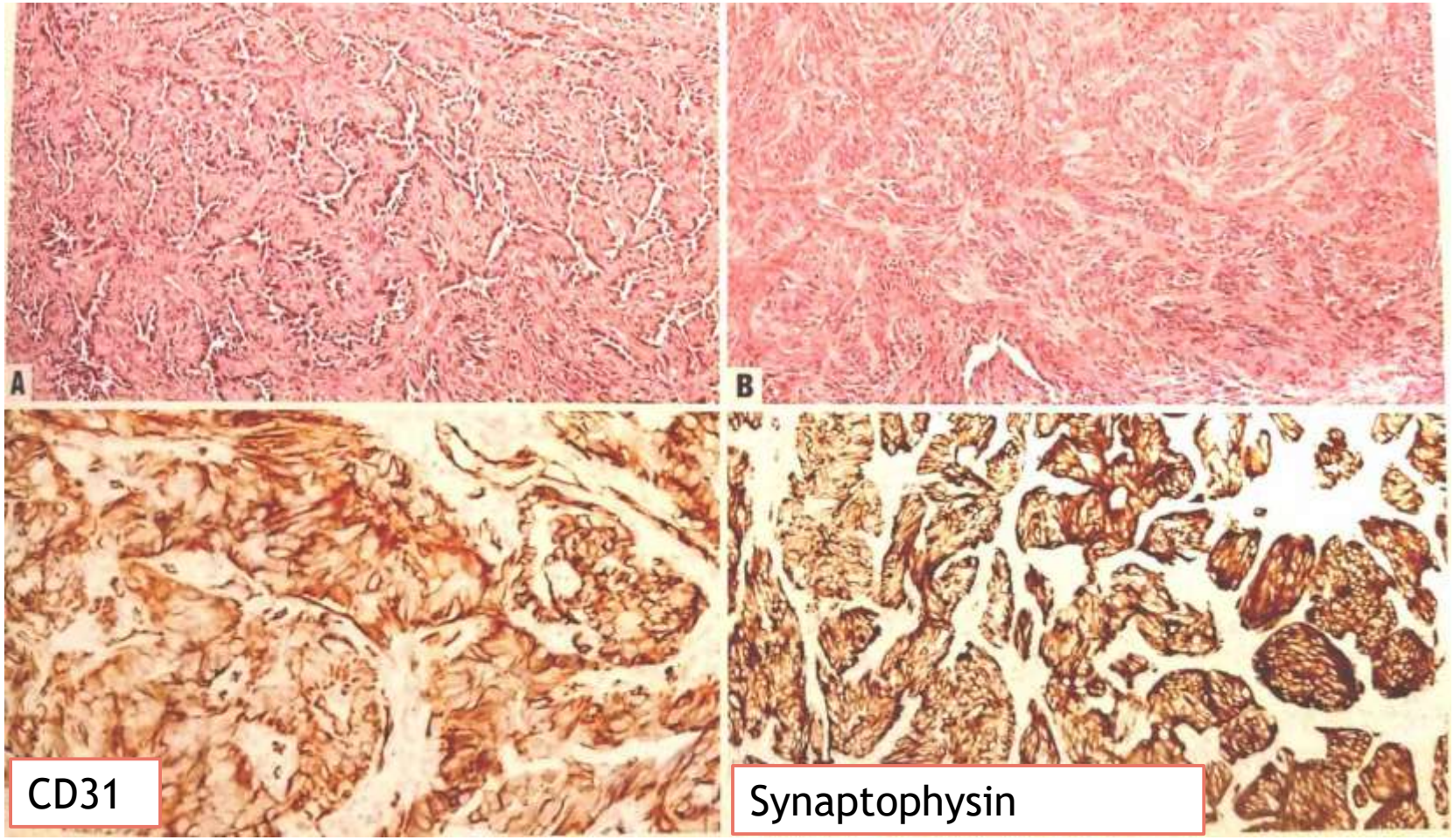




- **Strong expression in 6.4% of EHE**
- **Other neuroendocrine markers negative**
- **All cases had an atypical histology and pursued a very aggressive course**
  - ✓d.d from neuroendocrine carcinoma

Shibayama, AJSP 2021

Synaptophysin expressions in hemangioendothelioma



- Synaptophysin expression also described **in a subset of composite hemangioendothelioma** with aggressive behavior and in **hobnail hemangioendothelioma**

- A component of composite hemangioendothelioma may have features of **EHE (CAMTA1 negative)**

Perry, Mod Pathol 2017

Case Reports > Genes Chromosomes Cancer. 2020 Jul;59(7):389-395. doi: 10.1002/gcc.22839.
Epub 2020 Mar 20.

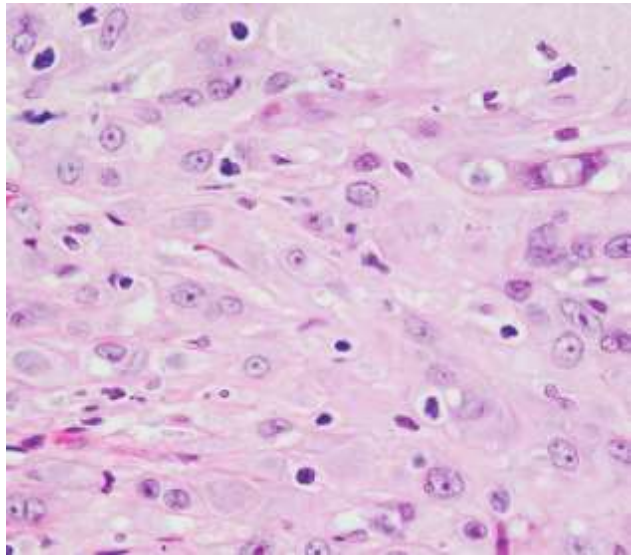
Variant WWTR1 gene fusions in epithelioid hemangioendothelioma–A genetic subset associated with cardiac involvement

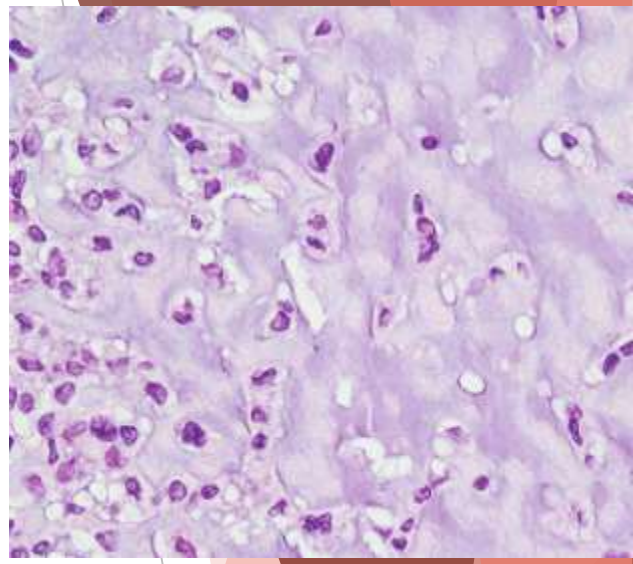
Albert J H Suurmeijer [1], Brendan C Dickson [2], David Swanson [2], Yun S Sung [3], Lei Zhang [3], Cristina R Antonescu [3]

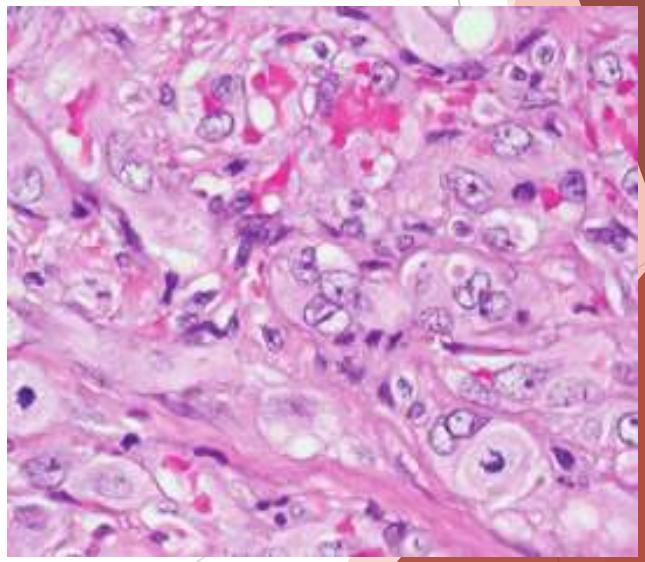
Affiliations + expand

PMID: 32170768 PMCID: PMC8258701 DOI: 10.1002/gcc.22839

- A subset of EHE cases contain novel WWTR1 fusions partners including MAML2 and ACTL6A
- **Variant WWTR1 EHE** shows a **striking predilection for cardiac presentation**
- ACTL6A is a subunit of the SW1/SNF complex and enhances the transcriptional activity of nuclear YAP/TAZ by inhibition of YAP proteosomal protein degradation







Morphologic spectrum of cardiac tumors with WWTR1 variant fusion

Comparative Study > Mod Pathol. 2020 Apr;33(4):591-602. doi: 10.1038/s41379-019-0368-8.
Epub 2019 Sep 19.

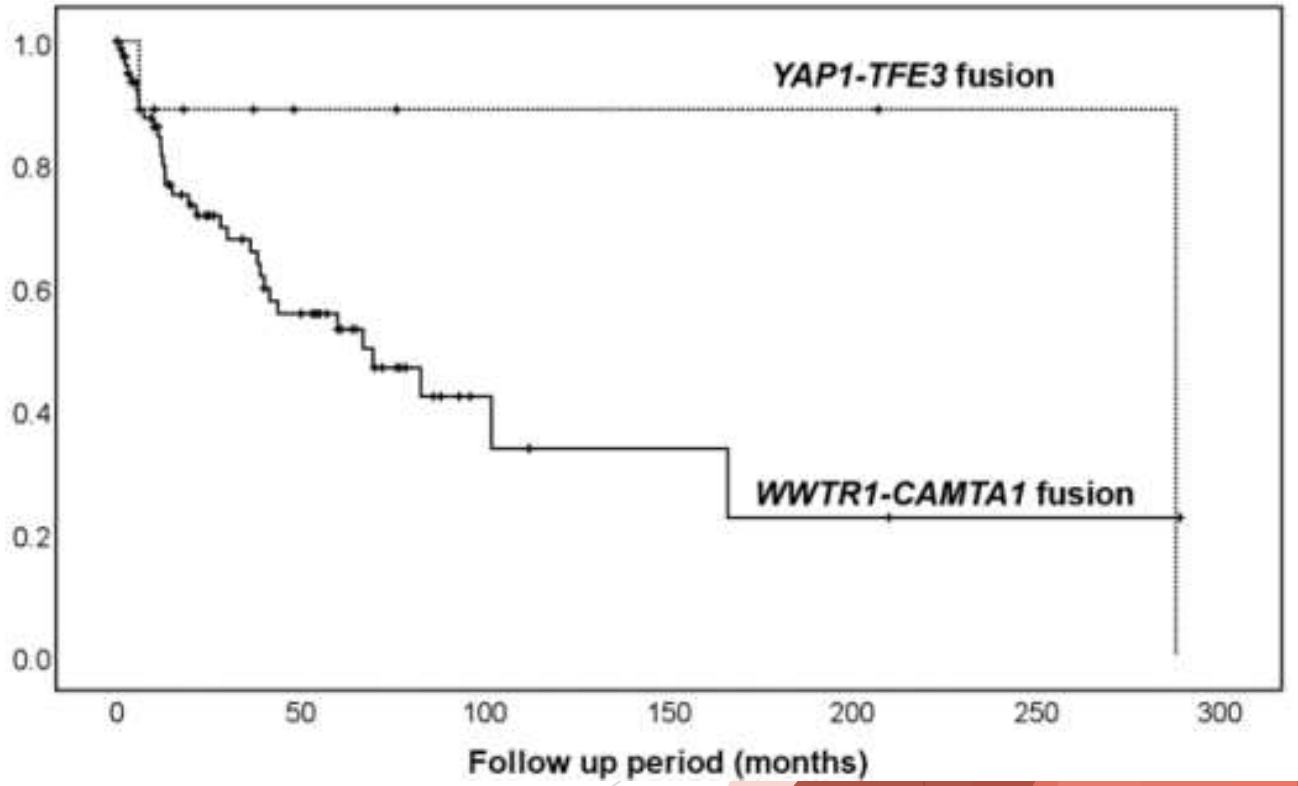
Prognostic stratification of clinical and molecular epithelioid hemangioendothelioma subsets

Evan Rosenbaum [1], Bhumika Jadeja [2], Bin Xu [3], Lei Zhang [3], Narasimhan P Agaram [3], William Travis [3], Samuel Singer [2], William D Tap [1 4], Cristina R Antonescu [5]

Affiliations + expand

PMID: 31537895 PMCID: PMC7228463 DOI: 10.1038/s41379-019-0368-8

- **Secondary genetic alterations in >50% of the cases**
- Conventional CAMTA-1 rearranged EHE less favorable outcome (59%) compared to YAP1-TFE3 rearranged subset (86%)
- Multifocality, pleural involvement, lymph node or distant metastases associated with a significantly worse outcome



> Am J Surg Pathol. 2020 Dec;44(12):1677-1684.
doi: 10.1097/PAS.0000000000001575.

Recurrent YAP1 and MAML2 Gene Rearrangements in Retiform and Composite Hemangioendothelioma

Cristina R Antonescu [1], Brendan C Dickson [2], Yun-Shao Sung [1], Lei Zhang [1], Albert J H Suurmeijer [3], Albrecht Stenzinger [4], Gunhild Mechtersheimer [4], Christopher D M Fletcher [5]

Affiliations + expand

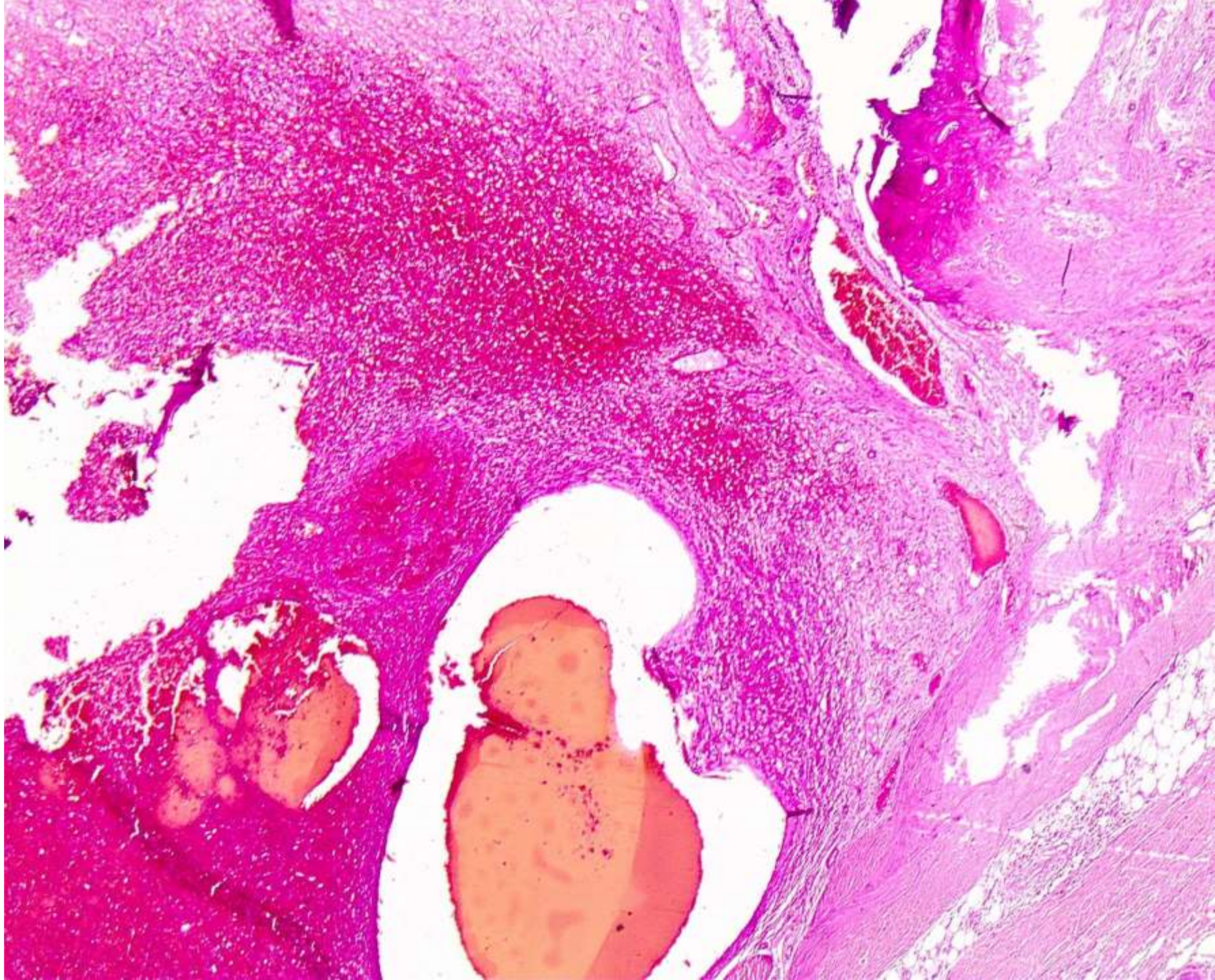
PMID: 32991341 PMCID: PMC7773139
DOI: 10.1097/PAS.0000000000001575

- **38% of retiform hemangioendothelioma (RHE) and 27% of composite hemangioendothelioma (CHE) showed YAP1 gene rearrangements (usually YAP1-MAML2 fusion)**
- YAP1 positive RHE preferentially occurred in moles and lower limb
- YAP1 positive CHE preferentially occurred in female children at acral sites
- **PTBP1-MAML2 fusion** was seen **in a neuroendocrine CHE** which appears to be genetically distinct from conventional RHE and CHE

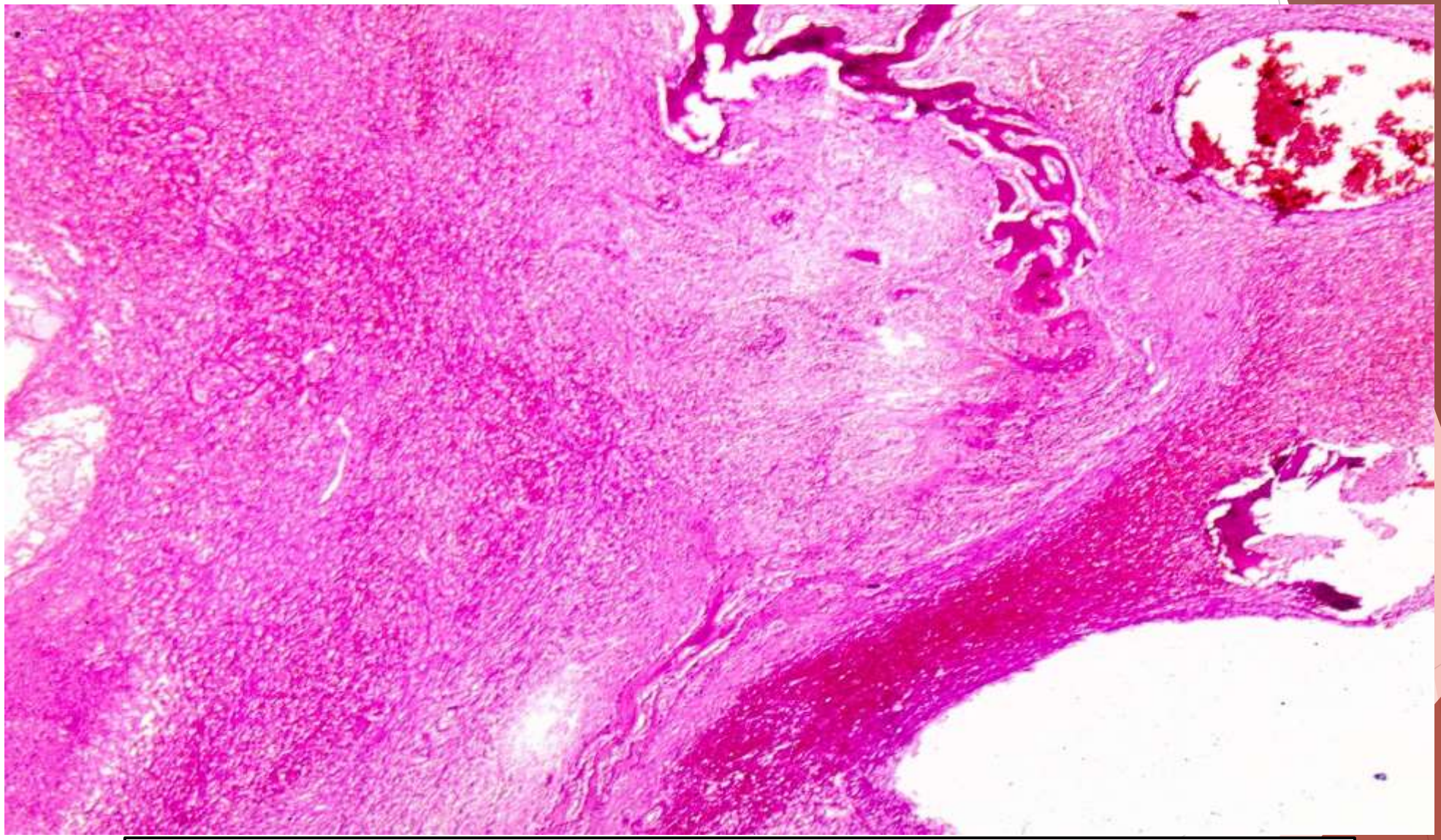
* **Both YAP1 and MAML2 related fusions are preferentially, but not exclusively, seen in vascular lesions**

Case #1

- Male, 40 year-old
- Rib tumor measuring 4.2cm extending into the surrounding soft tissues

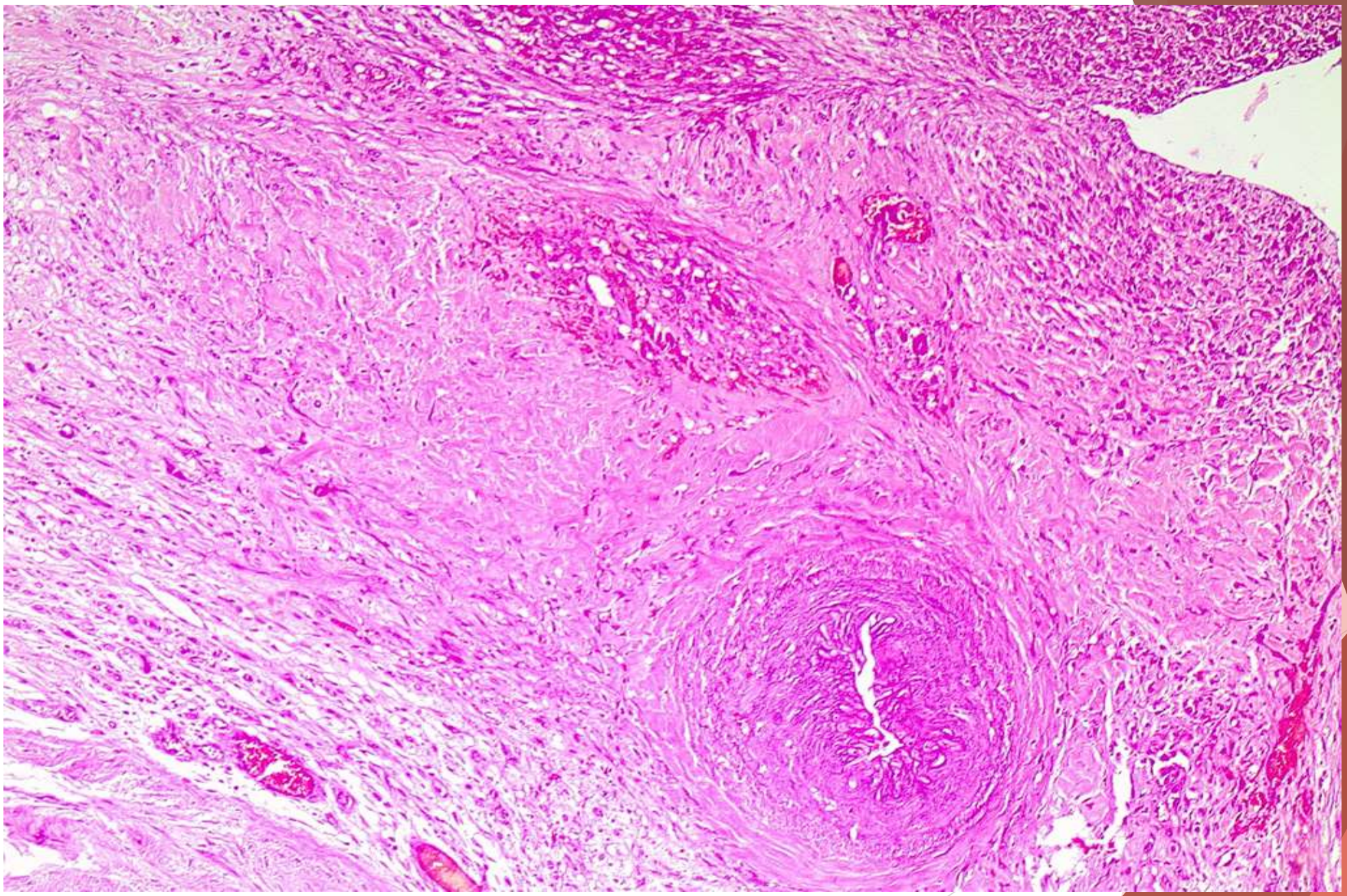


Case #1



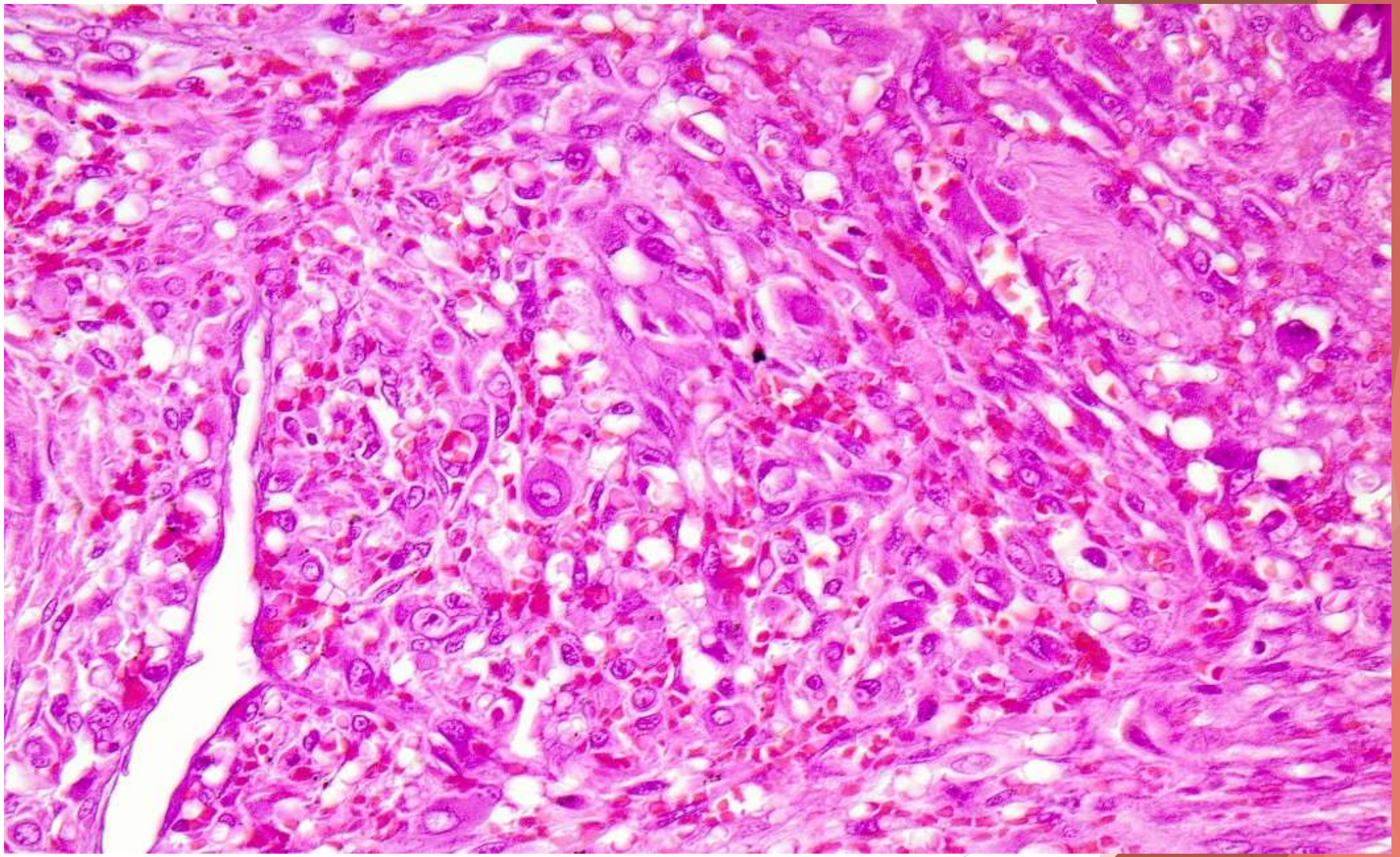
- Heavily hemorrhagic tumor permeating bone spicules
- Presence of ectatic blood filled vessels

Case #1



Neoplastic cells surrounding and invading venous vessels

Case #1

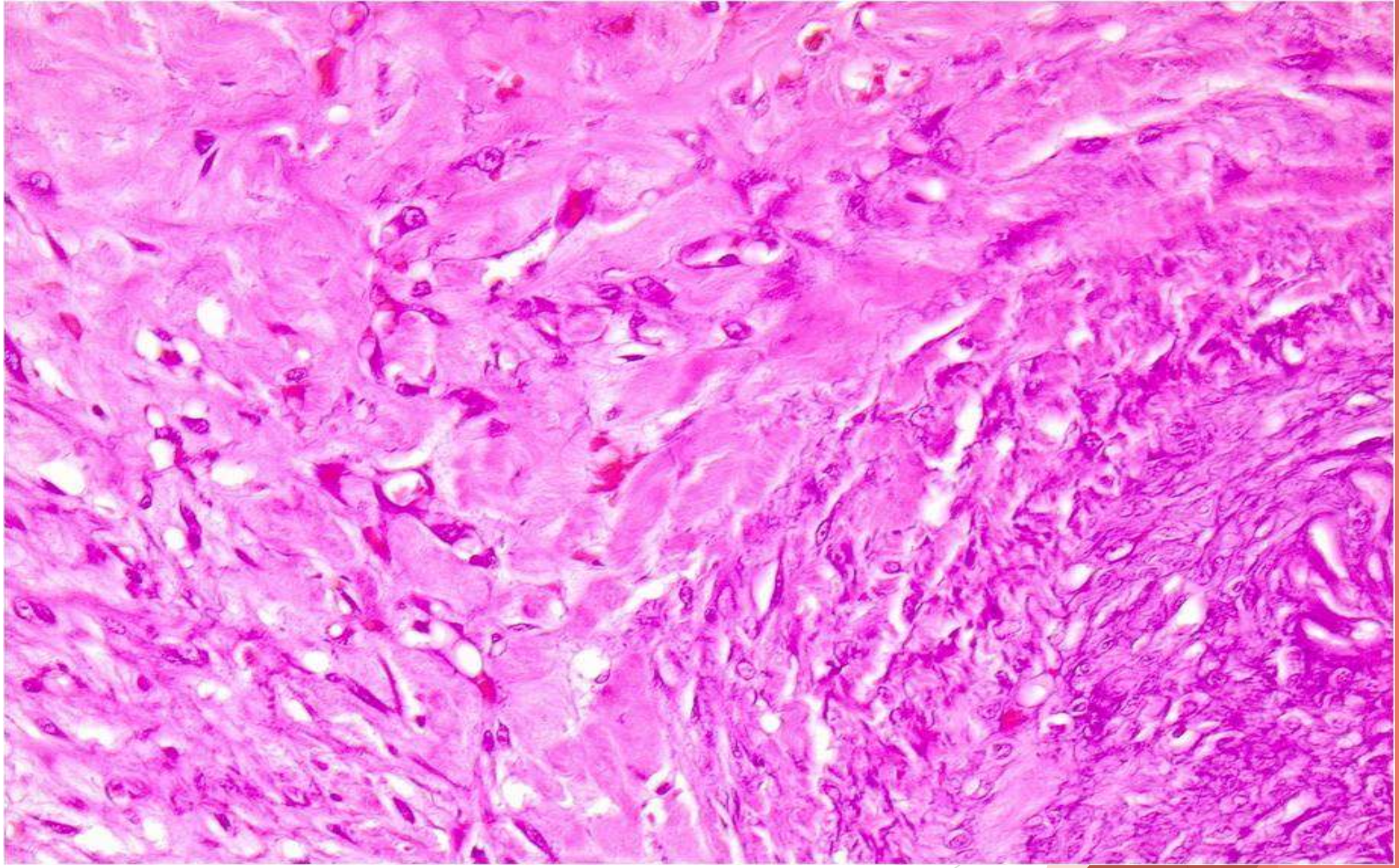


Vacuolated epithelioid cells with enlarged vesicular nuclei, small nucleoli and eosinophilic cytoplasm

Case #1

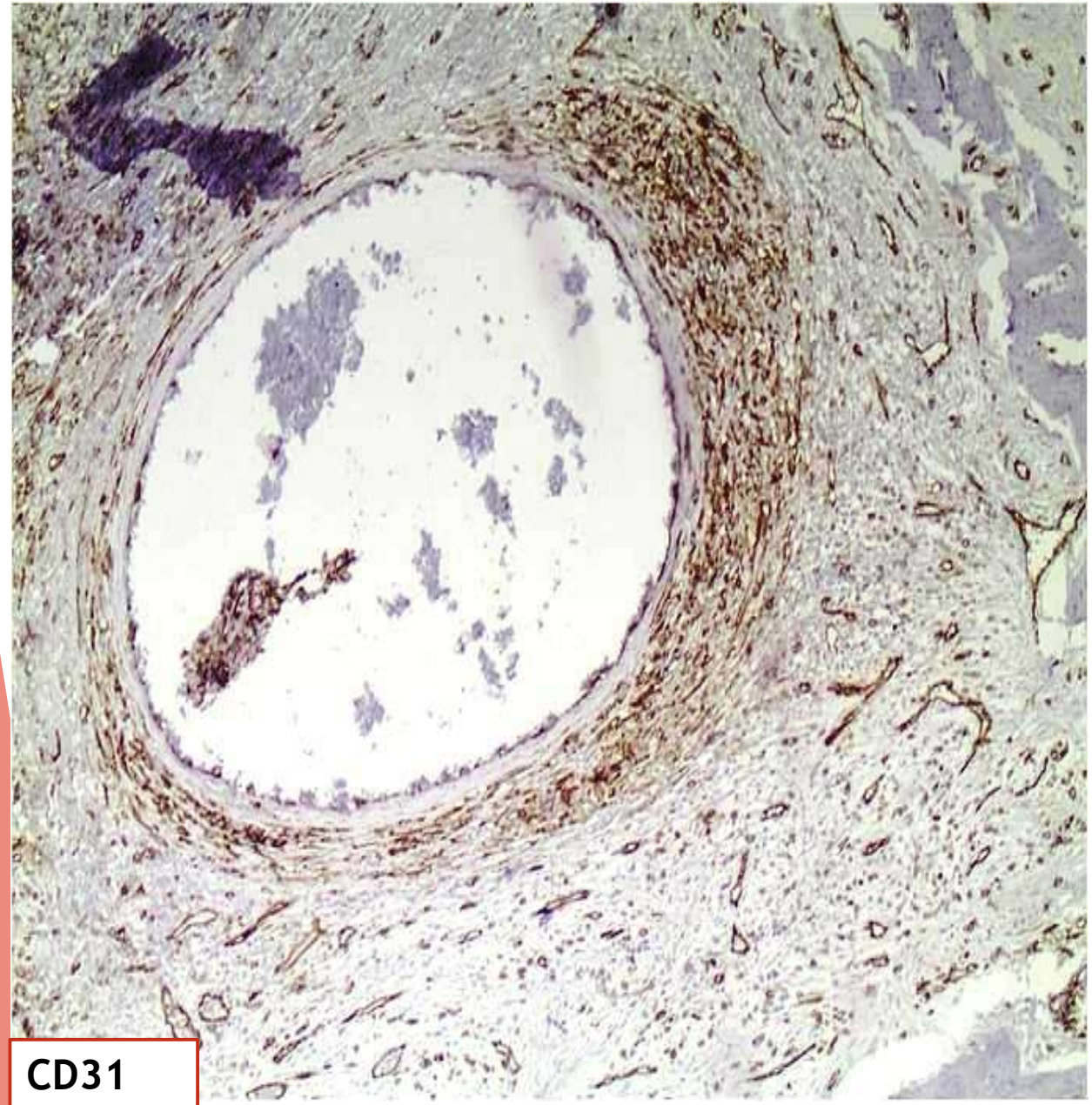
✓Mitoses very infrequent

✓Sparse inflammatory cells

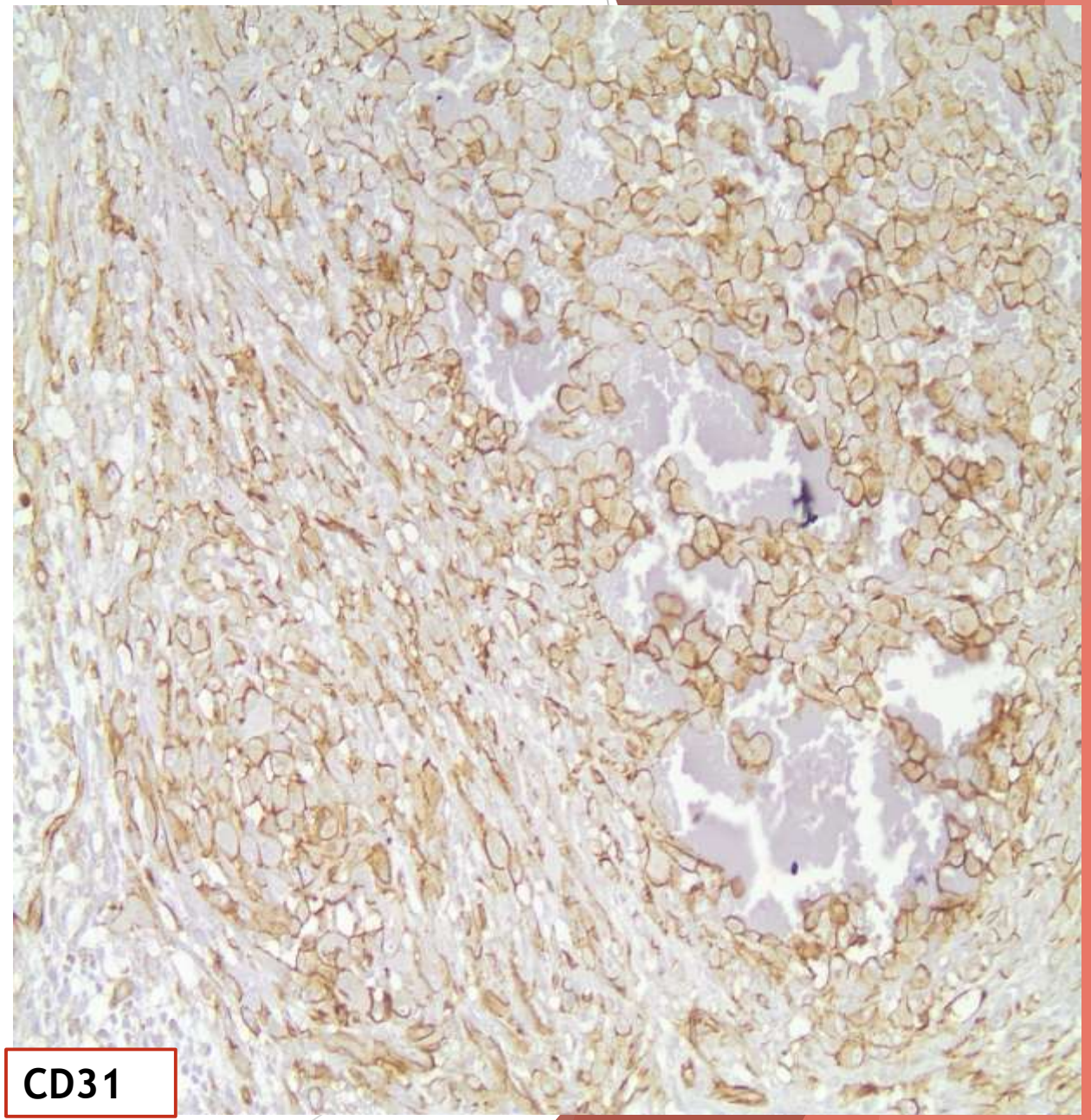


Epithelioid and spindle neoplastic cells arranged in cords and embedded in a myxohyaline stroma

Case #1

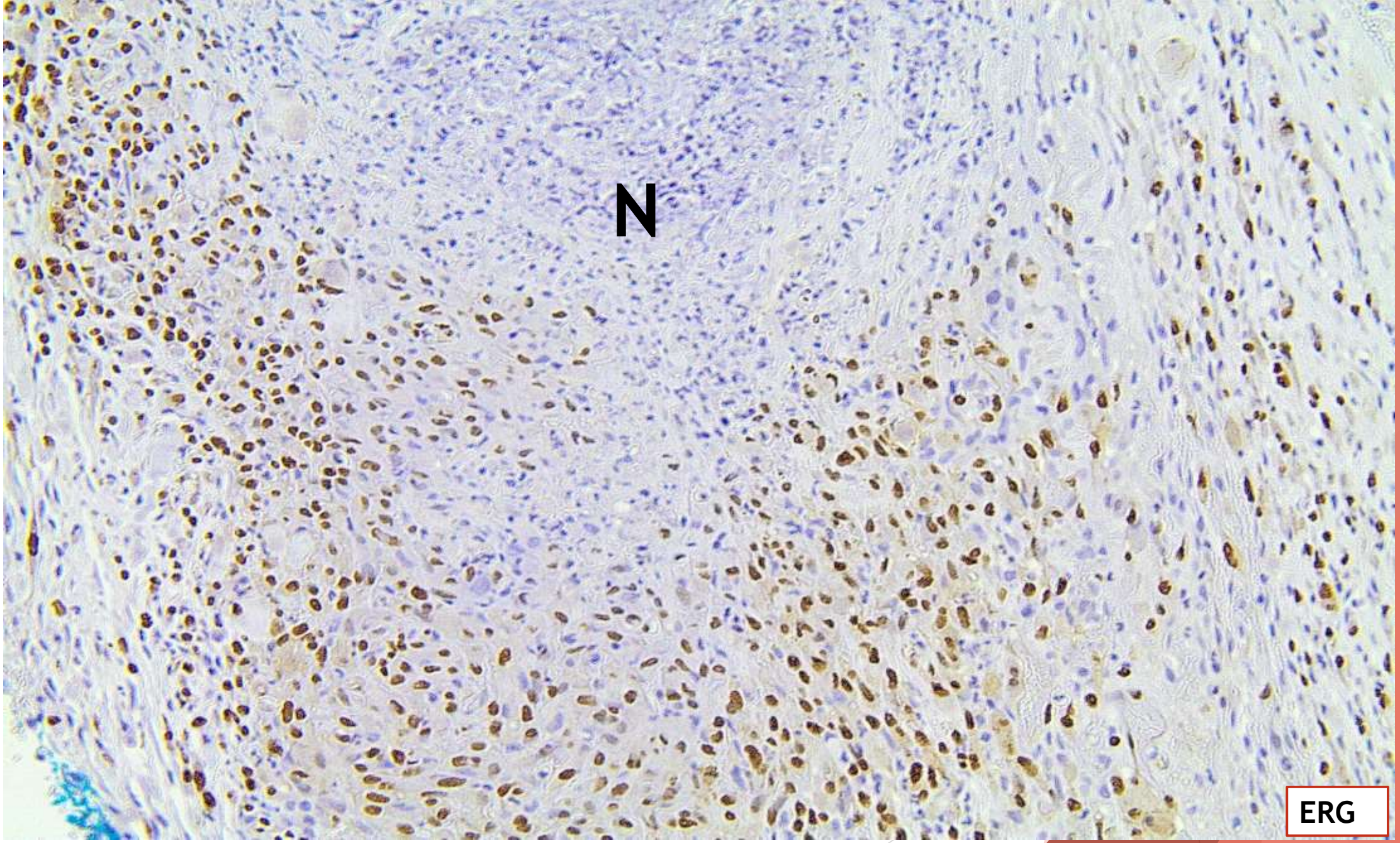


CD31



CD31

Case #1



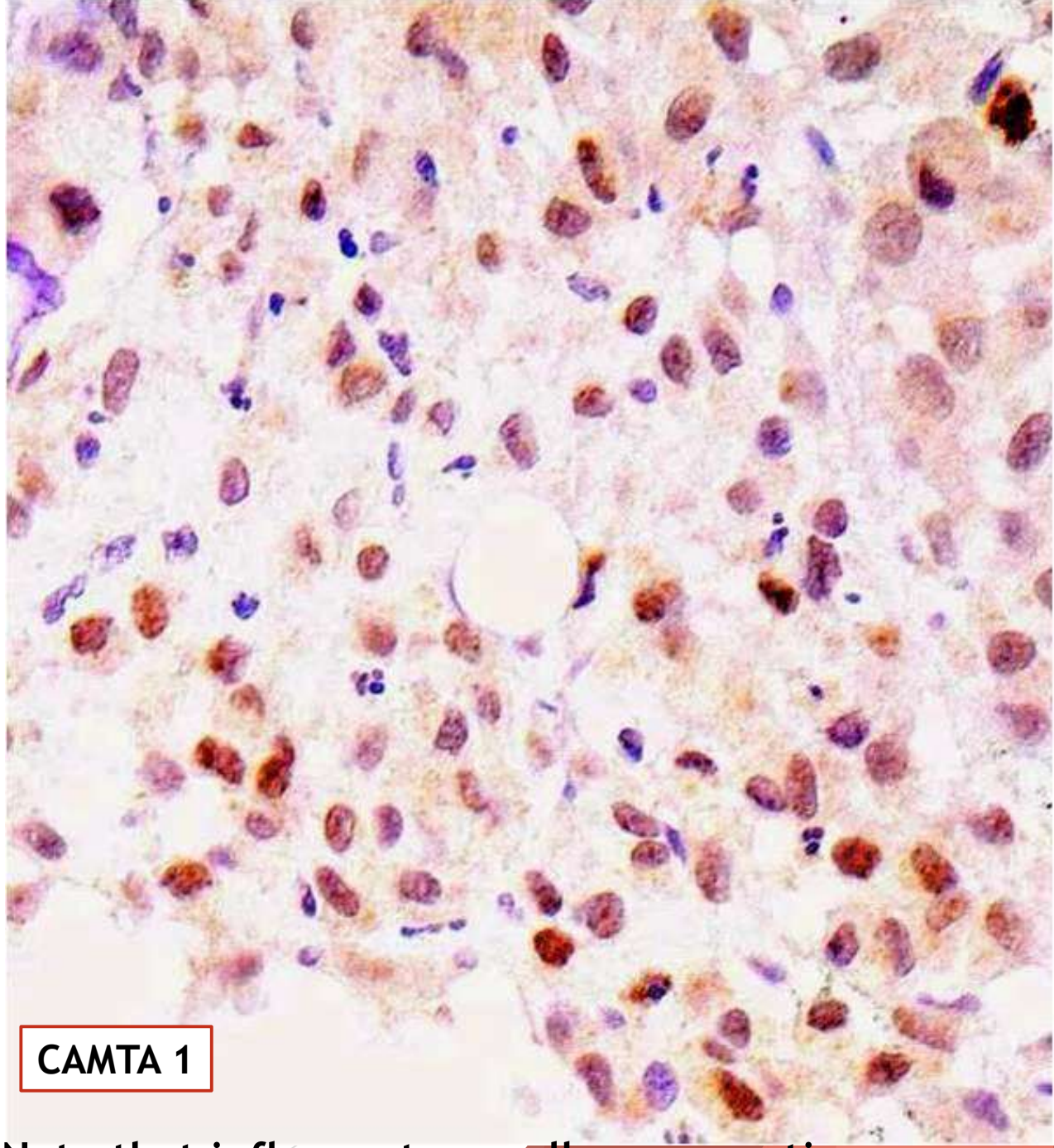
Coagulative necrosis (N)

Case #1

- **Diagnosis : Epithelioid hemangioendothelioma with atypical histology (size >3cm, necrosis, atypia)**
- **No correlation between**
  - ✓Histological features and prognosis for bone EHE in an earlier study (*Kleer, AJSP 1996*)
  - ✓*Histological risk stratification systems not tested in bone EHE*

- **Differential diagnosis:**
  - **Epithelioid angiosarcoma**
    -marked nuclear atypia absence of angiocentric growth
  - **Epithelioid hemangioma of bone**
    - -mild atypia, no macronucleoli, lobulated growth
    - -maybe locally aggressive
    - -acral bone involvement
    - -often no eosinophils
    - **Absence of CAMTA rearrangement/ immunoreactivity**

***Nielsen, AJSP 2009* &**
Doyle, AJSP 2016



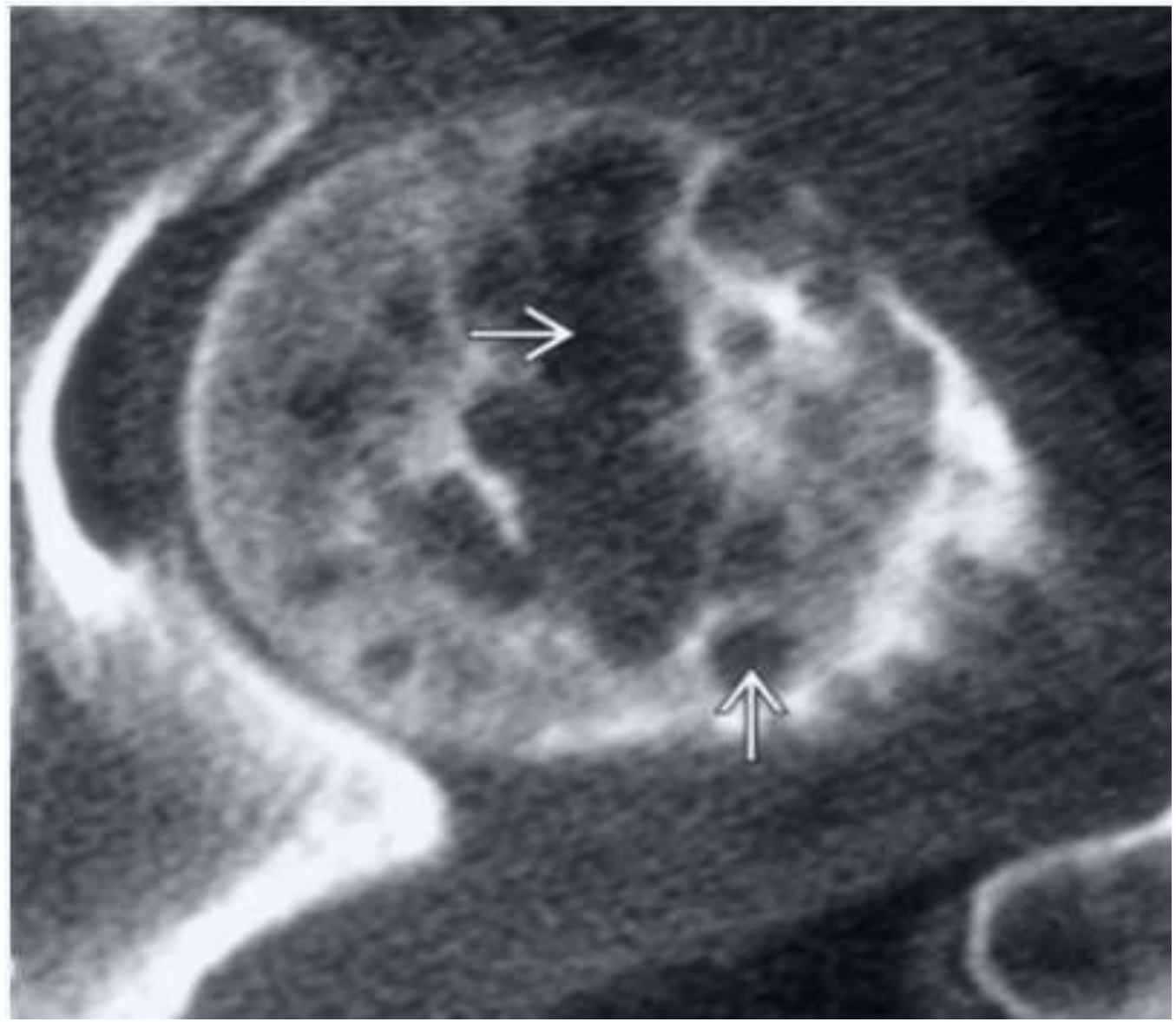
Note that inflammatory cells are negative

Comparison of EH and EHE

	EH	EHE
Sites	Long tubular bones (40%) Flat bones and vertebra (18%) Small bones (8%)	Long tubular bones of extremities (50-60%), pelvis, ribs, spine, small bones of hand and feet commonly involved
Multifocality	Maybe present (18-25%)	Lesions tend to cluster in an anatomical region Common (50-64%)
Radiographic Findings	Lytic, with well-defined margins	Lytic, rarely blastic lesion, with well or poorly defined margins; may expand the cortex and elicit a periosteal reaction
Molecular pathology	FOS rearrangements (1/3) ZFP36-FOSB in a subset with atypical features	WWTR1-CAMTA1 (85-90%) YAP1-TFE3 (5-10%)
Architecture	Lobulated growth with increasing vasoformation at the periphery	Infiltrative; paucity of well - formed vascular channels
Inflammatory infiltrate	Variable; when prominent may mimic osteomyelitis	Sparse
Clinical Behavior	Locally aggressive, local recurrence 10%	In the absence of parenchymal organ involvement, (10 year survival rate 92%)

Ramkumar 2021, Cureus *Nielsen, Diagnostic Pathology Bone 3rd edition 2021*

Case #1



Axial CT of EHE shows multiple well-defined, lytic lesions in the femoral head ➡ with relatively normal- appearing intervening bone. Few lesions are also seen in the acetabulum

Nielsen Diagnostic Pathology Bone 3rd edition

Case #1

› Rare Tumors. 2021 Apr 11;13:20363613211005593. doi: 10.1177/20363613211005593. eCollection 2021.

Epithelioid hemangioendothelioma of bone: A survival analysis of 50 cases from the SEER database (1992–2016)

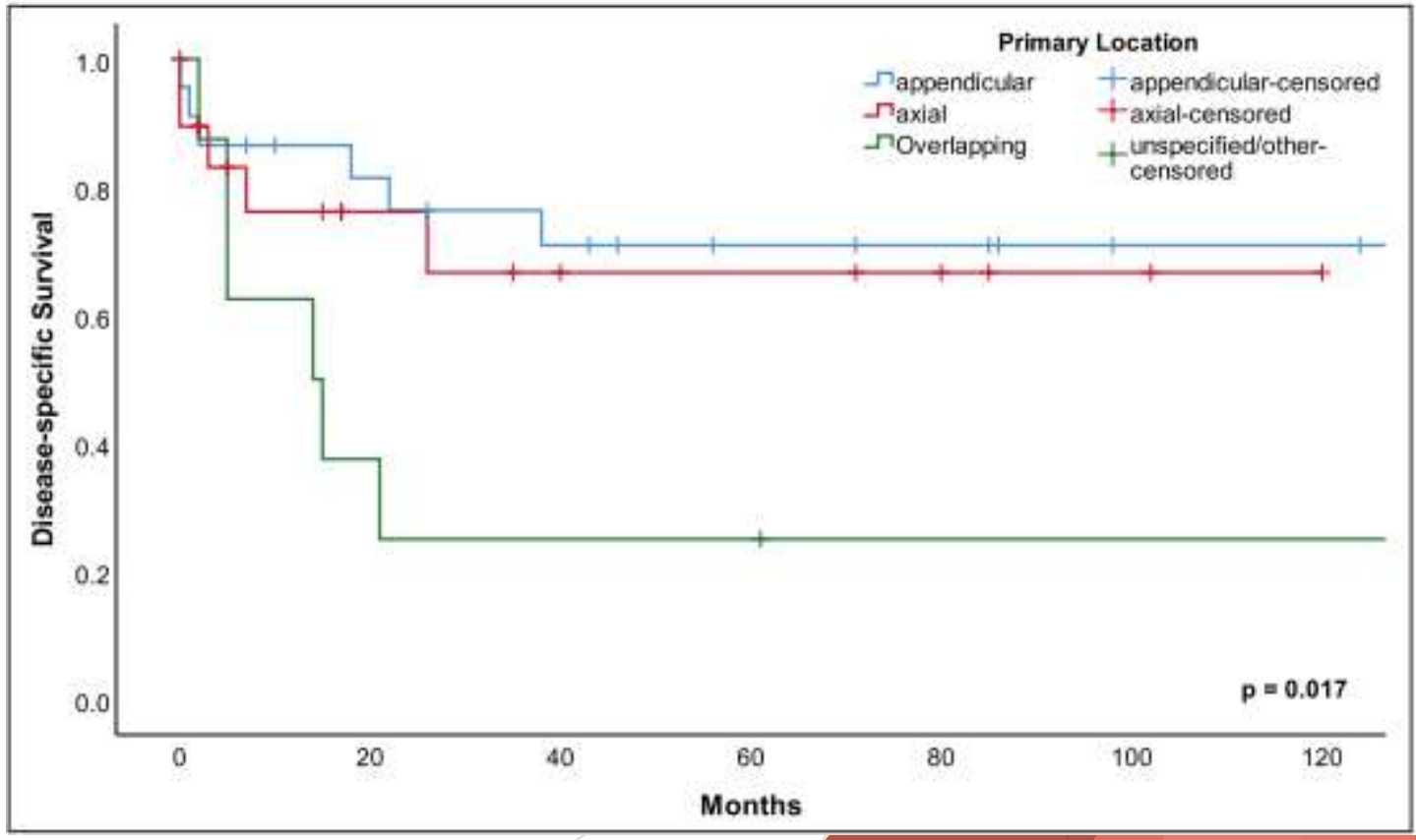
Charles A Gusho [1], Sarah C Tepper [1], Steven Gitelis [1], Alan T Blank [1]

Affiliations + expand

PMID: 33953894 PMCID: PMC8044559 DOI: 10.1177/20363613211005593

- Age (>50years), absence of surgery and tumor location (multicentric, overlapping) negative prognostic factors

- EHE of bone behaves as an intermediate grade tumor



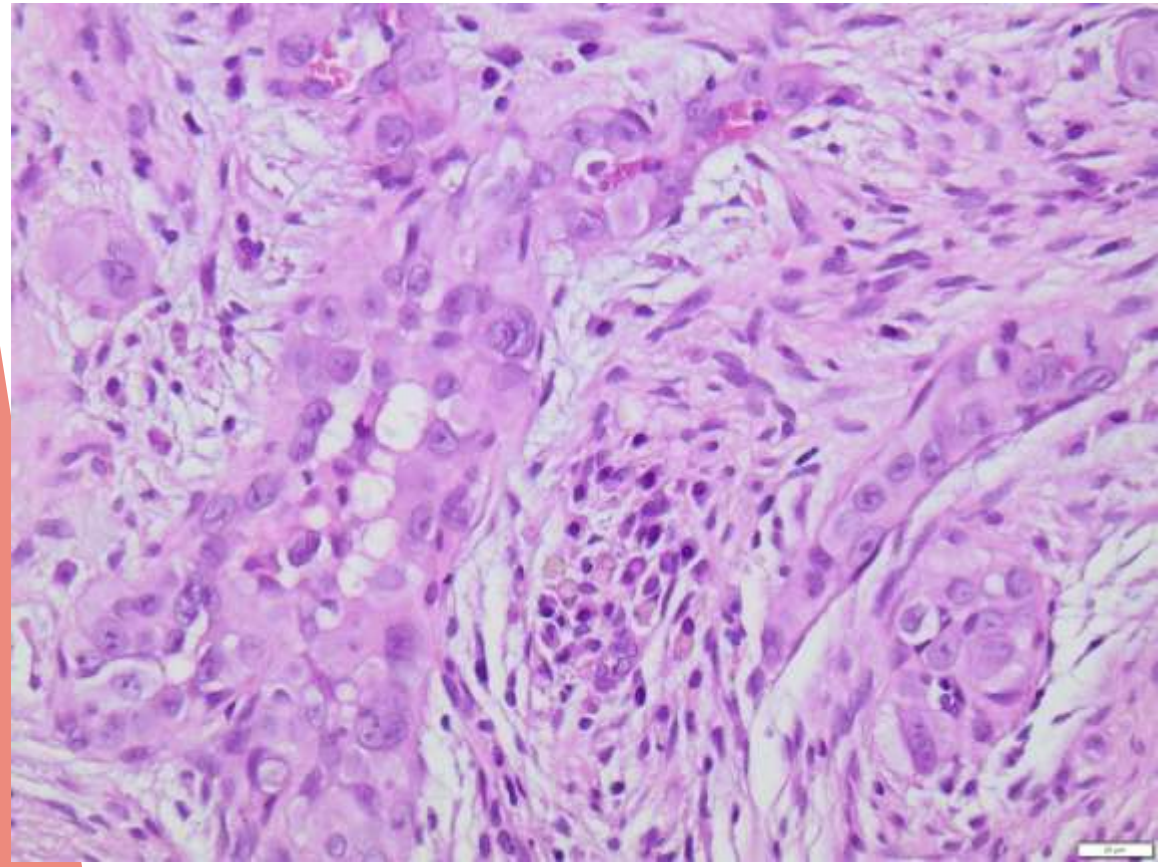
Pathologic Interpretation Pearls

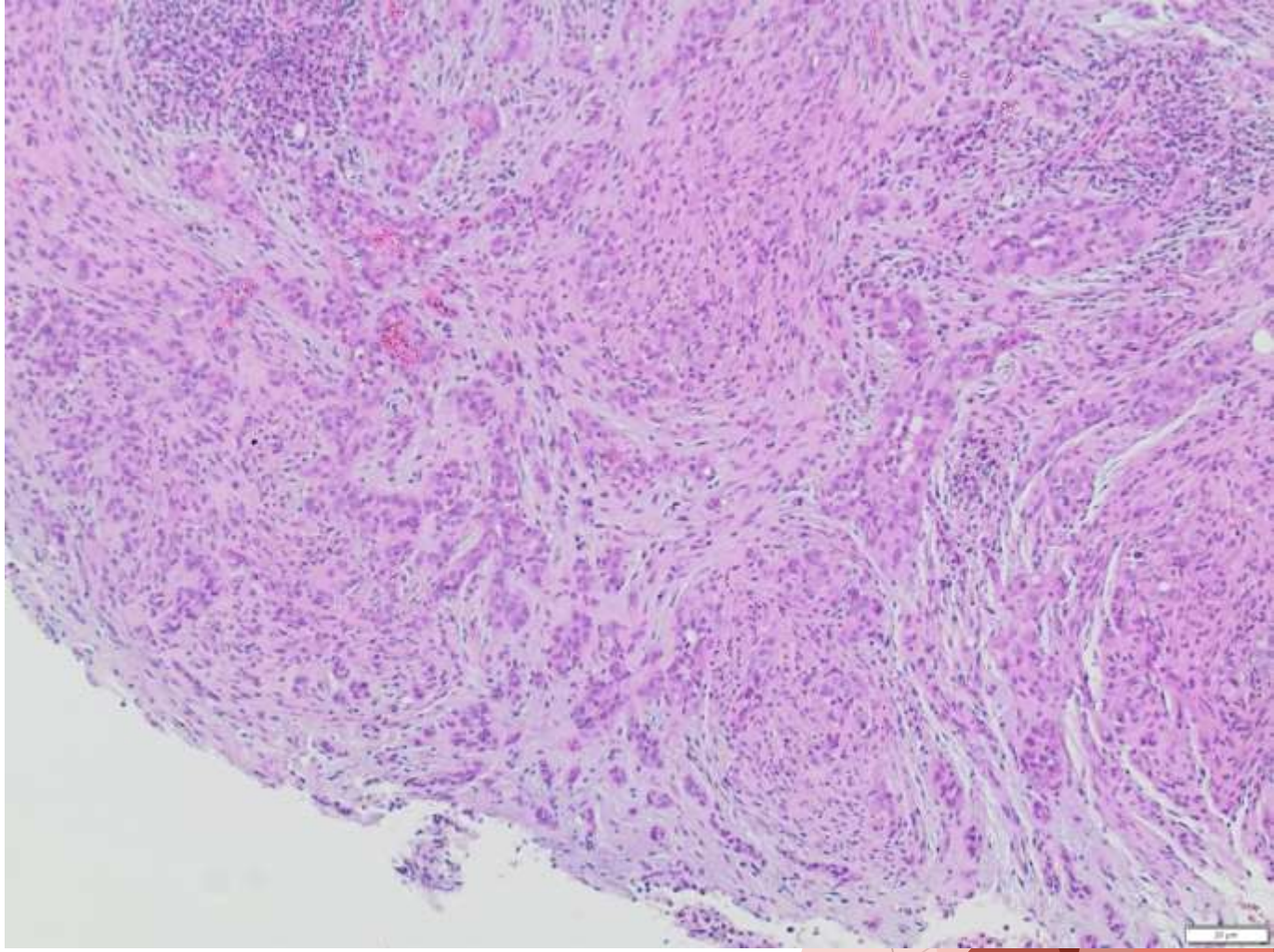
- **Always consider epithelioid vascular tumor in differential diagnosis of epithelioid tumor in bone**
- **Epithelioid vascular tumor can be keratin positive but stains for endothelial markers**
- When multifocal, can mimic metastatic carcinoma

Nielsen, Diagnostic Pathology Bone 3rd edition, 2021

Case #2

- Male, 62 year-old
- Multiple vertebral osteolytic lesions: clinical suspicion of metastatic carcinoma
- Bone marrow trephine taken to identify primary site

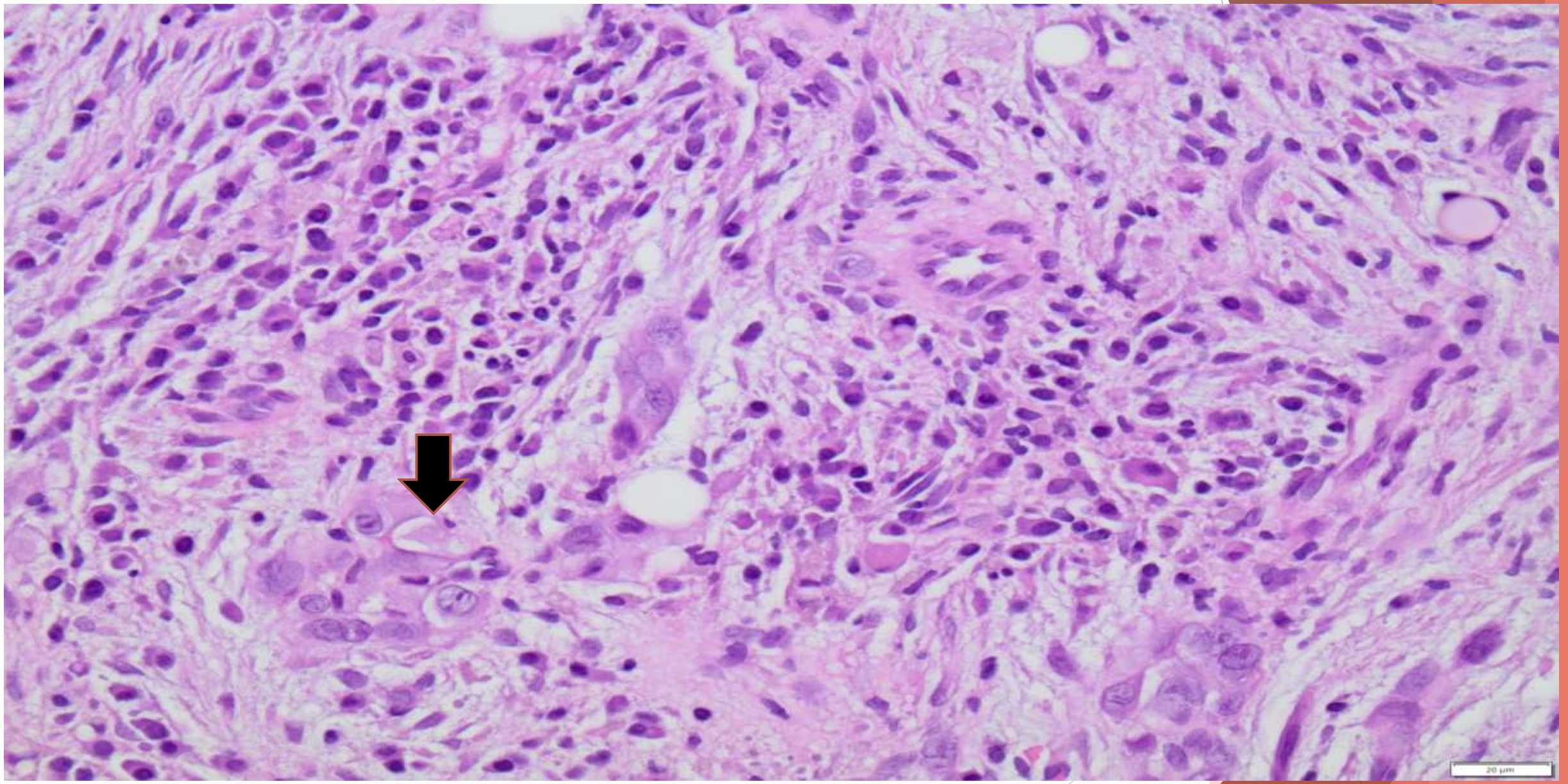




Epithelioid vasoformative vascular lesion invading cancellous bone

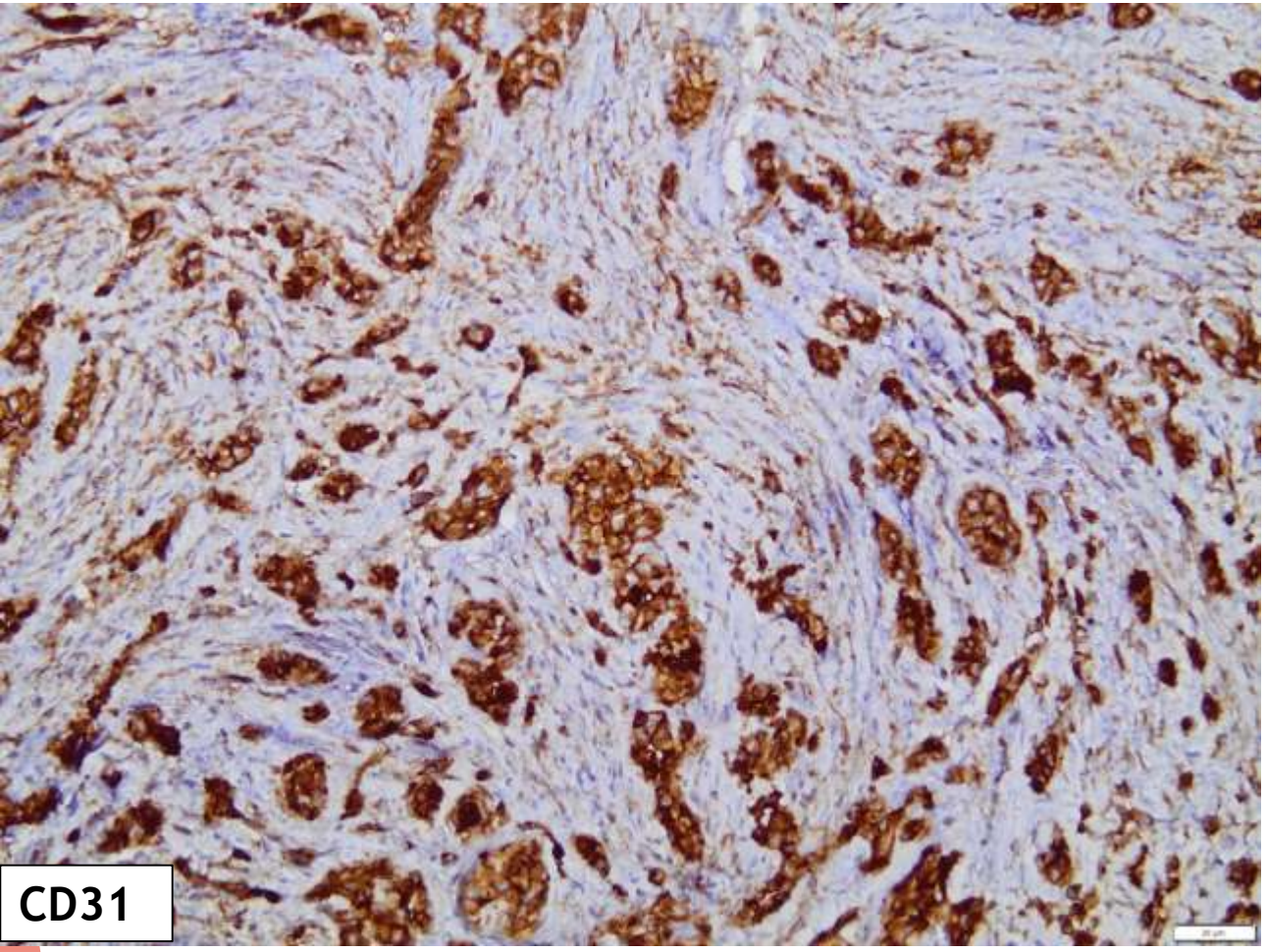
Neoplastic cells with mild atypia admixed with spindle cells and some inflammatory cells

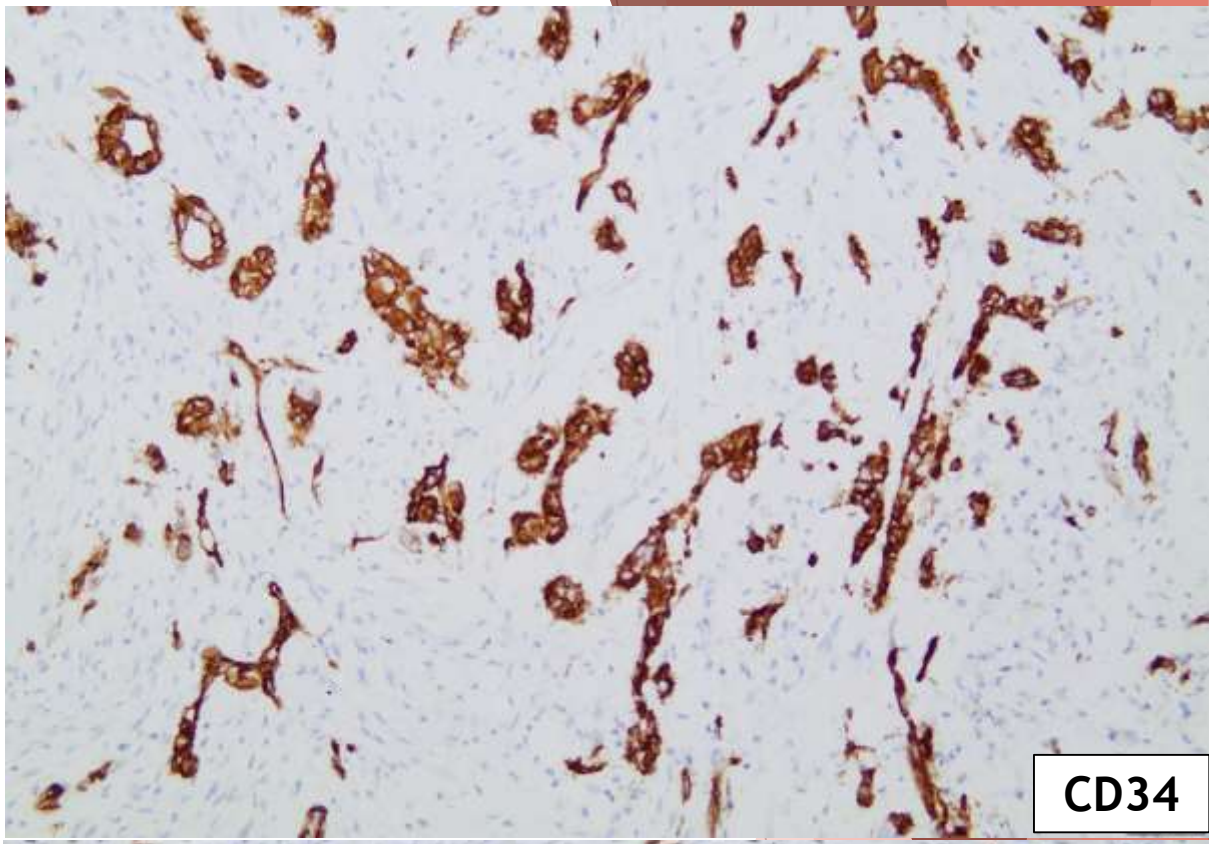
Case #2

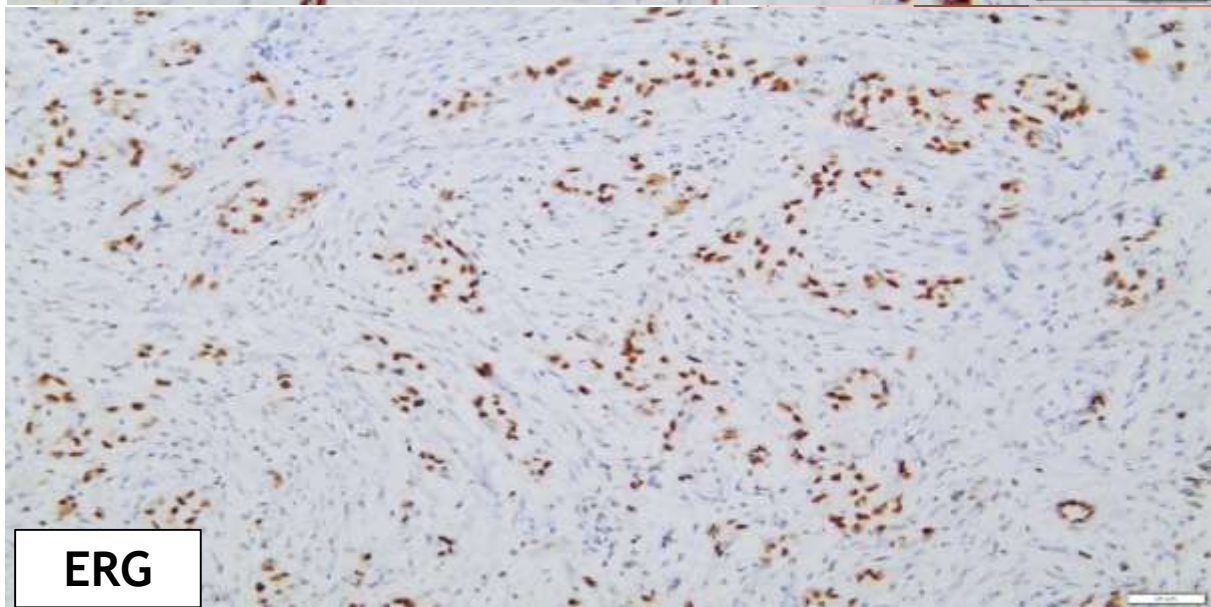


Prominent inflammatory infiltrate, mainly plasmacytic
Some intracytoplasmic vacuoles in neoplastic cells (Arrow)

Case #2

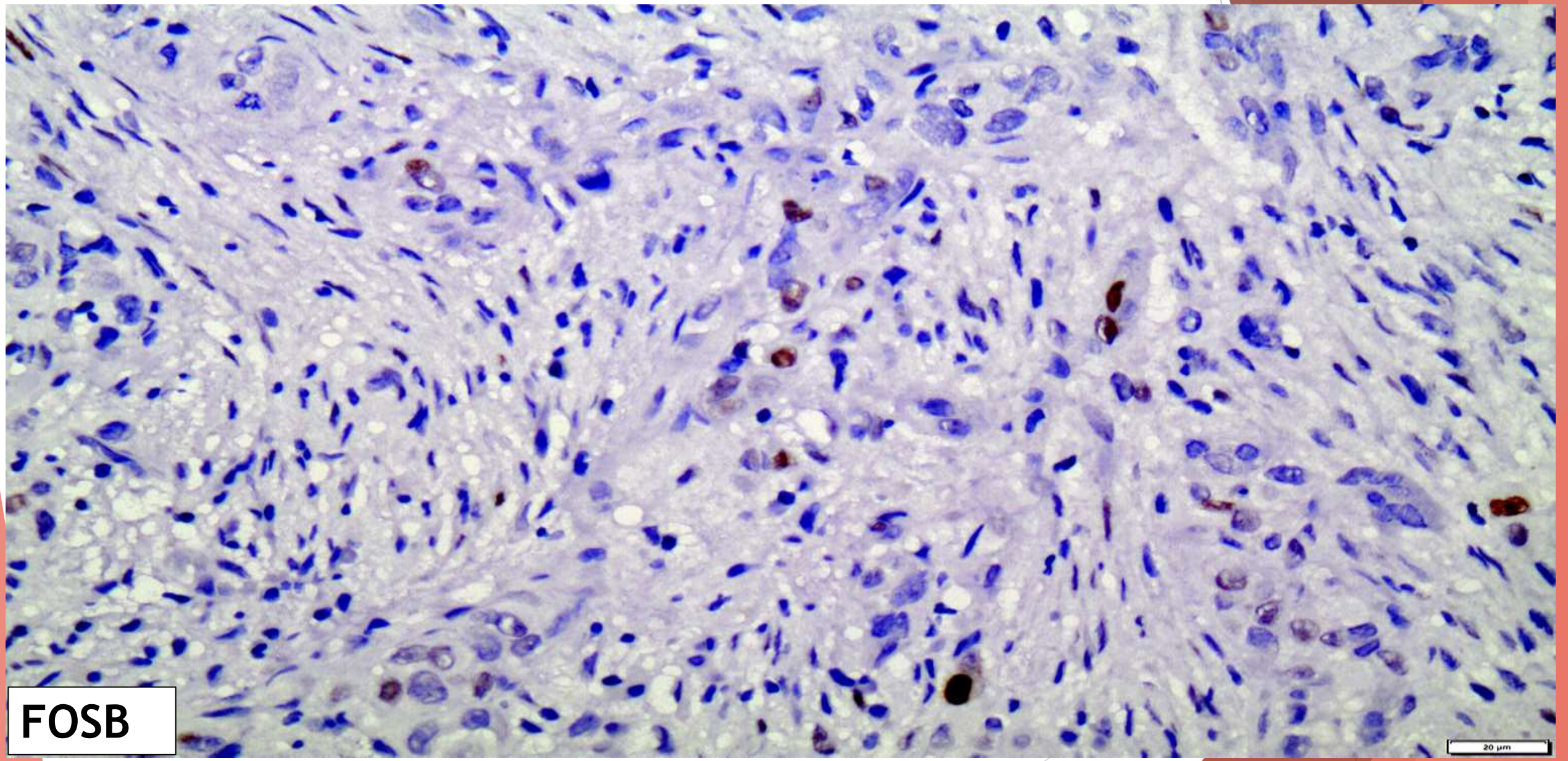






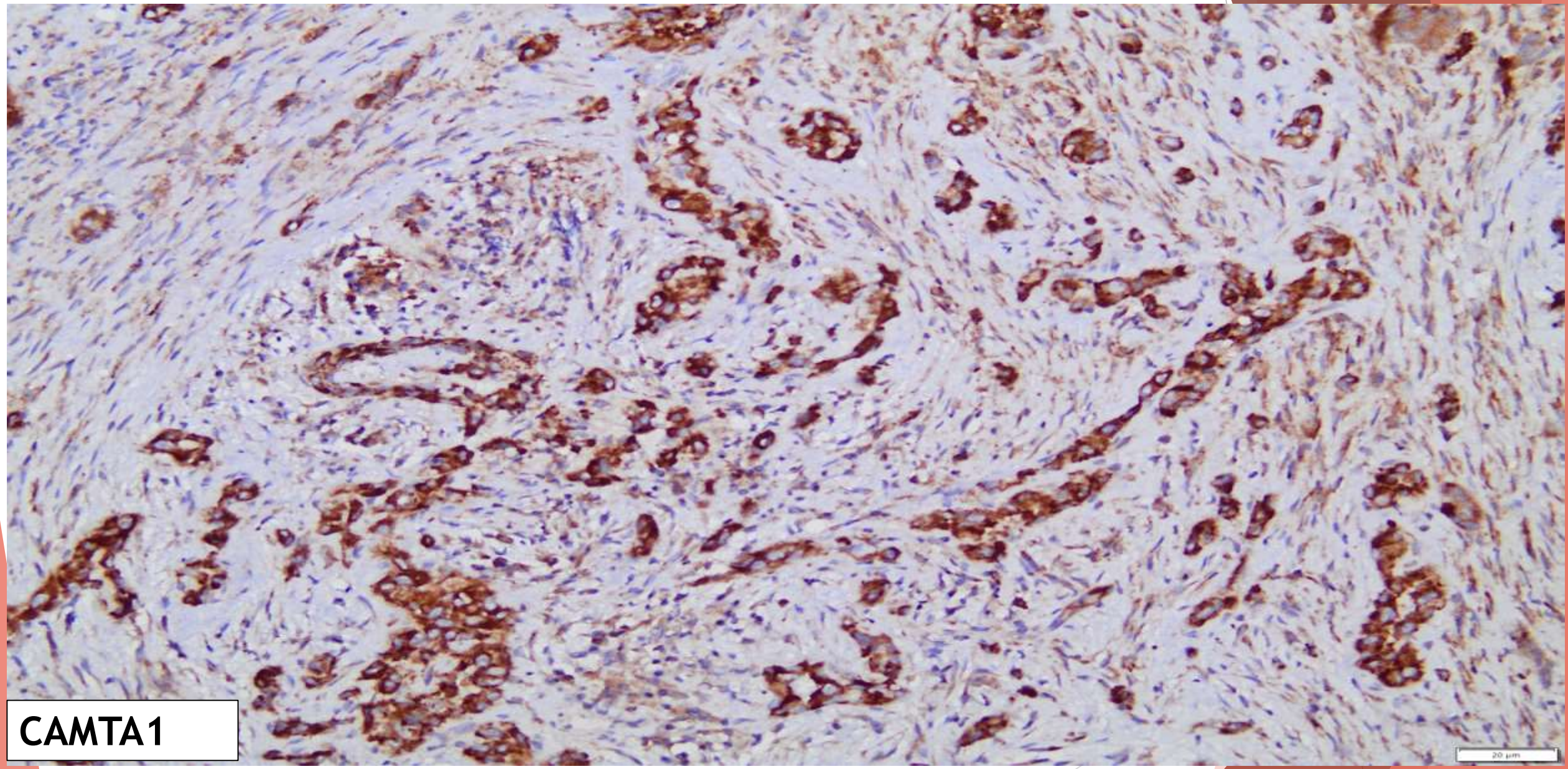
Diffuse positivity for CD32, CD34 and ERG

Case #2



Nuclear FOSB staining in several neoplastic cells with variable intensity

Case #2



Diffused cytoplasmic positivity **without nuclear staining**

TFE3 absence of nuclear staining

Case #2

Final Diagnosis: Multifocal Epithelioid Hemangioma in vertebral bones

Differential Diagnosis: Multifocal EHE

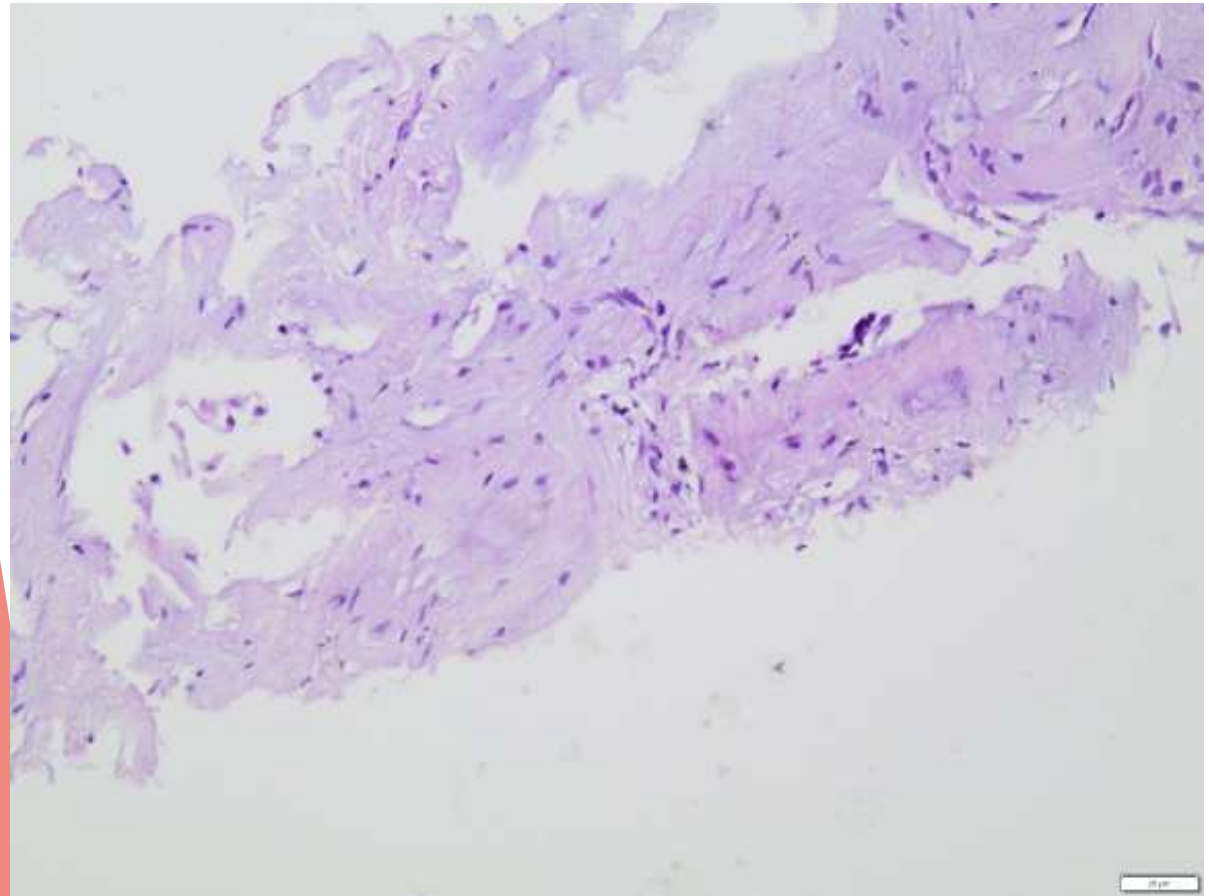
FOSB+ / CAMTA1- (Cytoplasmic staining non-specific)

FOSB expression may be entirely lost in decalcified sections

Righi 2020 AmJ Surg Pathol
Ramkuman 2021, Cureus

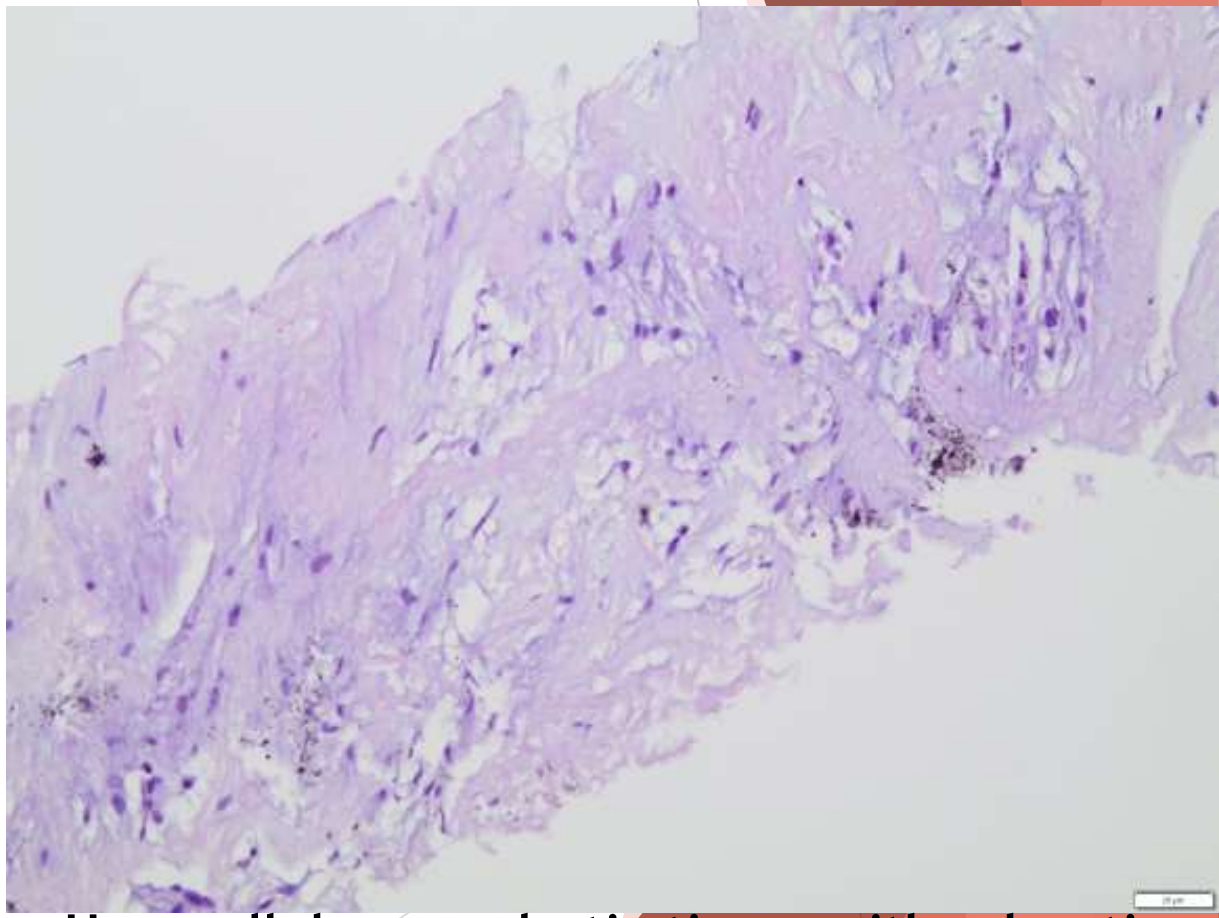
Case #3

- Male, 61 years-old
- Multiple bilateral parenchymal lung nodules
- Suspicion of metastatic carcinoma



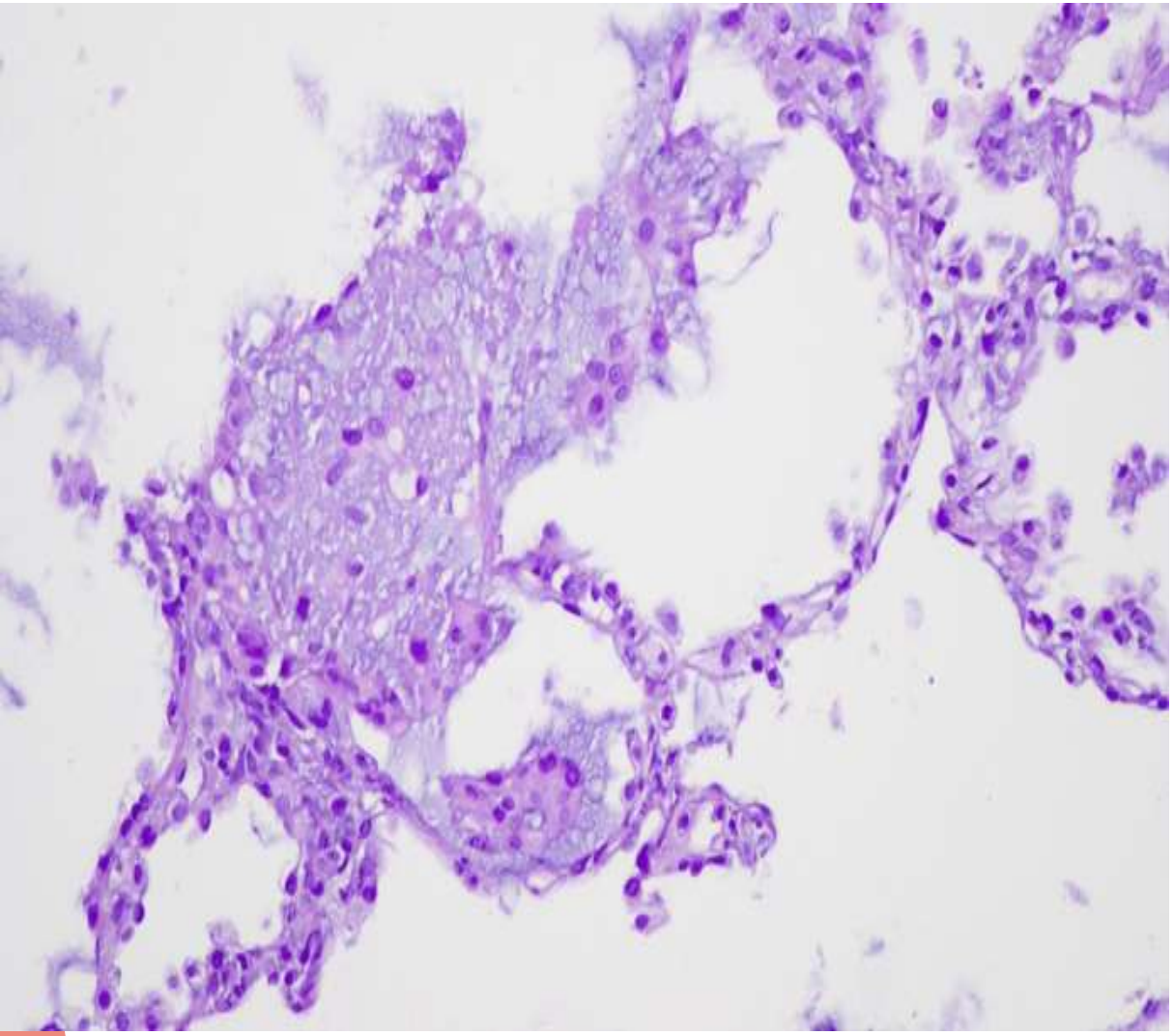
Consultation case:

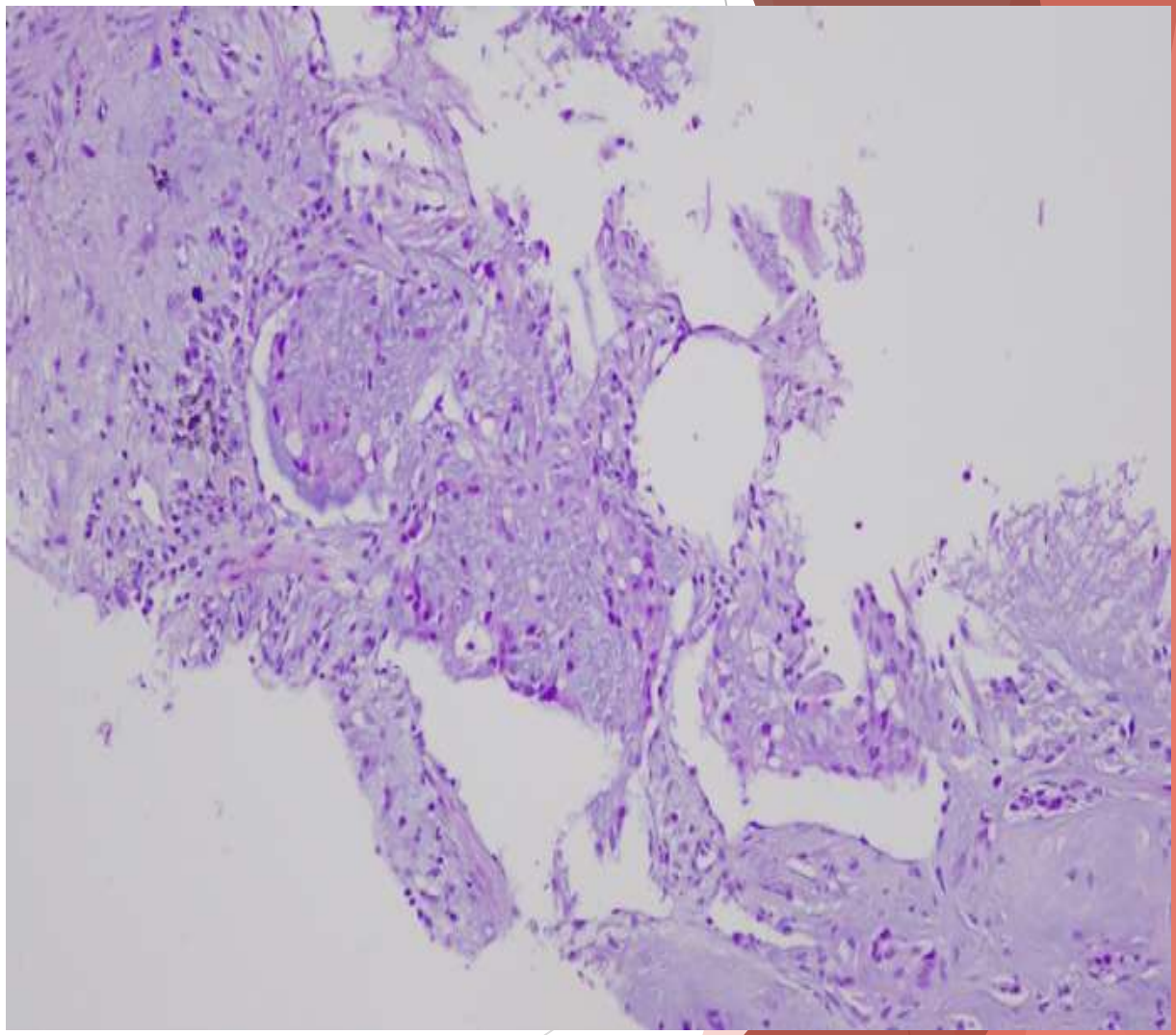
Referral diagnosis “probable adenocarcinoma, but negative epithelioid markers, TTF1 and napsin A”



Hypocellular neoplastic tissue with sclerotic stroma

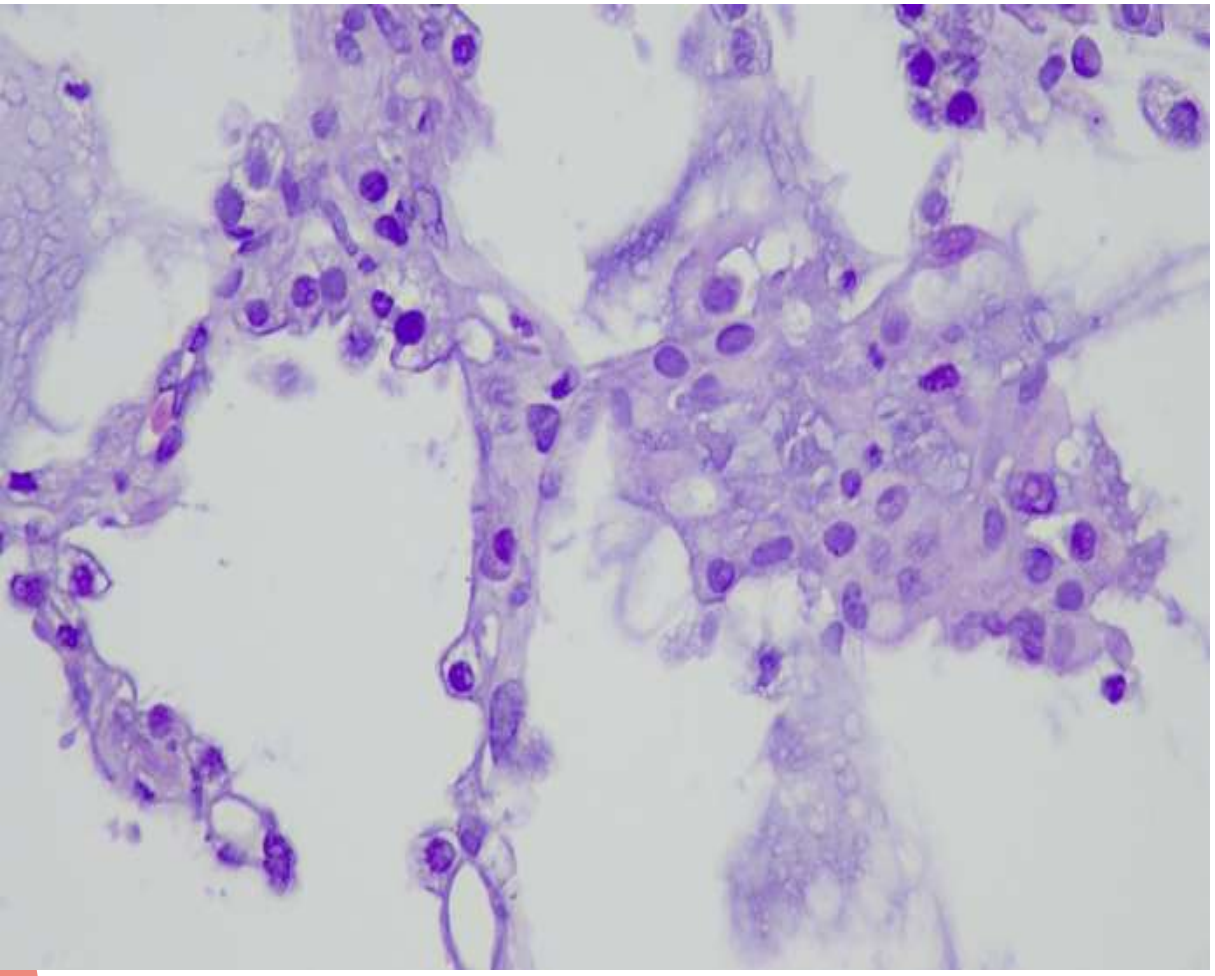
Case #3

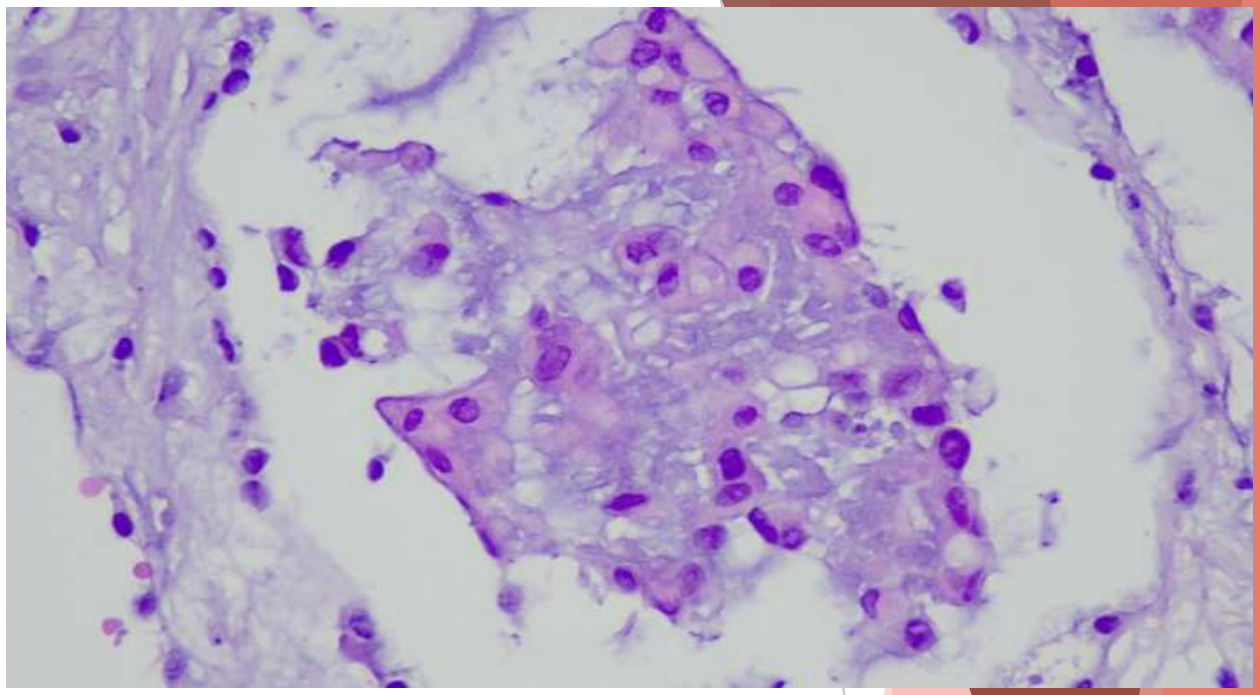


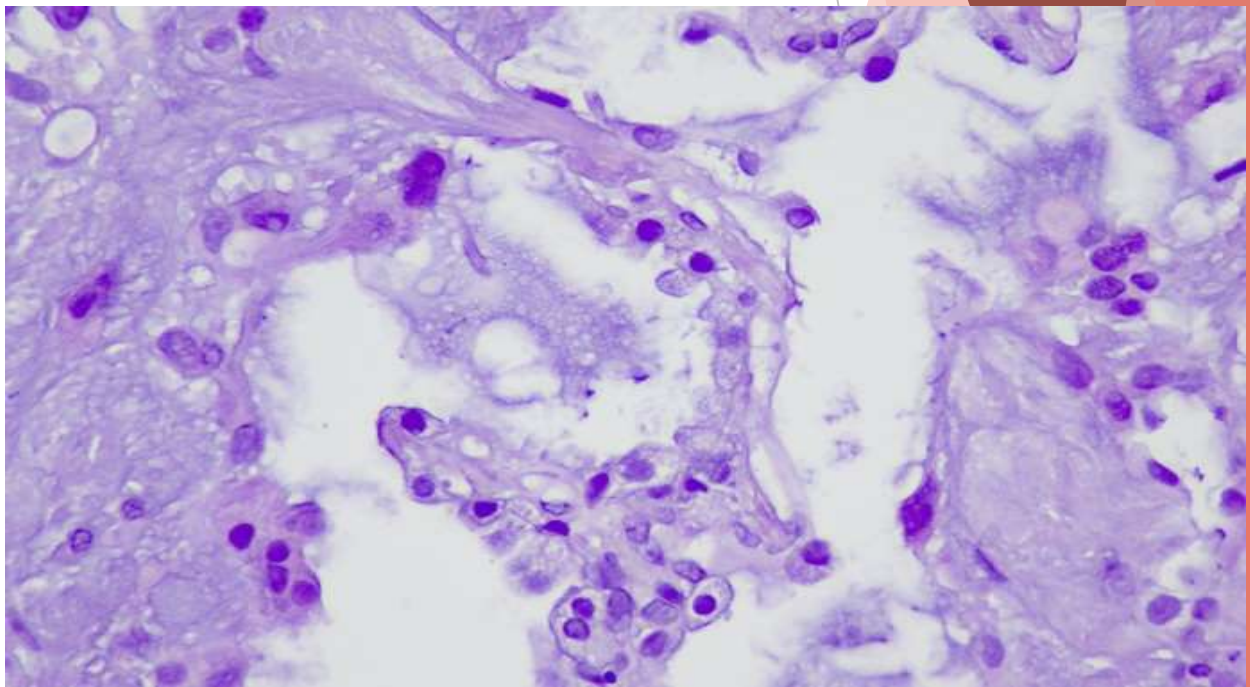


Neoplastic nodules within alveolar spaces

Case #3

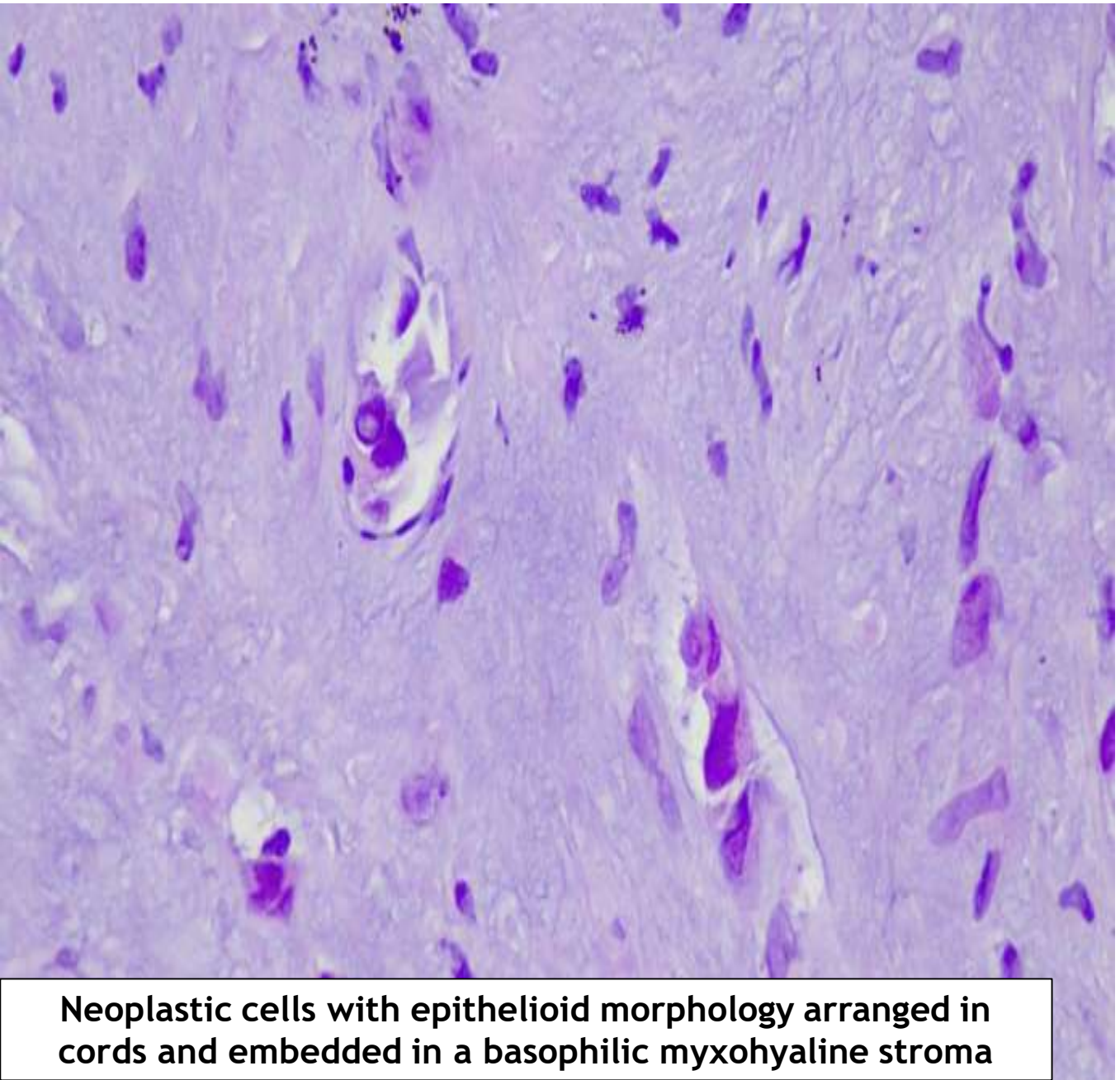




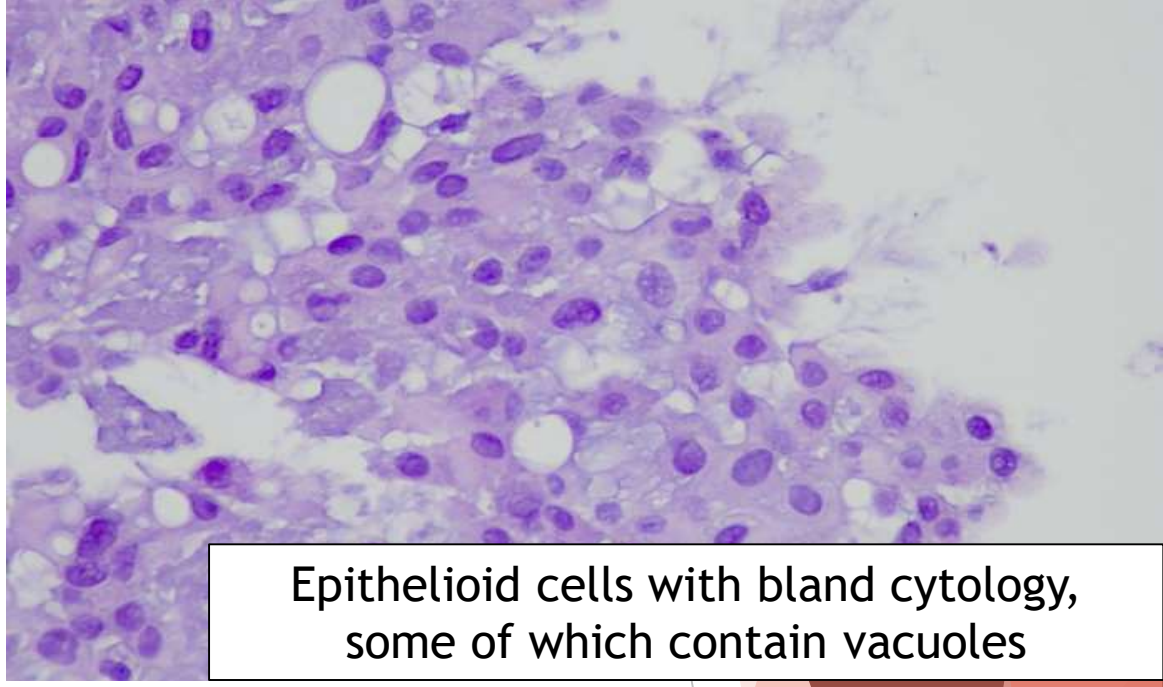


Neoplastic cells form papillary fronds protruding into alveolar spaces

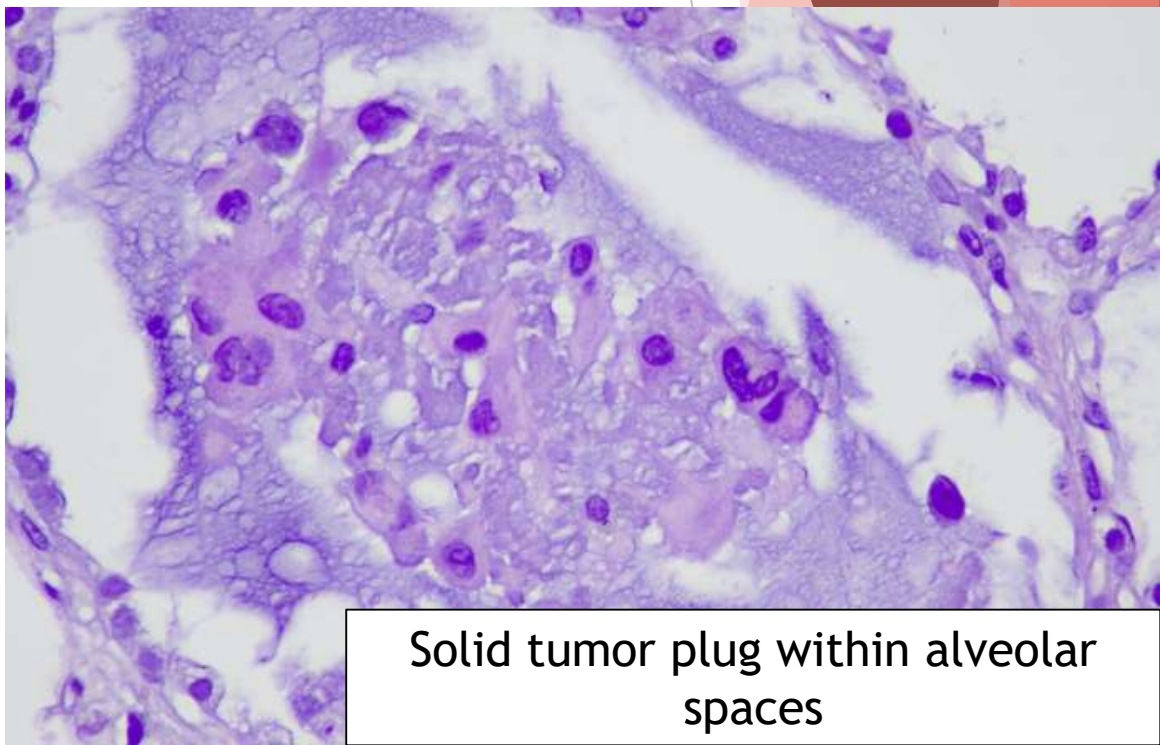
Case #3



Neoplastic cells with epithelioid morphology arranged in cords and embedded in a basophilic myxohyaline stroma

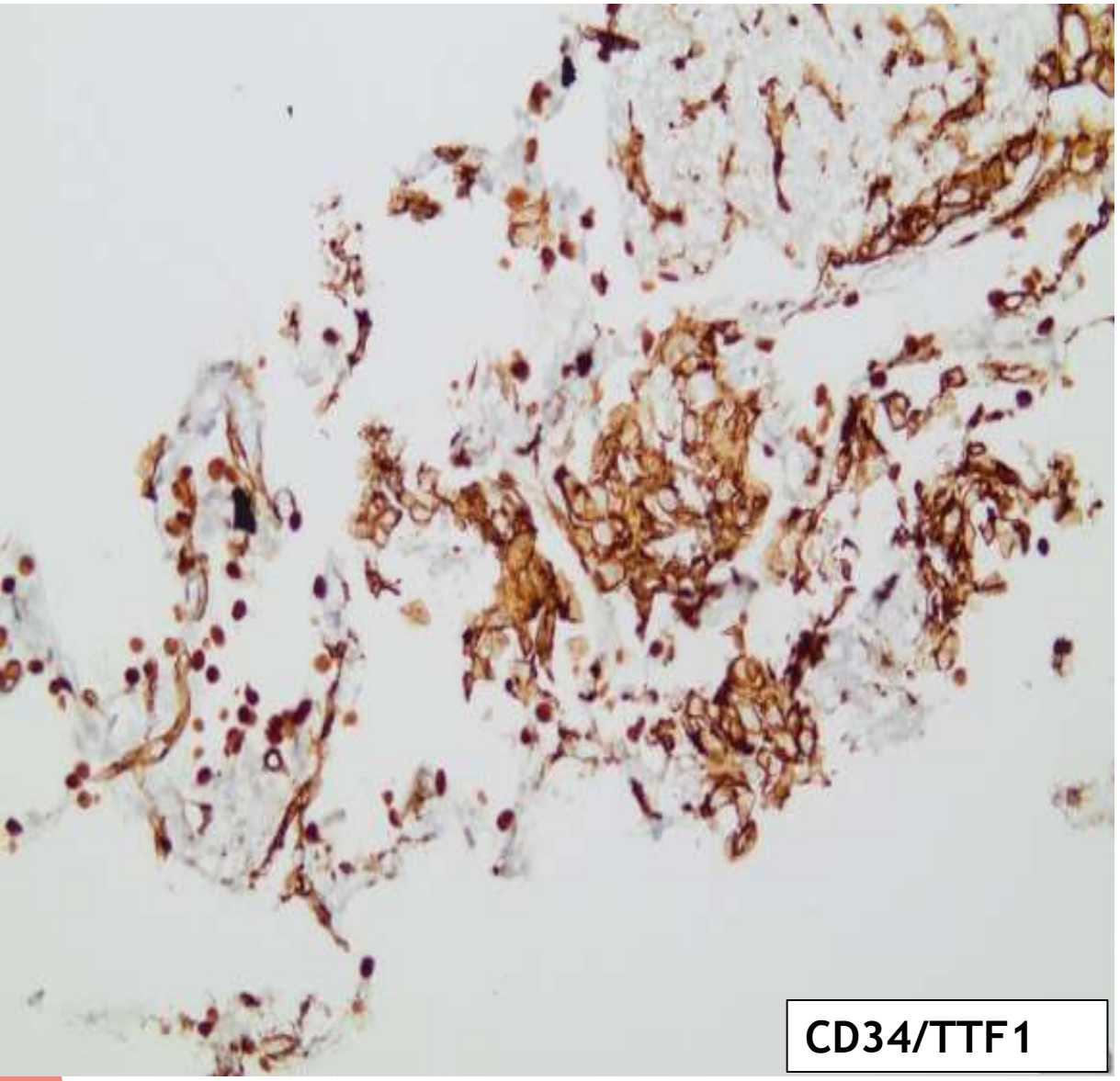


Epithelioid cells with bland cytology, some of which contain vacuoles

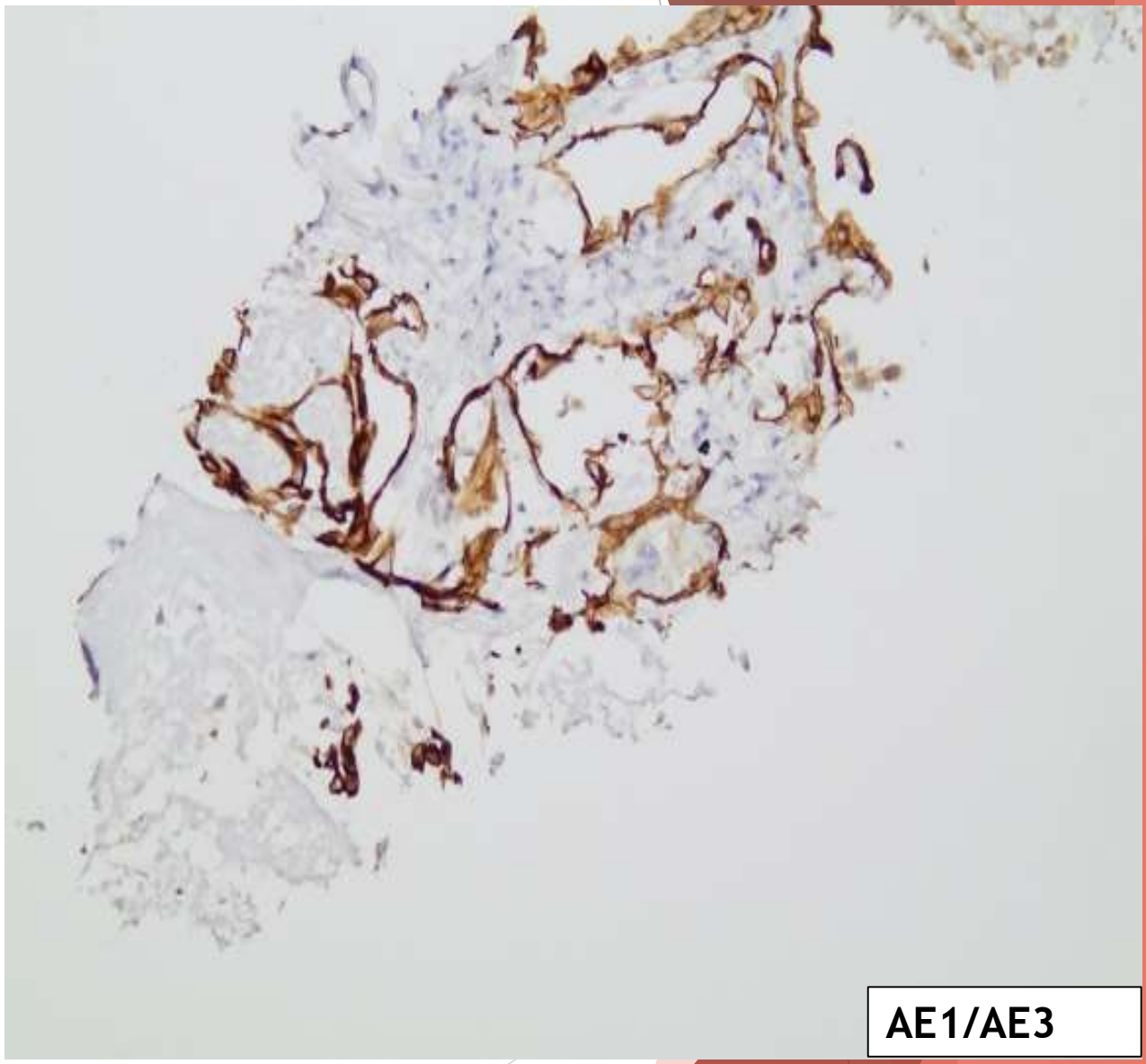


Solid tumor plug within alveolar spaces

Case #3

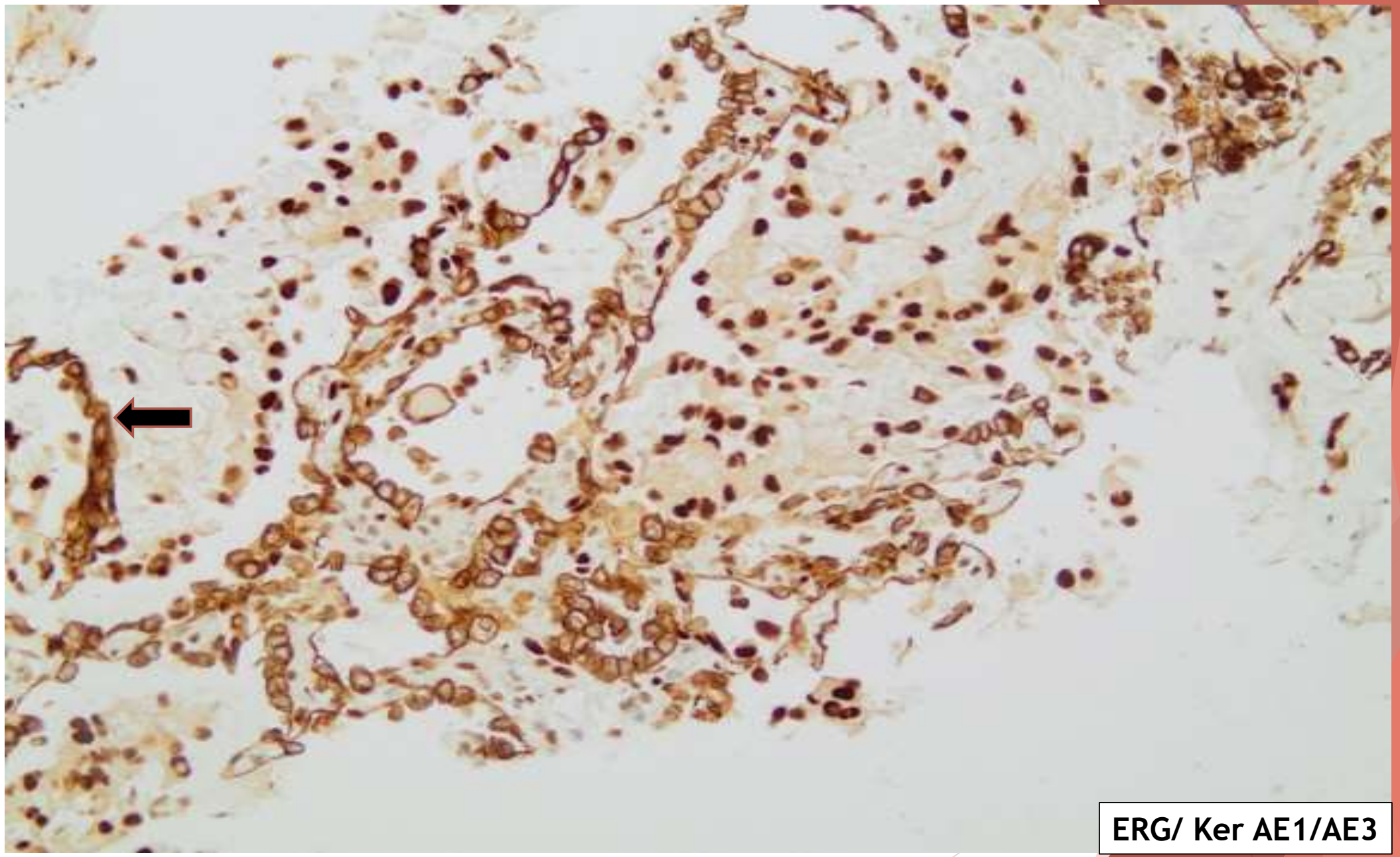


Strong positivity for CD34 of neoplastic cells



Neoplastic cells are negative as opposed to alveolar lining cells

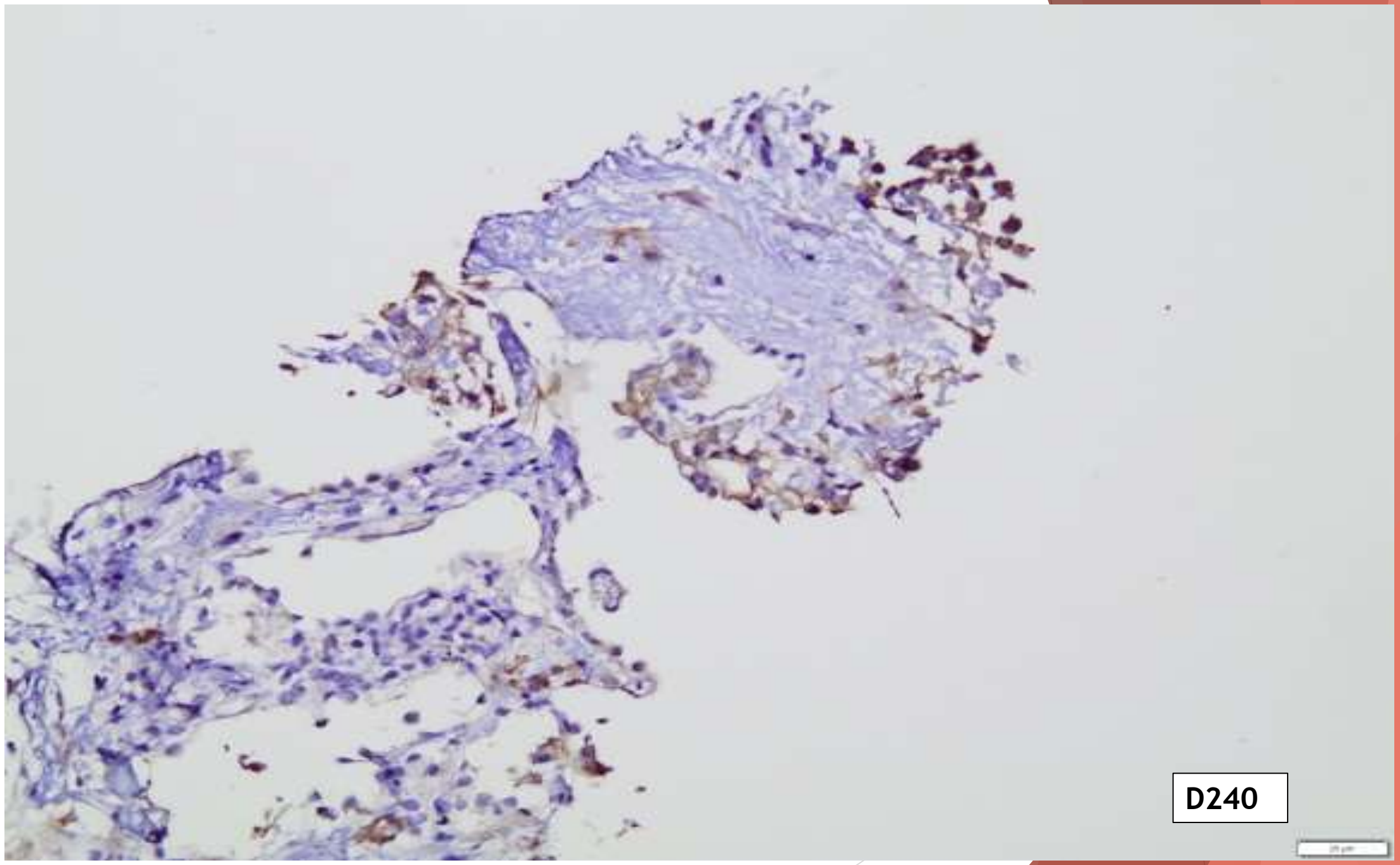
Case #3



ERG/ Ker AE1/AE3

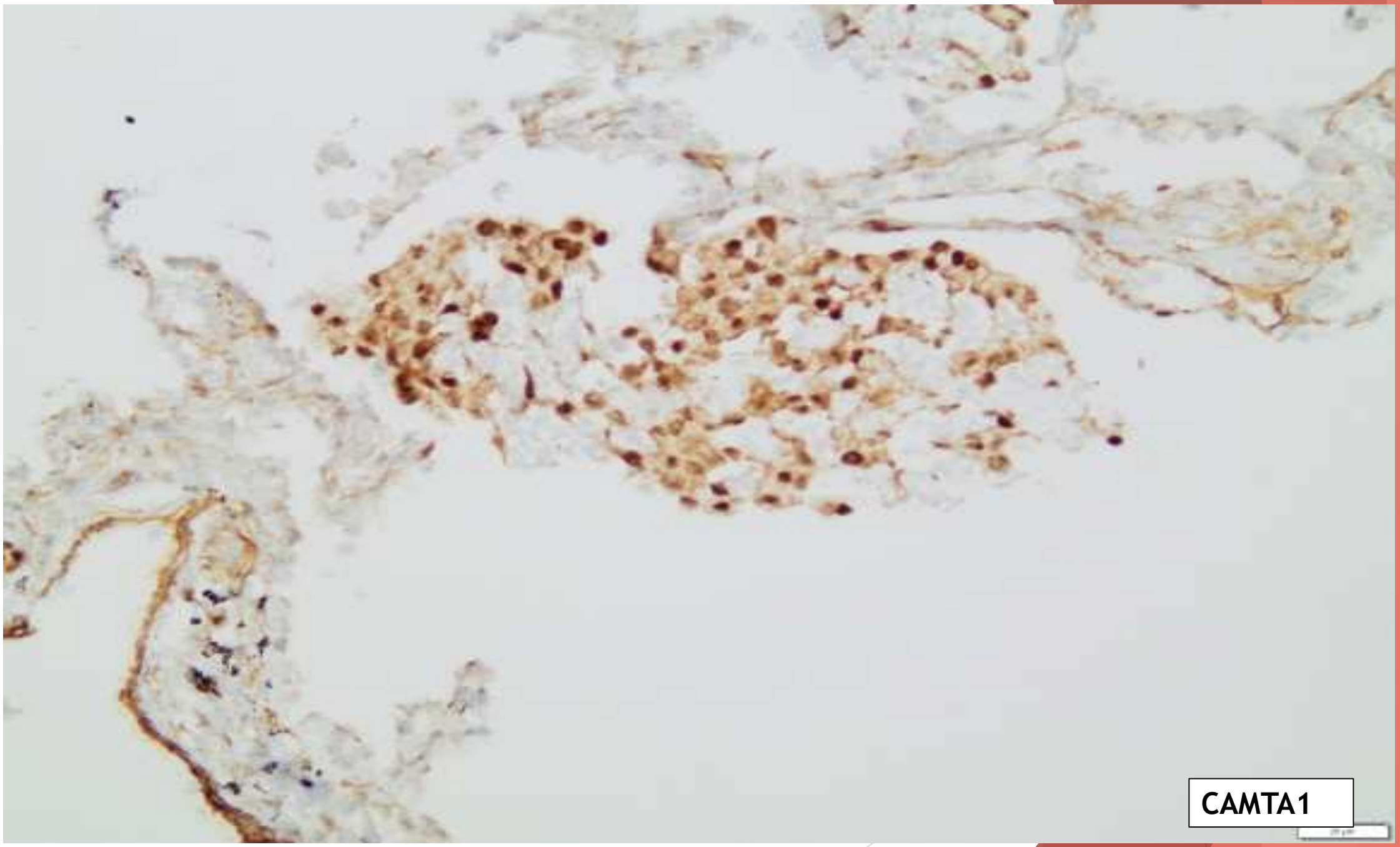
Diffuse nuclear expression of ERG (arrow)
Alverolar epithelial cells positive for KerAE1/AE3

Case #3



Neoplastic cells in papillary fronds are positive

Case #3



Diffuse strong nuclear expression of CAMTA1 in neoplastic cells

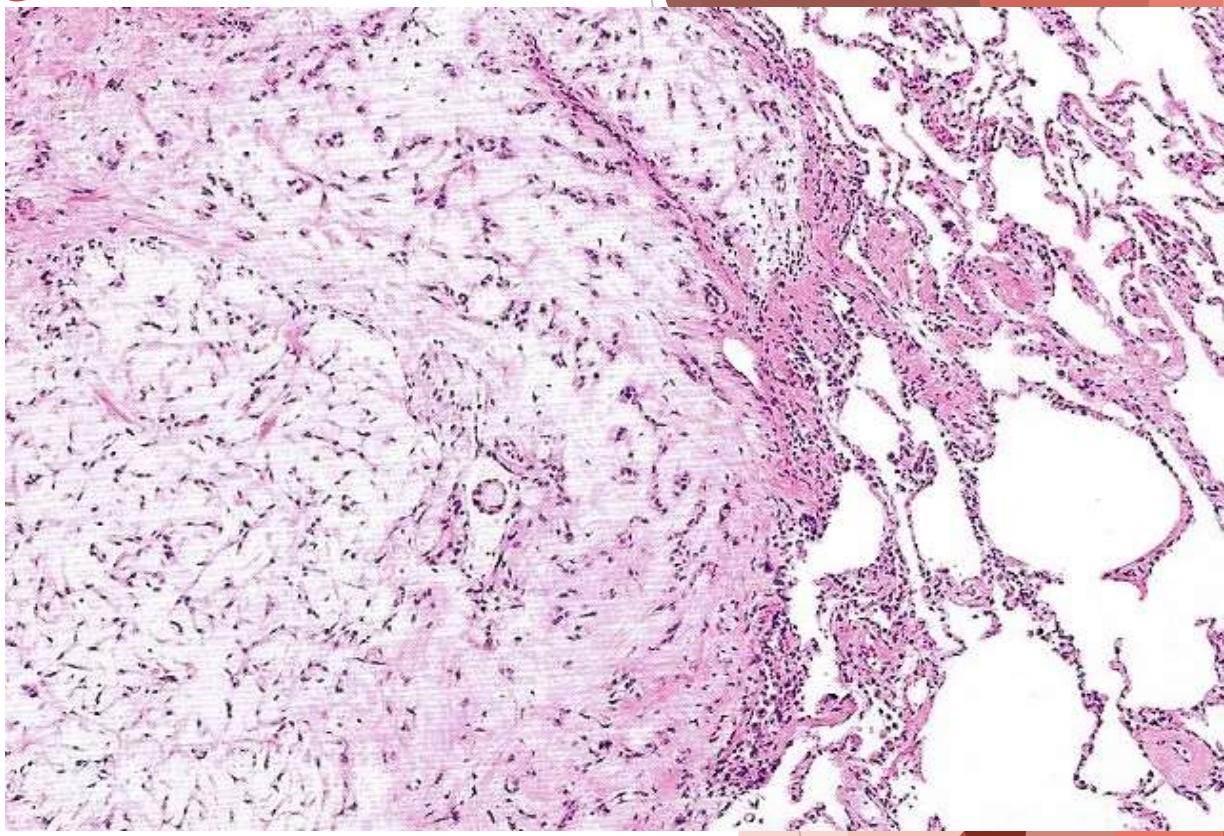
Case #3

Pathology of the Lung EHE

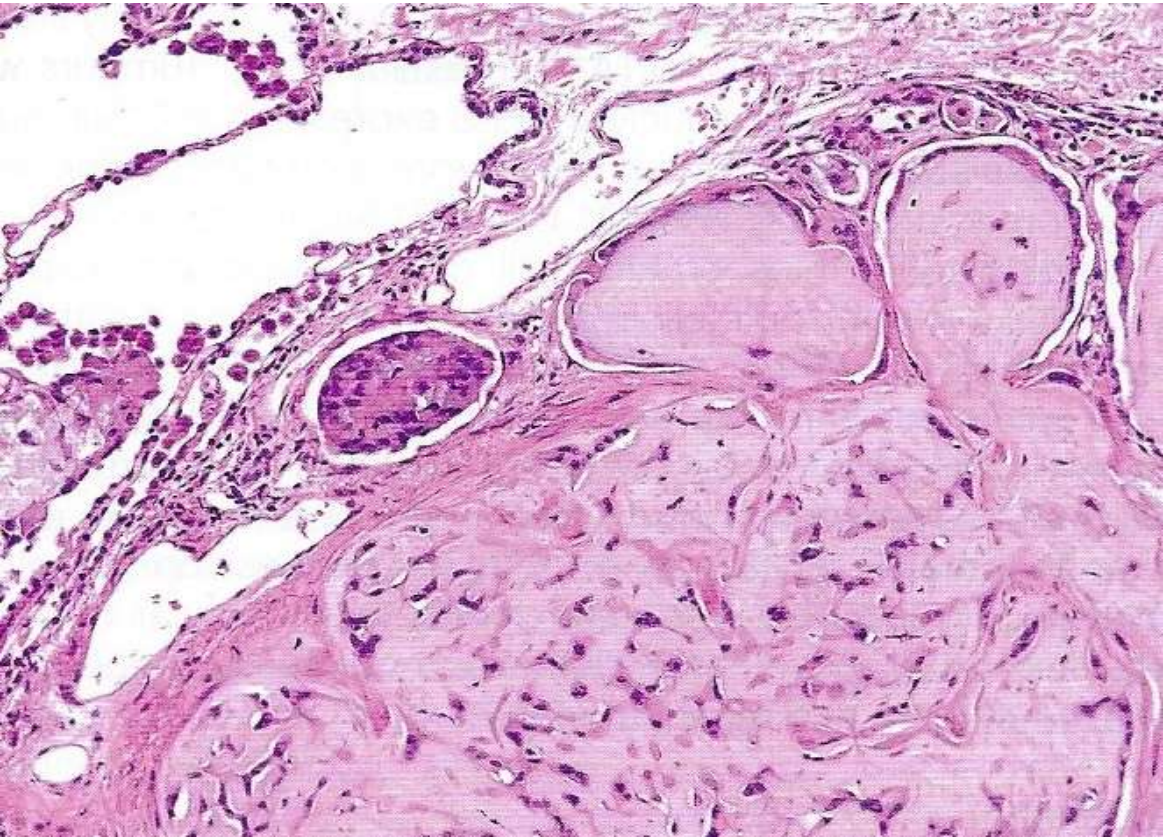
Diagnosis: Lung involvement by EHE

Pathology Interpretation Pearls (I)

- **In >60% of cases parenchymal lung disease is bilateral in the form of multiple nodules**
- Angiocentric origin may be evident



The tumor nodules are relatively well-circumscribed with a hypercellular periphery and hypocellular center



Papillary fronds covered by tumor cells project into the alveolar spaces ("intravascular bronchio alveolar tumor")

WHO Thoracic Tumours 2021

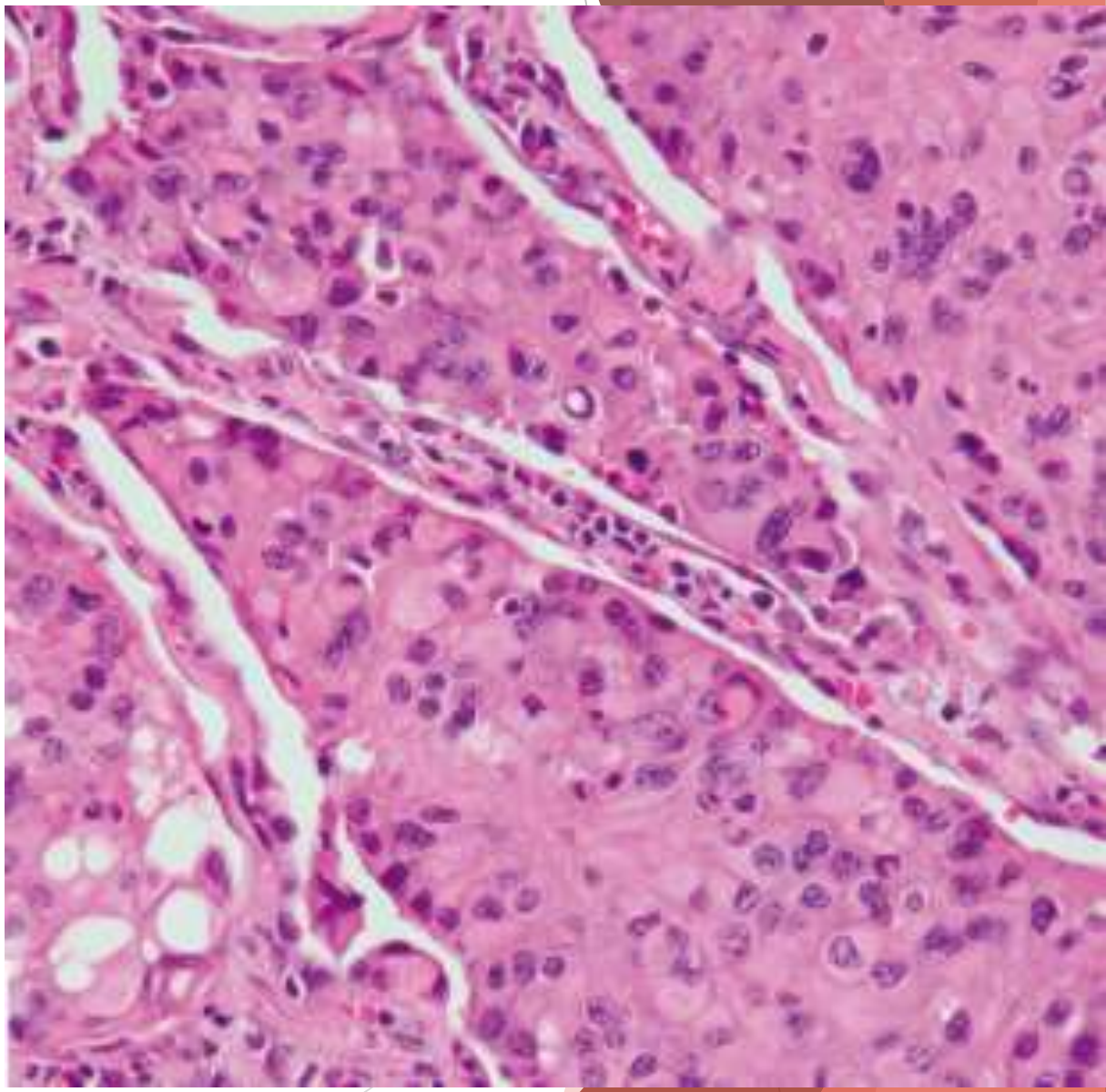
Case #3

Pathology of the Lung EHE

Diagnosis: Lung involvement by EHE

Pathology Interpretation Pearls (II)

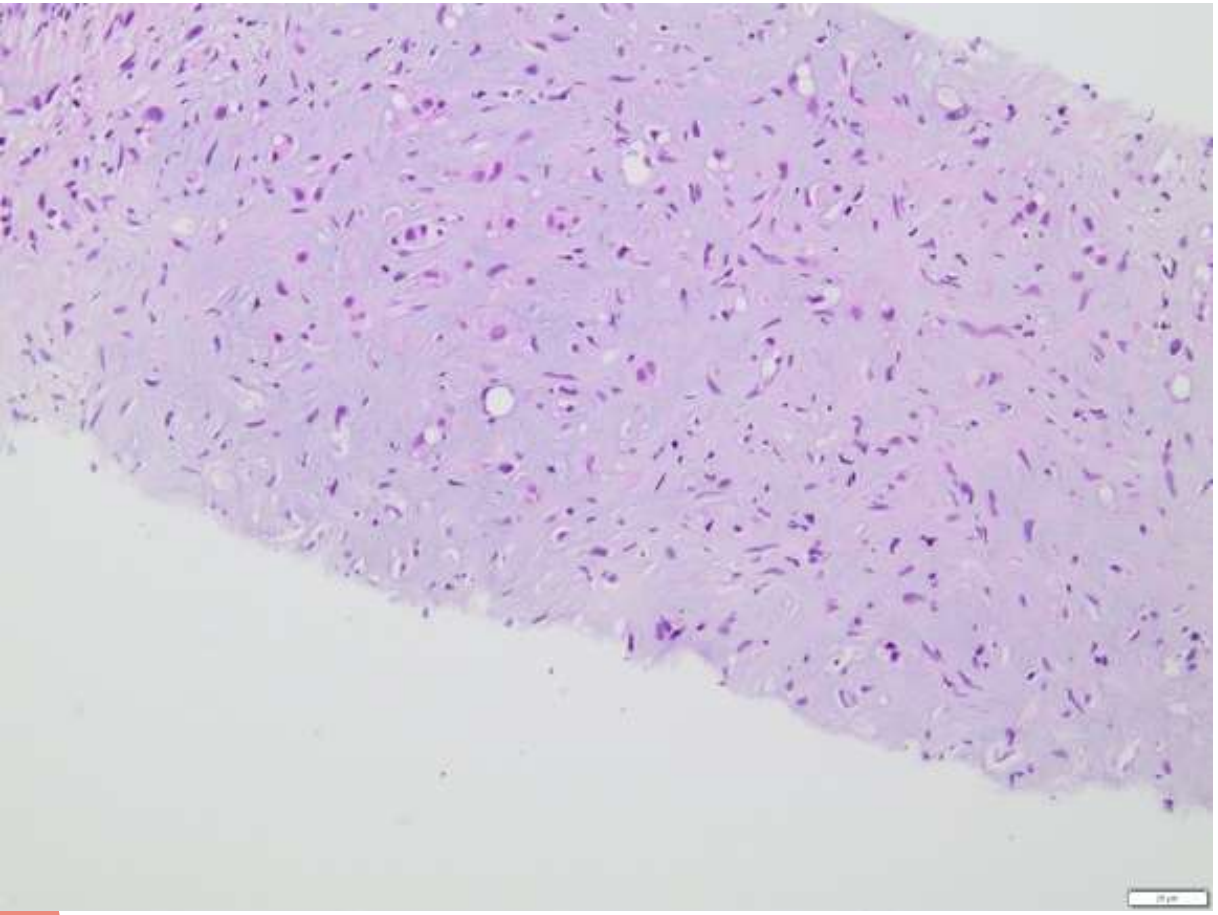
- **IHC:** ✓**ERG** distinguishes EHE from carcinoma and other sarcomas
  - ✓**CAMTA1 helpful in the distinction from angiosarcoma**
- **EHE in the lung is more aggressive than its soft tissue counterparts**
  - ✓**Pleural EHE is typically very aggressive**
  - ✓The metastatic rate may be as high as 50% in YAP1-TFE3 rearranged tumors



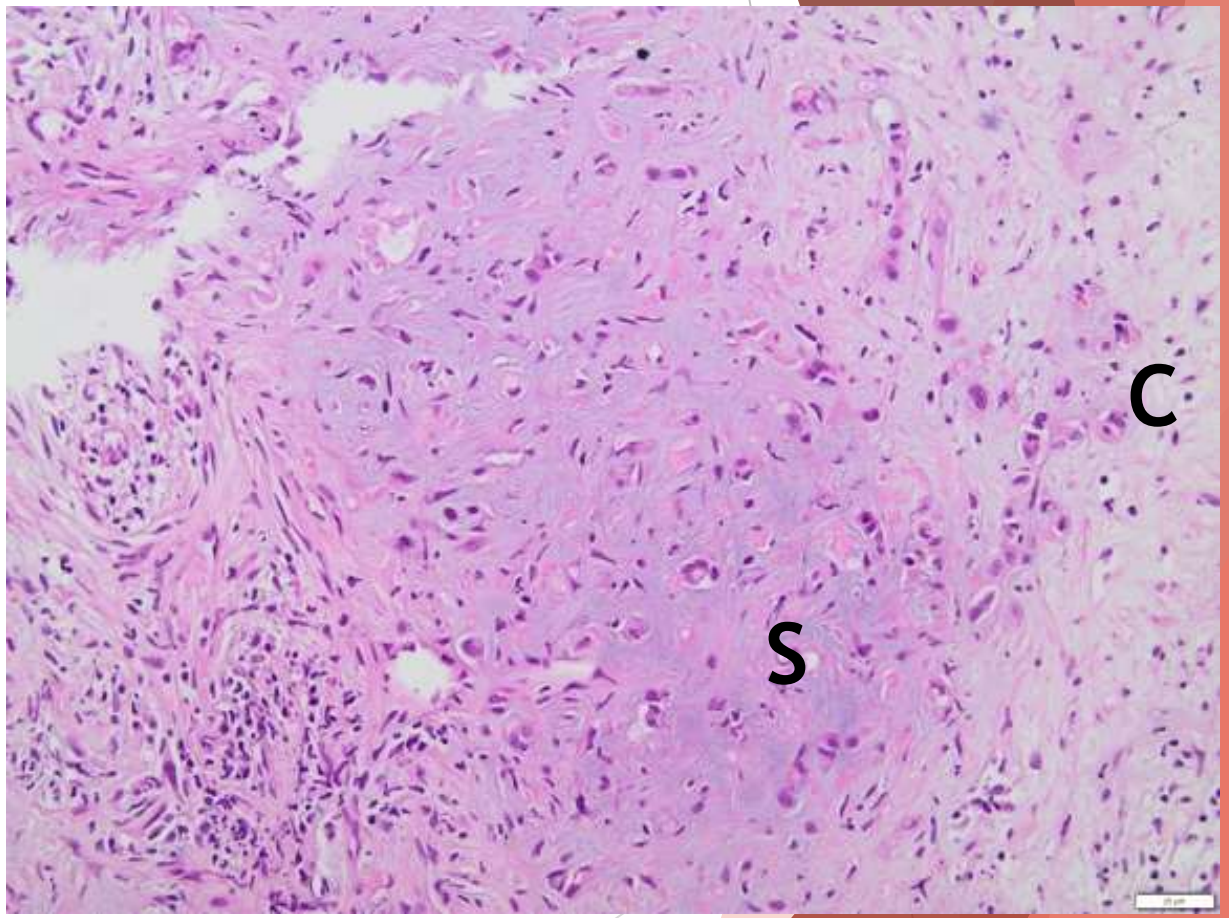
Tumor plugs within alveolar spaces

Case #4

- Female, 57 year-old
- Multiple liver lesions
- Clinical suspicion of metastatic carcinoma
- Needle liver biopsy

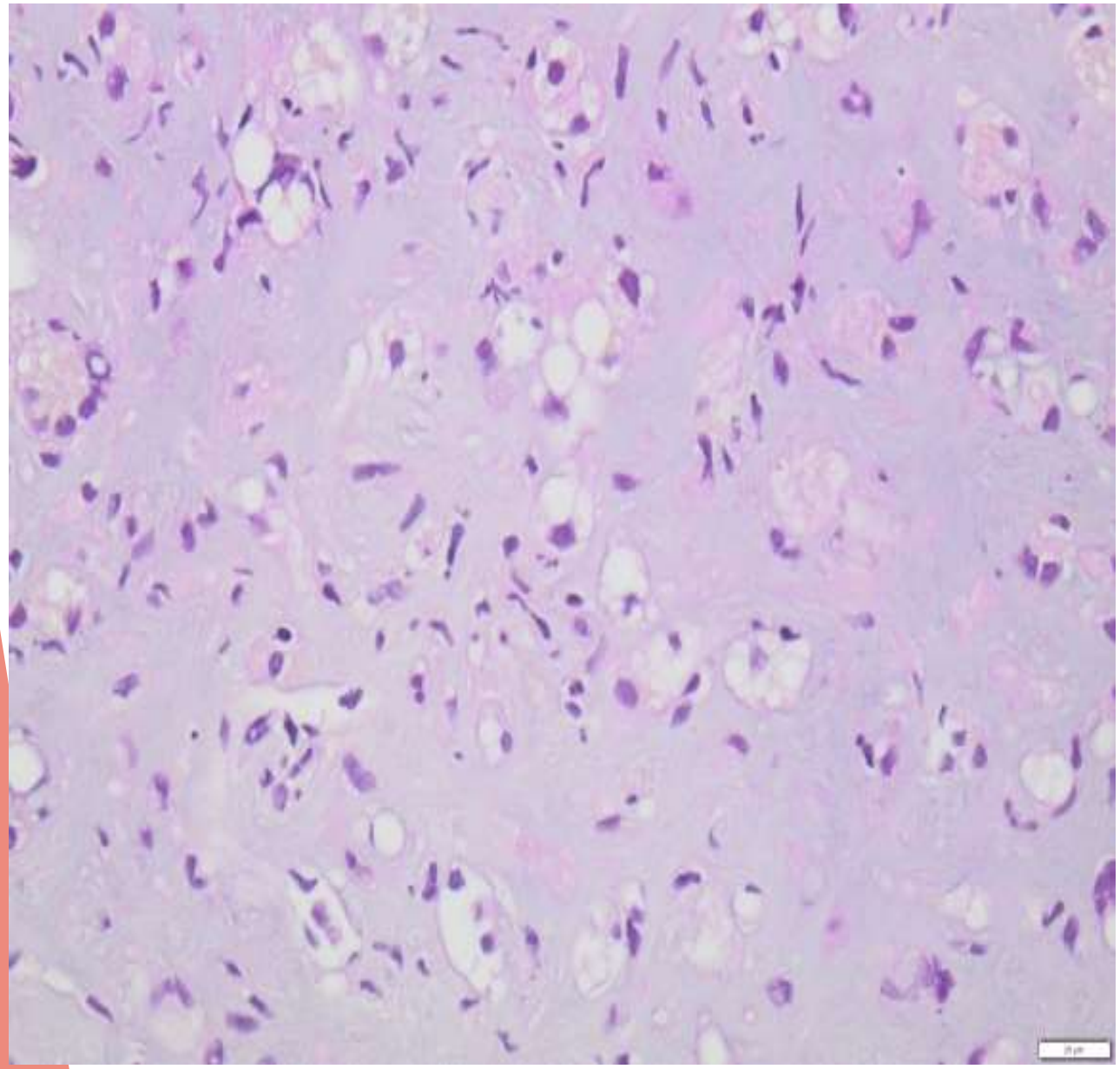


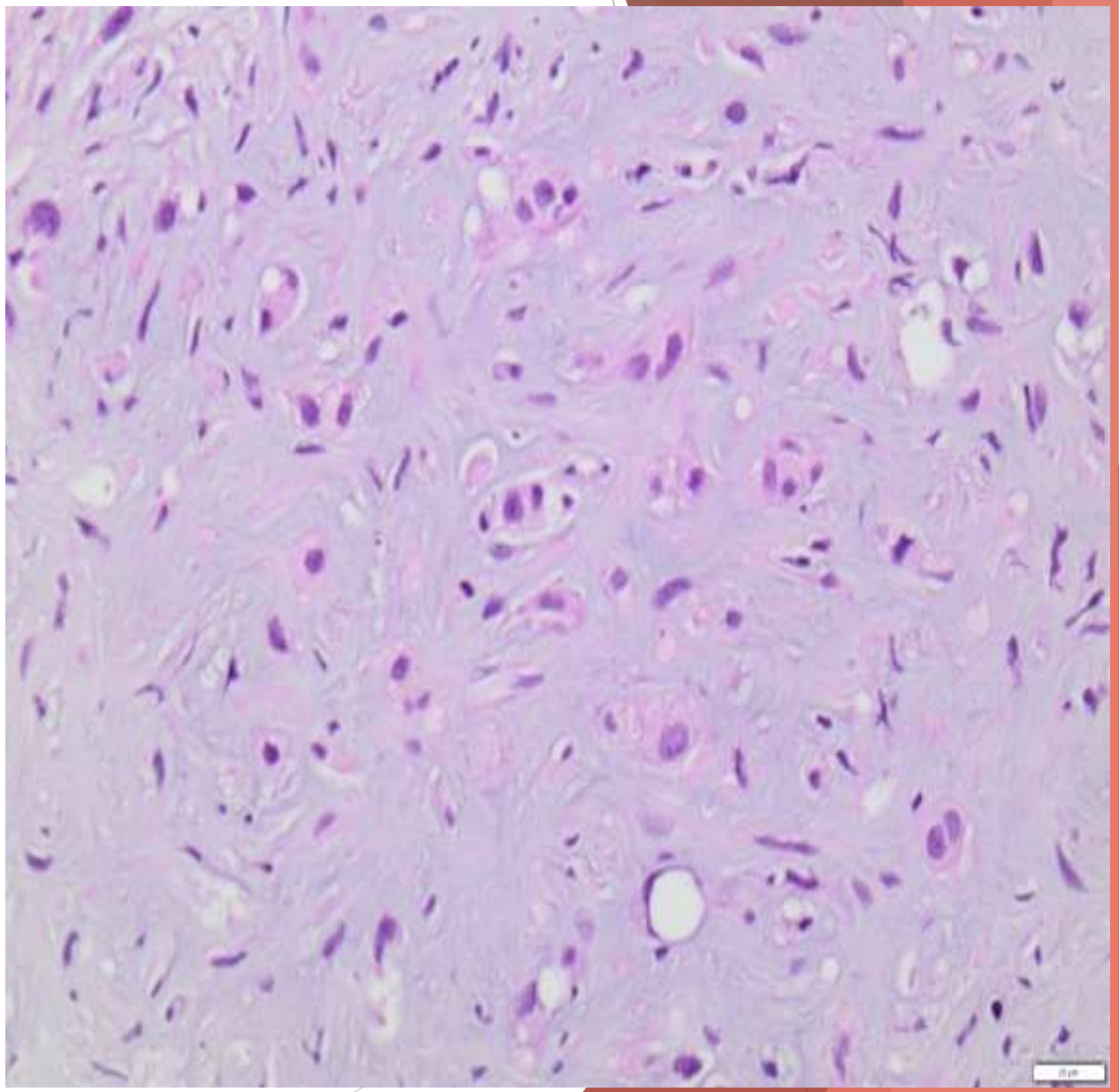
Hypocellular neoplastic tissue



Neoplastic cells embedded in basophilic stroma (S) and arranged in cords (C)

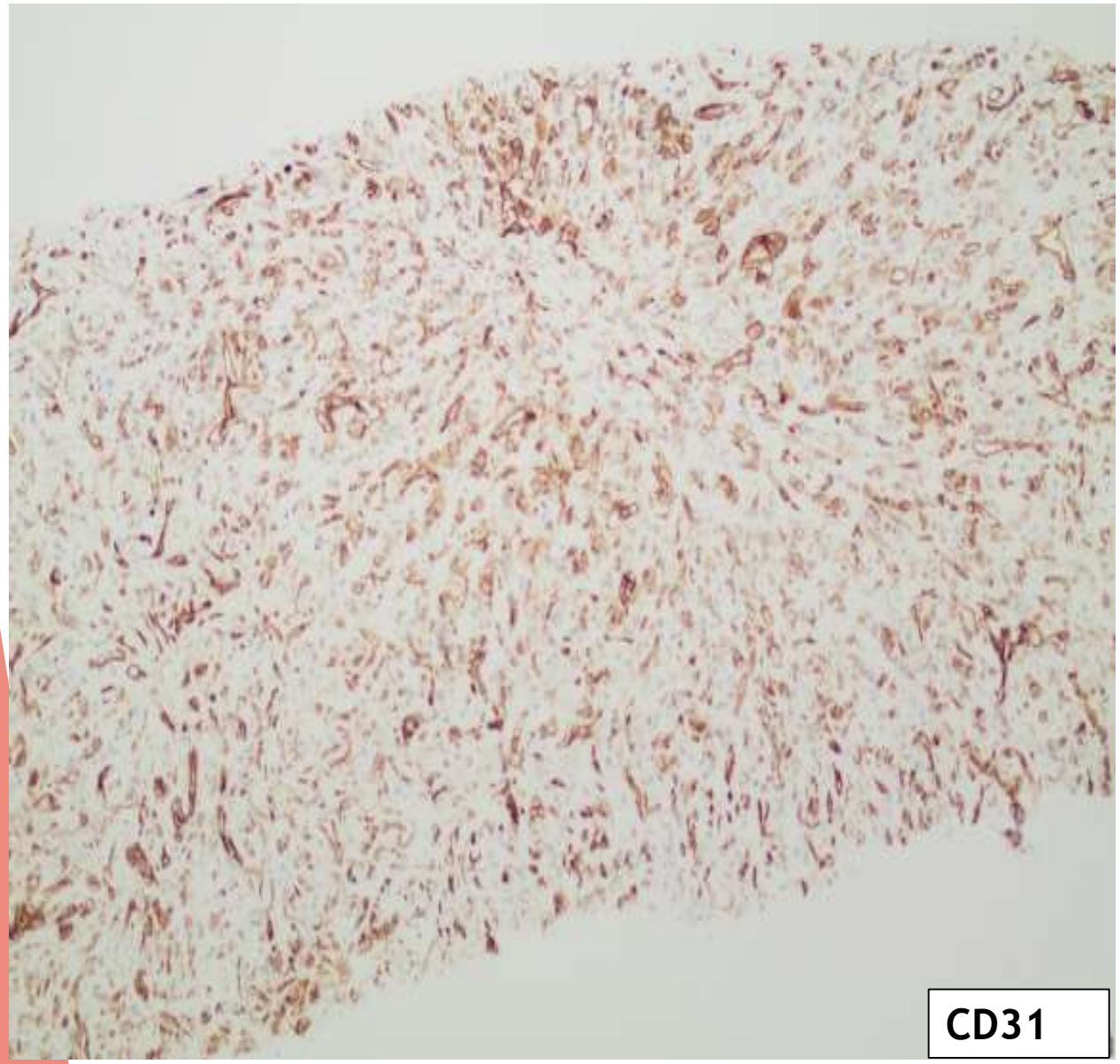
Case #4

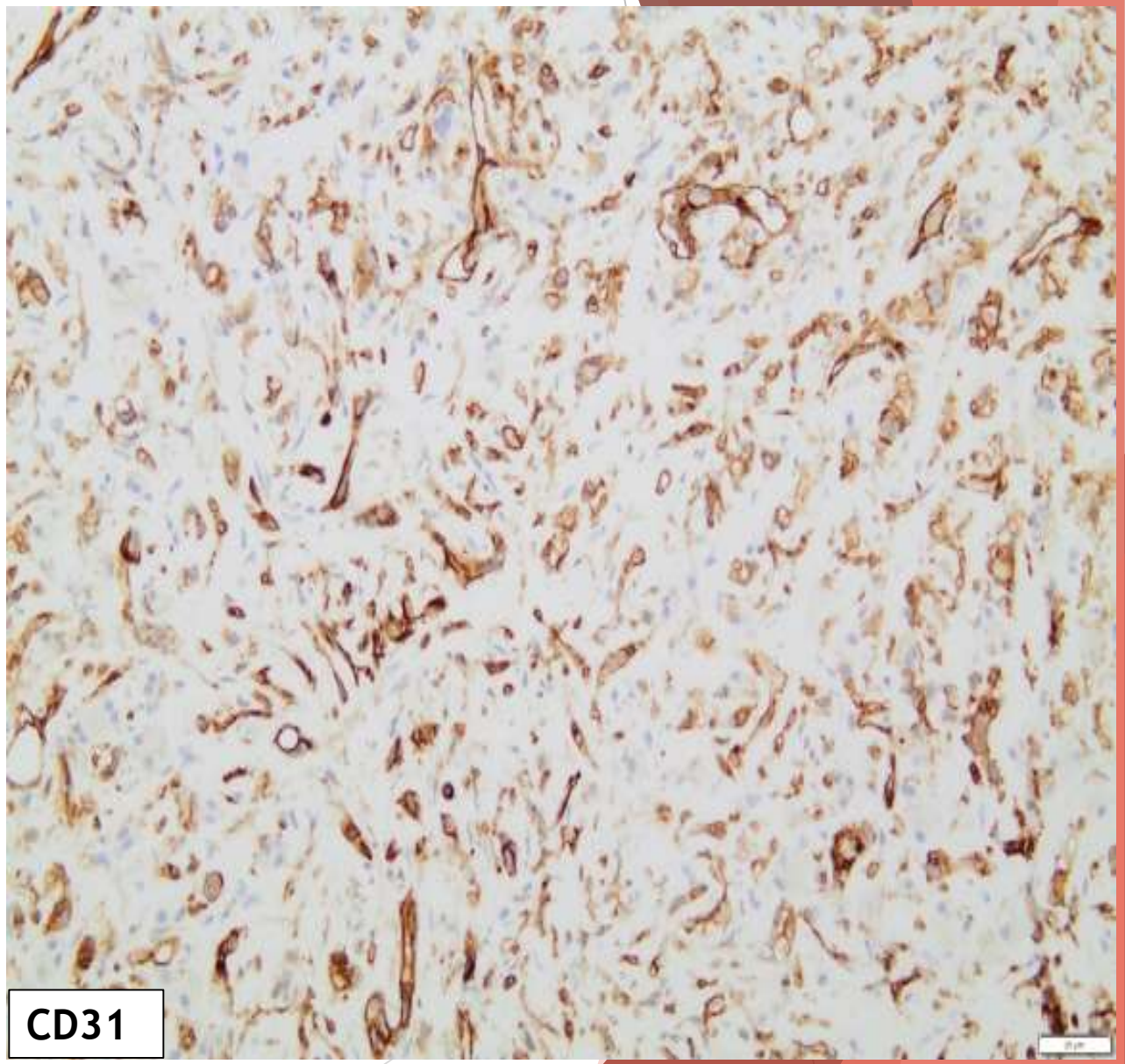




Bland neoplastic cells with epithelioid morphology and clear cytoplasmic vacuoles

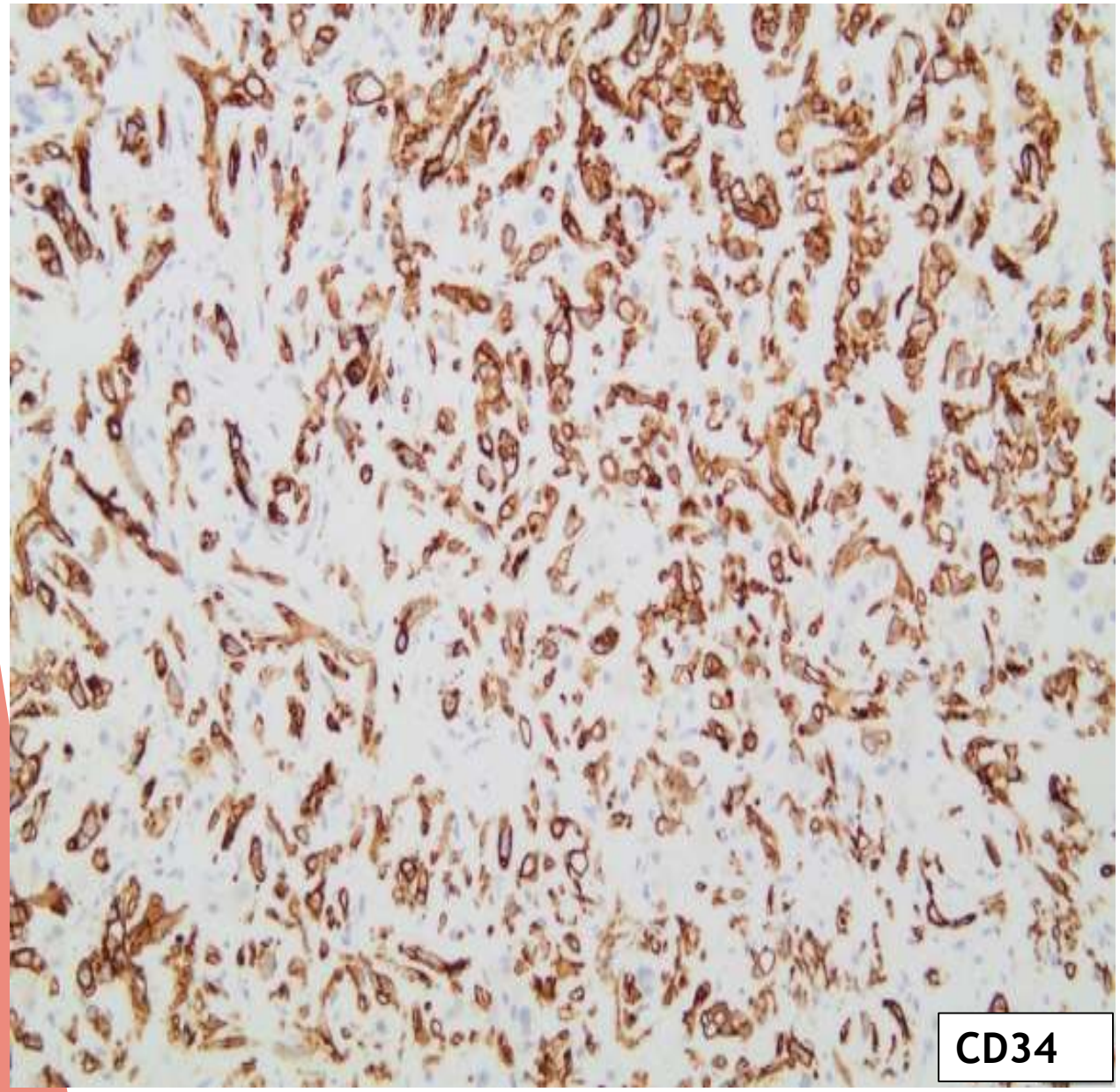
Case #4

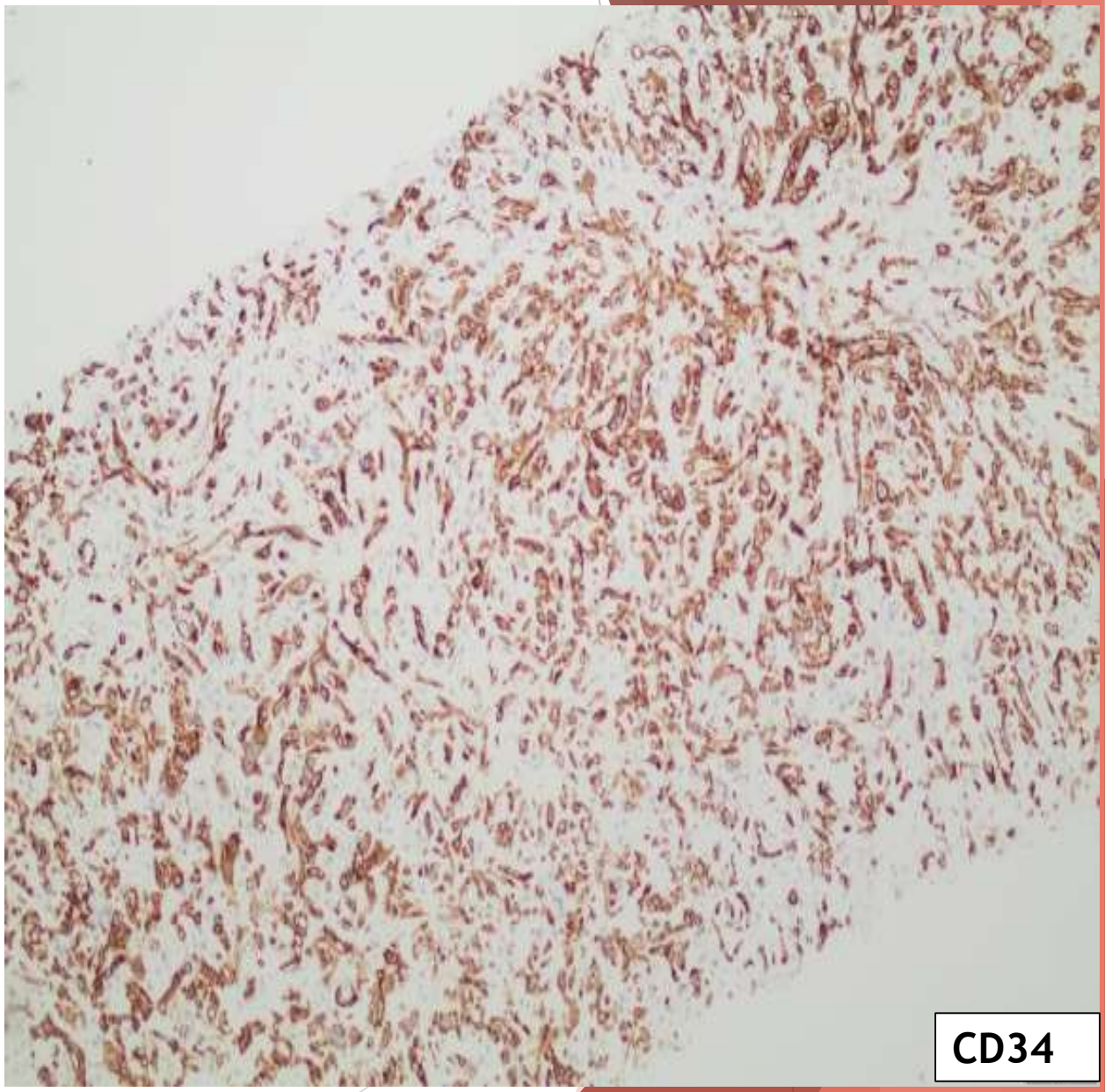




Diffuse positivity for CD31

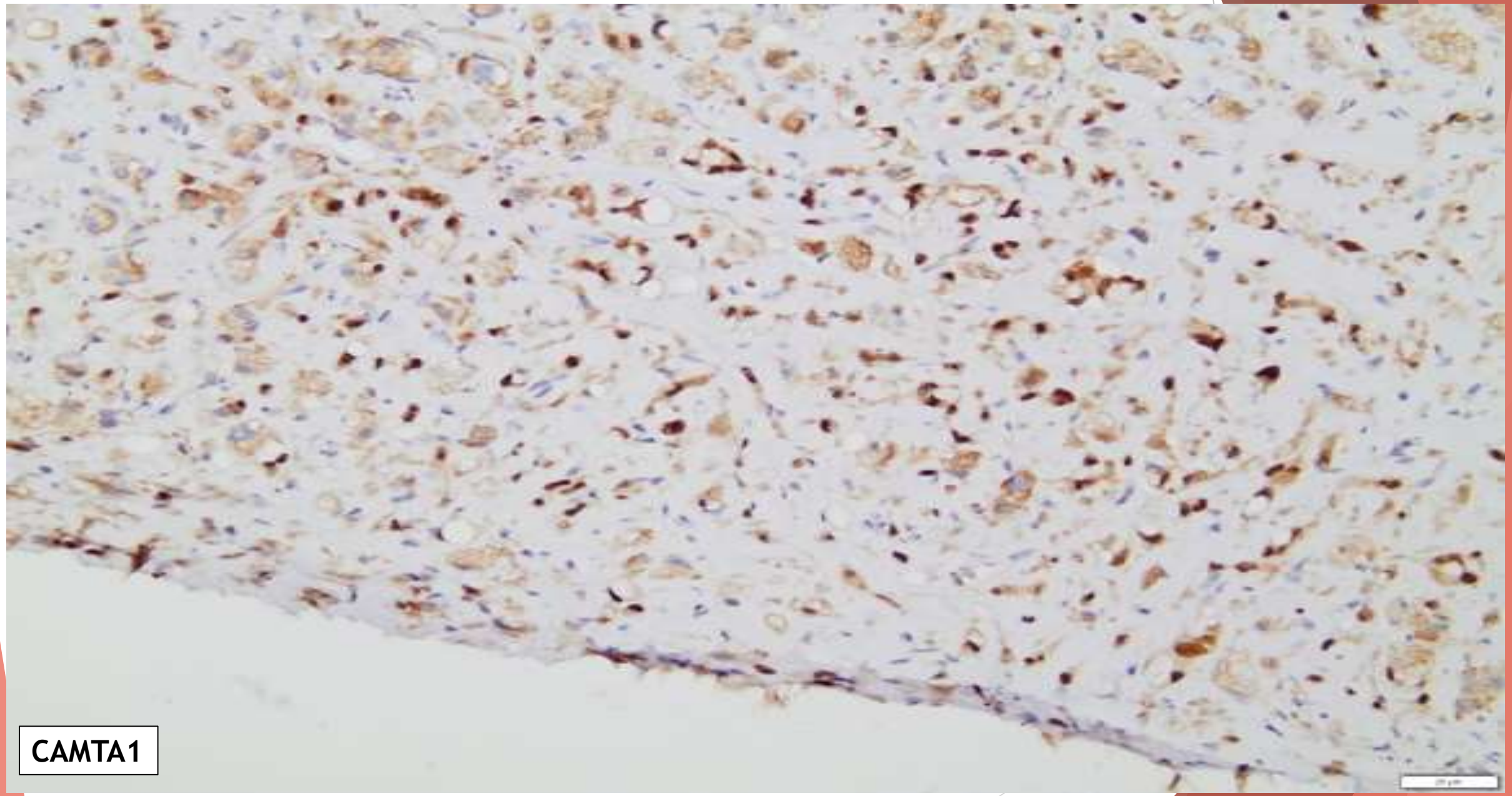
Case #4





Diffuse positivity for CD34

Case #4



Diffuse strong nuclear expression for CAMTA1

Case #4

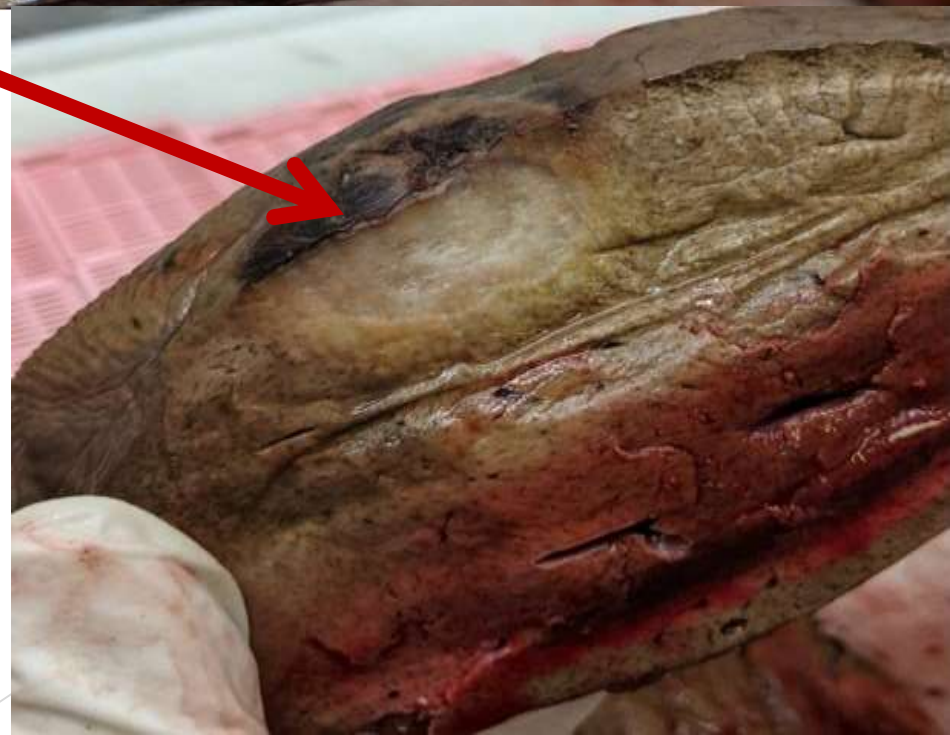
HEP-PAR highlights the atrophic hepatocytes, whereas neoplastic cells are uniformly negative

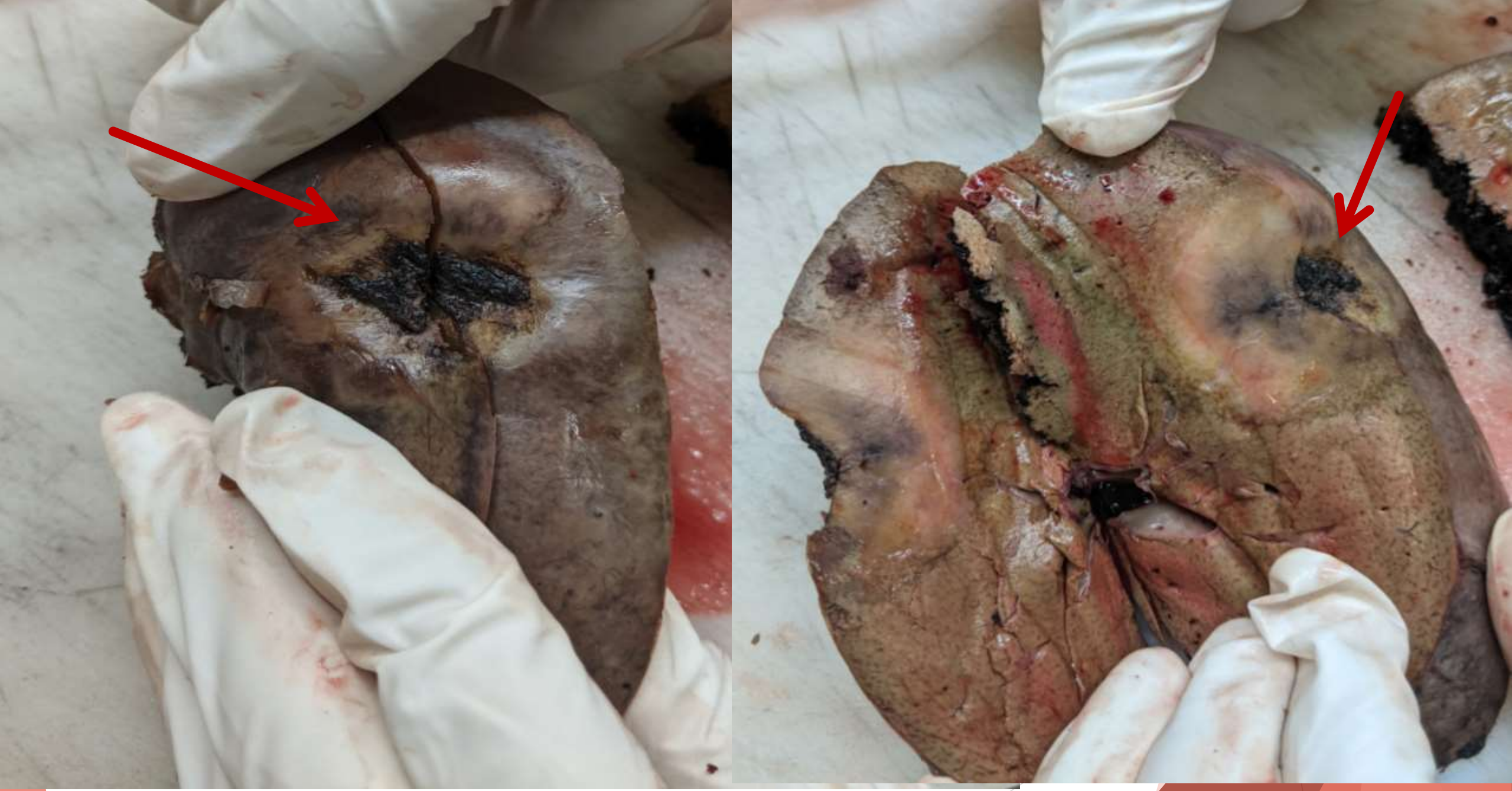
Case #4

Diagnosis: hepatic EHE

- Right hemi-hepatectomy specimen

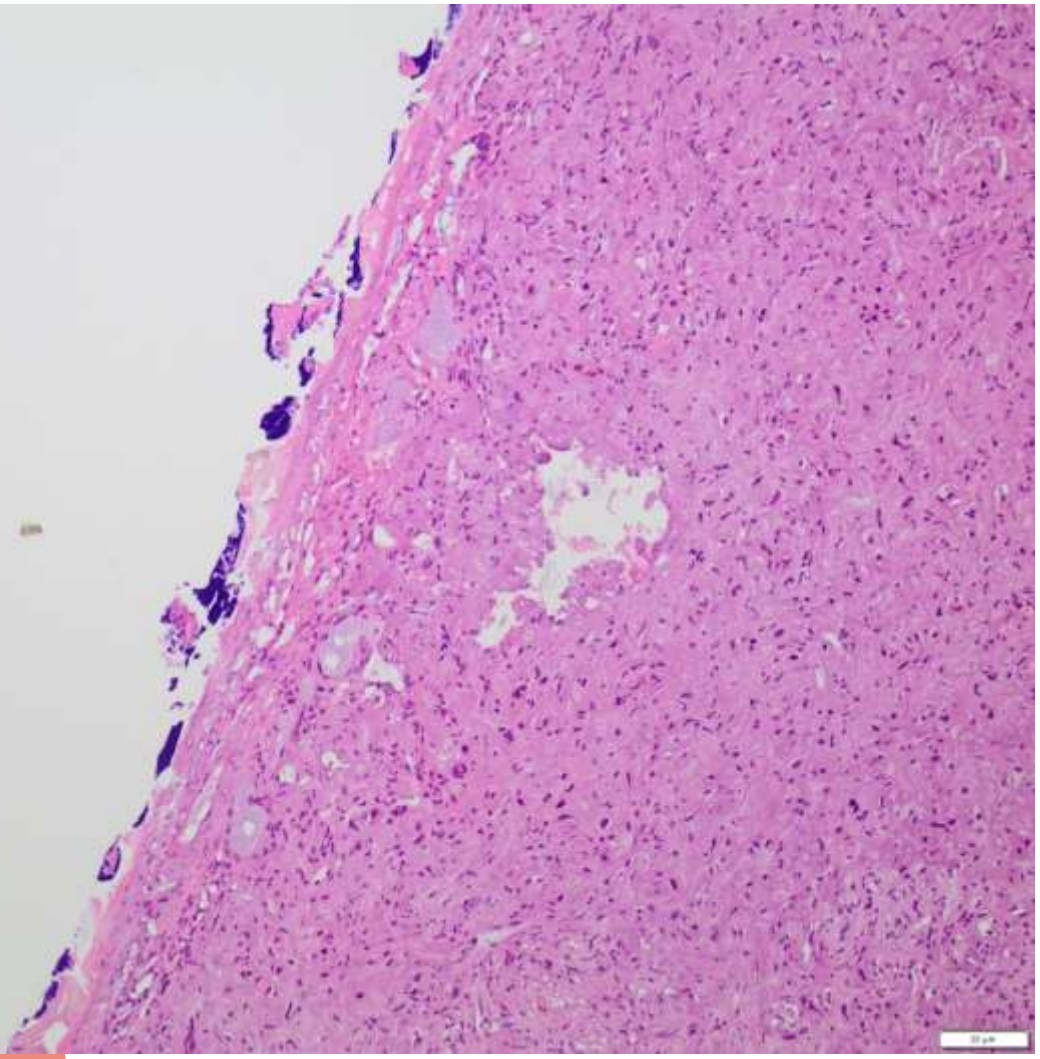
Multiple gray-tan tumor nodules up to 4cm in largest diameter

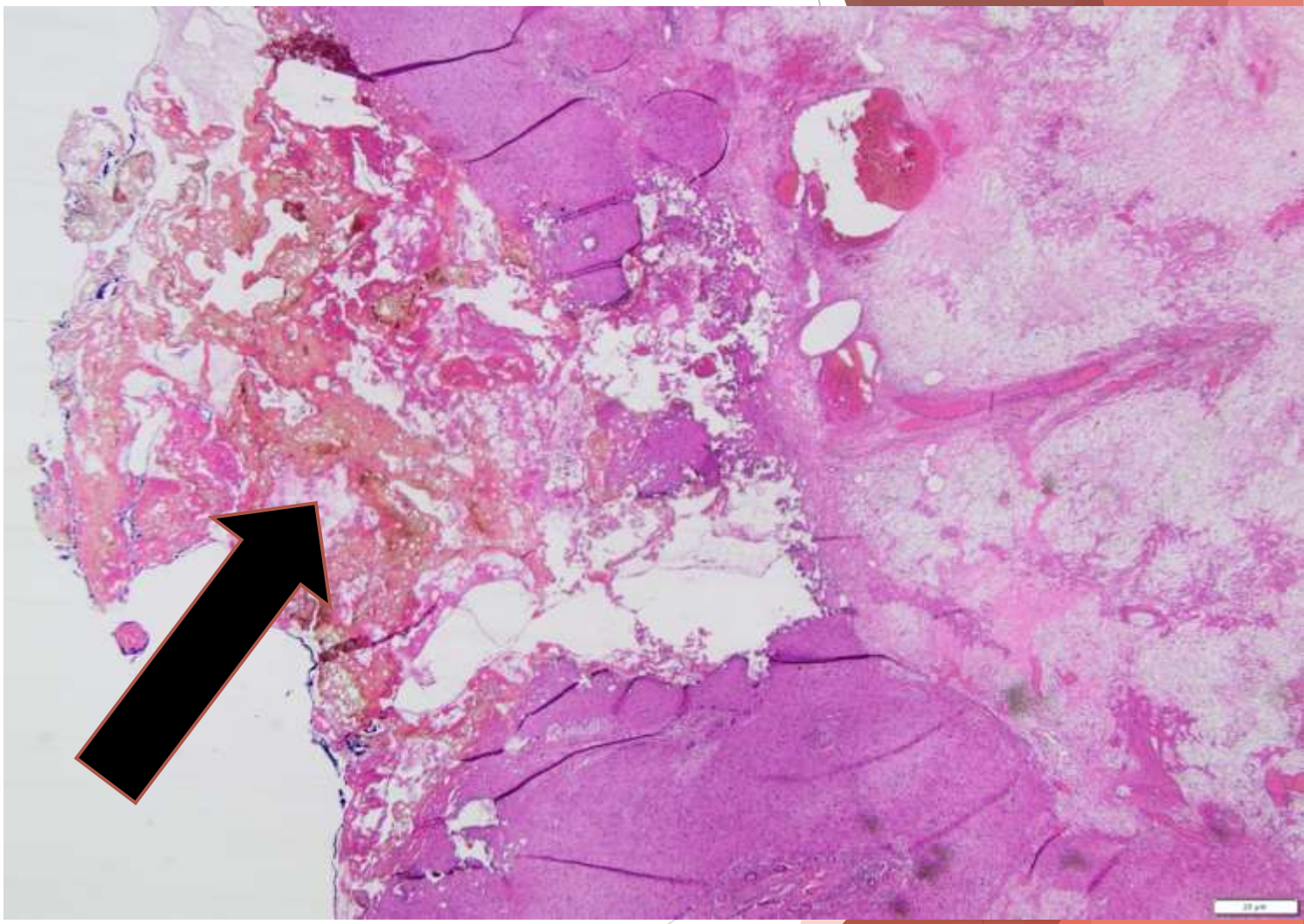




Capsular retraction

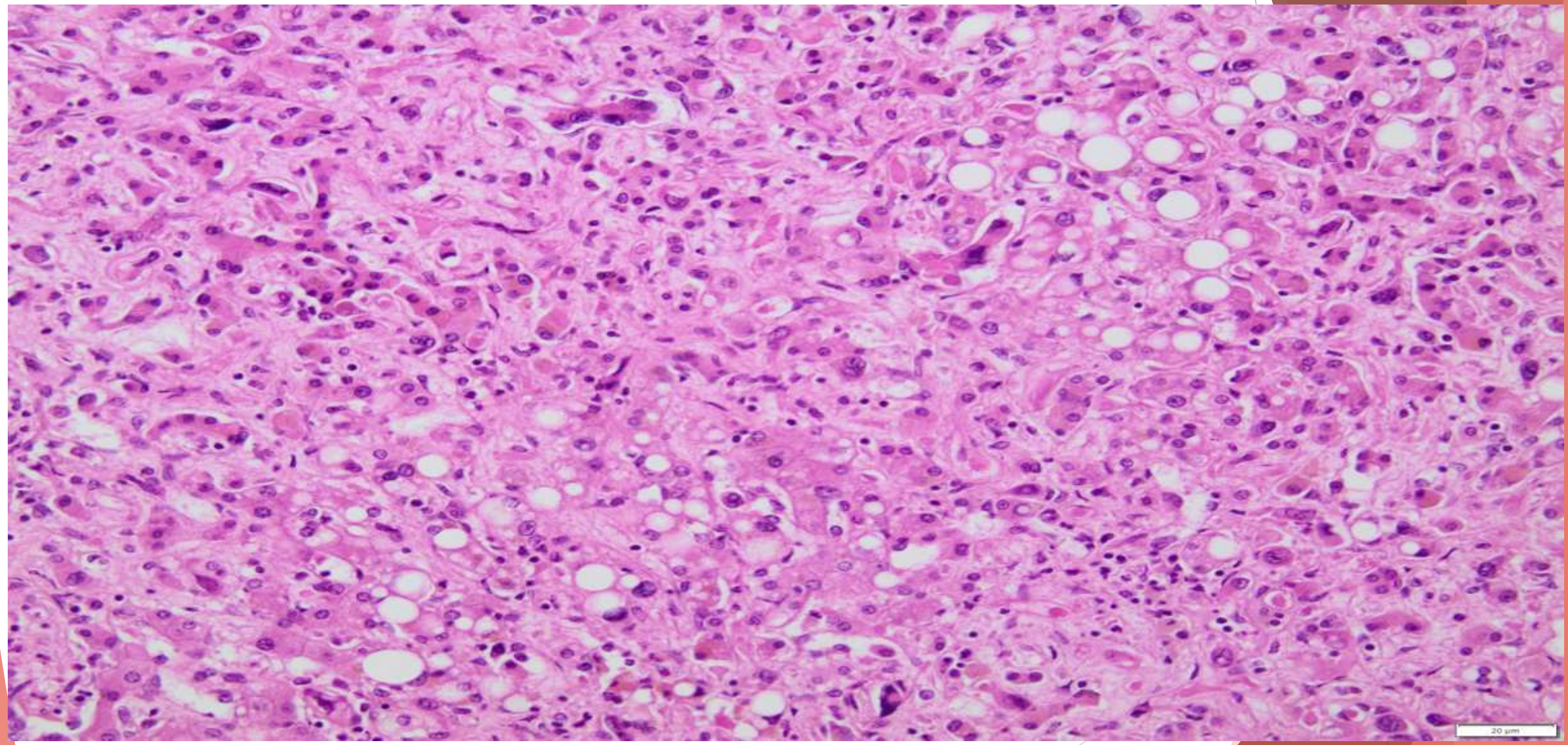
Case #4





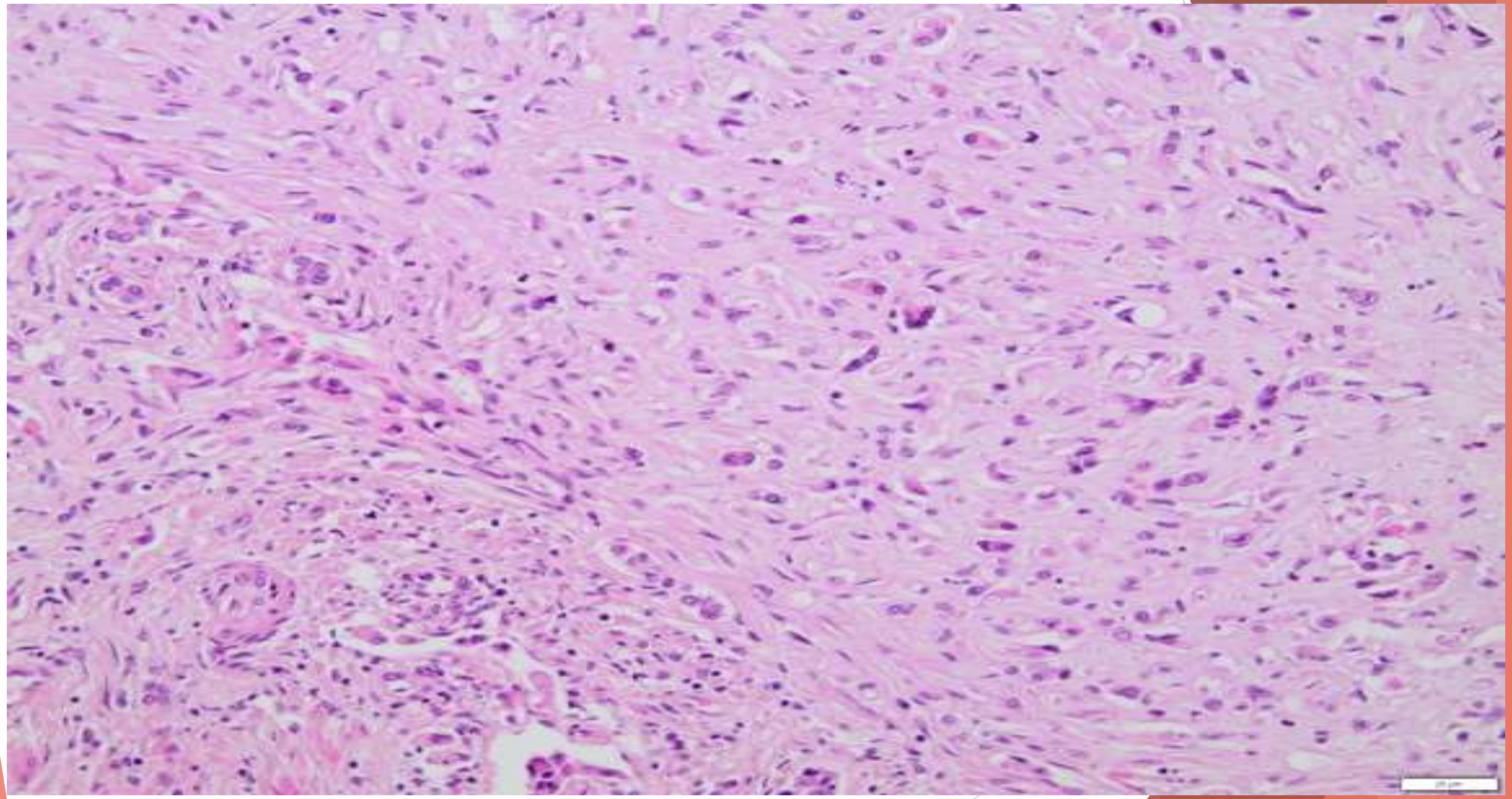
Tumor cells extend into liver capsule causing capsular retraction (Arrow)

Case #4



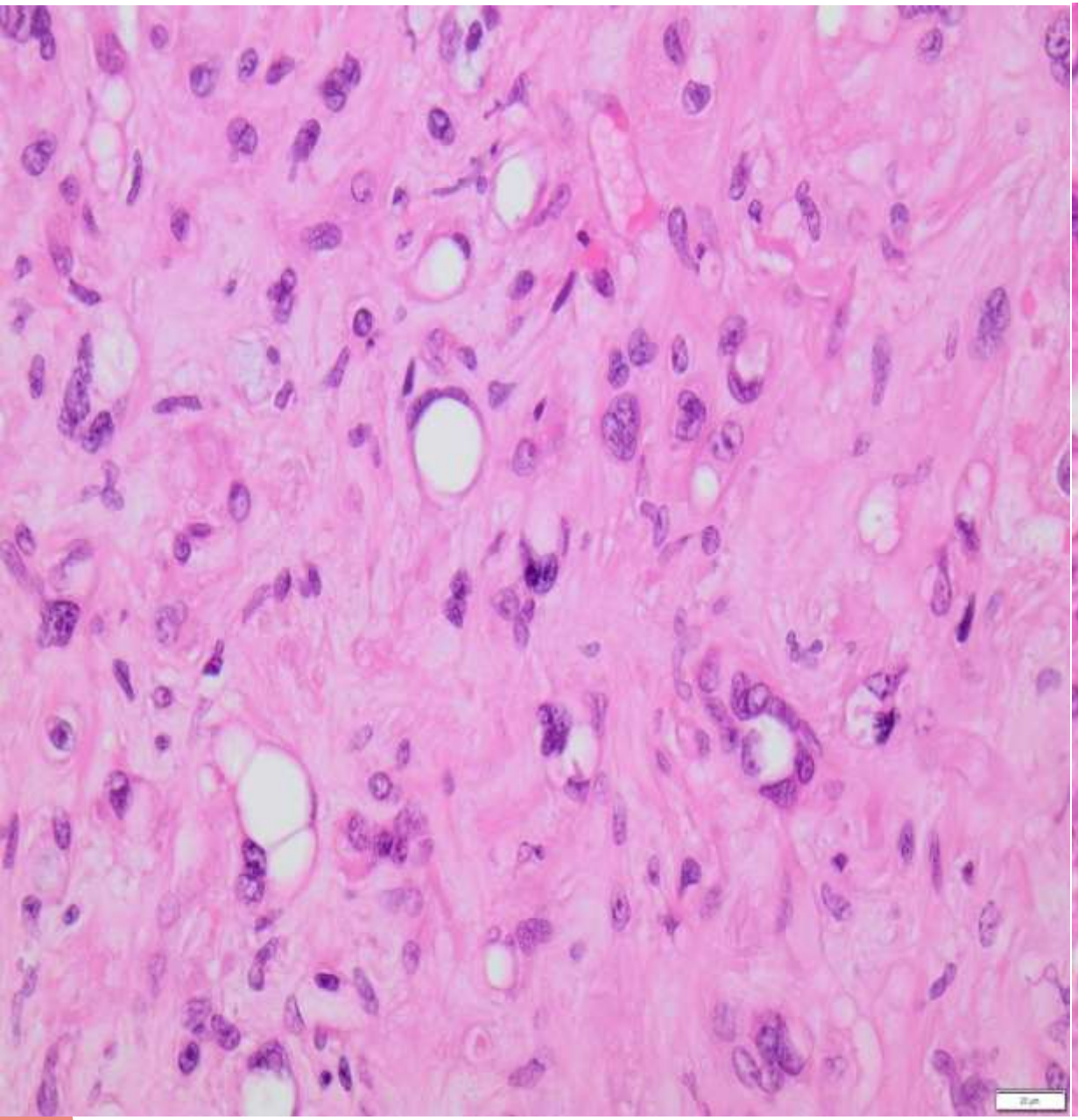
Neoplastic cells infiltrate the liver parenchyma causing atrophy of liver cell plates

Case #4

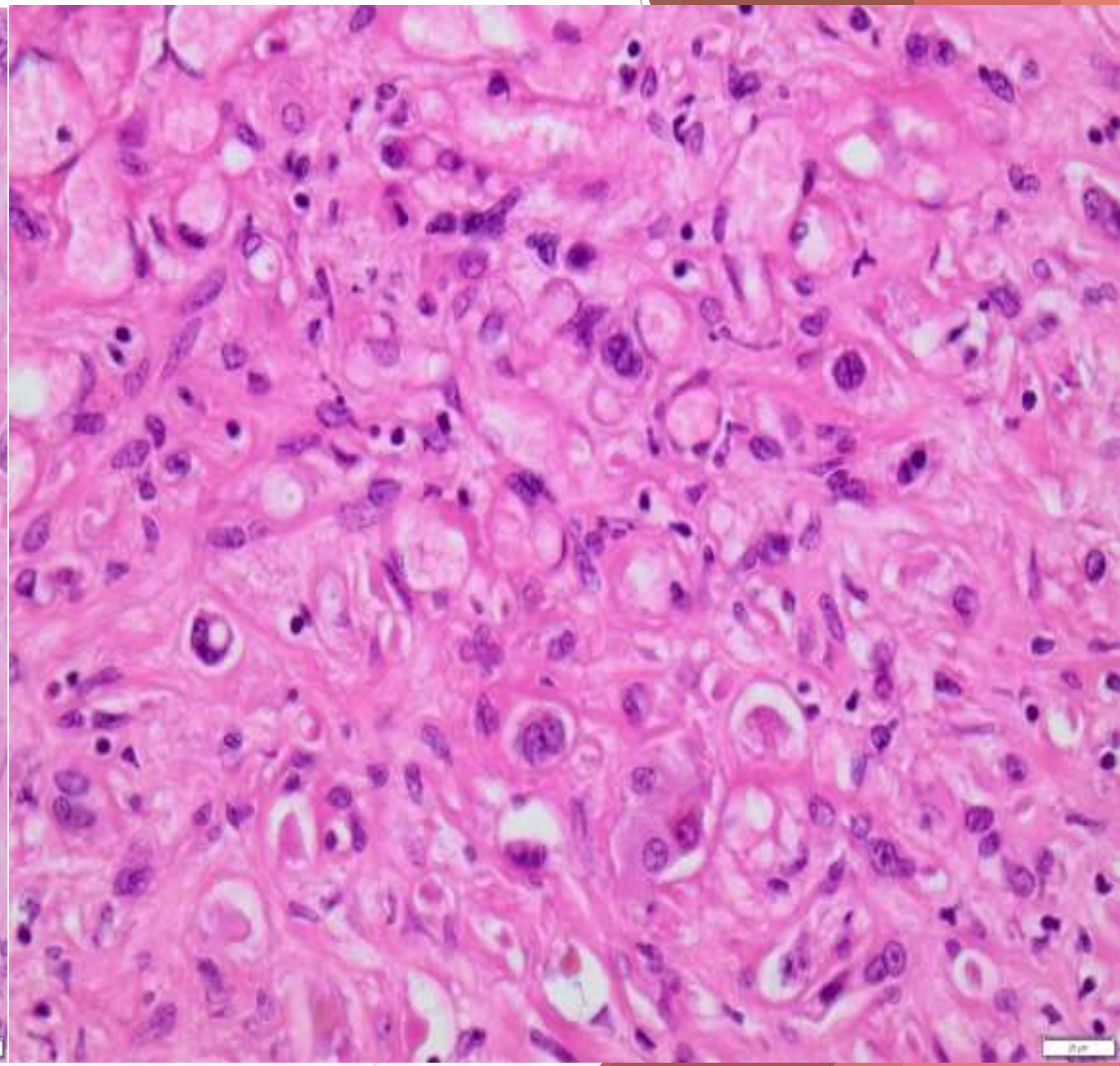


Myxohyaline stroma with “Chondroid” appearence

Case #4

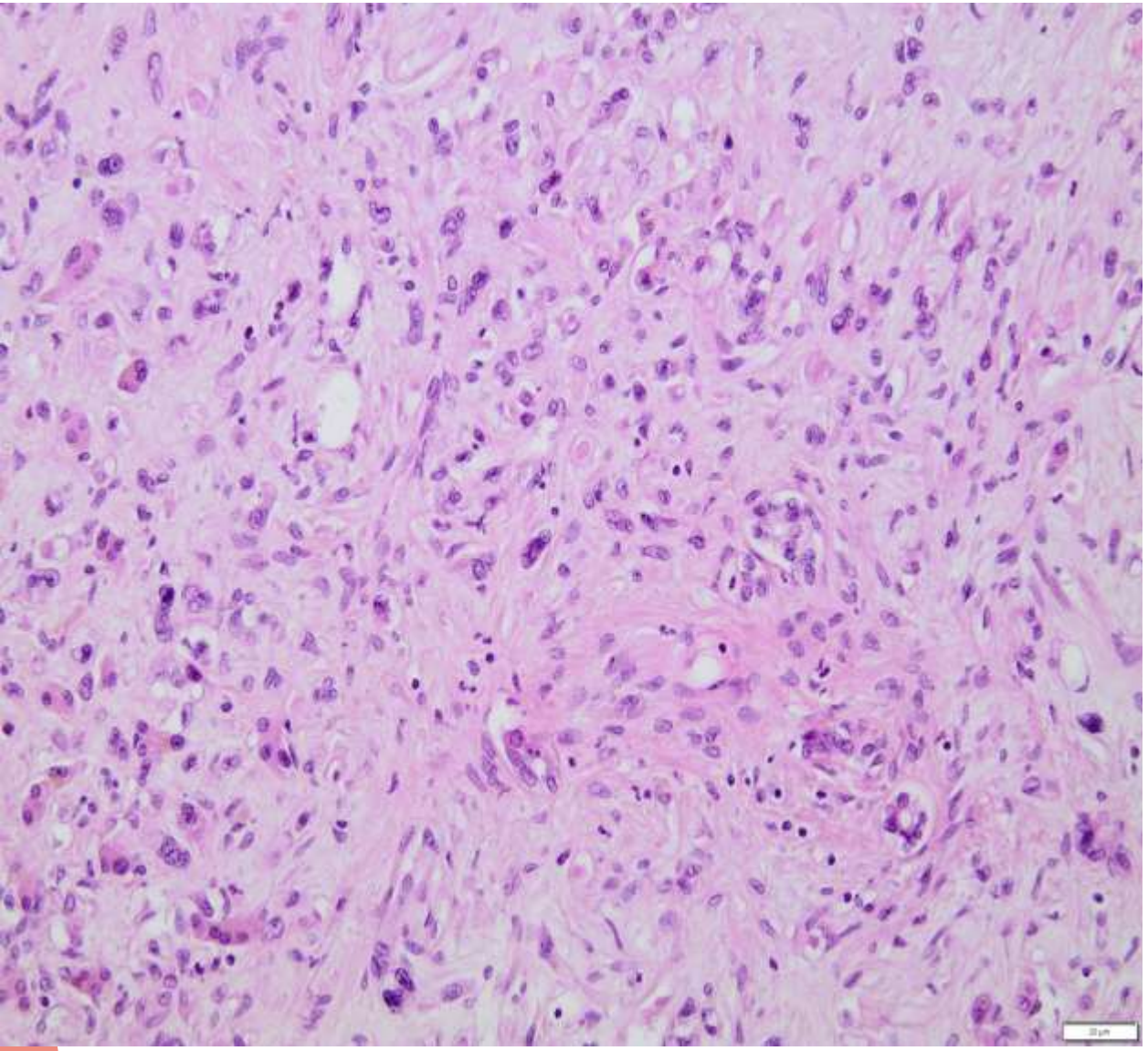


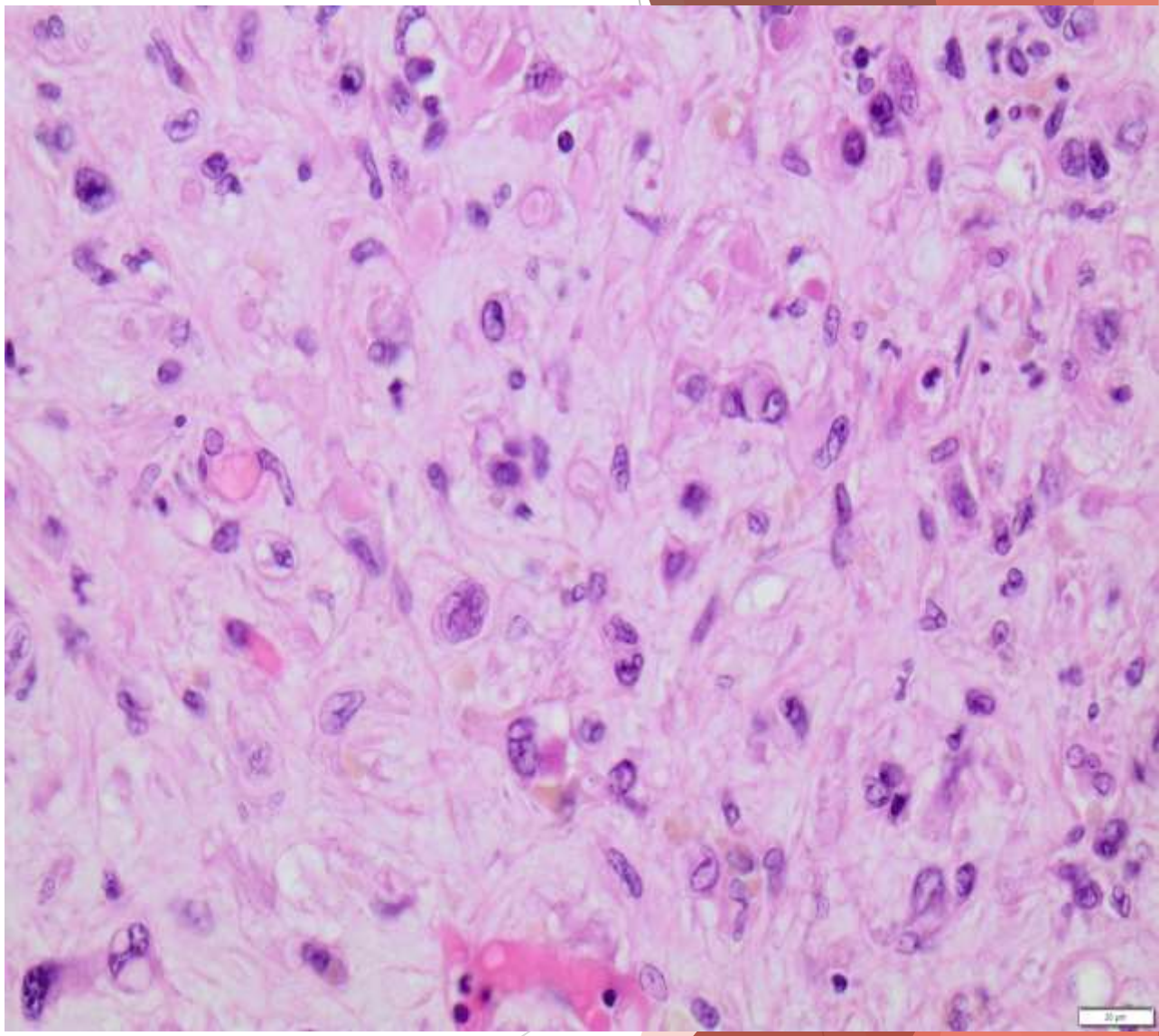
Cytoplasmic vacuoles of varying sizes



Eosinophilic neoplastic cells with cytoplasmic vacuoles

Case #4

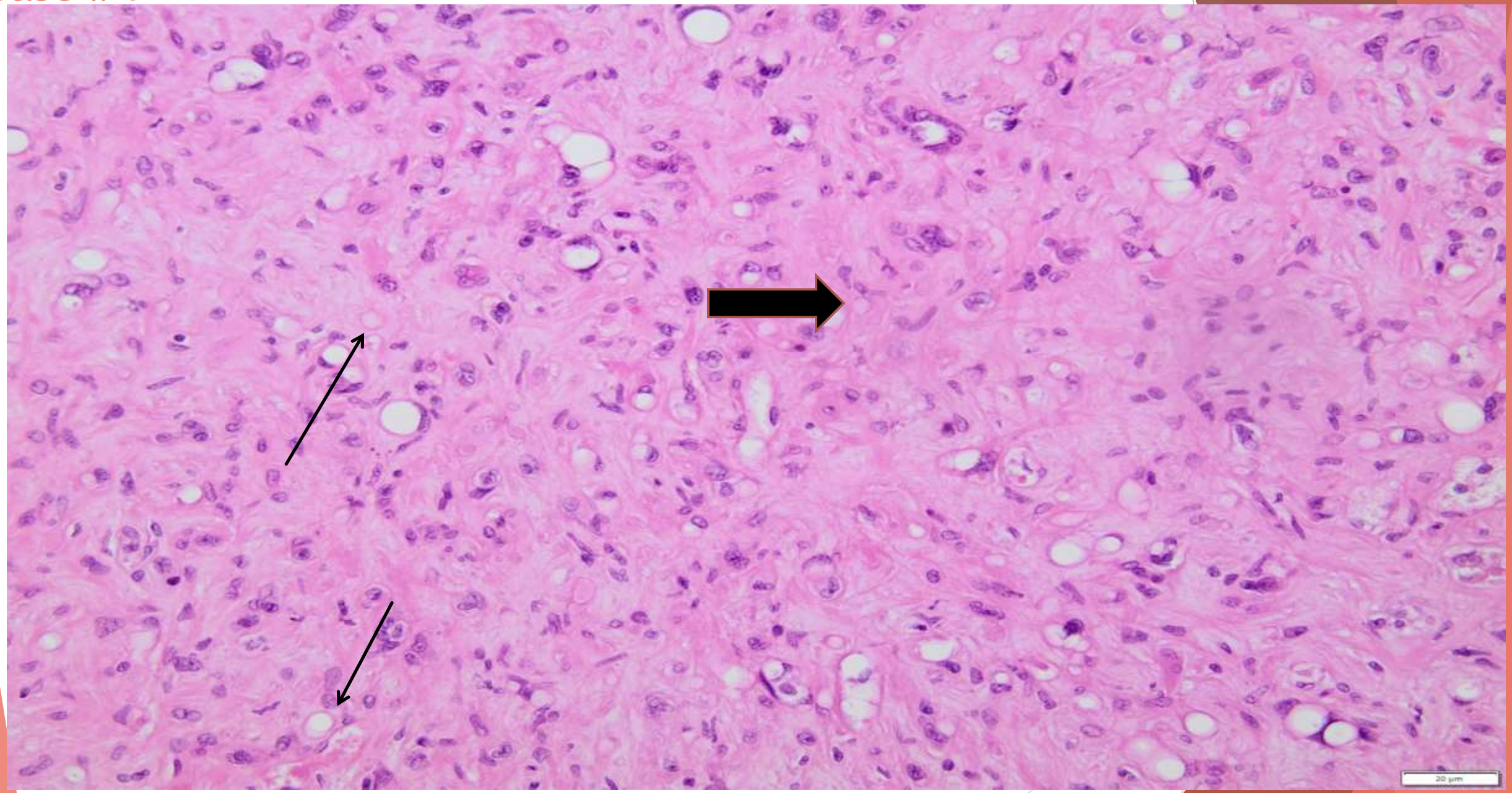




Neoplastic cells with enlarged hyperchromatic multilobated nuclei

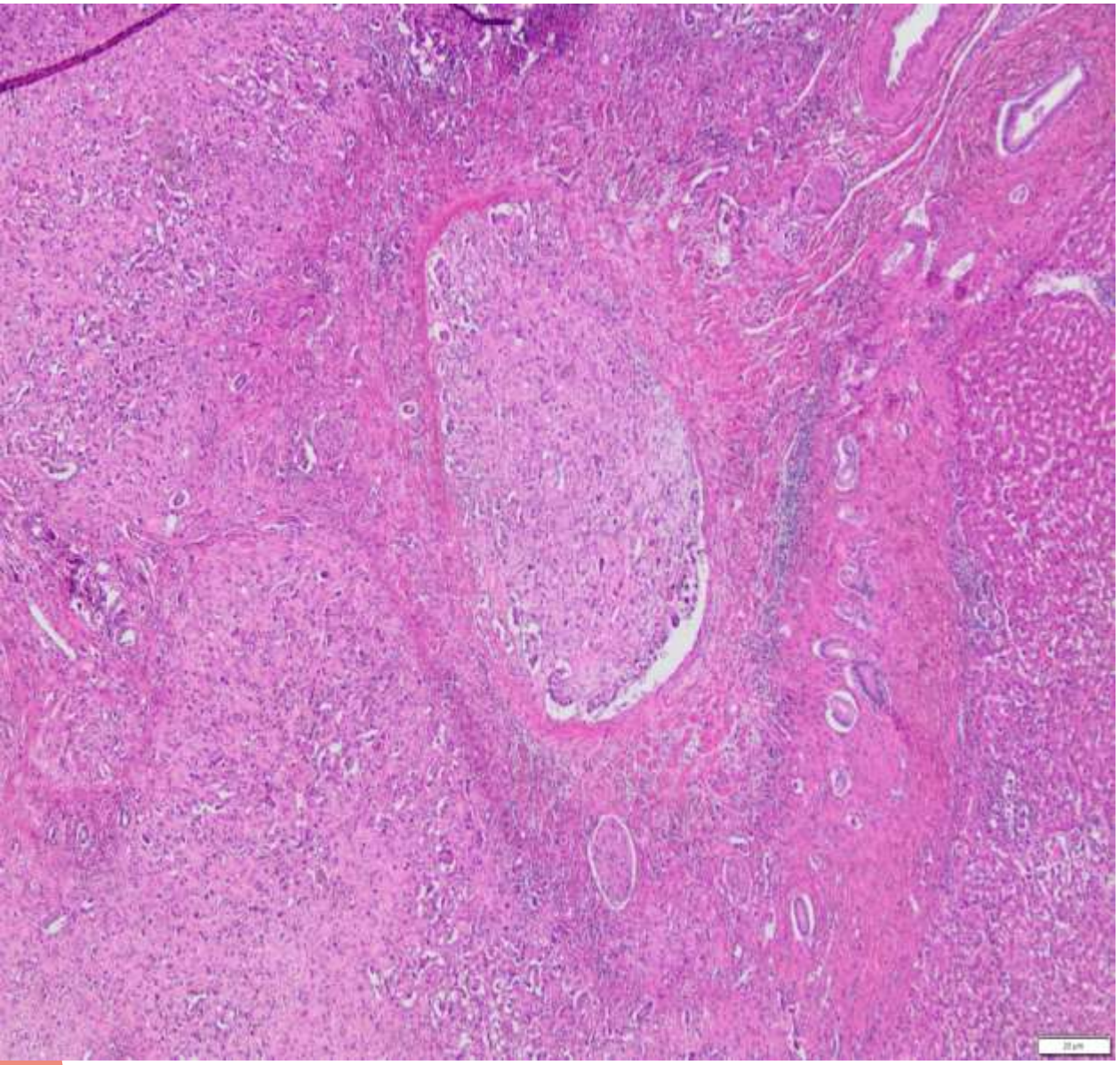
No mitotic figures

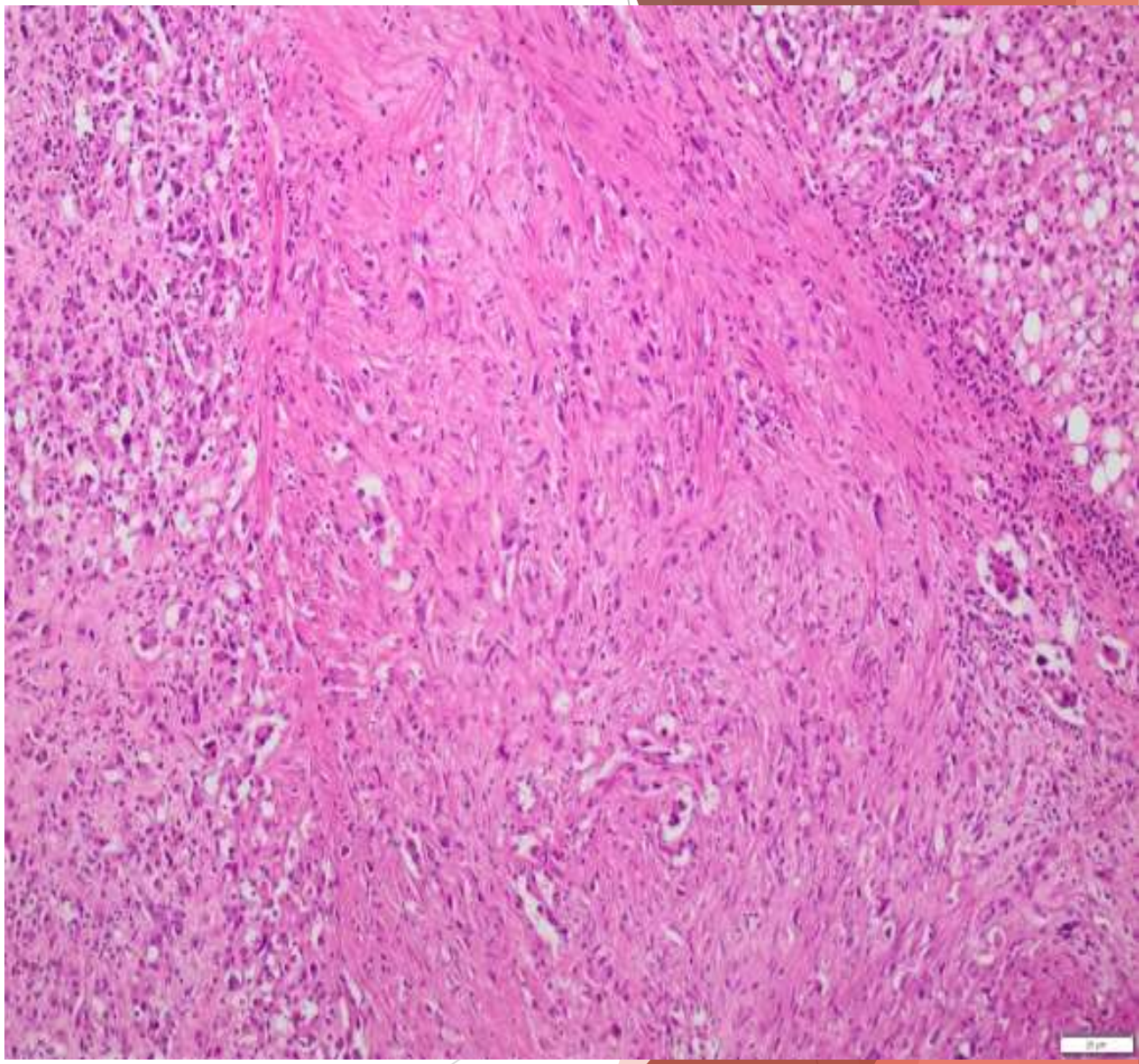
Case #4



Vacuolated cells mimicking “signet rings” (mucin stains negative) (Thick arrow)
Vacuoles also in fibrous stroma (thin arrows)

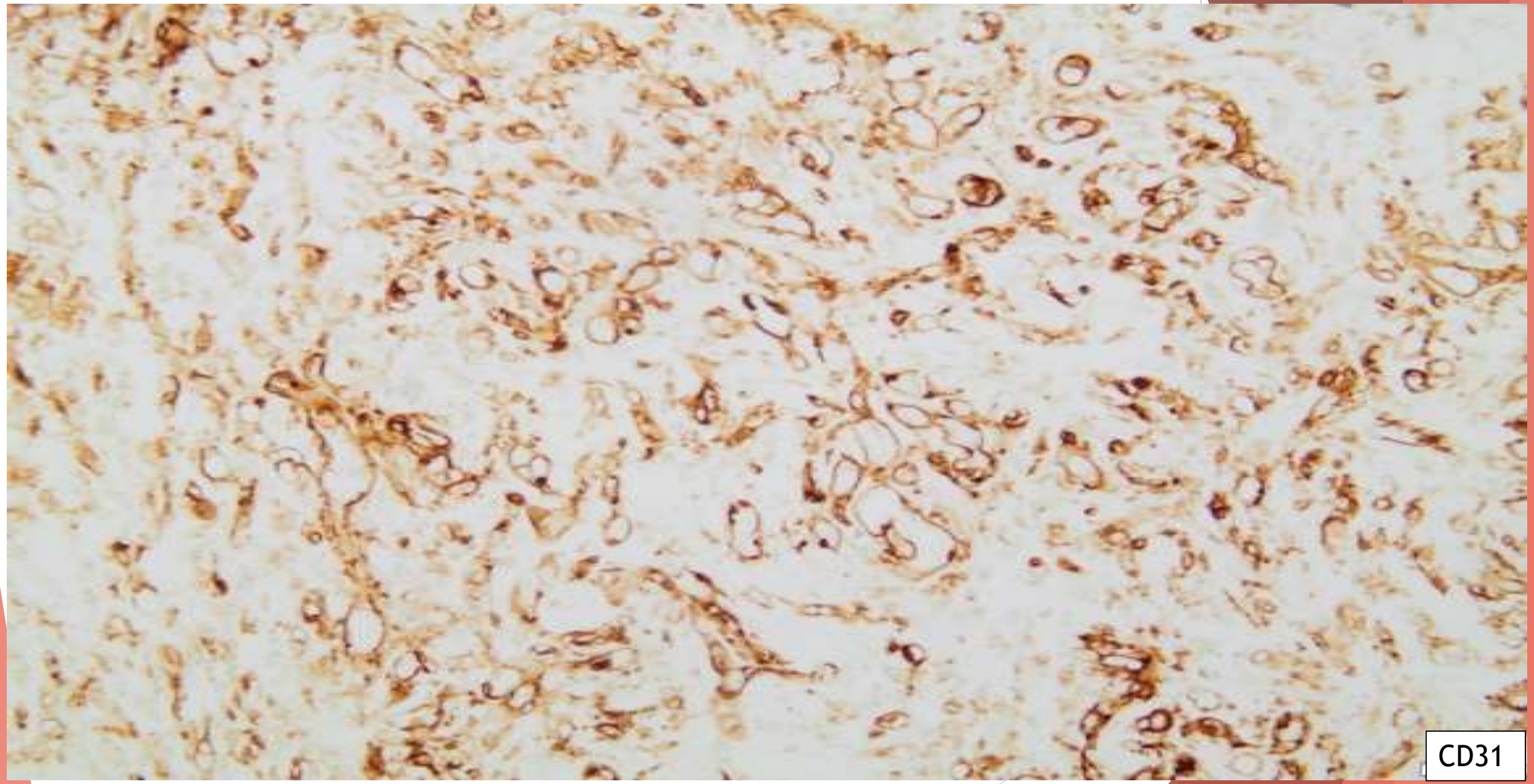
Case #4





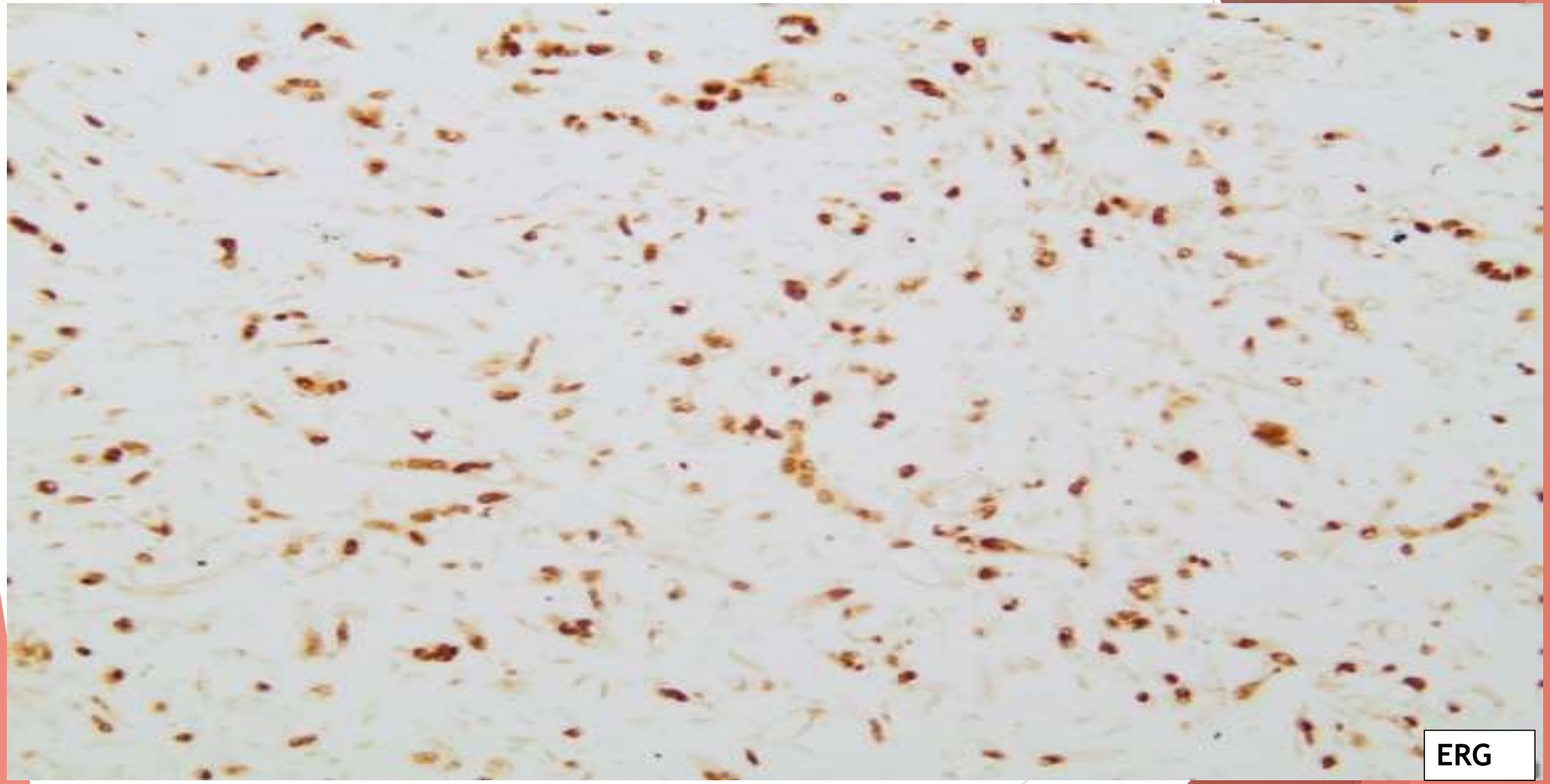
Multiple venous vessels involved by neoplastic cells obliterating the lumen

Case #4



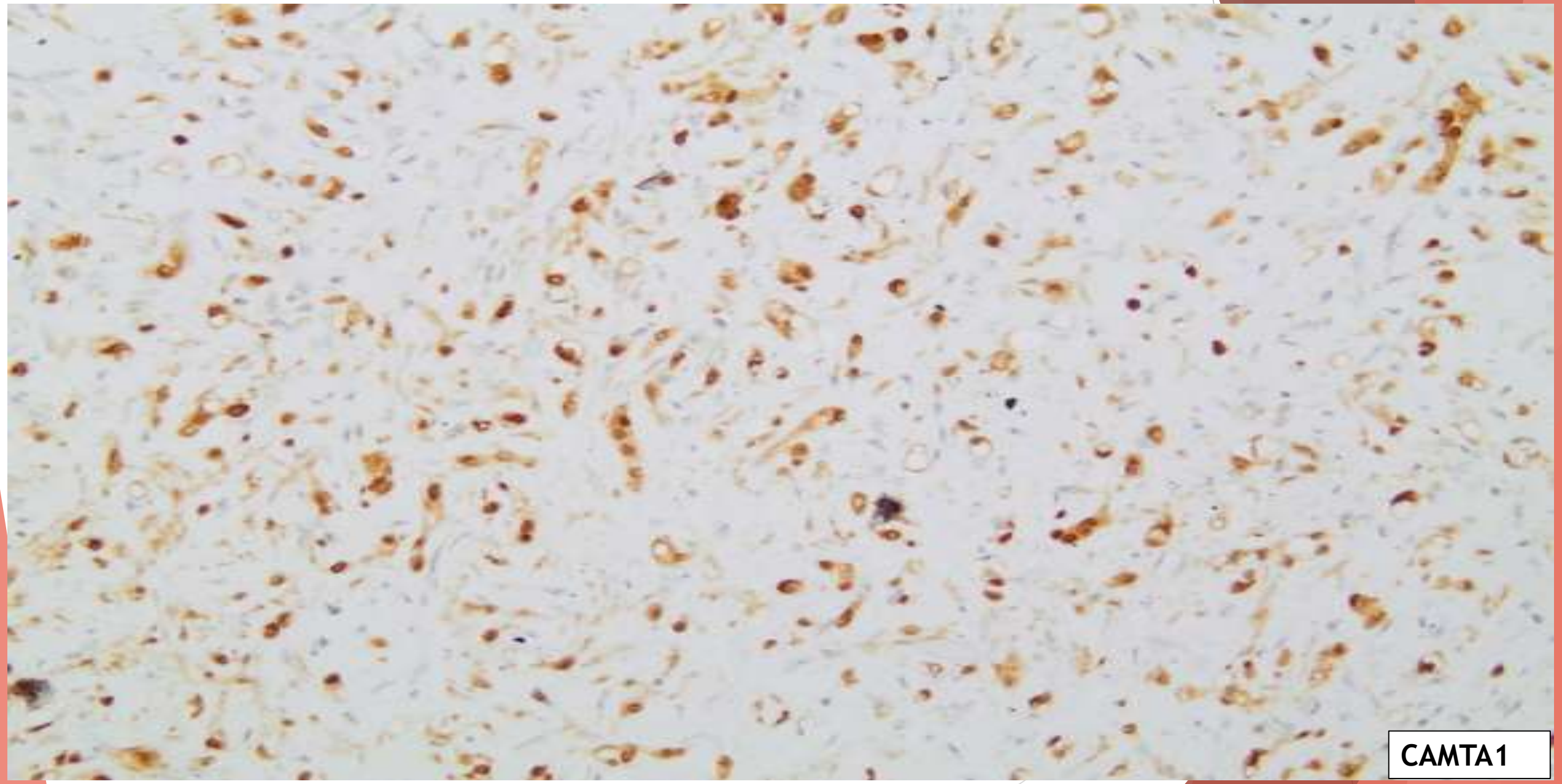
Diffuse expression of CD31

Case #3



Diffuse nuclear expression of ERG

Case #4



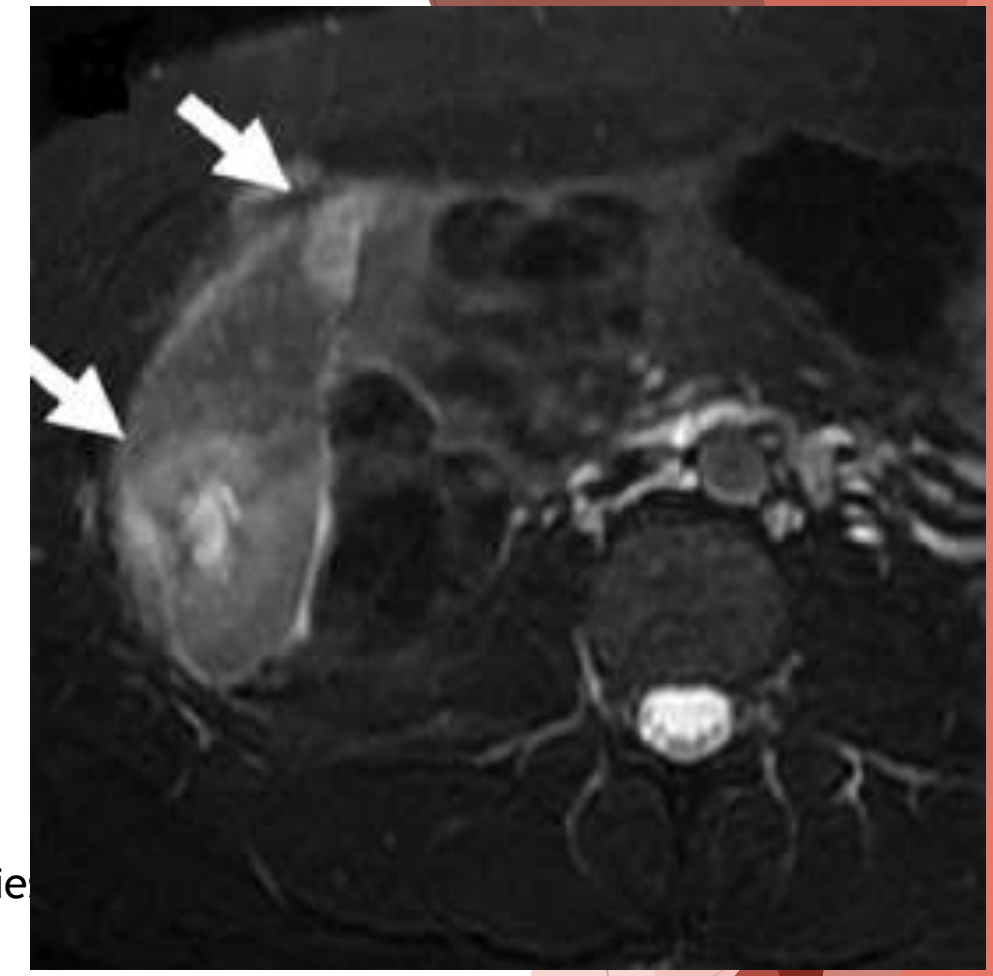
Diffuse nuclear expression of CAMTA1

Case #4 Hepatic EHE

Diagnosis: Multifocal involvement of right liver lobe by EHE

Pathology Interpretation Pearls

- **EHE of the liver pursues a variable clinical course**
- **Histological features do not reliably predict outcome**
- **Distant metastatic rate is 20-30%**
- **Target sign, lollipop sign, capsular retraction are typical of hepatic EHE**
- Differential diagnosis from angiosarcoma may be challenging in needle biopsie
- Nevertheless EHE has a much better prognosis than angiosarcoma of the liver
- **CAMTA1 valuable in the distinction between EHE and angiosarcoma**
  - **✓Positive only in 4% of angiosarcoma**



Some lesions showing no rim while others have a double- or triple-layered target pattern with a hyperintense center followed by alternating layers of T2 intermediate or hypointensity

Kou, World J Clin Cases 2020
Taniai, Case Rep Gastroenter 2020
WHO digestive system tumors 20189

EHE – Take home messages

- EHE is a malignant vascular tumor of variable clinical behavior, depending on the location
- Multifocal presentation common
- Histological features include primitive vasoformation in the form of intracellular vacuoles, epithelioid morphology and distinctive myxohyaline stroms
- Atypical histology (necrosis, atypia, increased mitoses) plus size (>3cm) associated with aggressive behavior and define risk stratification subsets, although not tested in every location
- Molecular subsets: WWTR1-CAMTA1 (85-90%), YAP1-TFE3 (5-10%), variant WWTR1 fusions, some of which with predilection for the heart
- Synaptophysin expression implies an aggressive behavior
- YAP1-TF3 molecular subset shows unique clinical and pathological features (? A distinct entity) - usually less aggressive than conventional EHE
- Differential diagnosis from epithelioid vascular and non-vascular tumors may be challenging

Thank you!