



Memorial Sloan Kettering
Cancer Center

Learning from Mistakes

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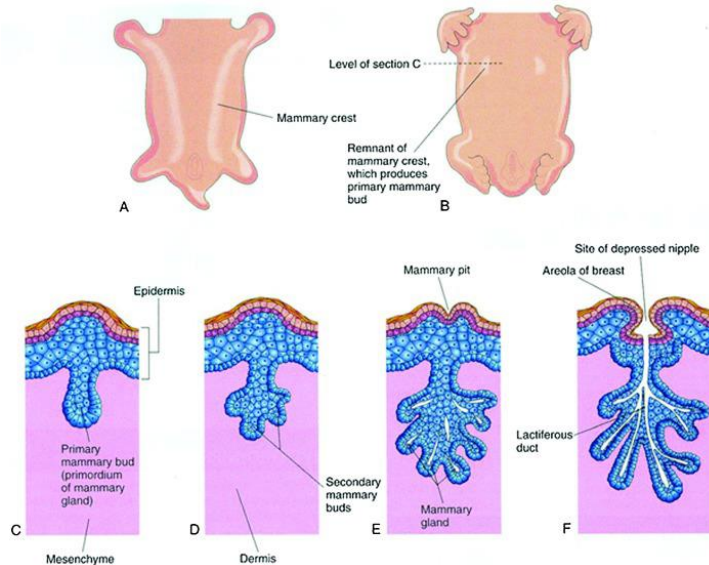
“Misdiagnoses”

- Skin lesions
- Vascular lesions

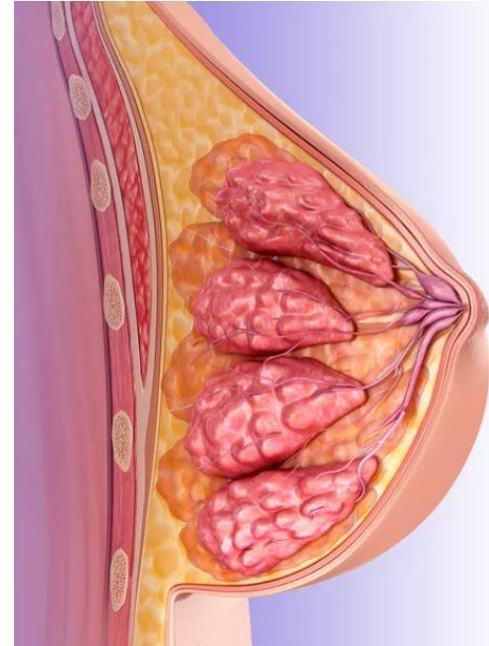


Breast = modified skin adnexal gland

Breast buds develop from the epidermis along the mammary crests



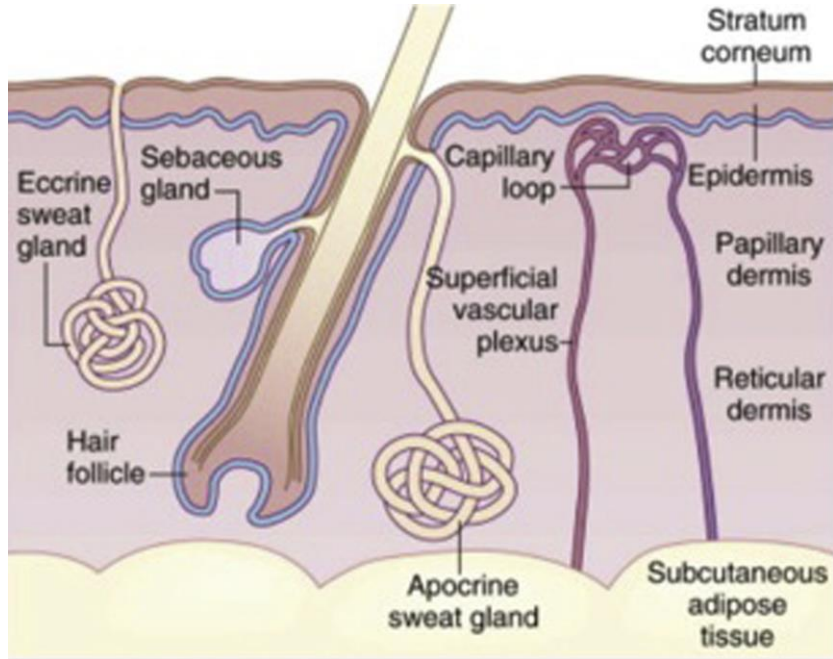
Breast covered by skin



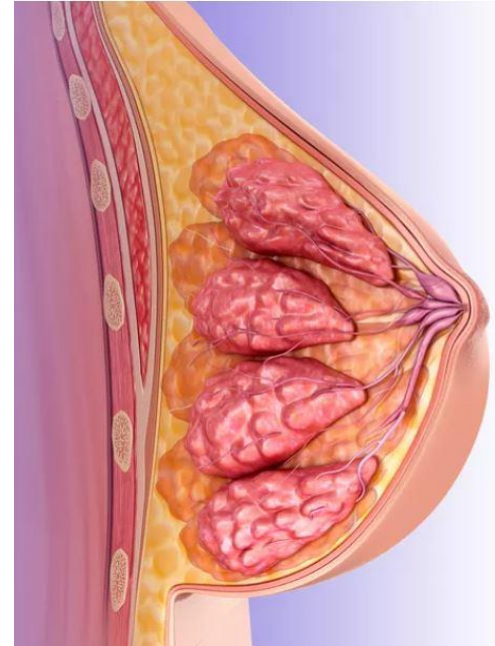
Moore KL, Persaud TVN, Torchia MG, *The Developing Human: Clinically Oriented Embryology*. 9th ed. 2013 Elsevier

Breast = modified skin adnexal gland

Skin components



Breast covered by skin



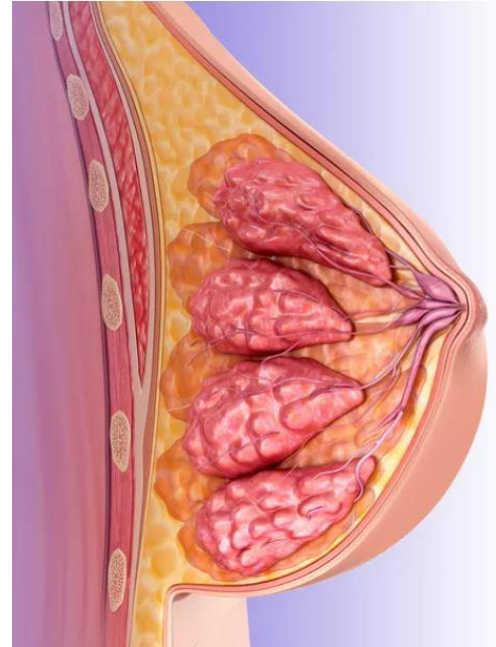
Skin epithelial neoplasms may mimic benign and

Cutaneous Malignancies

- May invade directly into the breast
- May metastasize to the breast

Benign cutaneous neoplasms

- May arise in the skin overlying the breast
- May arise in the breast



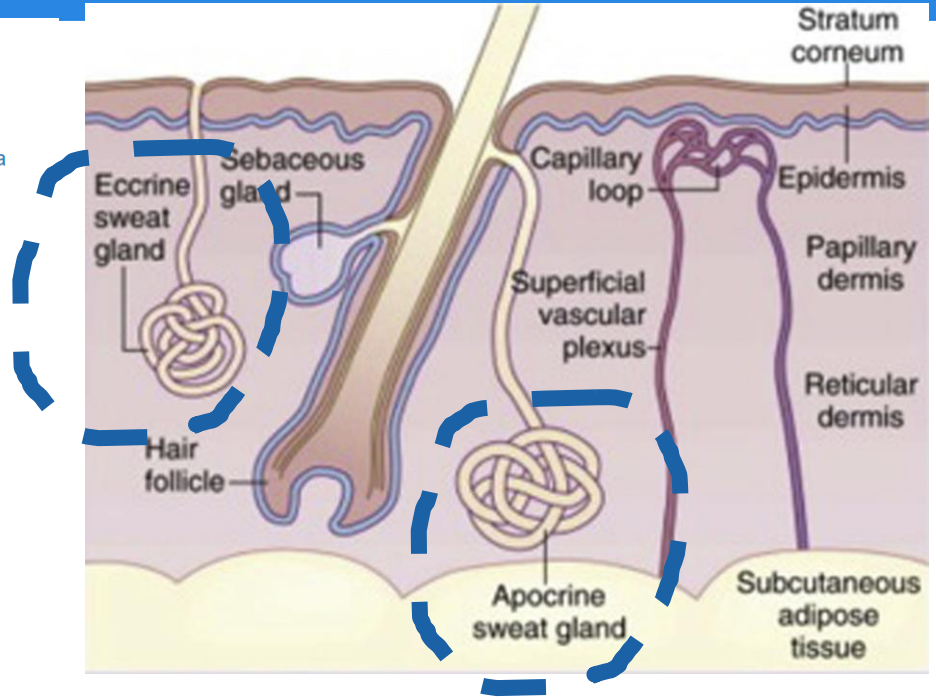
Skin tumors WHO 4th Ed. (2018)

Malignant tumours with apocrine and eccrine differentiation

- Adnexal adenocarcinoma not otherwise specified
- Microcystic adnexal carcinoma
- Porocarcinoma
- Malignant neoplasms arising from spiradenoma, cylindroma, or spiradenocylindroma
- Malignant mixed tumour
- Hidradenocarcinoma
- Mucinous carcinoma
- Endocrine mucin-producing sweat gland carcinoma
- Digital papillary adenocarcinoma
- Adenoid cystic carcinoma
- Apocrine carcinoma
- Squamoid eccrine ductal carcinoma
- Syringocystadenocarcinoma papilliferum
- Secretory carcinoma
- Cribriform carcinoma
- Signet-ring cell/histiocytoid carcinoma

Benign tumours with apocrine and eccrine differentiation

- Hidrocystoma/cystadenoma
- Syringoma
- Poroma
- Syringofibroadenoma
- Hidradenoma
- Spiradenoma
- Cylindroma
- Tubular adenoma
- Syringocystadenoma papilliferum
- Mixed tumour
- Myoepithelioma



Mammary vs skin adnexal origin

p63, p40
CK5/6

Highly expressed
in many cutaneous tumors

Usually negative/
only focally positive in BC

Ivan D et al. *J Cutan Pathol* 2007;34(6):474-80

Lee JJ et al. *Hum Pathol*. 2014;45(5):1078-83

Rollins-Raval M et al. *Arch Pathol Lab Med* 2011;135(8):975-83

GATA3

SOX10

ER, PR

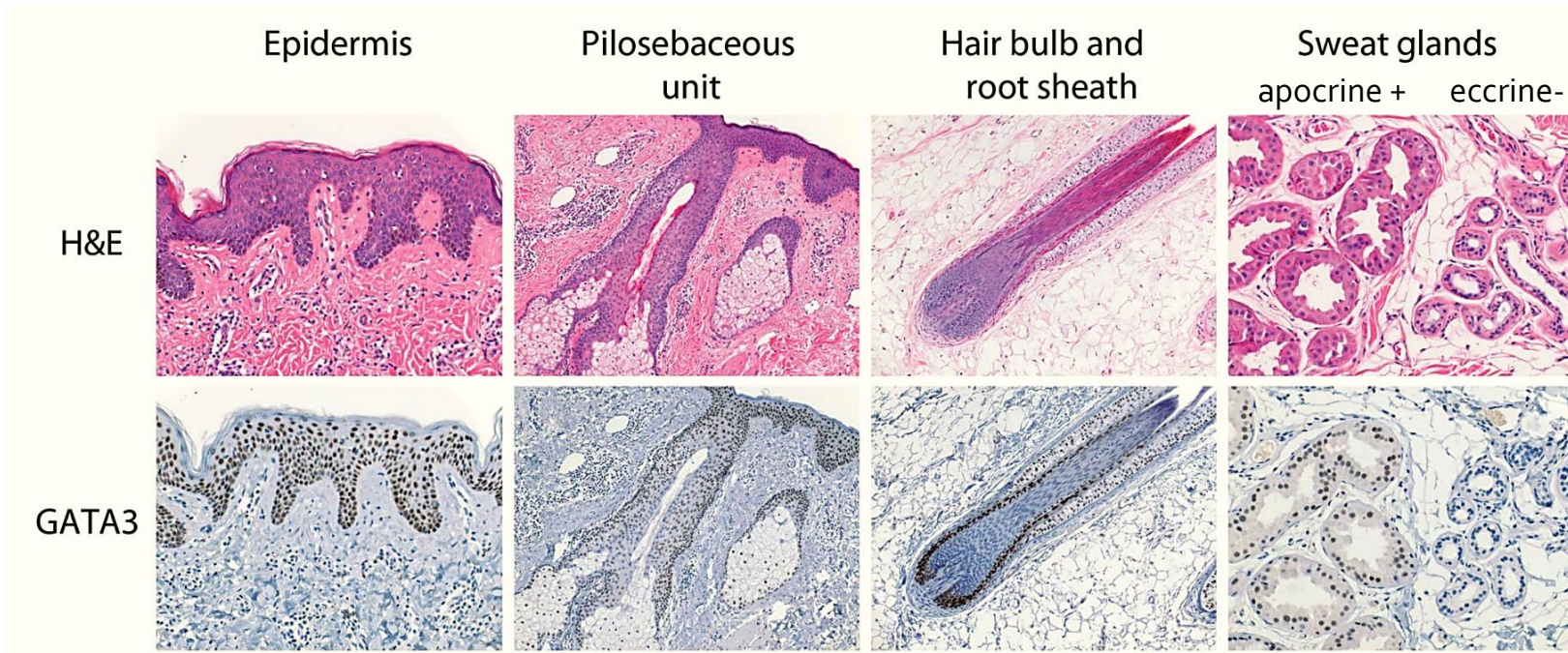
Mammaglobin

GCDFP15

Expressed in many
breast and skin tumors



GATA3 expression in normal skin and adnexa



Origin

GATA3 in benign and malignant skin neoplasms (%)

Squamous epithelium	<ul style="list-style-type: none"> Squamous cell carcinoma (100%) 	
Sebaceous glands	<ul style="list-style-type: none"> Sebaceous Carcinoma (93%) 	
Follicular neoplasms	<ul style="list-style-type: none"> Trichilemmal neoplasms, benign and malignant (100%) Basal cell carcinoma (100%) 	
Apocrine sweat glands	<ul style="list-style-type: none"> Apocrine carcinoma (93%) 	
Predominantly apocrine	<ul style="list-style-type: none"> Cylindroma (88%) Spiradenoma (62%); Spiradenocarcinoma (100%) Chondroid syringoma, apocrine type (67%) Malignant chondroid syringoma (75%) Hidradenoma papilliferum (100%) Syringocystadenoma papilliferum (67%) Microcystic adnexal carcinoma (42%) 	
Predominantly eccrine	<ul style="list-style-type: none"> Eccrine carcinoma (36%) Hidradenoma (100%), Hidradenocarcinoma (50%) Poroma (20%); Porocarcinoma (43%) 	
Others	<ul style="list-style-type: none"> Mucinous carcinoma (100%) Extramammary Paget disease (100%) Adenoid cystic carcinoma (20%) 	

modified from
 Pardal et al.
Am J Dermatopathol
 2017;39:279-286

Squamous cell carcinoma

Breast vs skin: morphologically indistinguishable

IHC similar

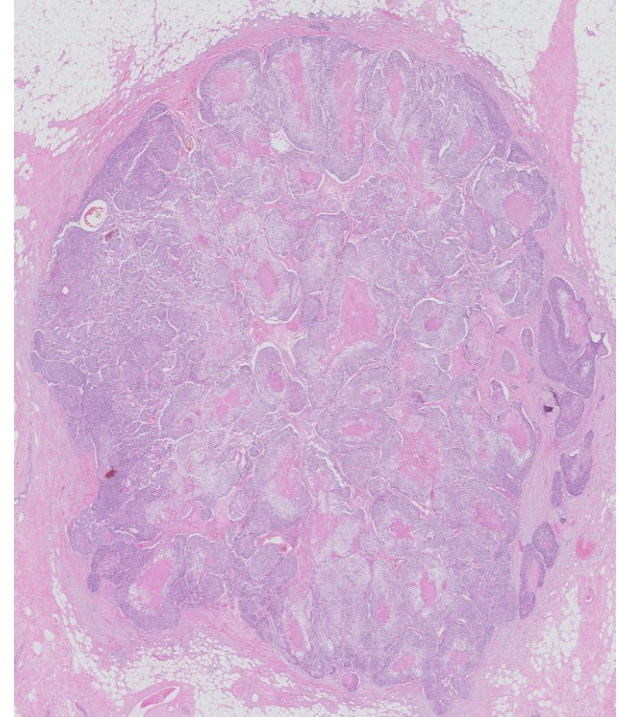
- CK5/6, p63, p40 and GATA3: diffusely and strongly(+) in both
- ER and PR usually(-) in both

Favor breast origin

- Location within breast + DCIS
- Associated invasive component NST (<10% of tumor)
- *TP53* and *EGFR* mutations

Favor cutaneous origin

- History of an enlarging skin nodule
- Superficial location in dermis/ near epidermis
- Carcinoma connects with epidermis/ SCC in situ in epidermis
- UV mutational signature (frequent C→T substitutions)



Apocrine carcinoma

Breast vs skin: morphologically similar

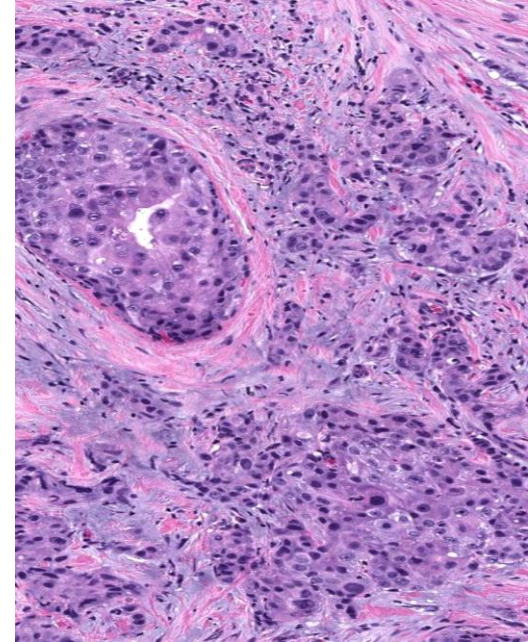
IHC similar

- GATA3(+) in both
- P63, p40, ER, PR usually (-) in both

Favor breast origin: Location within breast + DCIS

Favor cutaneous origin

- Location in dermis/ near epidermis
- CK5/6(+)?
- EGFR(+) (but 20% of BCs are EGFR+)
- calretinin(+)



Fernandez-Flores A. *Rom J Morph Embryol* 2012; Fernandez-Flores A. *Appl Immunohistochem Mol Morph.* 2010;
Busam K et al. *Mod Pathol* 1999; Fernandez-Flores A. *Rom J Morph Embryol* 2013



Adenoid cystic carcinoma

Salivary glands, breast, skin

Can occur at any age, also in men

Morphology: Conventional and solid basaloid

IHC:

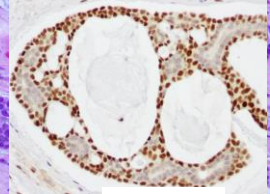
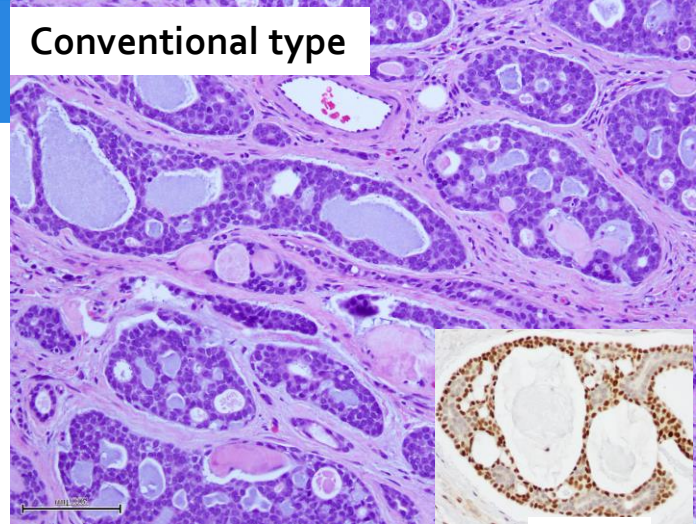
- (+): MYB, CD117, SOX10
- Conventional type: myoepithelial/ basal cells p63(+)
- Solid basaloid morphology: usually p63(-)
- ER, PR and HER2 (-)

Molecular:

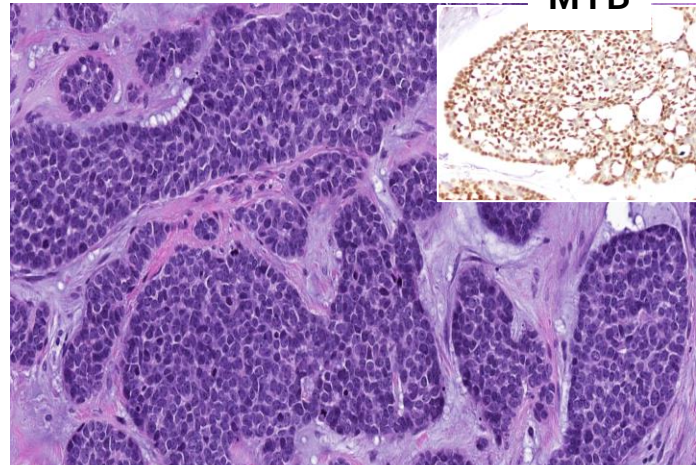
- *MYB-NFIB*, *MYB*-other partners, *MYBL1:NFIB*
- Solid basaloid: *NOTCH mutations* → worse prognosis

Ho AL et al. J Clin Invest 2019;129(10):4276-4289
Schwartz C et al Mod Pathol. 2022;35(2):193-201

Conventional type



MYB

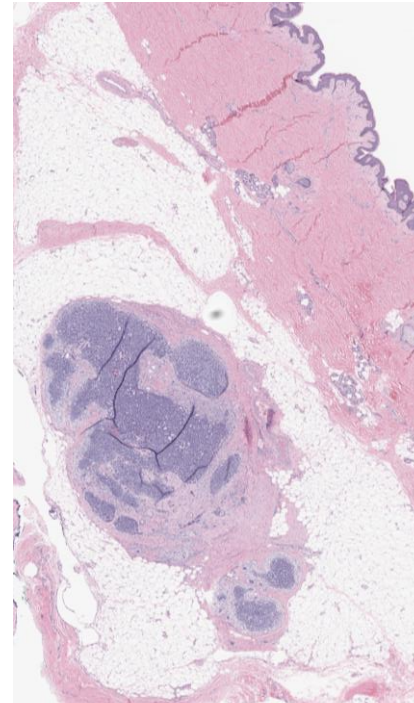


Solid basaloid type

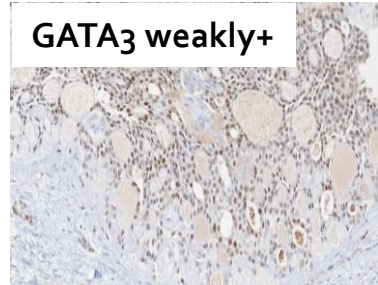
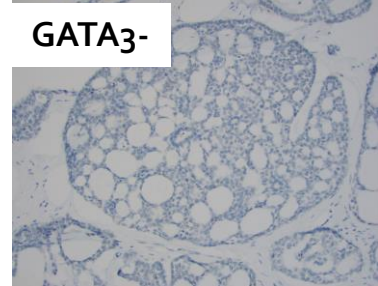
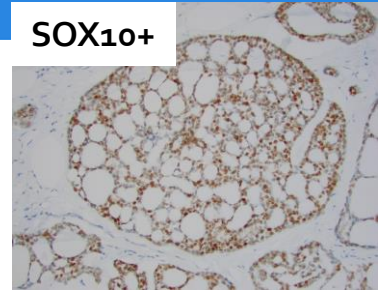
Adenoid cystic carcinoma (AdCC)

- SOX10(+)
 - GATA3(+) in
 - 20% skin AdCC
 - 45% salivary glands AdCC
 - Pardal et al. *Am J Dermatopathol* 2017;39:279-286
 - Adkins et al. *Head and Neck Pathology* 2020;14:406-411
 - breast AdCC: no published data
- personal observations:
most cases (-), rare weakly (+)

Clinical Hx!!!



chest wall recurrence
of breast AdCC

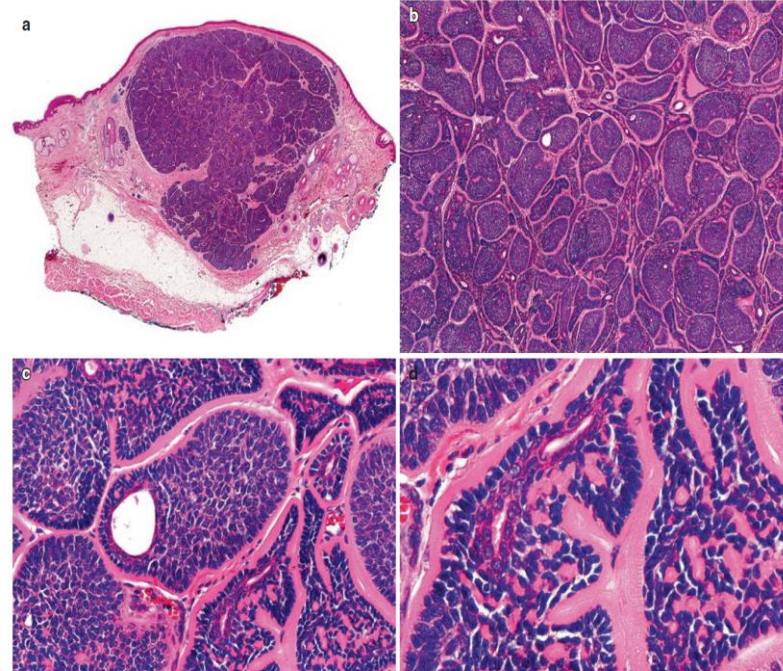


cylindroma

- Benign skin neoplasm, usually circumscribed
- Located in dermis, may extend into subcutis
- Biphasic: epithelial + myoepithelial cells
- IHC(+) similar to AdCC

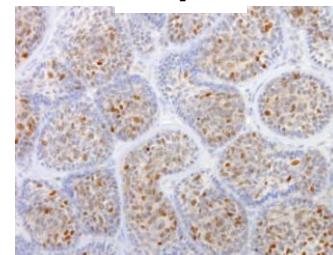
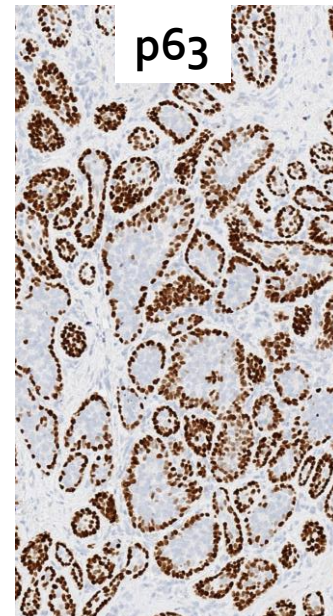
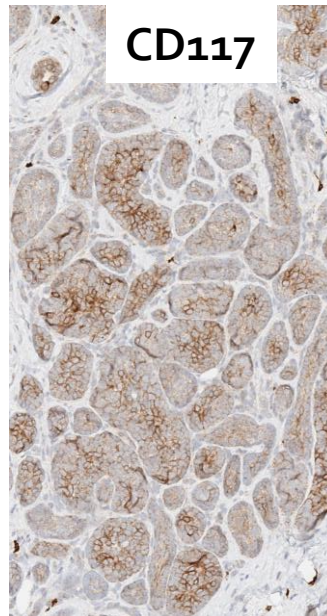
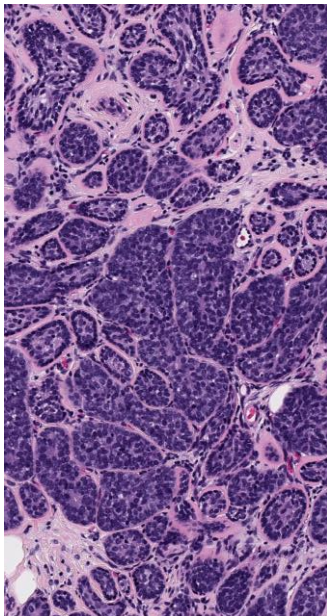
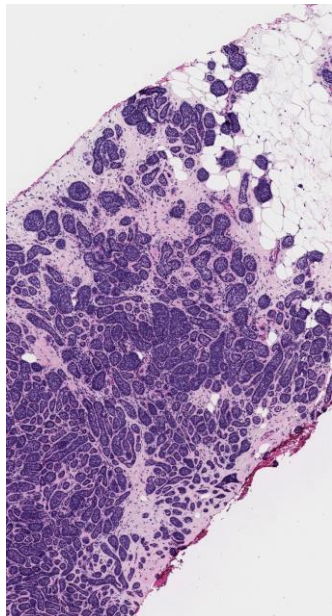
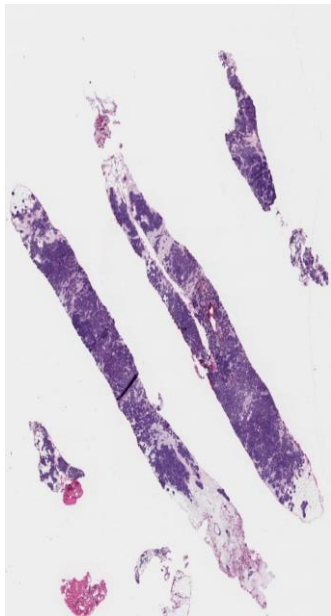
Sox10, calponin, p63, p40, CD117,
Myb

- *No MYB* alterations
- Brooke-Spiegler syndrome: autosomal dominant, *CYLD* mutations
- Sporadic cases *CYLD* somatic mutations

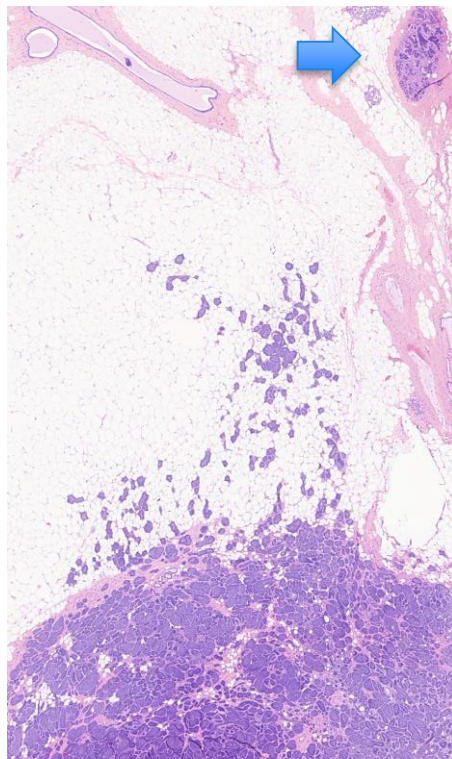


Case: AdCC vs cylindroma

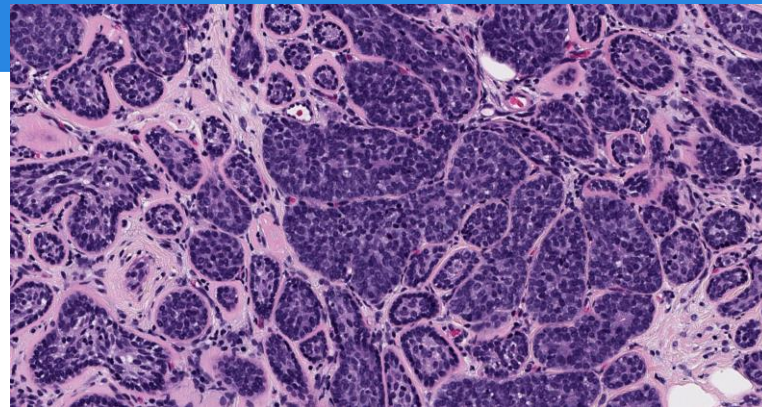
- 61 yo woman, with 10 mm mass near nipple
- Outside CNB Dx: Biphasic basaloid neoplasm, favor AdCC
- Our CNB Dx: Biphasic basaloid neoplasm, favor cylindroma



Case: AdCC vs Cylindroma Excision



Located in breast parenchyma (blue arrows)
Focal infiltrative growth



Final DX: Cylindroma

Next Generation Sequencing

Low mutation burden (3 mutations)
No specific diagnostic significance

RNA-sequencing: No fusion genes (no MYB-related alterations)



Cylindroma may arise within the breast

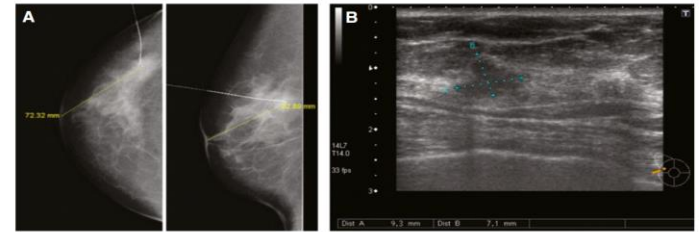
Reference No.	Clinical features	Family or previous history of cylindroma	Lesions, n	Size, mm
1	Incidental finding in lumpectomy for carcinoma	No	1	8
15	Ill-defined mass	Yes	1	12
9	Screen detected, incidental finding in mastectomy for ductal carcinoma in situ, nodule at the site of previous surgery, enlarging retro-areolar nodule	Yes in 1 patient ¹	4	7-13
6	Screen detected	No	1	16
22	Breast nodule	No	1	15
7	Two palpable nodules and two incidental findings in lumpectomy for invasive carcinoma	No	4	8-13
12	Palpable mass	No	1	
23	Mobile mass	Not stated	1	20
Current study	Two screen detected, 1 incidental finding in mastectomy for invasive carcinoma	No	3	7-12
Total			17	7-20

¹ Female patient with Brooke-Spiegler syndrome.

Rakha E, et al. *Pathobiology* 2015;82:172-178

Resolving quandaries: basaloid adenoid cystic carcinoma or breast cylindroma? The role of massively parallel sequencing

Nicola Fusco,^{1,2} Pierre-Emmanuel Colombo,³ Luciano G Martelotto,¹ Maria R De Filippo,¹ Salvatore Piscuoglio,¹ Charlotte K Y Ng,¹ Raymond S Lim,¹ William Jacot,³ Anne Vincent-Salomon,⁴ Jorge S Reis-Filho¹ & Britta Weigelt¹



Original DX: AdCC

Case re-reviewed for a study on AdCC

Low NG, thick BM around nests,
jigsaw puzzle

MYB(+) IHC, low level; no *MYB-NFIB*

Clonal somatic *CYLD* mutation

Tumor reclassified as Cylindroma

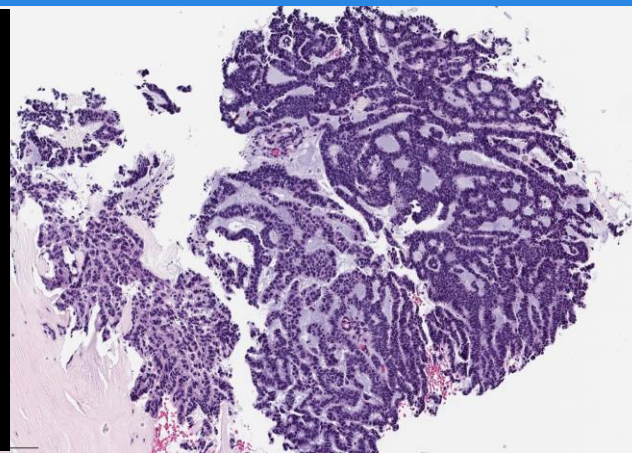
Fusco N et al. *Histopathology*. 2016;68(2):262-71



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Case

70 yo woman
Right axillary mass

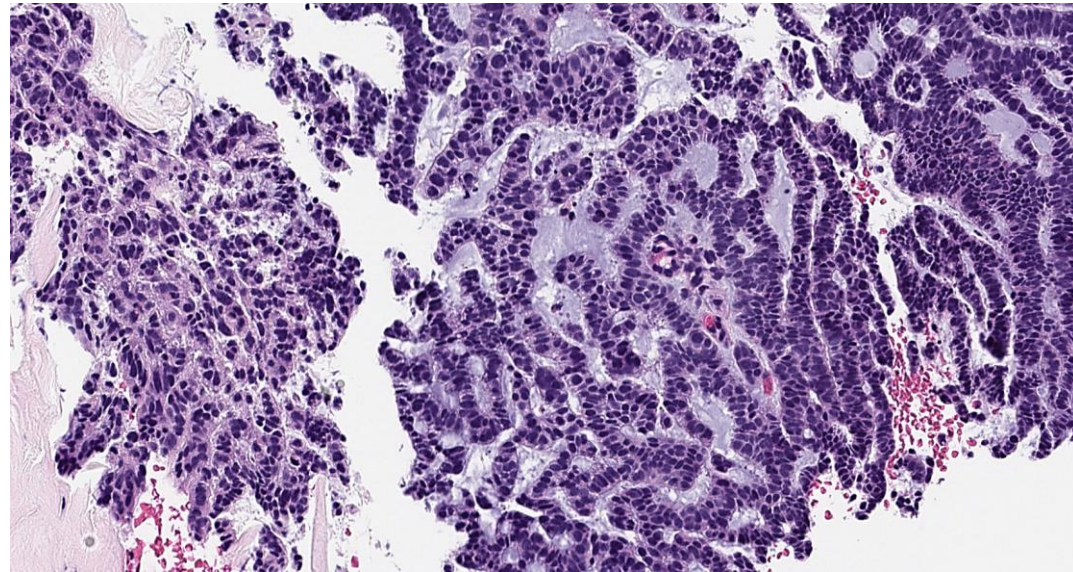


DX: Fragments of high grade papillary carcinoma

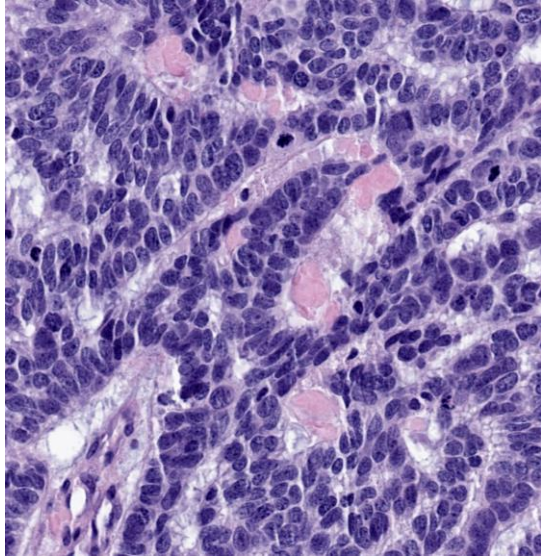
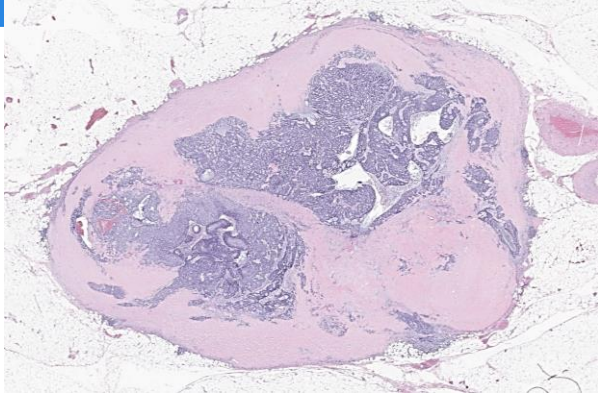
- no LN or breast tissue identified

DDX

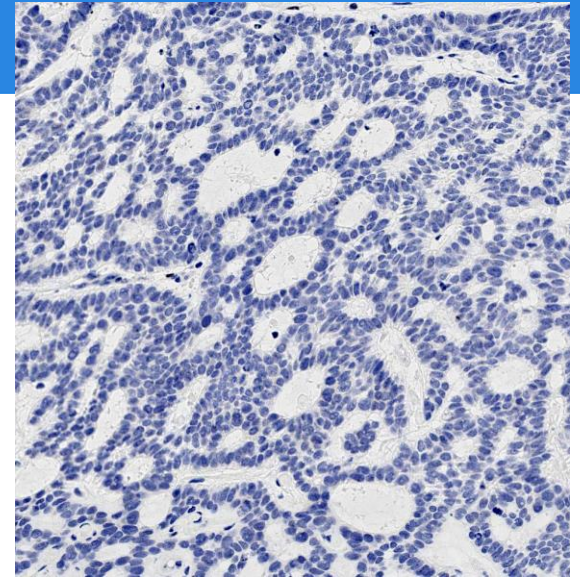
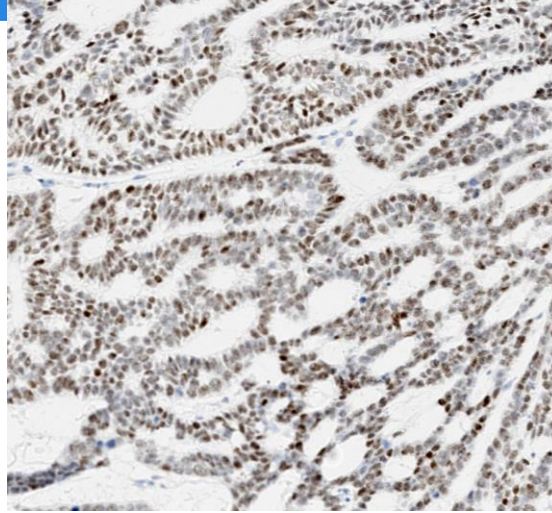
- Unusual mucin-producing carcinoma
- AdCC Skin; AdCC Breast
- Metastasis of an occult carcinoma



Axillary mass lumpectomy



GATA3 +



Negative:

ER, PR, HER2

Mammaglobin, CK7

Synaptophysin, INSM1

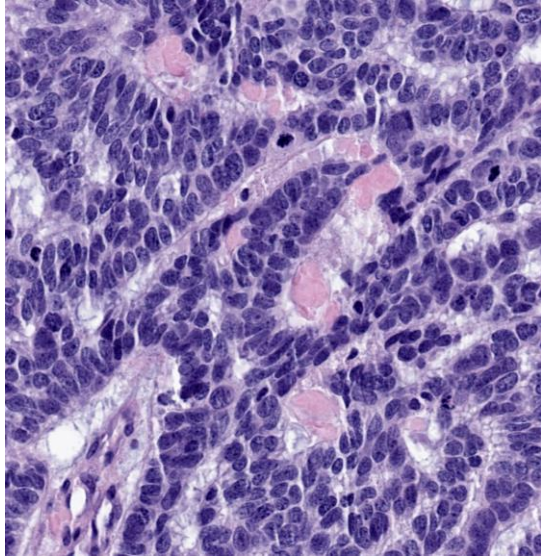
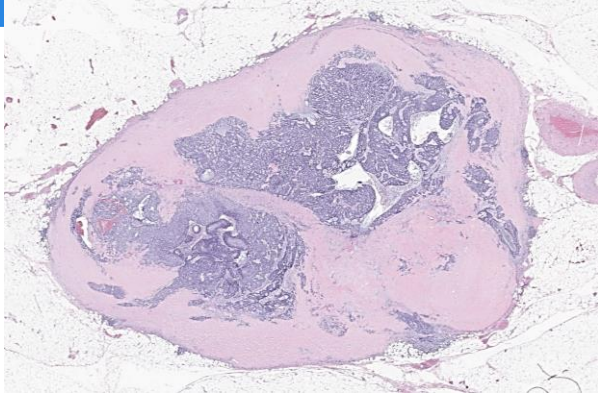
CD117, MYB

CDX2

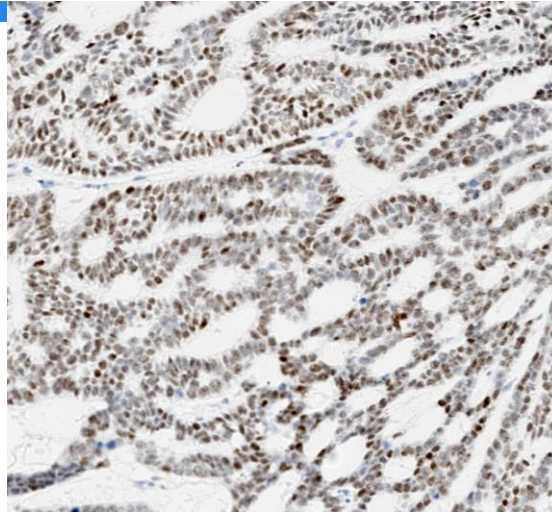
PAX8, WT1

mucicarmine

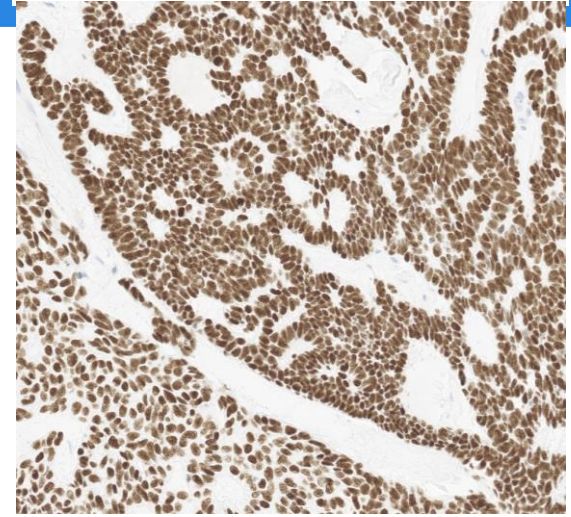
Axillary mass lumpectomy



GATA3 +



p63 and p40 +++



Negative:

ER, PR, HER2

Mammaglobin, CK7

Synaptophysin, INSM

1

CD117, MYB

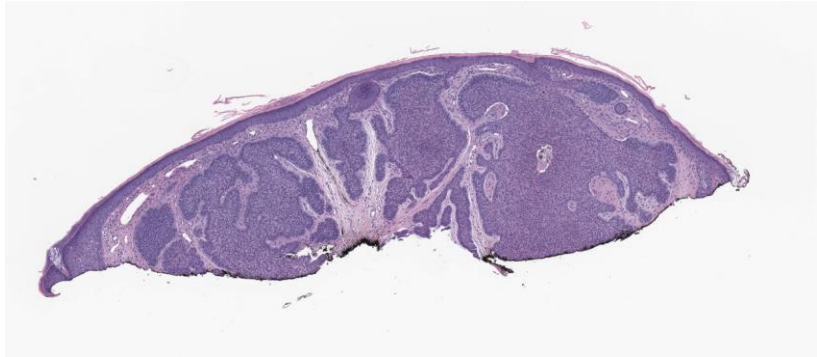
CDX2

PAX8, WT1

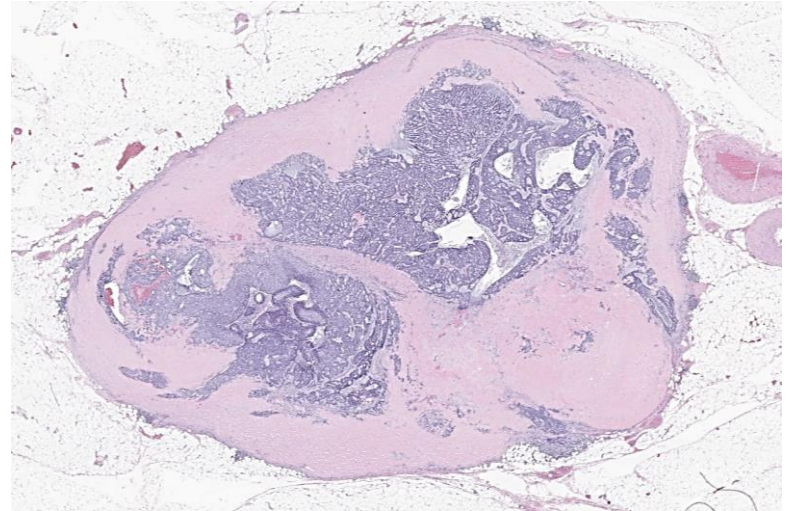
muscarinic

Patient had prior hx of multiple BCCs face and back

At least one nodular BCC

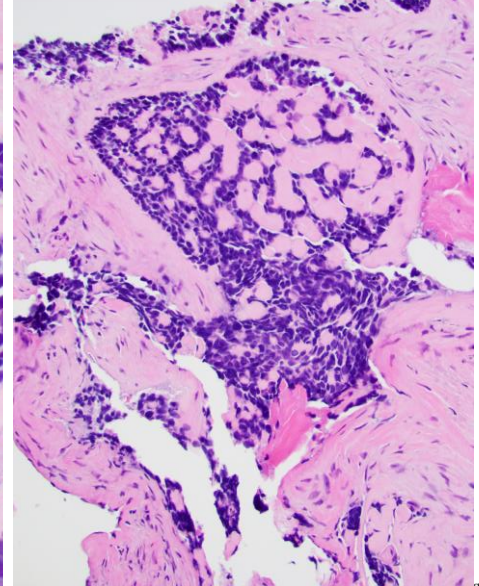
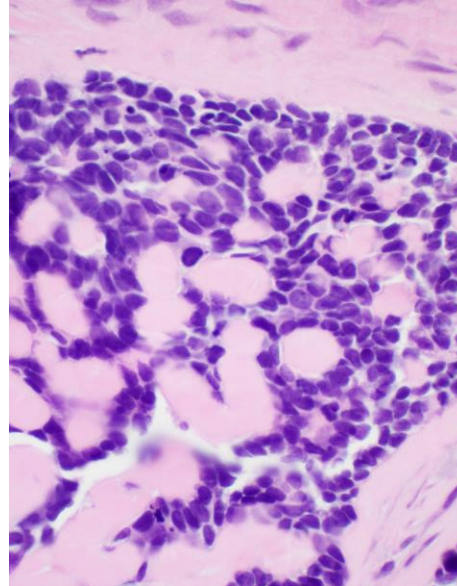
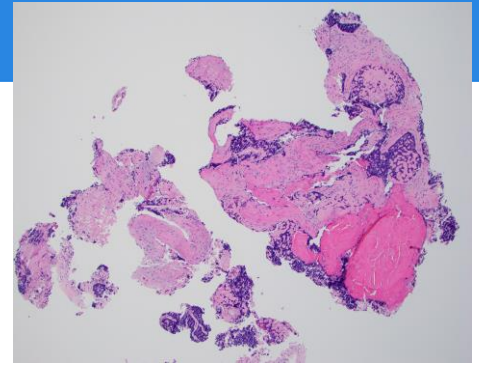


Axillary LN met of nodular BCC

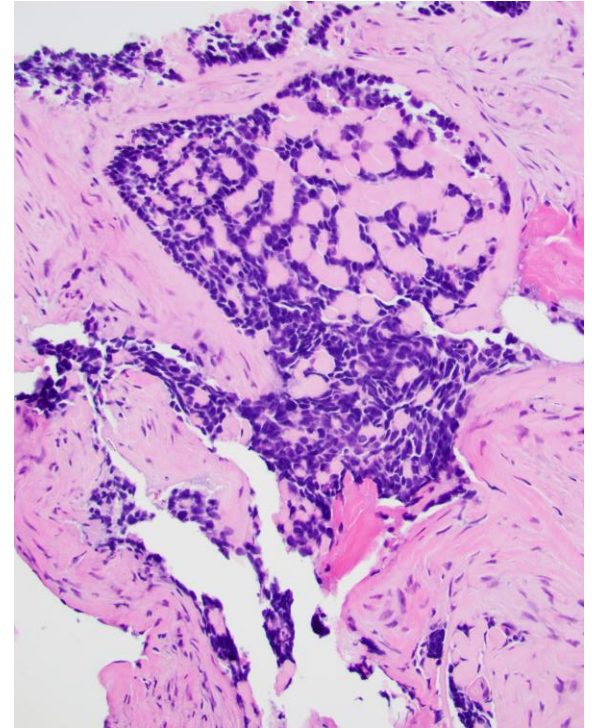
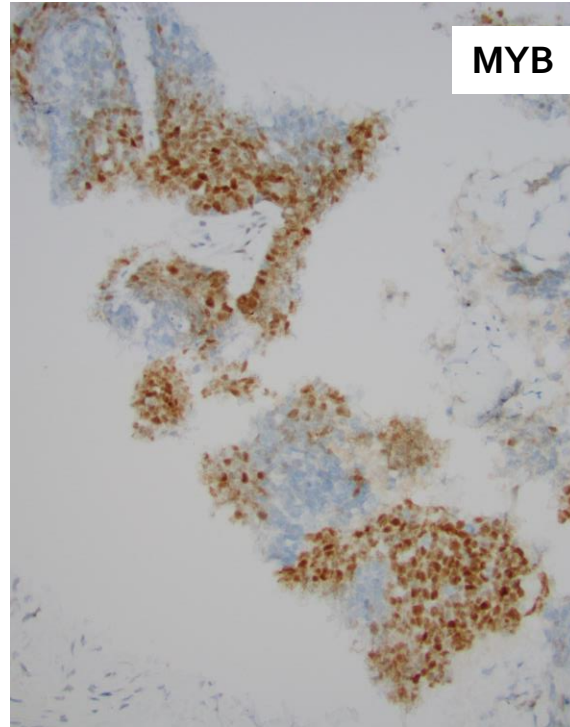
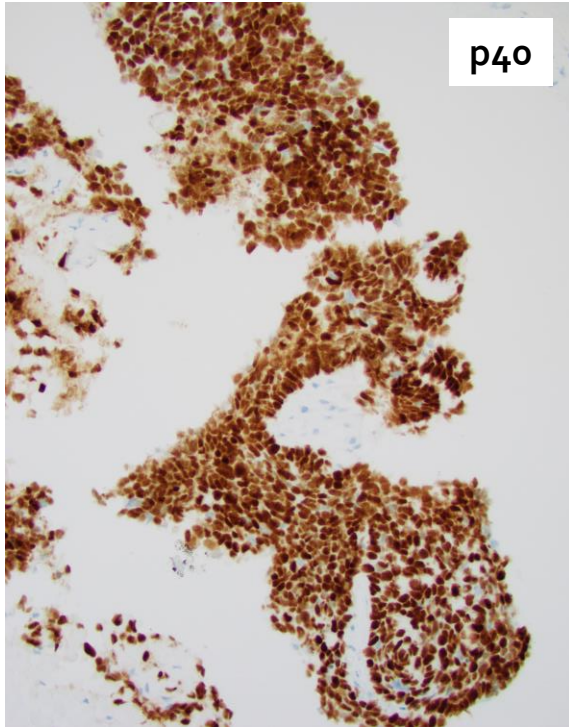


Case

- 70 yo male
- Bx of breast/ chest wall lesion
- DDX:
 - AdCC breast; AdCC skin
 - Metastatic AdCC
 - Metastatic carcinoma, unknown origin



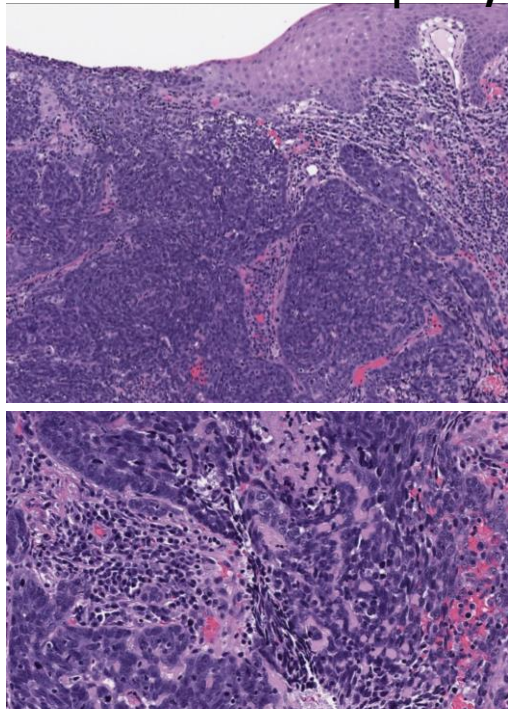
Adenoid cystic carcinoma???



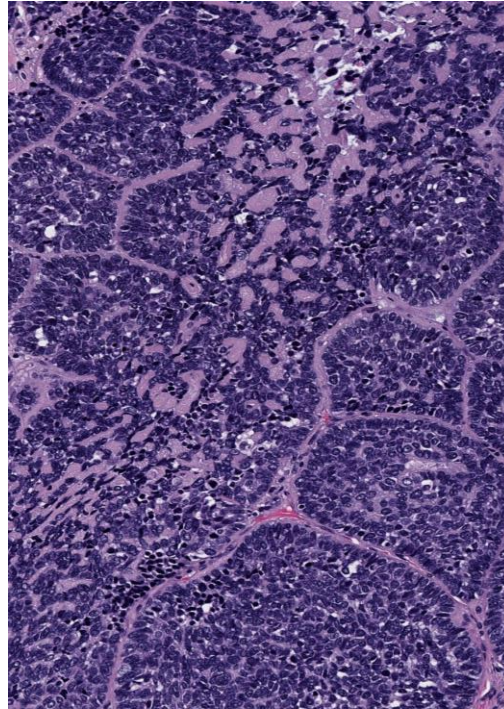
Prior history of basaloid squamous cell carcinoma of base of tongue

2016 tongue bx

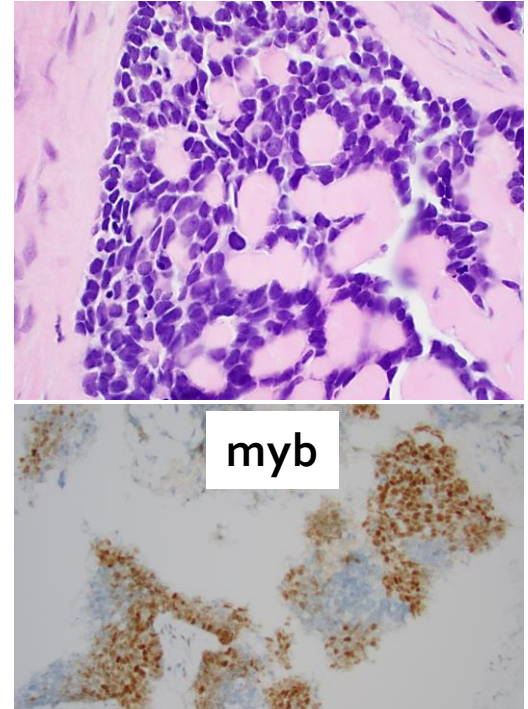
p16+, ISH HPV+



2021 lung met



2022 breast/chest

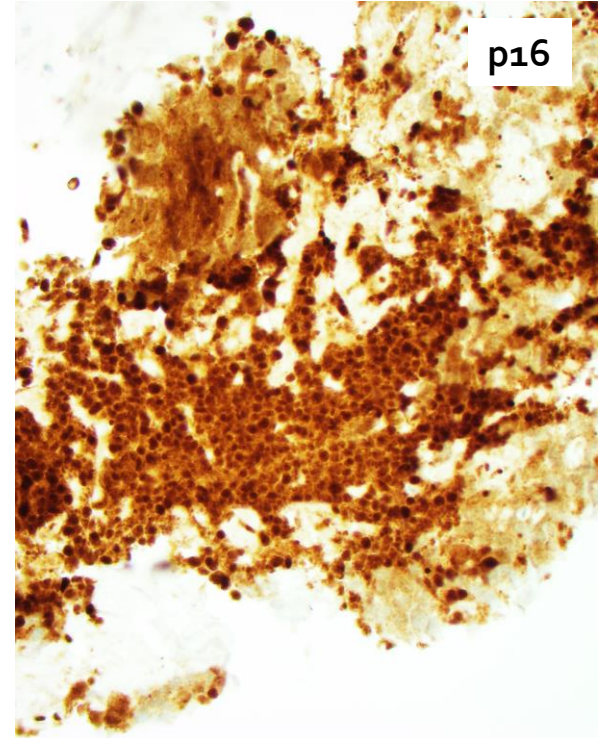
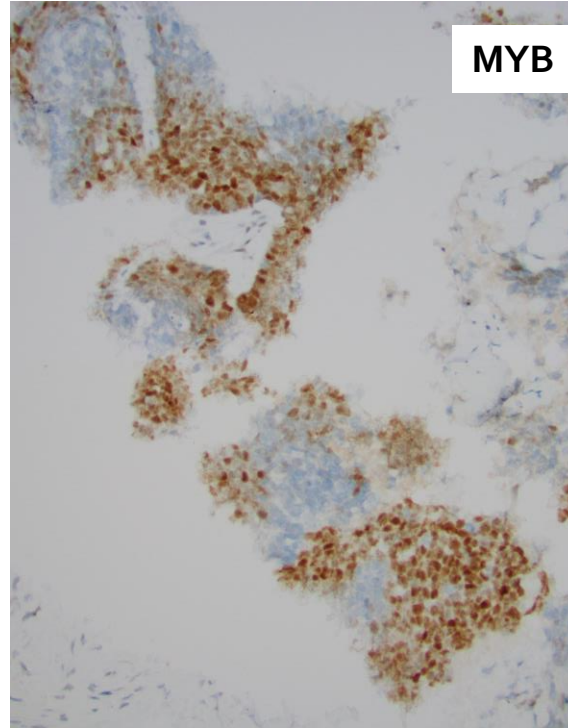
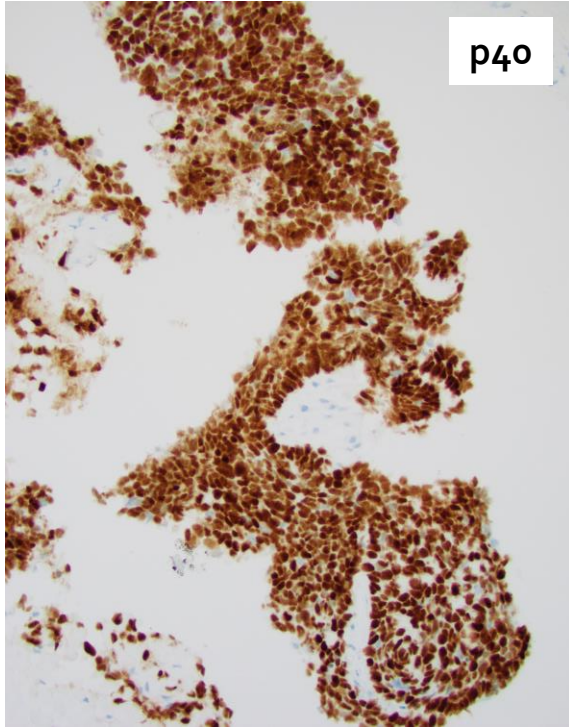


IHC MYB+ (not FISH) in HPV-related multiphenotypic sinonasal carcinomas (basaloid AdCC-Like, etc)

Bishop J et al. Am J Surg Pathol. 2017; Shah AA et al. Head and Neck Pathology 2019

Final Dx: Metastasis of basaloid SCC tongue

p40+, Myb+, p16+, ISH HPV+



Summary: AdCC differential diagnosis

Tumor type	location	Sox10	MYB	CD117	Other IHC	Molecular
Breast AdCC*	Deep in the breast	+	+	+	Gata3 -/+	<i>MYB/MYBL1:NFIB</i> or <i>MYB</i> amplification
Skin AdCC*	Dermis/ subcutaneous tissue	+	+	+	20% GATA3+	
Met salivary gland AdCC*	Dermis/ subcutaneous tissue	+	+	+	45% GATA3+	
Nodular BCC	Dermis/ subcutaneous tissue Connects with epidermis	-	-	-	GATA3+	UV mutation signature; <i>PTCH</i>
Metastatic basaloid SCC head neck	Dermis/ subcutaneous tissue	+ in 83% of HPV+ SCC (Rooper et al. Head and Neck Pathol 2019)	+ (Bishop et al. AJSP 2017)	-	P16+ (GATA3- ?)	HPV+
Cylindroma Bland histology Jigsaw pattern	Dermis/ subcutaneous tissue May arise deep in the breast	+	+	+	?	+/- <i>CYLD</i> mutation; no <i>MYB:NFIB</i>

*AdCC conventional: low grade, "cribriform" pattern; AdCC solid and basaloid: high grade

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Summary: AdCC differential diagnosis

Tumor type	location	Sox10	MYB	CD117	Other IHC	Molecular
Breast AdCC*	Deep in the breast	+	+	+	Gata3 -/+	MYB/MYBL1:NFIB or MYB amplification
Skin AdCC*	Dermis/ subcutaneous tissue	+	+	+	20% GATA3+	
Met salivary gland AdCC*	Dermis/ subcutaneous tissue	+	+	+	45% GATA3+	
Nodular BCC	Dermis/ subcutaneous tissue Connects with epidermis	-	-	-	GATA3+	UV mutation signature; <i>PTCH</i>
Metastatic basaloid SCC head neck	Dermis/ subcutaneous tissue	+ in 83% of HPV+ SCC (Rooper et al. Head and Neck Pathol 2019)	+ (Bishop et al. AJSP 2017)	-	P16+ (GATA3- ?)	HPV+
Cylindroma Bland histology Jigsaw pattern	Dermis/ subcutaneous tissue May arise deep in the breast	+	+	+	?	+/- <i>CYLD</i> mutation; no <i>MYB:NFIB</i>

*AdCC conventional: low grade, "cribriform" pattern; AdCC solid and basaloid: high grade

Summary: AdCC differential diagnosis

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*AdCC conventional: low grade, "cribriform" pattern; AdCC solid and basaloid: high grade

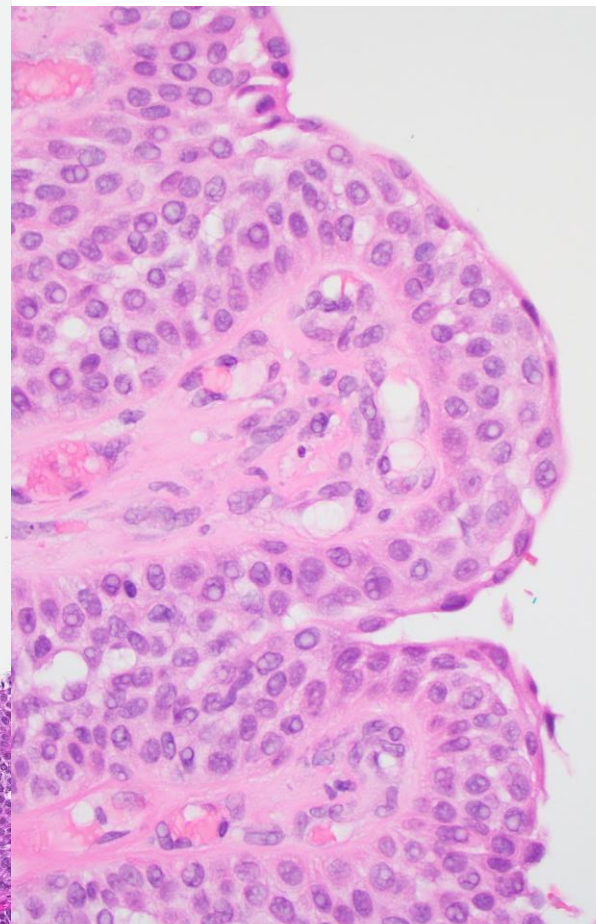
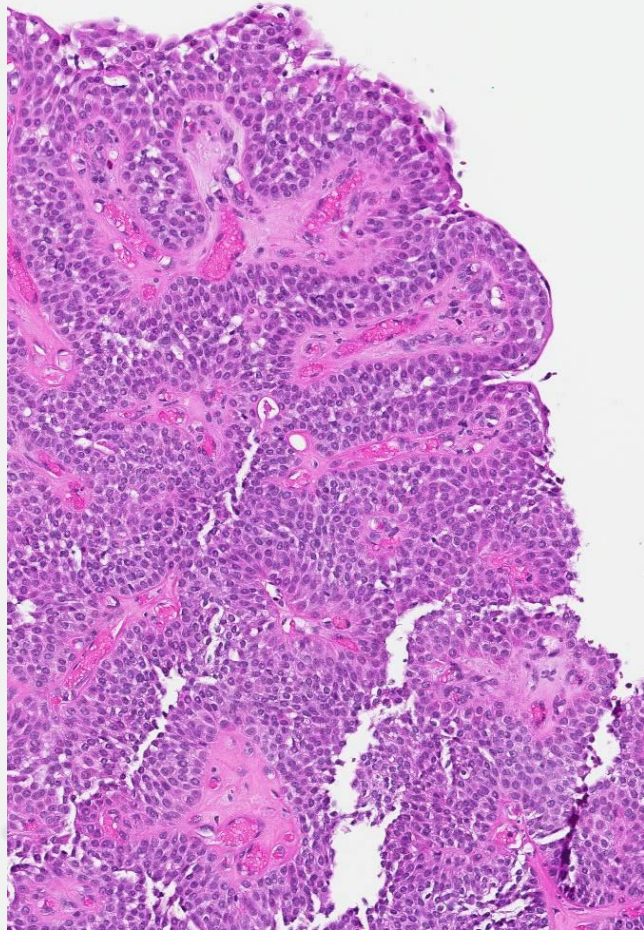
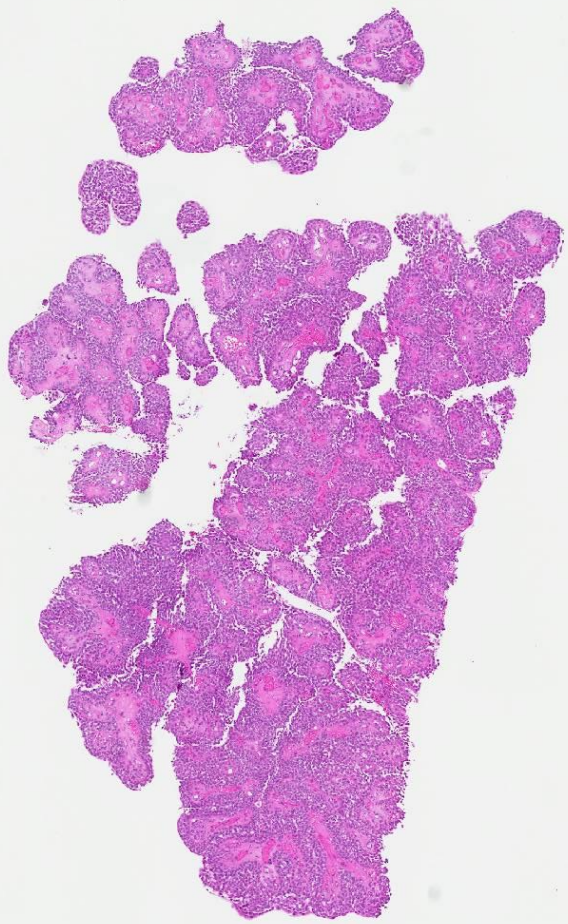
Take home messages

AdCC breast vs AdCC skin vs AdCC salivary gland met vs skin cylindroma vs others (nodular BCC and HPV+ SCC)

- Clinical history!!!
- Location in the skin vs breast
- IHC overlap: SOX10, CD117, MYB
- AdCC
 - conventional: low grade, “cribriform” pattern
 - solid basaloid: high grade, p63 and p40 usually (-)
 - *MYB-NFIB*, *MYB* or *MYB-like1* amplification in 70-90% cases of conventional AdCC
- Cylindroma: epithelial+ myoepithelial, bland cytology, jigsaw pattern, usually *CYLD* mutation; no *MYB-NFIB*

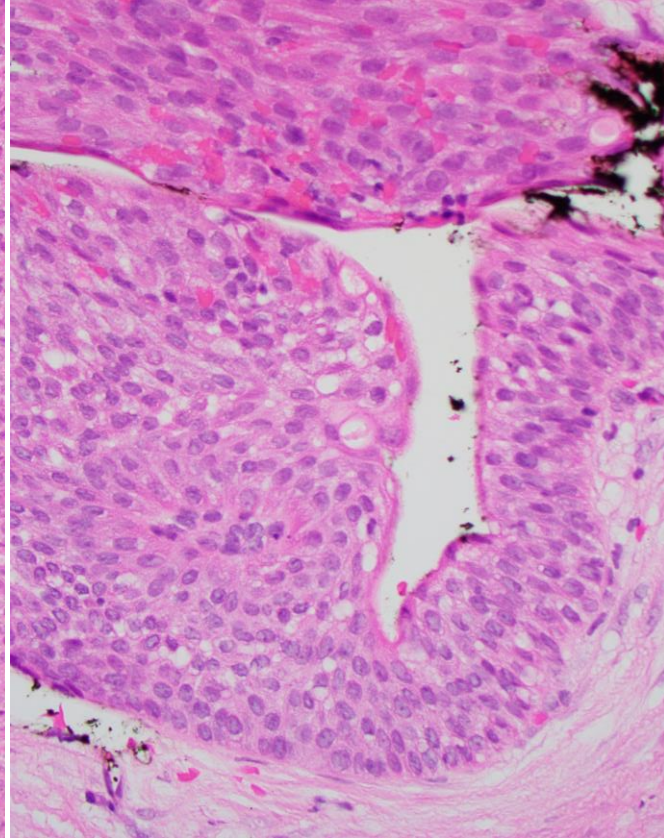
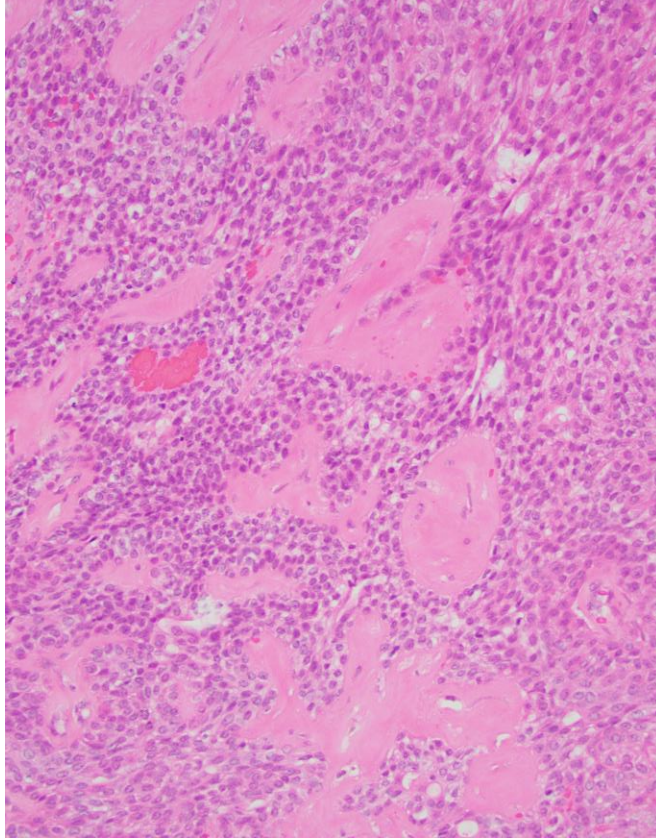
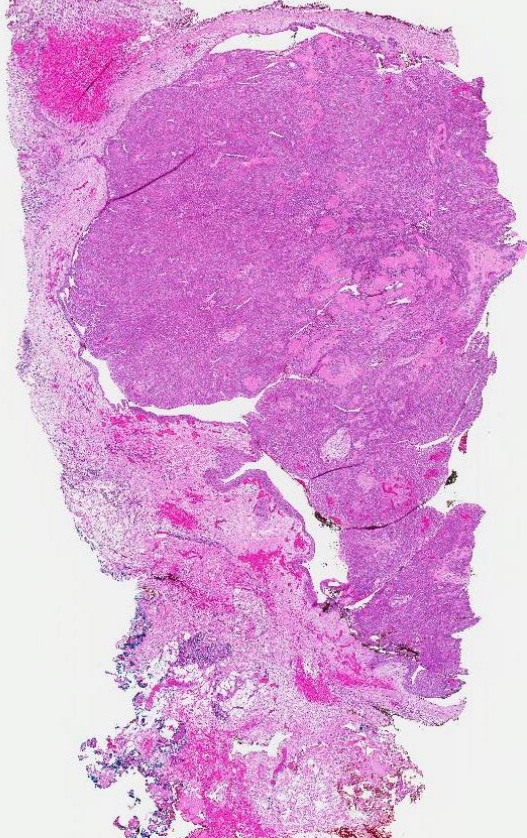


Case: 37 yo female; CNB of 2 cm solid-cystic mass near the nipple;
Original DX: Atypical papilloma

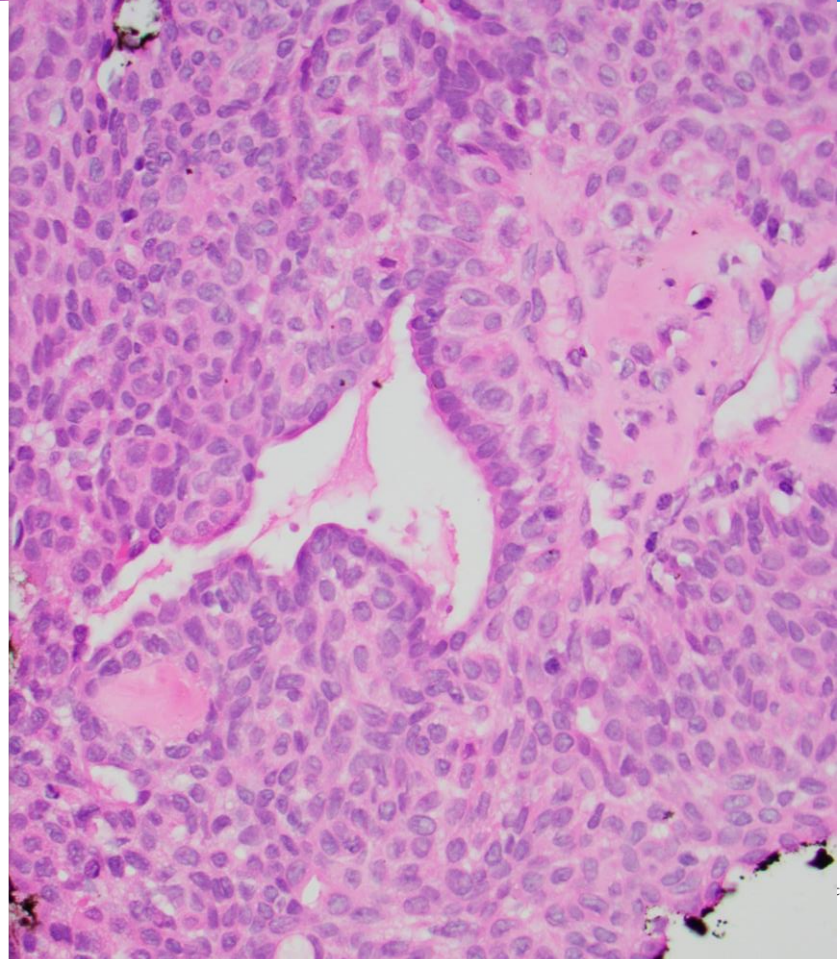
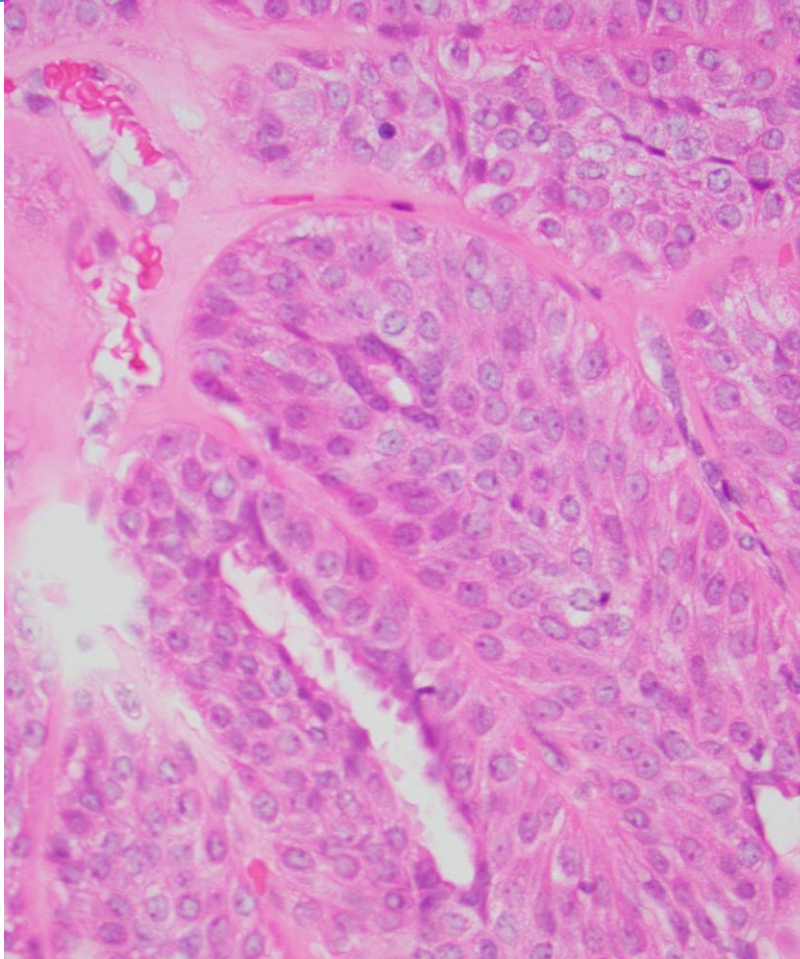


Excision

Solid+papillary; low grade; attenuated surface epithelium; hyaline fibrovascular cores



Small tubules and glands



Case seen in consultation

Dear Dr. Brogi,

I would like to submit a papillary lesion for your review and consultation. She had an imaging study which showed a complex cystic mass which measures 1.8 x 1.6 x 1.0 cm. Vascular flow is seen within the solid component. This lesion shows an unusual immunohistochemical profile with proliferative cells showing diffuse strong staining for CK5/6, P63, P40 and without clear evidence of myoepithelium along fibrovascular cores and wall of the lesion (CD10, S100 and SMMS) . ER is patchy positive and chromogranin is negative and the cells have a somewhat clonal /homogeneous appearance with possibly some squamous or myoepithelial differentiation

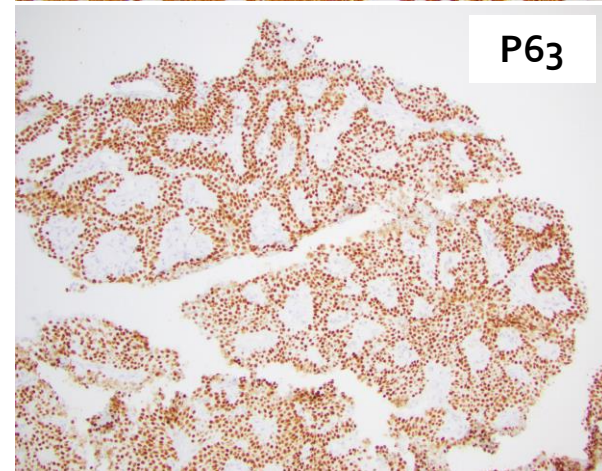
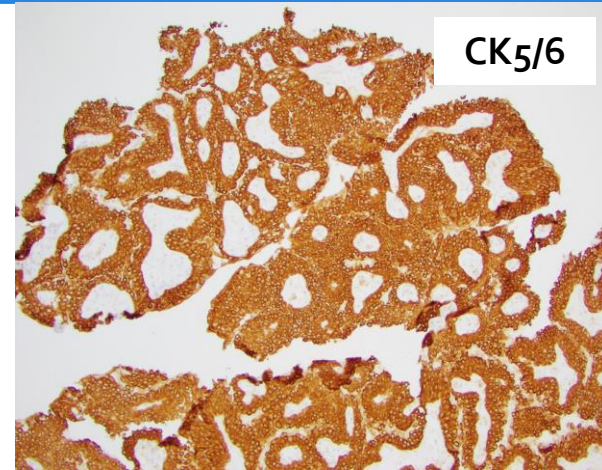
I see features concerning for carcinoma.
I enclosed all H&E slides and IHC.

Thank you in advance for your thoughtful consultation.



Immunohistochemistry

Antigen	Result
p63	Positive
p40	Positive
CK5/6	Positive
Smooth muscle myosin	Negative
CD10	Negative
Estrogen Receptor	Negative (<1%)
Progesterone Receptor	Negative
Chromogranin	Negative



Papillary Transitional Cell Carcinoma of the Breast: A Report of Five Cases with Distinction from Eccrine Acrospiroma

Mod Pathol 1999;12:287-

Eoghan E. Mooney, M.B., M.R.C.Path., Fattaneh A. Tavassoli, M.D.

“No evidence of recurrent or metastatic disease was found in the four patients for whom follow-up was available; the length of follow-up ranged from 18 months to 11 years.

... The transitional-like variant seems to behave in a fashion similar to that of other types of papillary carcinoma of the breast. Distinction of this malignant lesion from various benign lesions that occur in the same region is mandatory.”

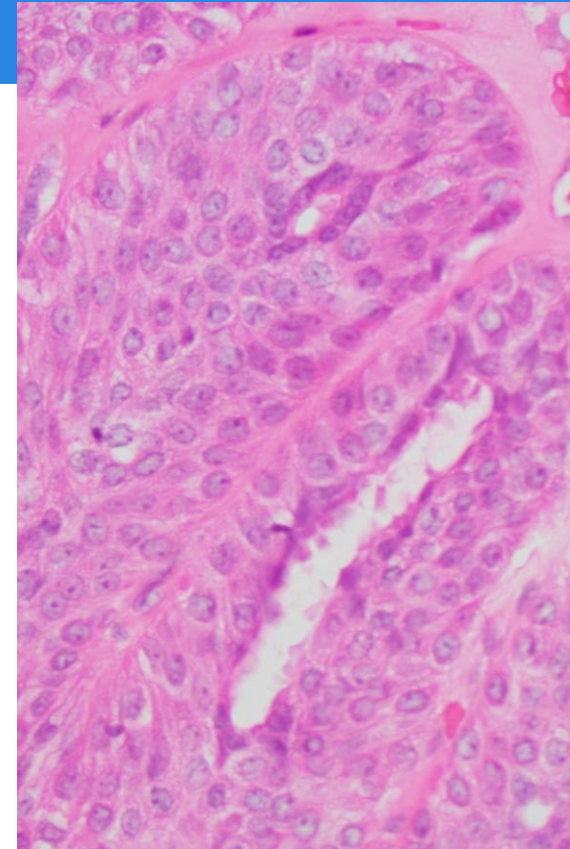


FIGURE 1. PCTF: hyalinized fibrovascular cores surrounded by a solid proliferation of cells with oval nuclei. The superficial cells are flattened.



Final DX: Hidradenoma (eccrine acrospiroma)

- Benign skin adnexal neoplasm
- Sporadic lesion, men=women, usually adults
- Scalp, trunk, proximal extremities, hands+feet, eyelids
- Nodular or solid & cystic mass in the dermis
 - Size usually <2 cm, but up to 5-6 cm reported
- Morphology
 - Clear / pale cells containing glycogen (clear cell hidradenoma)
 - Squamoid cells: central nucleus + eosinophilic cytoplasm
 - Mucinous cells
 - Cuboidal to columnar cells lining small tubules
 - Hyalinized fibrovascular cores common
- IHC(+): p63, p40, CK5/6, GATA3
- IHC(-): ER, PR, (SOX10?)
- Complete excision is curative; malignant transformation uncommon



Hidradenoma of the breast

Hidradenoma of the breast: A source of diagnostic confusion

Case report of an hidradenoma misdiagnosed twice as:

- Sclerosing intraductal papilloma
- Carcinoma with urothelial differentiation

Vasconcelos I. et al. *Breast J.* 2015;21(6):681-2.



Hidradenoma of the breast

Nodular Hidradenoma: a rare adnexal tumor that mimics breast carcinoma, in a 20-year-old woman

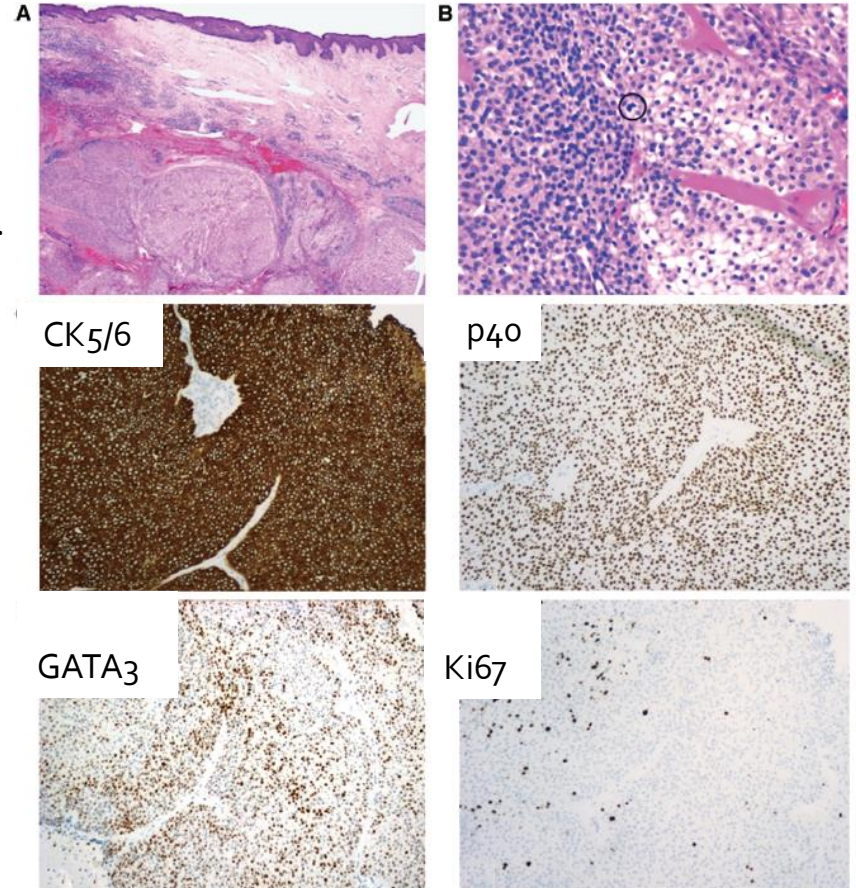
Jaitly V, et al. *Lab Med.* 2019;16;50(3):320-325.

5 cm mass near the nipple, with skin ulceration

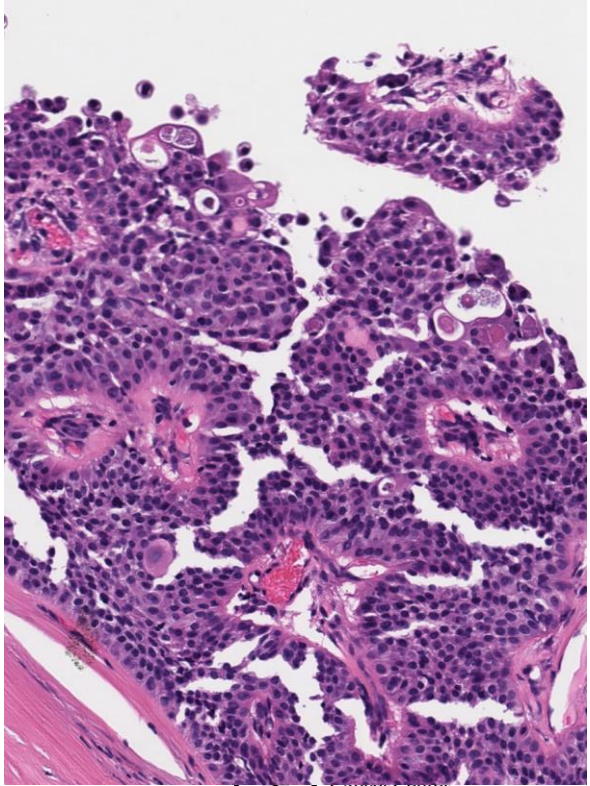
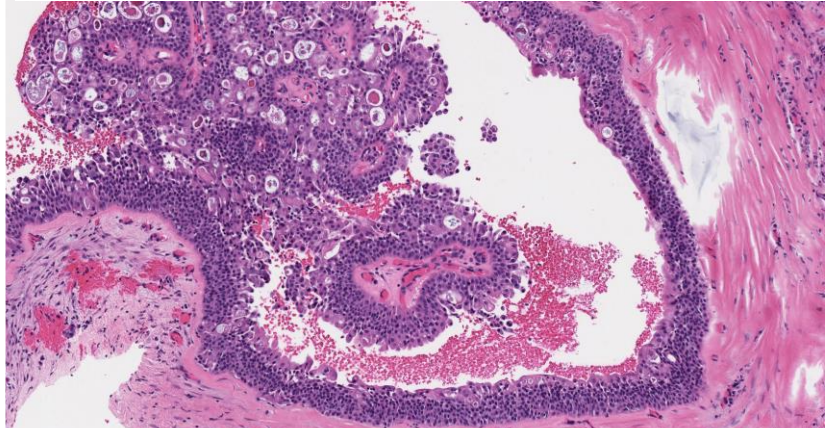
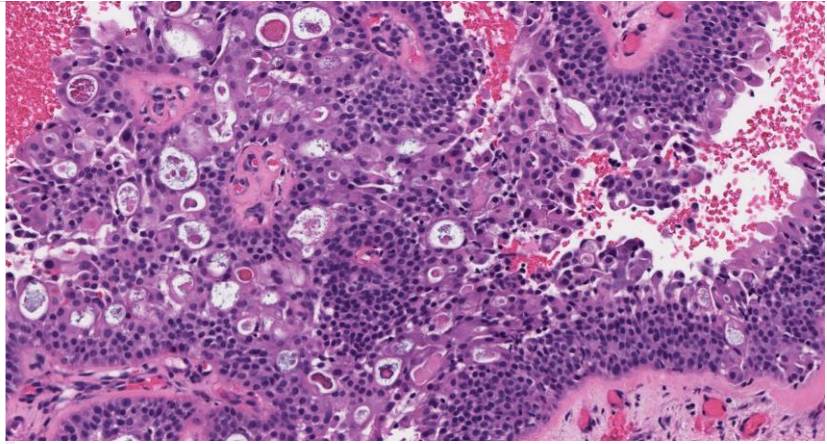
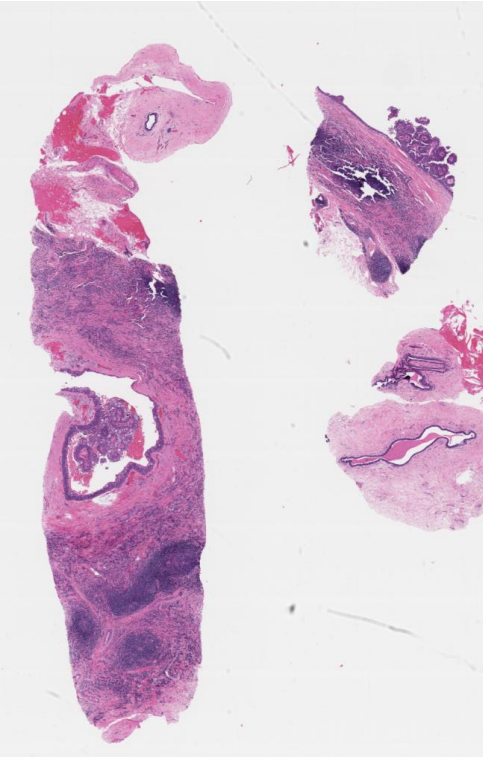


Image 1

Tumor mass in the upper outer quadrant of the right breast with ulceration and serosanguinous discharge.



Another case: 30 yo woman; CNB of a palpable periareolar mass



Another case: 30 yo woman; CNB of a palpable periareolar mass

Original CNB diagnosis

Surgical Pathology Final Report

.Clinical Information:

Ultrasound guided biopsy left breast 7 periareolar palpable complex cystic mass

Operation: Left breast 7 periareolar

Specific questions to be answered: None

Molecular Algorithm work flow selected on Surgical Pathology requisition: No

Specimen:

1 Breast, Core Biopsy, Left Breast 7:00 periareola

.Final Diagnosis:

1. Breast, left, 7:00 periareola, core biopsy:

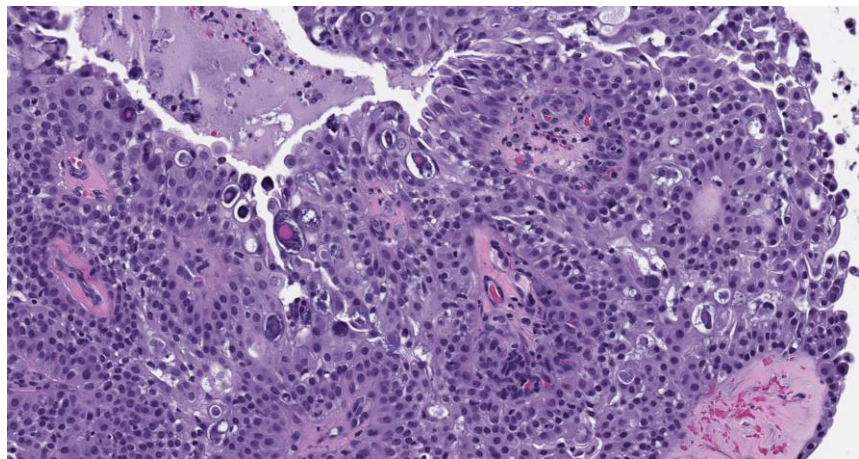
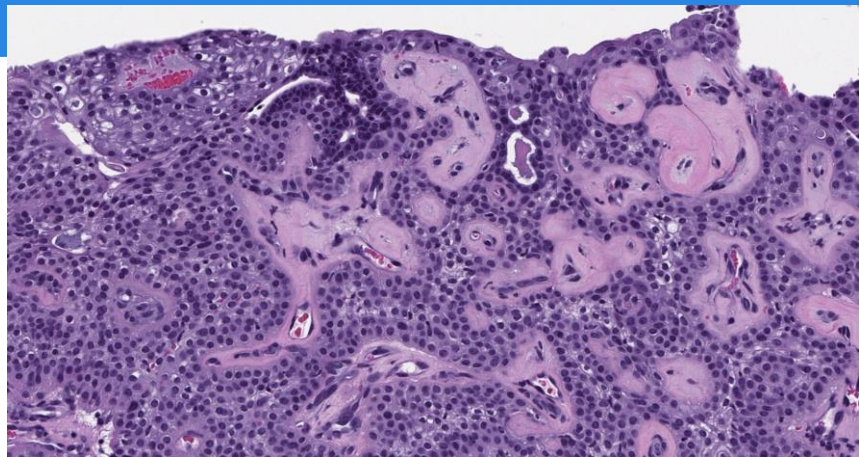
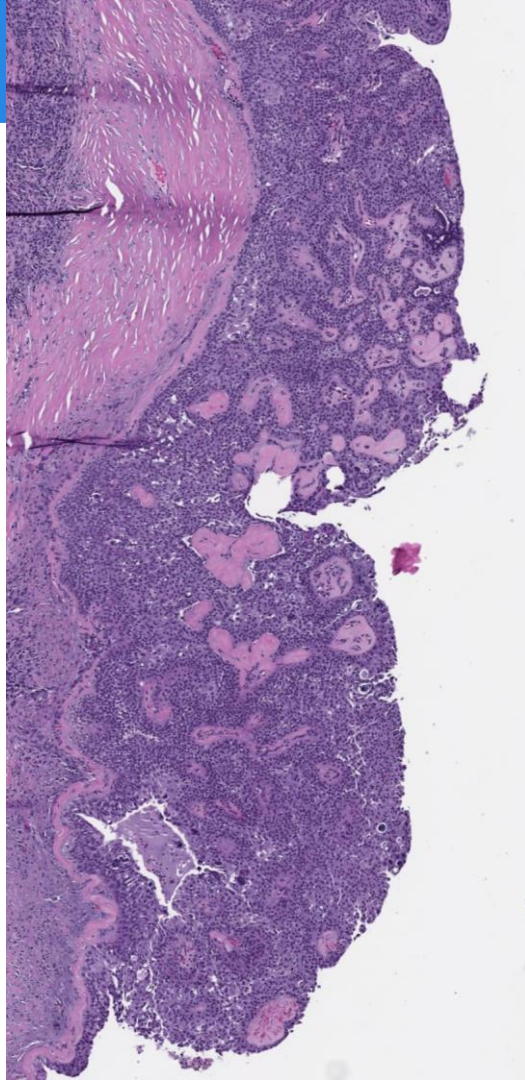
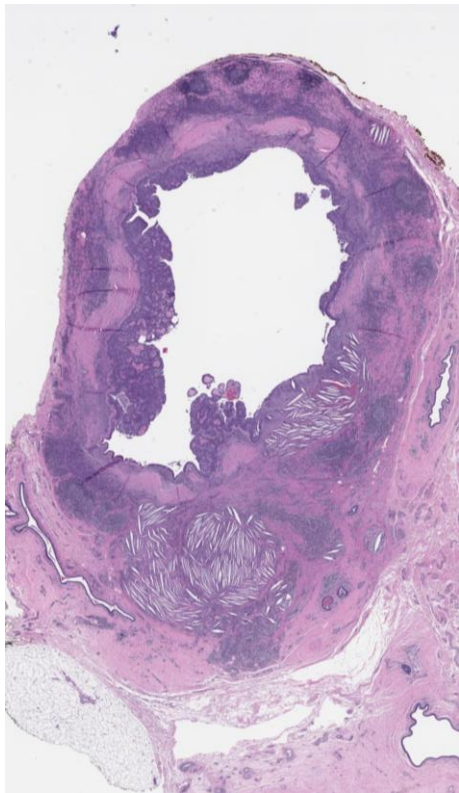
- Intraductal carcinoma (cribriform and micropapillary type with secretory features, EORTC at least intermediate nuclear grade) involving an intraductal papilloma. Secondary cystic duct dilatation with surrounding severe chronic inflammation.



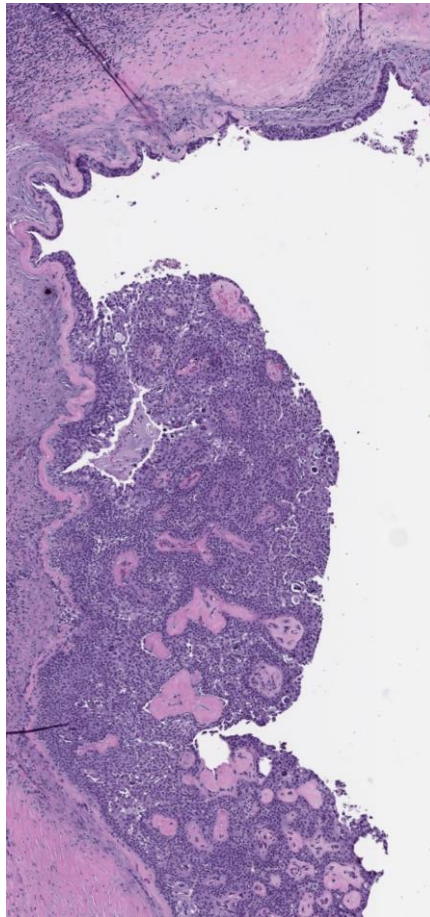
Final CNB diagnosis: Atypical papillary lesion



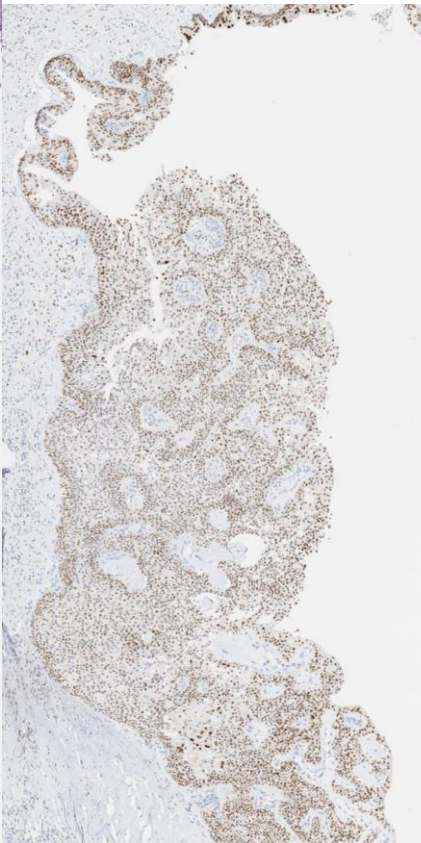
Excision



Final diagnosis: Hidradenoma



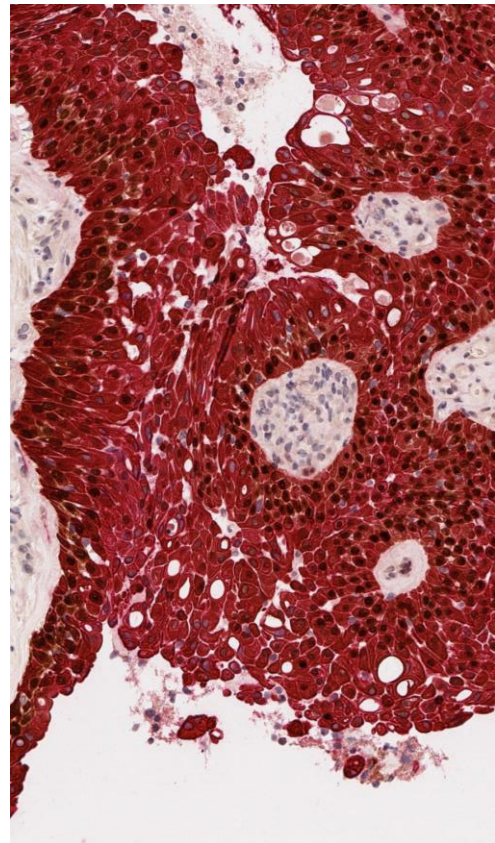
GATA3



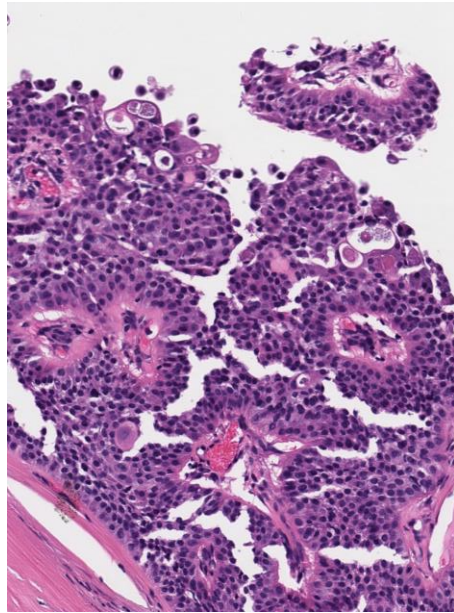
34βE12



ADH5



Hidradenoma or low grade mucoepidermoid carcinoma?



Tumor	Genetic alteration	frequency
Hidradenoma (skin)	CRTC1::MAML2 fusion CRTC3::MAML2 fusion	50–75% rare
	Yoshimi, K. et al. <i>J. Derm.</i> 2017, 44, e190–e191 Kyrpychova, L et al. <i>Ann. Diagn. Pathol.</i> 2016, 23, 8–13	
Mucoepidermoid carcinoma (salivary glands, breast, lung, and pancreas)	salivary glands CRTC1::MAML2 fusion CRTC3::MAML2 fusion	34–70% cases rare
	Seethala RR et al. <i>AJSP.</i> 2010, 34, 1106–1121 Jee KJ et al. <i>Mod. Pathol.</i> 2013, 26, 213–222 Nakayama T et al. <i>Mod. Pathol.</i> 2009, 22, 1575–1581	

Clear cell papillary neoplasm of the breast with MAML2 gene rearrangement: Clear cell hidradenoma or low-grade mucoepidermoid carcinoma? Memon RA, Prieto Granada CN, Wei S. *Pathol Res Pract.* 2020 Oct;216(10):153140.

Clear cell hidradenoma of the breast with MAML2 gene rearrangement. Hsieh MS, Lien HC, Hua SF, Kuo WH, Lee YH. *Pathology.* 2017 Jan;49(1):84-87.

Case: 64 yo male; CNB of breast/ chest wall mass

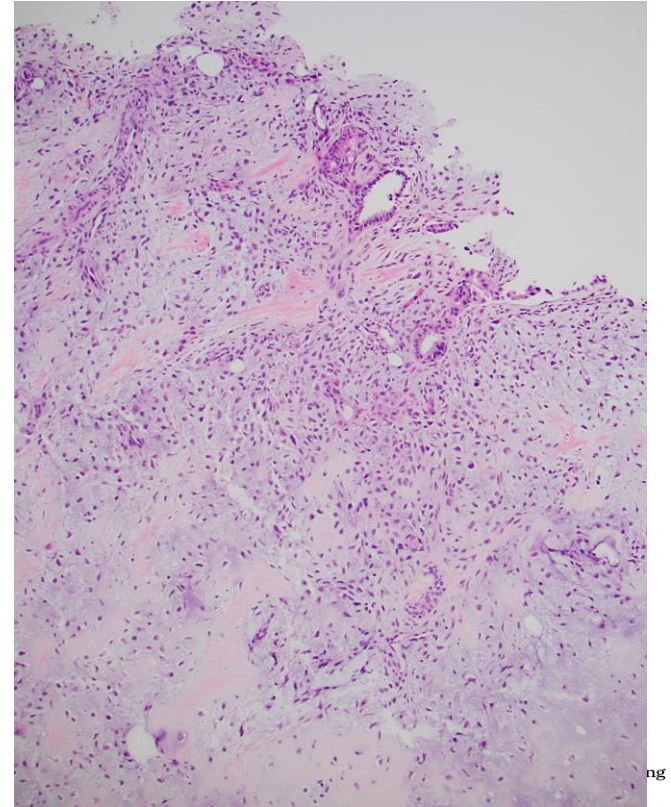
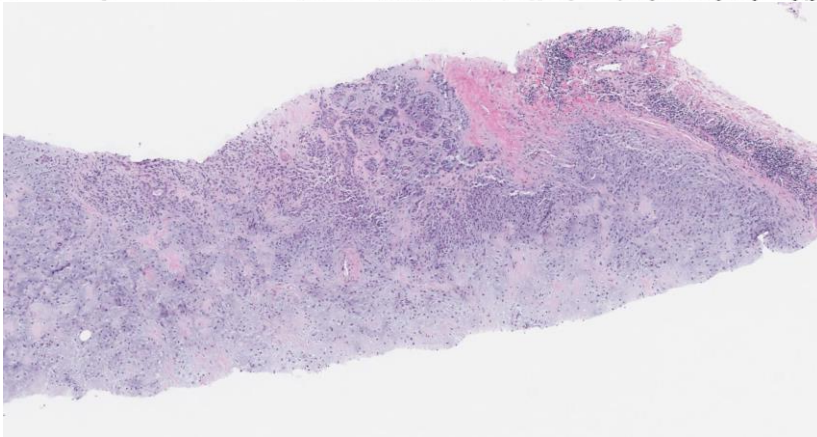
Breast, core biopsies – Invasive poorly differentiated duct carcinoma with predominantly chondroid matrix (metaplastic carcinoma) (8mm in greatest microscopic dimension).

Immunohistochemical stains were performed and show positive staining of carcinoma with keratins (AE1/3, Cam5.2, CK5/6, CK7), p63 and focally with EMA. GATA3 is negative.

ESTROGEN RECEPTOR PROTEIN (ER- clone SP1)*: NEGATIVE (0%)

PROGESTERONE RECEPTOR PROTEIN (PR- clone 1E2)*: NEGATIVE (0%)

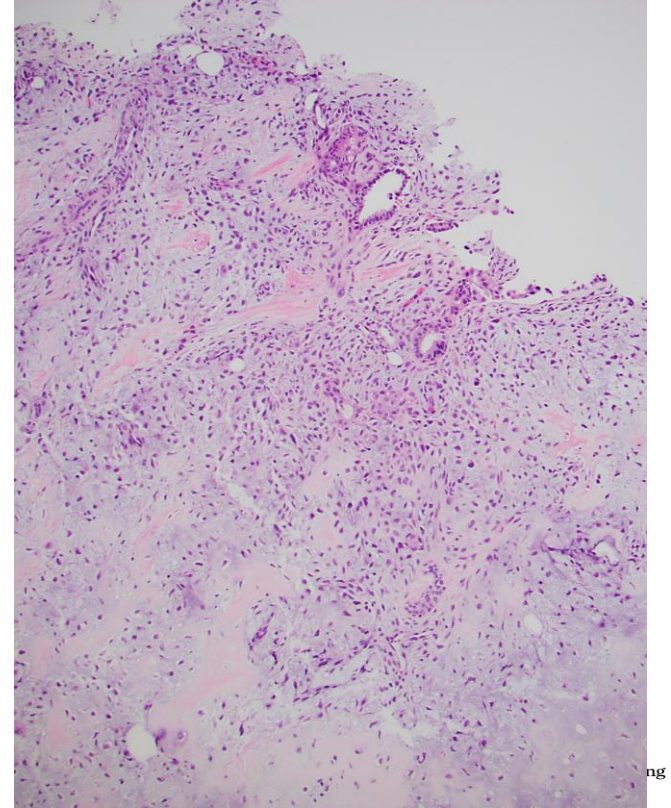
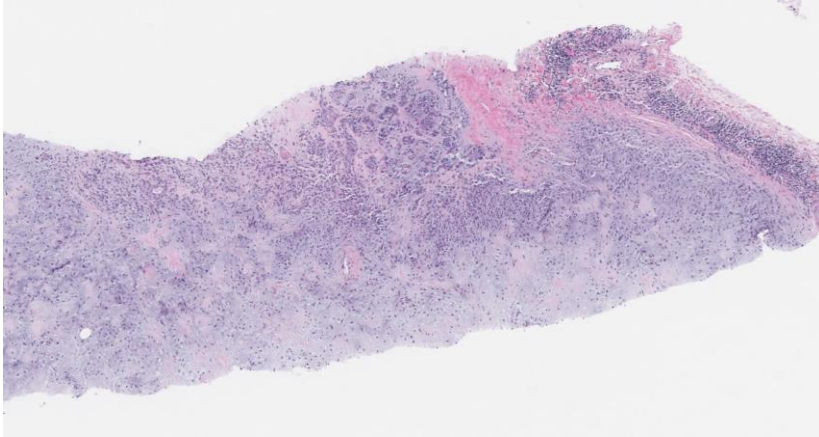
HER-2-NEU oncoprotein**: NEGATIVE (1+ 60%)



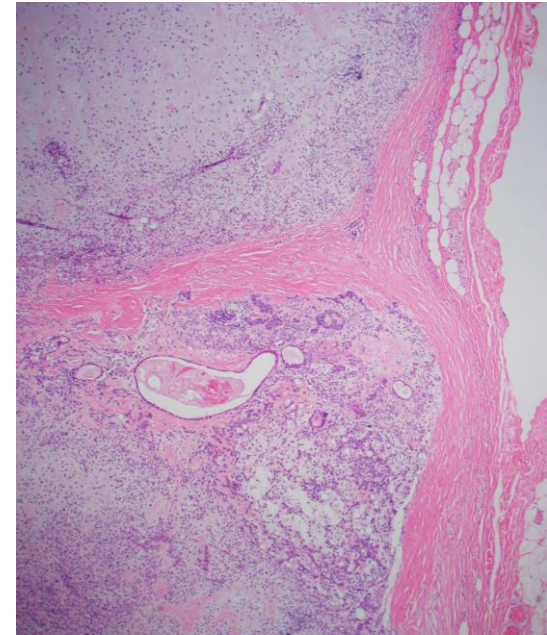
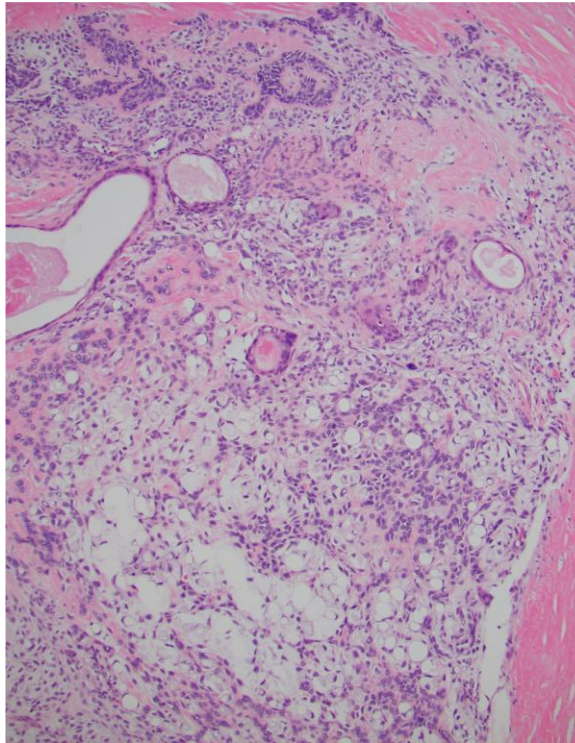
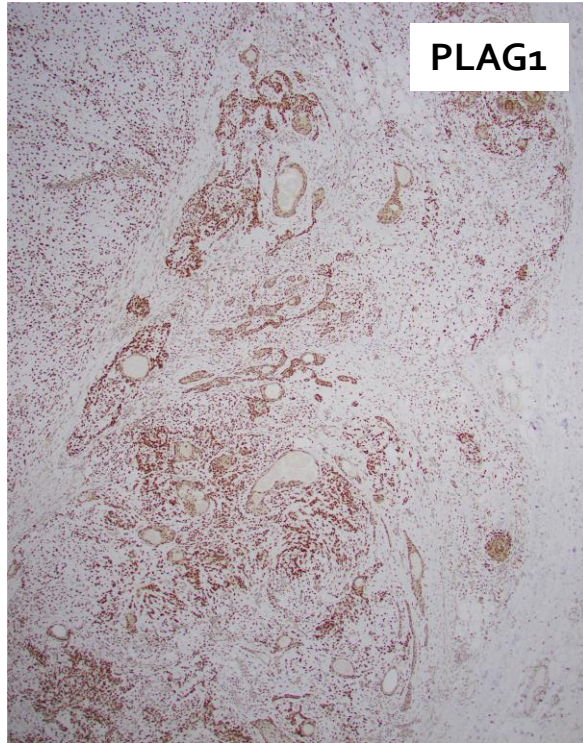
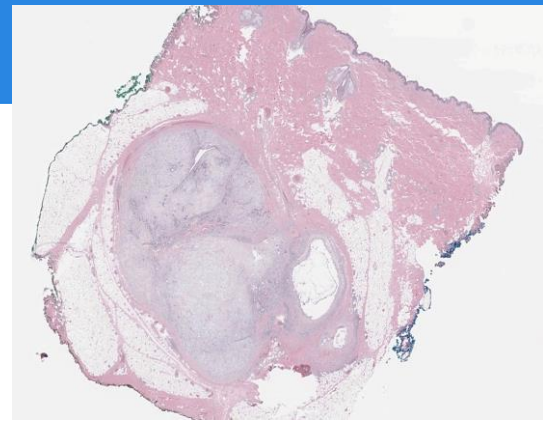
Case: 64 yo male; CNB of breast/ chest wall mass

Final CBX DX: Matrix-producing neoplasm.

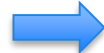
Although this tumor could be compatible with metaplastic carcinoma, this diagnosis is exceedingly rare in men. No breast parenchyma or in situ carcinoma is identified. Clinical correlation recommended.



64 yo male with breast/ chest wall mass
Excision: Final DX: Mixed Tumor of skin



Most frequent molecular alterations in skin adnexal neoplasms



Diagnosis	Molecular Alteration	Frequency (%)
Adenoid cystic carcinoma	<i>MYB::NFIB</i> fusion	73–83%
	<i>MYBL1::NFIB</i> fusion	20–23%
Cutaneous mixed tumor	<i>PLAG1</i> fusion	33%
	<i>HMGA2</i> fusion	unknown
Cylindroma	<i>CYLD</i> inactivation	near 100%
Spiradenoma	<i>CYLD</i> inactivation	29%
	<i>ALPK1</i> p.V1092A mutation	43%
Spiradenocarcinoma	<i>CYLD</i> inactivation	8%
	<i>ALPK1</i> p.V1092A mutation	33%
Hidradenoma	<i>CRTC1::MAML2</i> fusion	50–75%
	<i>CRTC3::MAML2</i> fusion	rare
Hidradenocarcinoma	<i>CRTC1::MAML2</i> fusion	unknown
Myoepithelioma	<i>EWSR1</i> fusion	82%
	<i>FUS</i> fusion	18%
Poroma	<i>YAP1</i> fusion	88%
	<i>NUTM1</i> fusion	17–55%
Porocarcinoma	<i>YAP1</i> fusion	8–63%
	<i>NUTM1</i> fusion	11–54%
Secretory carcinoma	<i>ETV6::NTRK3</i> fusion	near 100%
Syringocystadenoma papilliferum and tubular adenoma	<i>BRAF</i> p.V600E mutation	50–64%
	<i>HRAS</i> p.G13R mutation	7–26%
	<i>KRAS</i> p.G12D mutation	rare

Take home messages

Cutaneous epithelial neoplasms can closely mimic epithelial neoplasms of the breast

When dealing with a tumor with unusual morphology

→ Obtain clinical history + review prior material

→ Consider DDx of cutaneous (adnexal) neoplasms

include BENIGN skin adnexal neoplasms in the DDx

Beware: substantial overlap of the IHC profiles of skin and breast epithelial neoplasms

– GATA3, ER, PR, AR, SOX10

– BUT strong and diffuse positivity for p63/ p40/ basal keratins favors cutaneous origin

Exception: mammary metaplastic squamous cell carcinoma

Cutaneous Squamous and Basal cell carcinomas have UV mutational signatures

Skin adnexal tumors often harbor specific genomic alterations → possible use for Dx

– Possible overlap with tumors primary at other sites, interpret in context

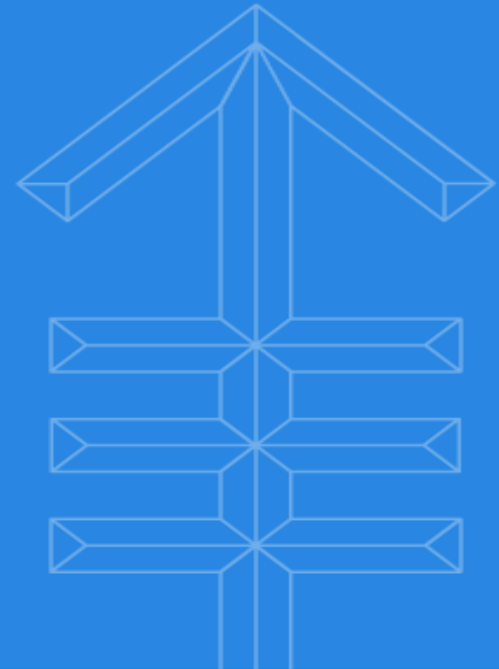




Memorial Sloan Kettering
Cancer Center

Learning from Mistakes

Vascular lesions - Pitfalls



Vascular lesions in the breast

- *Dilated lymphatics/ vessels*
- Hemangioma (various types)
- Atypical hemangioma
- Angiolipoma
- “Angiomatosis”
- **Angiosarcoma (AS)**
 - **Primary**
 - **Secondary (radiation-induced)**

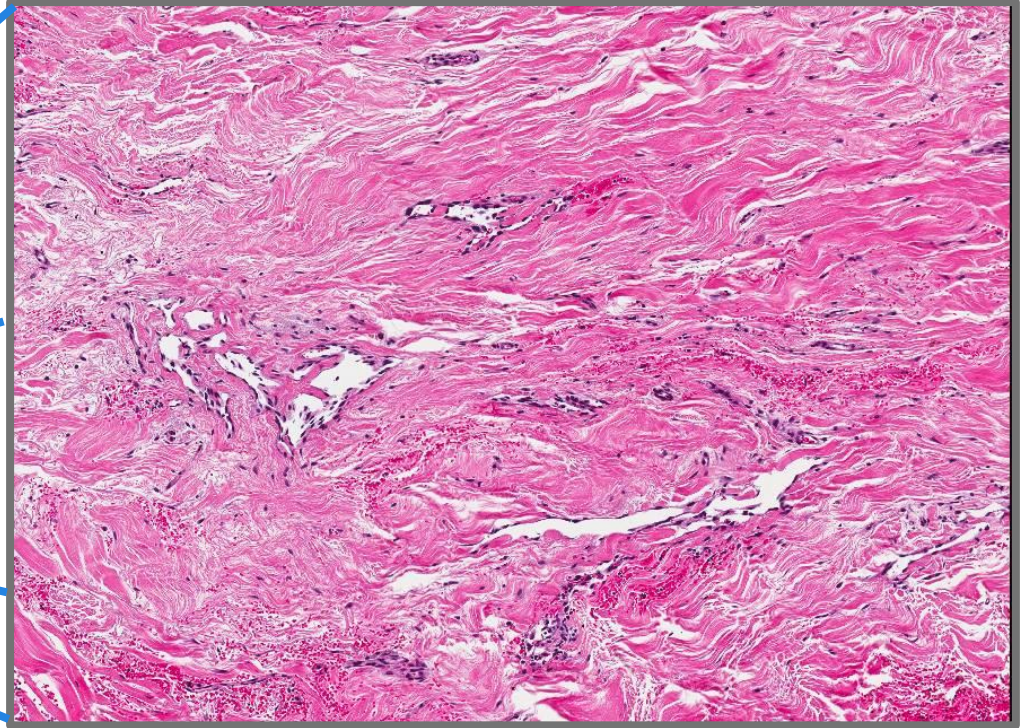
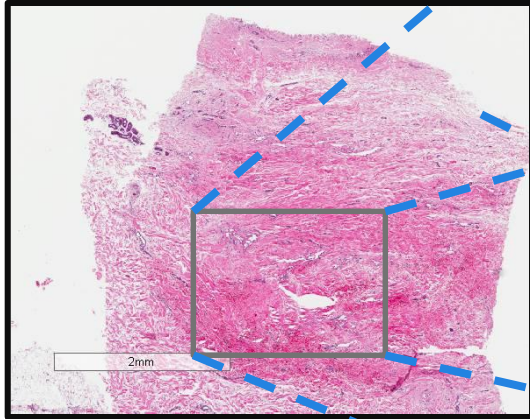


Case – 38 yo F

- No prior significant history
- Skin discoloration overlying an ill-defined palpable left breast mass
Skin punch biopsy: Original DX: Benign
- 3 months later:
CNB of the breast mass: Original DX: Poorly differentiated invasive ductal carcinoma, triple negative
- Patient referred to MSKCC for neoadjuvant chemotherapy
- All pertinent pathology material was reviewed

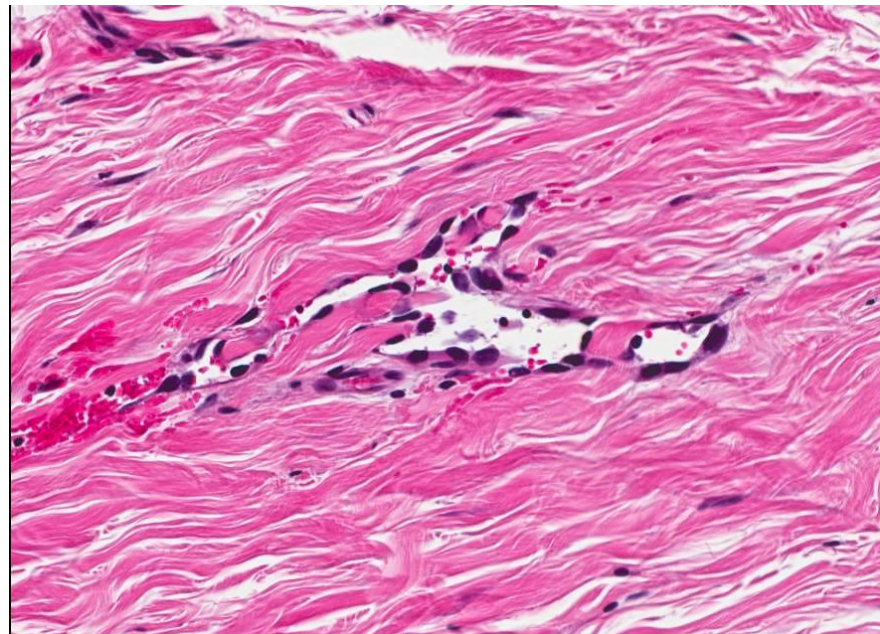
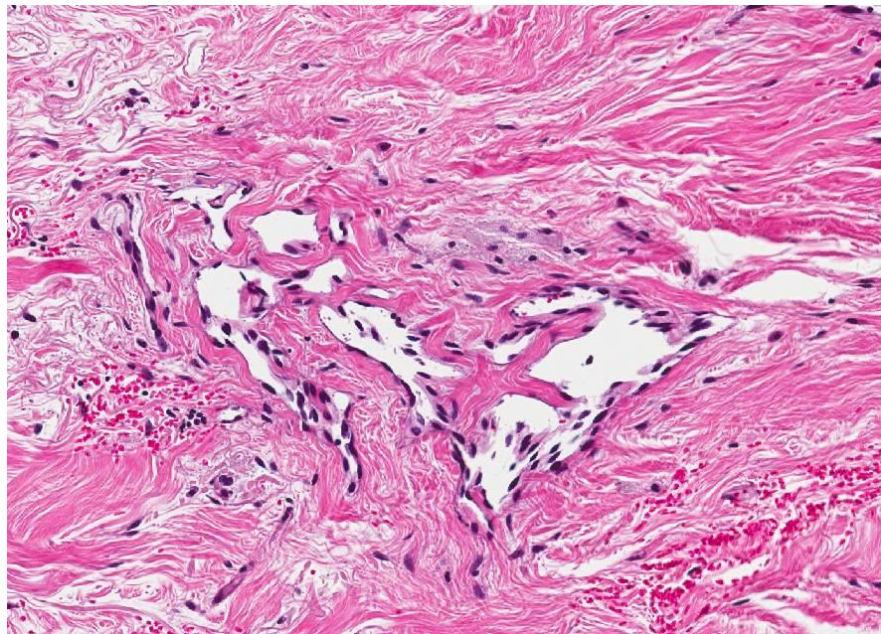


Skin punch biopsy

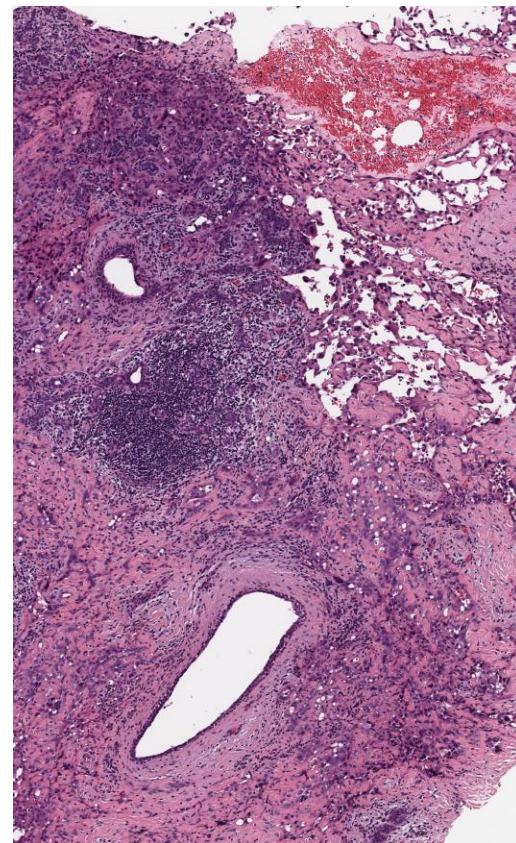
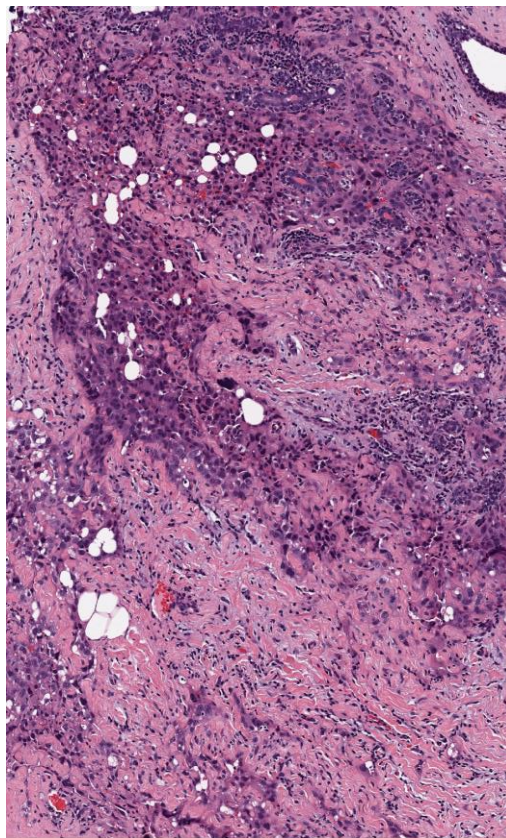
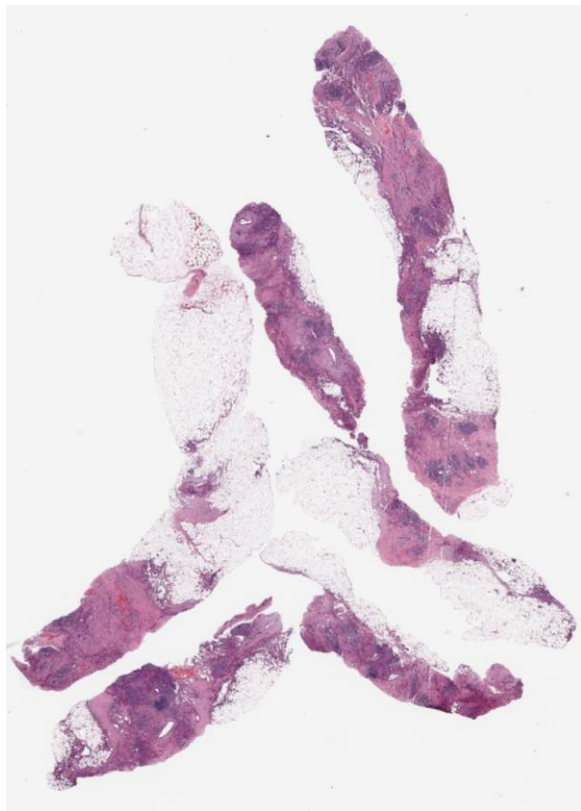


Skin punch biopsy

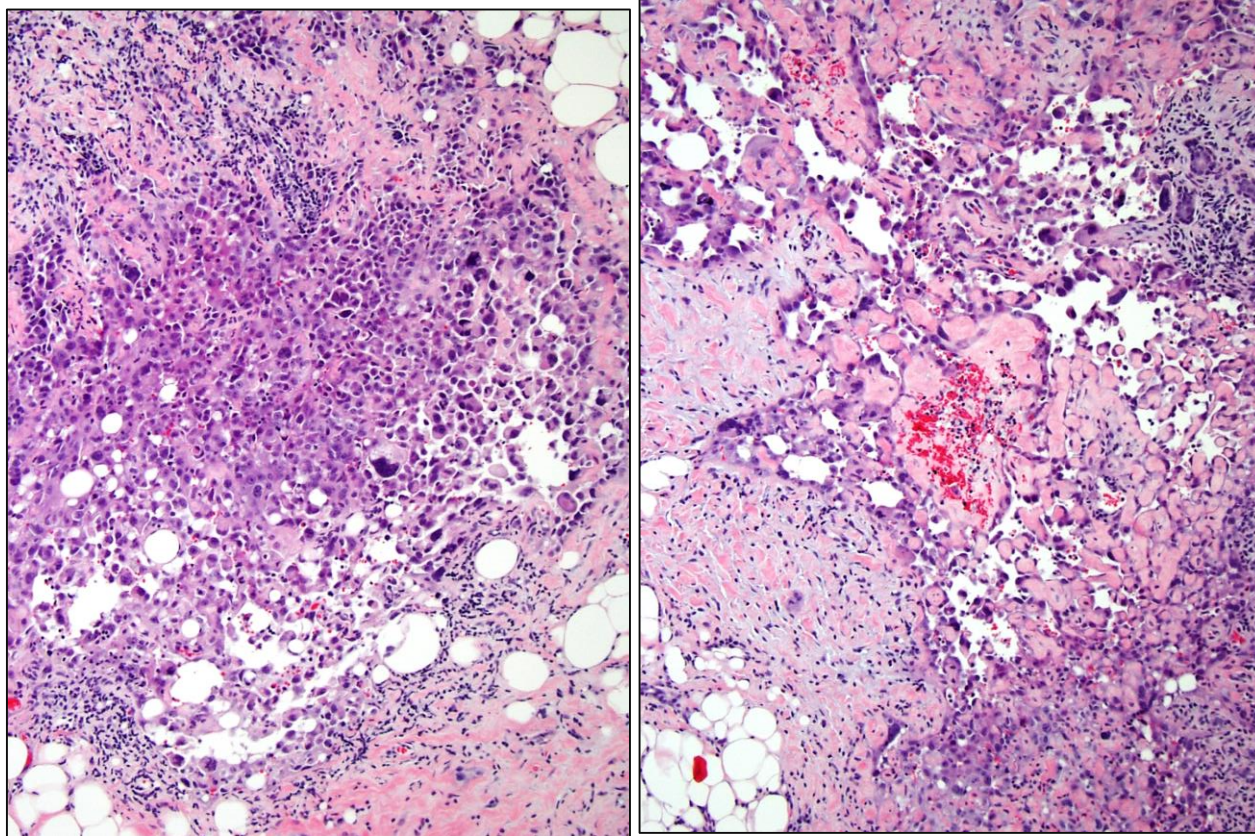
Final DX: Atypical vascular proliferation, suspicious for low grade AS



CNB of the underlying breast mass



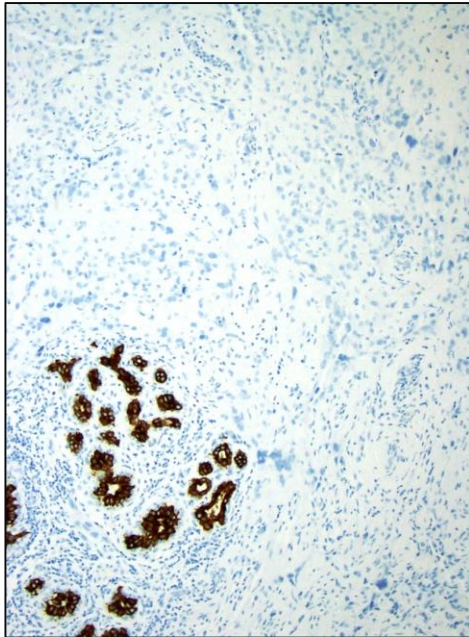
CNB of the underlying breast mass



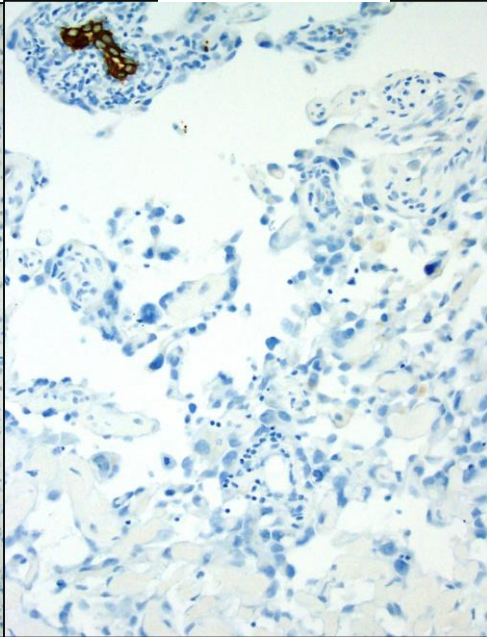
CNB of the breast mass

Final DX: High grade angiosarcoma, epithelioid and spindle

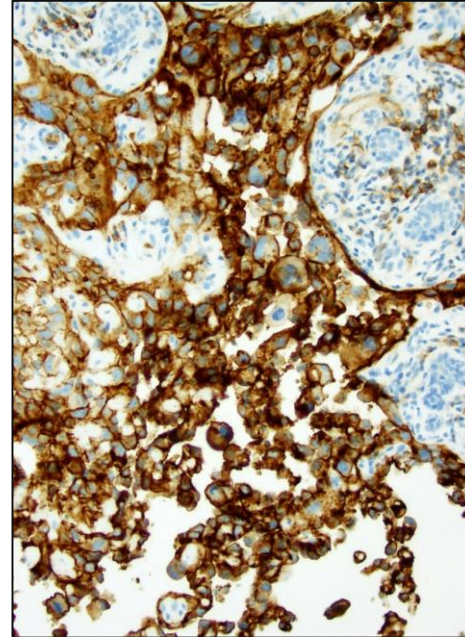
CAM5.2



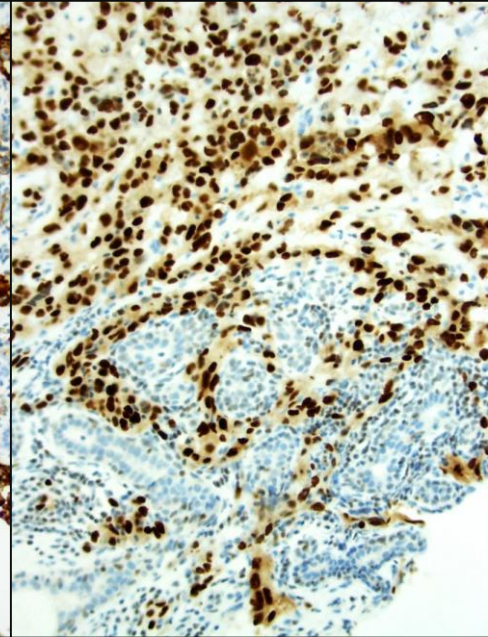
AE1/AE3



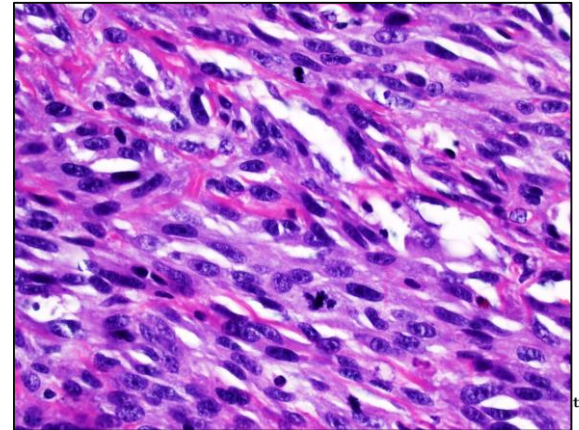
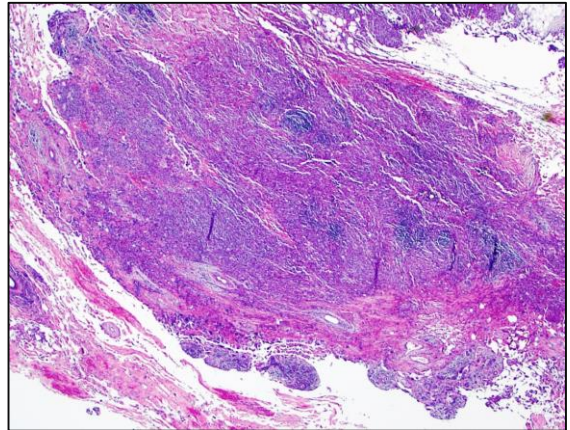
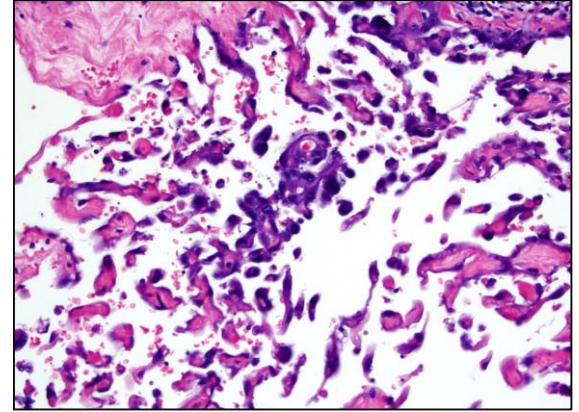
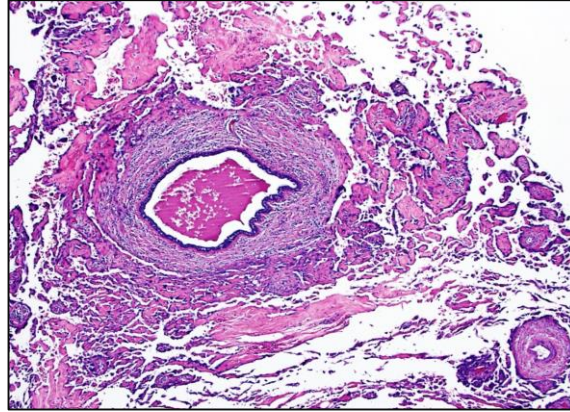
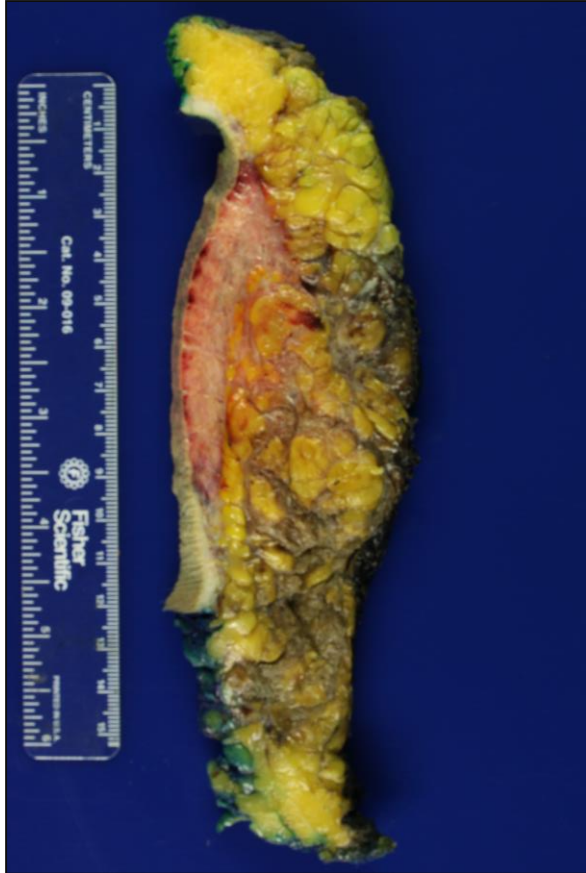
CD31



ERG

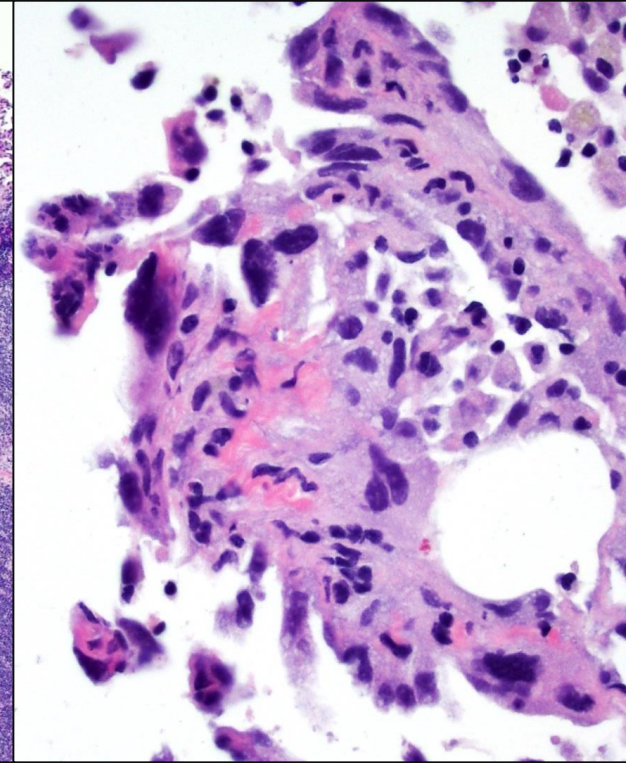
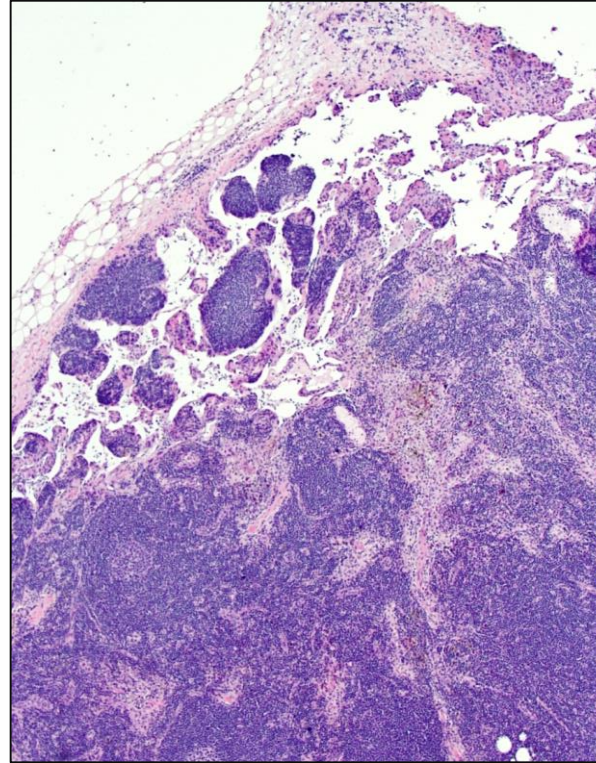
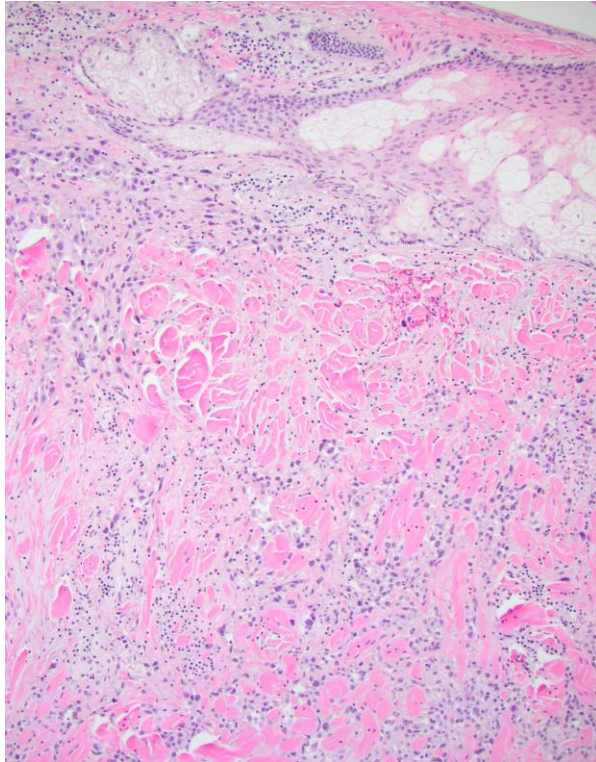


Mastectomy



Dermal involvement

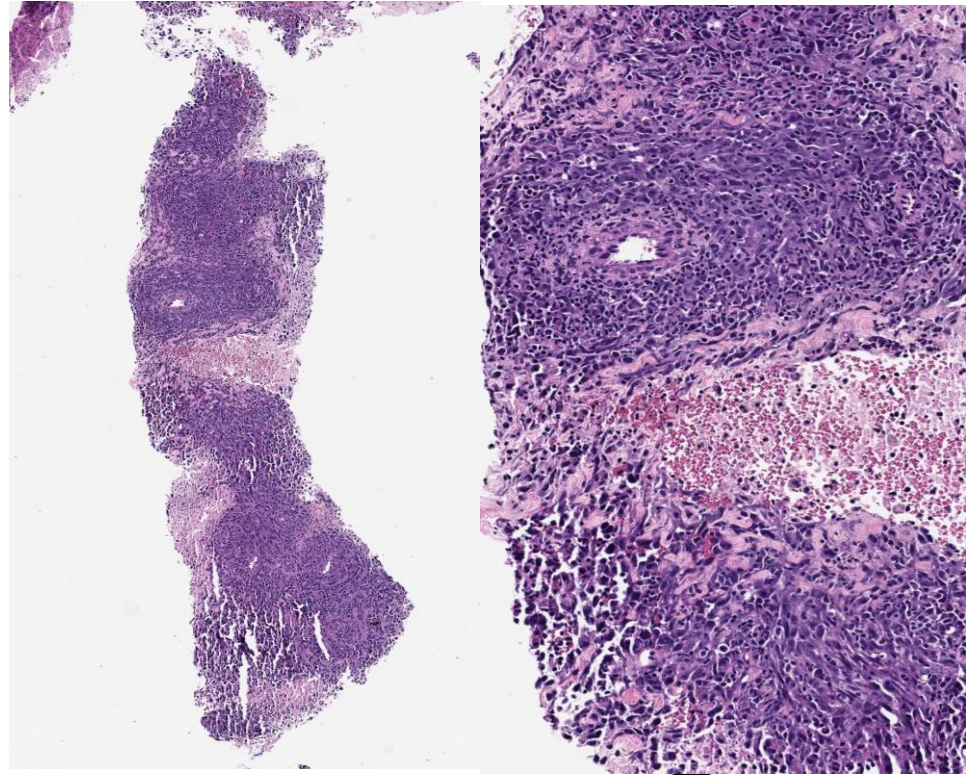
Metastatic AS in one LN



Another case

58 yoF, CNB of a breast mass in 2021

**Original DX: Invasive lobular carcinoma, triple negative
E-cadherin stain is negative,
supporting lobular phenotype**



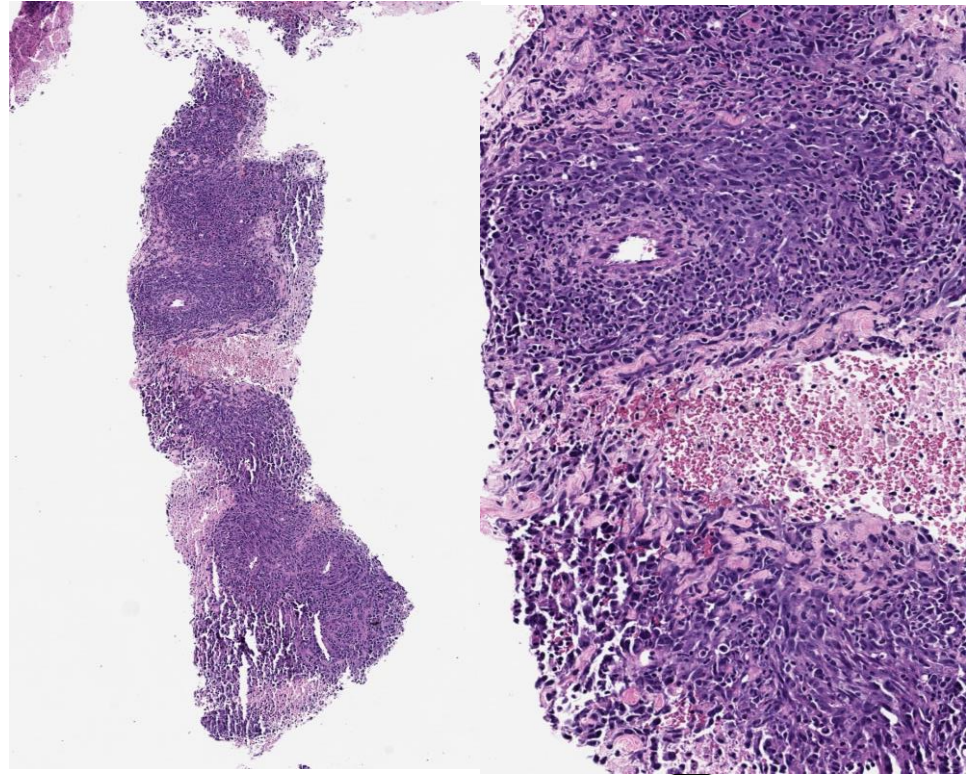
Another case

58 yoF, CNB of a breast mass in 2021

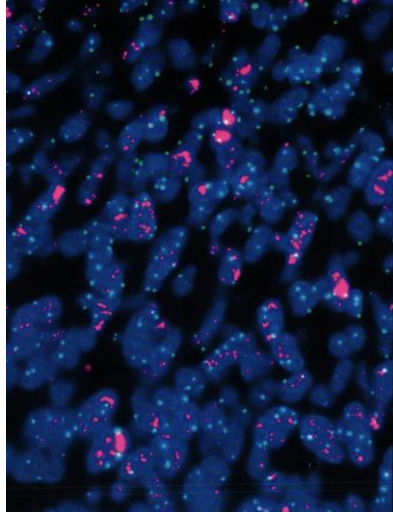
Patient transferred care @MSK
CNB reviewed

Prior Hx obtained

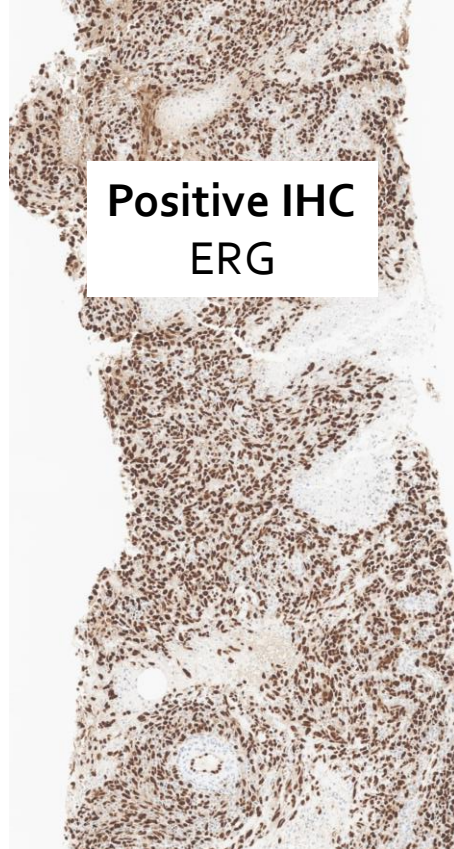
In 2009: Ipsilateral invasive triple
negative DUCTAL carcinoma →
Lumpectomy + **radiotherapy** +
adjuvant chemotherapy



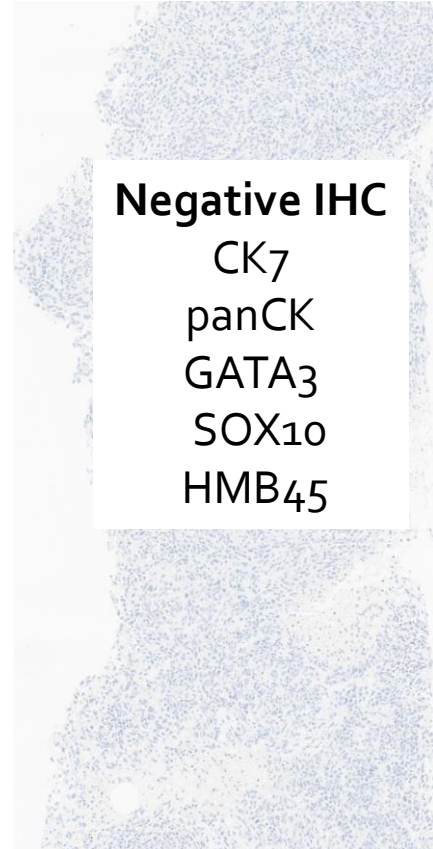
CNB final DX: (Radiation-induced) Angiosarcoma



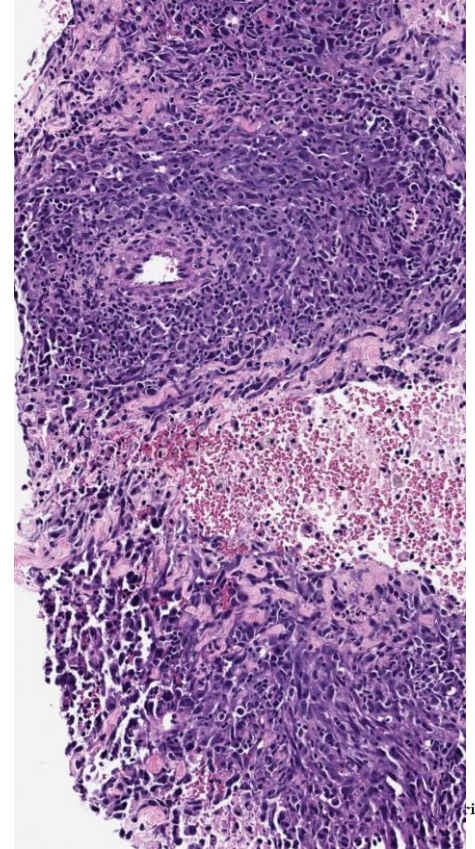
**MYC
amplification**



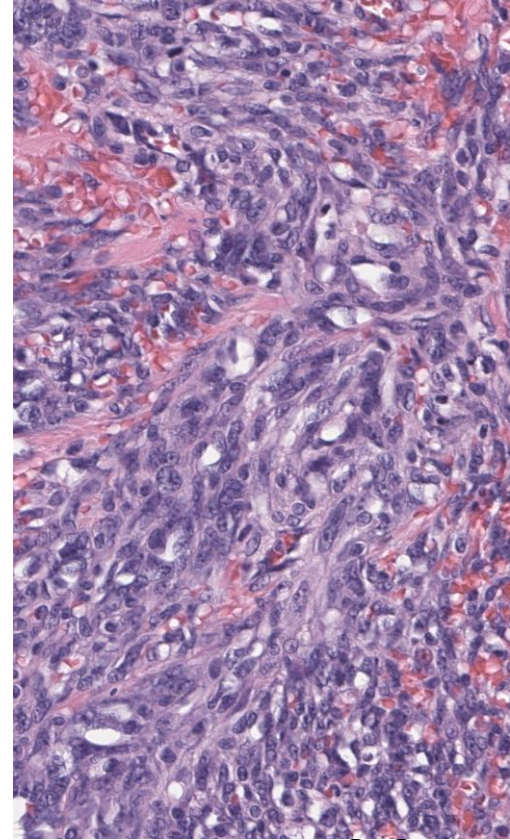
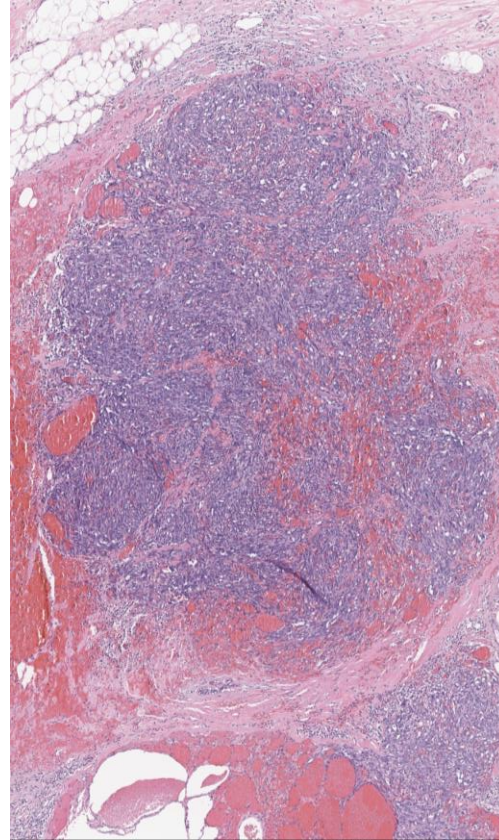
**Positive IHC
ERG**



Negative IHC
CK7
panCK
GATA3
SOX10
HMB45

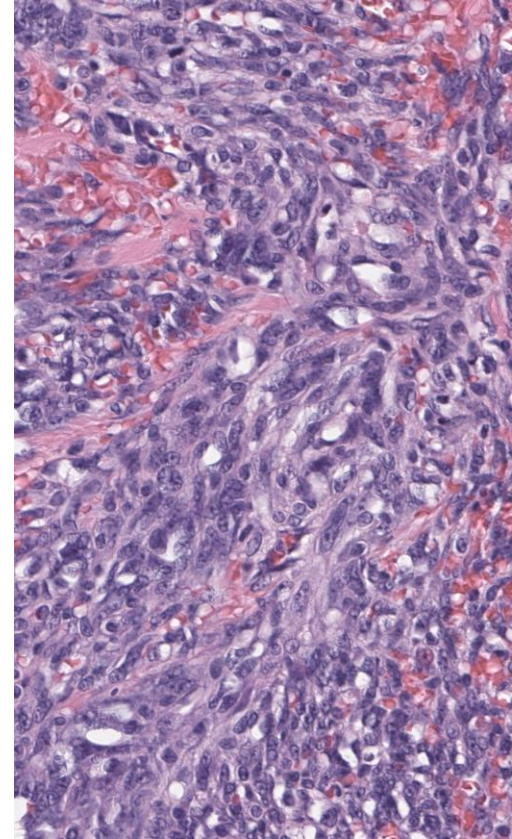
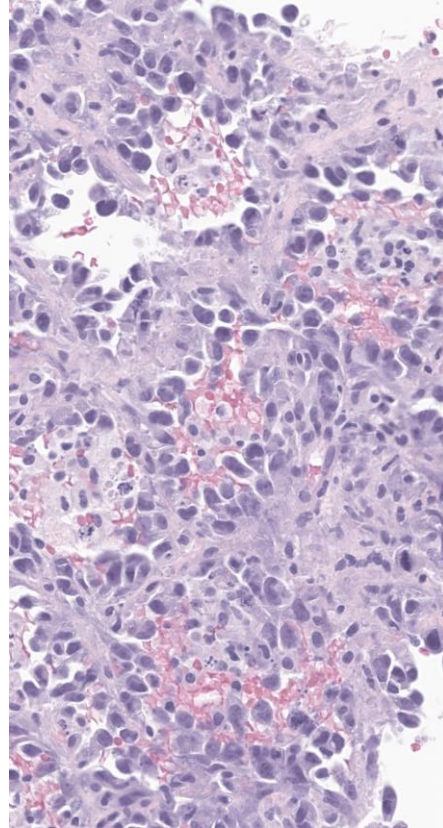
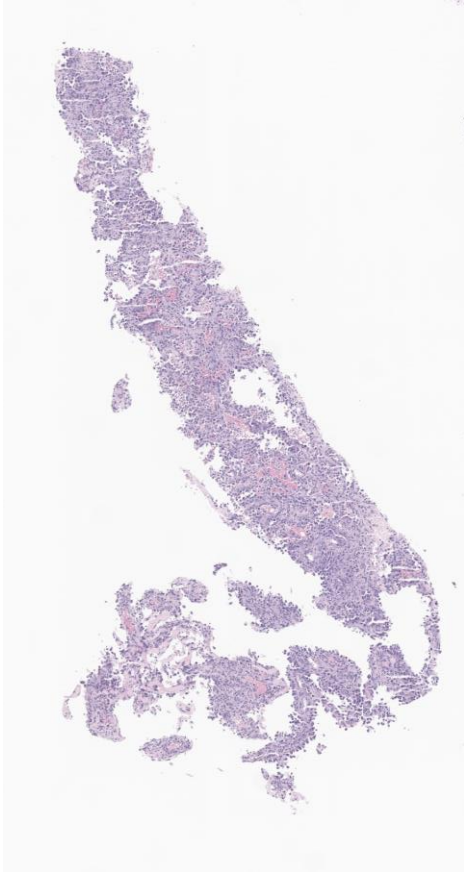


Mastectomy (October 2021)



February 2022: bx of an inguinal mass

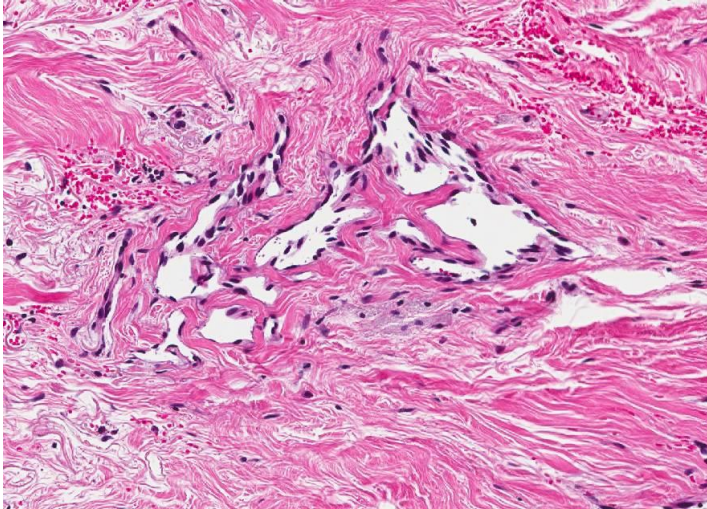
October 2021: Mastectomy



Angiosarcoma – Pitfalls in Dx

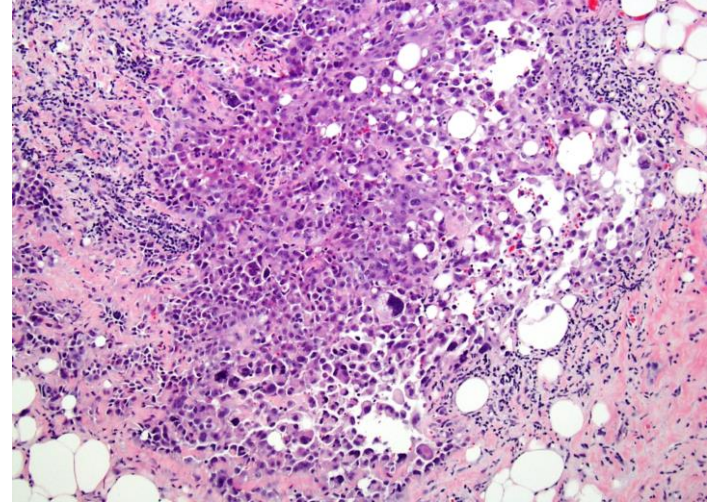
Low grade AS

- Often inconspicuous
- Dilated vessels, irregular outline
- Nuclear atypia, hyperchromasia



High grade AS, epithelioid

- DDx High grade carcinoma, triple neg
- Bloody background? → consider AS
 - do IHC for CKs and ERG

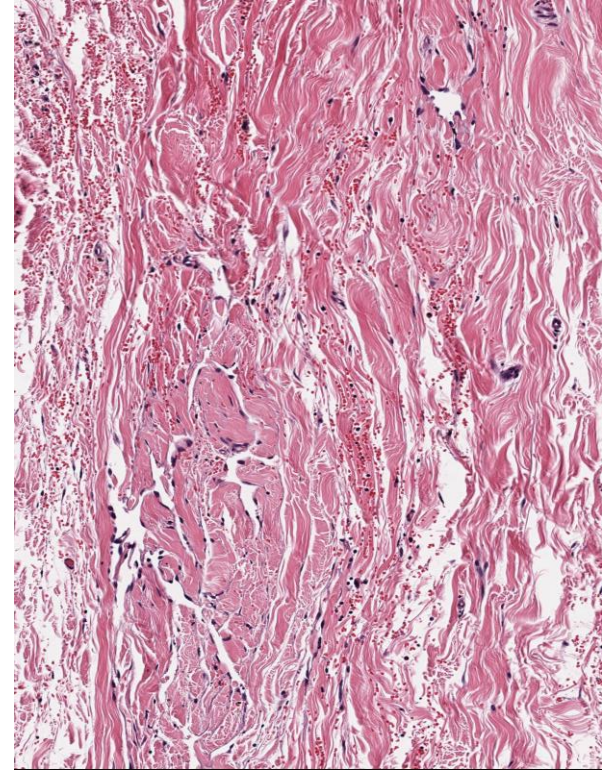
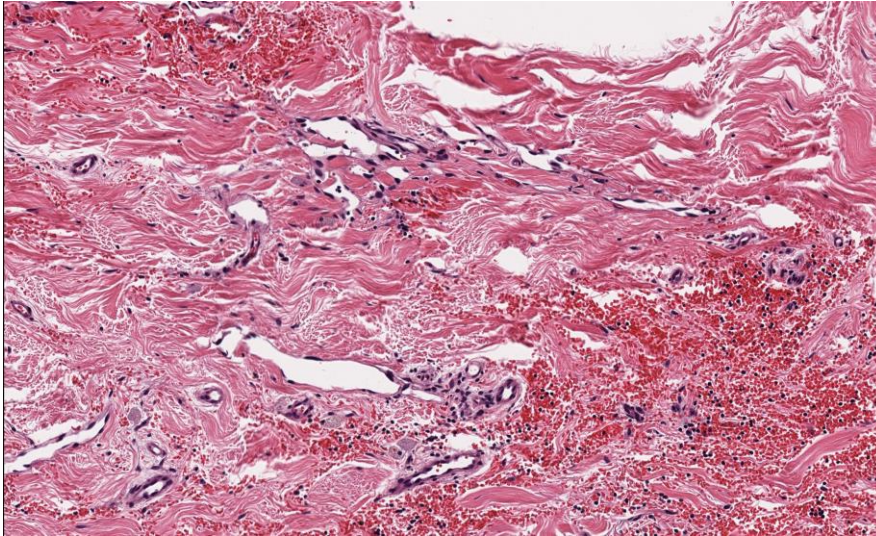


Clinical History

Any skin discoloration/ bruising? Prior radiotherapy?

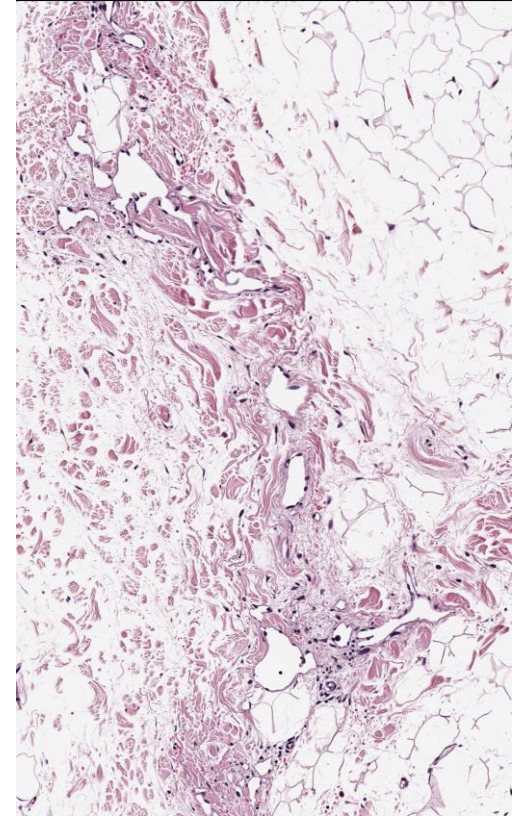
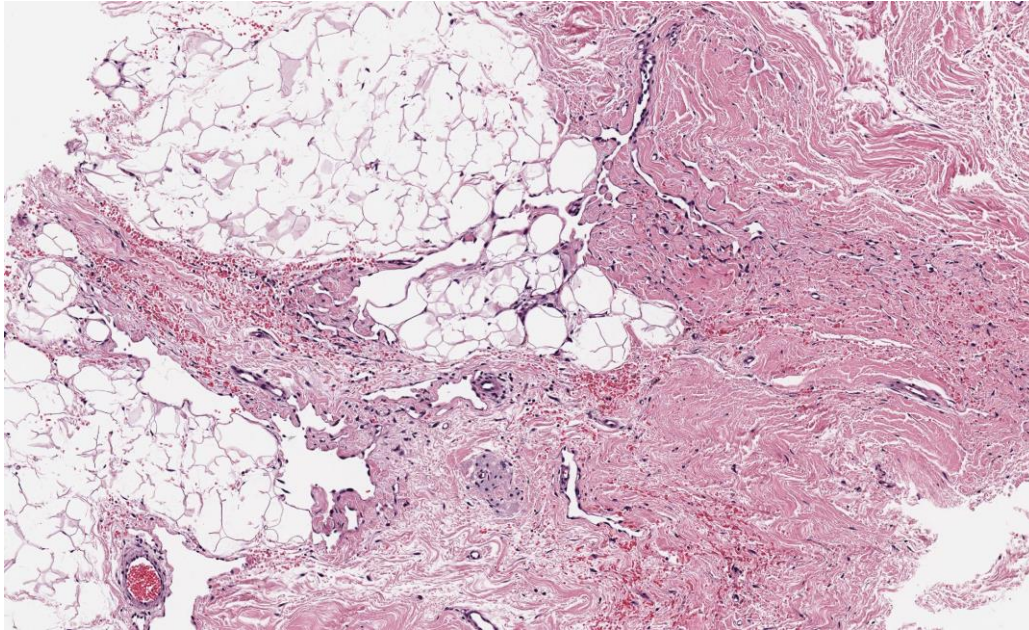
Features suggestive of a vascular lesion

- Bloody tissue fragments
- Hemorrhagic background

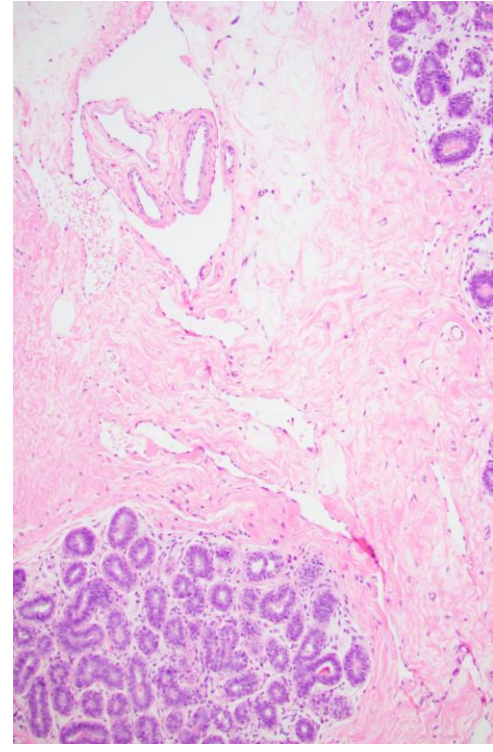
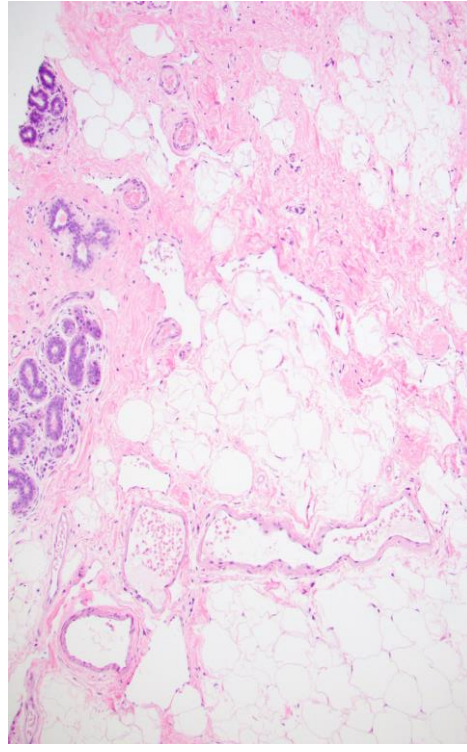
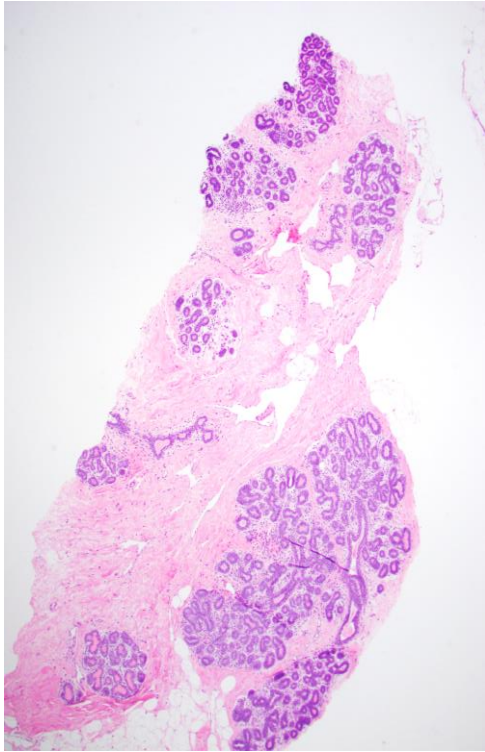
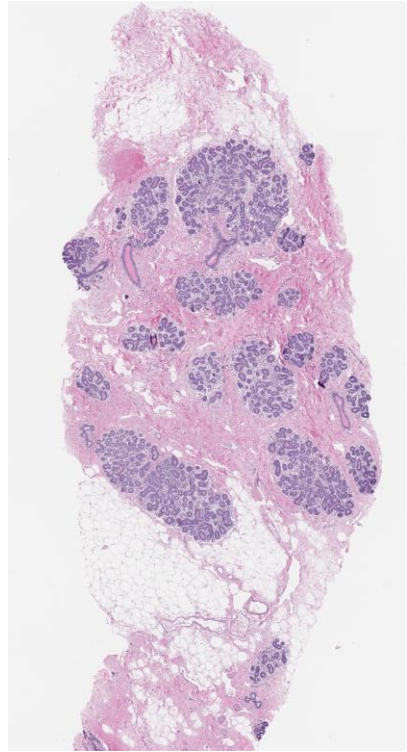


Features suggestive of atypical vascular lesion/ AS

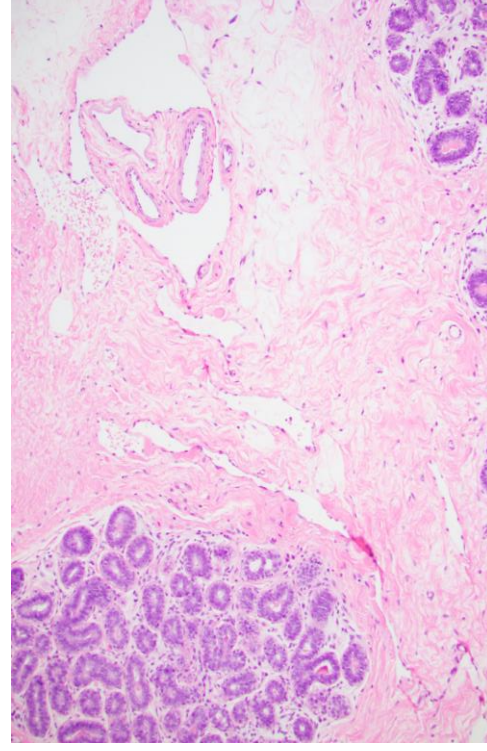
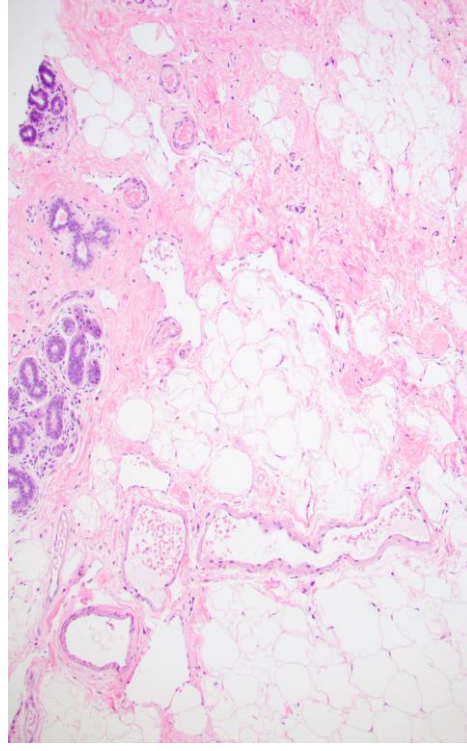
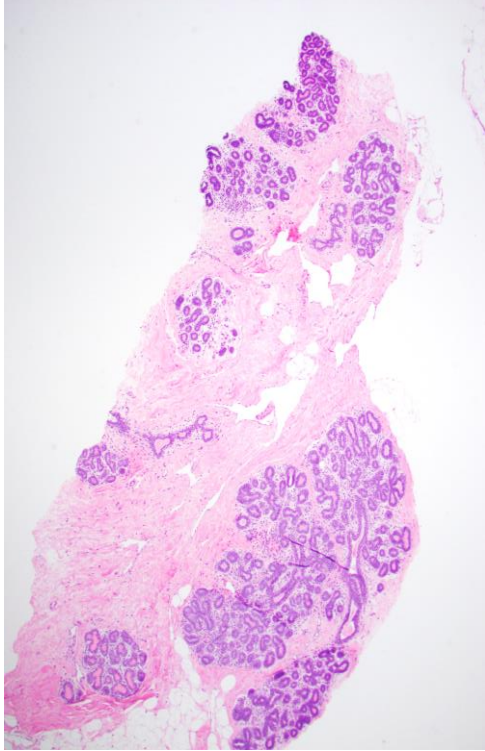
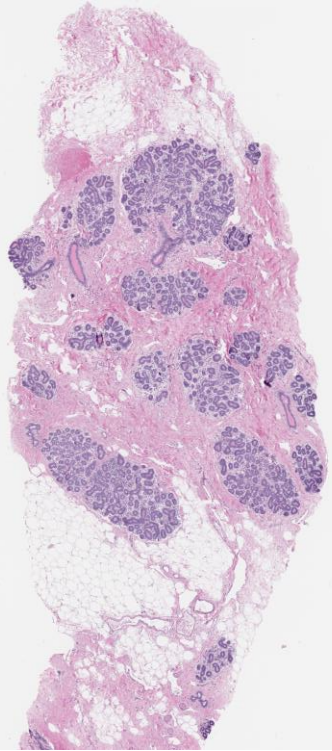
- Irregular/ dissecting vascular spaces
- Hyperchromatic/ hobnail nuclei



48 yo woman - high risk screening CNB of MRI non-mass enhancement



Original CNB DX: prominent vascular spaces, cannot rule out vascular lesion → Excision: Benign with bx site

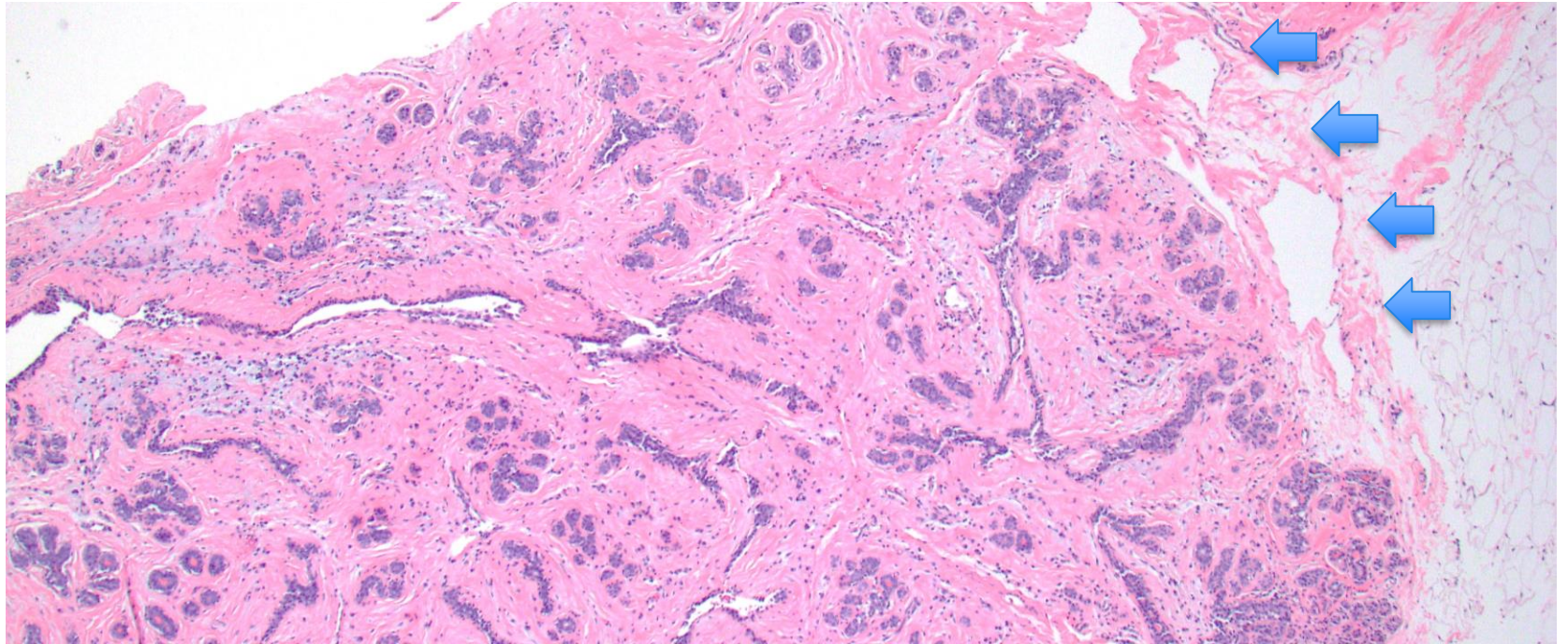


MRI-guided CNB

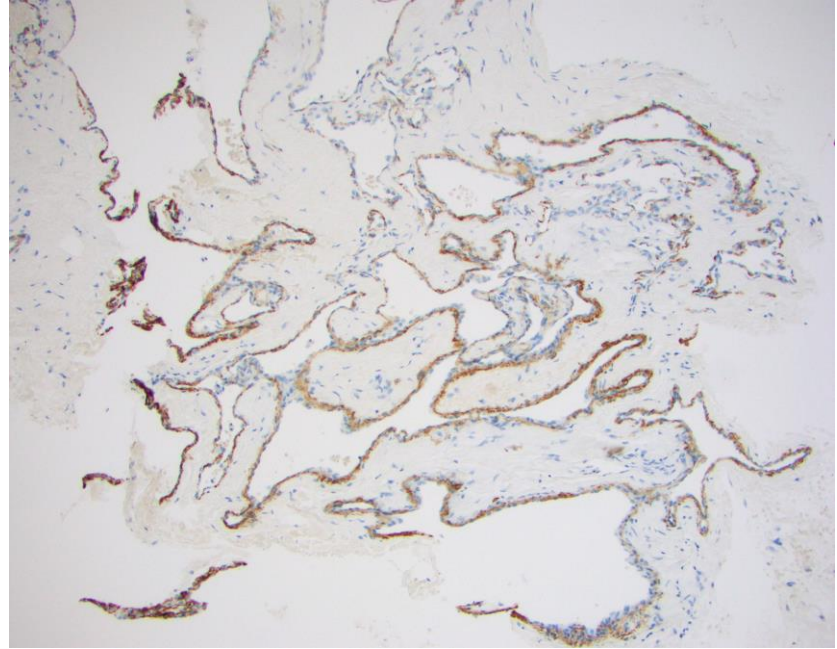
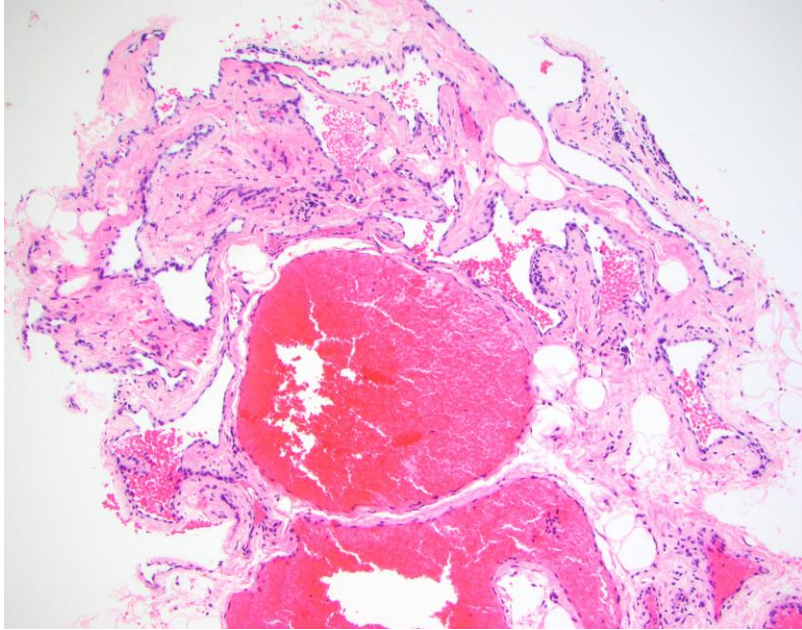
patient is in prone position



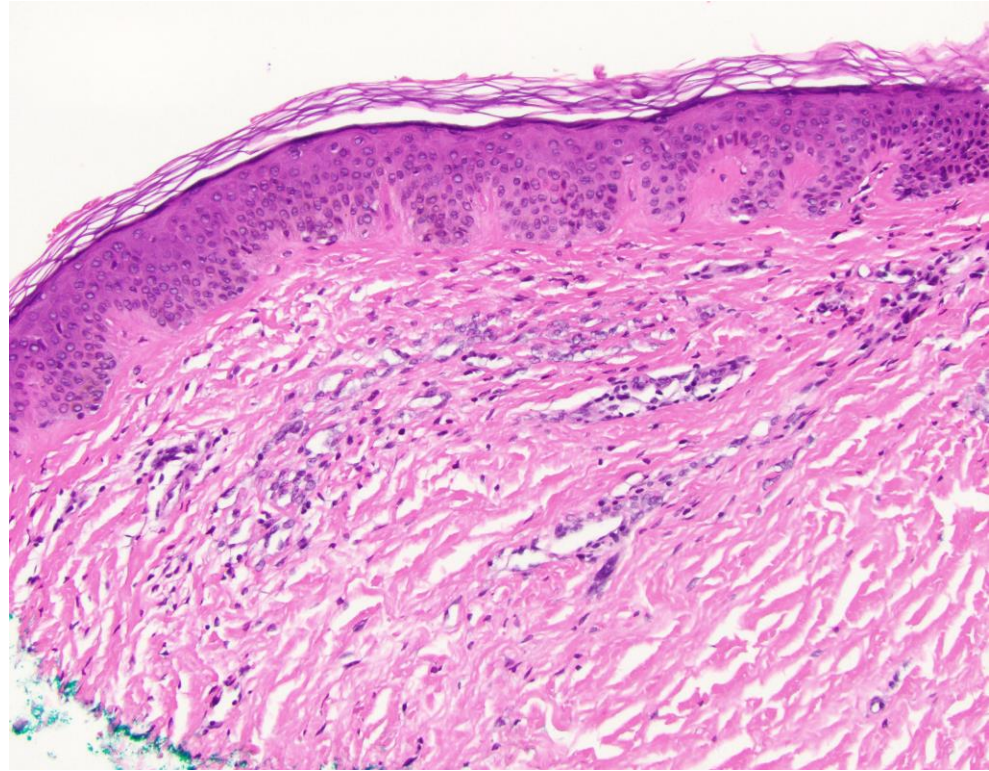
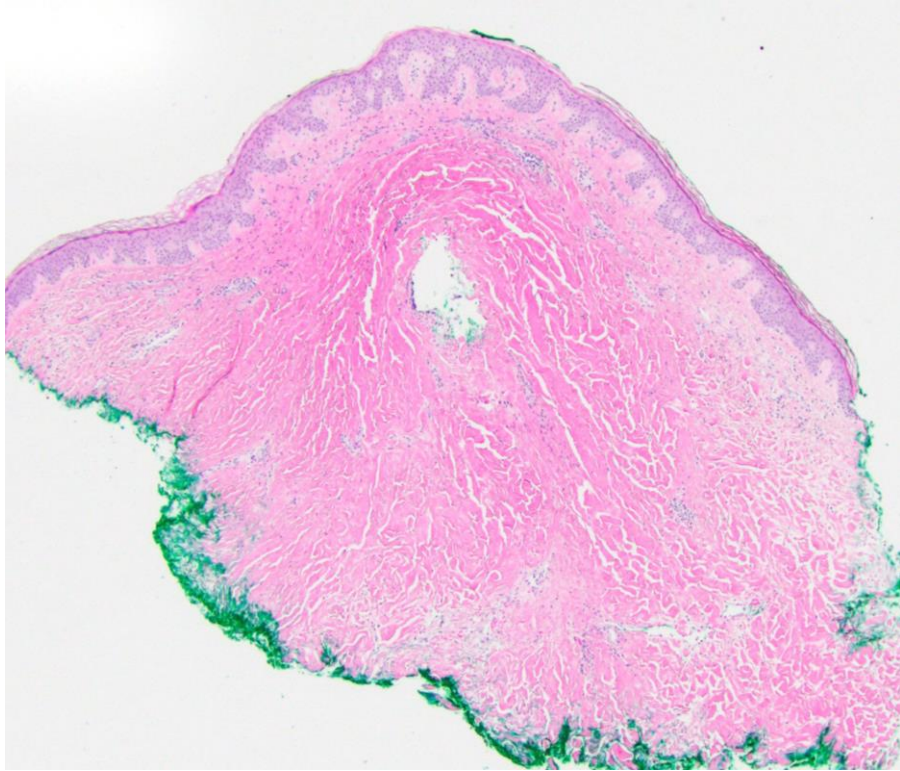
Dilated lymphatic vessels common in MRI-guided CNB



SMA(+) cells around dilated vessels: benign vascular

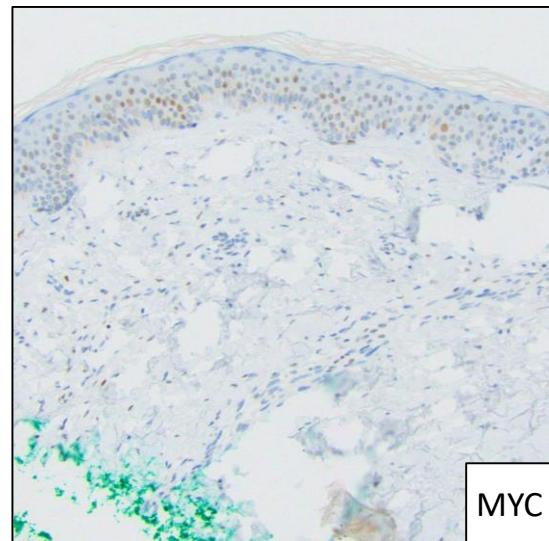
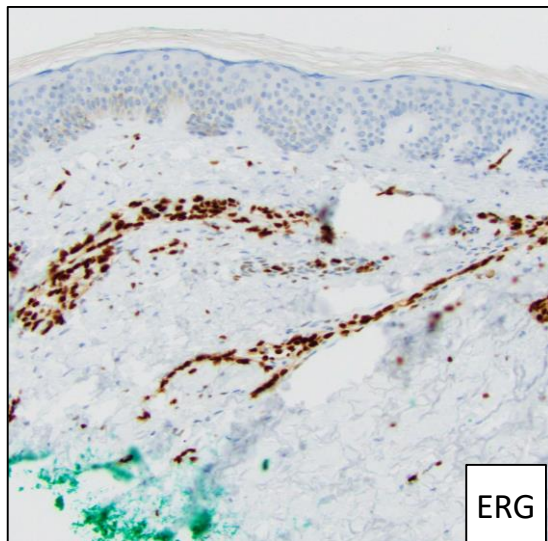
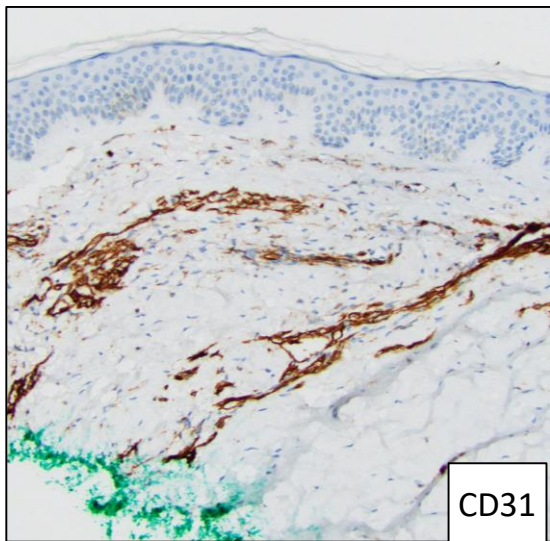


Another case: 58 yoF, s/p radioTP for BC 10 yrs before
Skin punch biopsy for slight skin discoloration



Left breast punch biopsy DX

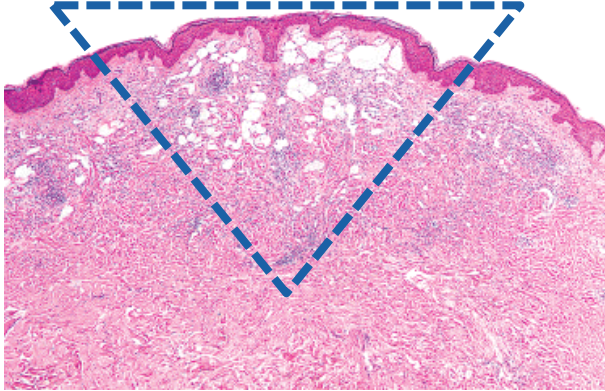
Atypical vascular lesion (MYC-negative)



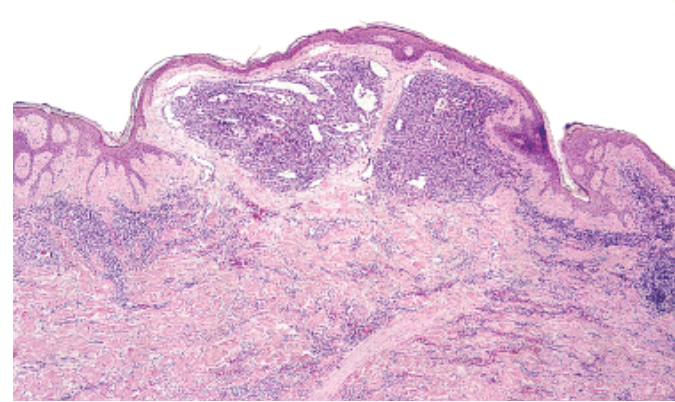
Post-RT AVL

vs

angiosarcoma



- Small, circumscribed
- Wedge-shaped, usually symmetrical
- Limited to superficial-mid dermis
- Does not involve subcutaneous tissue



- Poorly circumscribed
- Diffusely infiltrative
- Extends into subcutaneous tissue and breast parenchyma

MYC-amplification is a diagnostic feature of radiation-induced angiosarcoma

- MYC amplification detected by FISH in radiation-induced AS
- MYC amplification present also in primary AS, but levels are usually lower
- **No MYC amplification in AVLs**
- IHC for MYC may be useful in some cases, but its validity has not been proven in large series

Manner J, et al. **MYC high level gene amplification is a distinctive feature of angiosarcomas after irradiation or chronic lymphedema.** Am J Pathol. 2010 ;176(1):34-9

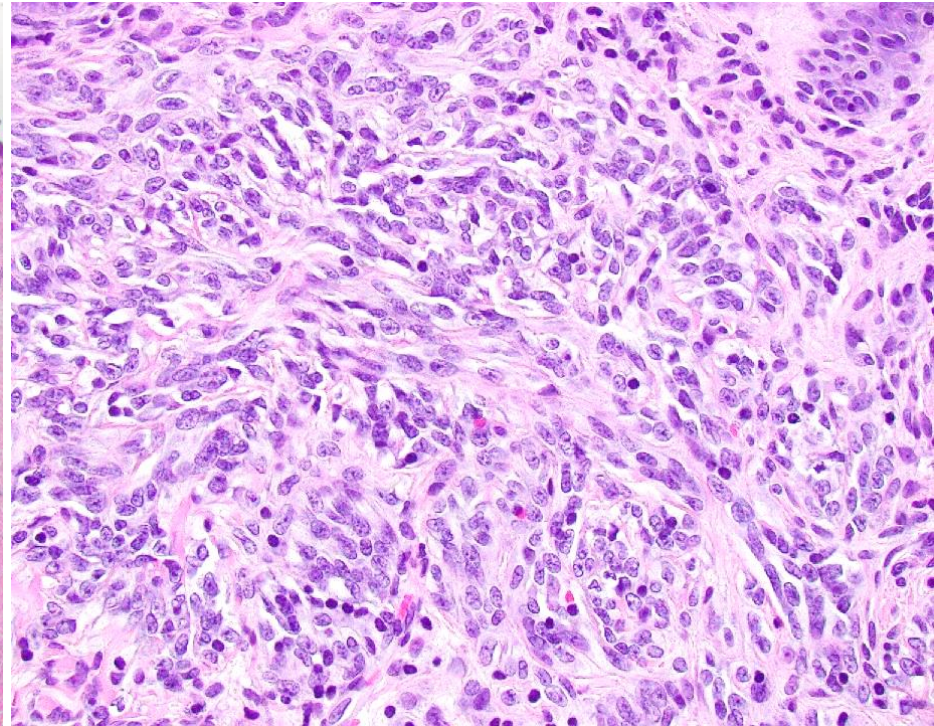
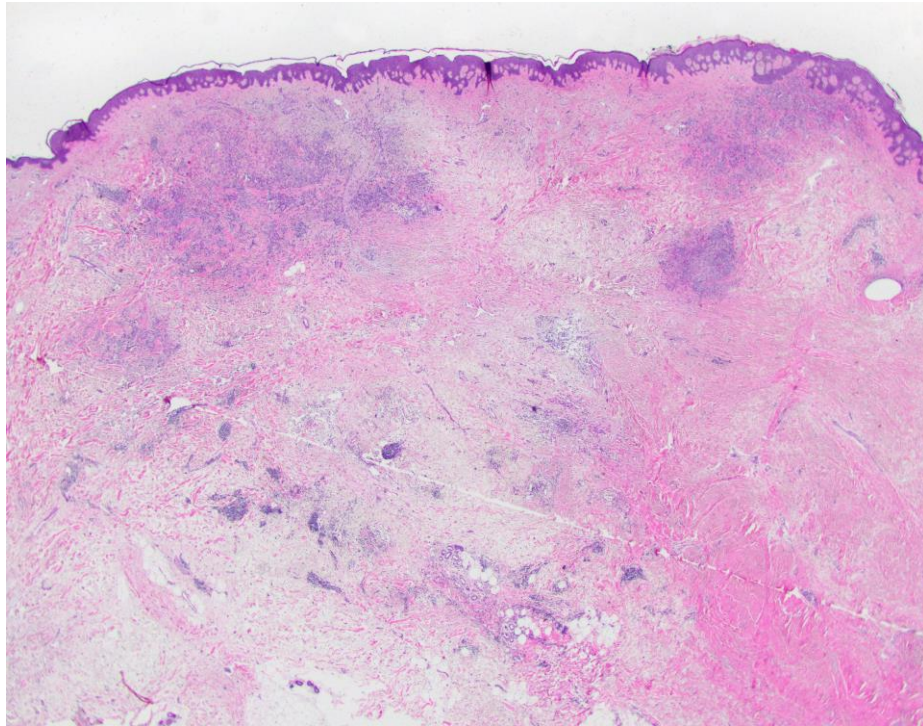
Guo T et al. **Consistent MYC and FLT4 gene amplification in radiation-induced angiosarcoma but not in other radiation-associated atypical vascular lesions.** Genes Chromosomes Cancer. 2011 ;50(1):25-33 (IMAGES)

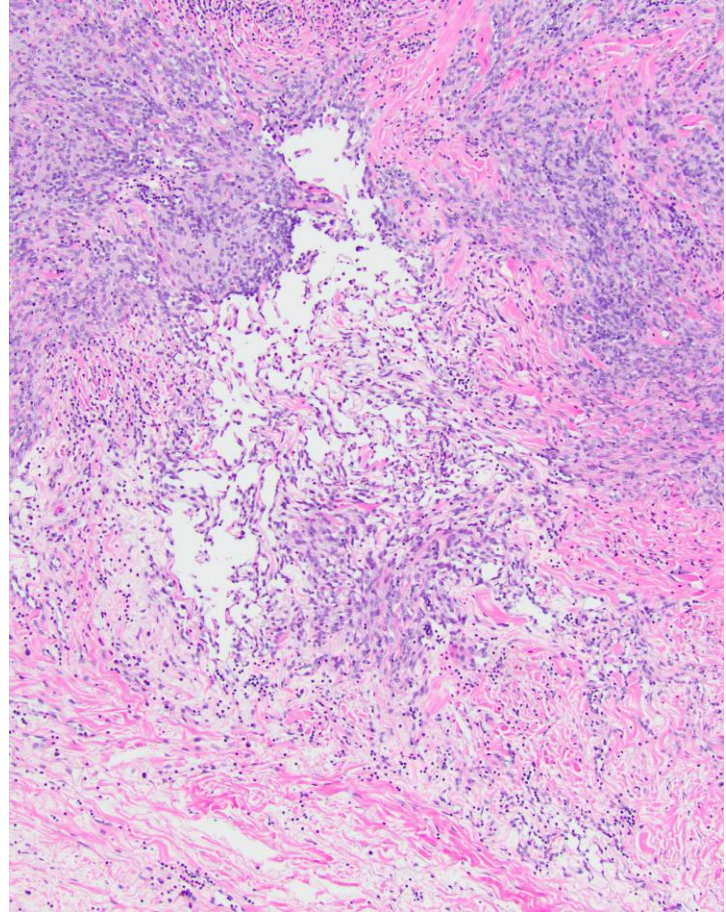
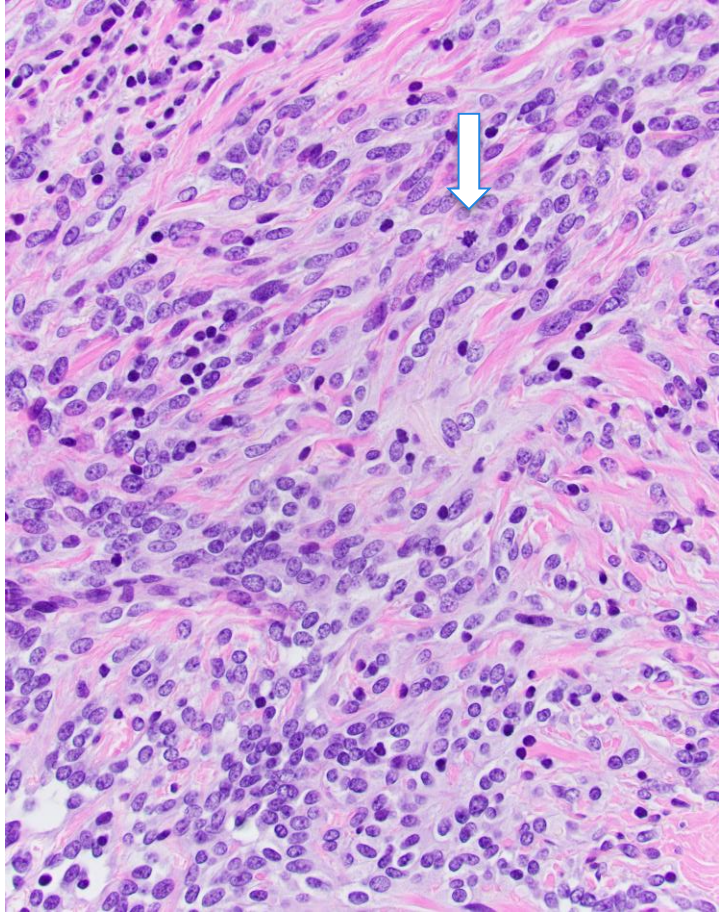
Mentzel T et al. **Postradiation cutaneous angiosarcoma after treatment of breast carcinoma is characterized by MYC amplification in contrast to atypical vascular lesions after radiotherapy and control cases: clinicopathological, immunohistochemical and molecular analysis of 66 cases.** Mod Pathol. 2012;25(1):75-85.

Ginter PS et al. **Diagnostic utility of MYC amplification and anti-MYC immunohistochemistry in atypical vascular lesions, primary or radiation-induced mammary angiosarcomas, and primary angiosarcomas of other sites.** Hum Pathol. 2014 ;45(4):709-16.

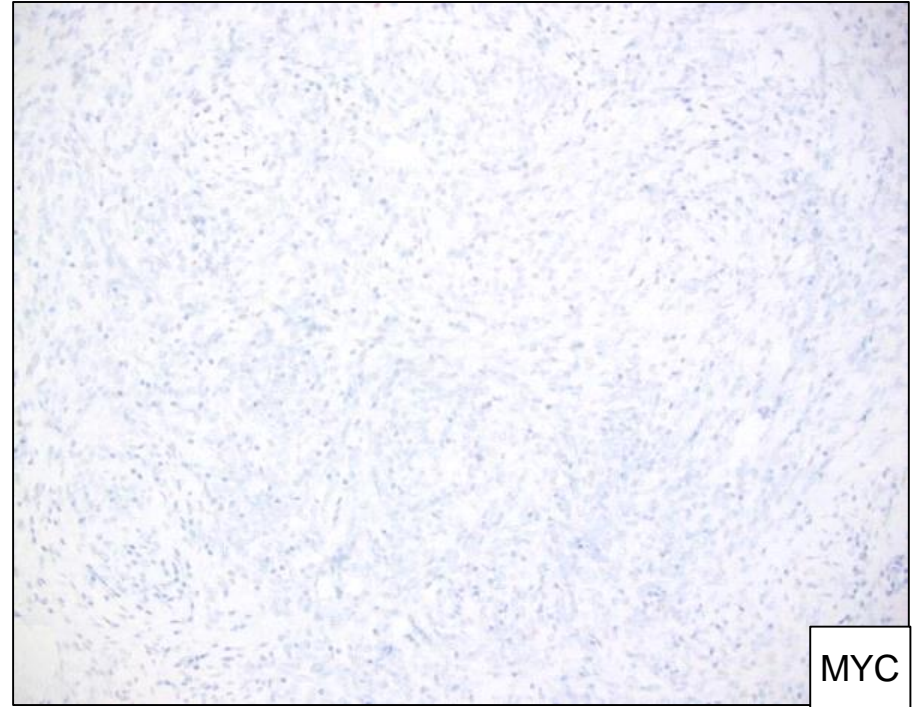
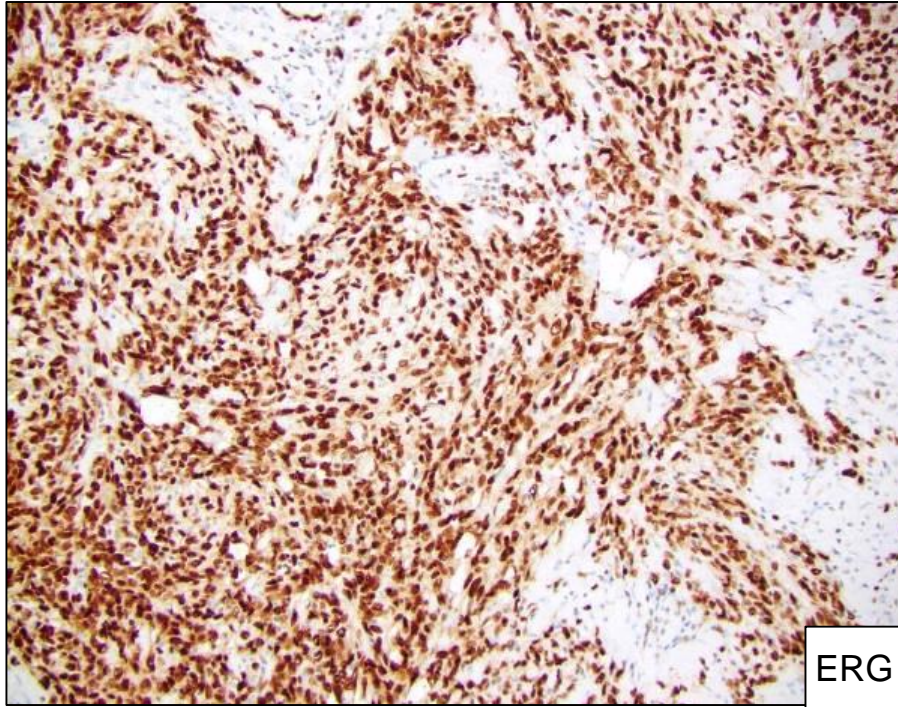


6 months later: Patient underwent left breast excision





Left breast excision



FISH: negative for MYC amplification

DX: Radiation-induced Angiosarcoma, non *MYC*-amplified

Total 81 Radiation-induced Angiosarcomas (1998-2019)

- **73 (90%) *MYC*-amplified**
median patient age 69 years, range 45-96
- **8 (10%) *MYC*-non-amplified**
median patient age 61 years; range 48-76

Latency time: 7.5 years for both groups

AS has poor prognosis: 56% rate of 5-year disease-specific survival
47% rate of 5-year overall survival

Worse prognosis associated with older age, larger tumor size, positive margins and *MYC* amplification.

Vascular lesions - Take home messages

- **Bloody background – r/o a vascular lesion**
Any irregular dissecting and interconnecting vascular spaces?
Any nuclear atypia, hyperchromasia, hobnailing of the nuclei?
- **Some radiation-induced AS are not MYC-amplified**
Close F/U of *MYC*-negative AVL recommended
If AVL size or contour changes → excision
- **Dilated vascular spaces common in MRI-guided CNBs**
No hemorrhage, no nuclear atypia → do not overinterpret
SMA(+) pericytes → benign vascular lesion
- **Obtain prior clinical history**
- **Let the morphologic findings guide your DX, not vice versa**



Thank you for your attention

