



# **INTERESTING CASES FROM THE U OF U RAD-PATH CONFERENCE 2019: DIFFERENTIATING CHALLENGING ENTITIES**

**Eugene Kim, M.D., Radiology**

**Rachel Factor, M.D., Pathology**

# OBJECTIVES

- **At the conclusion of this activity, participants will be able to:**
  - **Discuss radiologic and pathologic features of three interesting breast cases**
  - **Use these features to guide the evaluation of the differential diagnoses**
  - **Identify some important entities to exclude from the differential**
  - **Recall pertinent immunohistochemical and molecular data to help solidify the diagnoses**

***\*We have no disclosures\****

# CASE 1

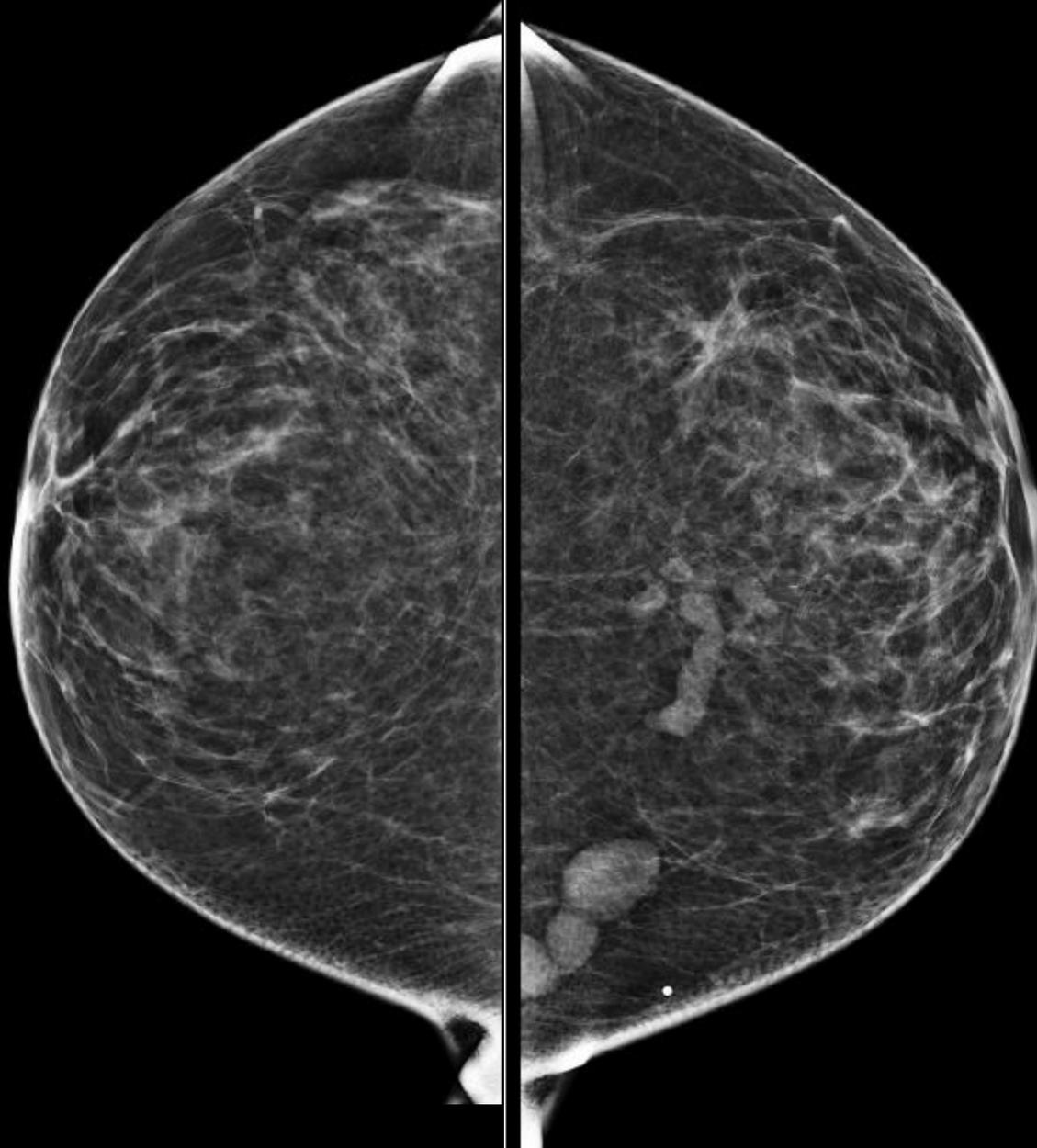
- **Patient is a 36 yo female**
- **Complains of left breast pain x20 years**
- **Palpable mass in the upper inner quadrant**
- **Prior left breast surgery at age 14 (possible lipoma)**
- **Pain to light touch**

# RADIOLOGY

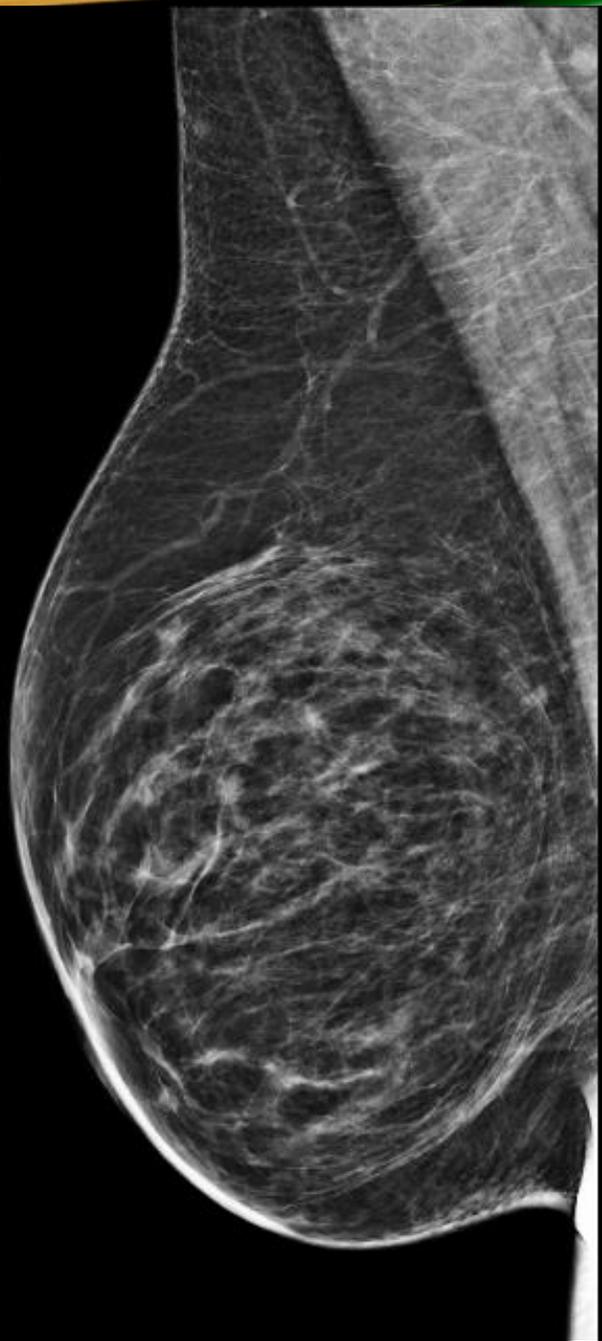
- **Patient was referred for imaging**

[M  
S] RCC

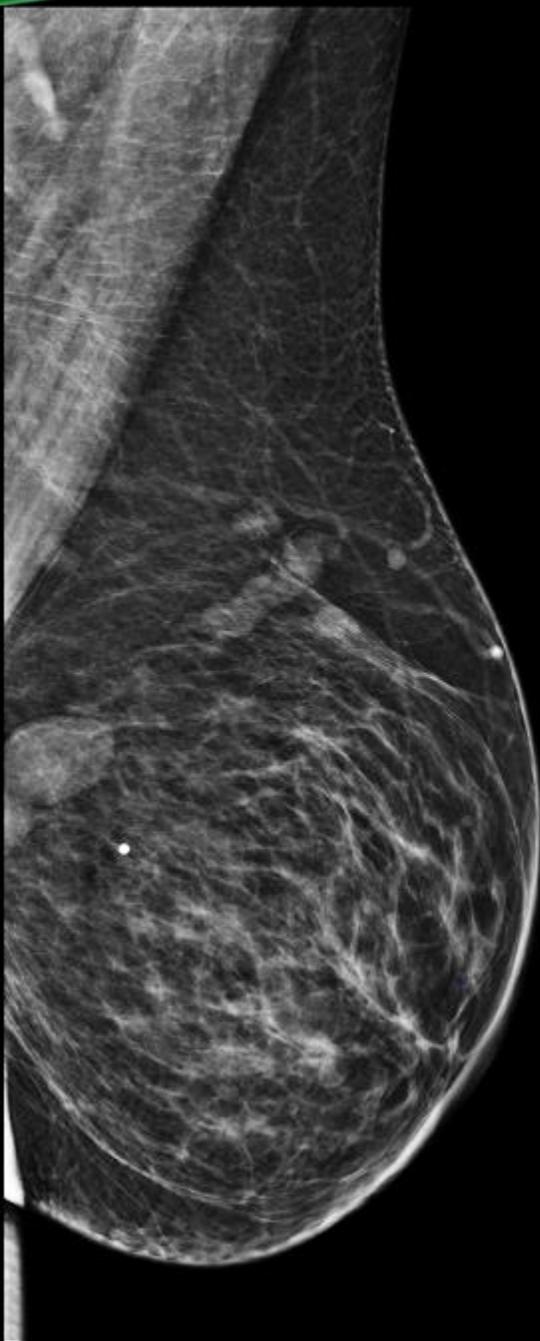
[M  
S] LCC

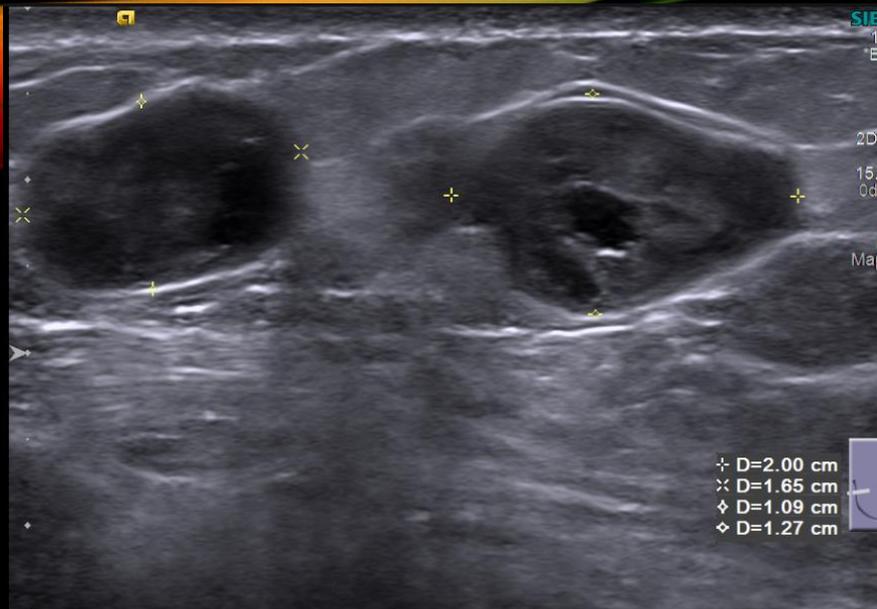


RMLO

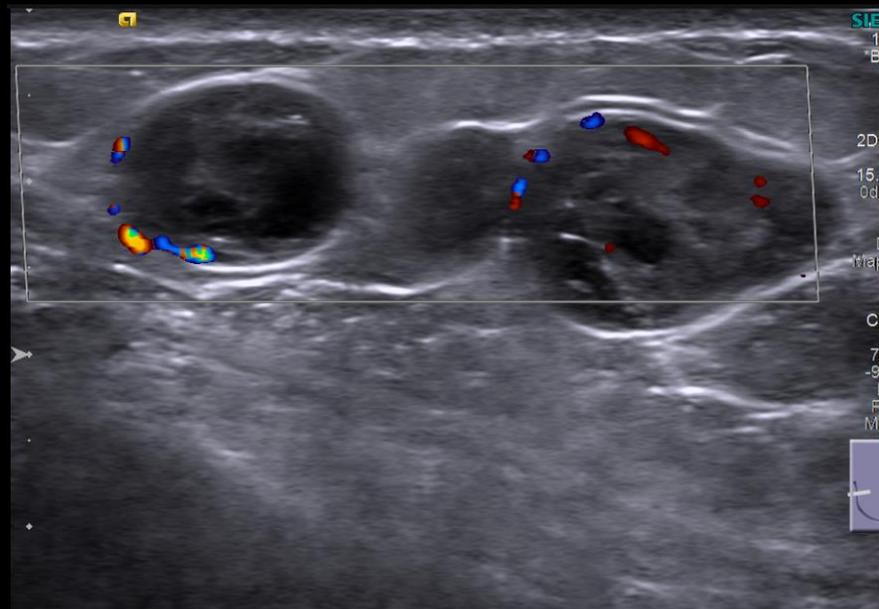


LMLOAX

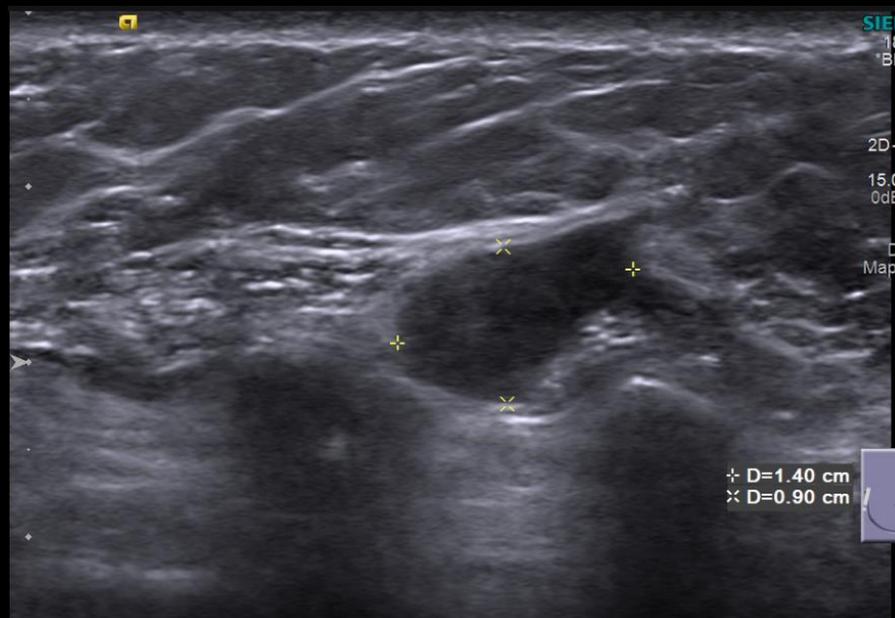




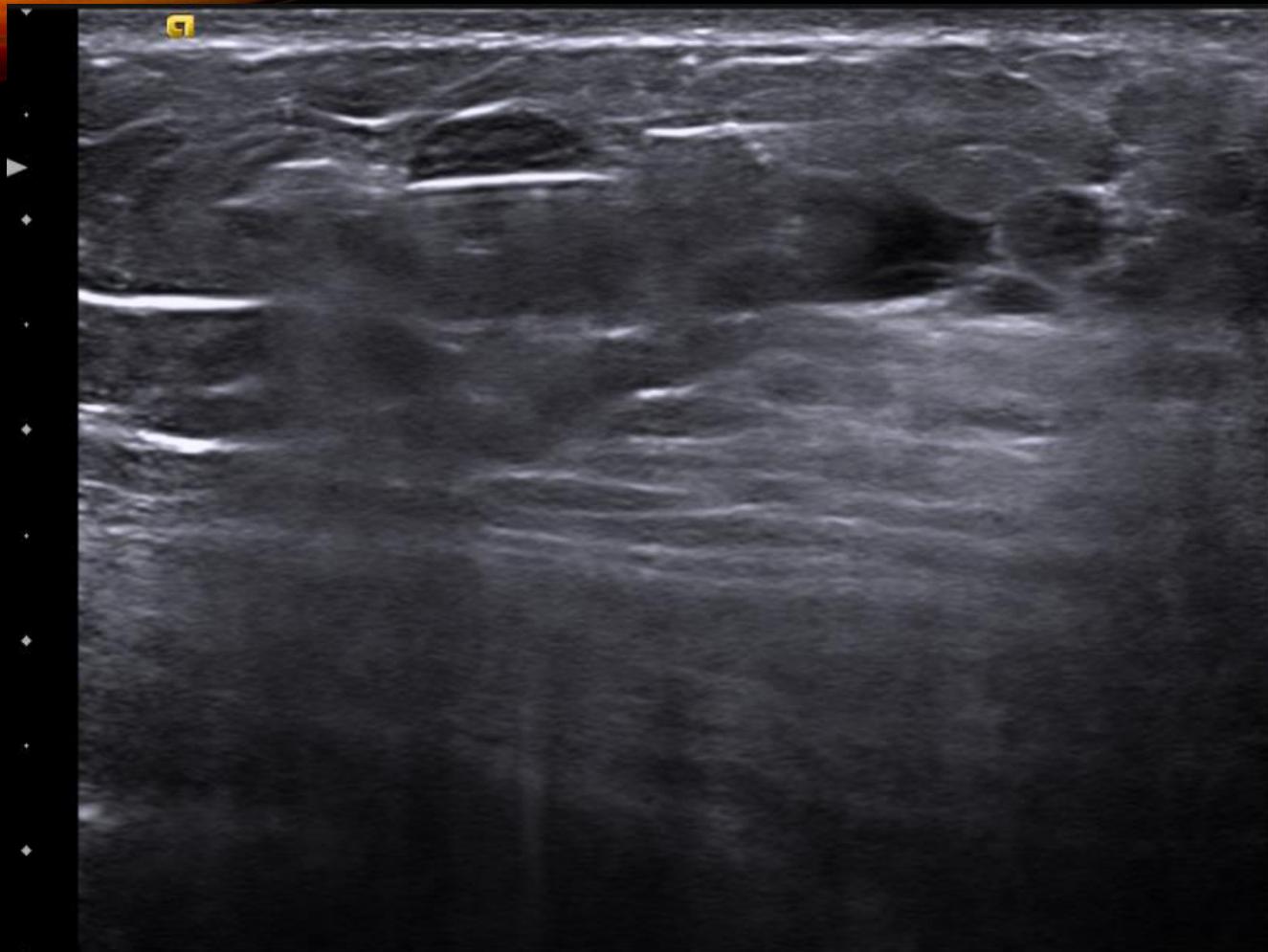
LT BREAST UPPER INNER 11 O'CLOCK 12 CMFN \_



LT BREAST UPPER INNER 11 O'CLOCK 12 CMFN \_



LT BREAST UPPER INNER 11 O'CLOCK 12 CMFN \_



LT BREAST BX 2\_  
11 O'CLOCK 12 CMFN

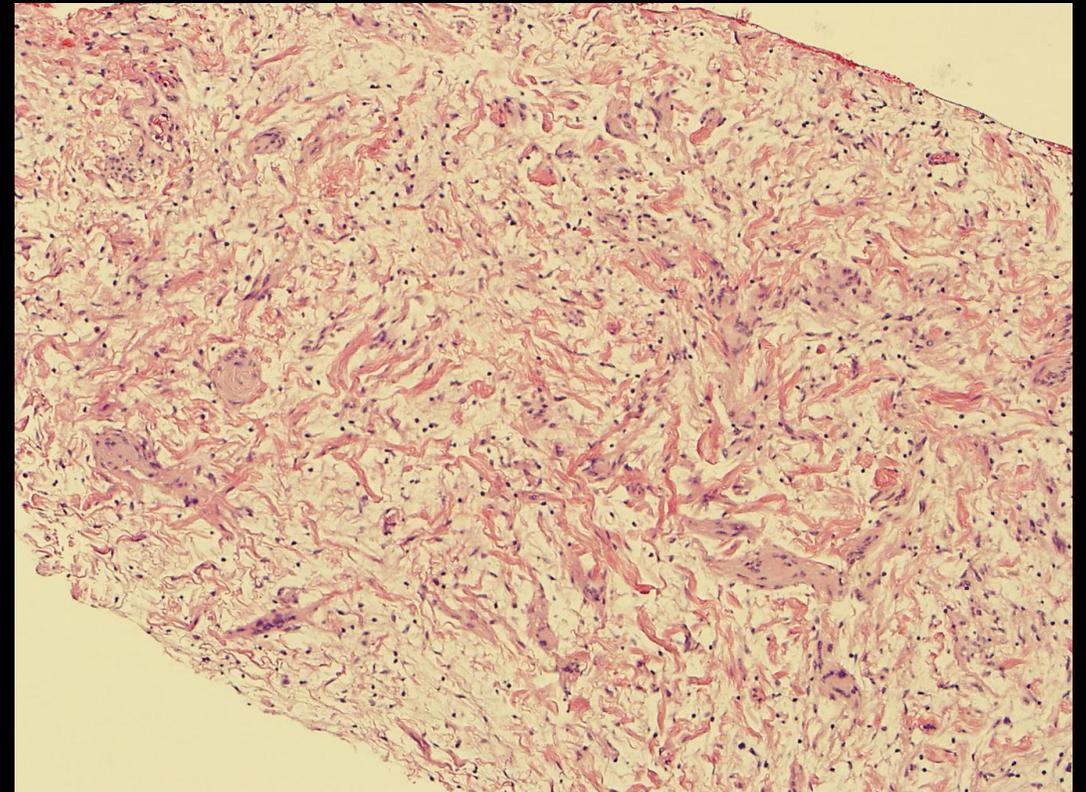
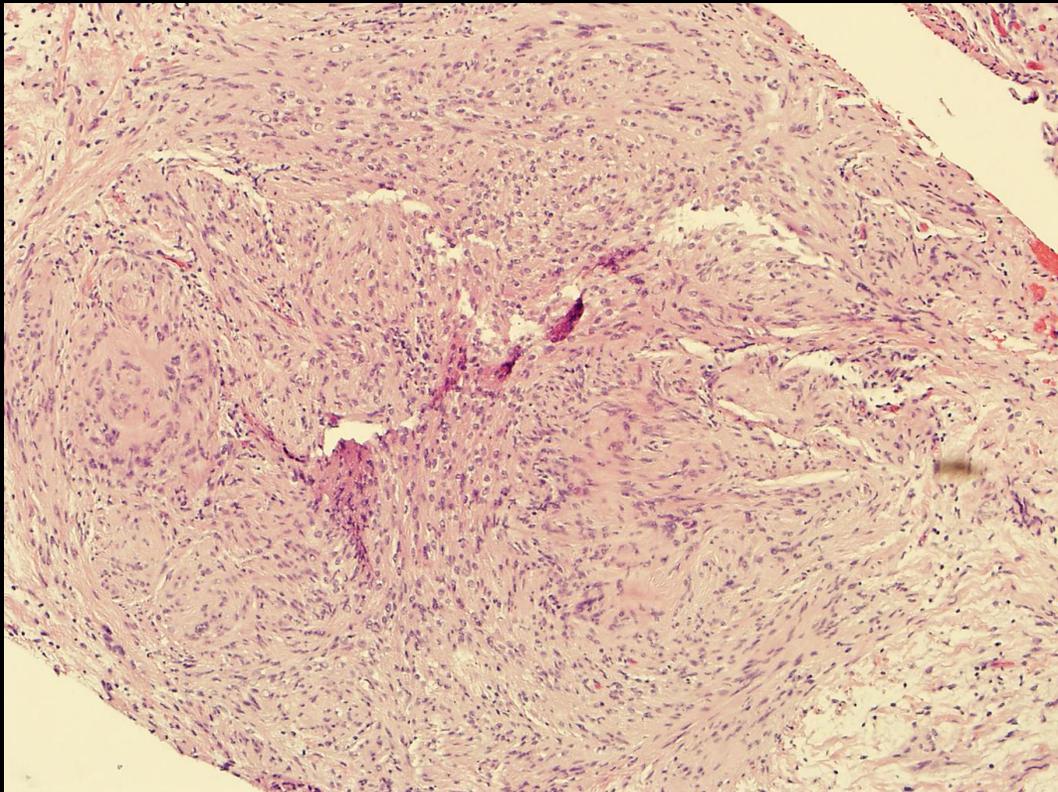
4.5cm

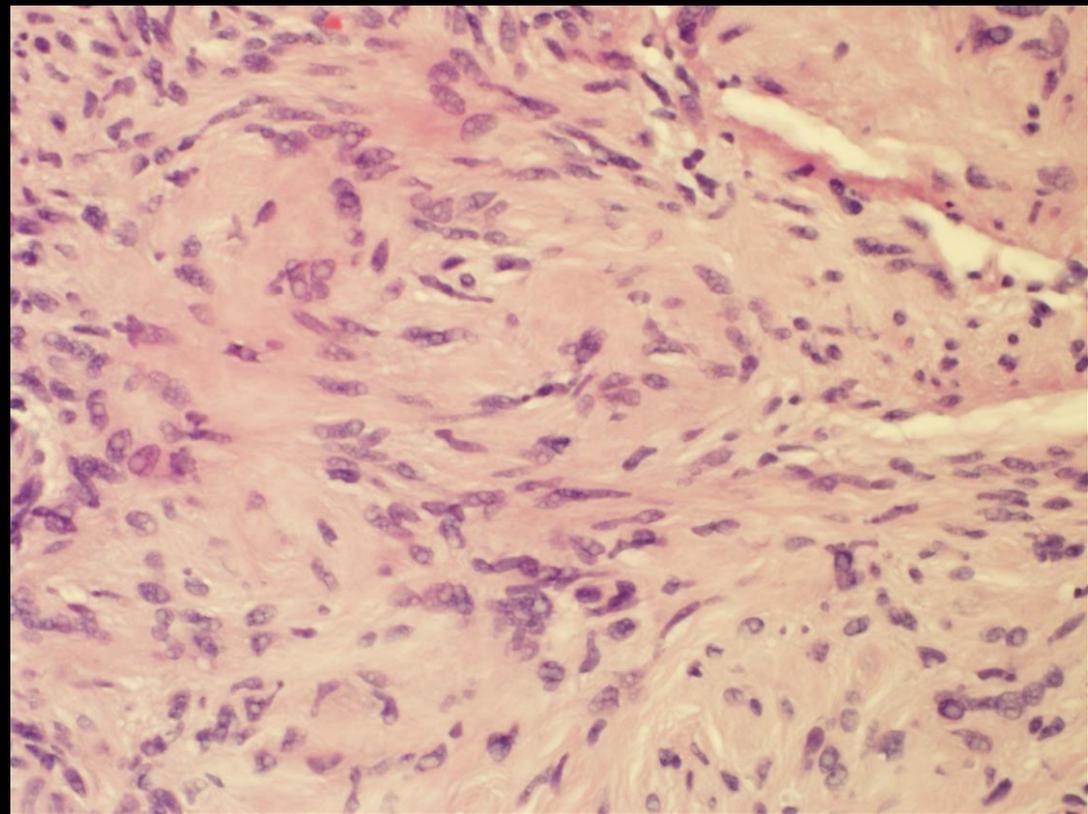
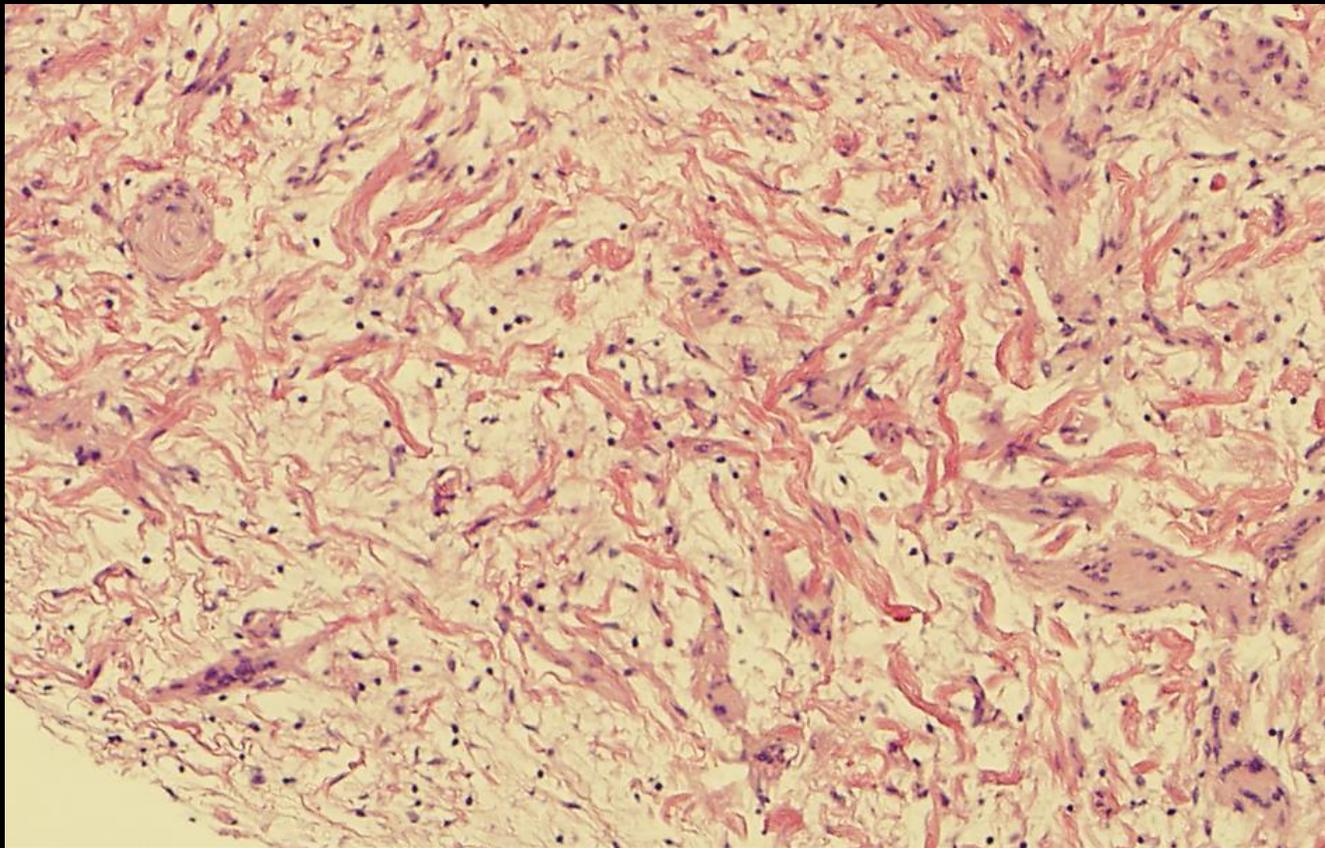
# BIOPSY PERFORMED

- **Radiology differential:**
  - **Fibroadenomas**
  - **Complicated / complex cysts**
  - **Infection**
  - **Vascular lesion**
  - **Malignancy**
- **US guided core needle biopsies of mass at 11:00 axis**
  - **14 gauge core biopsies**

# PATHOLOGY

- **Left breast biopsy at 11 o'clock:**





# DIFFERENTIAL: SPINDLE CELL LESIONS OF THE BREAST

- **Metaplastic carcinoma (spindle cell)**
- **Low grade myofibroblastic sarcoma**
- **Benign phyllodes tumor**
- **Desmoid-type fibromatosis**
- **Myofibroblastoma**
- **Schwannoma**

# METAPLASTIC CARCINOMA

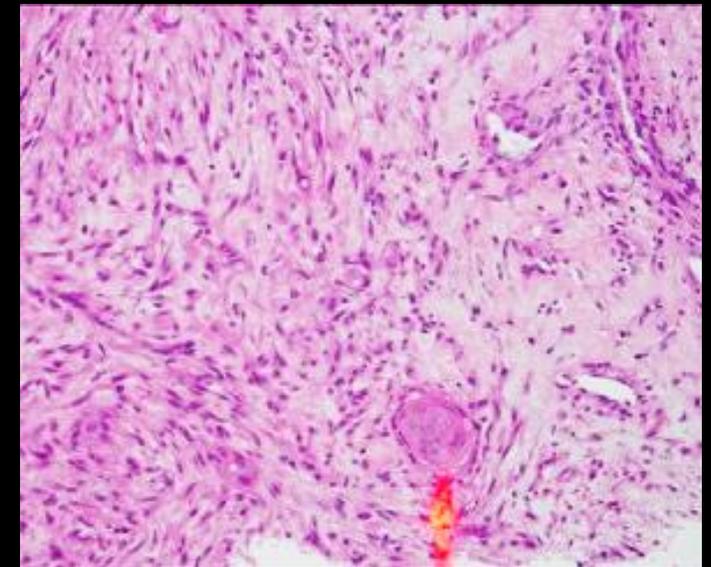
- **Includes many morphologic entities**
- **All have carcinomatous and mesenchymal differentiation**
- **Similar clinical presentations to invasive mammary carcinomas**
- **May be well-circumscribed or infiltrative**
- **Rarely show axillary lymph node metastases**

# SPINDLE CELL CARCINOMA

- **Encompasses “myoepithelial carcinoma”**
- **Variant: low grade fibromatosis-like metaplastic carcinoma**
- **May be bland, and mimic other entities**
- **Important to exclude**

# SPINDLE CELL CARCINOMA: HISTOLOGY

- **Atypical spindle cells arranged in long or short fascicles, sometimes storiform, fasciitis-like or fibromatosis-like**
- **Mitoses are present, but variable**
- **Stromal inflammatory cells usually present**
- **Helps to have a background of DCIS**



# HELPFUL IMMUNOHISTOCHEMISTRY

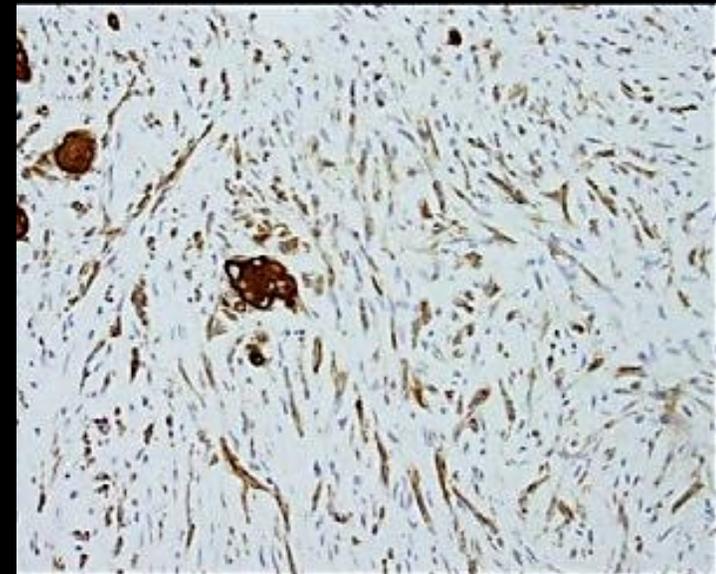
- **Positive:**

- **High molecular weight keratin**
  - **Broad spectrum: AE1/AE3, MNF116**
  - **Basal type: 34betaE12, CK5/6**
- **p63**
- **SMA**

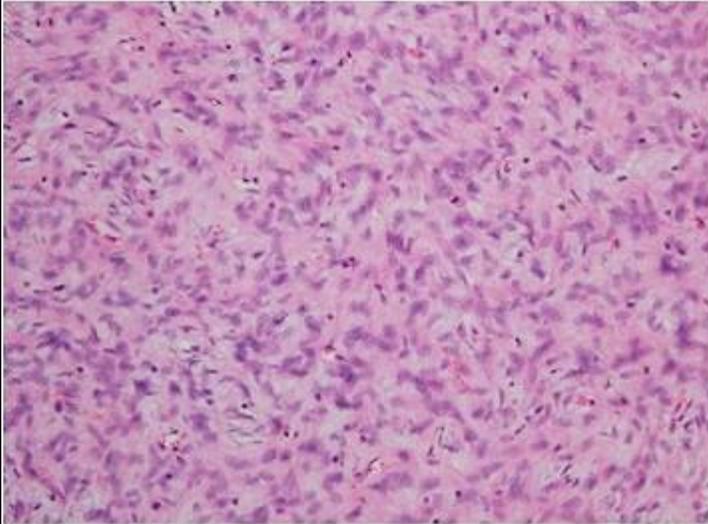
- **Negative:**

- **Low molecular weight keratin (CAM 5.2)**
- **Triple negative (ER/PR/HER2)**

AE1/AE3



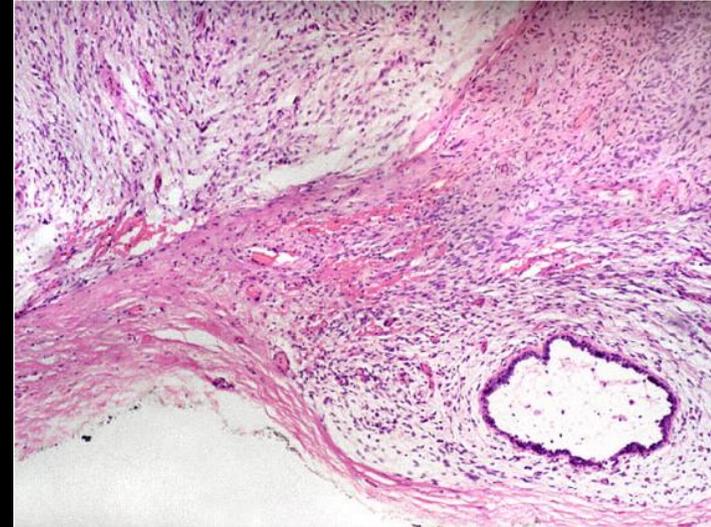
## Low grade myofibroblastic sarcoma



Diag Pathol. 2016; 11:33

**Usually in head/neck**  
**Fascicular, spindle cells**  
**Stromal collagen**  
**Diffusely infiltrative**  
**Positive: SMA, Desmin**  
**Neg: Keratin, CD34, S-100, B-cat**

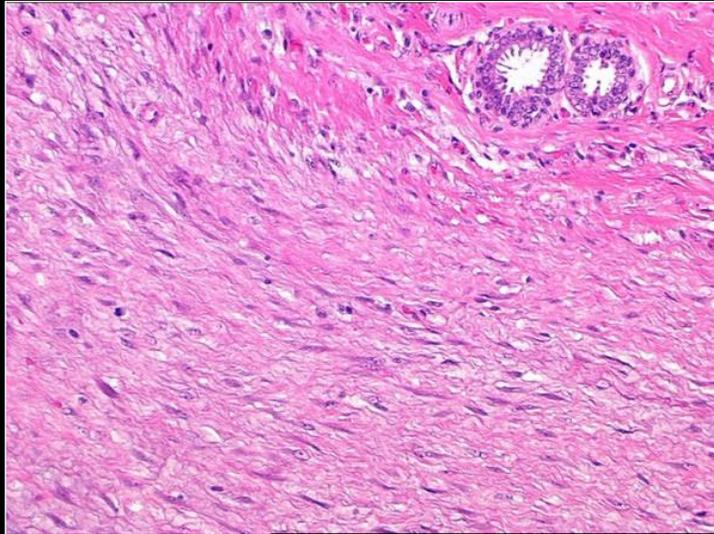
## Benign Phyllodes Tumor



Digital Atlas of Breast Pathology, M Singh

**Expansile, fibroepithelial lesion**  
**Pushing border**  
**Hypo/hypercellular areas**  
**Bland spindle cells**  
**Positive: CD34**  
**Negative: Keratin, p63**

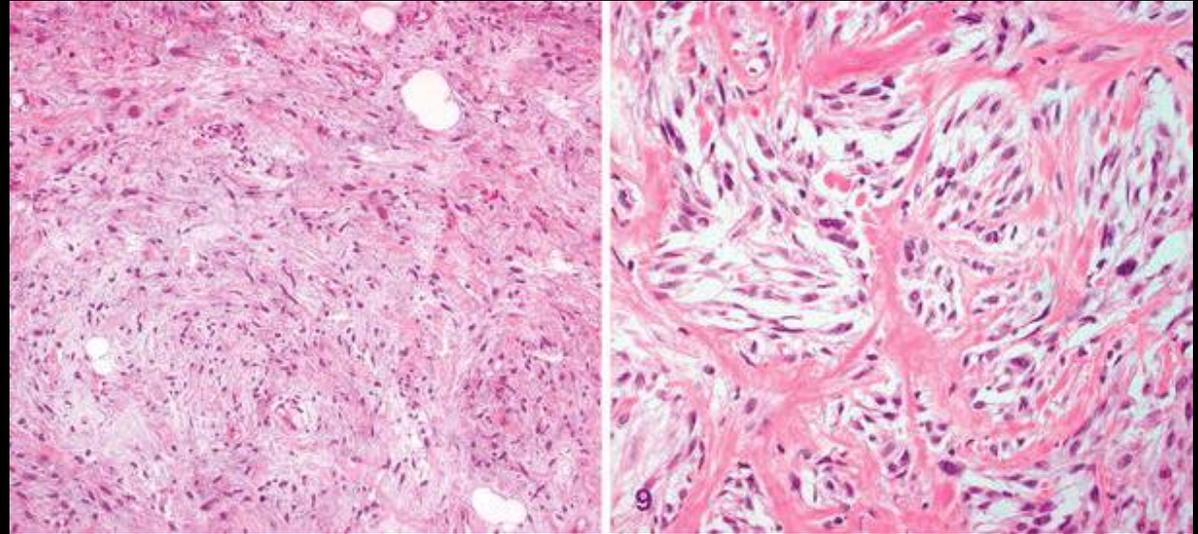
## Fibromatosis



World J Surg Oncol. 2006;4:32

**Infiltrative into surrounding tissue**  
**Entrap benign epithelium**  
**Often hypocellular**  
**Bland spindle cells**  
**Positive: B-catenin (nuclear), SMA**  
**Negative: Keratin, ER, CD34, p63**

## Myofibroblastoma

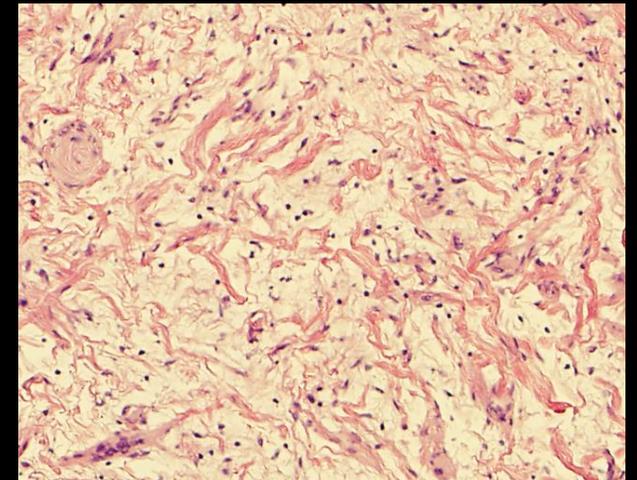
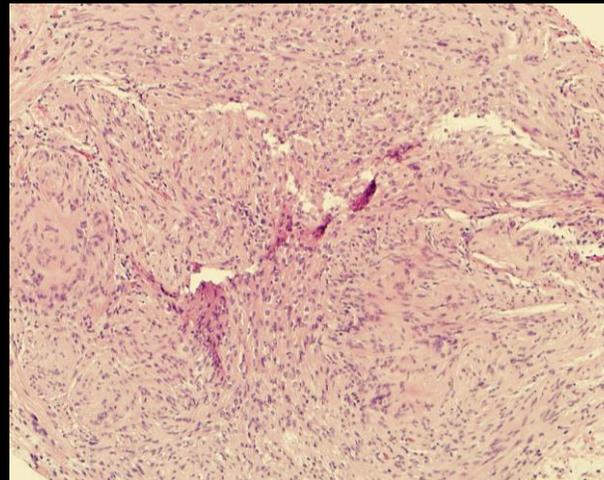


Archives of Pathology

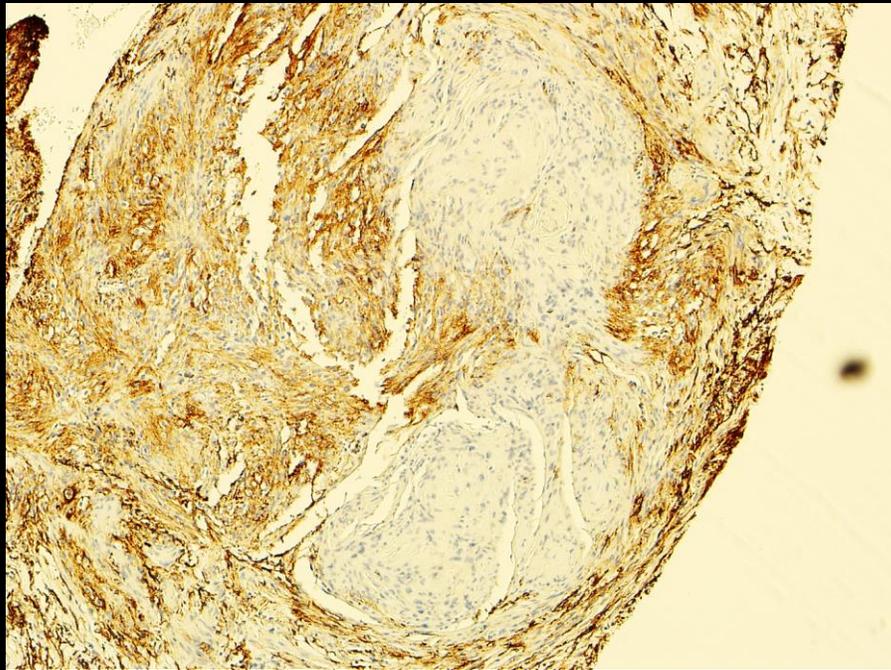
**Well circumscribed, fibroadenoma-like**  
**Bland spindle cells grow in short fascicles**  
**Rare mitoses**  
**Stroma with hyalinized collagen and mast cells**  
**Positive: ER, PR, CD34, Desmin**  
**Negative: Keratin, S-100**

# OUR CASE: REVISITED

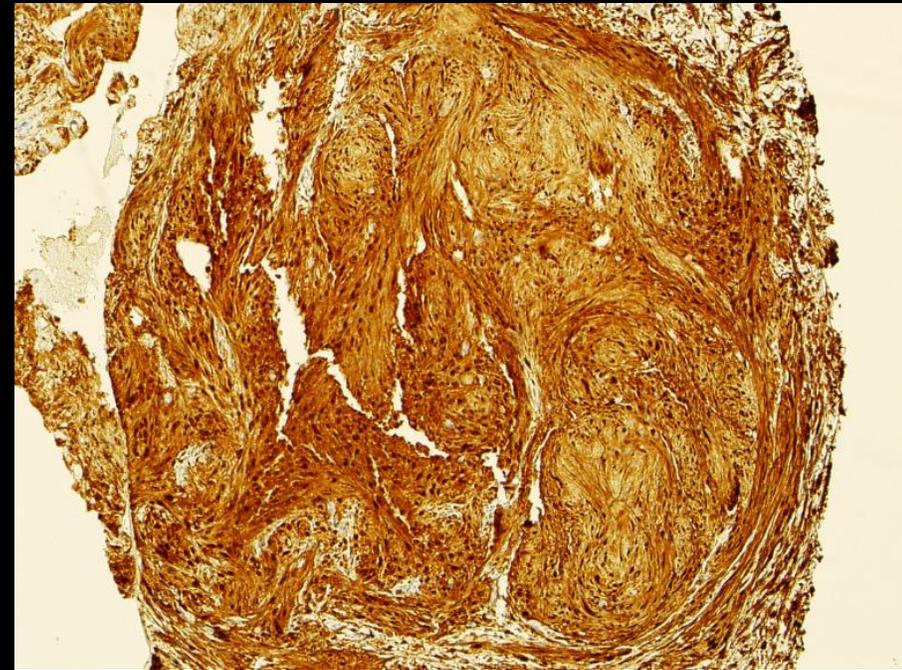
- **Spindle cell lesion**
- **Absence of breast elements**
- **Fascicular with hypercellular and hypocellular areas**
- **Bland cytology: intranuclear vacuoles, no mitoses**
- **No necrosis**
- **Nerves present**



# OUR CASE: IMMUNOHISTOCHEMISTRY



**Negative: keratin, CD34**



**Positive (strong, diffuse): S-100**

# DIAGNOSIS

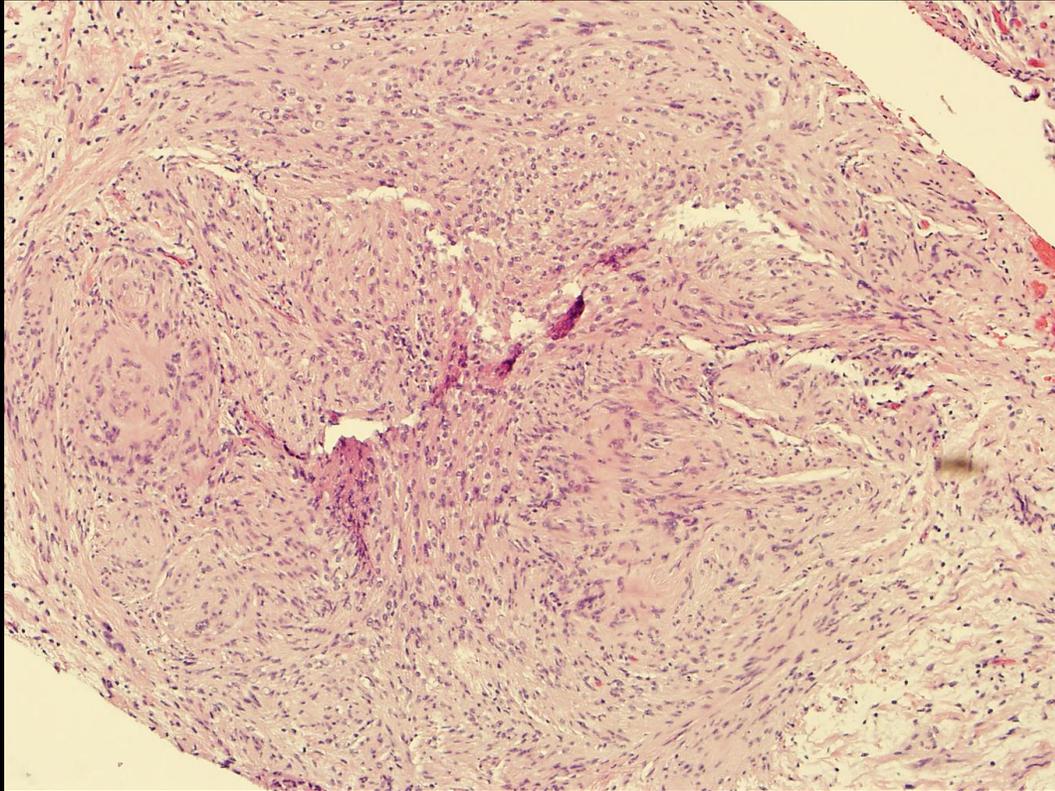
- **Intramammary schwannoma**



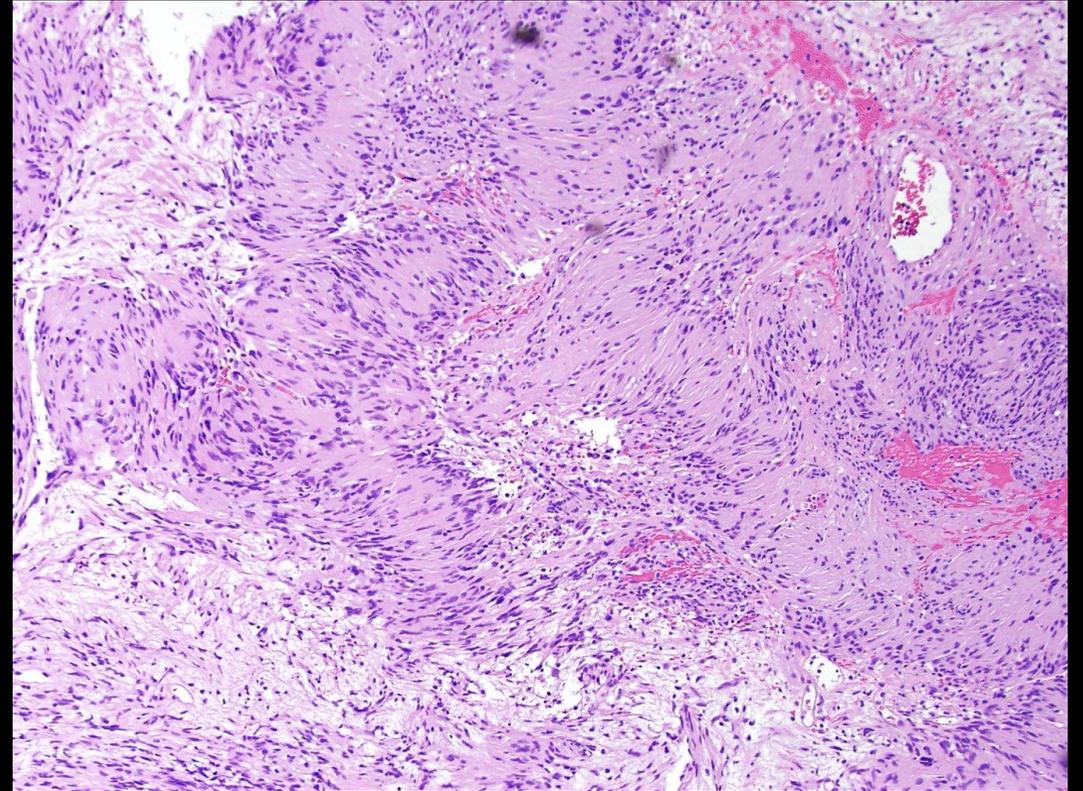
# SCHWANNOMA

- **In breast: only about 30 cases in the literature**
- **Benign, slow growing tumors of the peripheral nerve sheath**
- **Common in upper limbs, head and neck**
- **Also in the posterior mediastinum, GI tract, bone, liver**

**Left breast mass**



**Right arm mass**



- \*Bland spindle cells, palisading hypercellular (Antoni A) and hypocellular (Antoni B) areas**
- \*Associated with a nerve**
- \*Strongly positive for S-100**

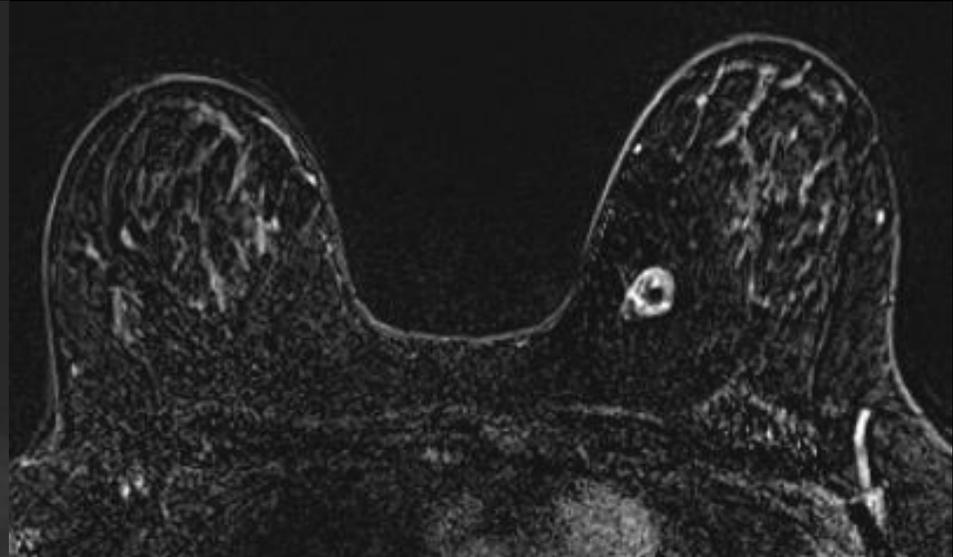
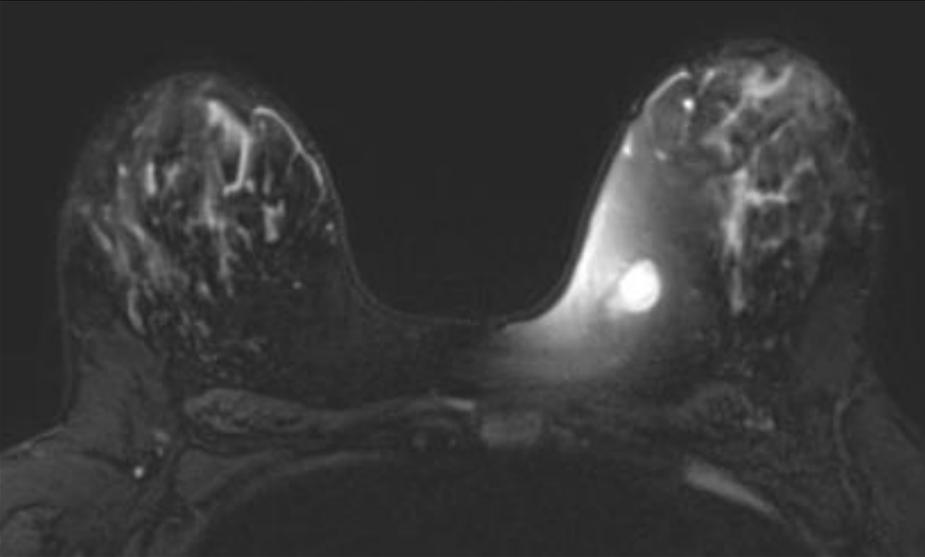
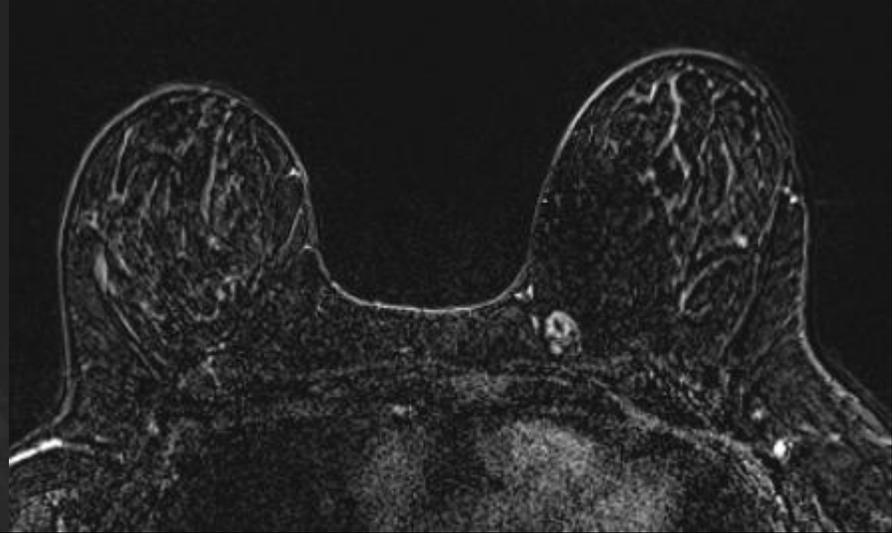
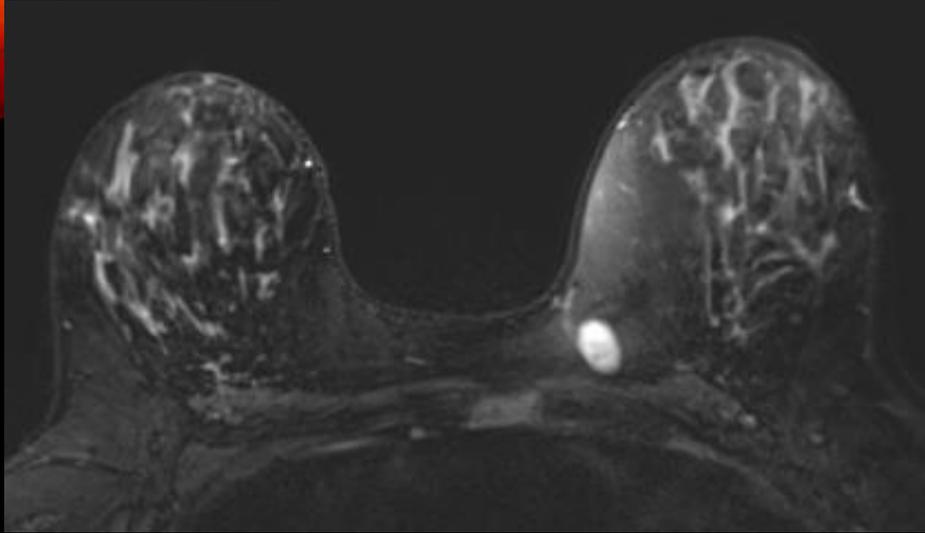
# CLINICAL

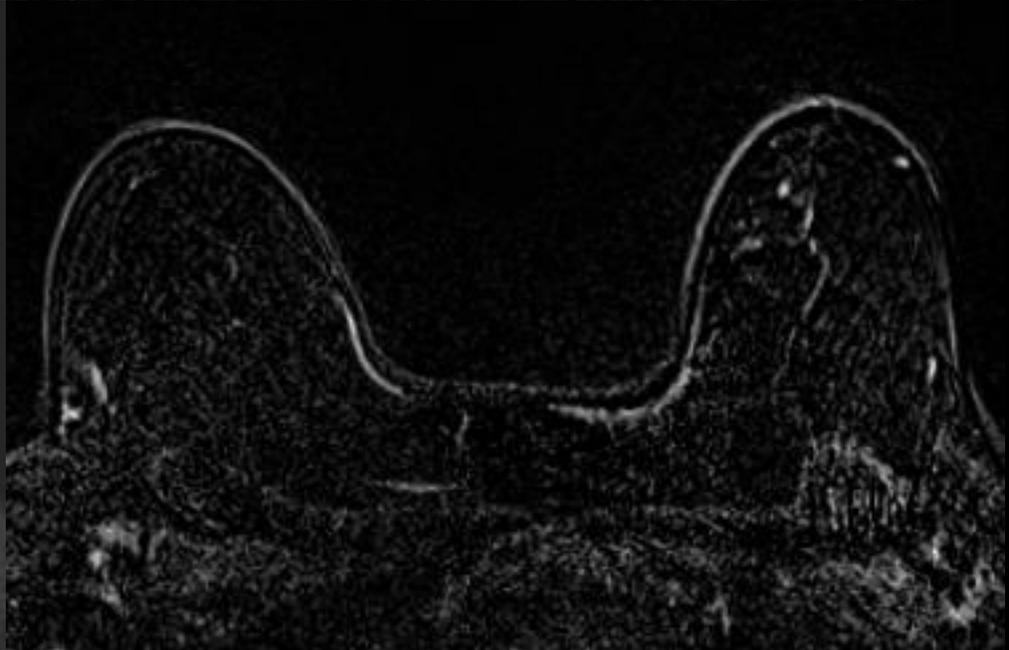
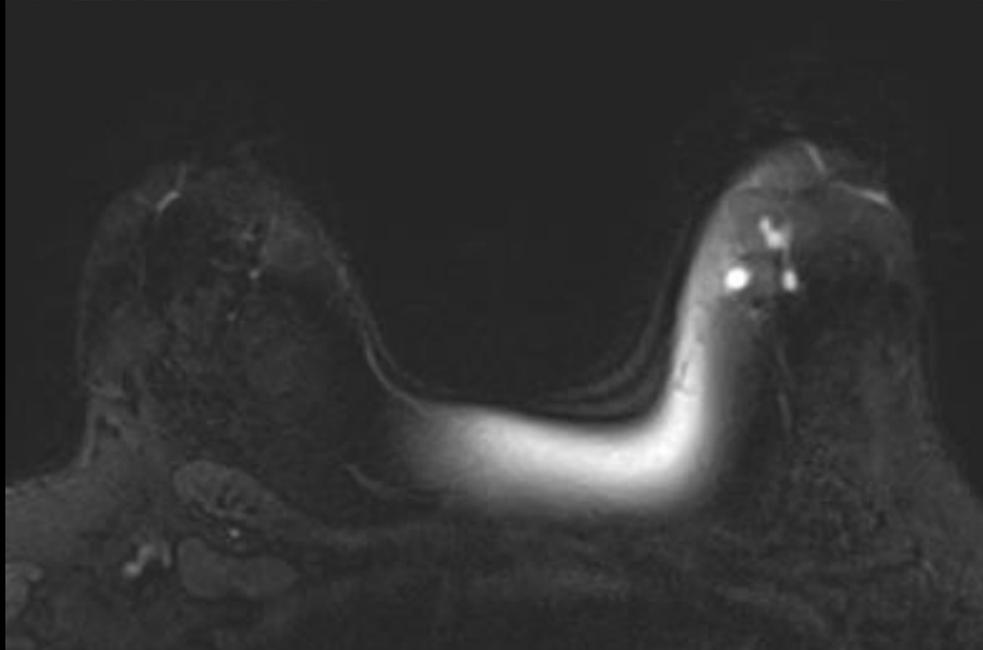
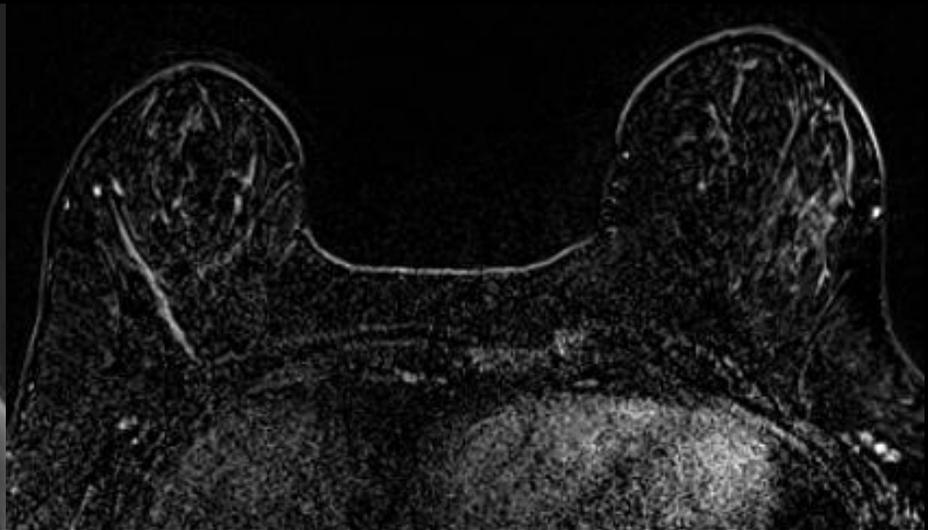
- **Not usually painful, but described for large tumors**
- **90% sporadic; <5% are associated with Neurofibromatosis Type II**
- **Malignant transformation is rare**
- **~25% of malignant schwannomas are associated with NFII**
- **Treatment: excision**

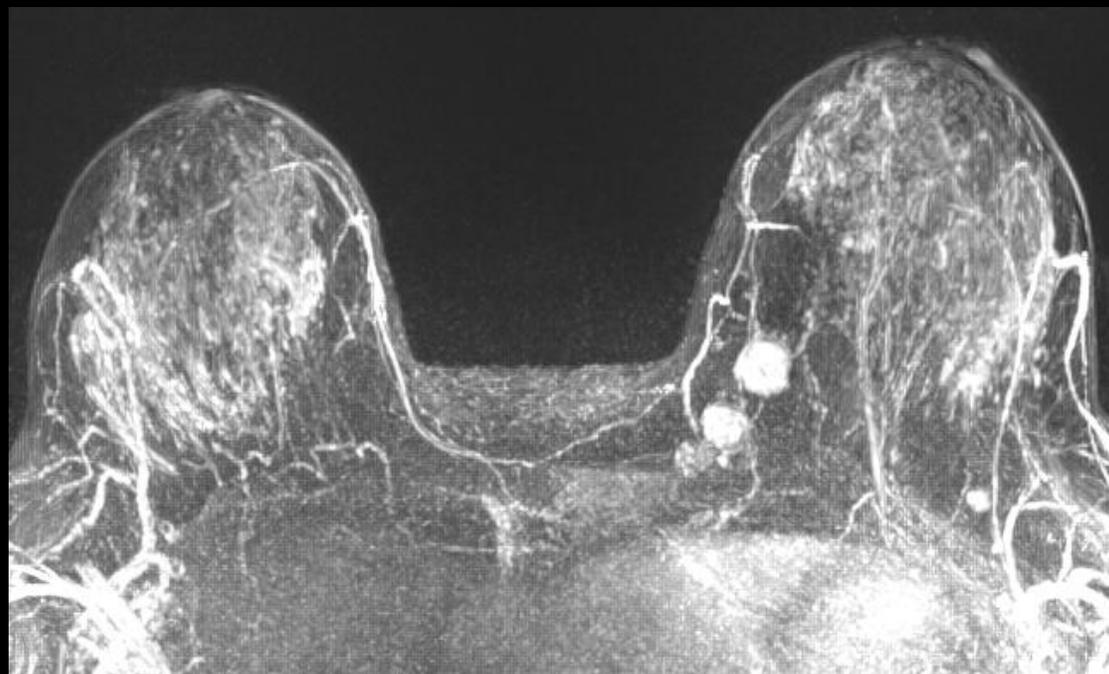


# OUR PATIENT

- **MRI performed to evaluate extent**





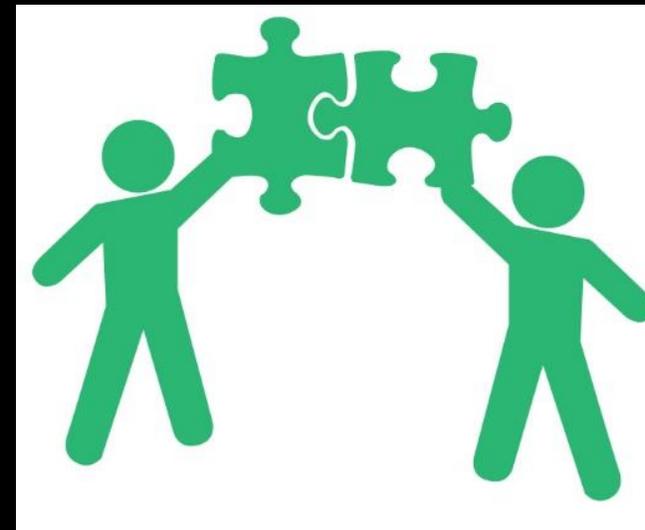


# PATIENT MANAGEMENT

- **Referral to neurosurgery and genetic counseling**
- **Pregnant: surgery postponed**

# RAD-PATH DISCUSSION

- **Radiologic correlation- does the diagnosis make sense?**
- **When we agree with each other, we feel more comfortable making the diagnosis**



## CASE 2

- **Patient is a 38 year old female**
- **Bilateral silicone implants**
- **Breast lump noted 2 years ago, mammo normal**
- **Now tender, palpable lump, growing x1 month**
- **Feels firm. Under the nipple to lateral breast**
- **No waxing/waning**

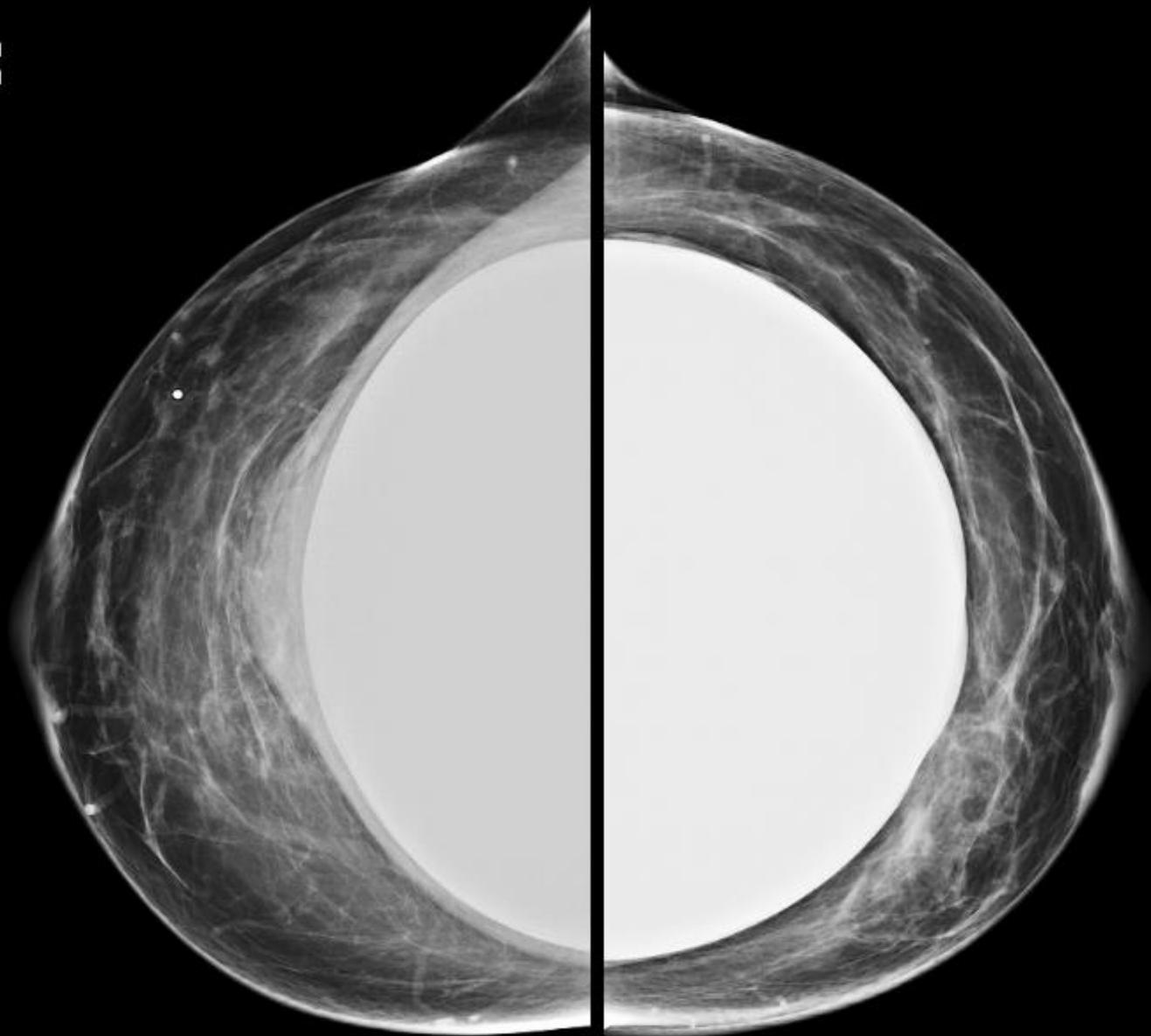


# RADIOLOGY

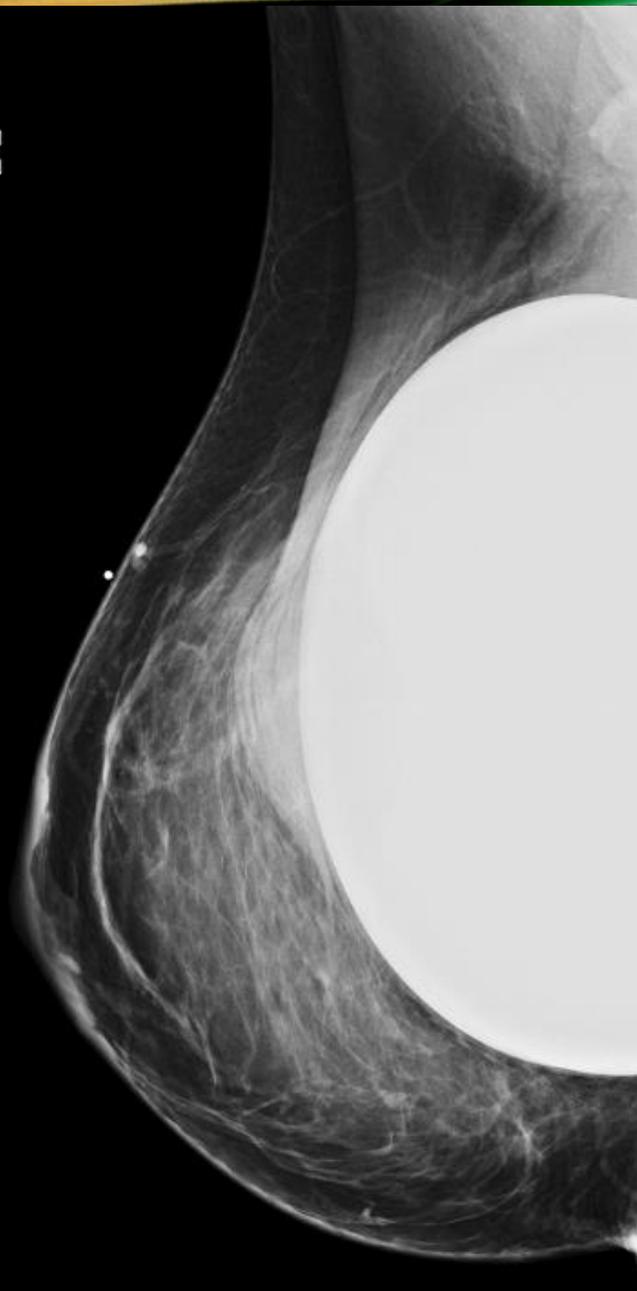
- **Patient was referred for imaging and biopsy**

RCC

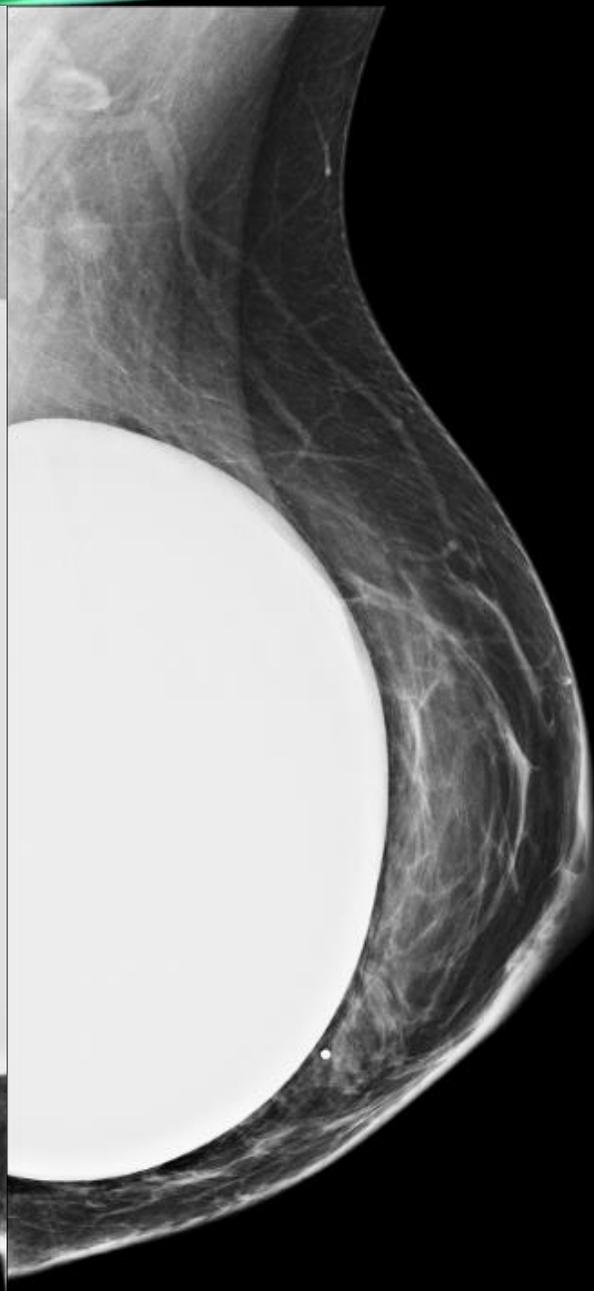
LCC

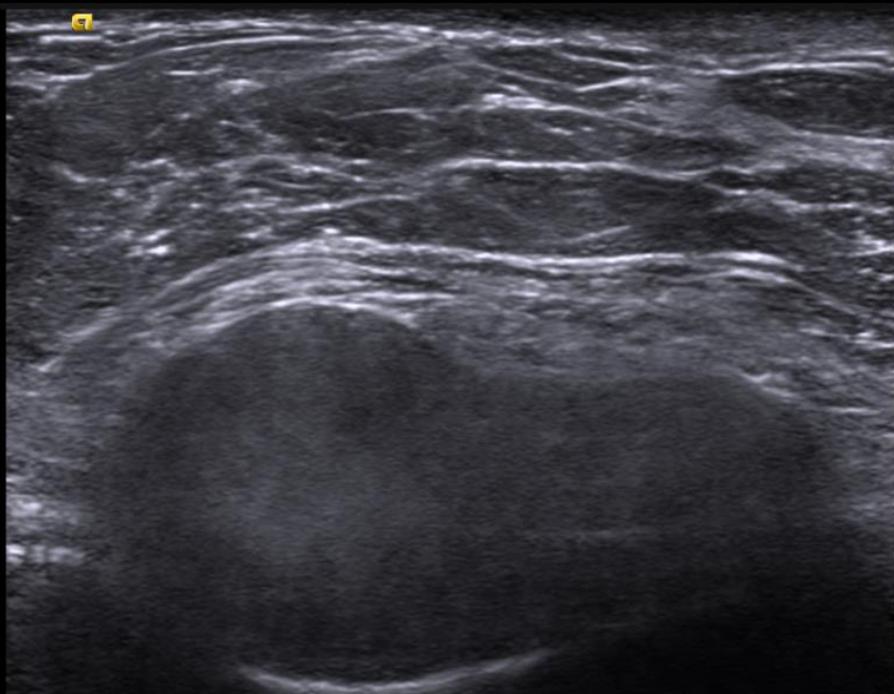


RMLO

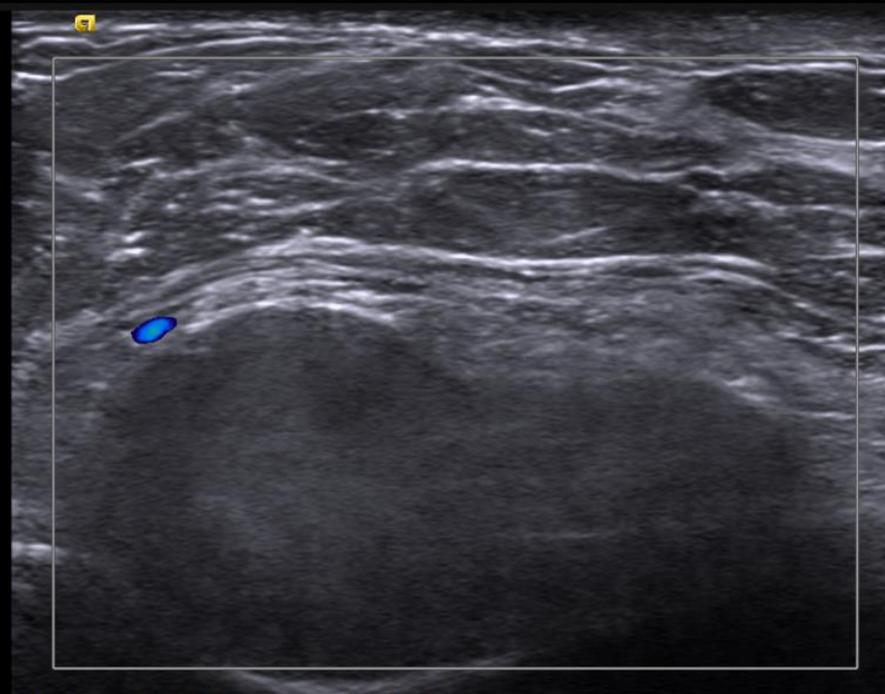


LMLO

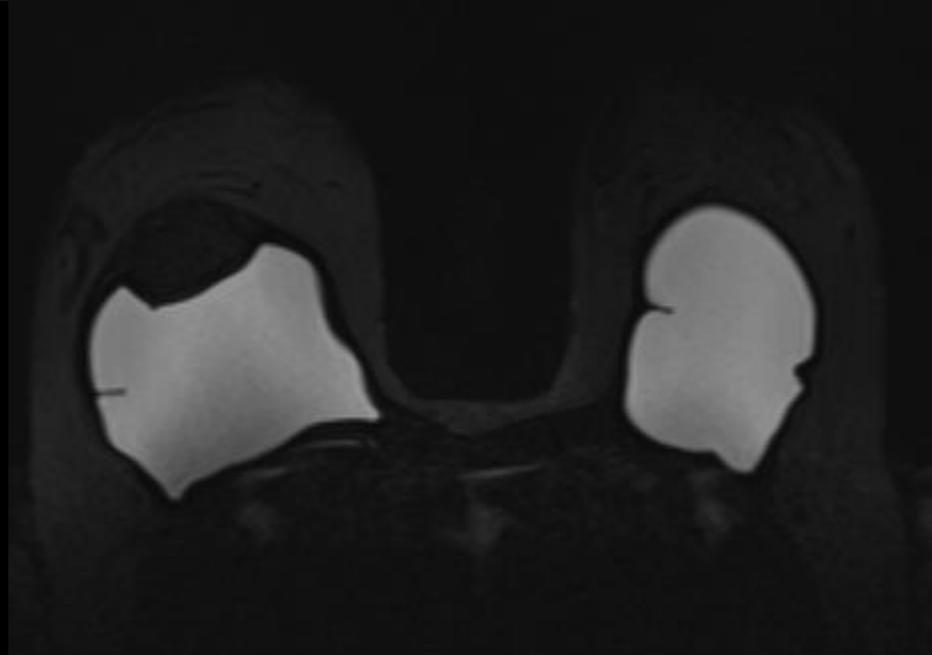
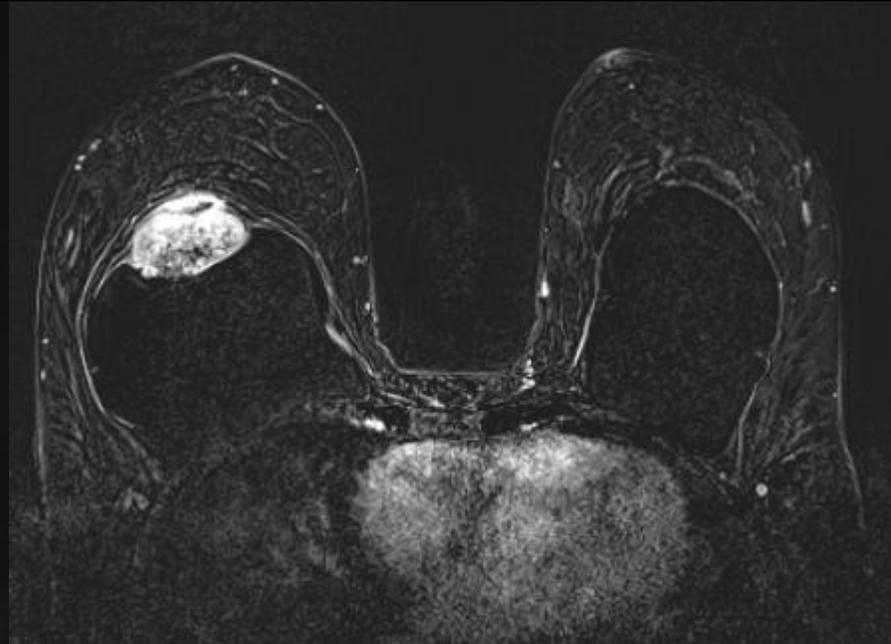
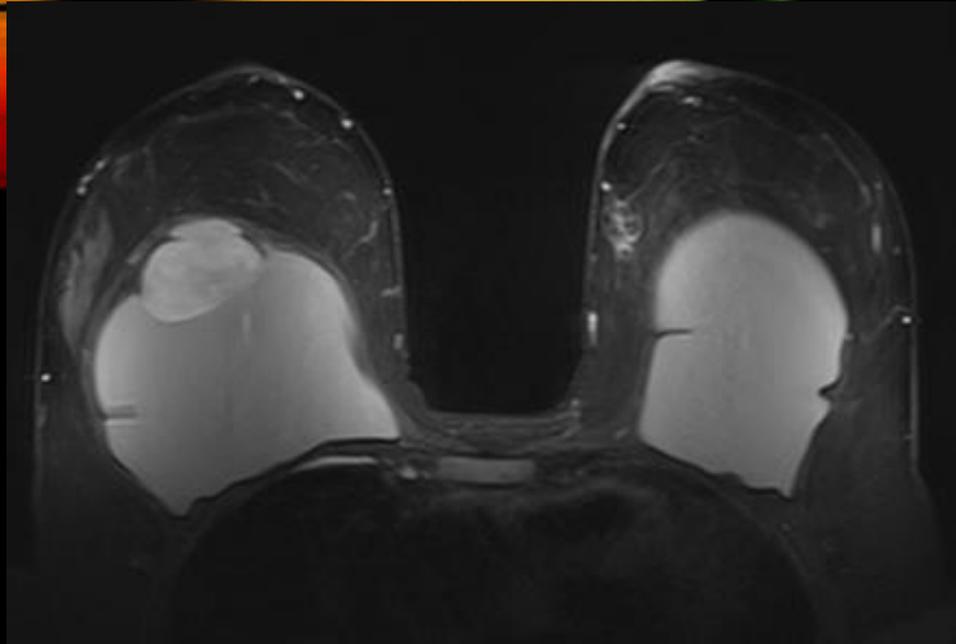


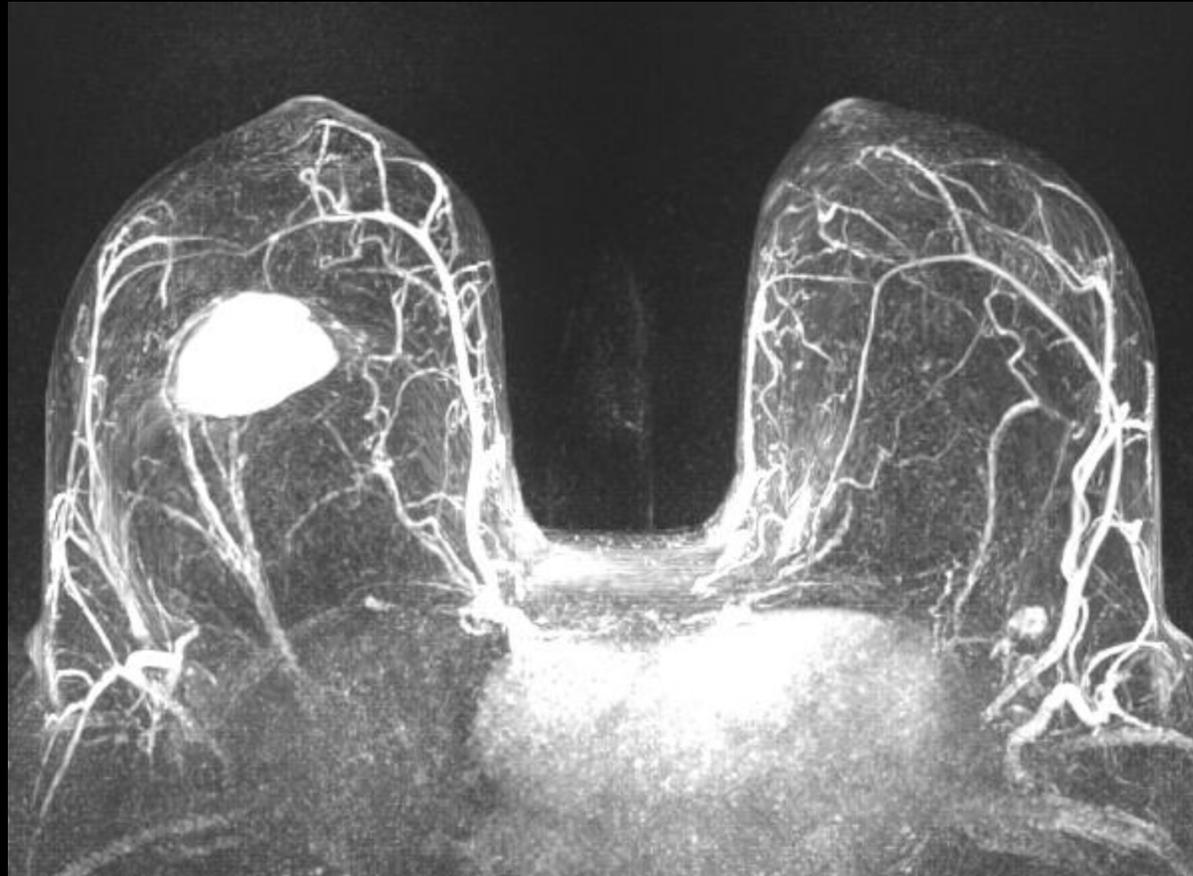


RT BREAST 11 O'CLOCK 2 CMFN TRANS PALP \_



RT BREAST 11 O'CLOCK 2 CMFN TRANS \_

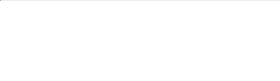
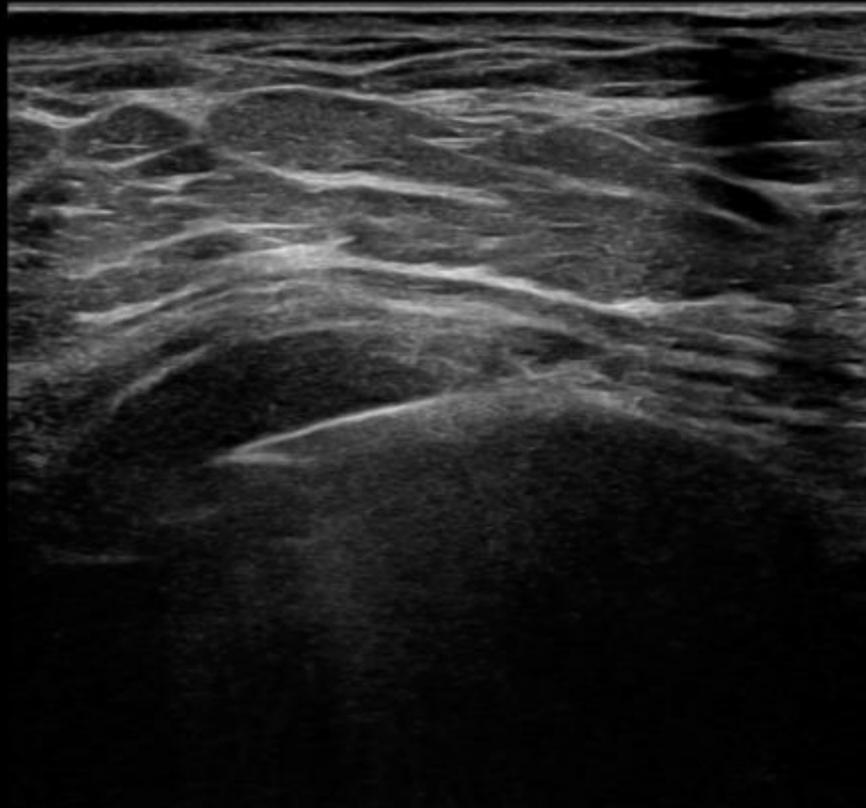




# BIOPSY PERFORMED

- **US guided biopsy taken of 11:00 axis mass**
  - **14 gauge core biopsies**
- **Radiology differential:**
  - **Abscess**
  - **Hematoma**
  - **Seroma**
  - **Implant rupture**
  - **Implant associated anaplastic lymphoma**
  - **Sarcoma**

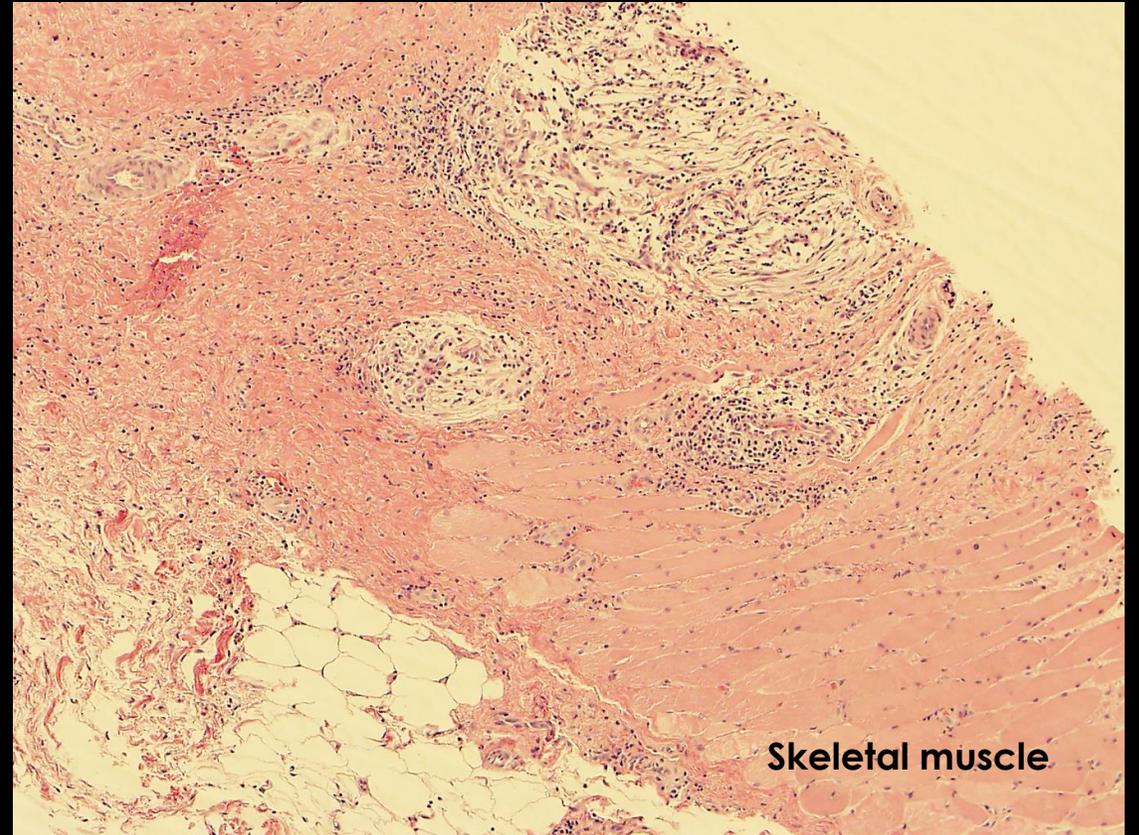
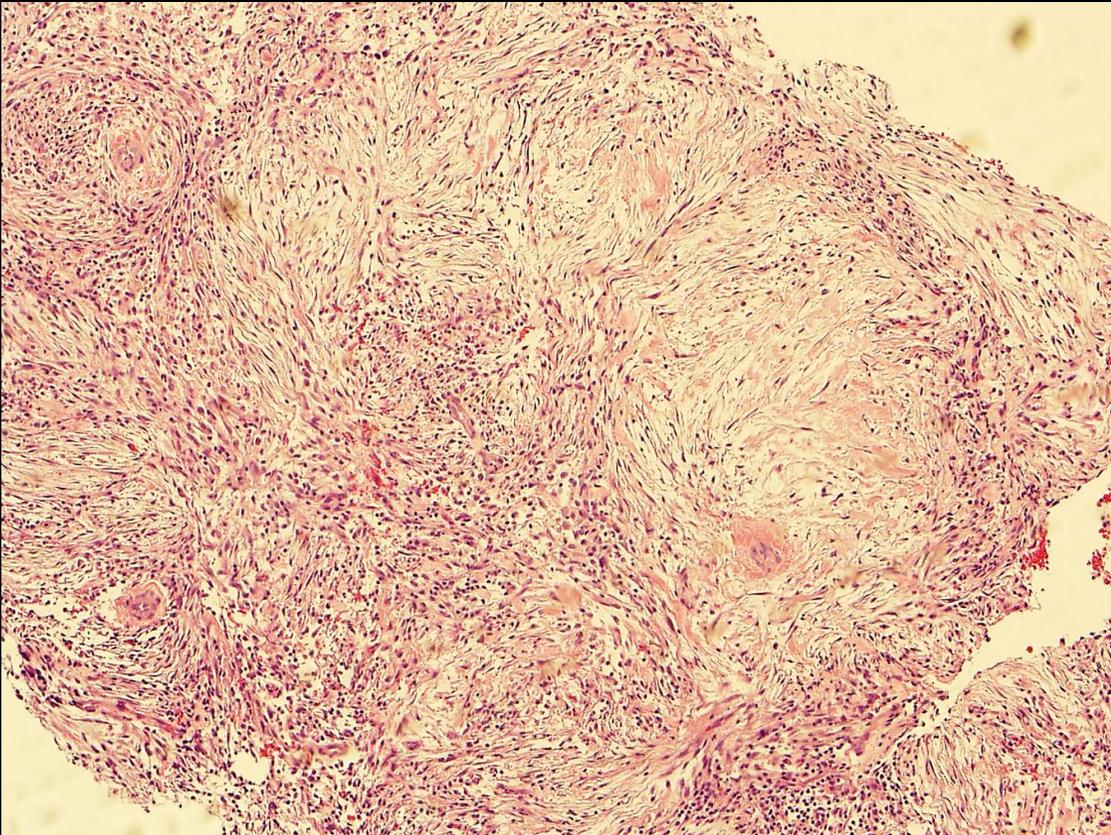
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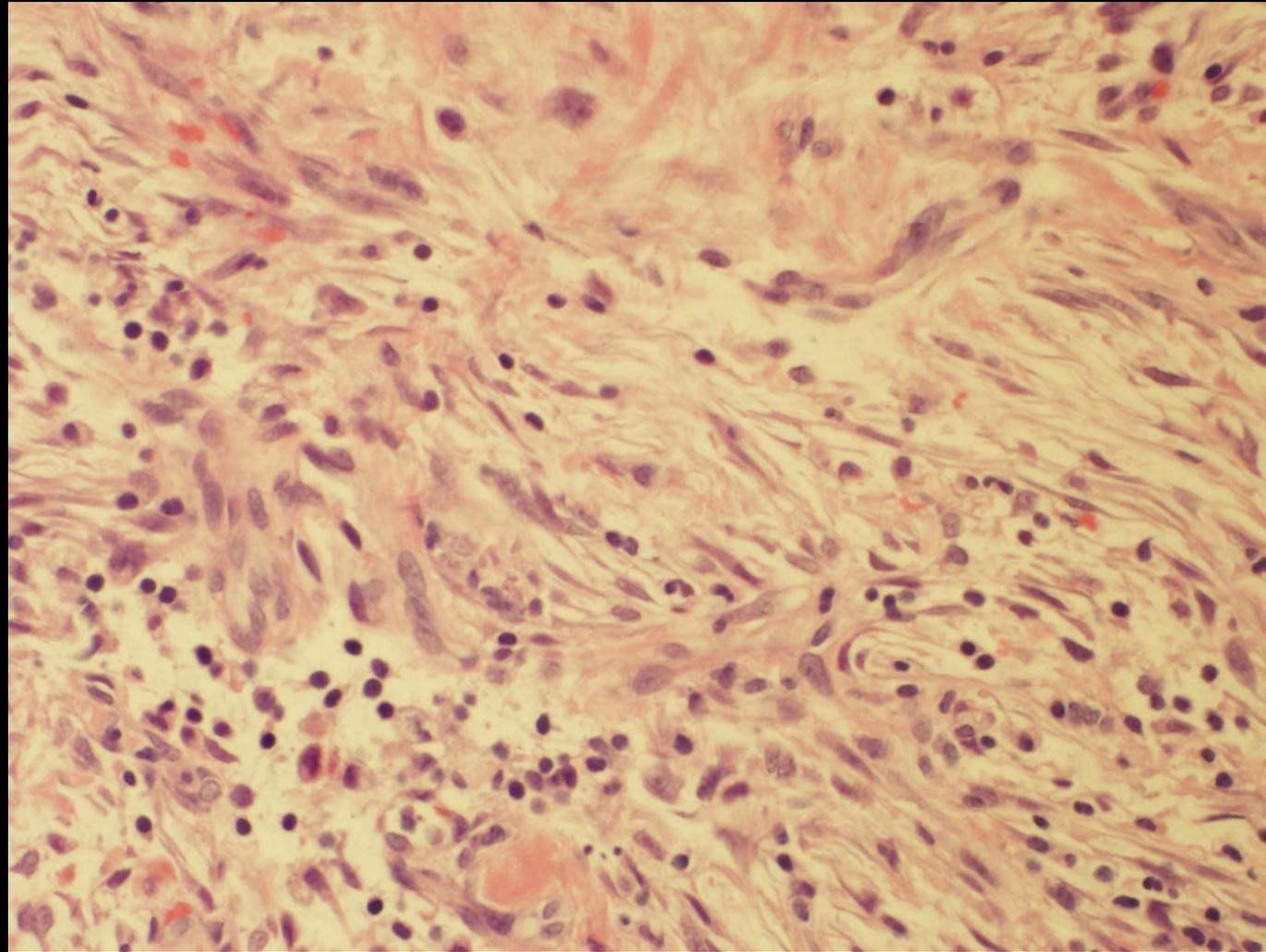


RIGHT BREAST 11:00 2 CM FN PRE BIOPSY1

# PATHOLOGY

- **Right breast biopsy:**





# DIFFERENTIAL DIAGNOSIS

- **Scar**
- **Mastitis**
- **Fibroepithelial lesions with myxoid change**
- **Inflammatory myofibroblastic tumor**
- **Low grade myofibroblastic sarcoma**
- **Low grade spindle cell metaplastic carcinoma**
- **Nodular fasciitis**

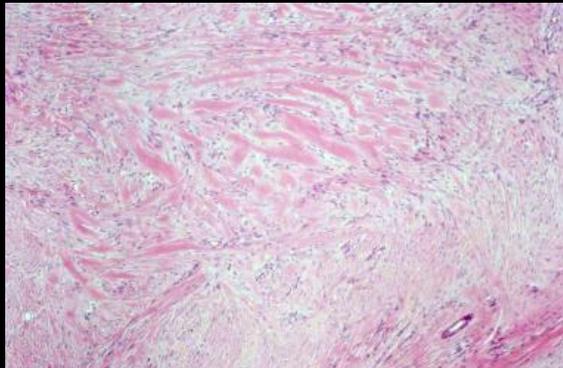
# THINKING IT THROUGH

## Scar

Would see in the setting of prior surgery

Fibroblasts, tend to be horizontal to epidermis

Expect hypocellular and less inflammation



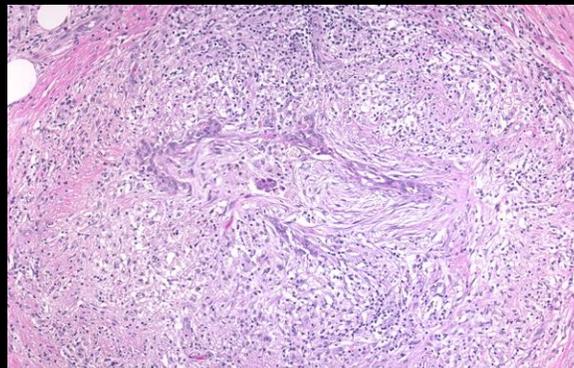
Medscape.com

## Idiopathic granulomatous mastitis

Lobulocentric process

Expect to see ducts/lobules

Inflammation, including giant cells and neutrophils



Webpathology.com

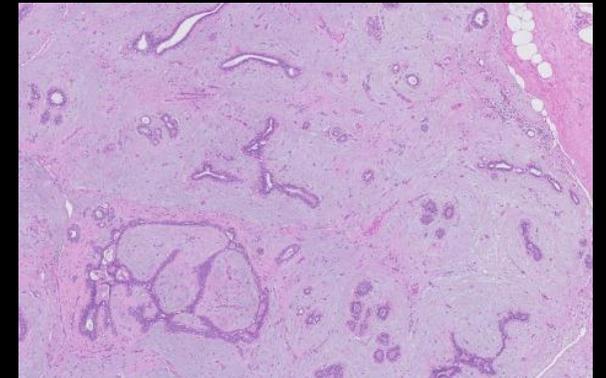
## Fibroepithelial lesion, myxoid

Epithelium and stroma present

Relatively hypocellular

Prominent myxoid change

Rare mitoses, rare inflammation

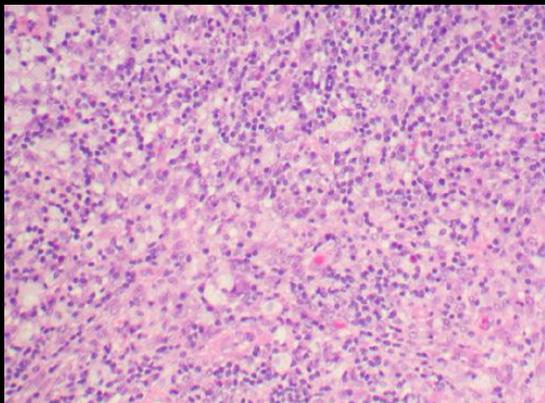


Sciencedirect.com

# DIFFERENTIAL CONTINUED

## Inflammatory myofibroblastic tumor

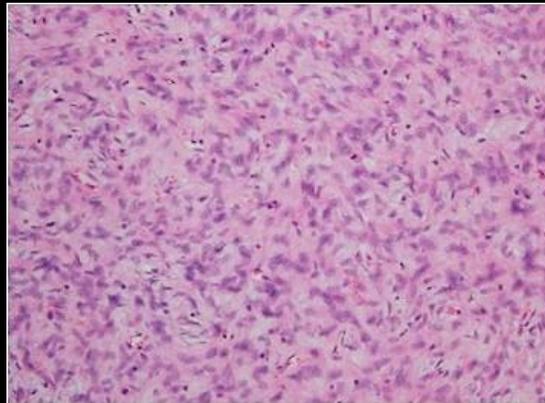
Very rare, forms nodular lesion  
May be hypocellular (scar-like)  
Or inflammatory  
Positive for SMA, keratin, IgG4  
ALK rearrangements seen



Digital atlas of breast pathology

## Low grade myofibroblastic sarcoma

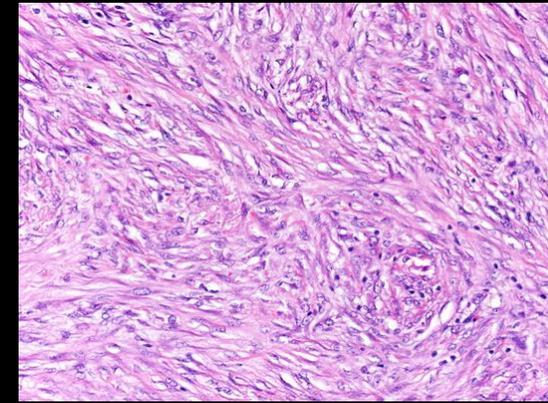
Mostly seen in head/neck  
Spindle cells  
Diffusely infiltrative  
Positive for SMA, Desmin



Diag Pathol. 2016; 11:33

## Spindle cell carcinoma

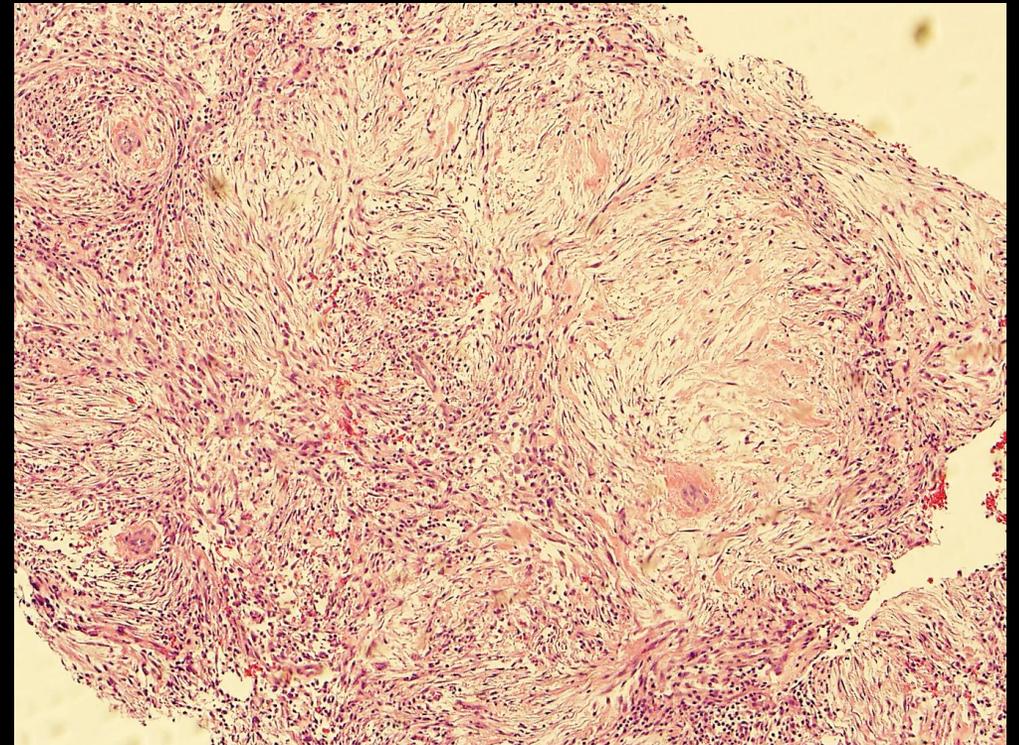
Infiltrative spindle cell lesion  
Look for epithelial components  
Heterologous elements  
Positive for keratin, p63



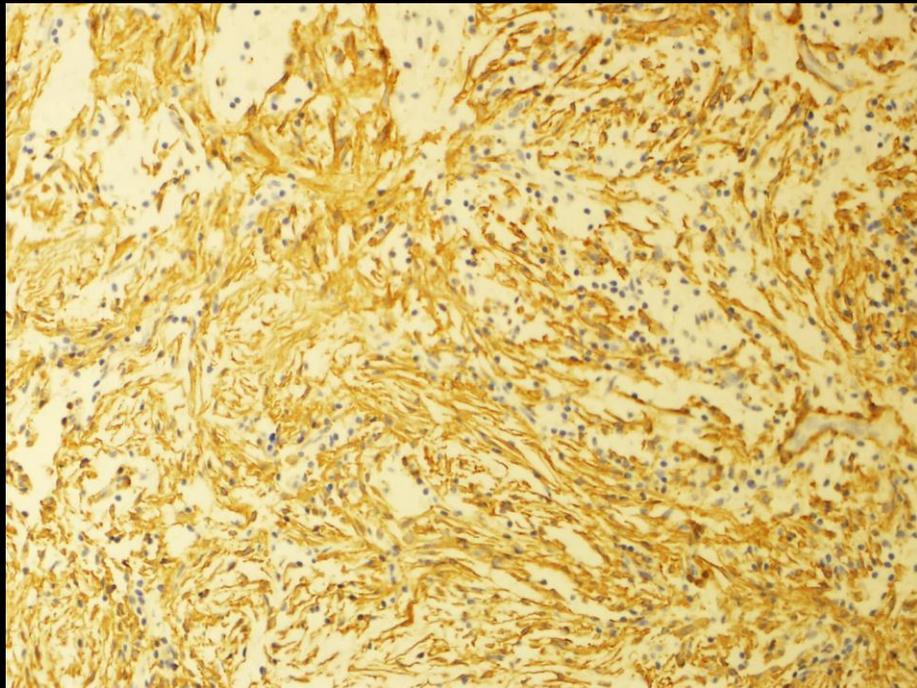
Webpathology.com

## OUR CASE REVISITED

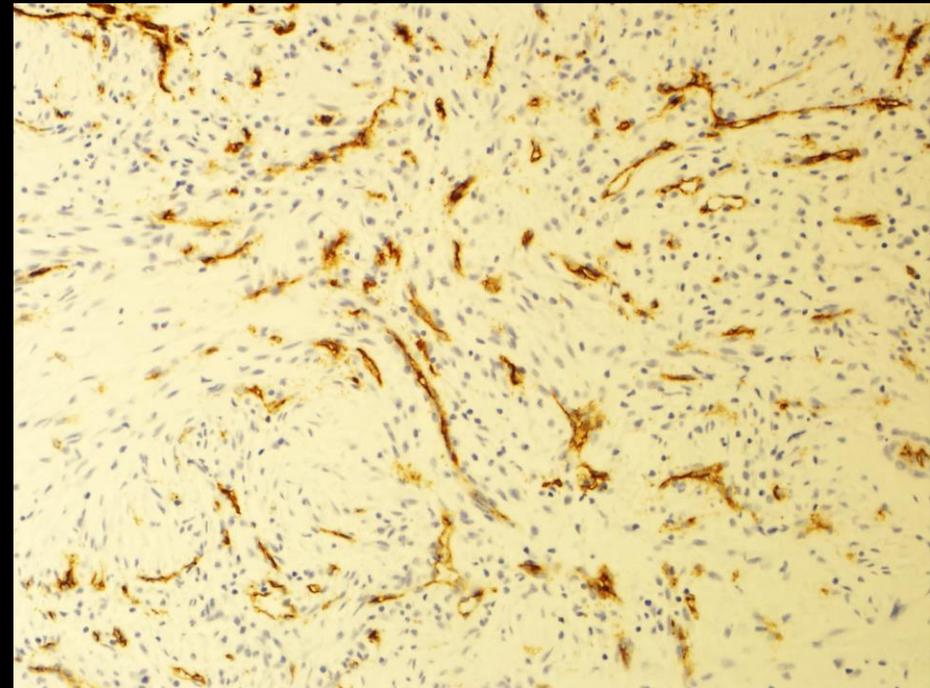
- **Absence of breast epithelium**
- **Bland spindle cells**
- **Variable cellularity**
- **“Tissue culture like” growth pattern**
- **Inflammatory cells**
- **Extravasated red blood cells**



# IMMUNOHISTOCHEMISTRY



**Positive: SMA**



**Negative: K903, AE1/AE3, CD34, Desmin,  
S-100, ALK-1**

# DIAGNOSIS

- **Nodular fasciitis of the breast**



# NODULAR FASCIITIS

- **Very uncommon benign breast lesion**
- **Usually occurs in extremities, head/neck, trunk**
- **Usually in young and middle aged adults, equal male:female**
- **No longer thought to arise following trauma**
- **Fusion gene MYH9-USP6 is common**

# DIAGNOSING NODULAR FASCIITIS IN THE BREAST

- **Clinically: firm or hard mass**
- **Often rapid growth, concerning for malignancy**
- **May be painful**
- **Histologically distinctive**

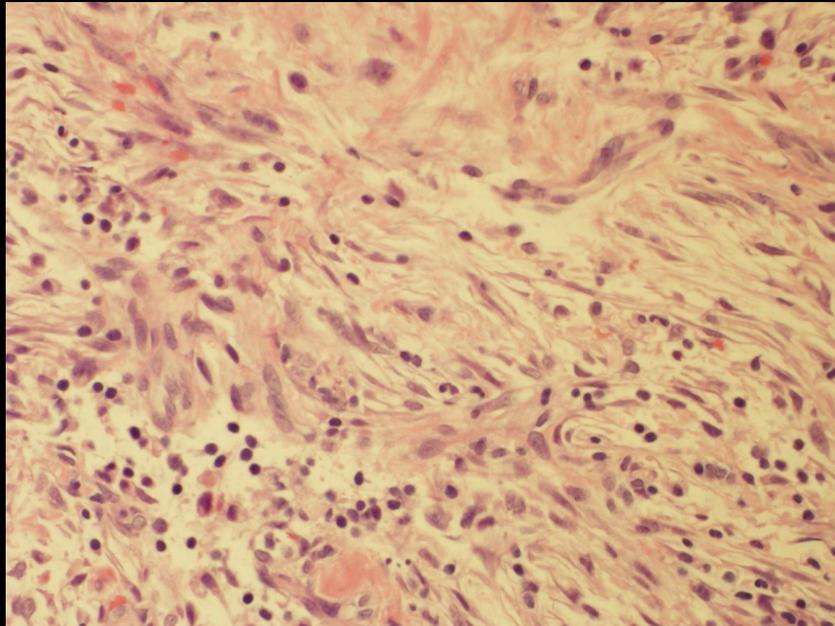
# HISTOLOGY

- **Myxoid to collagenous stroma**
- **Cellular at first, cystic degeneration common**
- **Spindle cells are fibroblasts and myofibroblasts**
- **Plump, may have prominent nucleoli, mitoses common**
- **Grow in loose fascicular and storiform pattern, “tissue culture like”**
- **Inflammatory cells and extravasated erythrocytes present**
- **SMA and CD68 positive, other IHC negative**

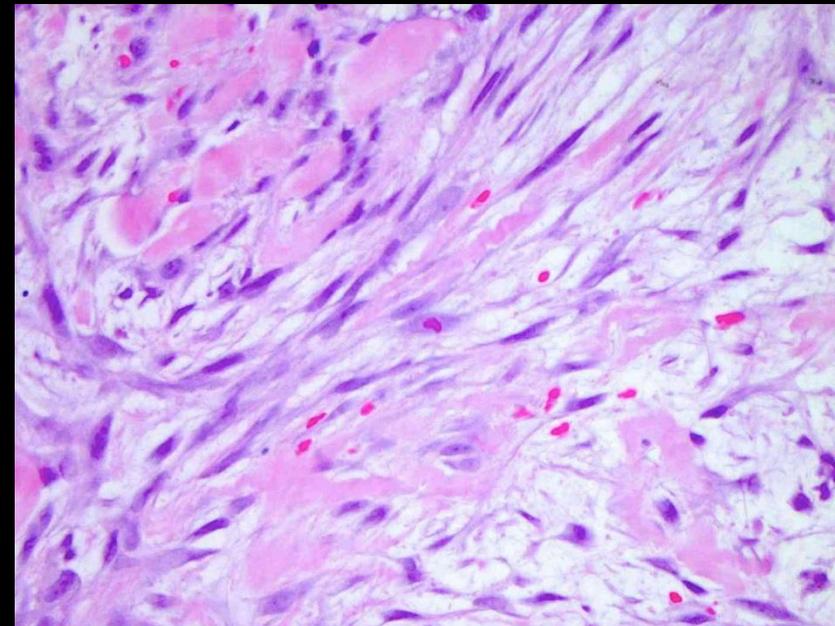
# HISTOLOGY

- **Epithelial elements not usually present**

Our case: in the breast



Nodular fasciitis of the neck



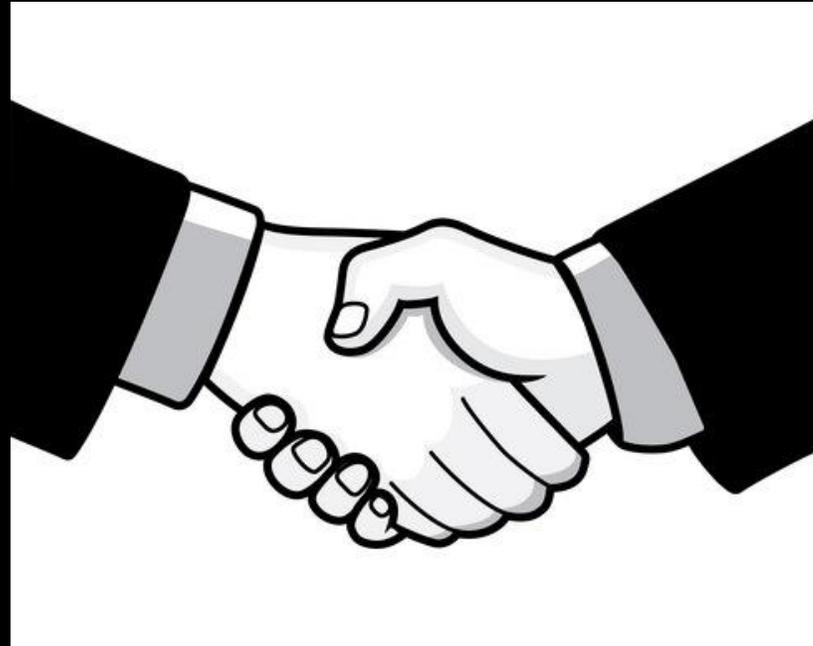
# MANAGEMENT OF NODULAR FASCIITIS IN THE BREAST

- **Exclude other diagnostic entities**
- **Excision is mainstay**
- **Can watch: spontaneous resolution occurs**
- **Prognosis is excellent**

## **BOTTOM LINE**

- **Rare lesion of the breast**
- **Don't forget about it!**
- **May mimic growth of malignant tumors**
- **Exclude metaplastic carcinoma**
- **Correlate with radiology**

# RAD-PATH DISCUSSION

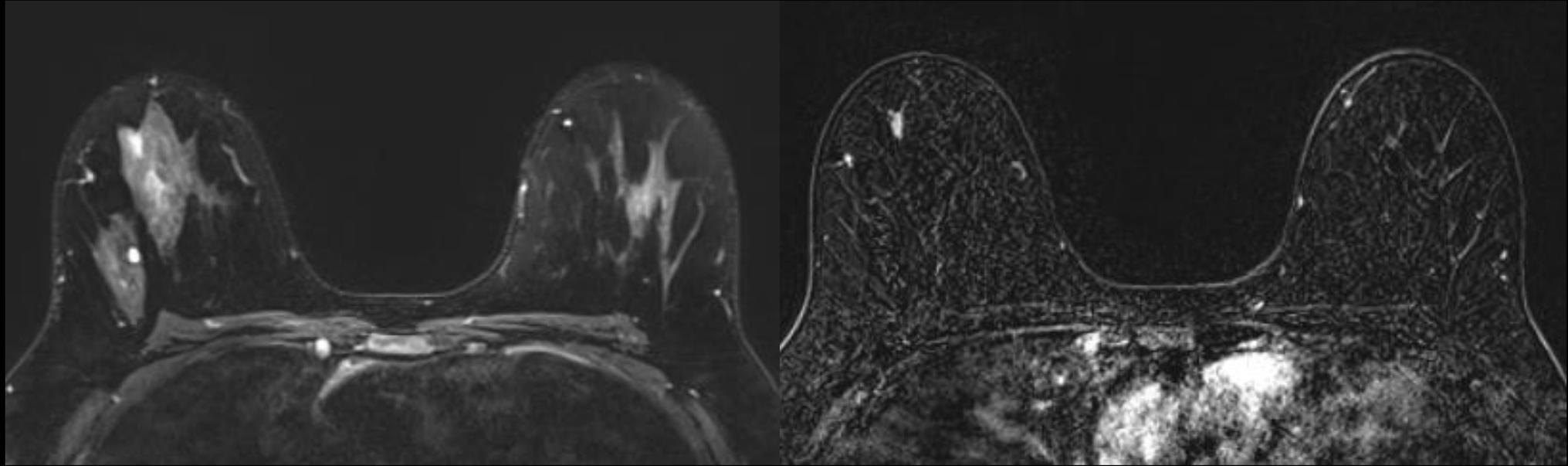


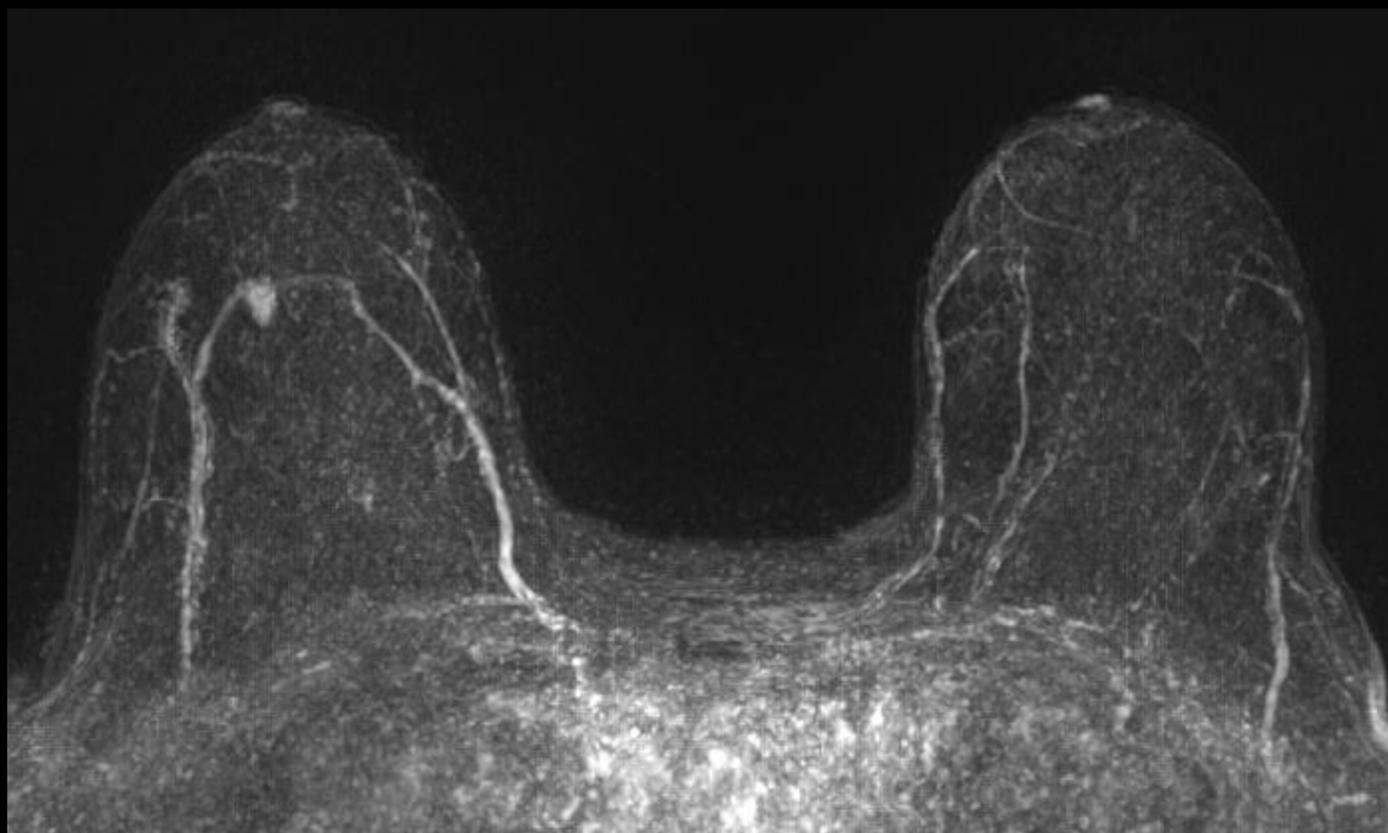
## CASE 3

- **40 year old female**
- **Two aunts and her mother with breast cancer**
- **2015: Underwent genetic testing → BRCA-1**
- **Has undergone surveillance with MRI/mammo**
- **Breast MRI August 2018 → negative**
- **Mammo Feb 2019 → negative**
- **Now for MRI June, 2019**

# RADIOLOGY

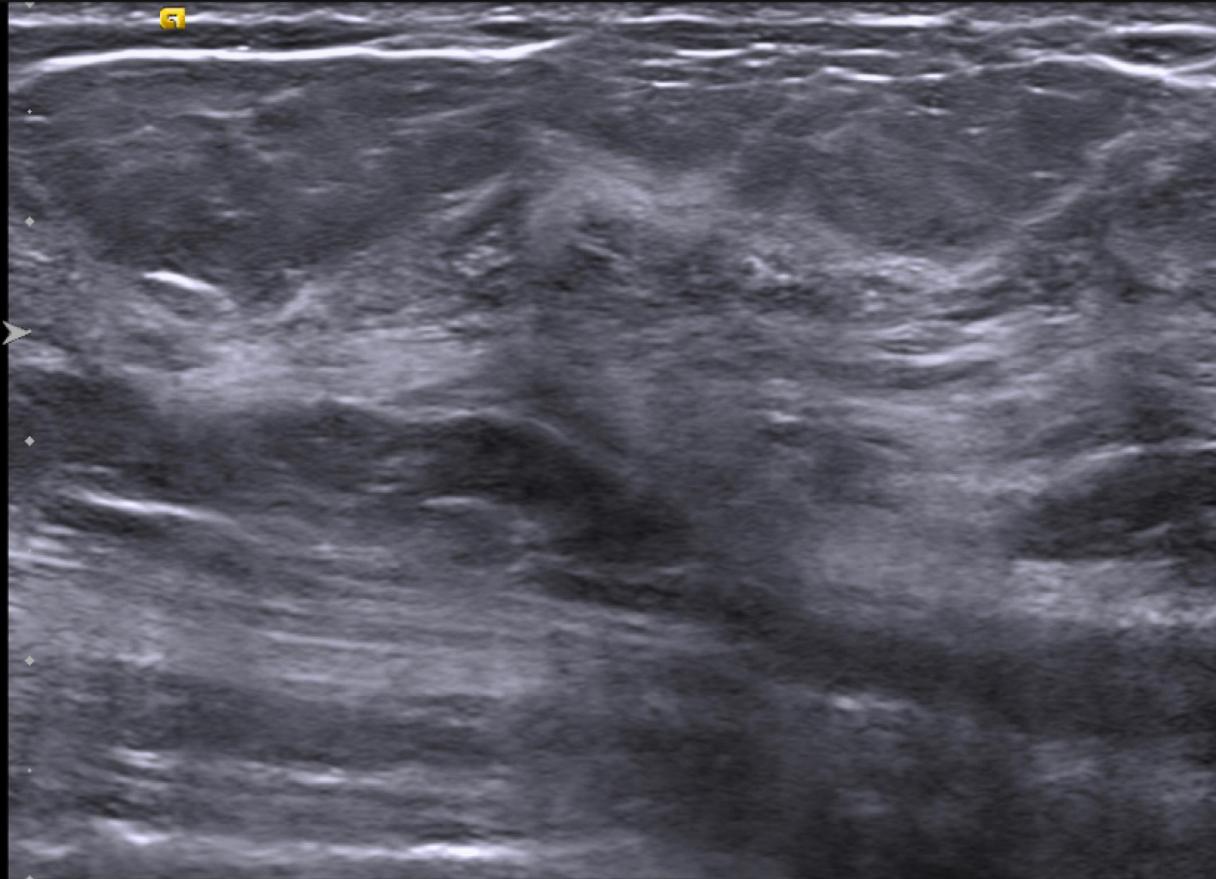
- **Patient presented for 6 month surveillance MRI**



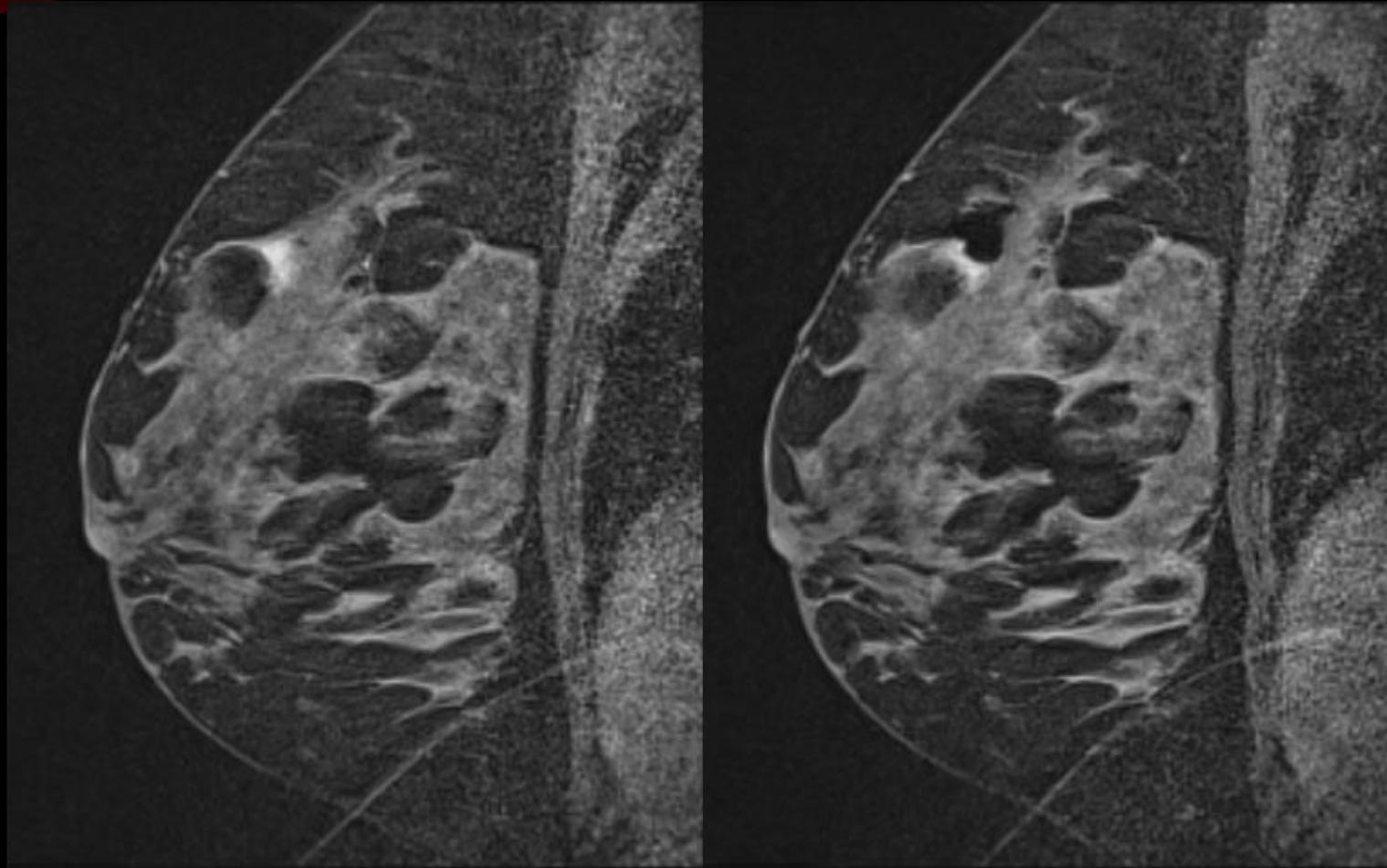


11

5



RT BREAST UOQ\_

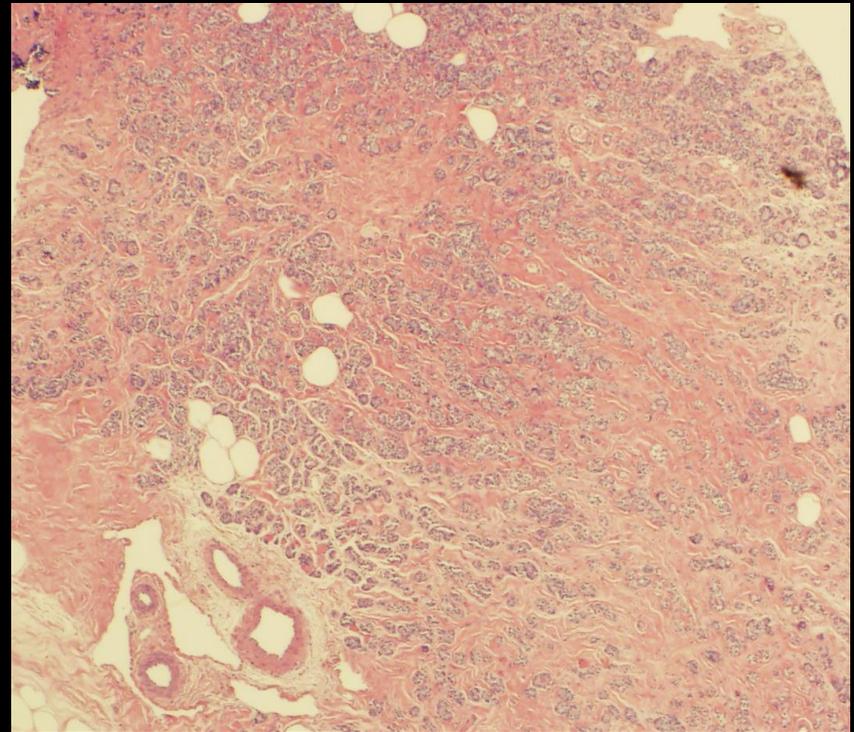
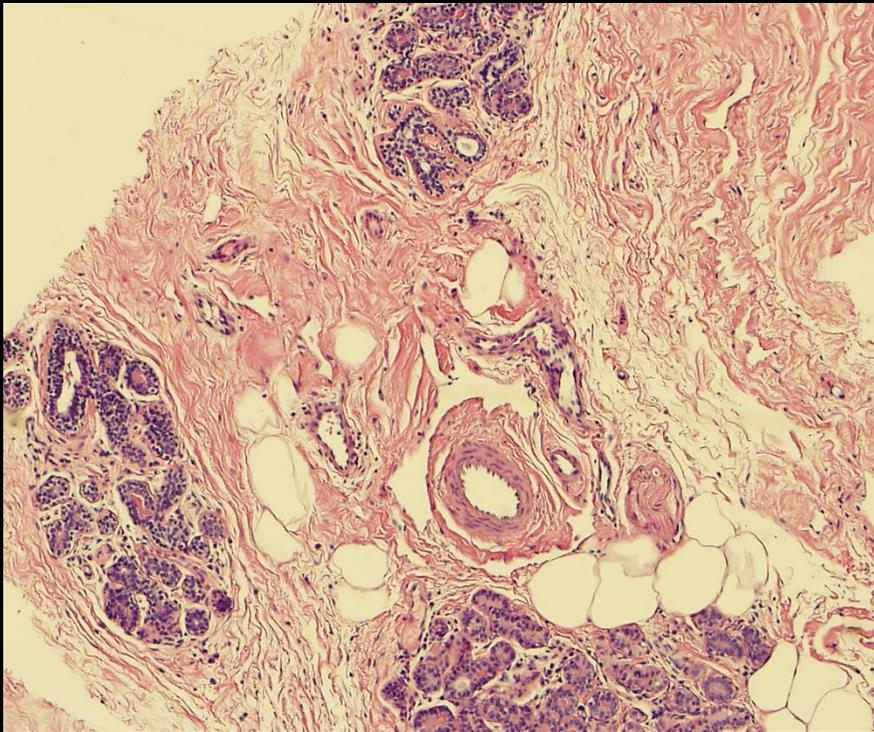


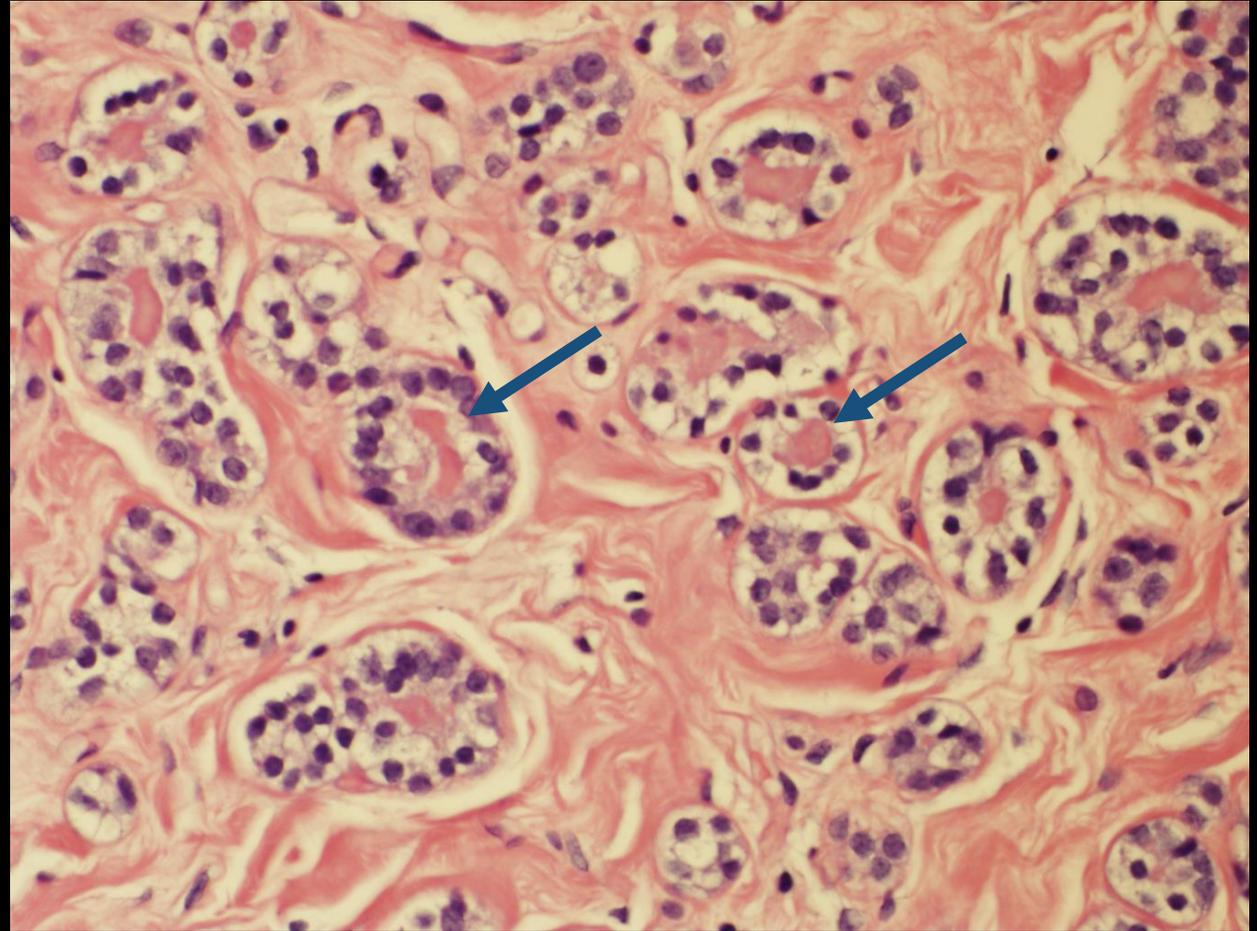
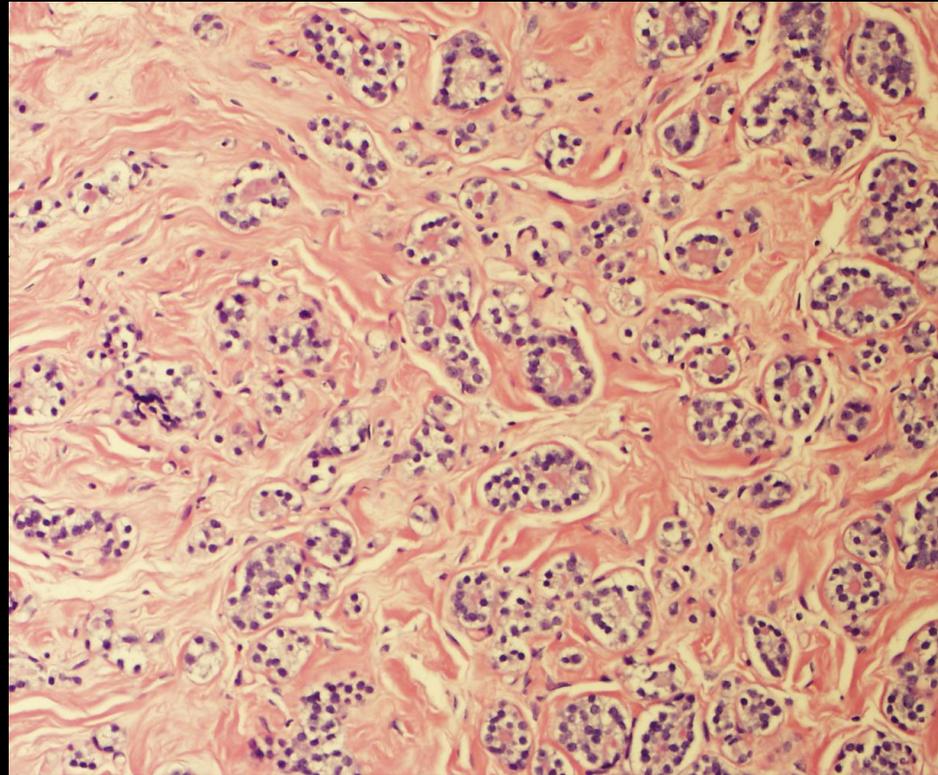
# BIOPSY PERFORMED

- **Radiology differential:**
  - **DCIS**
  - **Invasive cancer**
  - **Sclerosing adenosis**
  - **Fibrocystic change**

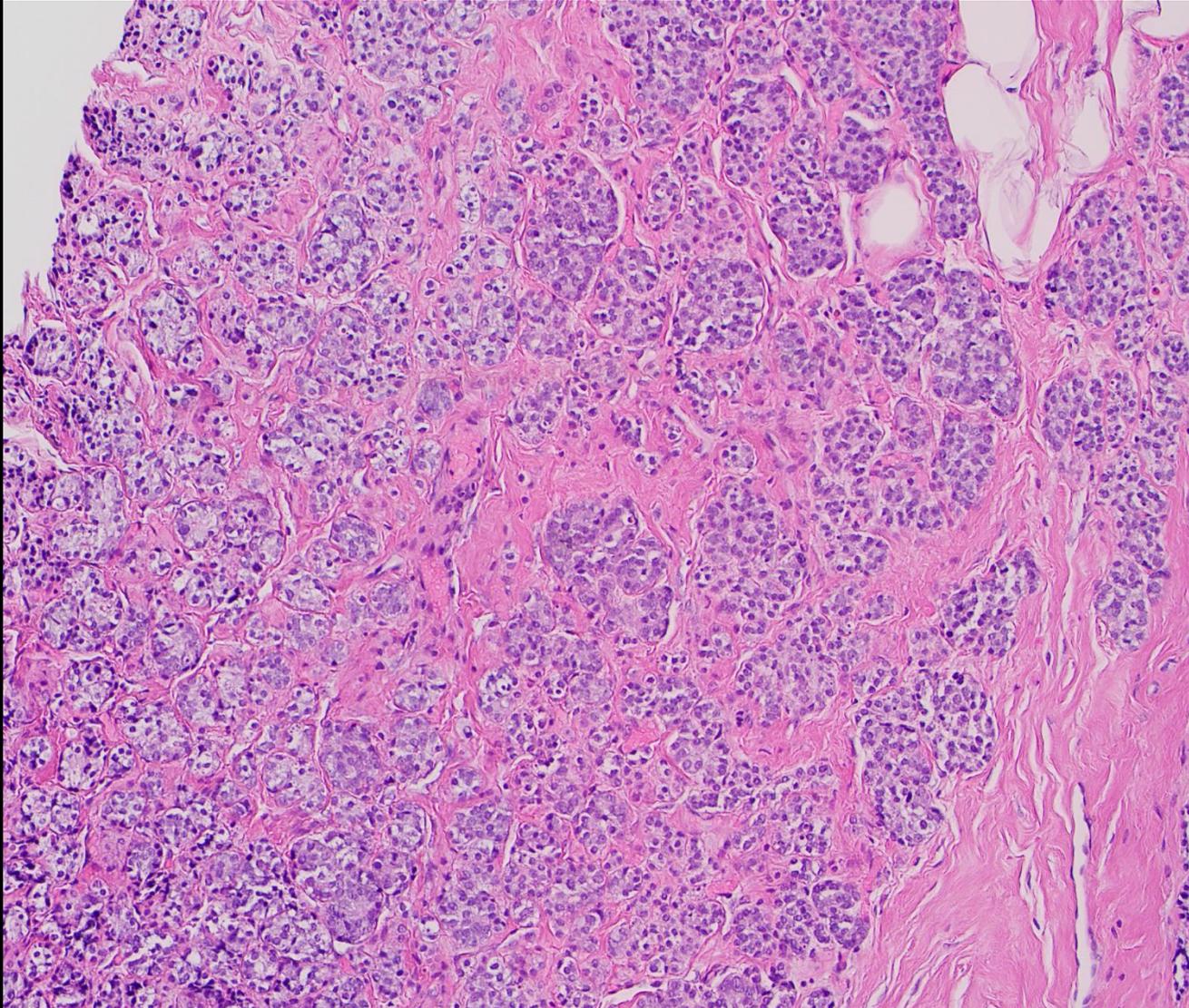
# PATHOLOGY

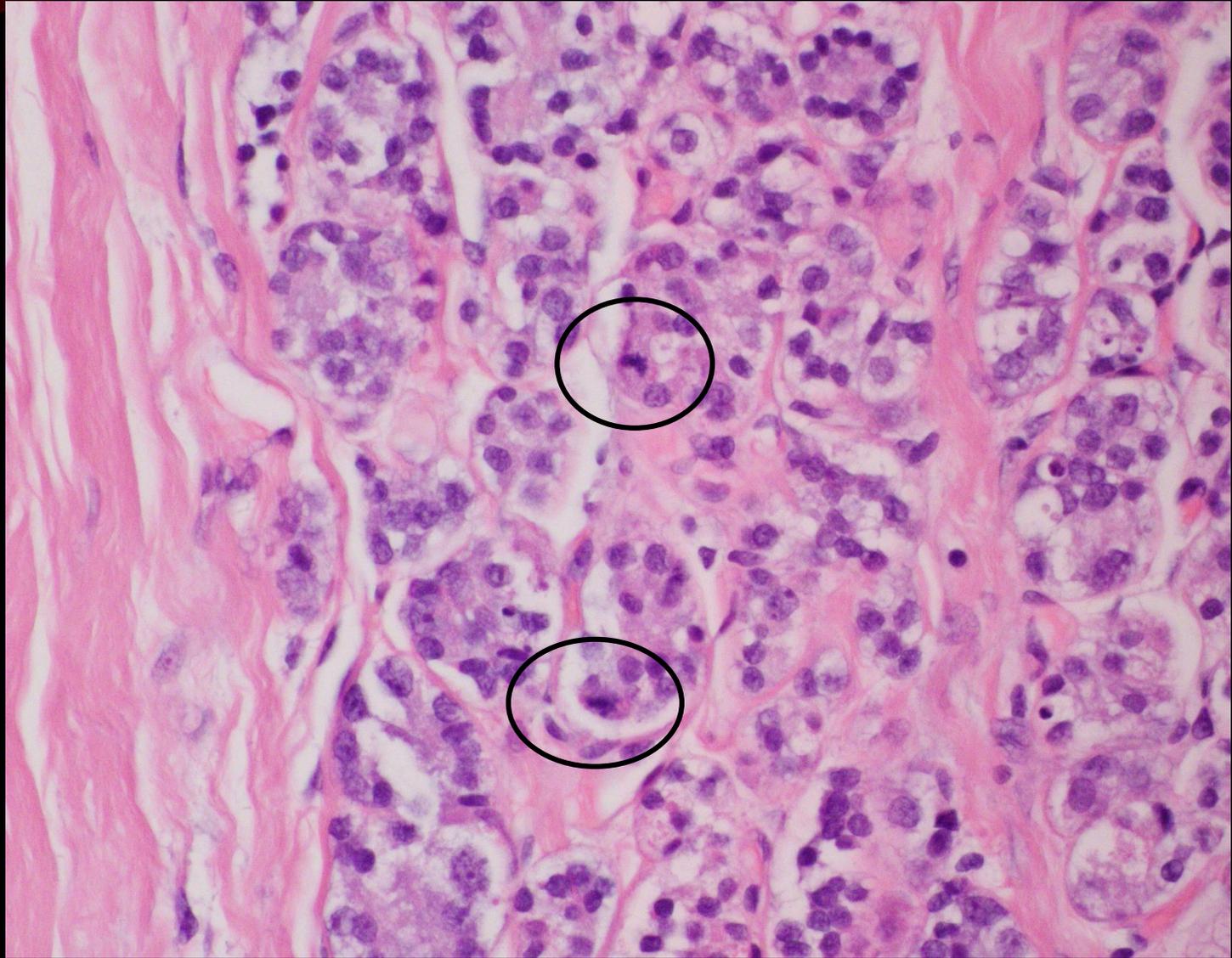
- **Right breast mass, biopsy:**





# OTHER AREAS





# DIFFERENTIAL DIAGNOSIS

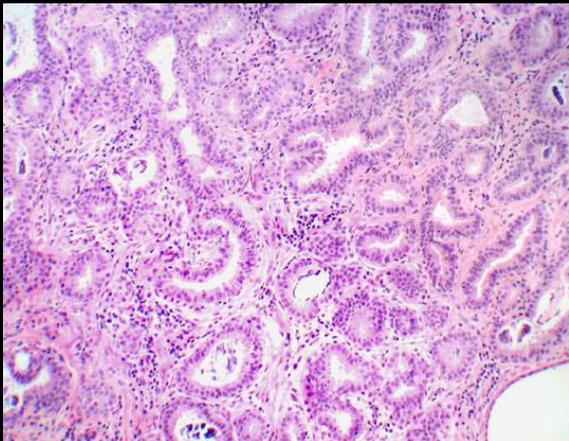
- **Adenosis**
- **Tubular adenoma**
- **Tubular carcinoma**
- **Microglandular adenosis**

# THINKING IT THROUGH

## Adenosis

**Hyperplasia: normal ducts but many of them**

**Myoepithelial cells present**



Digital Atlas of Breast Pathology

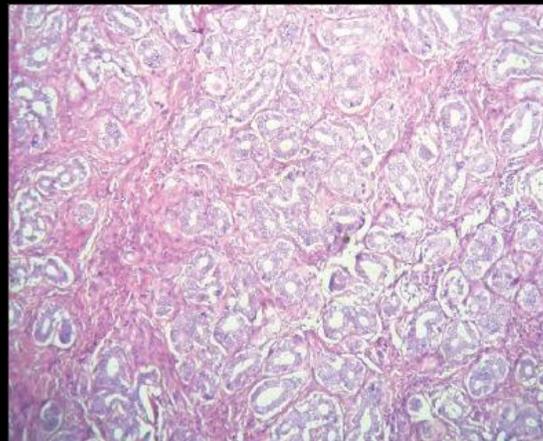
## Tubular adenoma

**Florid, back to back tubules**

**Minimal intervening stroma**

**No pleomorphism**

**Myoepithelial cells present**



Research Gate

## Tubular carcinoma

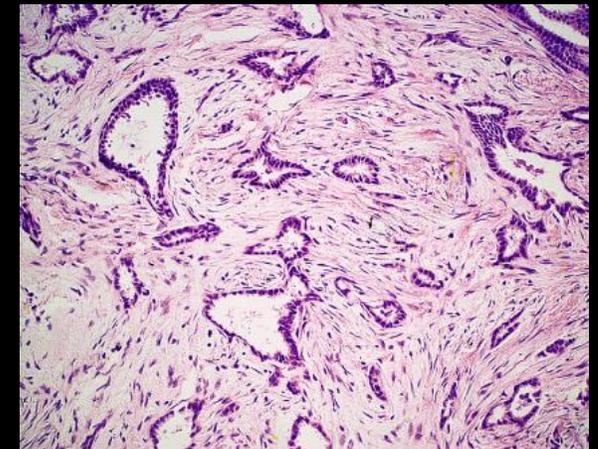
**Well differentiated IDC**

**Angulated tubular structures**

**Luminal secretions common**

**Infiltrative, desmoplastic stroma**

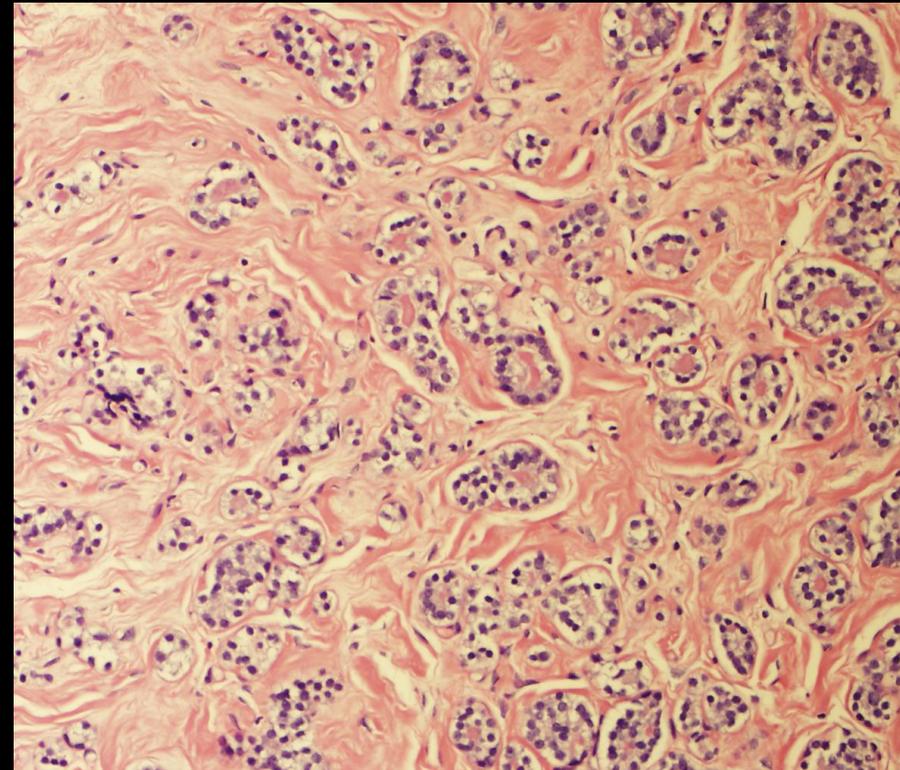
**ER, PR positive**



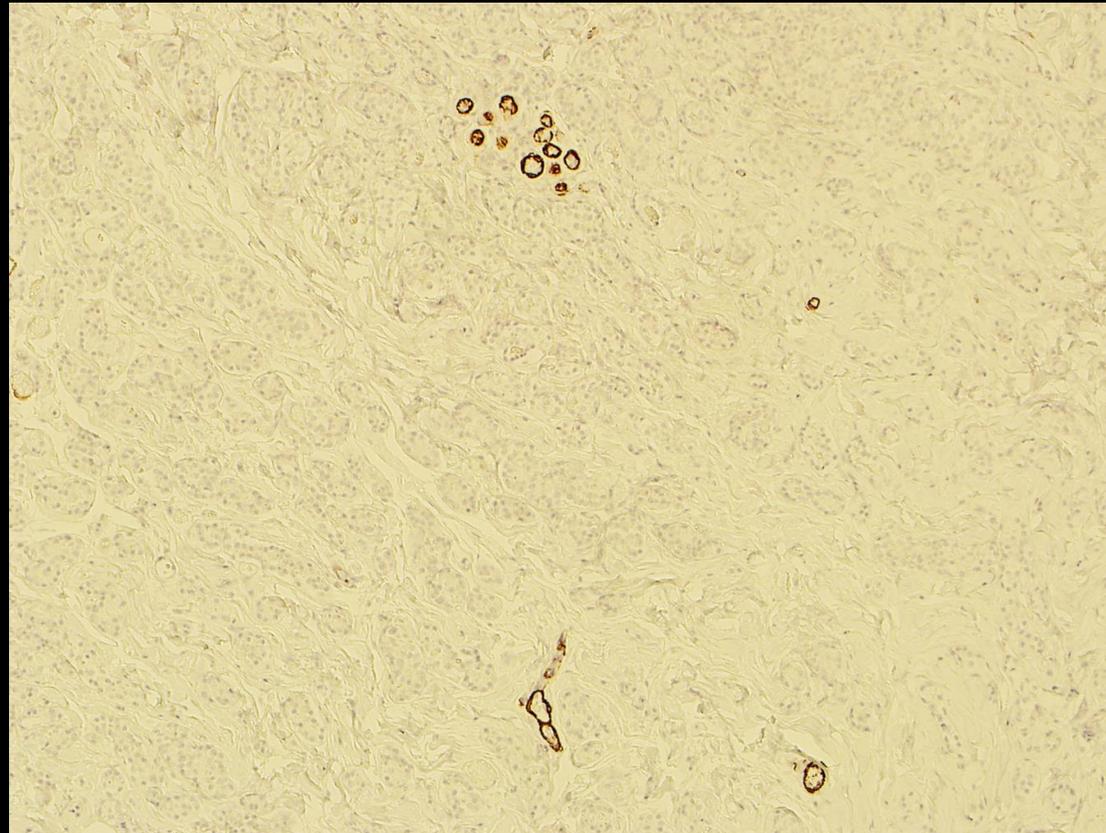
Rosal and Ackerman, 2004

# OUR CASE REVISITED

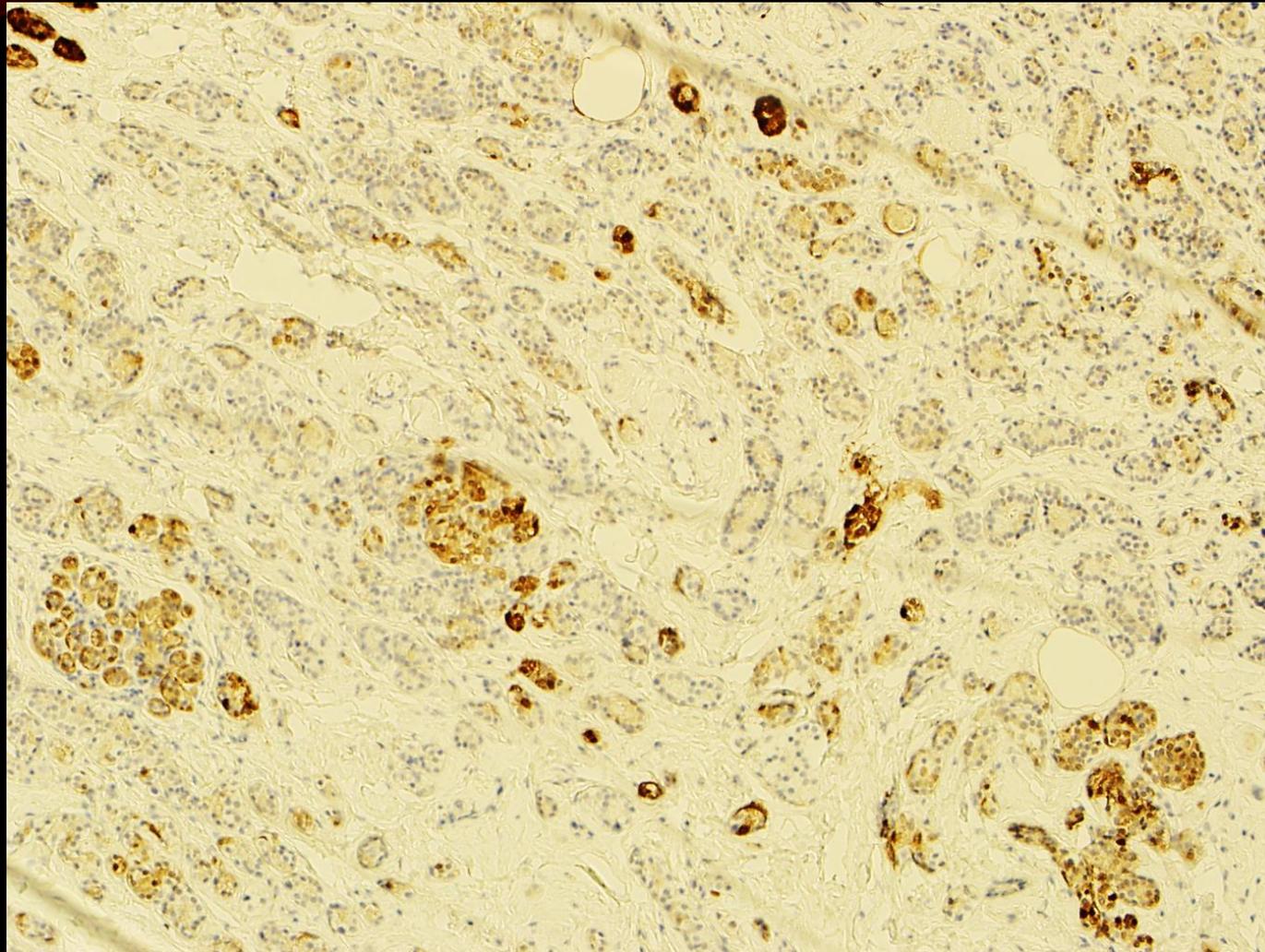
- **Tubules with bland nuclei**
- **Intraluminal eosinophilic secretions**
- **No desmoplastic stroma**
- **No DCIS**



# IMMUNOHISTOCHEMISTRY



Negative: p63, Myosin, Estrogen receptor



**Positive: S-100**

# DIAGNOSIS

- **Microglandular adenosis**



# MICROGLANDULAR ADENOSIS

- **Uncommon lesion of the breast (<0.1% breast biopsies)**
- **May be incidental or form a mass**
- **Infiltrative, may mimic invasive carcinoma**

# PRECURSOR LESION?

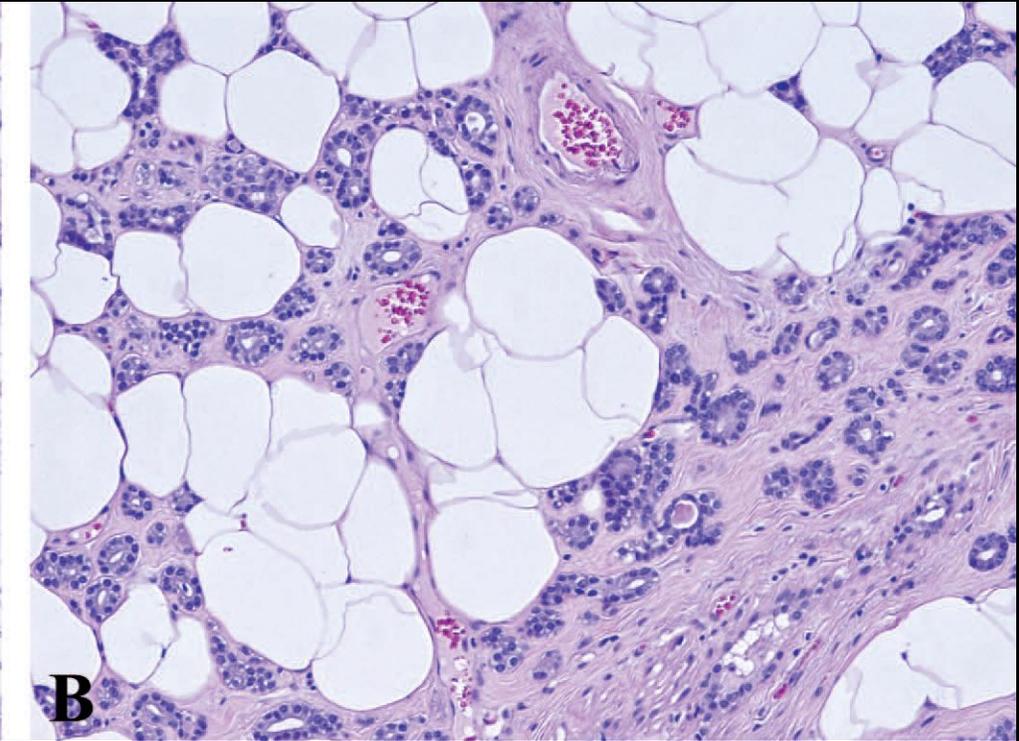
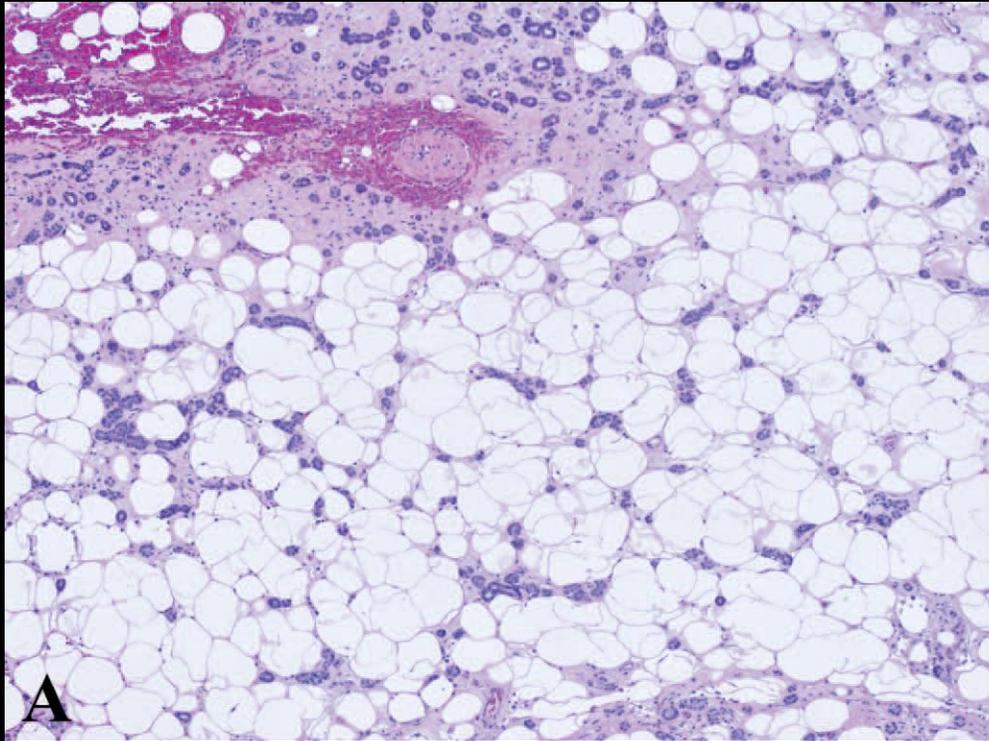
- **Usually indolent and benign**
- **Considered “borderline neoplasia”**
- **~25% of cases are associated with invasive carcinoma**
- **Morphology and staining pattern is distinctive**
- **Tubular lesion with bland nuclei that lack myoepithelial cells**

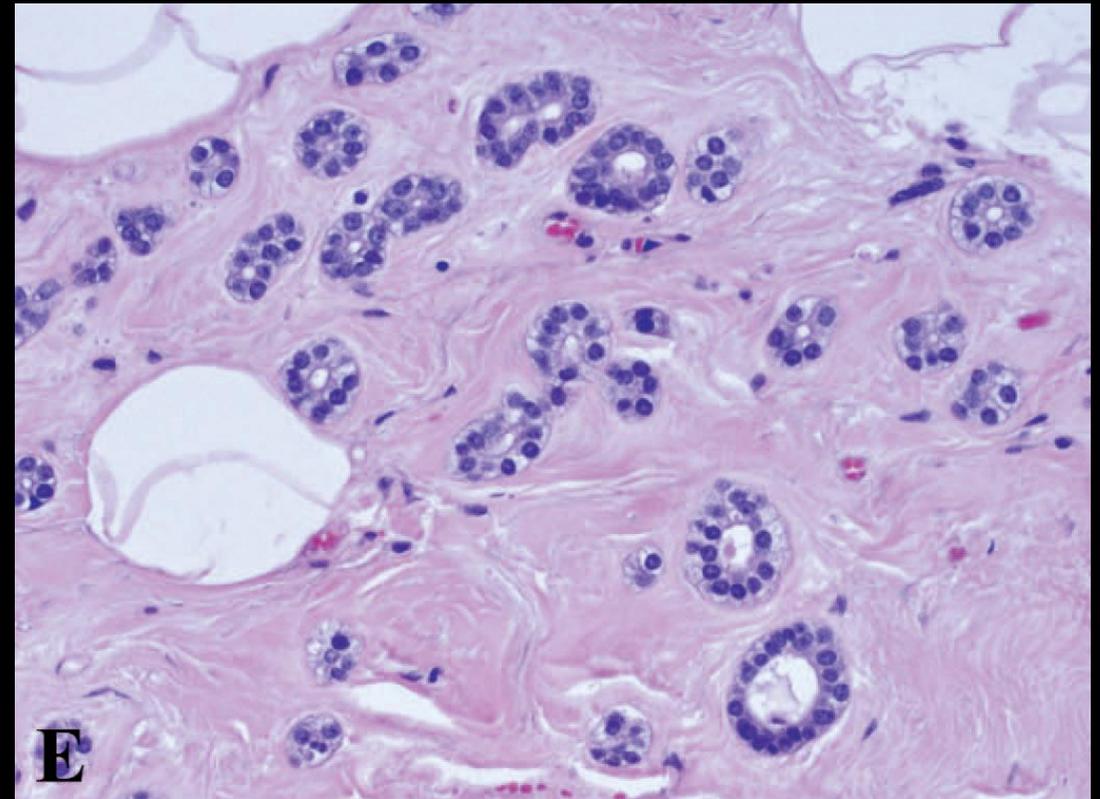
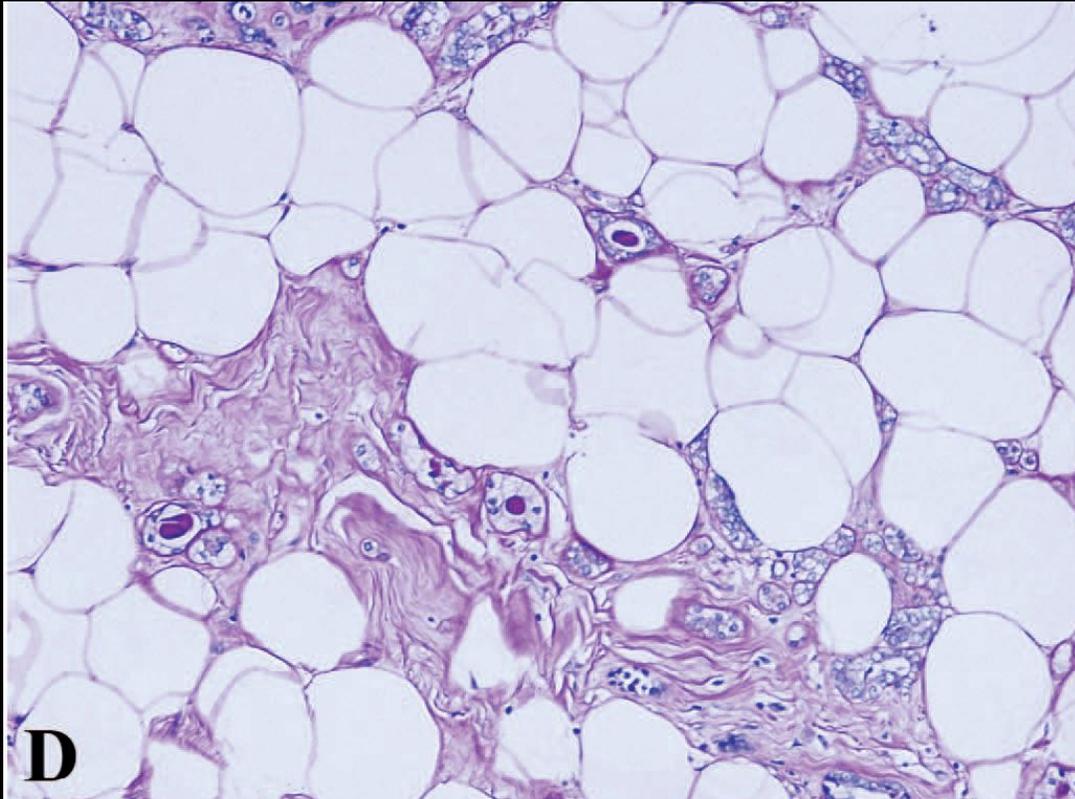
# HISTOLOGY

- **Haphazard growth pattern, appears infiltrative**
- **Small tubules with round lumina**
- **Bland nuclei, inconspicuous nucleoli, moderate foamy cytoplasm**
- **Intraluminal secretions: eosinophilic, PAS+/PAS-D+**
- **Rare mitoses**
- **No desmoplastic stromal reaction**

# HISTOLOGY

Kravtsov O, Jorns J. Microglandular adenosis and associated invasive carcinoma. Arch Pathol Lab Med. (2019) In Press

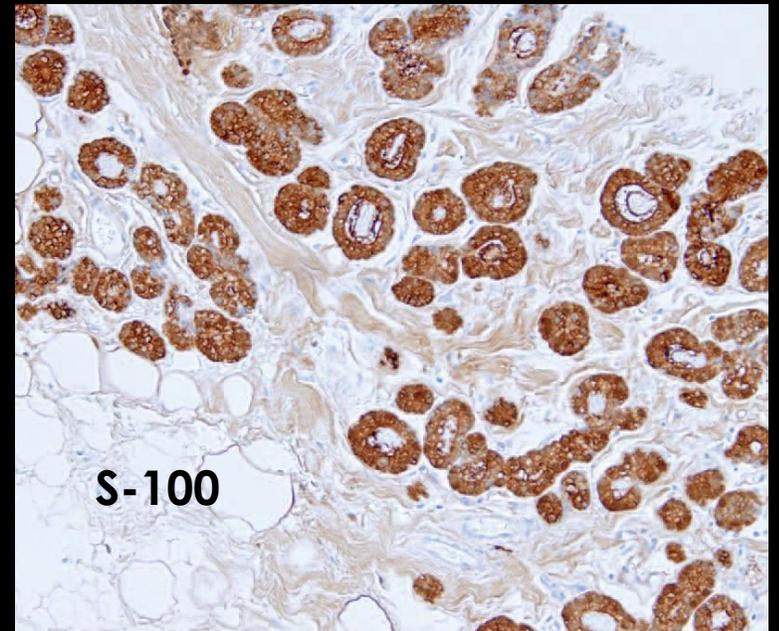




Kravtsov O, Jorns J. Microglandular adenosis and associated invasive carcinoma. Arch Pathol Lab Med. (2019) In Press

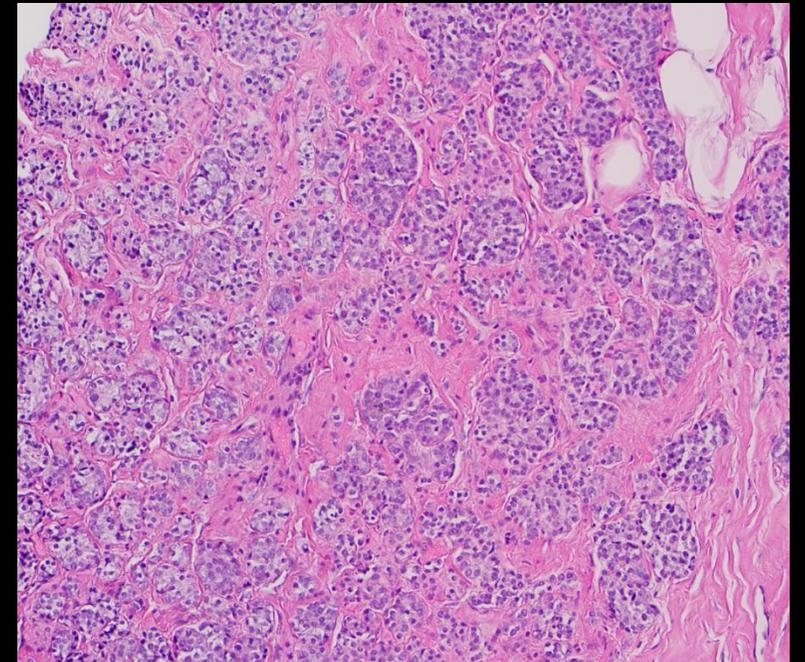
# IMMUNOHISTOCHEMISTRY

- **Basement membrane positive for Collagen IV and laminin**
- **Negative for myoepithelial markers (p63, Calponin, Myosin, etc.)**
- **Positive for S-100**
- **Negative for ER, PR, HER2**



# ATYPICAL MICROGLANDULAR ADENOSIS

- **Cytologic and architectural atypia**
- **Larger, hyperchromatic nuclei with prominent nucleoli**
- **Mitoses and apoptotic cells**
- **Crowded glands, possible cribriforming**
- **Haphazard growth pattern is maintained**

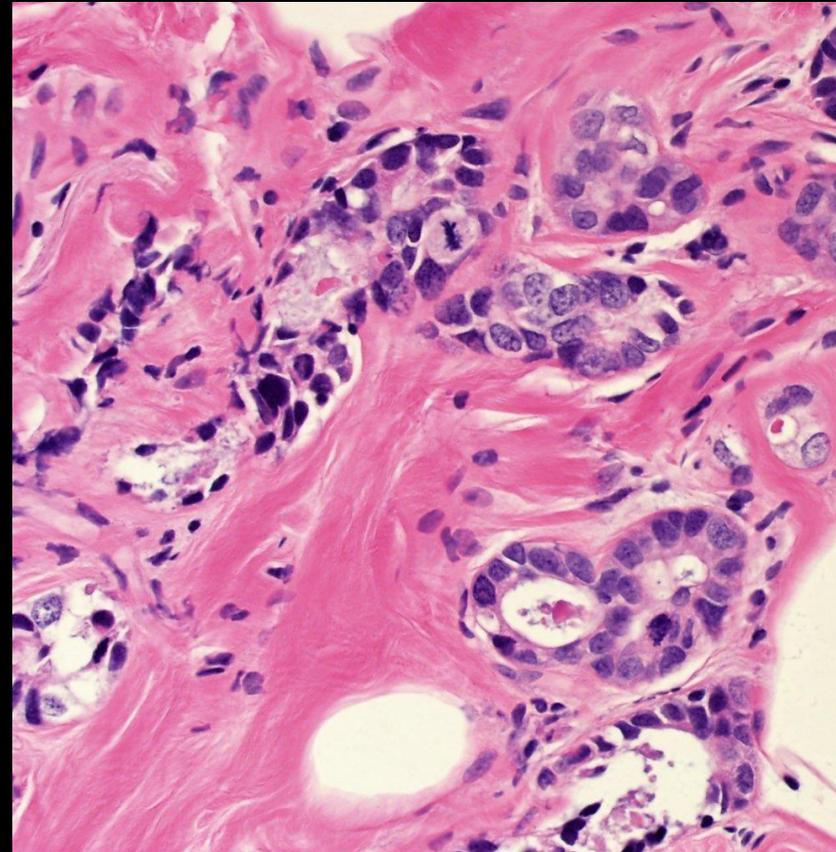
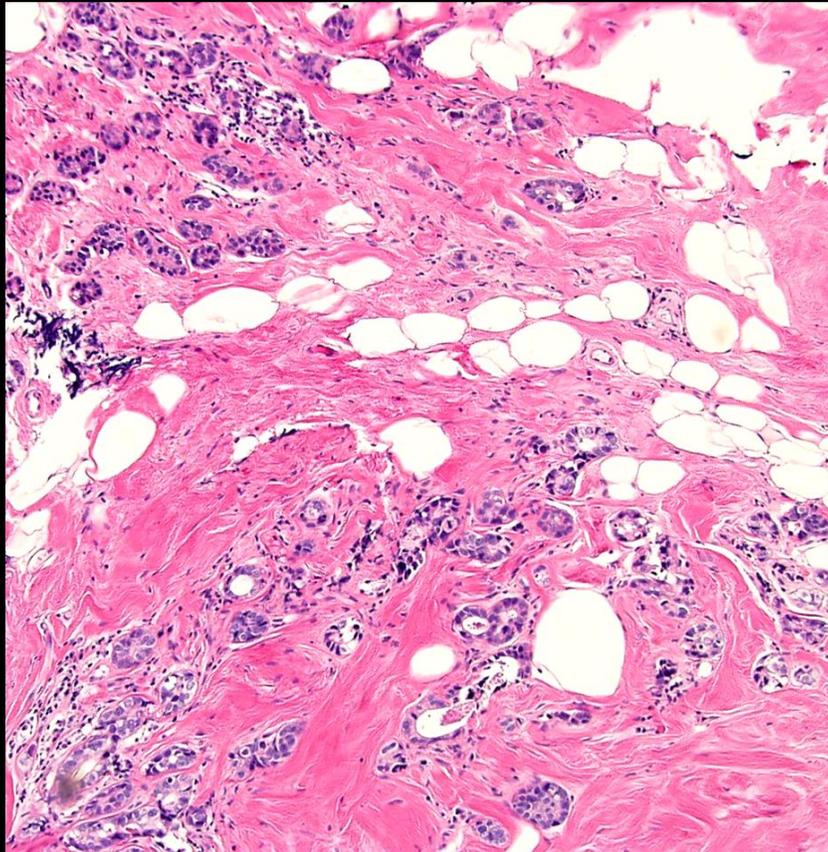


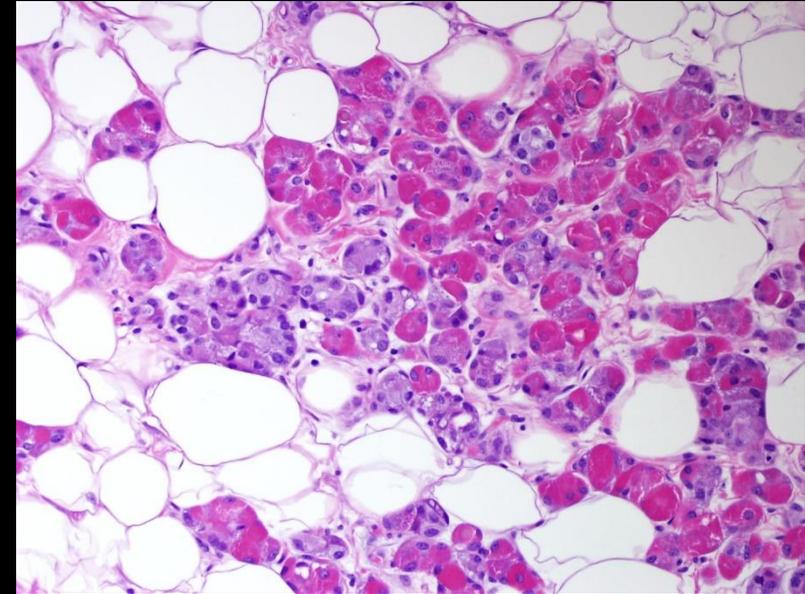
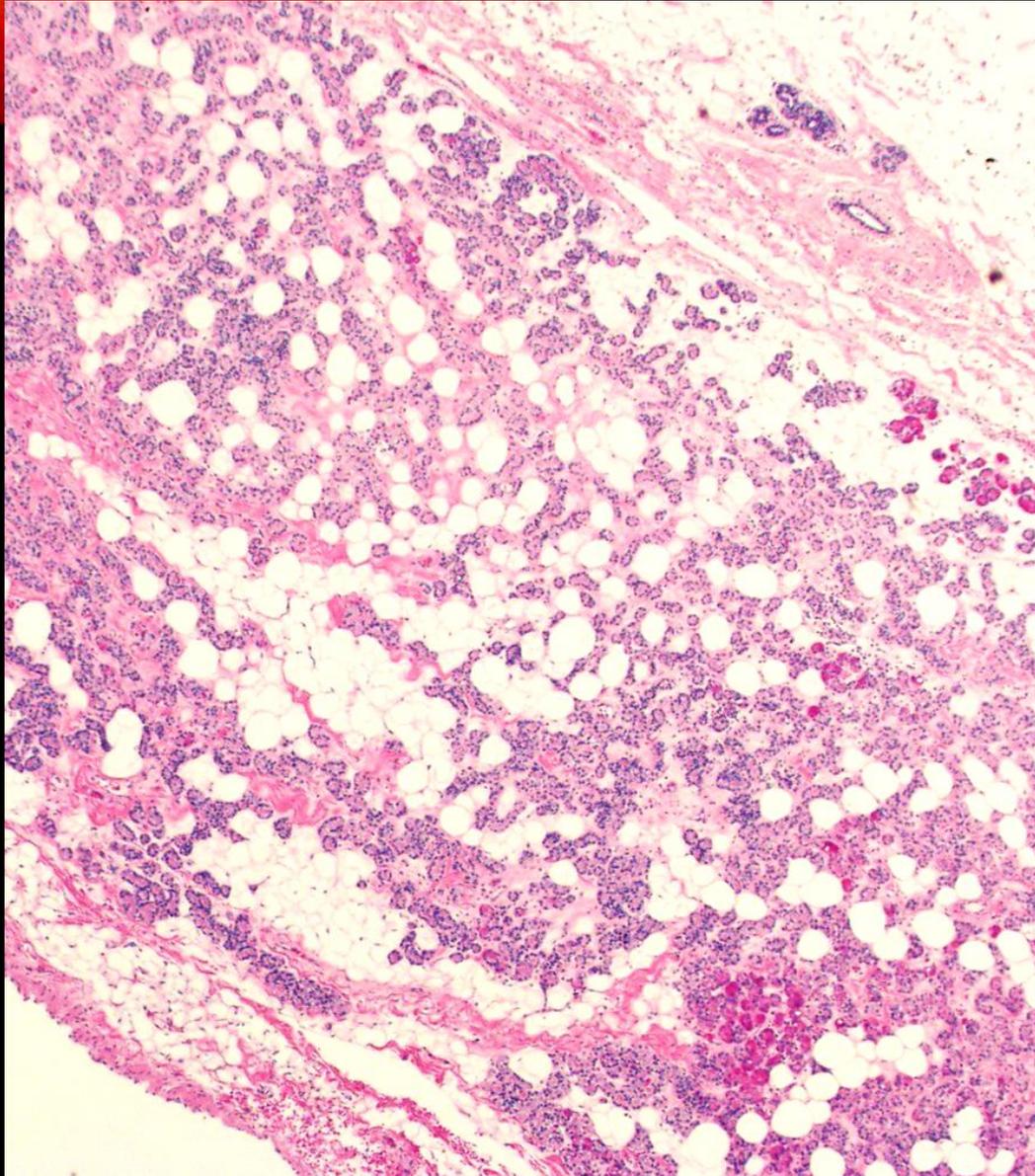
# MGA ASSOCIATED CARCINOMA

- **Invasive carcinoma, tubules with open lumina**
- **Nuclear pleomorphism, increased mitoses**
- **Triple negative (ER, PR, HER2 negative)**
- **May retain S-100 positivity**

# SOMETIMES WITH RARE ASSOCIATIONS

**Case from 2010**





**Diagnosis:**  
**Acinic cell-like carcinoma of the breast  
with Paneth cell like granules arising from  
microglandular adenosis**

**3 Similar cases described:**  
Huo L, Bell D., et al. Paneth cell-like eosinophilic  
cytoplasmic granules in breast carcinoma. *Annals of  
Diagnostic Pathology* 15 (2011) 84-92

# **MGA ASSOCIATED INVASIVE CARCINOMA (ACINIC CELL)**

**Geyer FC, et al. Genetic analysis of microglandular adenosis and acinic cell carcinomas of the breast provides evidence for the existence of a low grade triple negative breast neoplasia family. Mod Pathol. 2017 Jan; 30(1):69-84**

- **Molecular analysis demonstrates similarities between MGA, Atypical MGA and Acinic cell carcinoma, suggesting they are a spectrum of low grade triple negative breast neoplasia/carcinoma**
- **Pure MGA often lacks mutations, but may be a neoplastic precursor lesion**
- **Most common mutated gene in atypical MGA and carcinoma is TP53**
- **Mutations also seen in PIK3CA, PTEN and BRCA1**

**Kravtsov O, Jorns J. Microglandular adenosis and associated invasive carcinoma.  
Arch Pathol Lab Med. (2019) In Press**

Key Features in the Differential Diagnostics of Microglandular Adenosis (MGA)						
	MGA	Atypical MGA	MGA-Associated Invasive Carcinoma	Well-Differentiated Invasive Ductal Carcinoma	Invasive Tubular Carcinoma	Sclerosing Adenosis
Collagen IV	Positive	Positive	Negative	Negative	Negative	Positive
S100	Positive	Positive	Positive/negative	Negative	Negative	Negative
ER/PR	Negative	Negative	Negative	Positive (diffuse)	Positive (diffuse)	Positive (patchy)
Myoepithelial markers	Negative	Negative	Negative	Negative	Negative	Positive
EMA	Negative	Negative	Negative	Positive	Positive	Positive
Desmoplasia	Absent	Absent	Present	Present	Present	Absent
Cytologic atypia	Minimal	Minimal to mild	Moderate to severe	Minimal to mild	Minimal to mild	Minimal
Growth pattern	Infiltrative	Infiltrative	Infiltrative	Infiltrative	Infiltrative	Lobulocentric to infiltrative
Gland shape	Round with secretions	Variable (round to angulated, fused, complex)	Irregular	Variable (round to angulated, fused, complex)	Angulated	Compressed
Apical cytoplasmic snouts	Absent	Absent	Absent	Absent	Present	Absent

# THE PATIENT

- **Lesion was identified by q6 month surveillance**
  - **Radiology had a low threshold for biopsy**
- **Underwent bilateral mastectomies earlier than she hoped**
  - **Additional atypical MGA found**
    - **KI67 15%, p53 wild type**
  - **No invasive carcinoma identified**
  - **Consultation with MD Anderson**

# CONCLUSION

- **Rare entities in the breast can be diagnostically challenging**
- **Use clinical, radiology and pathology information**
- **Rad-Path discussions are helpful**
  - **Provide a multidisciplinary approach**
  - **Learn from each others disciplines**
  - **Makes arriving at the diagnosis interesting and fun**

**THANK YOU**

