



Diagnostic and Differential Considerations in Squamous Breast Lesions

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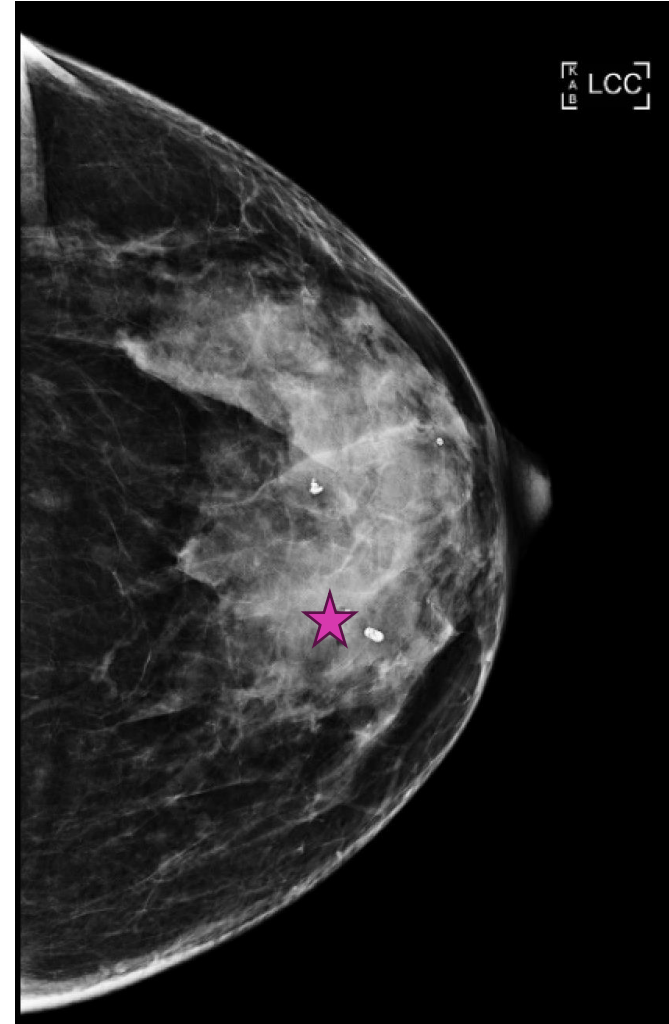
I have no relevant conflict of interests to disclose.

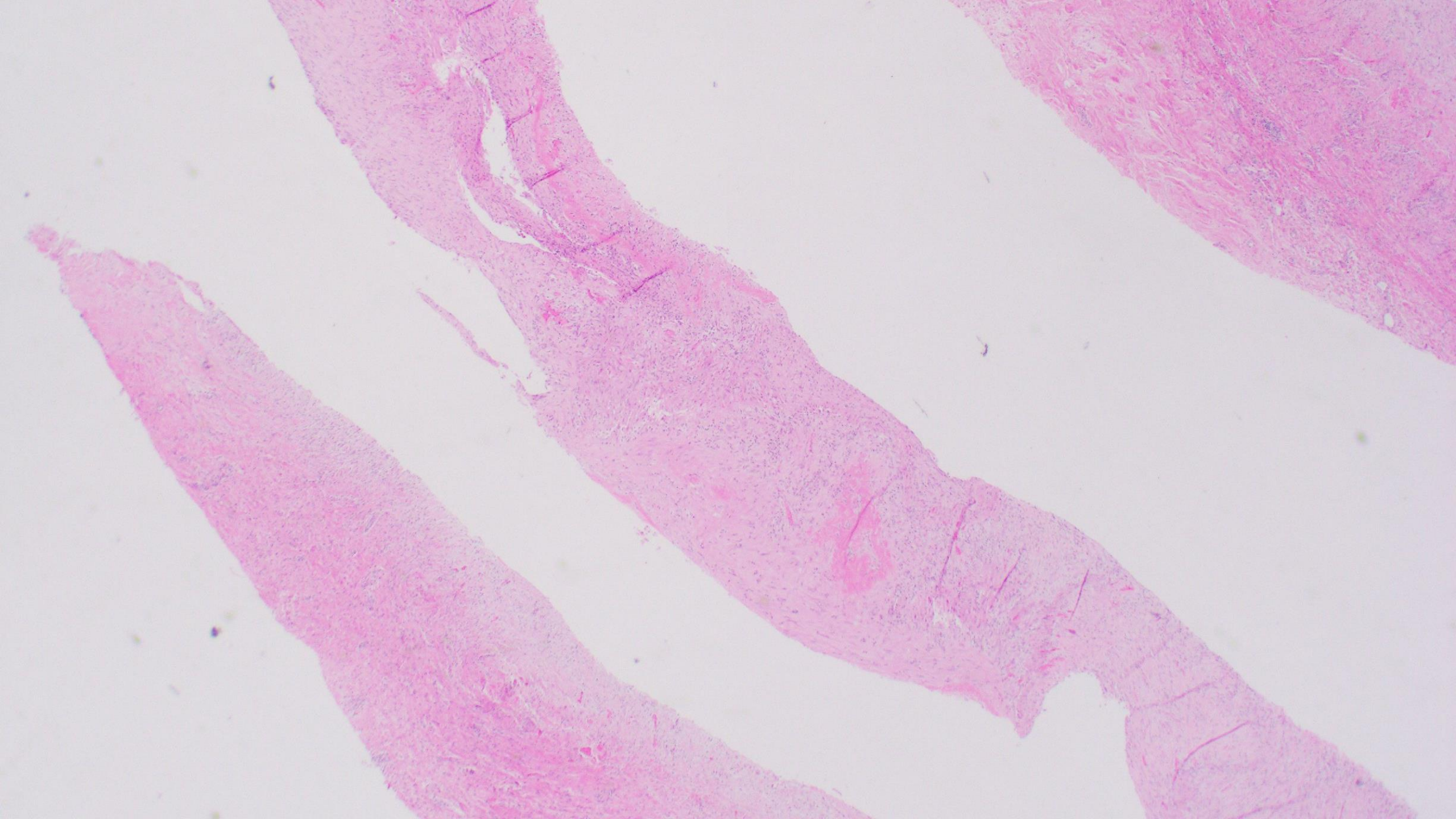
Objectives and presentation outline

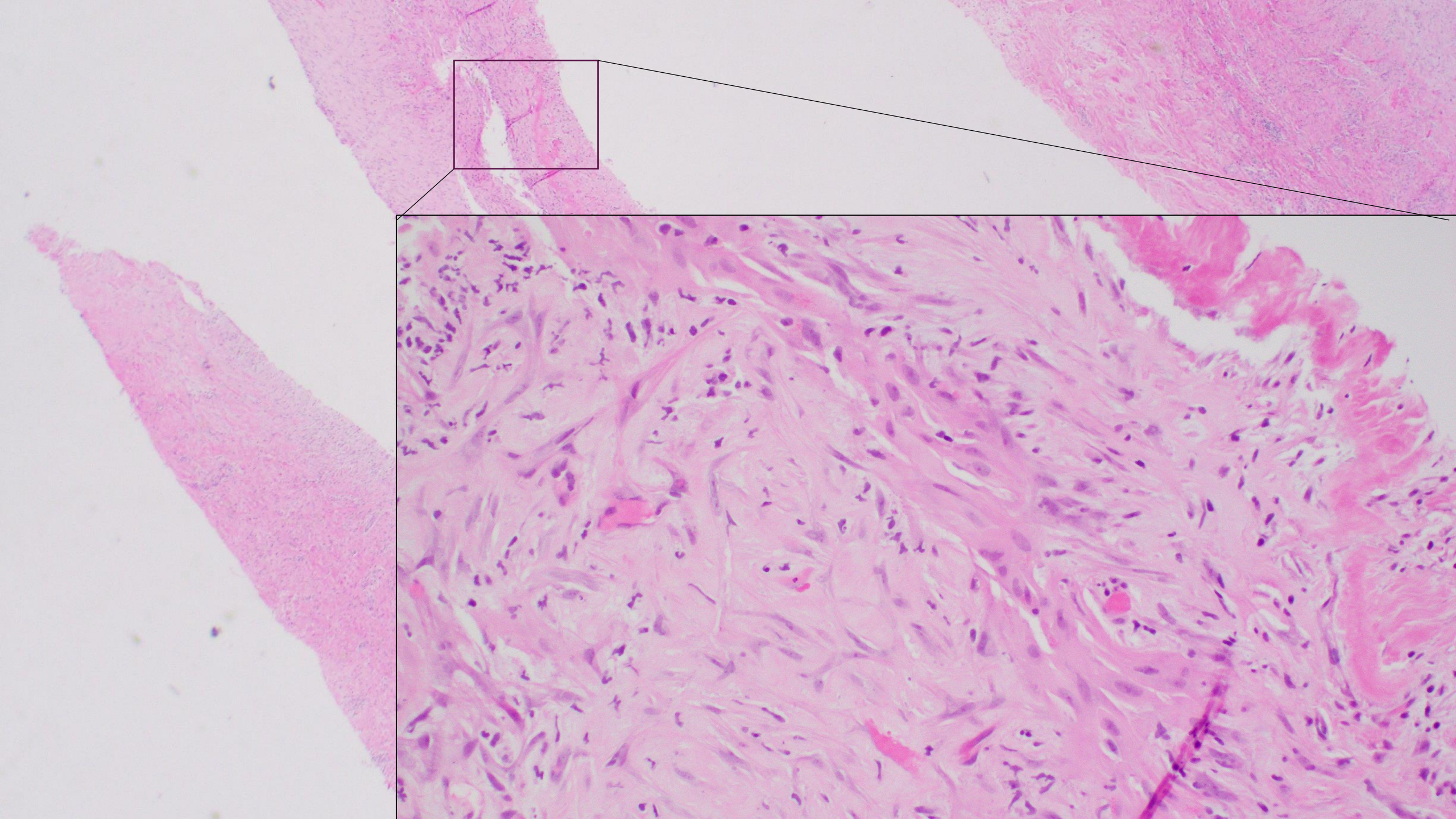
- Outline
 - 5 cases
 - Each case will have a discussion of differential considerations and literature review
 - Take home message
 - References
- Objectives
 - Breast biopsy shows a benign appearing cyst with squamous lining. What is the differential diagnosis?
 - What is the differential diagnosis for radial scar with squamous metaplasia?
 - Is squamous metaplasia in mammary tissue very rare?
 - What is the differential diagnosis for breast biopsy showing carcinoma with squamous differentiation?

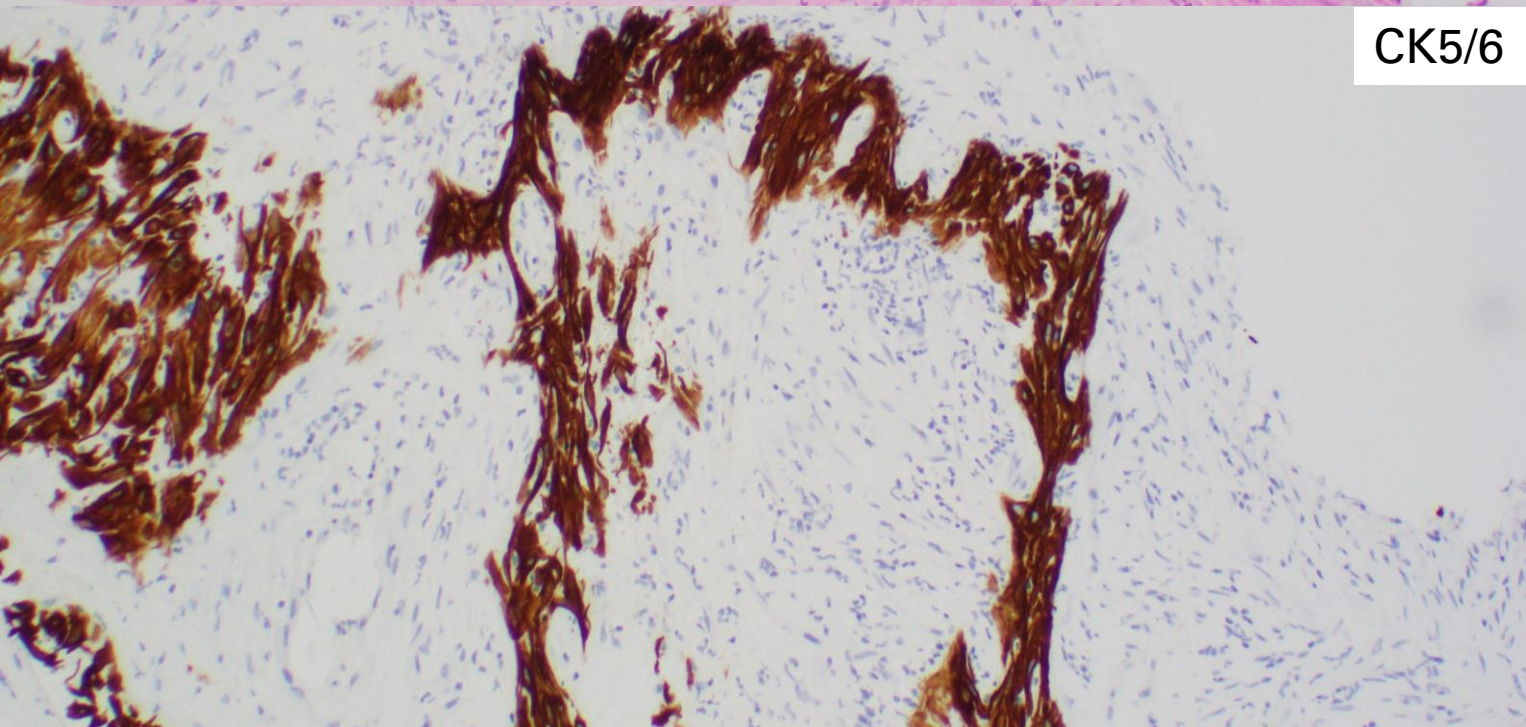
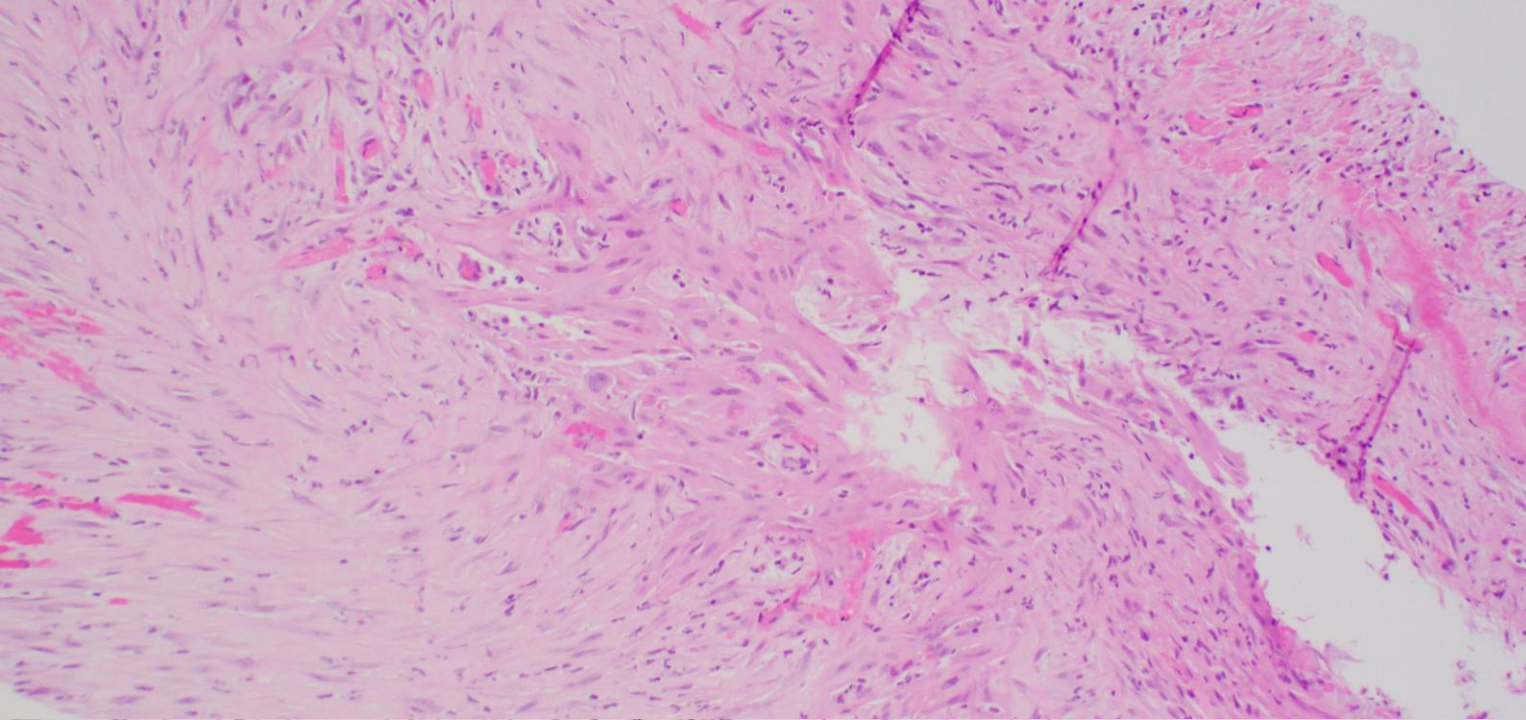
CASE 1

- 51-year-old female presents for a lump in her left breast
- Imaging showed an oval, complex cystic and solid mass measuring 2 cm, found 1 cm from nipple
- Ultrasound guided biopsy was obtained
- BI-RADS category 4





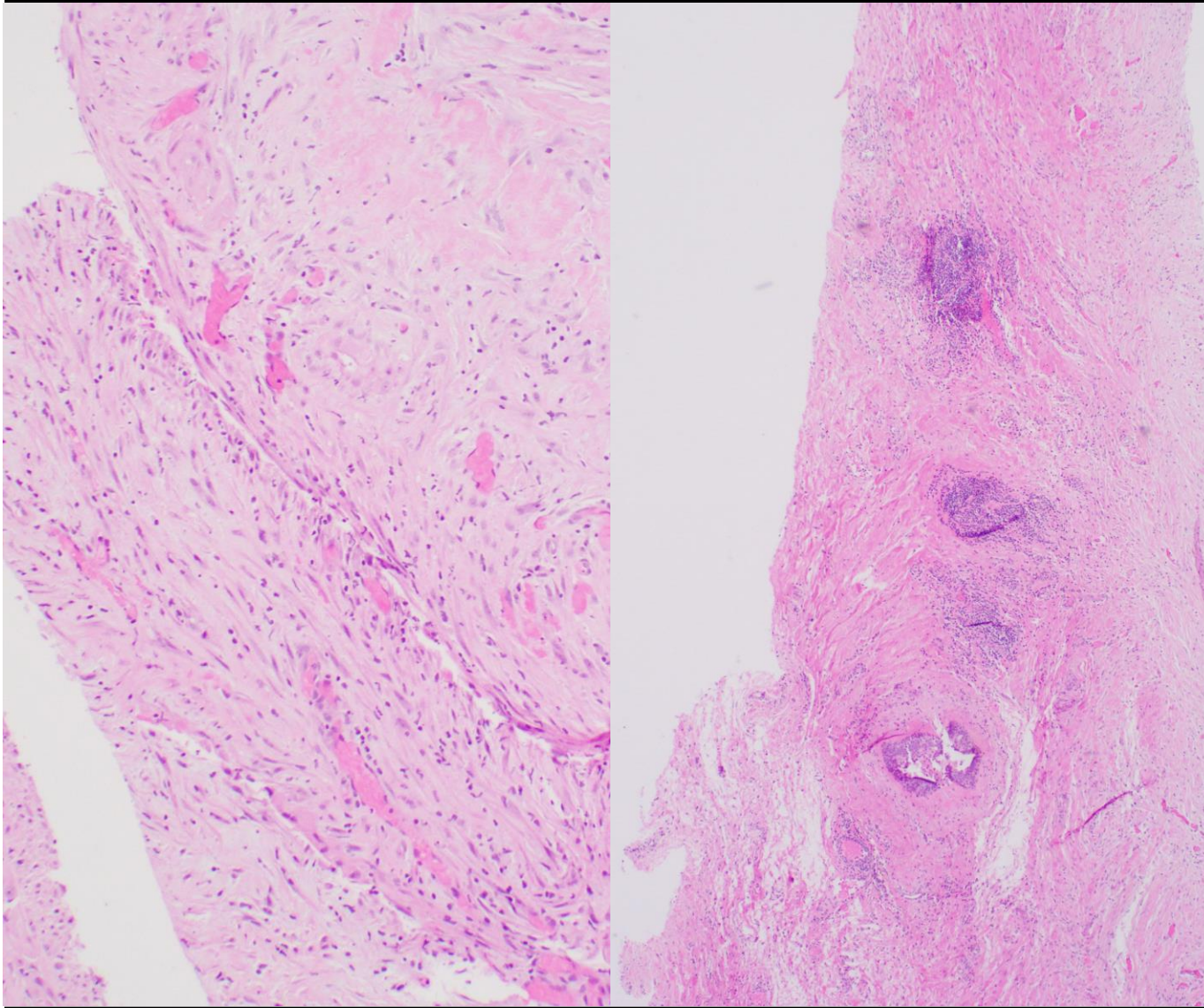




CK5/6

- The epithelium stains positive for AE1/AE3, CAM5.2, CK5/6, K903, and shows multifocal staining for p63
- The spindle cells stain positive for SMA and show multifocal staining for CD34 but are negative for cytokeratins (AE1/AE3, CAM5.2, CK5/6, K903) and p63

Cystic structure and chronic inflammation



Differential considerations

- Epidermal inclusion cyst
- Squamous metaplasia of lactiferous ducts (SMOLD) or a cyst with squamous metaplasia
- Metaplastic (squamous) carcinoma

Final Diagnosis: Cyst lining with squamous metaplasia and reactive inflamed stroma

- Patient didn't get a resection
- There are no updates in her clinical chart (it has been two years since the biopsy)
- Detailed review of her clinical chart revealed smoking history

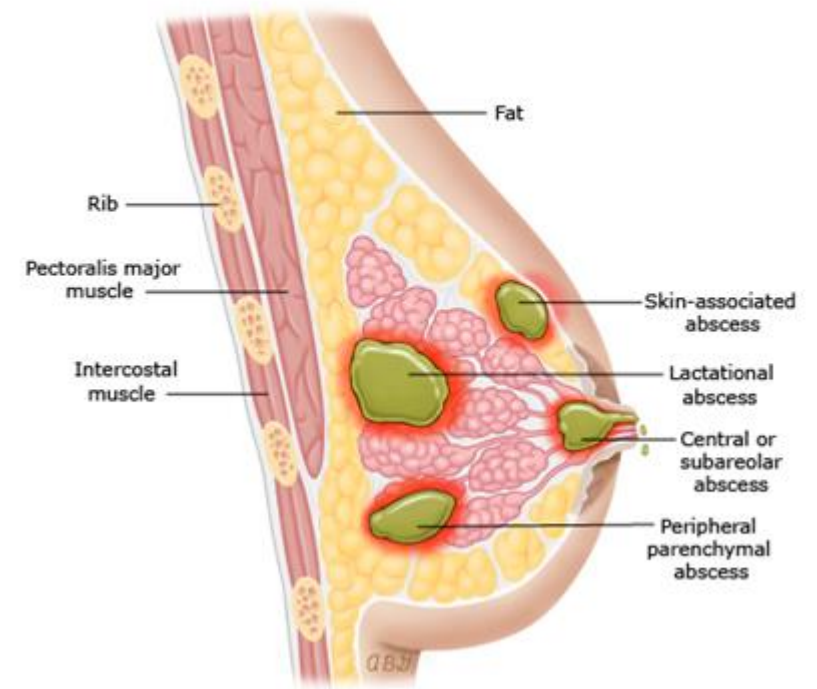
Squamous metaplasia of the breast

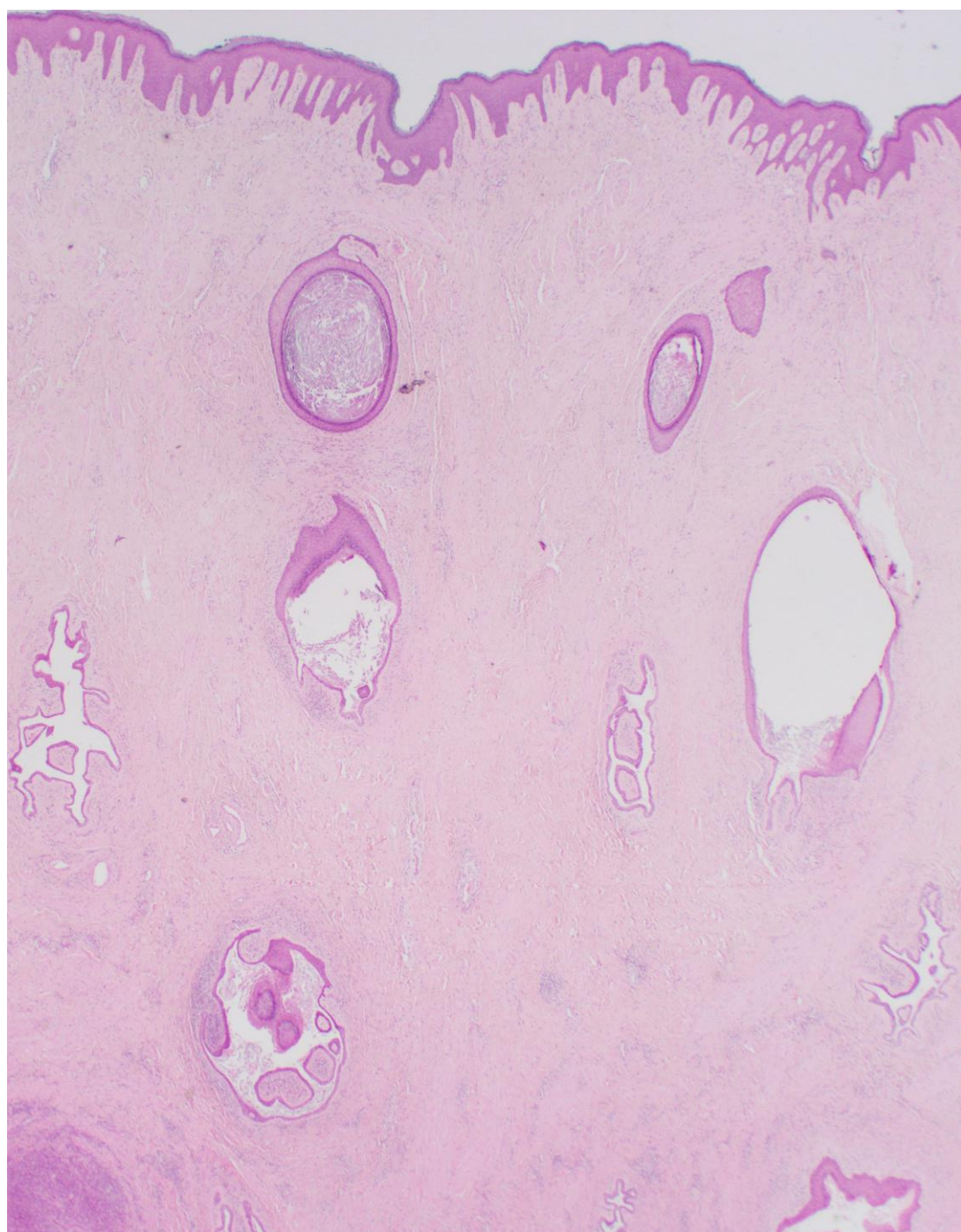
- Very rare in breast tissue
- Reported in association with fibrocystic changes, radial scars, papillomas, fibroadenomas, adenomyoepithelioma and phyllodes tumors (mostly in the form of case reports)
- A special consideration would include squamous metaplasia of lactiferous ducts (SMOLD) also called periductal mastitis, which occurs around the nipple and may cause pain, masses, nipple discharge, abscesses and fistula formation

Squamous metaplasia of lactiferous ducts (SMOLD)

- Occurs in women and men often in 4th to 5th decade
- Associated with smoking history
- The pathophysiology includes accumulation of keratin secondary to squamous metaplasia in deeper lactiferous ducts with subsequent blockage
- Classic histologic findings include expanded ducts with keratin debris, periductal acute and chronic inflammatory cell infiltrate with foreign body giant cell reaction

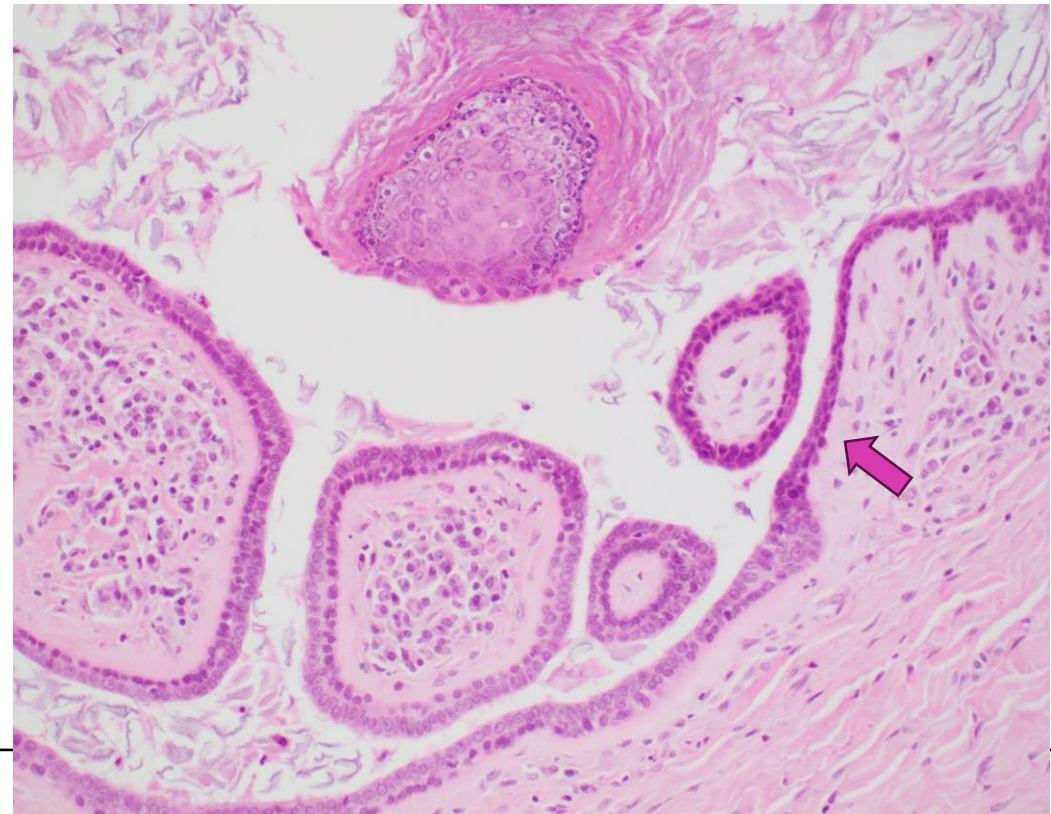
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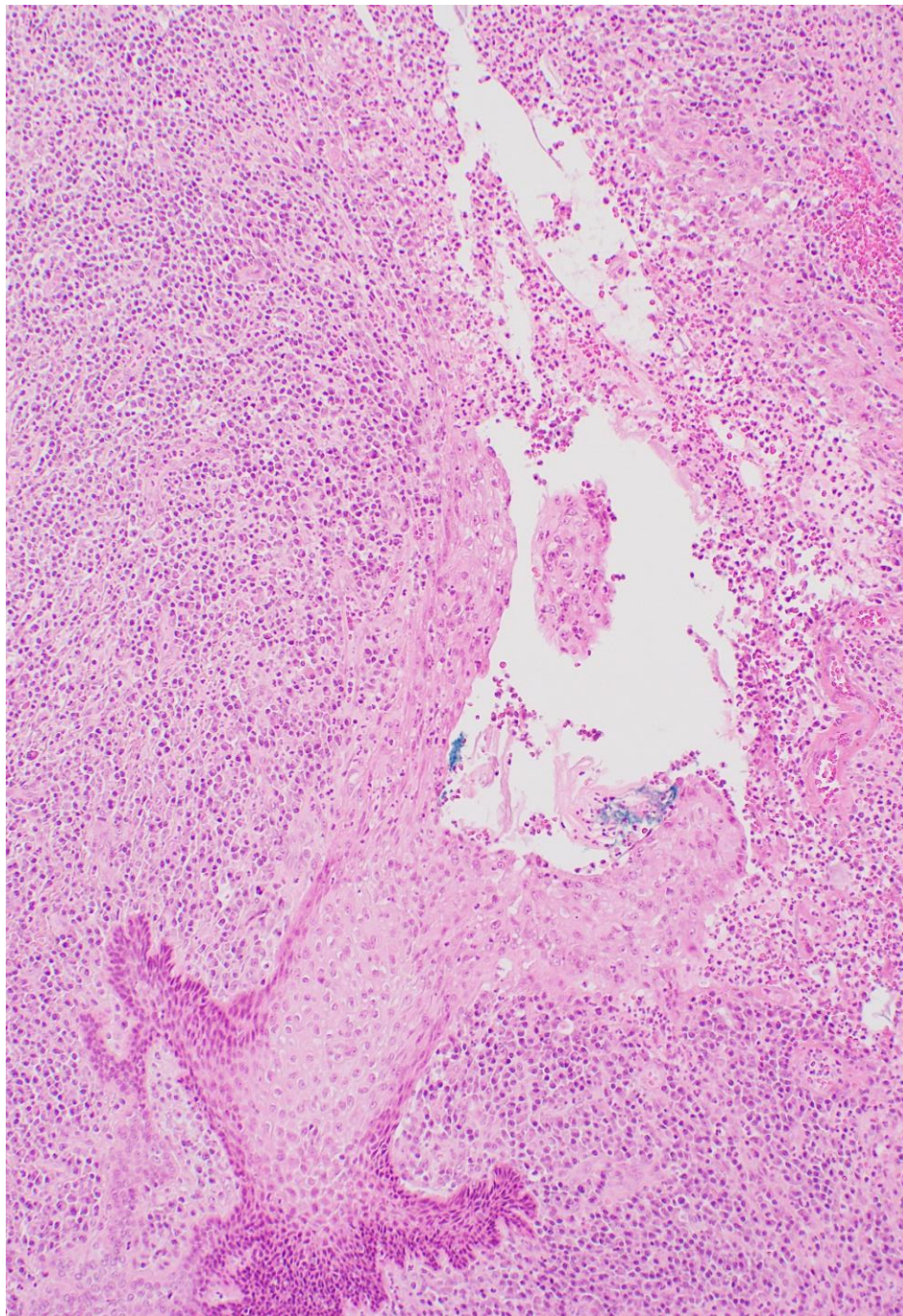




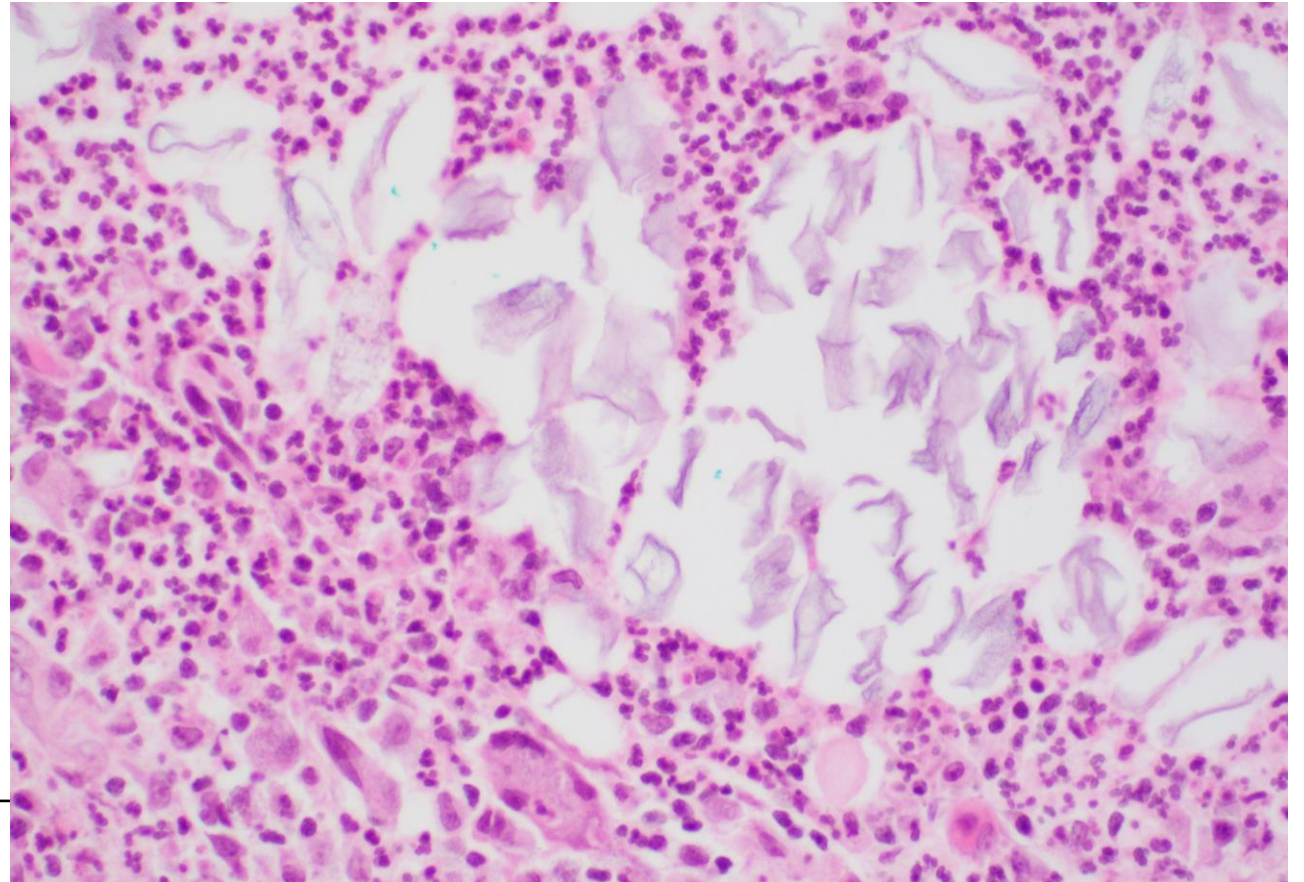
Squamous metaplasia of lactiferous ducts (SMOLD)

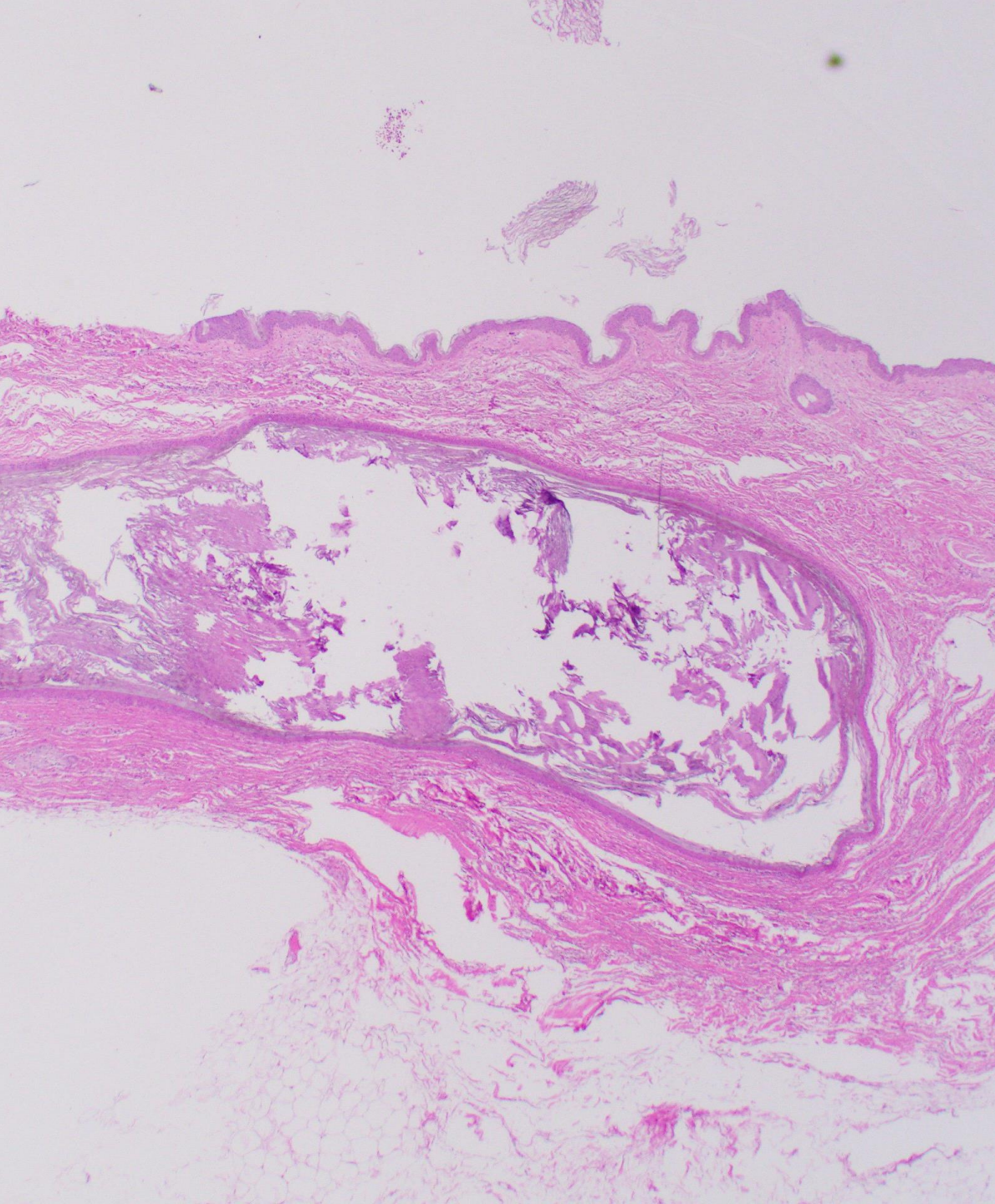
- Lactiferous duct variably involved by squamous metaplasia
- Squamous metaplasia is found below the normal transition zone (0.1-0.2 cm beneath the epidermal surface)





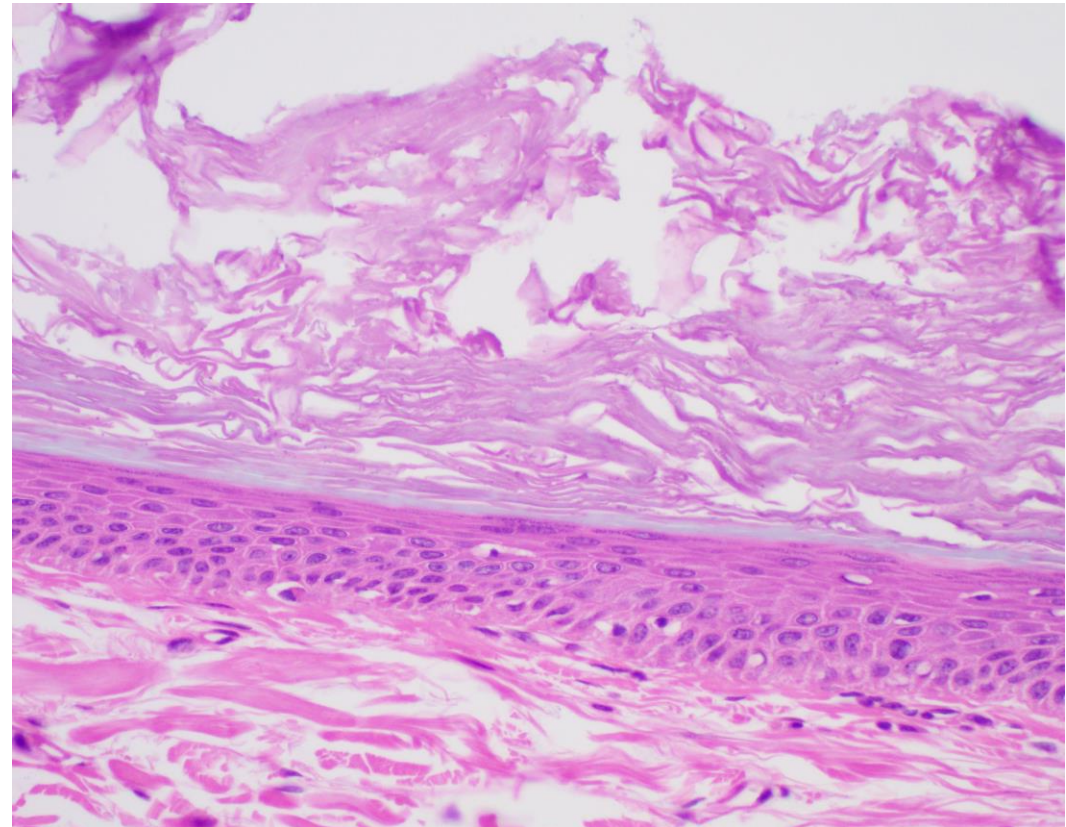
SMOLD with rupture and keratin debris
associated with foreign body giant cell reaction
and acute neutrophilic inflammation

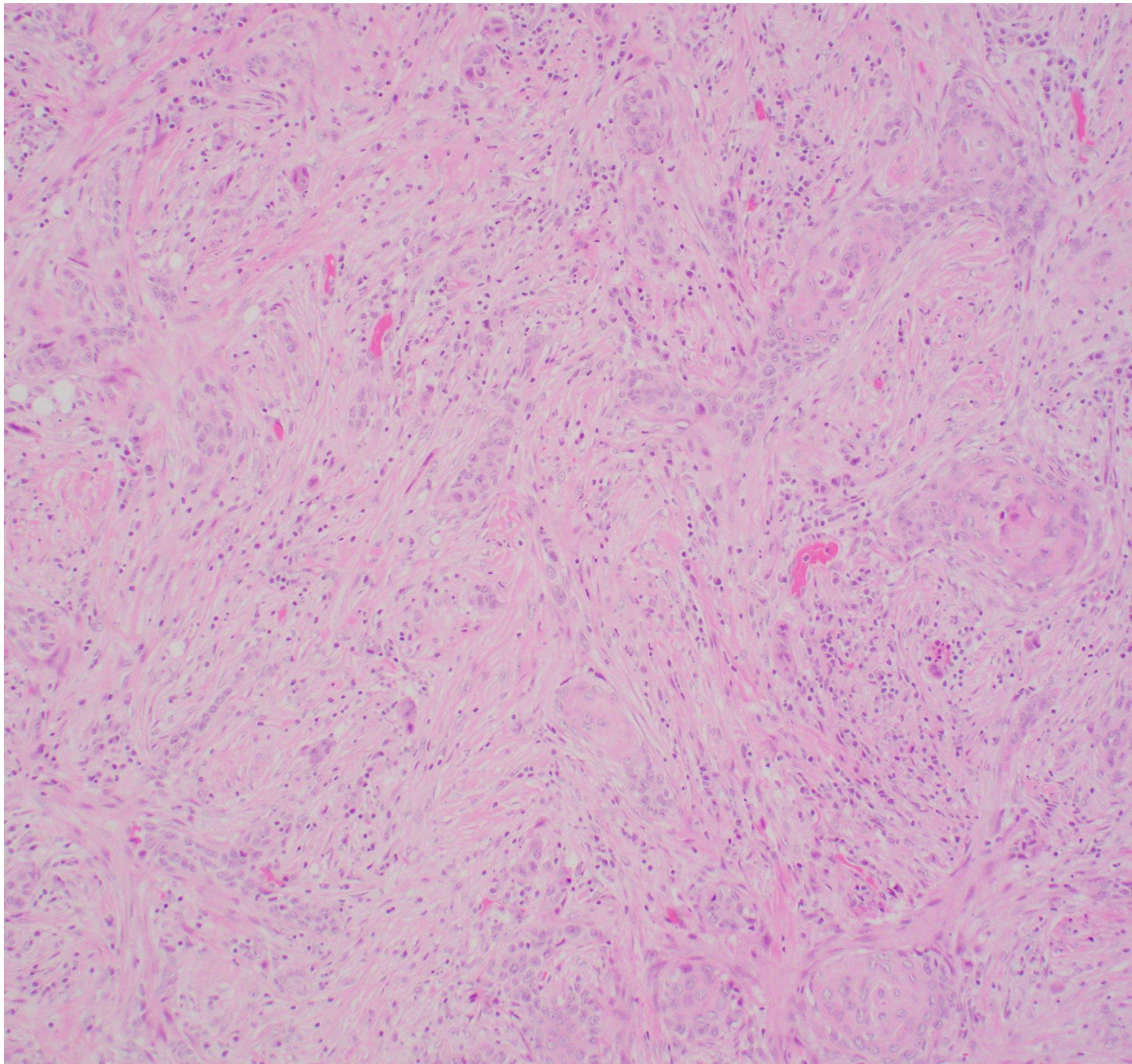




Epidermal inclusion cyst

- Cyst with benign squamous lining filled with keratin debris
- No connection to lactiferous ducts

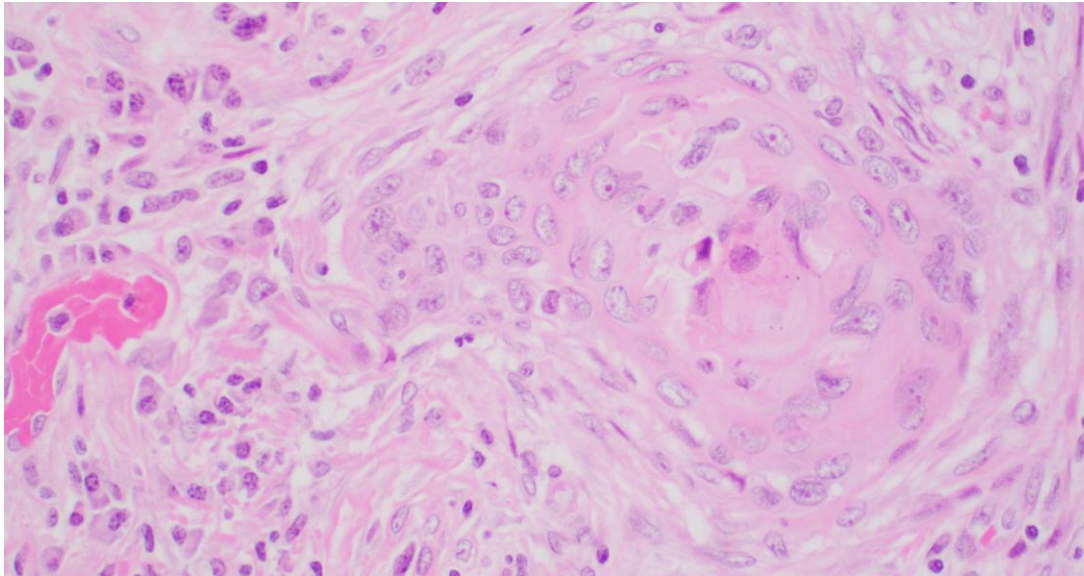




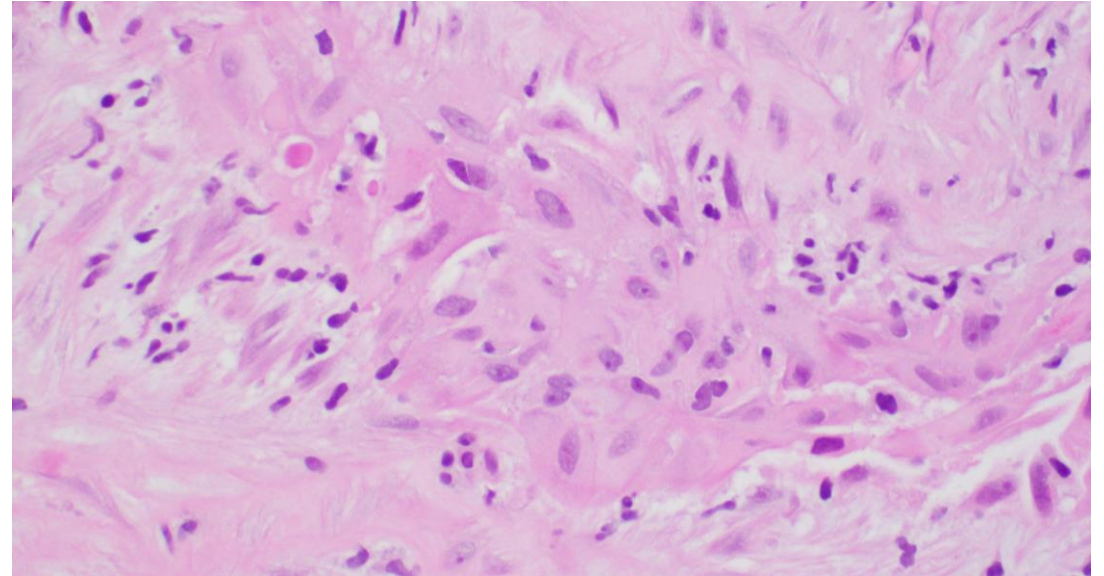
Metaplastic carcinoma

1. Carcinoma with squamous features may be pure or mixed [Pirot et al. 2020]
2. Pure metaplastic squamous cell carcinoma usually presents as a cystic lesion in which the cavity is lined by squamous cells
3. This picture was obtained from a resection case of low-grade adenosquamous carcinoma
 - The neoplastic cells infiltrate the adjacent stroma in the form of sheets cords and nests
 - Variable degrees of squamous differentiation
 - Conspicuous stromal reaction
 - Prominent inflammatory infiltrates

Metaplastic carcinoma on high magnification



Current case with squamous metaplasia

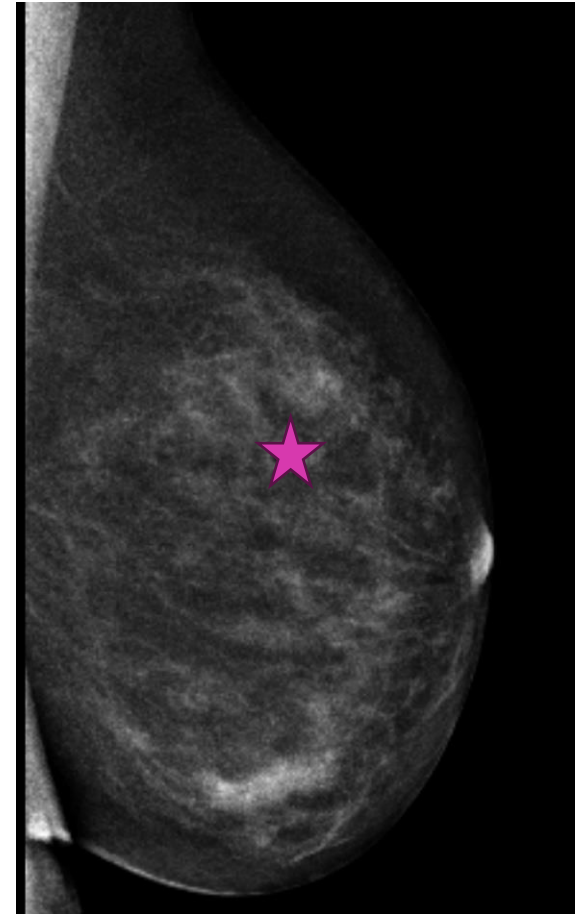


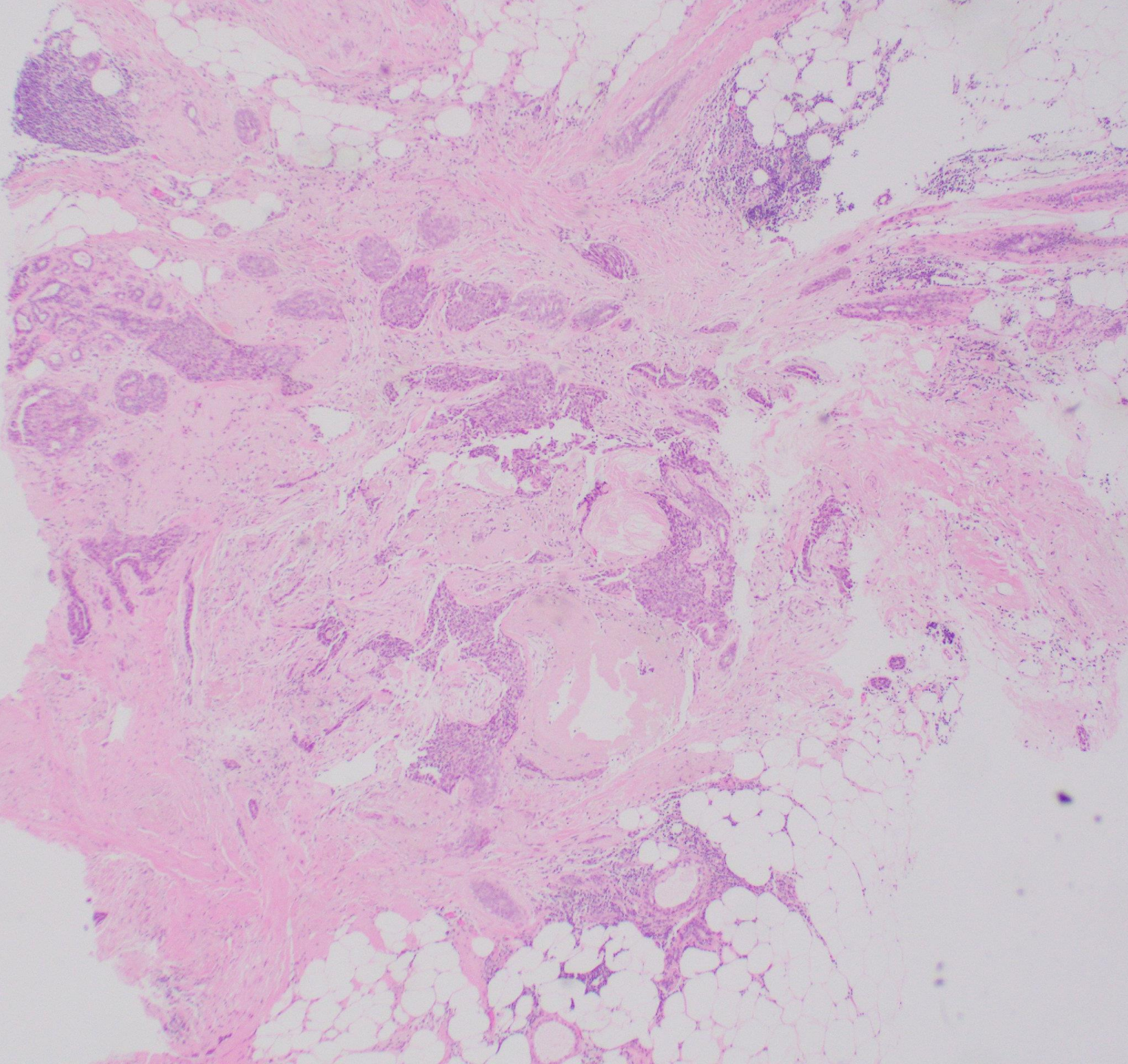
Summary

- SMOLD is a retroareolar inflammatory lesion due to lactiferous duct blockage and rupture with keratinizing squamous metaplasia of the ducts
 - Recurrence is common without definitive treatment, including excision of the affected duct and smoking cessation. Breast duct irrigation may also yield good outcomes [Xu et al. 2021]
 - Secondary infection or abscess may occur
 - Fistula tract usually forms beneath smooth muscle of areola, which is a path of least resistance
- Squamous metaplasia is a rare incidental finding of no real clinical concern
- Epidermal inclusion cyst should not recur if completely excised [Paliotta et al. 2016]
- Carcinoma requires staging and oncologic management and needs to be ruled out

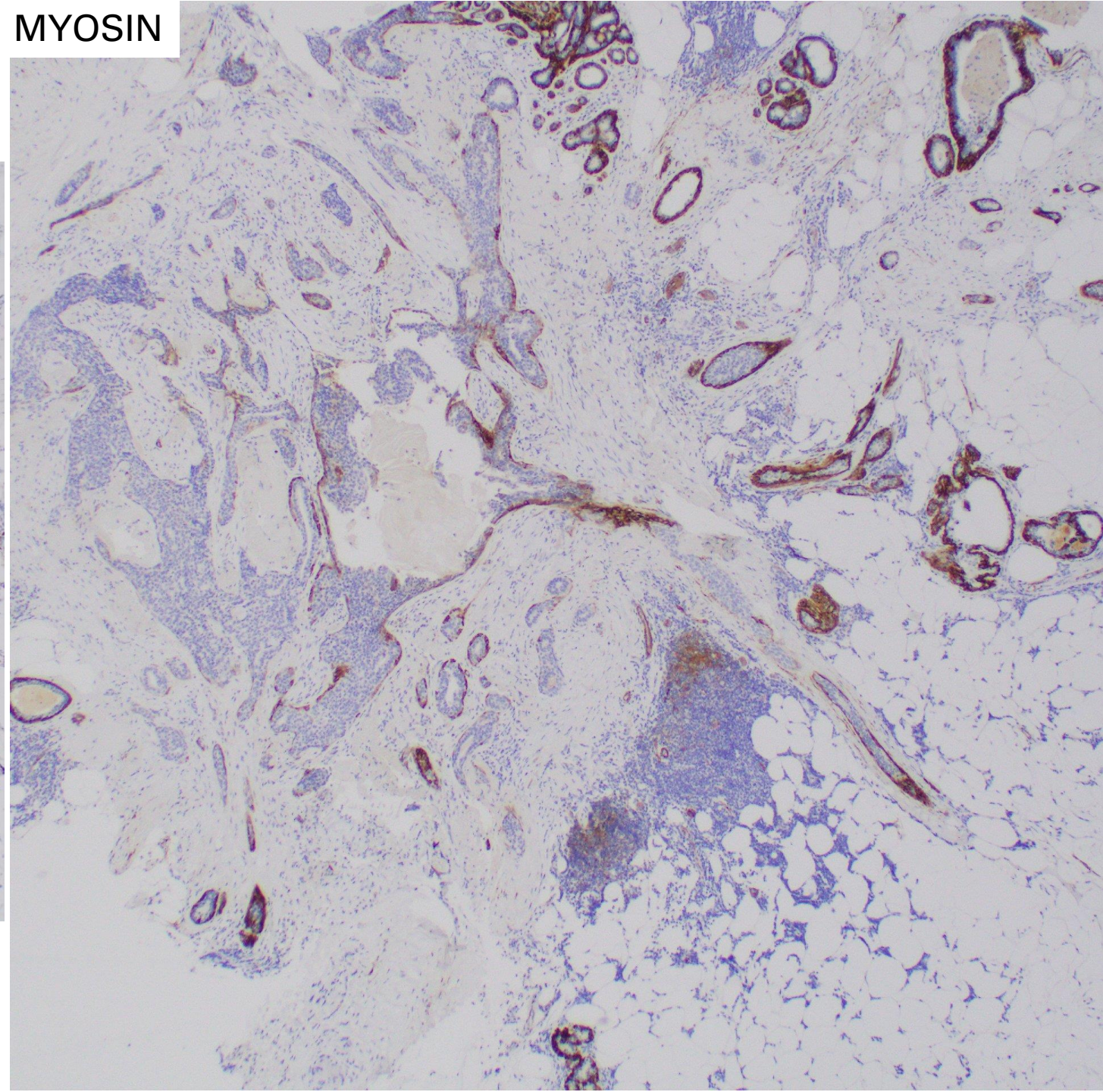
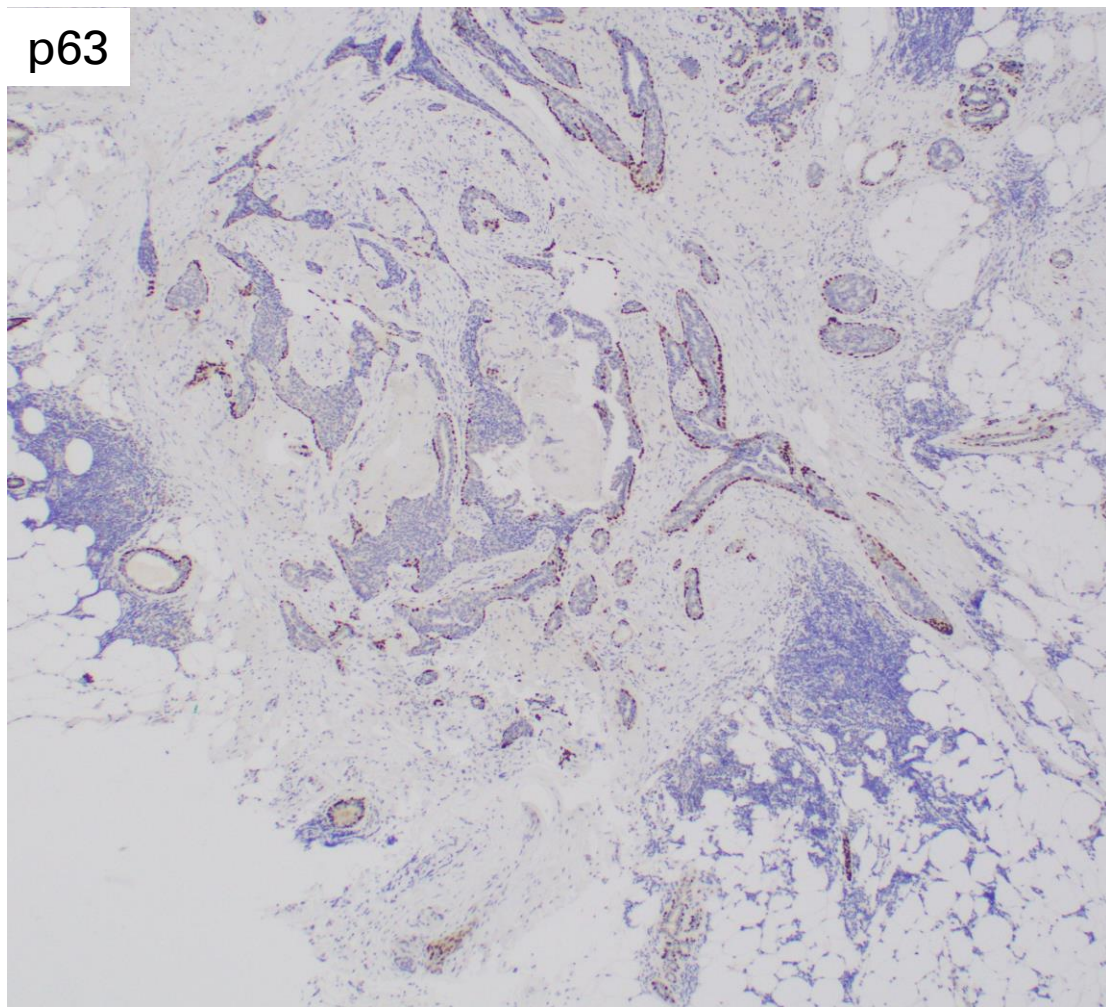
CASE 2

- 60-year-old female with an area of architectural distortion in the upper outer quadrant of the breast on screening mammogram
- This is a new finding since her mammogram done one year prior
- Stereotactic biopsy was performed



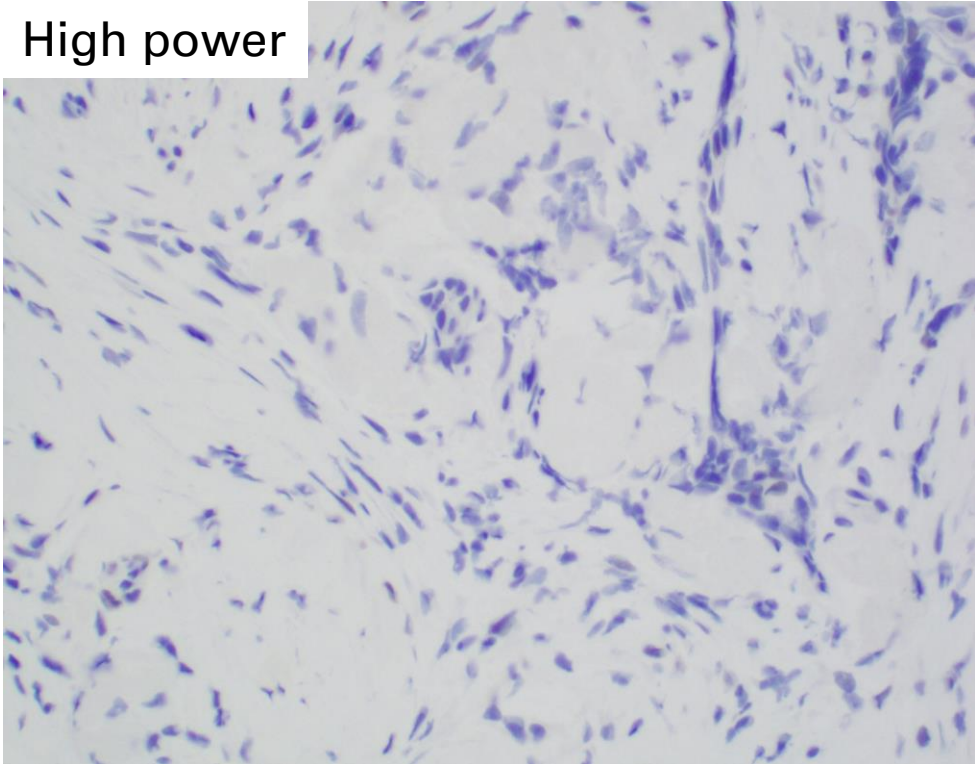


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- Epithelial proliferations
 - Stellate appearance on low magnification
 - Lymphoid aggregates around the periphery
 - Cellular stroma

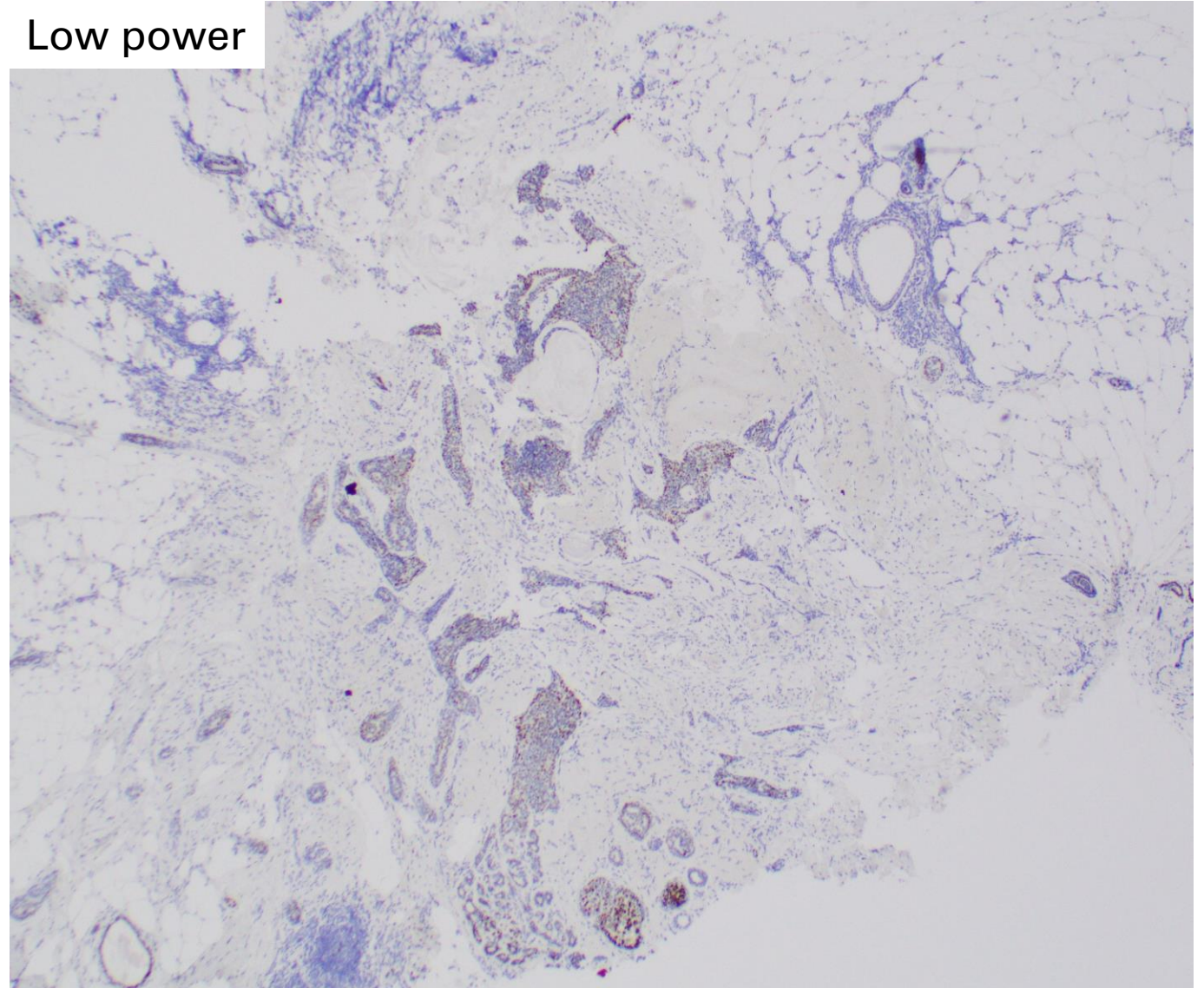


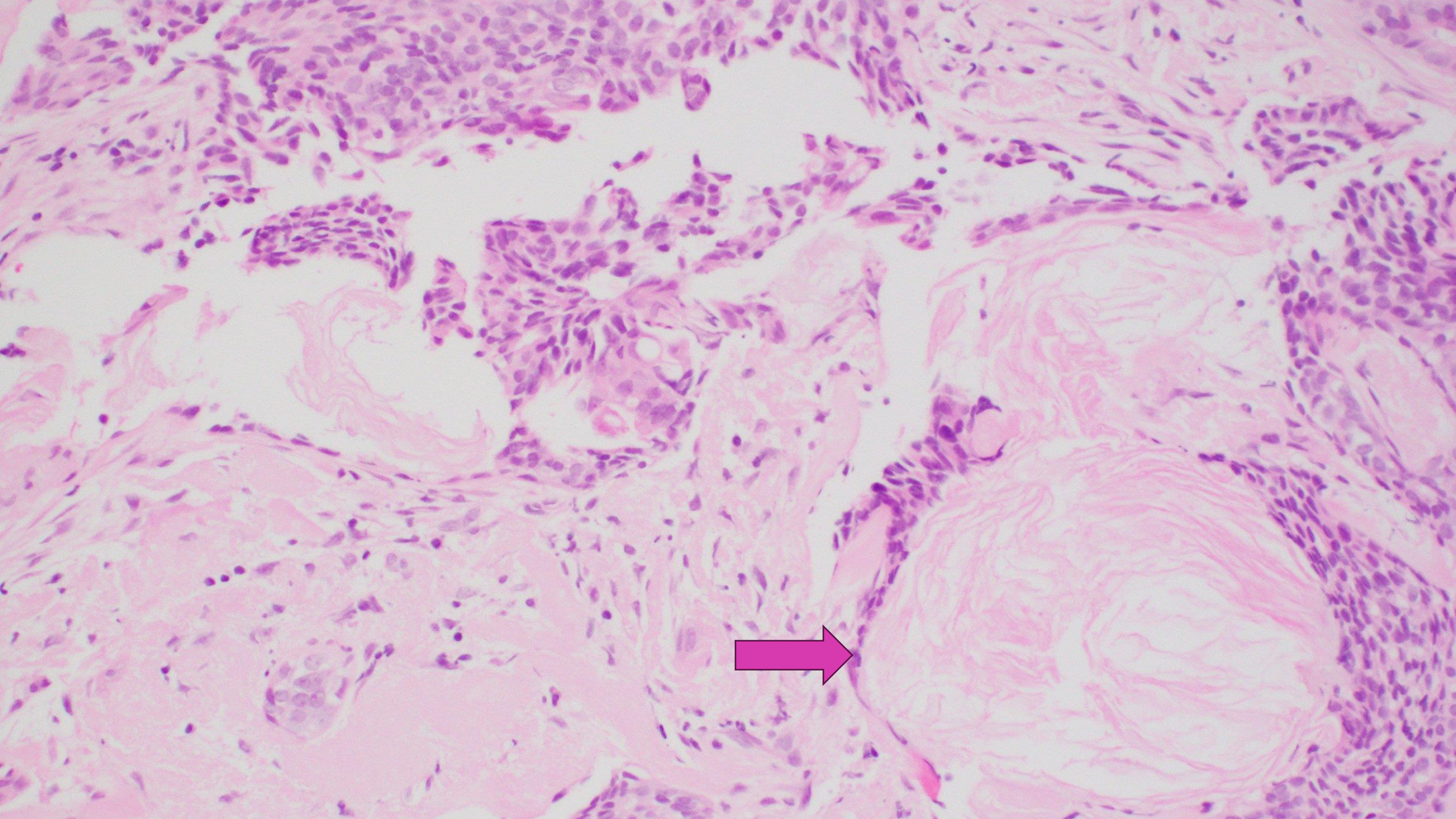
Estrogen Receptor stain

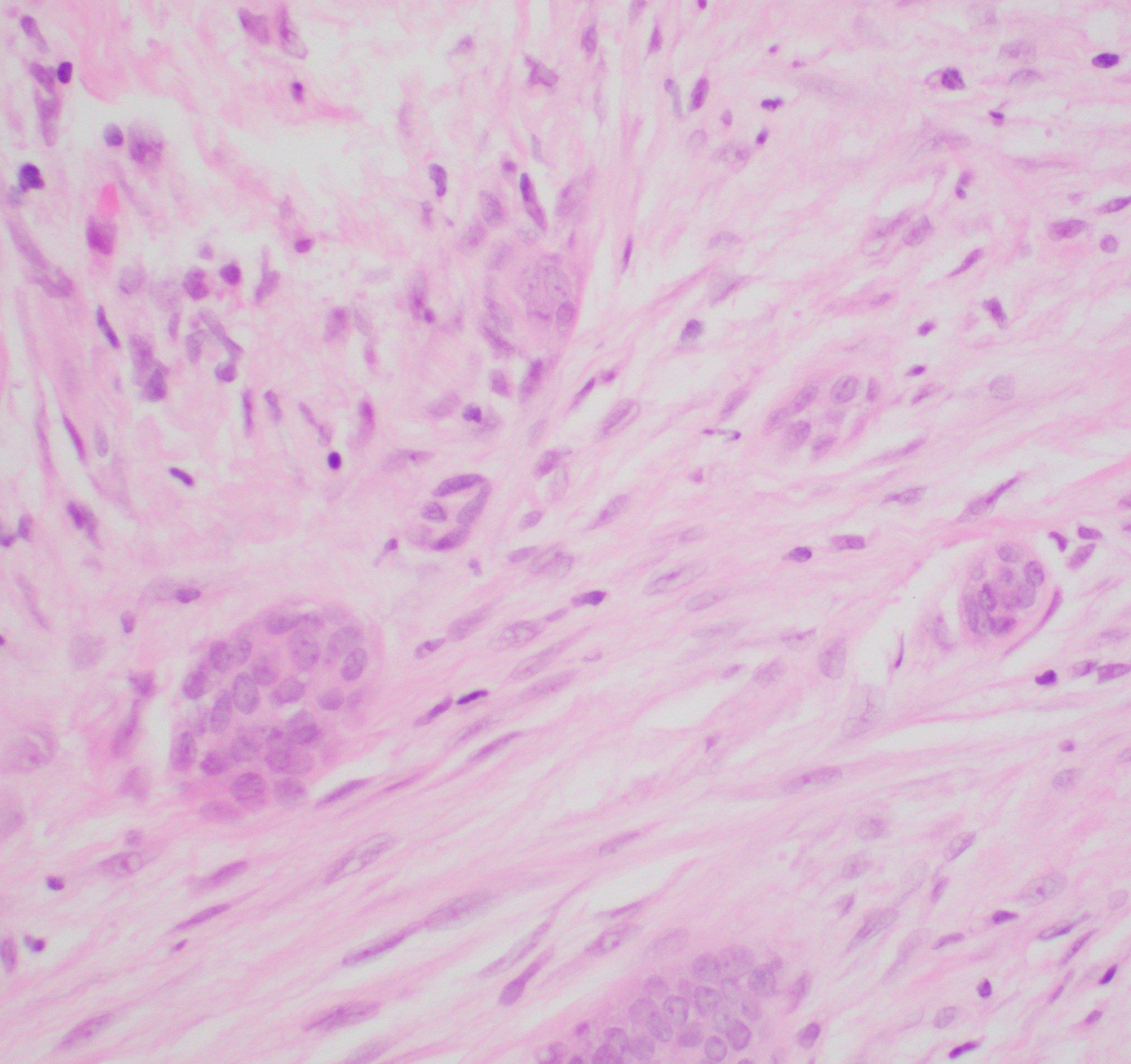
High power



Low power

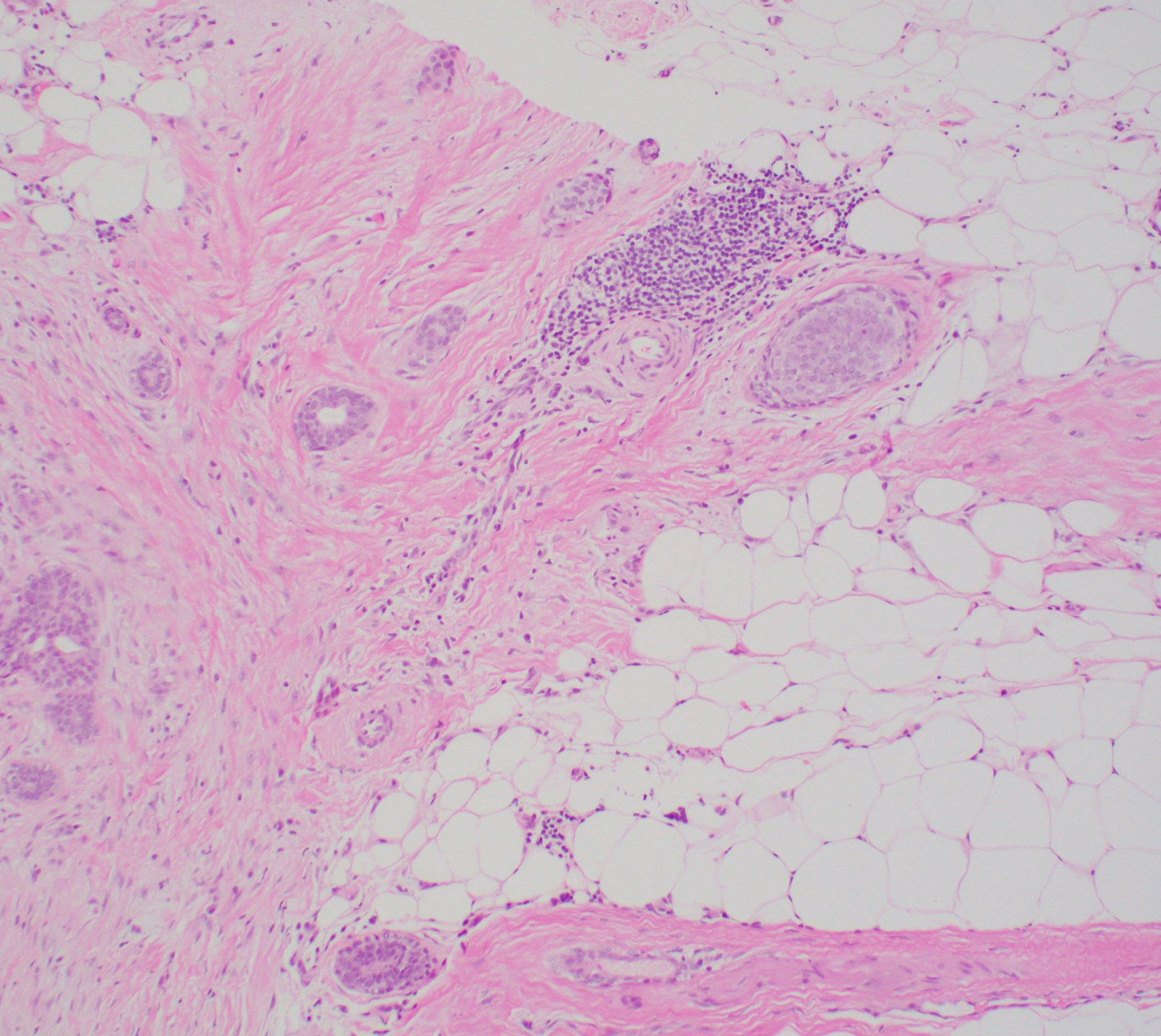




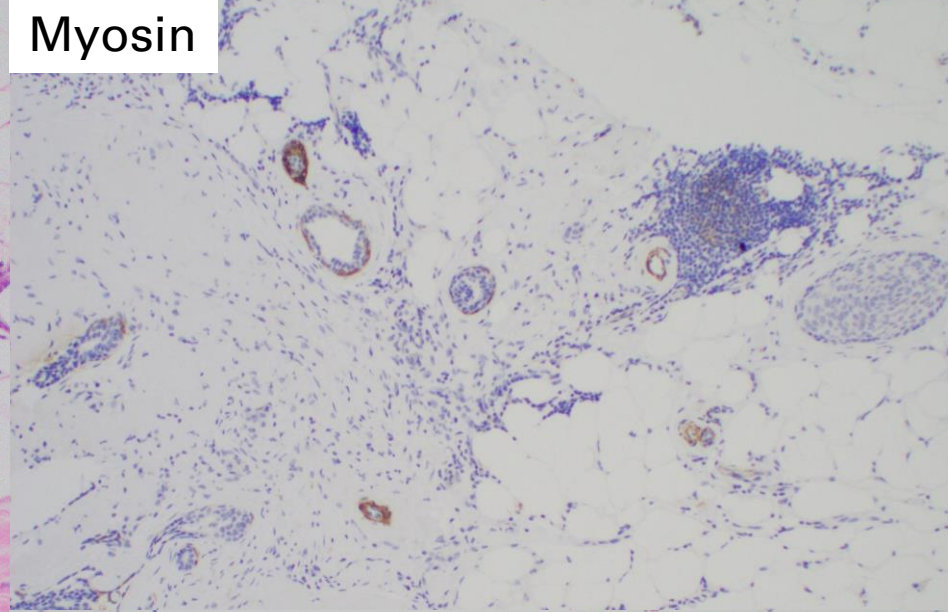


HIGH MAGNIFICATION

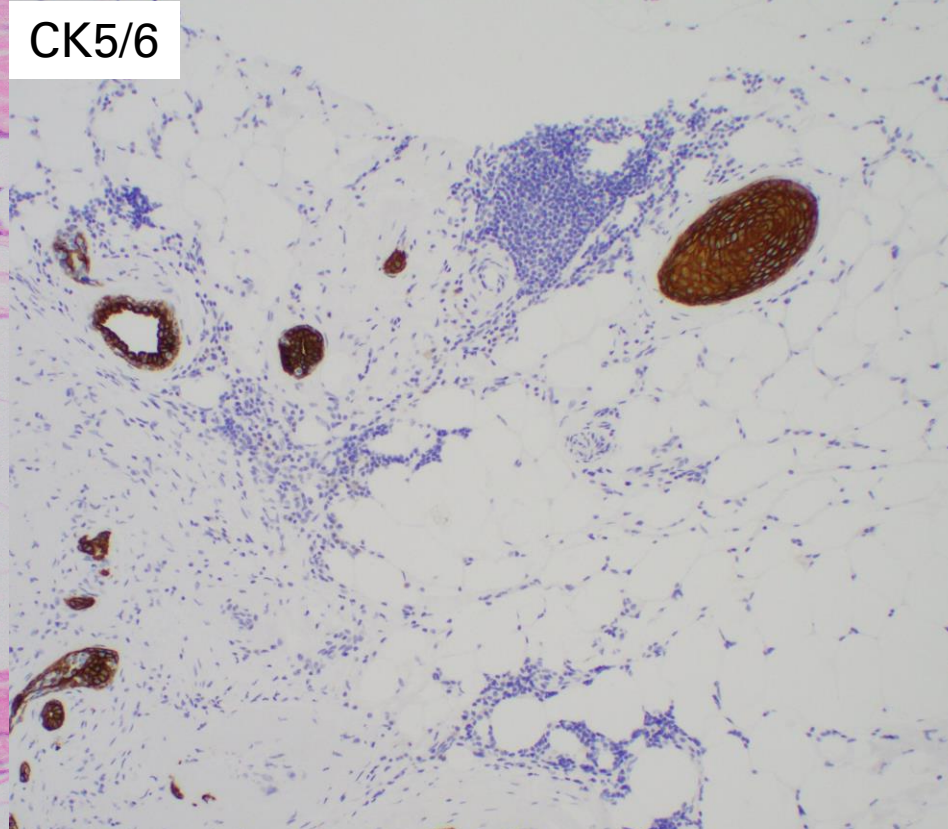
- Cellular spindle cell stroma
- Bland nuclear appearance
- Nests of epithelial cells



Myosin



CK5/6



Differential considerations

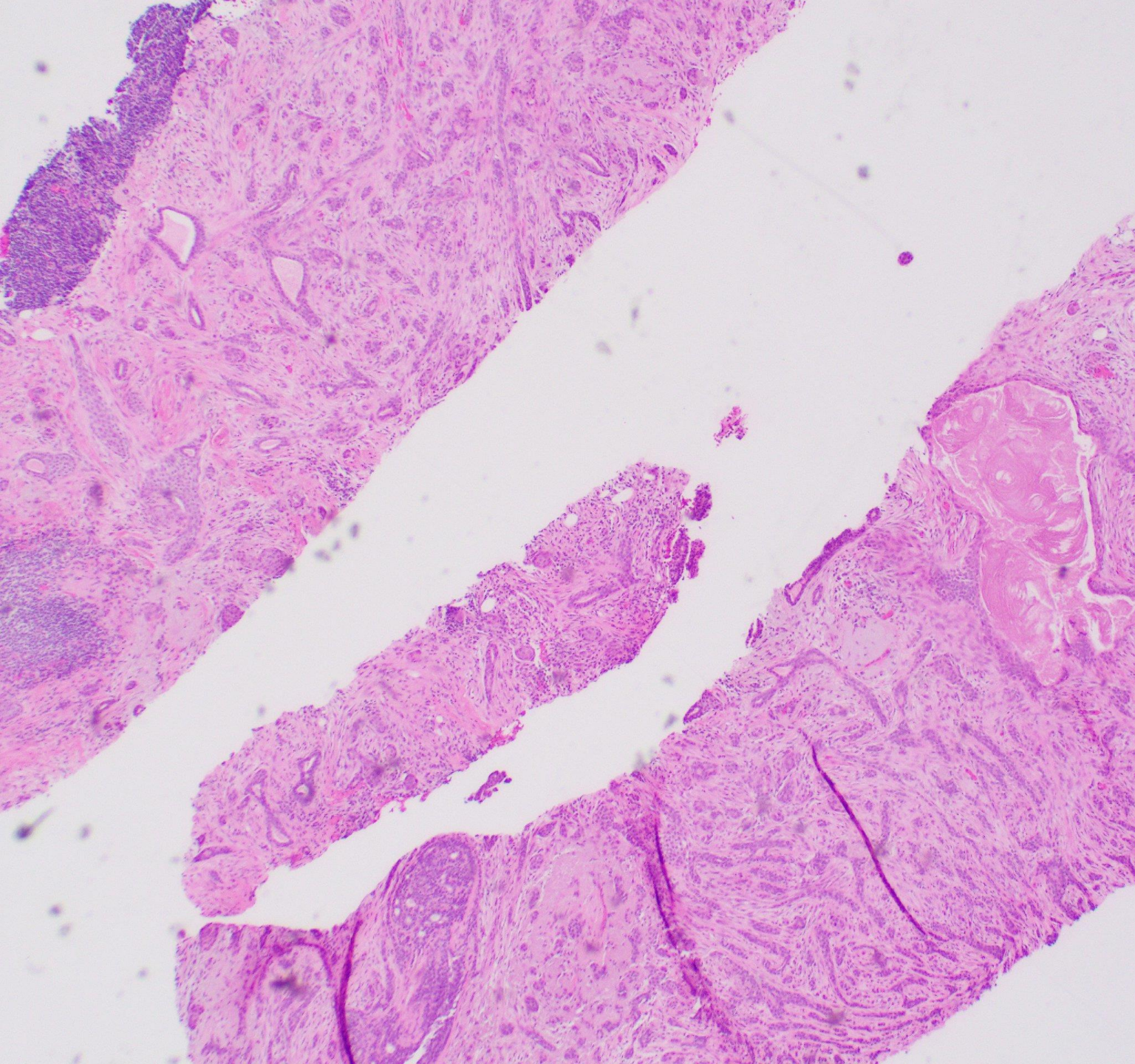
- Radial scar with squamous metaplasia
- Low-grade adenosquamous carcinoma

Final diagnosis: Atypical radial sclerosing lesion (with a comment recommending excision)

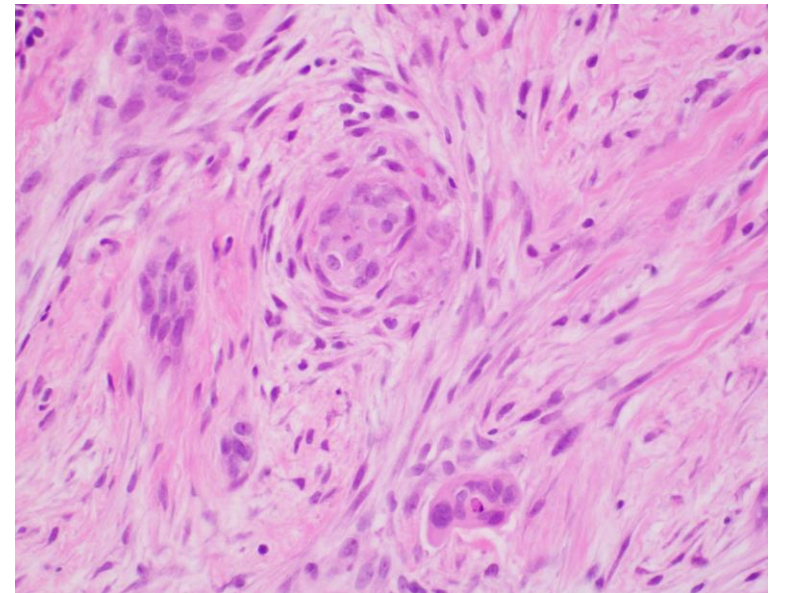
- Lumpectomy was performed which was signed out as low-grade adenosquamous carcinoma
- Patient had one benign lymph node excised
- Received radiation therapy
- No recurrences on 9 months follow-up

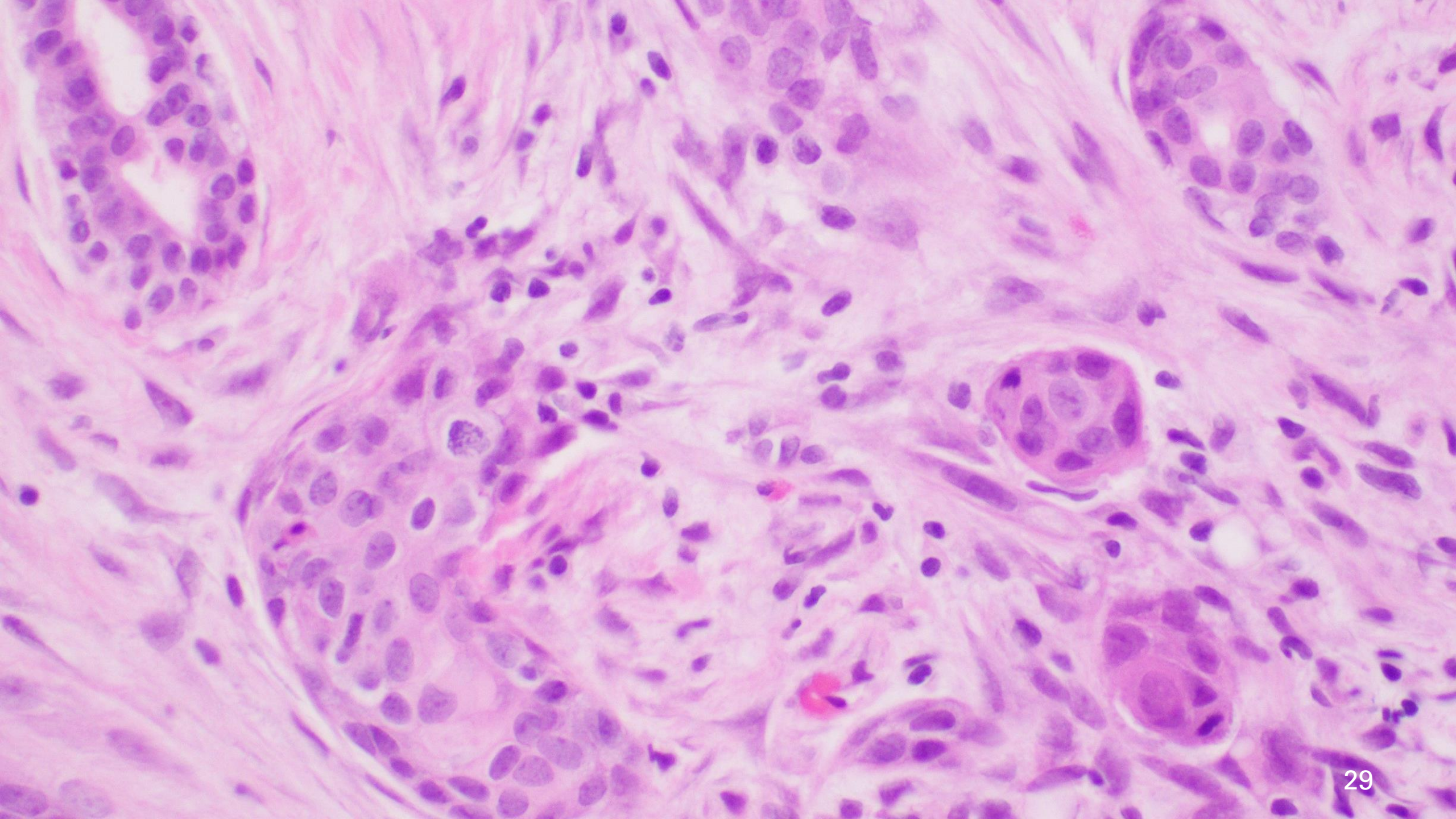
Low-grade adenosquamous carcinoma

- Definition:
 - Low-grade tumor with two coexisting components (glandular and squamous)
 - Peripheral clusters of lymphocytes in a “cannon ball” pattern
 - Cellular stroma
 - ER/PR/HER2 negative or triple negative tumor (typically)
- Rare with <1% of overall breast cancers
 - Usually in peri- or post menopausal women
- The optimal treatment strategy for LGASC is still unknown
 - Breast conserving surgery with adjuvant radiation therapy is today the preferred therapeutic approach to this cancer because of the very low incidence of nodal or distant metastases

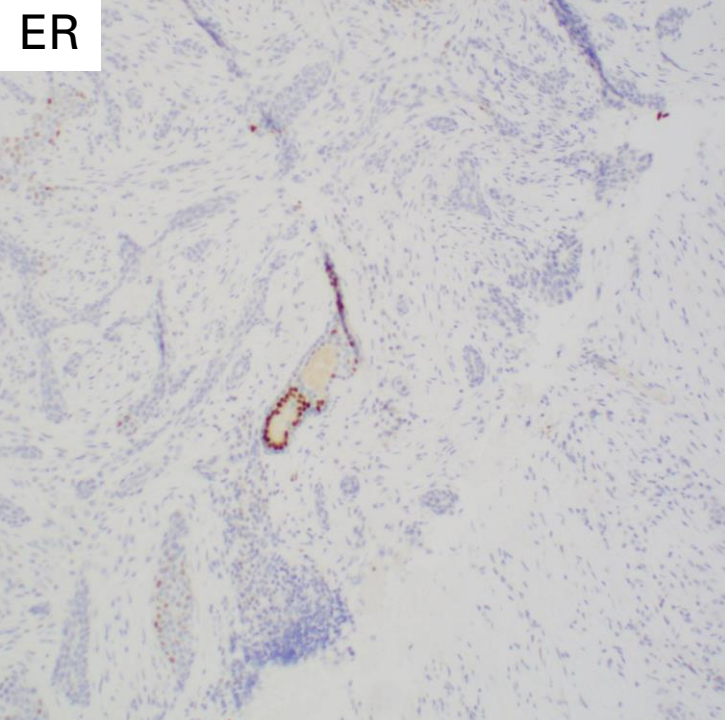


Low-grade adenosquamous carcinoma

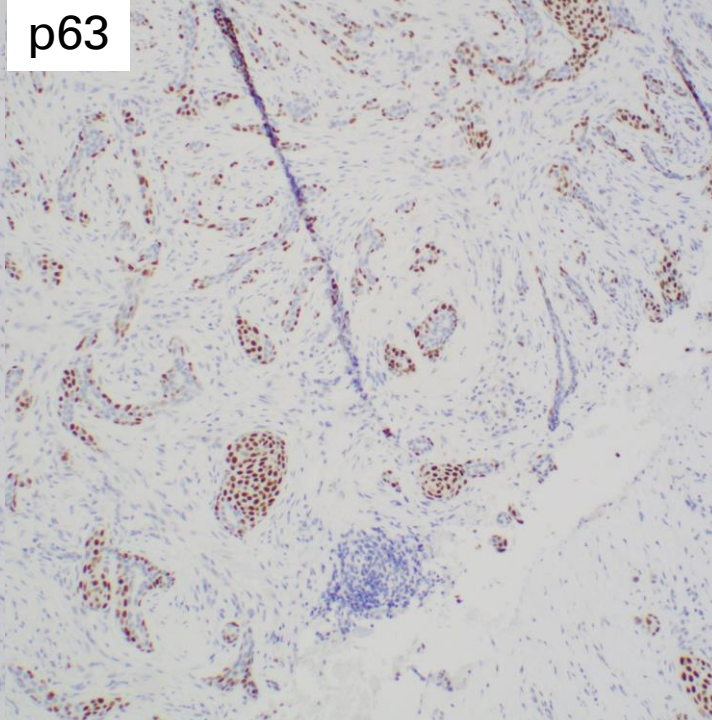




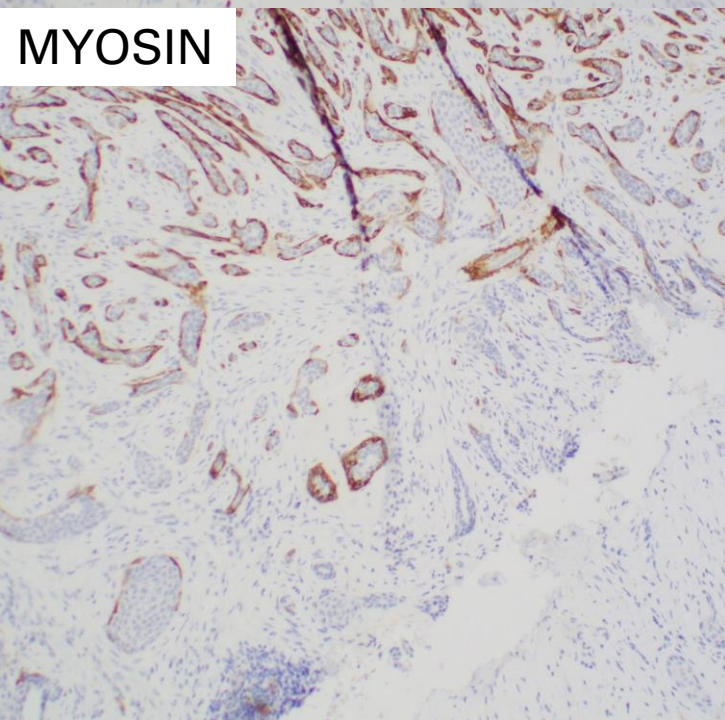
ER



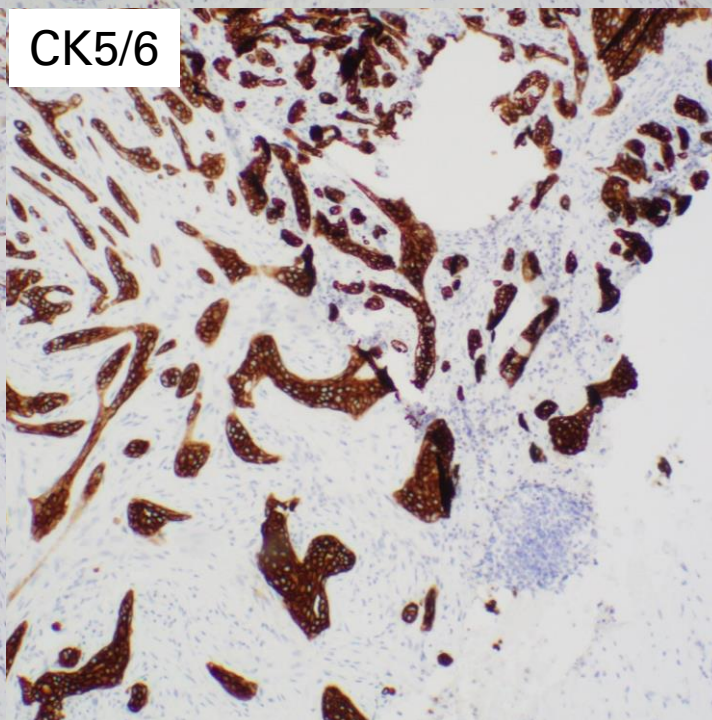
p63



MYOSIN

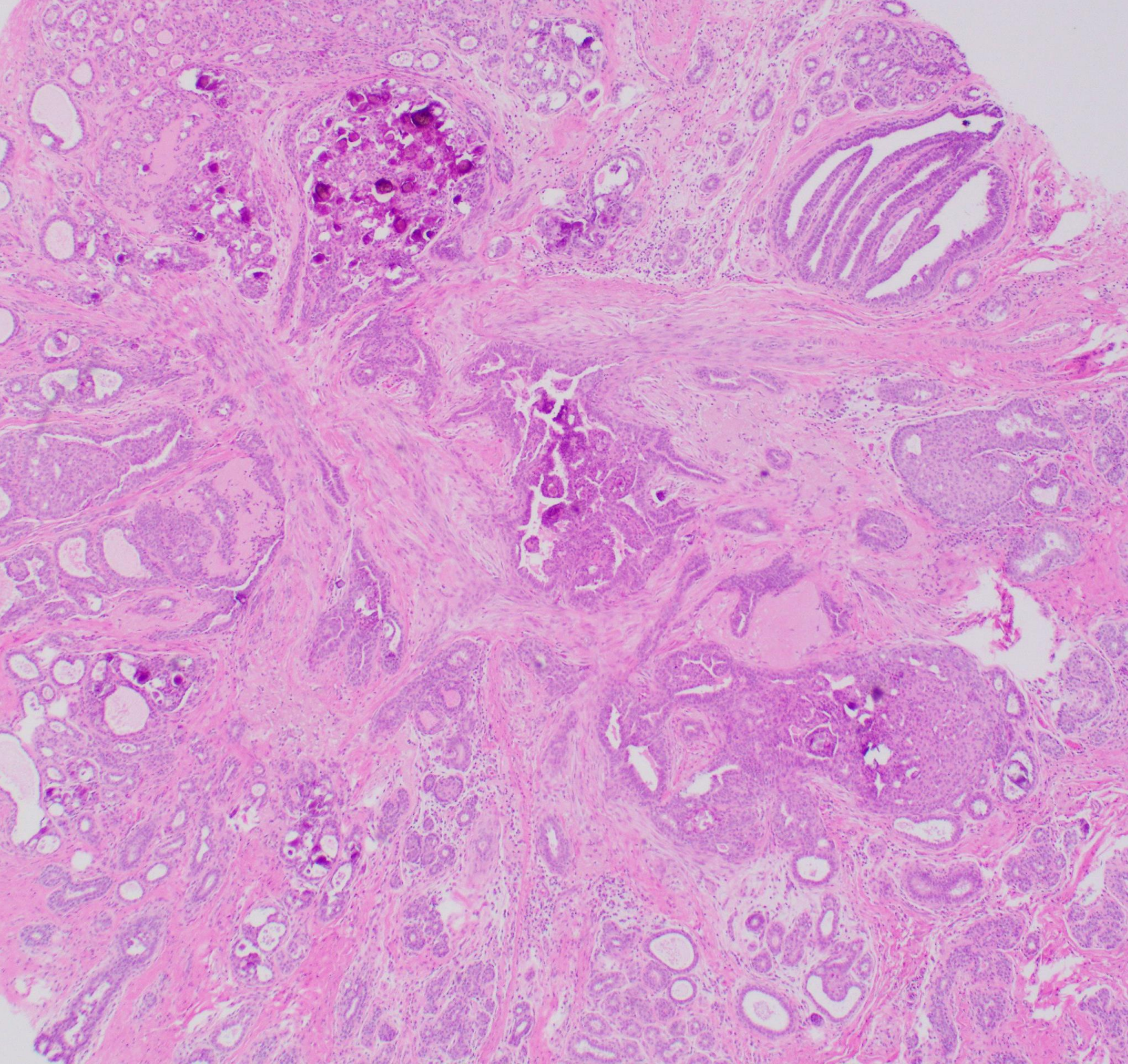


CK5/6



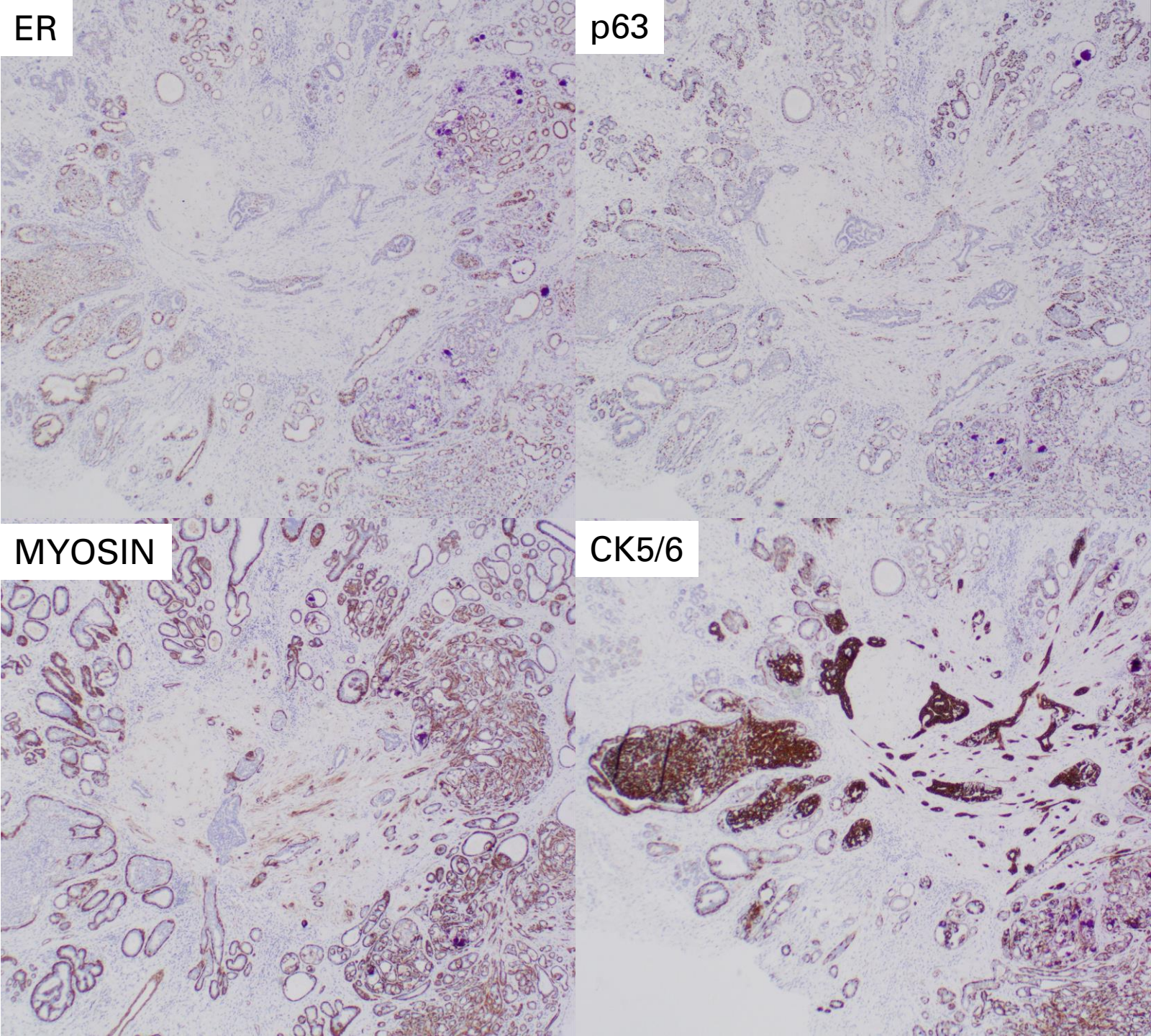
Low-grade adenosquamous carcinoma

- Variable p63 and myosin staining
- Prominent staining on CK5/6
- Low to negative ER



Radial sclerosing lesion

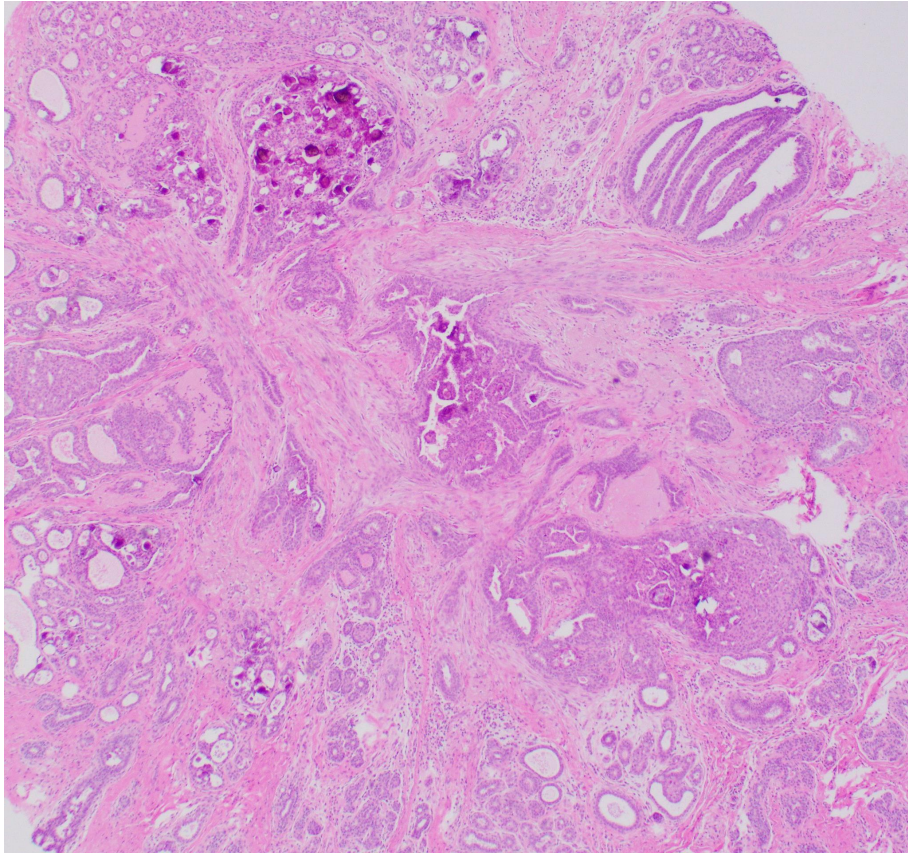
- Central fibroelastotic stroma
- Radial arrangement of glands
- Often stroma is densely sclerotic
 - Early radial scars may show stromal cellularity



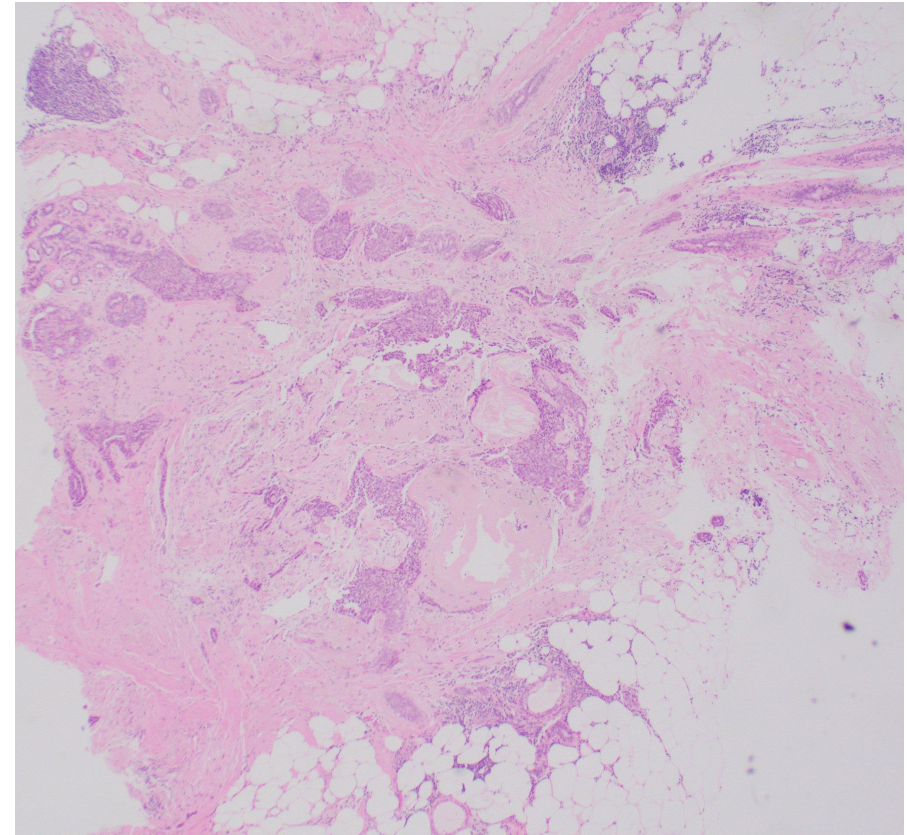
Radial sclerosing lesion

- Intact myoepithelium on p63 and myosin
- Patchy positive ER in epithelium
- Heterogenous expression on CK5/6
 - Without concurrent p63 overexpression
 - No definitive squamous differentiation

Radial scar



Current case



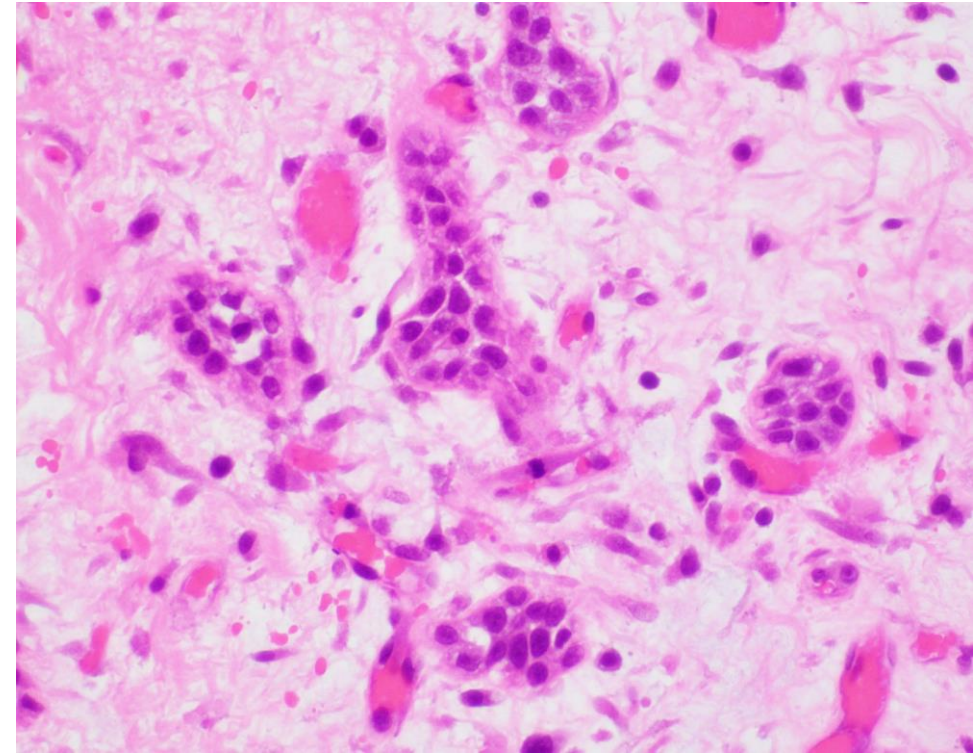
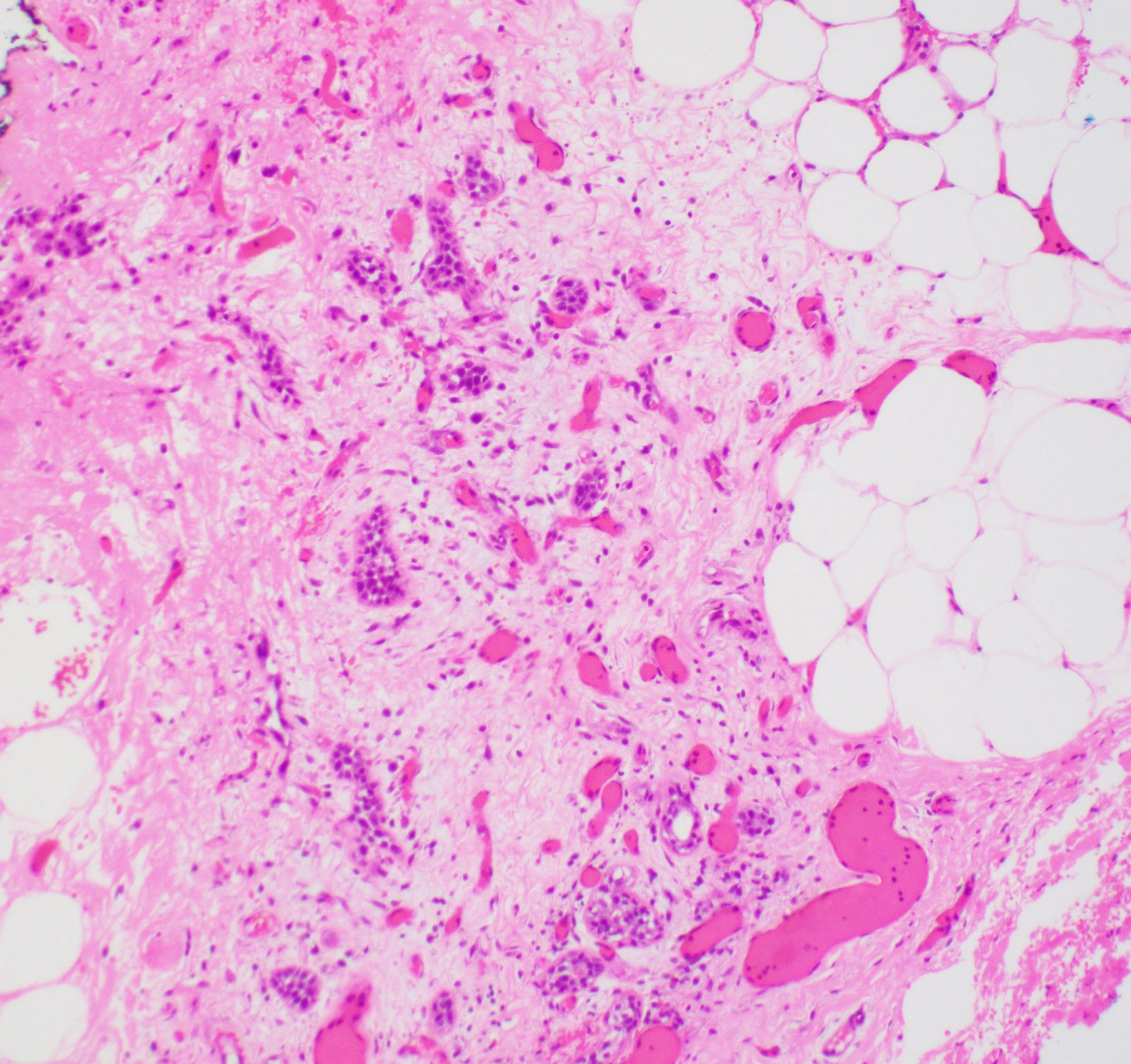
Summary

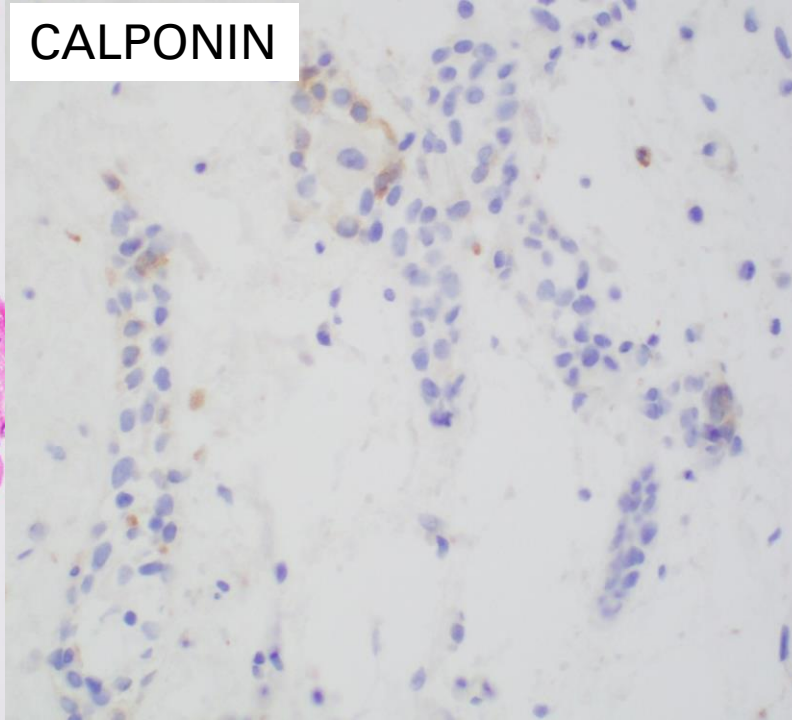
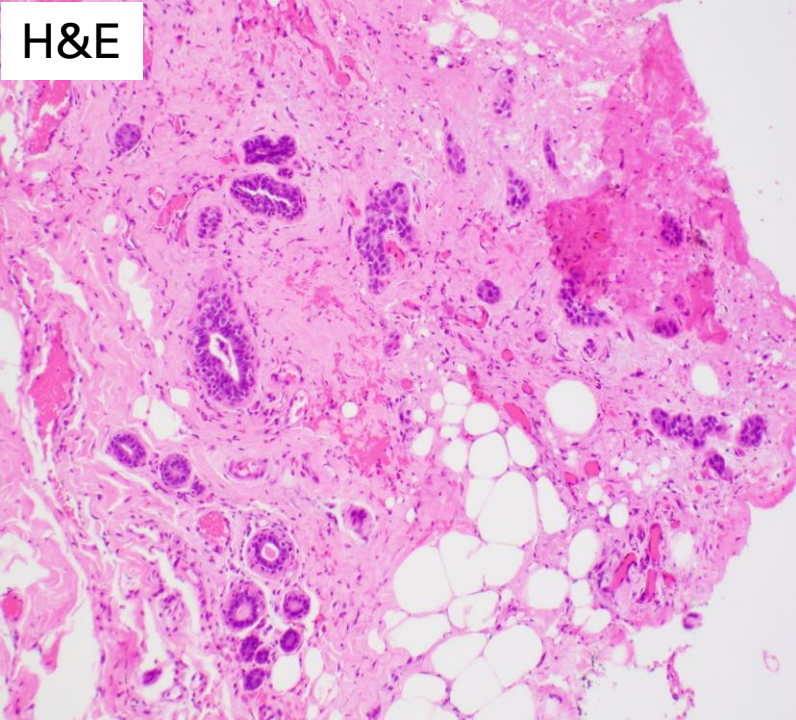
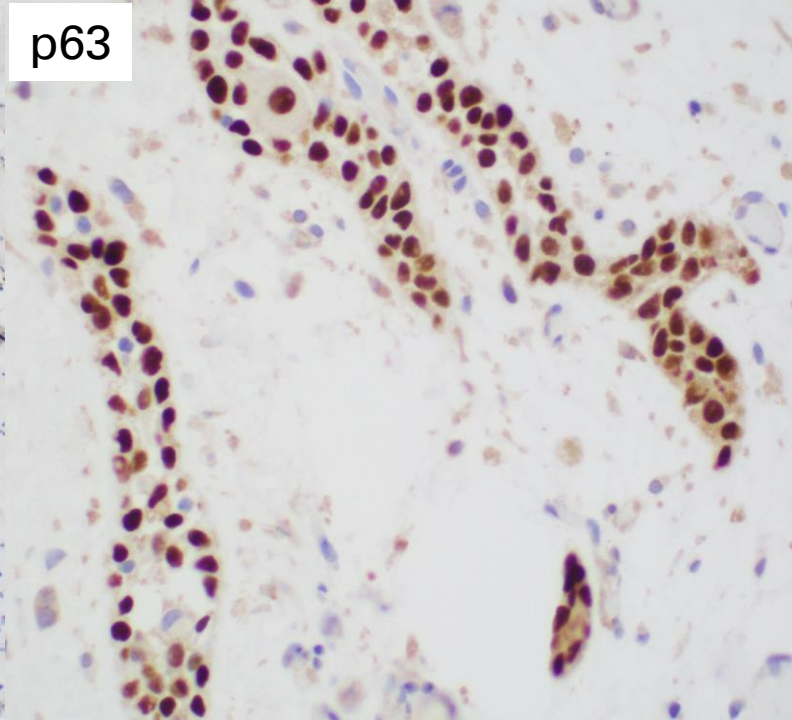
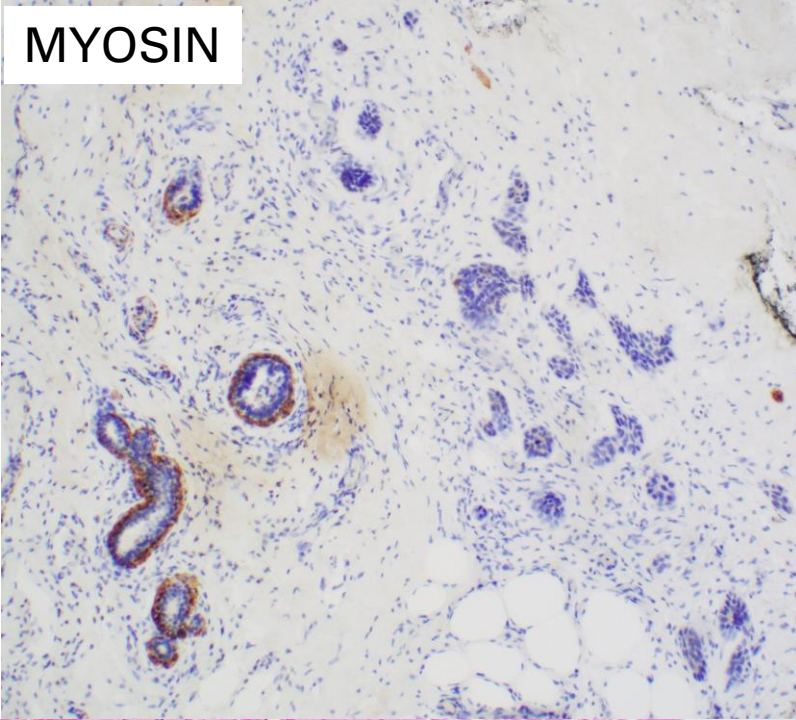
- Low-grade adenosquamous carcinoma can arise within radial scars, papillomas and adenomyoepithelioma [Scali et al. 2013, Romanucci et al. 2021, Denley et al. 2000]
 - May recur locally
 - Rarely metastases
 - Few reported cases of evolution into a more aggressive form of metaplastic carcinoma
- Radial scar can look very similar to low-grade adenosquamous carcinoma [Bachert et al. 2023]
 - Early radial scars show stromal cellularity
 - Radial scar can show squamous metaplasia in the central nidus
 - Radial scar with concerning features may require excision to rule out malignancy
- In the nipple, the differential should also include syringomatous adenoma [Li et al. 2012]

CASE 3

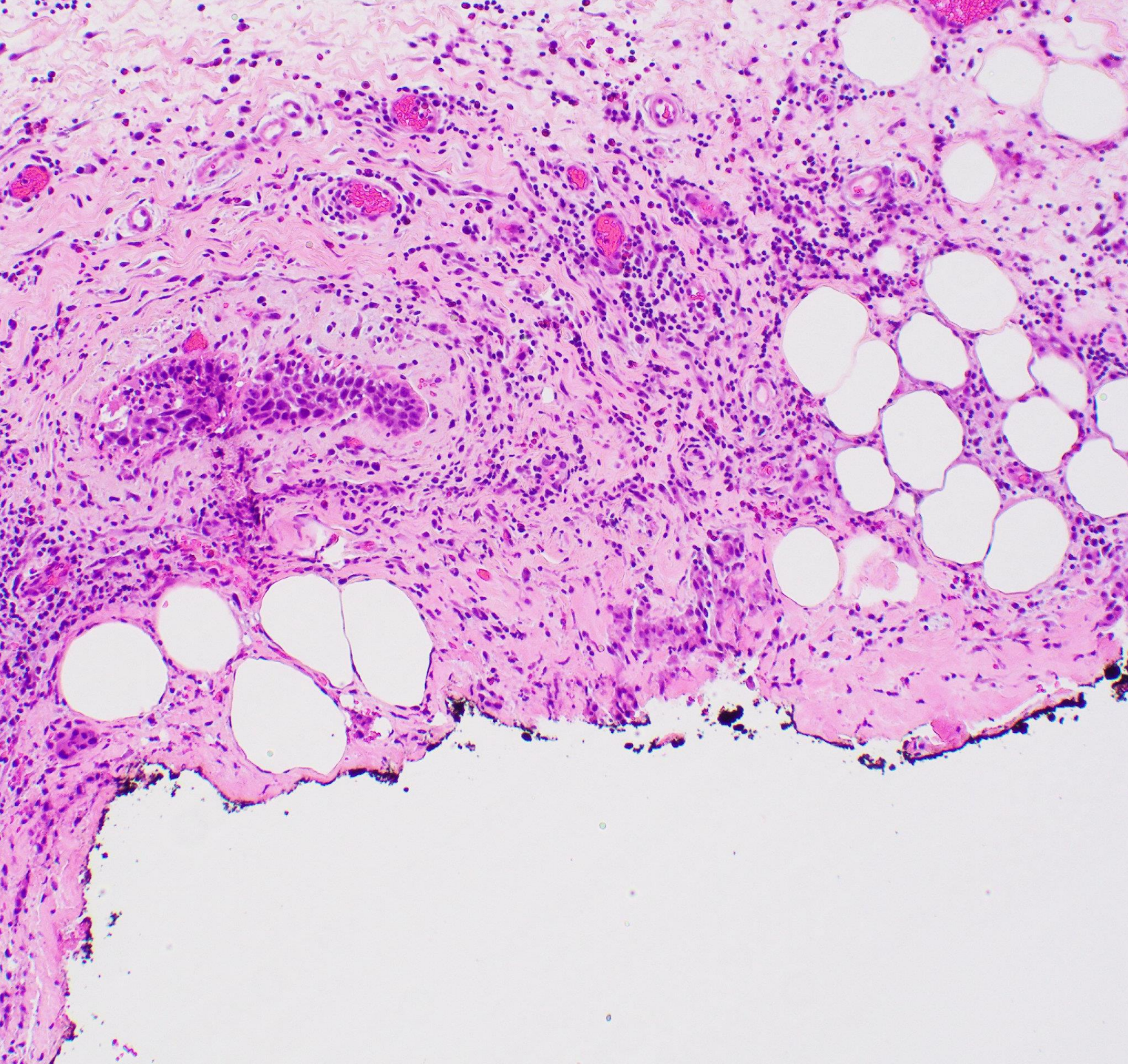
- 74-year-old female with history of prior lumpectomy for invasive ductal carcinoma with lobular features and DCIS with positive margins
- She presents with surgical re-excision of margins
- Consultation case from outside hospital

EXTENDED INFERIOR MARGIN

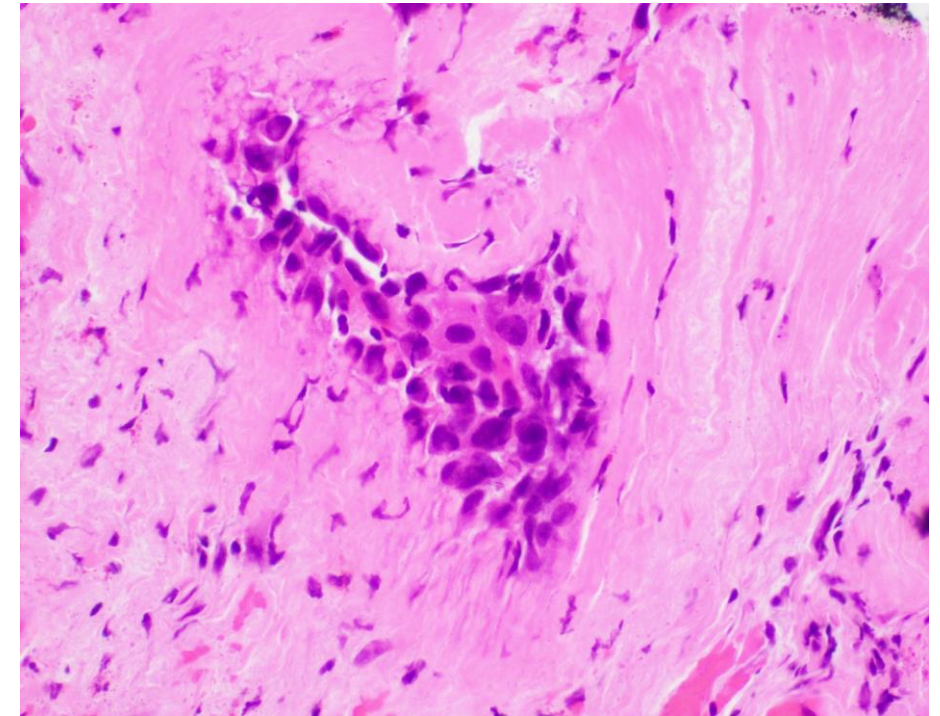


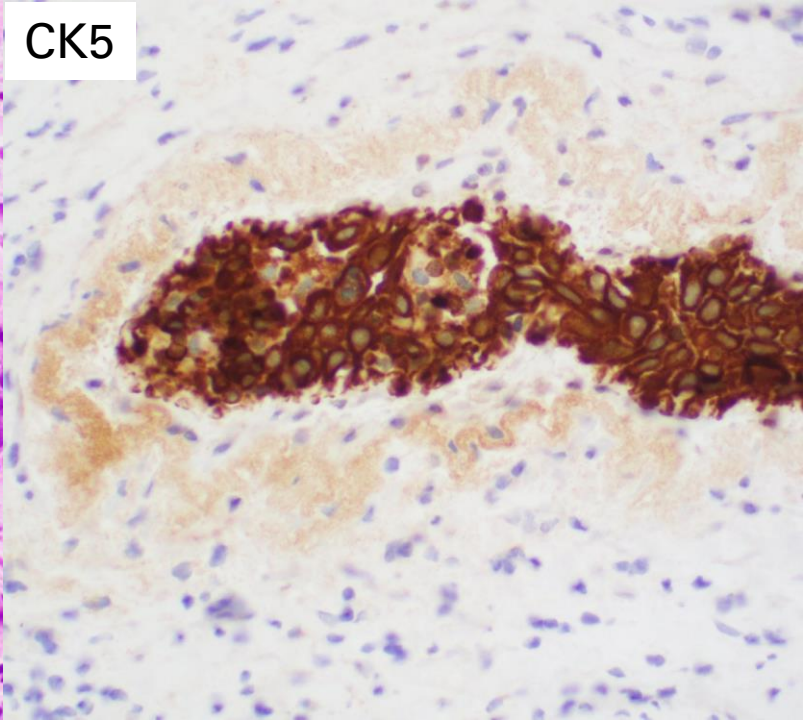
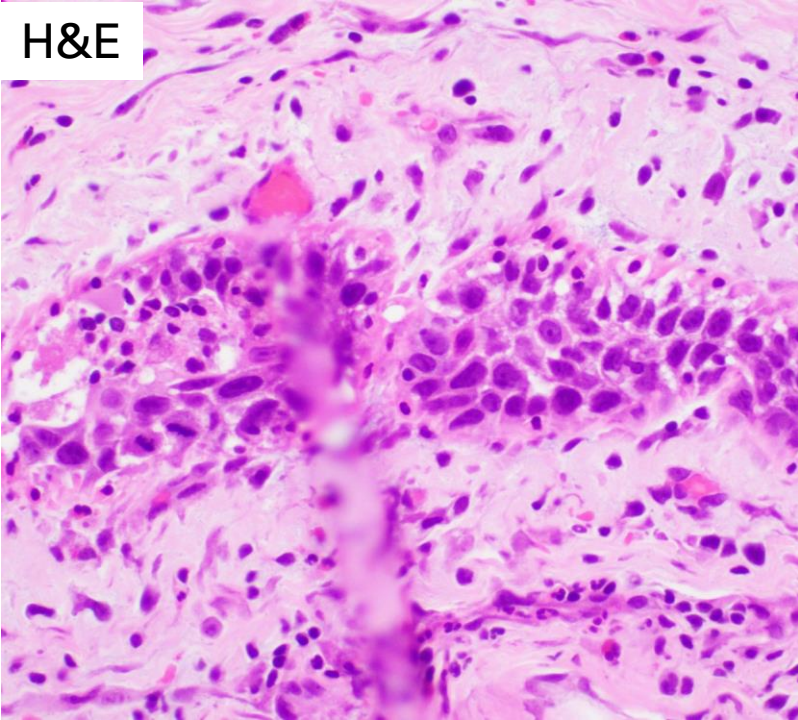
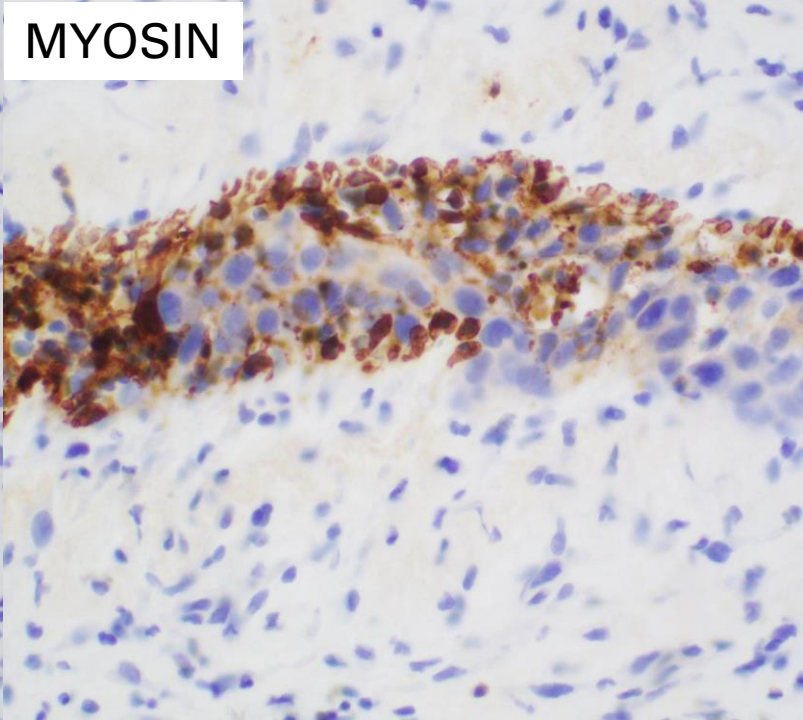
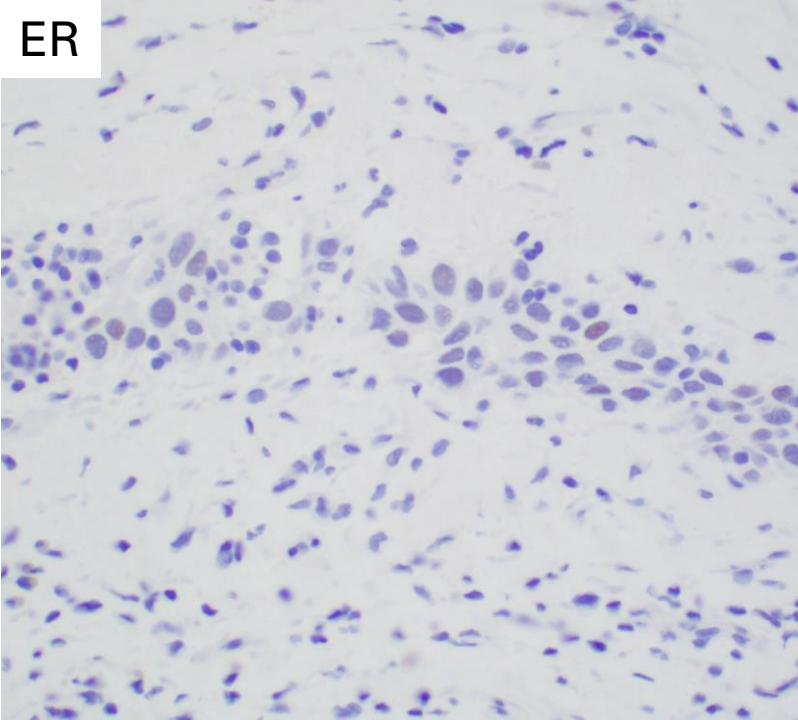


EXTENDED
INFERIOR
MARGIN



EXTENDED LATERAL MARGIN





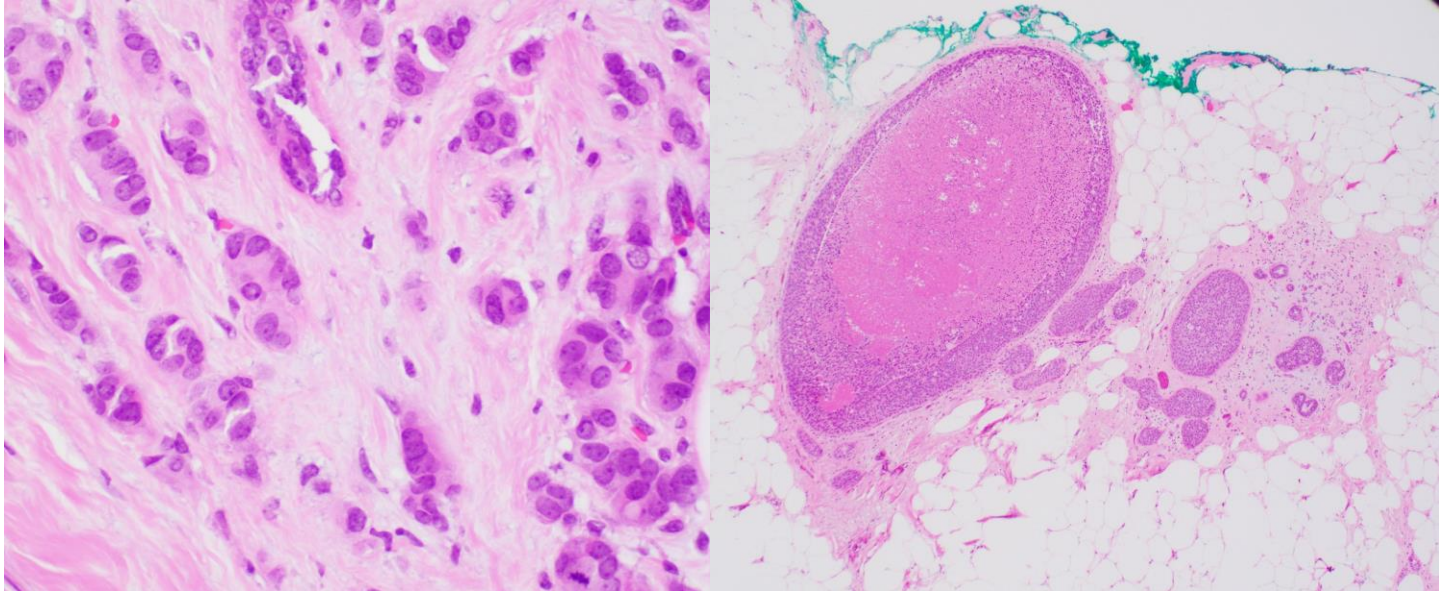
EXTENDED
LATERAL
MARGIN

Differential considerations

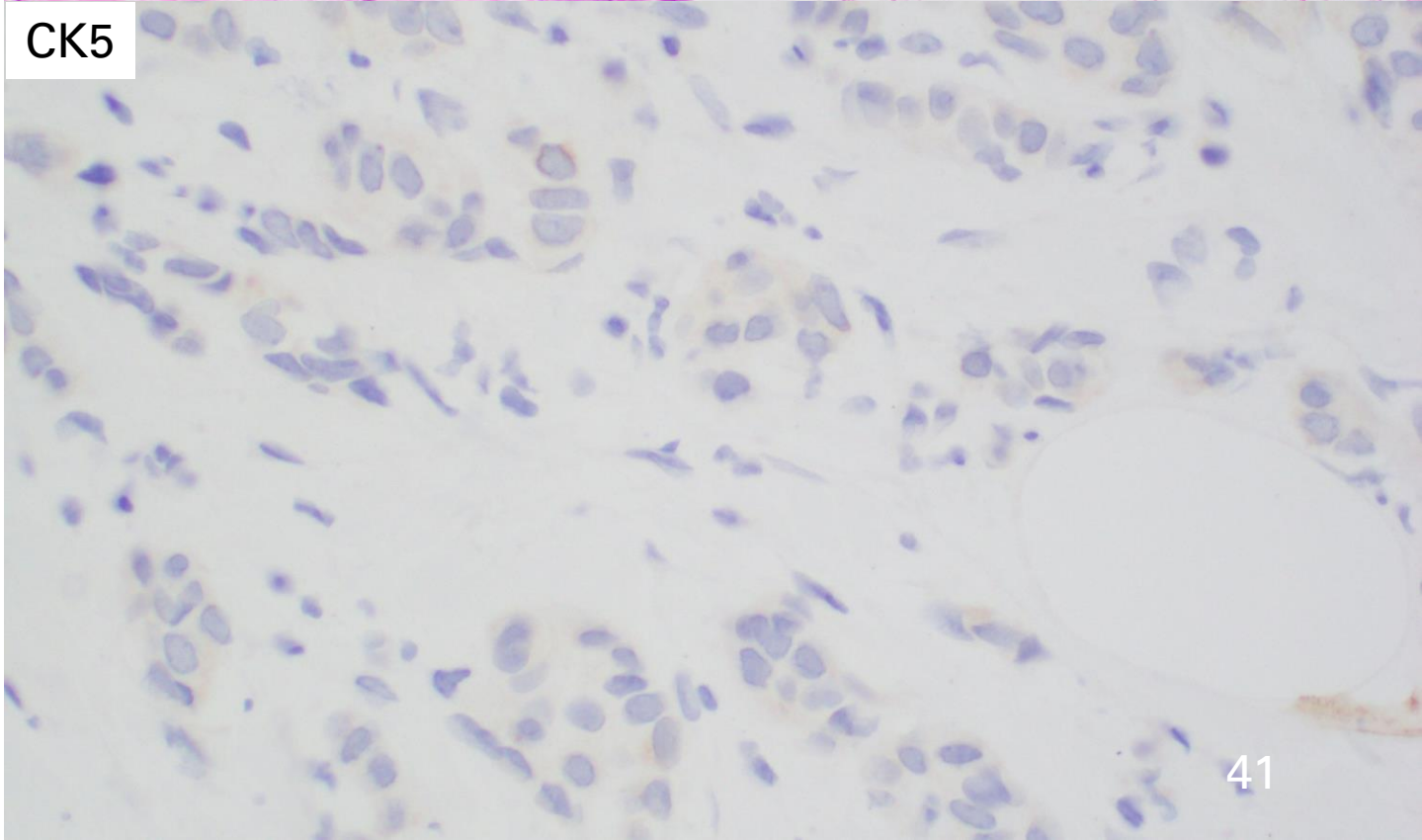
- Extended inferior margin:
 - Invasive carcinoma
 - Benign ducts with squamous metaplasia
- Extended lateral margin:
 - DCIS
 - Benign ducts with usual ductal hyperplasia
 - Benign ducts with squamous metaplasia

What else is helpful?

- Histologic comparison with the prior resection may be helpful which shows that this patient had:
 - *Invasive ductal carcinoma with lobular features that was ER /PR positive (90%, strong) and HER2 negative*
 - *Focal high-grade DCIS*



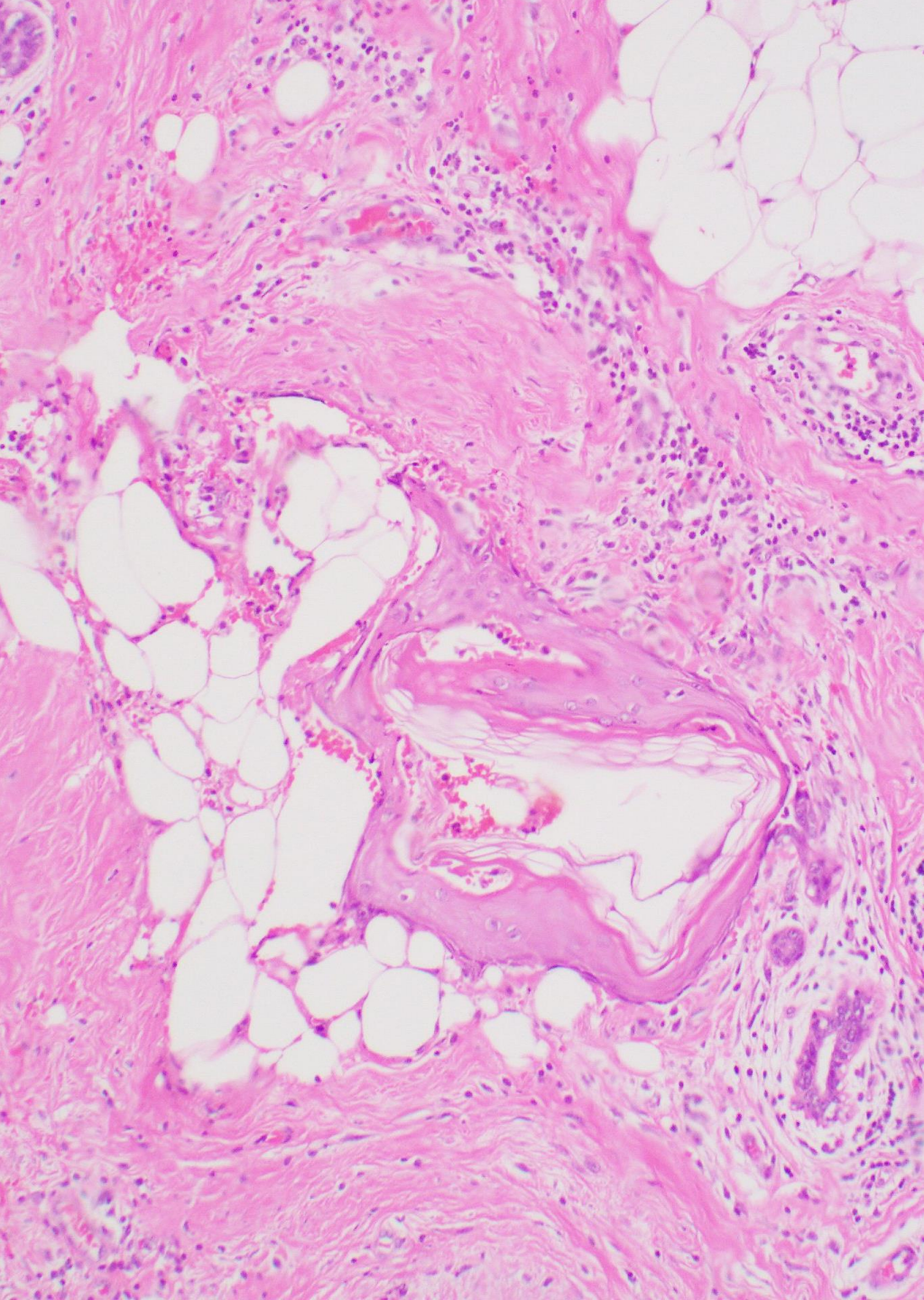
CK5



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- The patient in the current case had a prior resection that showed luminal A breast cancer (ER/PR positive and HER2 negative) with positive margin on initial lumpectomy
 - Re-excision was performed to obtain negative margins and showed concerning areas
 - Extended inferior margin: focus of epithelial cells that were p63 positive and showed loss of calponin and myosin
 - Extended lateral margin: focus with atypical duct (largely intact myosin), pretty much negative ER and positive CK5
 - Invasive breast carcinoma and DCIS can express p40, p63 and CK5, often described as basal-like triple negative breast cancer (also has EGFR mutation) [Gazinska et al. 2013]
 - Metaplastic (squamous) carcinoma will also show positivity for p40, p63 and CK5 immunohistochemical stains and will often be triple negative
 - Breast tissue after prior procedure can often show squamous metaplasia and displacement of the epithelium so interpretation is difficult

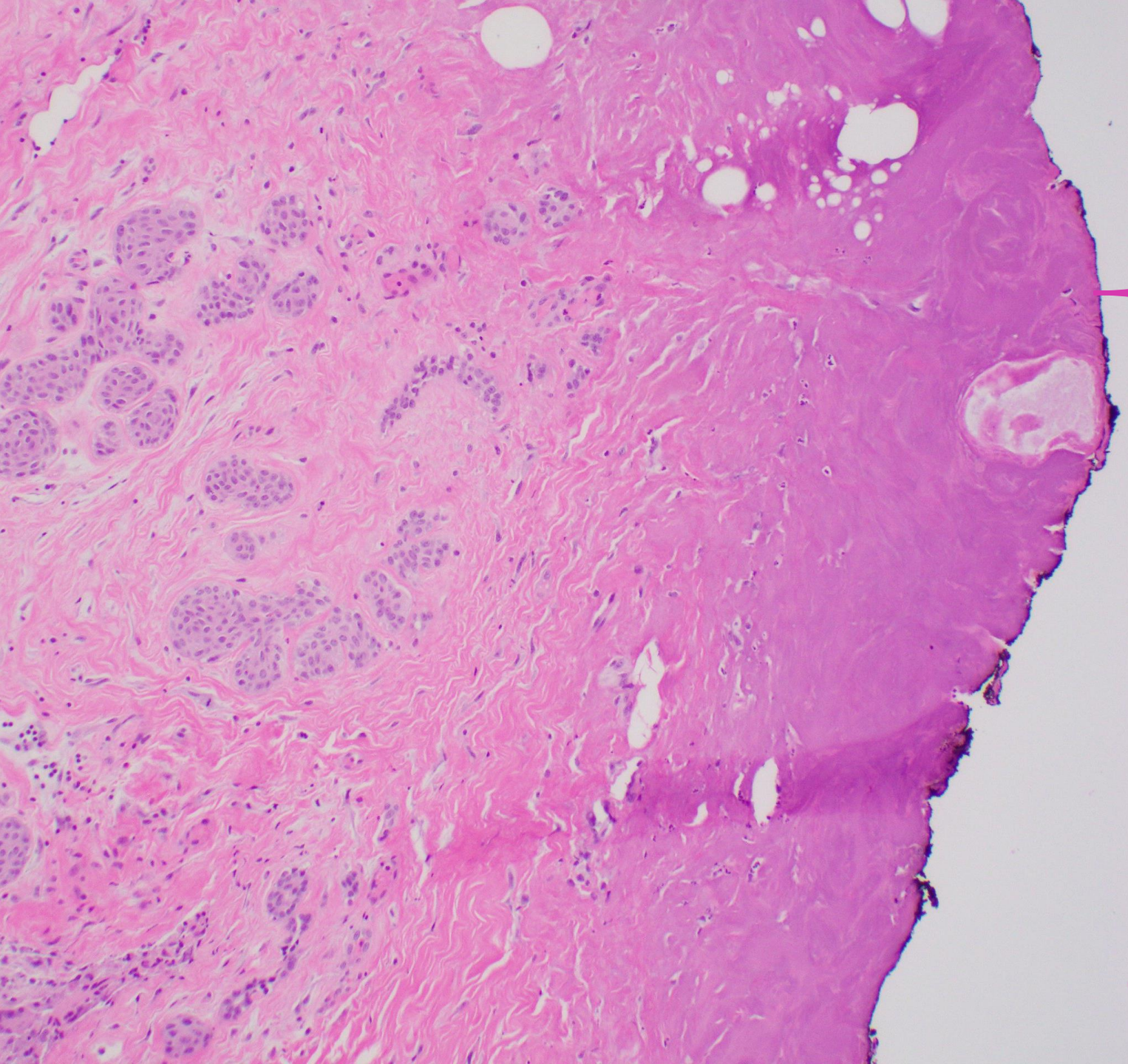
Final diagnosis

- Extended inferior margin:
 - Atypical epithelium, favor invasive carcinoma less than 0.1 cm to margin
- Extended lateral margin:
 - Atypical epithelium, favor DCIS about 0.15 cm to margin



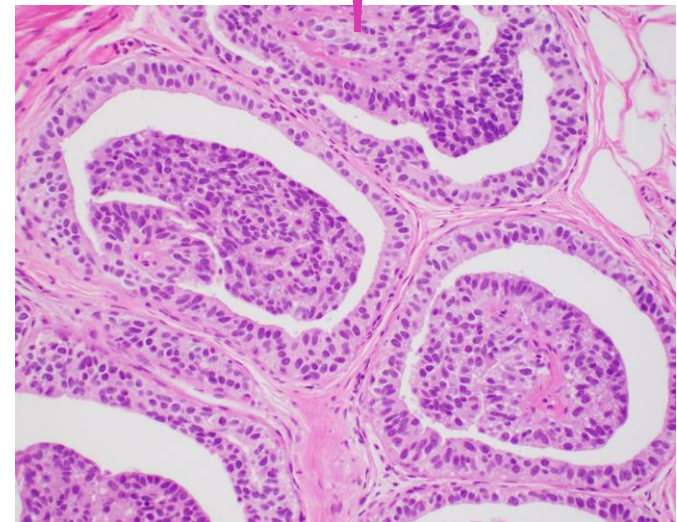
Is squamous metaplasia common after a prior procedure?

- Layfield et al. reported squamous metaplasia in 6 out of 100 cases (6%) in his pathologic reviews of mastectomies with prior biopsy/excision (2015)
 - “The presence of atypical duct-like structures, atypical squamous metaplasia, abnormal vessels, and single apparently infiltrative atypical epithelial cells do raise the differential diagnosis with malignancy”

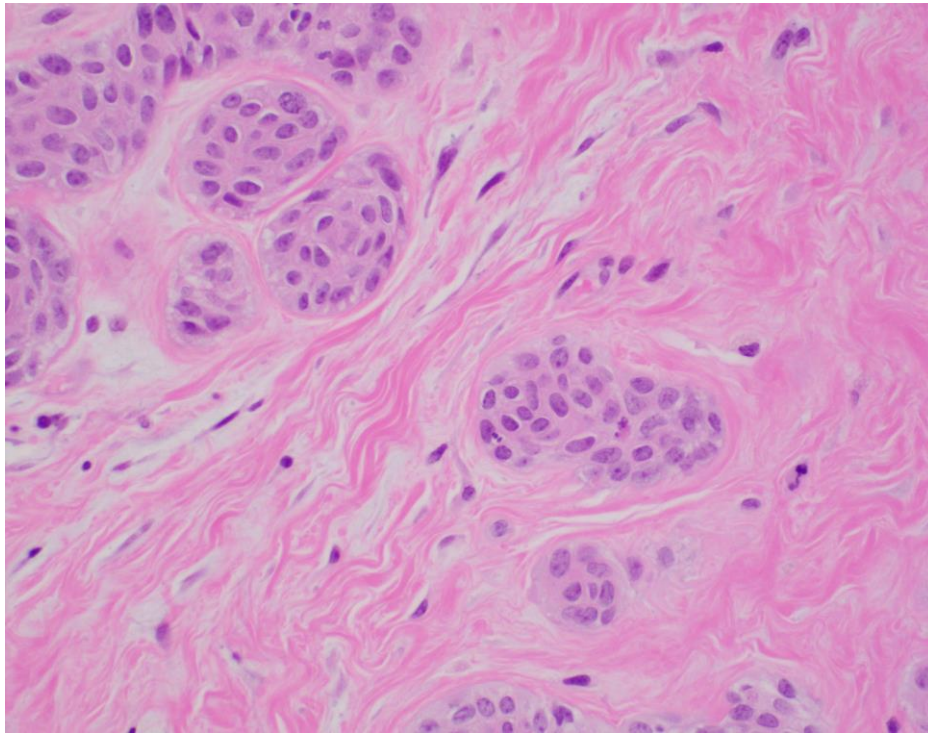


Incidental squamous metaplasia involving lobules found in the re-excision for DCIS

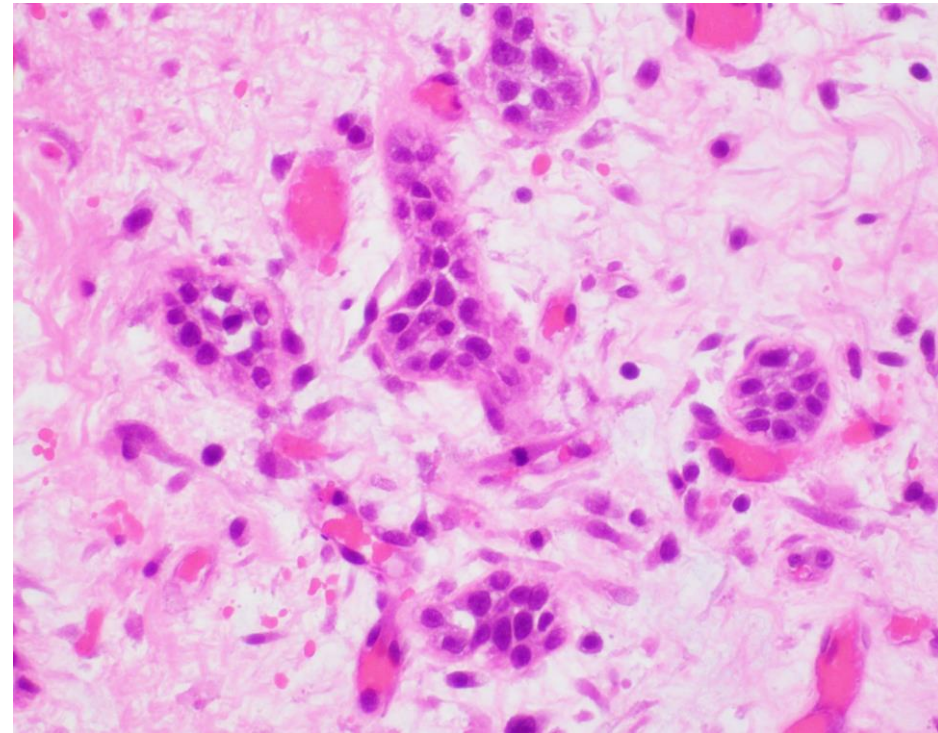
Patient's DCIS for comparison

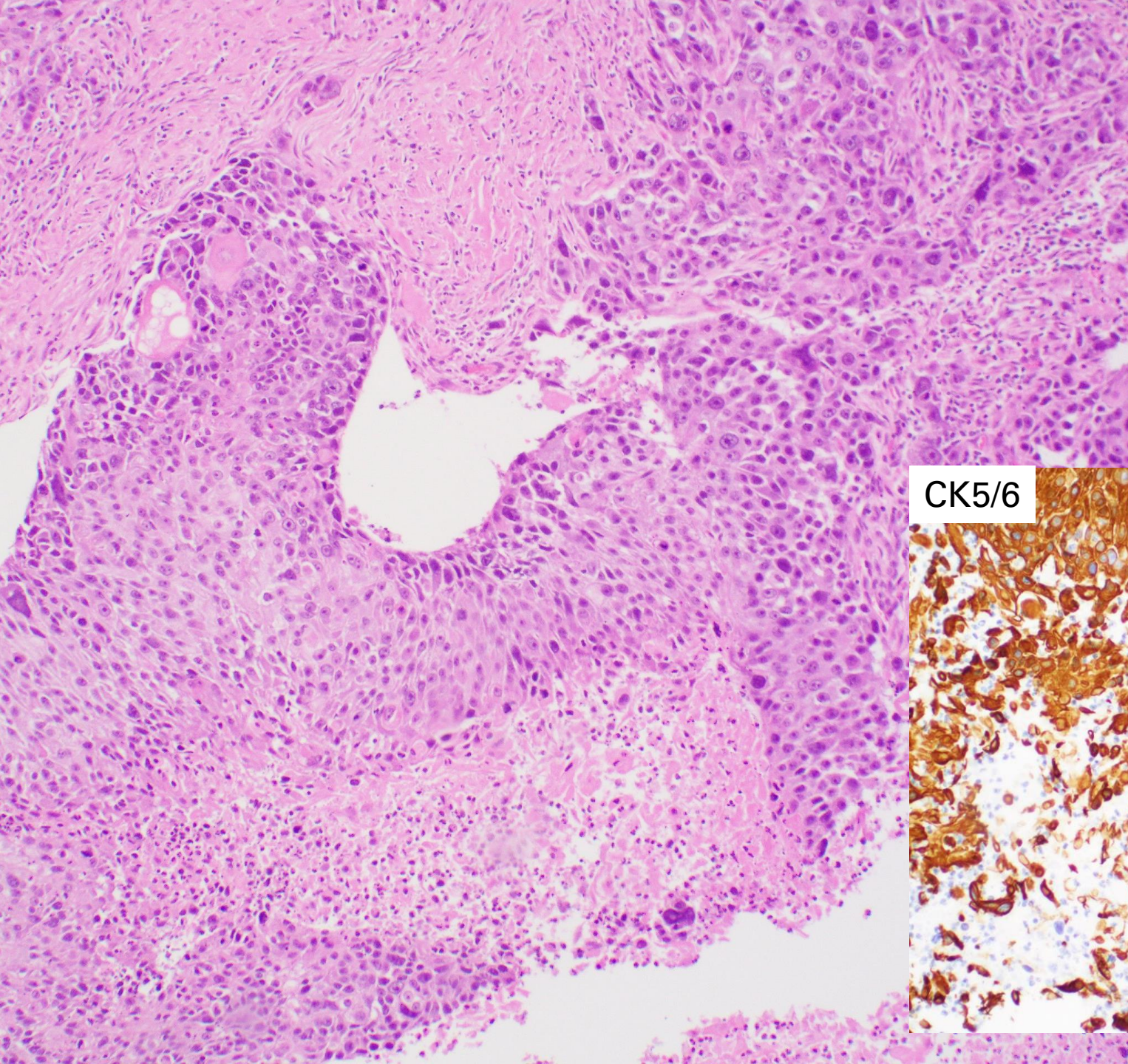


Squamous metaplasia



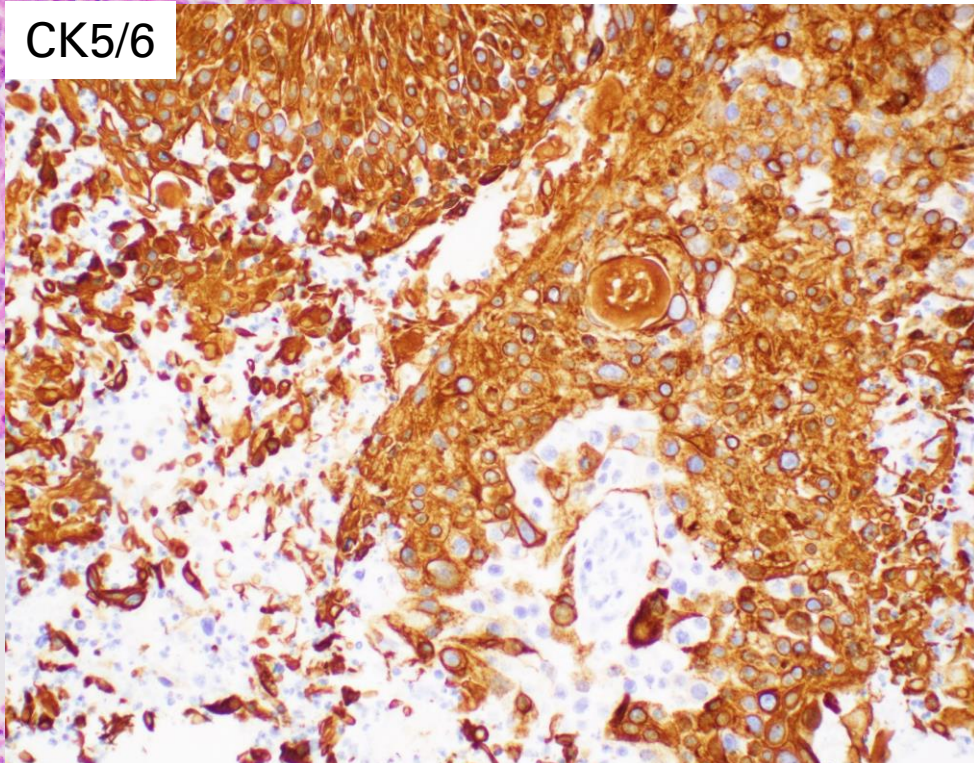
Current case (from extended inferior margin)

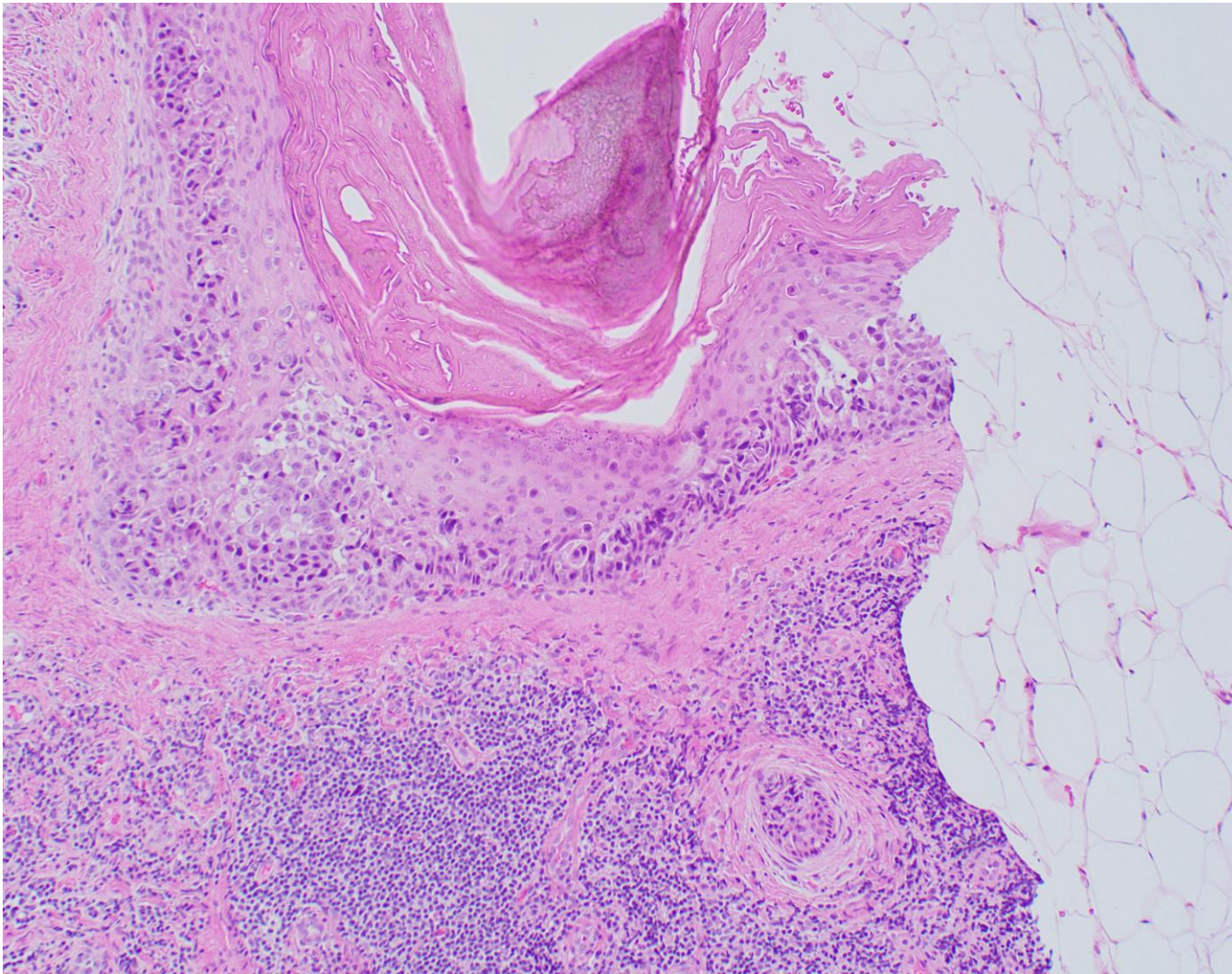




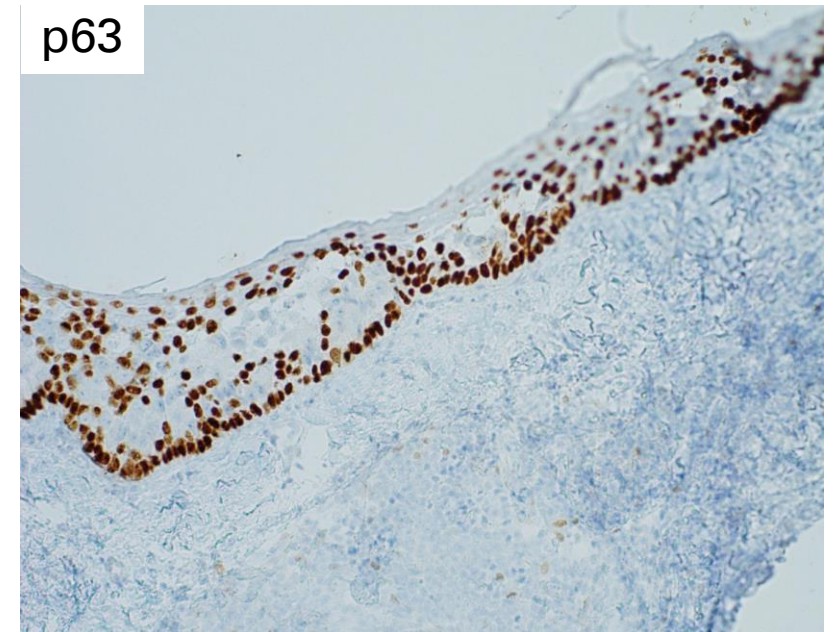
Metaplastic carcinoma with squamous differentiation

- Positive CK5/6 and p63
- Tumor cells with eosinophilic cytoplasm and keratinization focally





Ductal carcinoma in situ (DCIS) and squamous metaplasia

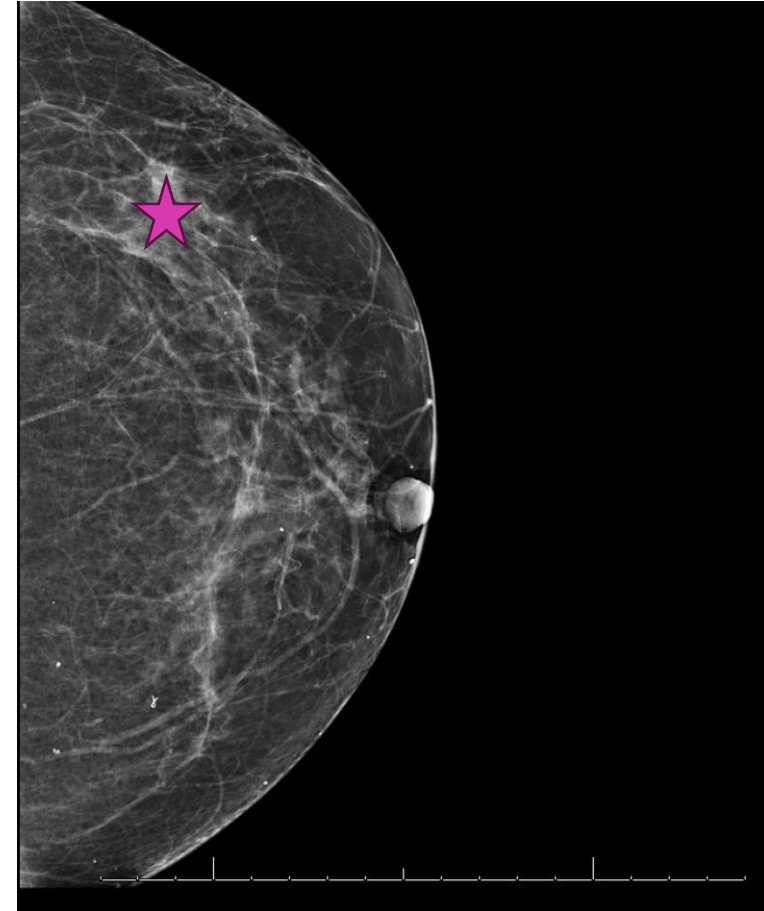


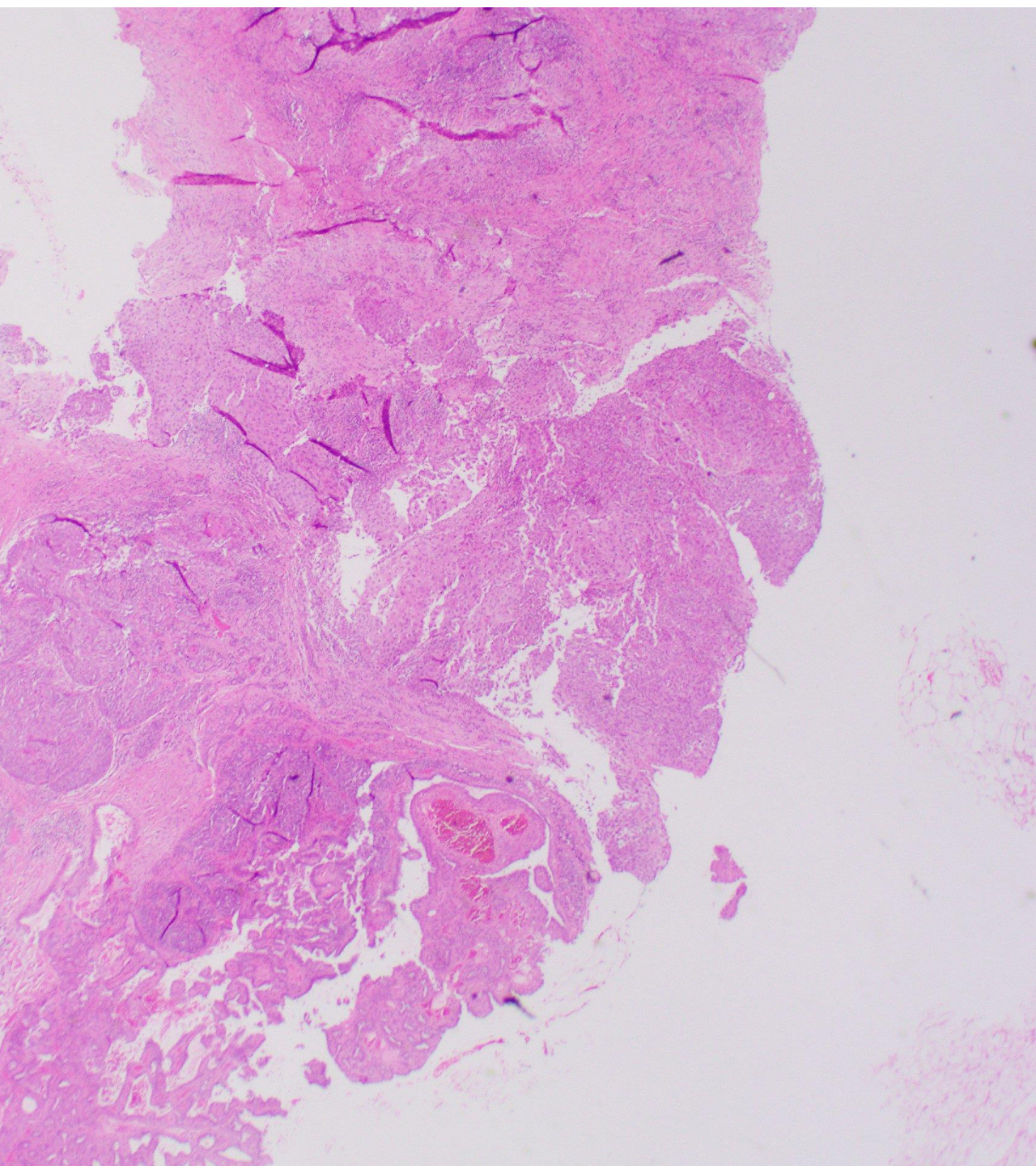
Summary

- Squamous metaplasia is rare in breast, unless there was a previous biopsy or excision [Layfield et al. 2015]
 - Prior biopsy site change may cause epithelial displacement and reactive atypia
 - Myoepithelial stains may be helpful
- Breast cancer can be positive for p63 and CK5/6 immunostains or show overt squamous features
- Comparison with prior specimen if available can help establish the diagnosis

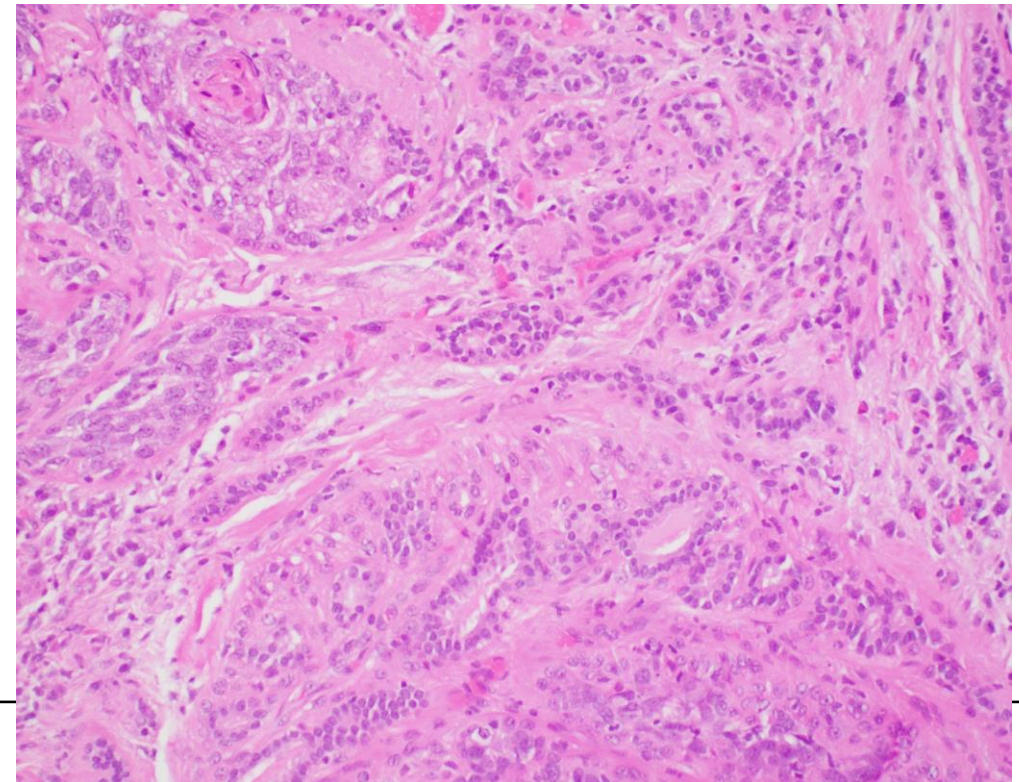
CASE 4

- 72-year-old female who presented with left breast calcifications on screening mammogram
- She has a history of cancer in contralateral breast
- Left breast imaging showed increased predominantly amorphous grouped calcifications associated with a stable focal density at 2 o'clock posteriorly
- BI-RADS category 4
- Stereotactic core needle biopsy was performed

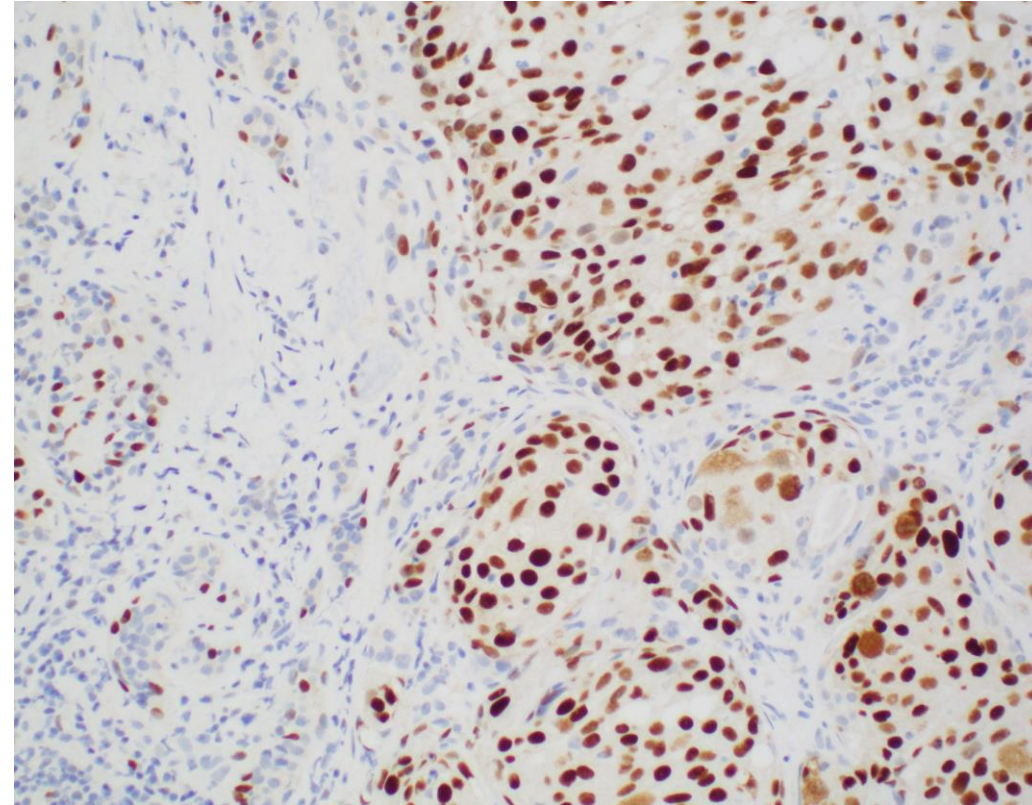
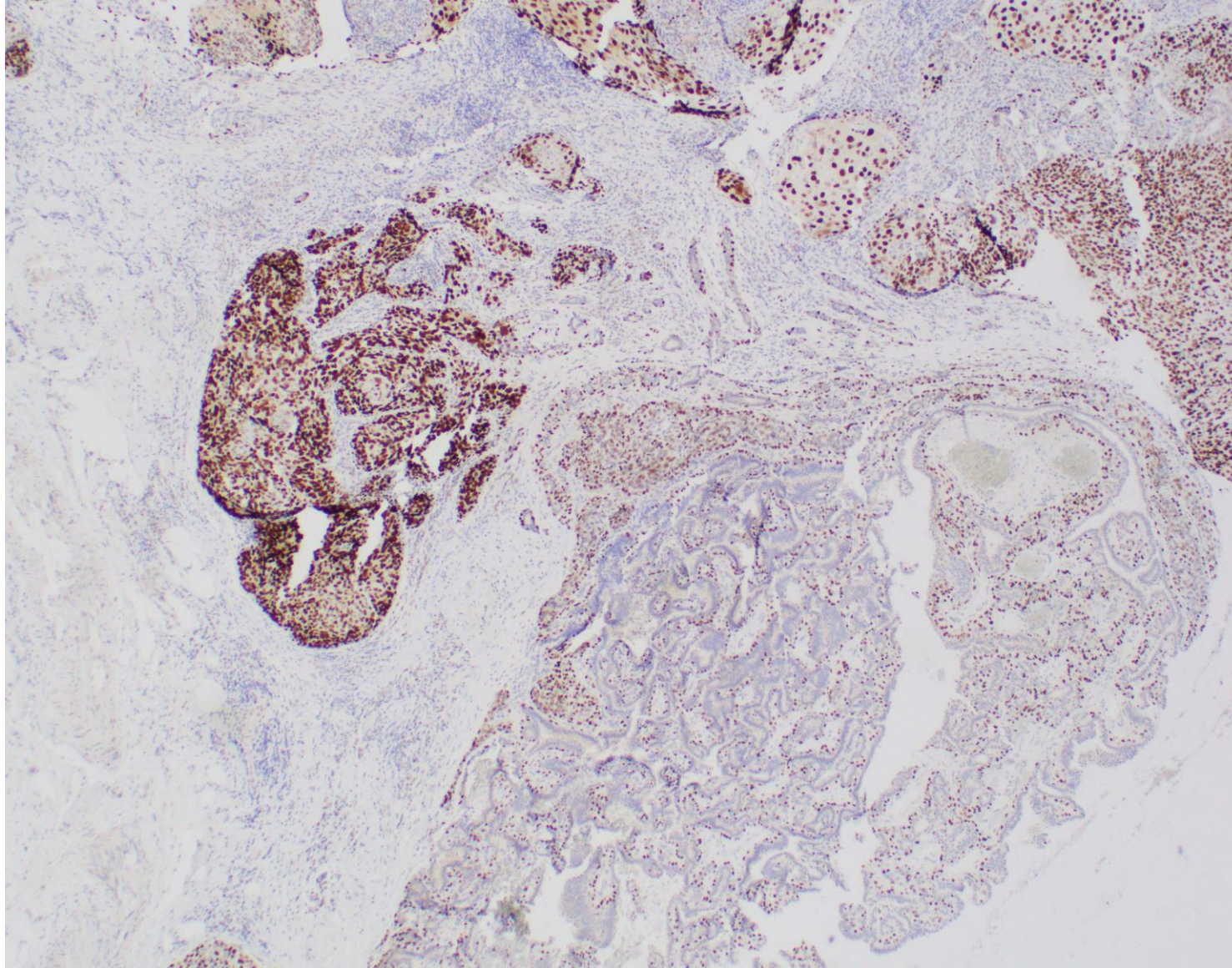




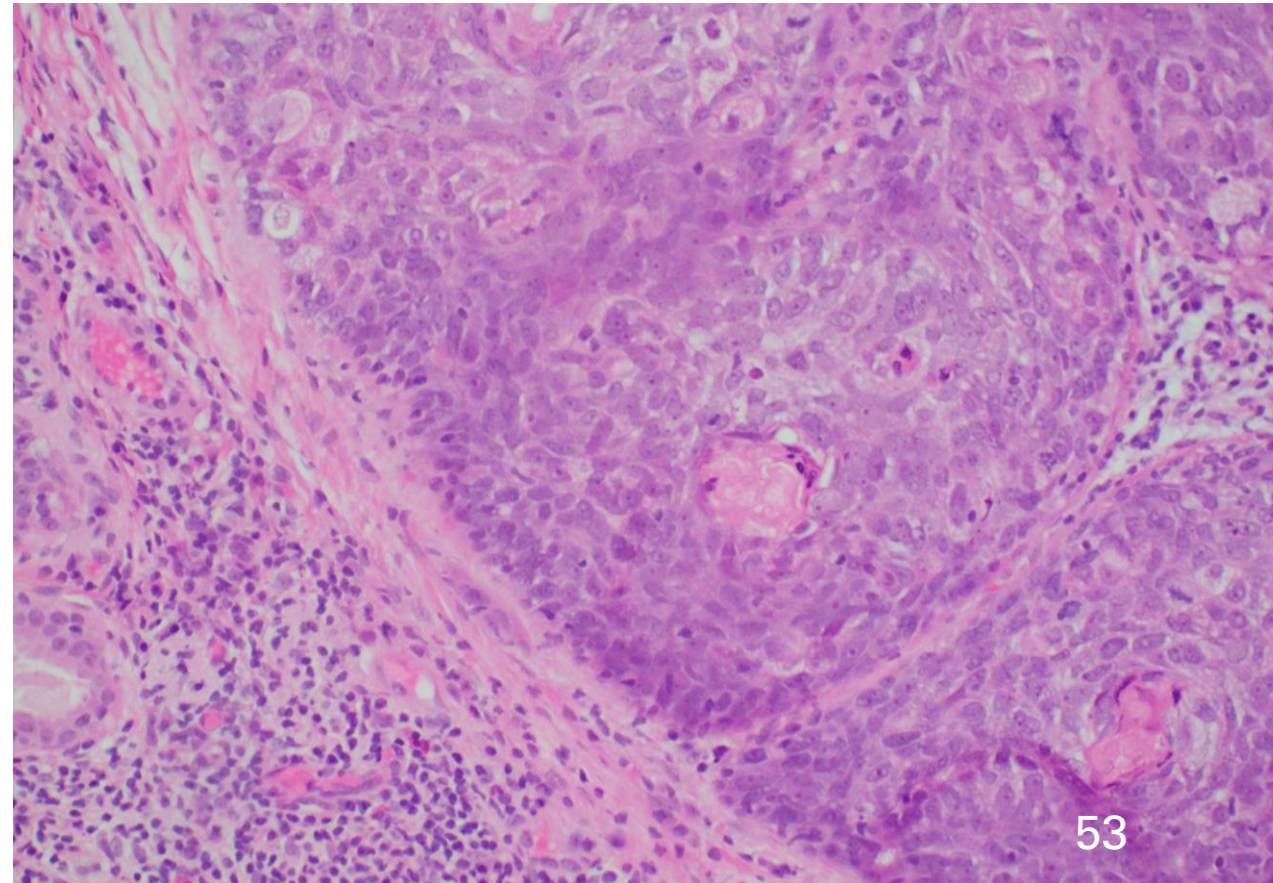
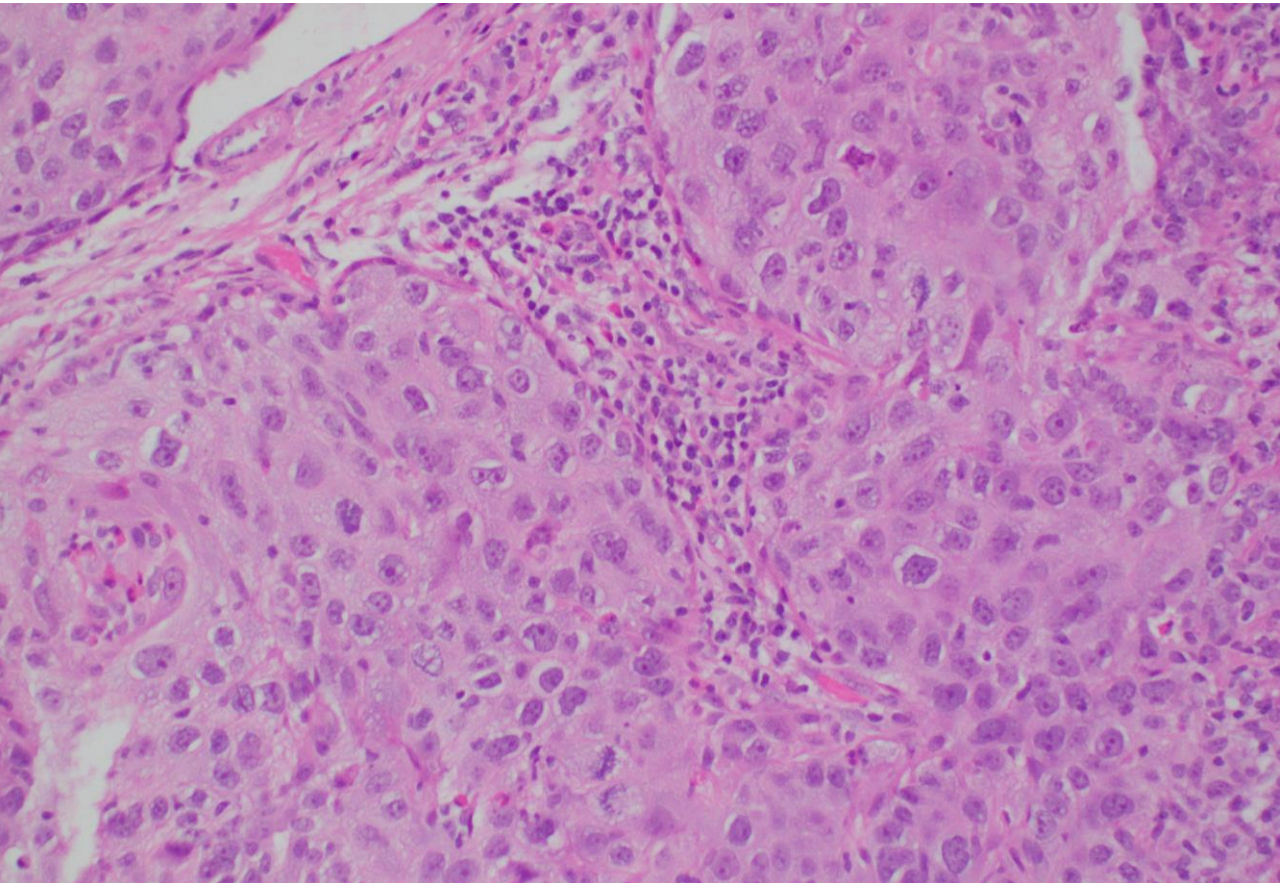
-
- Areas with fibrovascular cores in keeping with a papilloma
 - Prominent intraductal proliferation

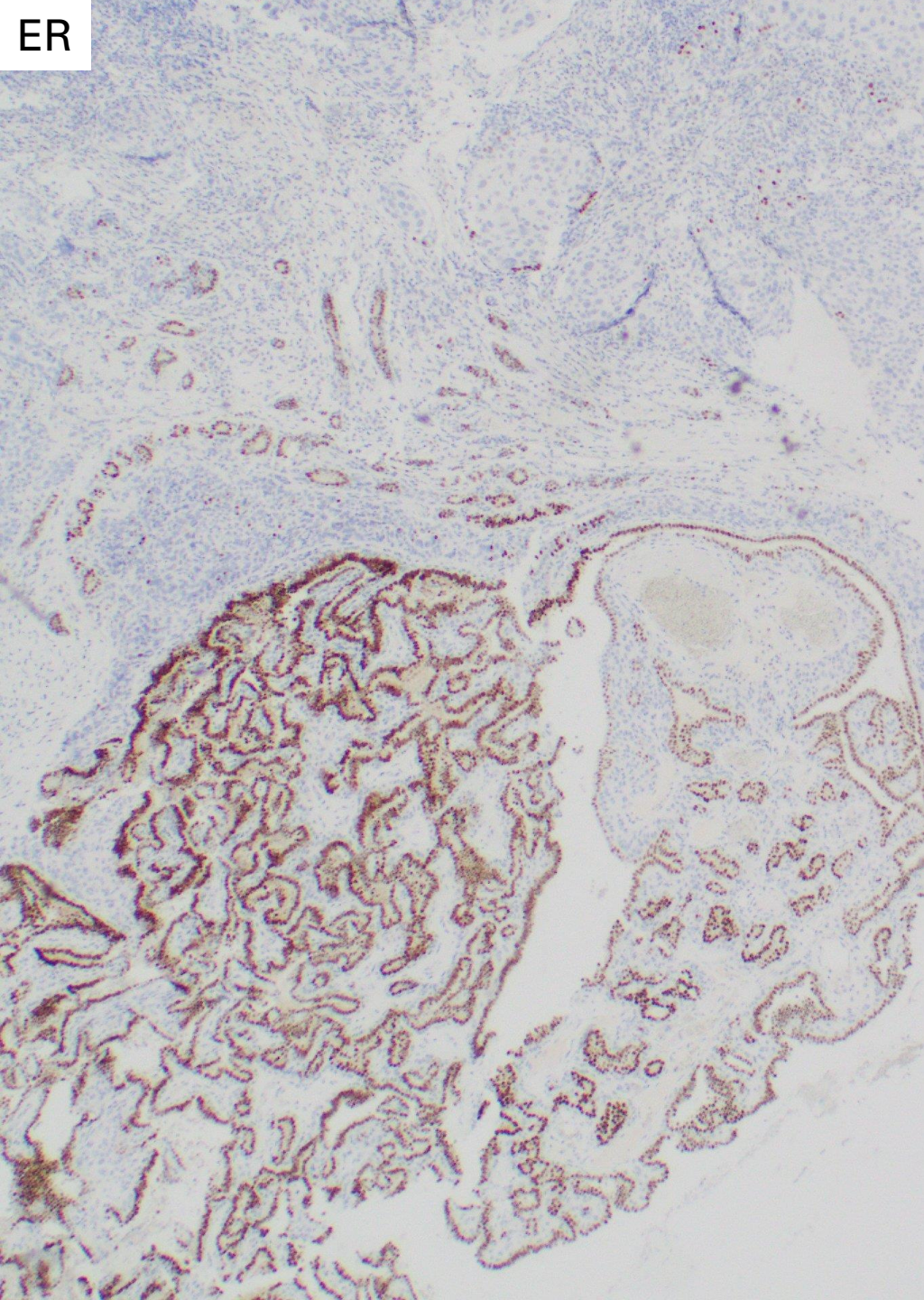


P63 immunostain



Additional images showing intraductal proliferation at high magnification with sheet like appearance and keratinization





Differential considerations

- In situ carcinoma involving intraductal papilloma
- In situ carcinoma involving intraductal papilloma with an invasive carcinoma component
- HER2, estrogen and progesterone receptor stains were negative

Final diagnosis: Squamous cell carcinoma involving sclerotic intraductal papilloma (0.8 cm)

- No definitive invasion
- Excision showed no residual cancer
- No radiation
- No recurrences on subsequent mammogram 1 year later

The pure squamous form of DCIS has been reported in literature, but it is rare

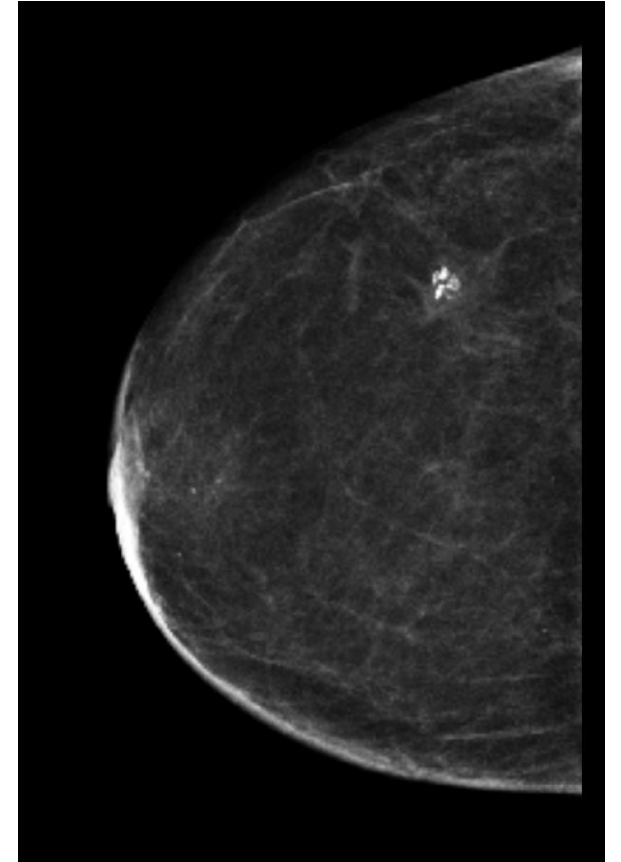
	Patient demographics	Treatment	Follow up
Hayes et al.	59-year-old female with 5 mm lesion detected on screening in the left breast	Wide excision +radiation	18 months with no recurrence
Hayes et al.	35-year-old female with retro areolar 20 mm lump in the left breast	Simple mastectomy with negative sentinel nodes sampling	15 months with no recurrence
Hayes et al.	51-year-old female with 18 mm lesion detected on screening in the left breast	Wide excision +radiation with negative sentinel nodes sampling	10 months with no recurrence
Arafah et al.	73-year-old female with 16 mm lesion in the left breast	Simple mastectomy with negative sentinel nodes sampling	11 years with no recurrence
Lu et al.	85-year-old female with 16 mm lesion detected on screening in the right breast	Simple mastectomy with negative sentinel nodes sampling	38 months with no recurrence

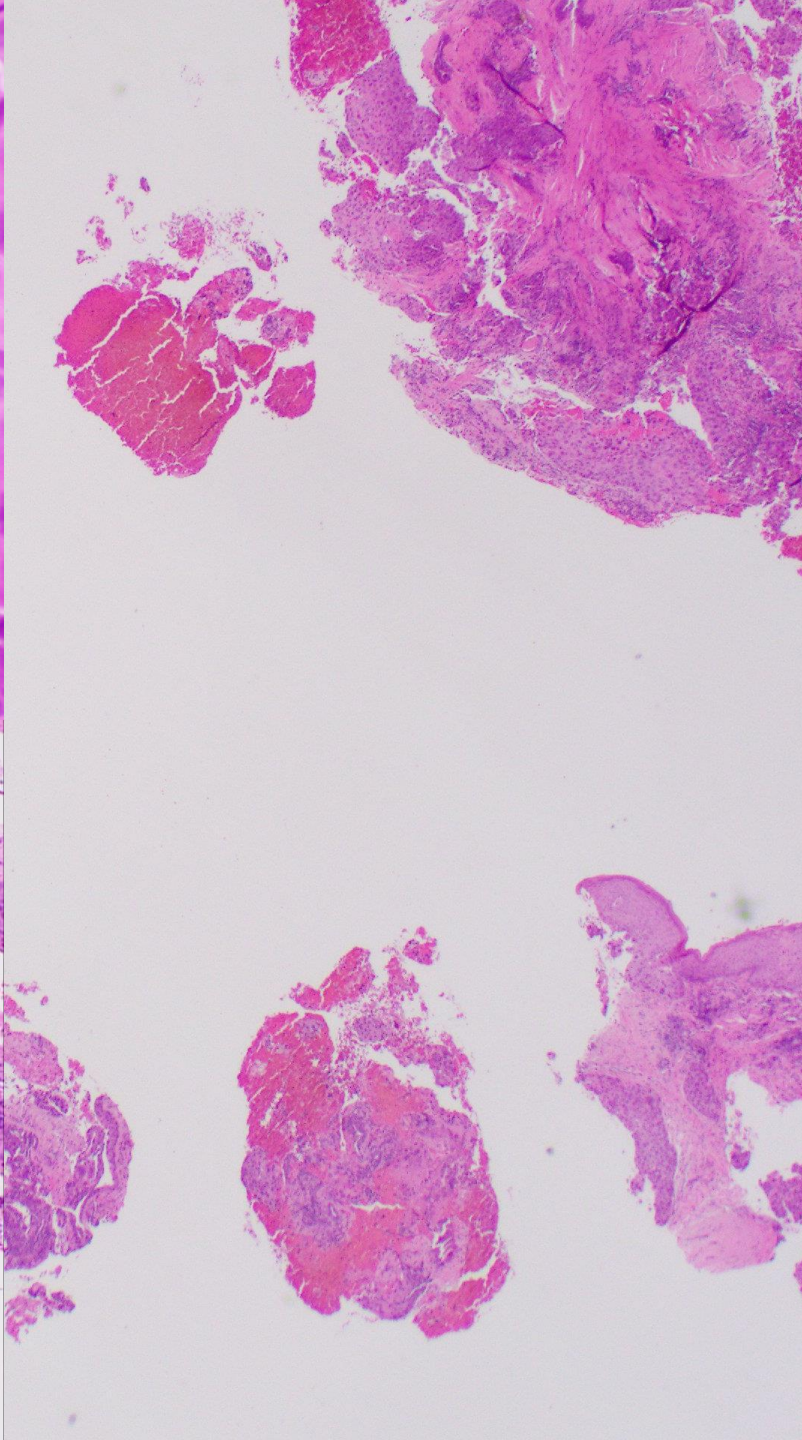
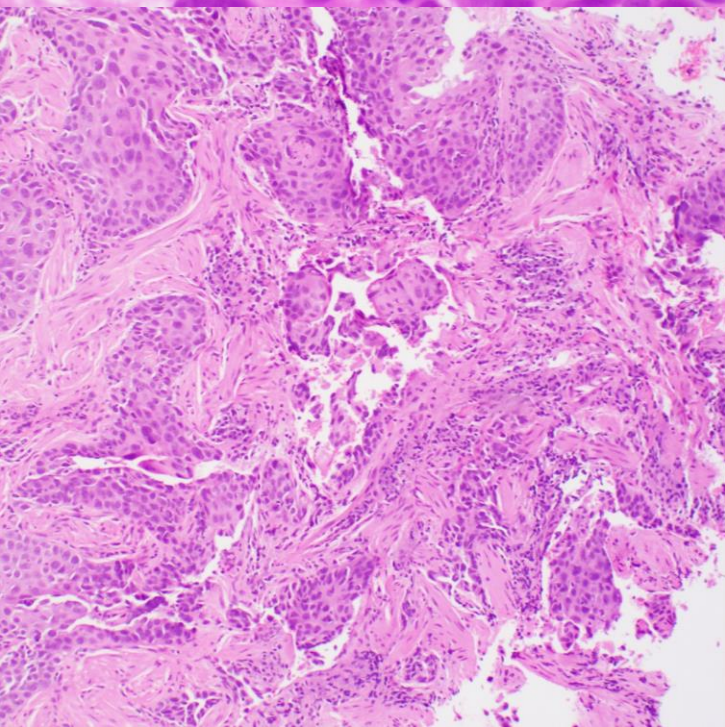
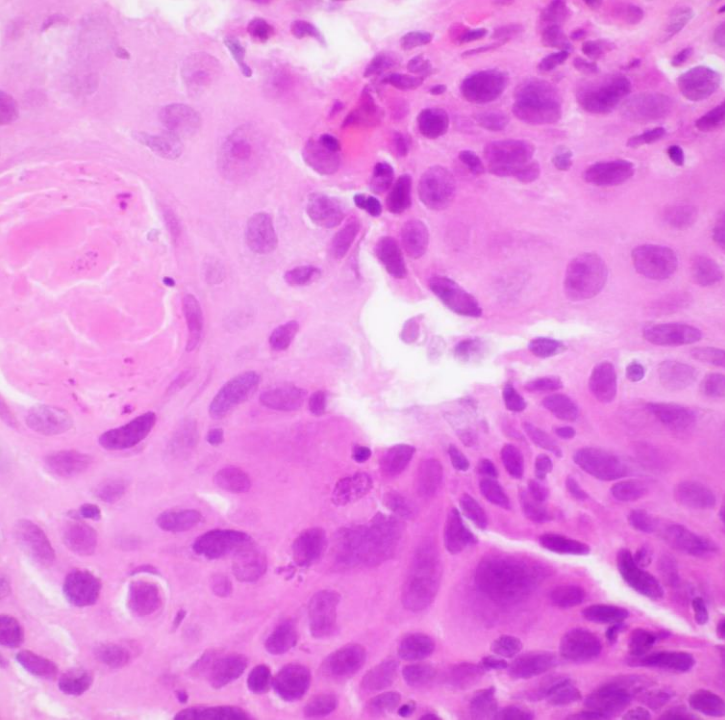
Summary

- There are several types of DCIS listed in the WHO classification including cribriform, flat, micropapillary, papillary, solid, apocrine, clear cell, comedonecrosis, neuroendocrine, signet ring, and squamous
- The diagnosis of pure squamous cell carcinoma in the breast requires squamous differentiation in a significant portion of the tumor (more than 90%)
- Invasive squamous cell carcinoma of the breast is a form of metaplastic carcinoma that may present as abscesses, long-standing or recurrent cyst, in a chronic sinus or in the capsule of a breast implant [Kinslow et al. 2023]
 - Typically occurs in women and often shows cystic degeneration
 - Rarely associated with squamous DCIS
 - Aggressive tumor with potential for locoregional relapse and poor prognosis [Hennessy et al. 2005]
 - Pure squamous carcinomas may have better prognosis than metaplastic carcinomas with squamous differentiation/features [Pirot et al. 2020]

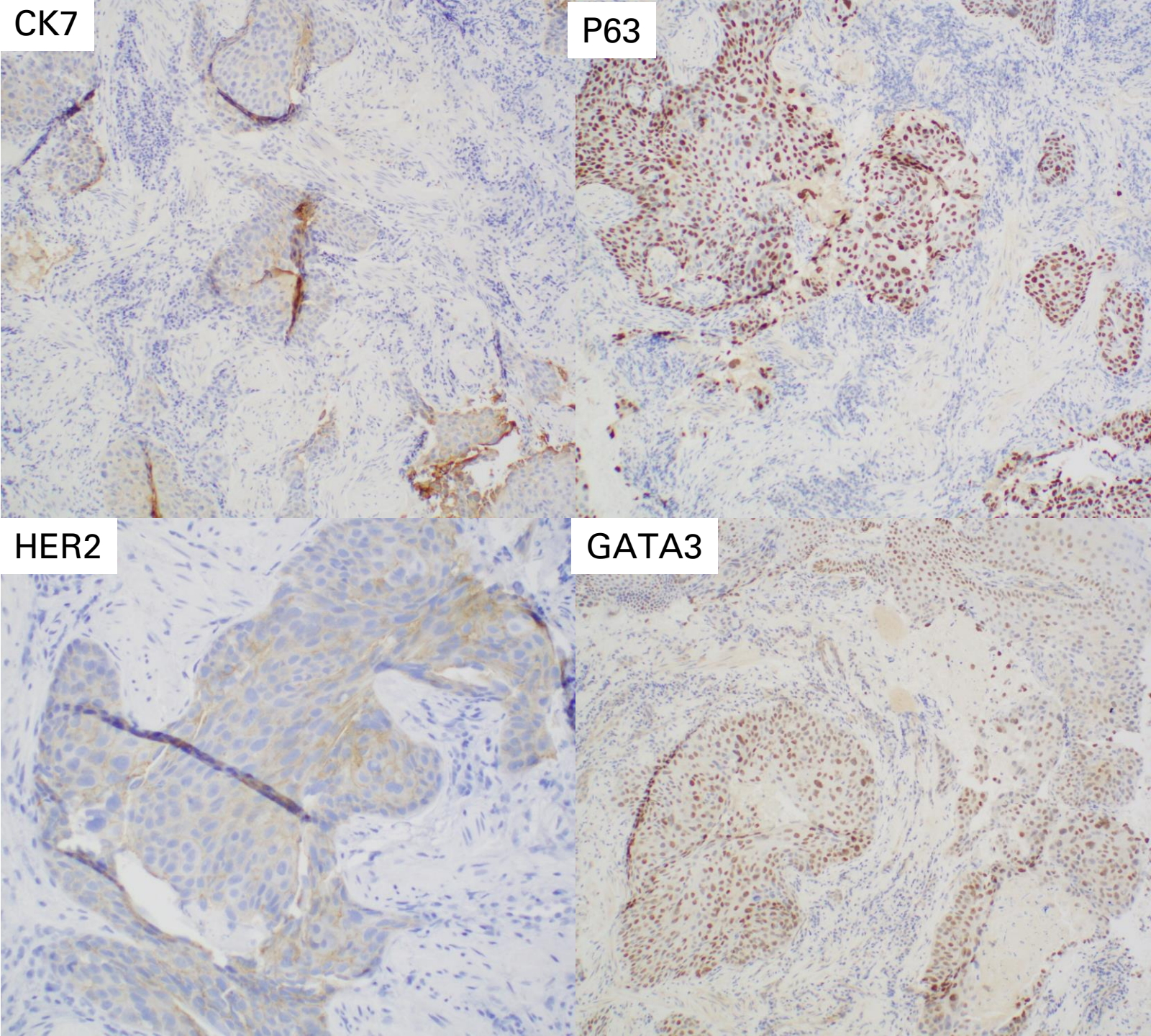
CASE 5

- 76-year-old female with right nipple bloody discharge and remote history of breast cancer (moderately differentiated invasive ductal carcinoma of the right breast, 9 years ago)
- Clinical appearance concerning for Paget's disease
- Imaging showed right nipple thickening without other lesions
- Punch biopsy was performed





-
- Multiple fragments of tissue
 - Some showing intact squamous epithelium
 - Some irregular nests of malignant appearing cells with sheeting and squamous pearls



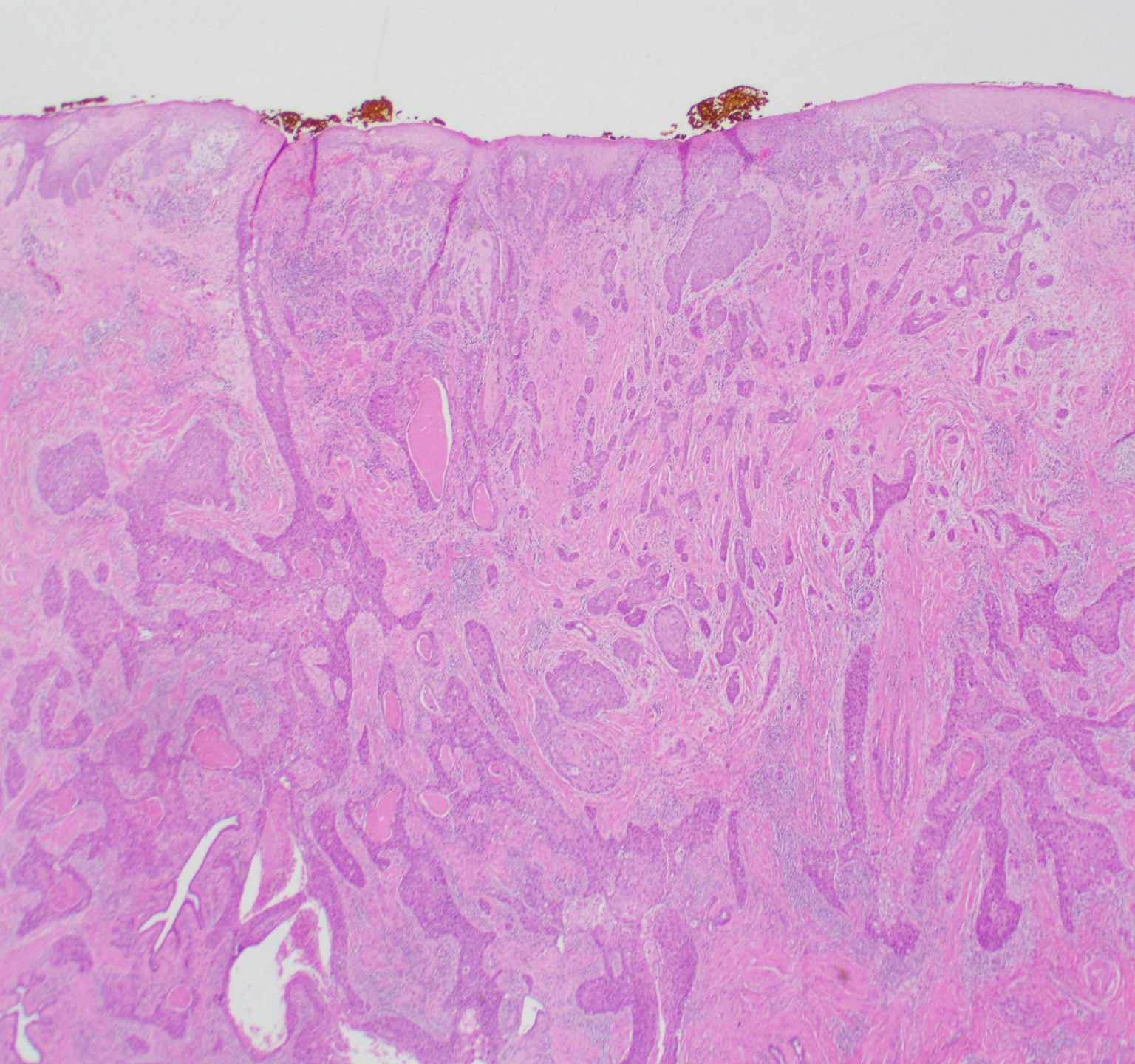
- ER was positive weak in 10%
- PR negative
- HER2 FISH: non-amplified

Differential considerations

- Metaplastic squamous carcinoma
- Cutaneous squamous cell carcinoma
- Metastatic squamous cell carcinoma

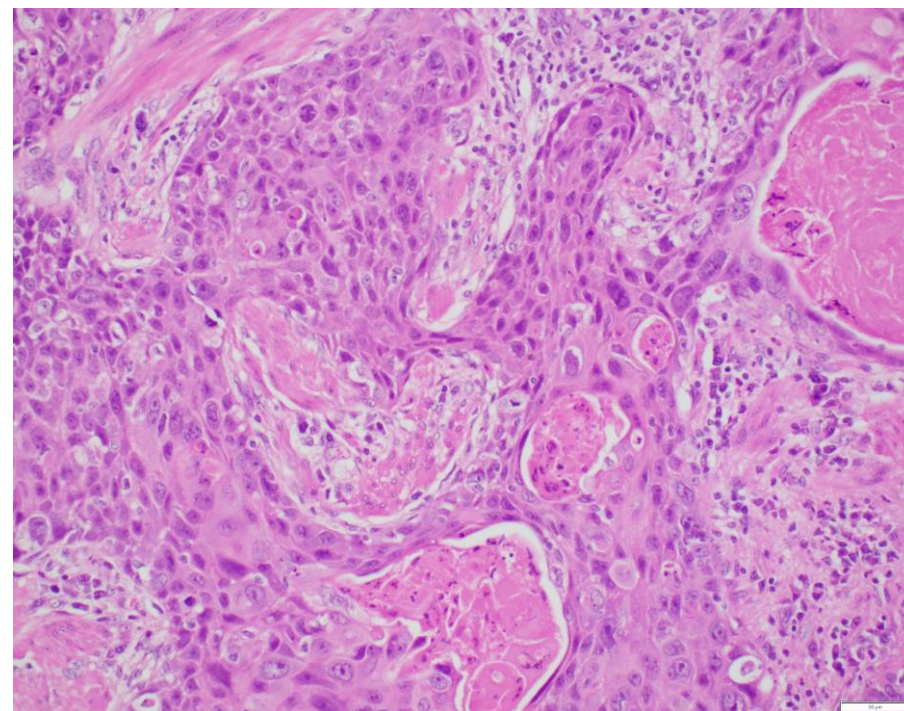
Final diagnosis (biopsy): High grade carcinoma with squamous differentiation

- Central lumpectomy was performed with a nipple resection



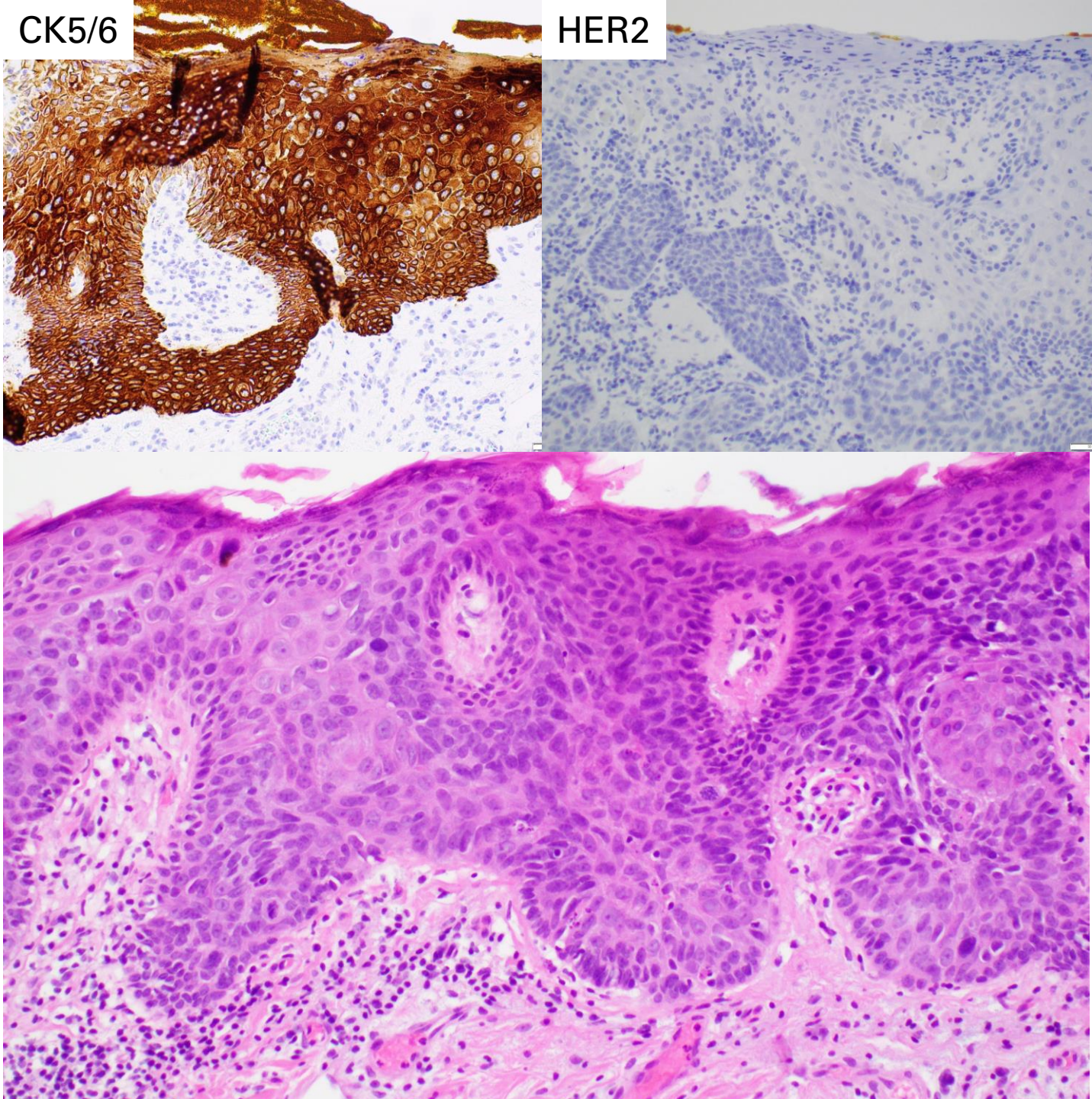
CENTRAL LUMPECTOMY SPECIMEN (NIPPLE SECTION)

- Positive p40 and CK5/6
- Patchy weak CK7 and GATA3
- Negative HER2 (score 0+)



EPIDERMIS AROUND THE PERIPHERY

- In situ component with strong positivity on CK5/6 and negative HER2 and focal CK7

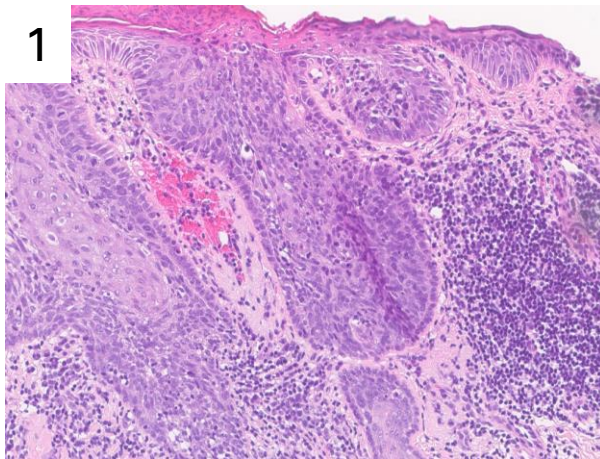


Final diagnosis (resection)

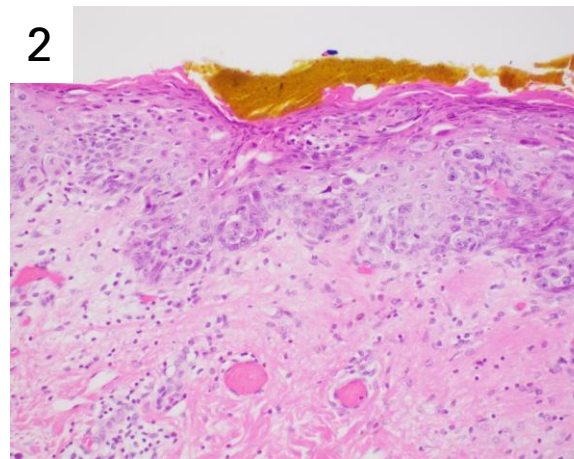
- Invasive moderately to poorly differentiated squamous cell carcinoma arising in the nipple with depth of invasion of 0.8 cm (with a comment favoring cutaneous origin rather than breast origin)
- Margins were negative
- No lymphovascular or perineural invasion were identified
- No lymph nodes sampling was done
- No radiotherapy was done
- No recurrence on almost 3 year follow up

Invasive squamous cell carcinoma of the nipple

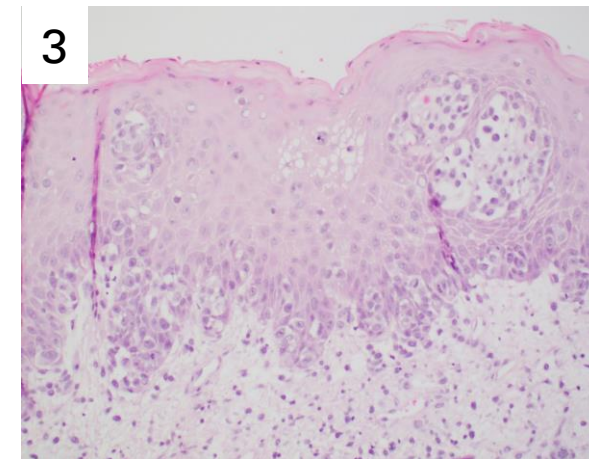
- Very rare diagnosis (about 8 reported cases in English literature)
- Limited data on treatment and outcome
- Bowen's disease¹ of the nipple (in-situ carcinoma) is the precursor lesion (which must distinguish from Paget's disease² and in-situ melanoma³)



+p63, +p40 and +HMWCK



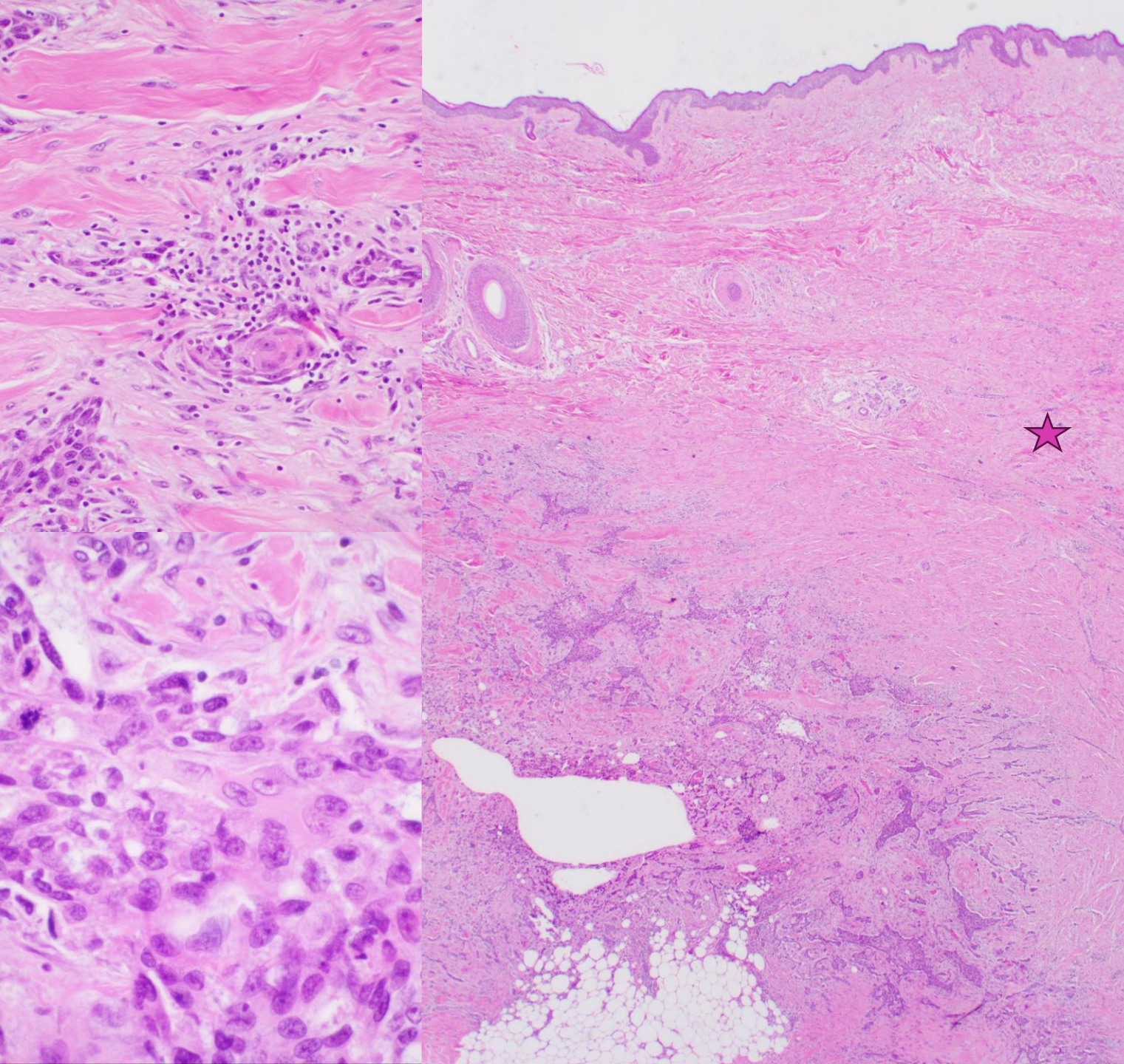
+CK7, +HER2, +CAM5.2



+SOX10, +S100, +MelanA

Table summarizing case reports with invasive squamous cell carcinoma of the nipple

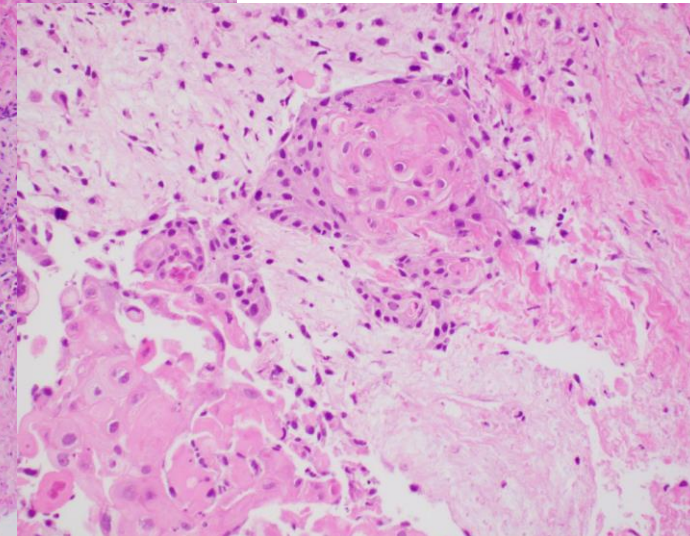
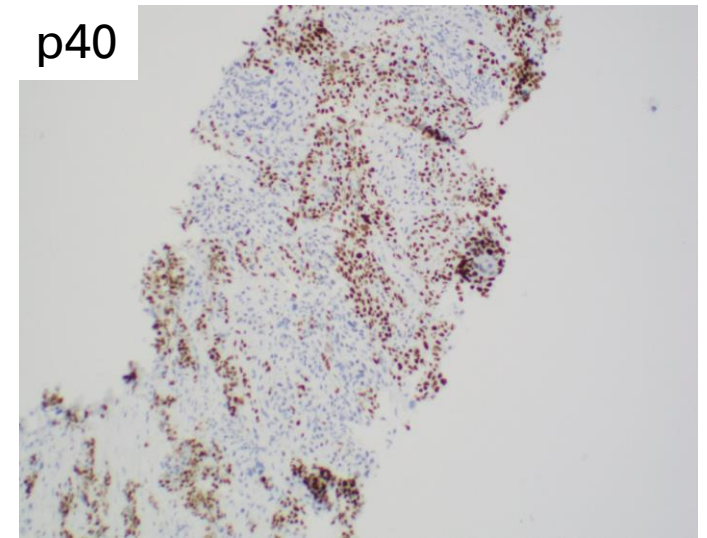
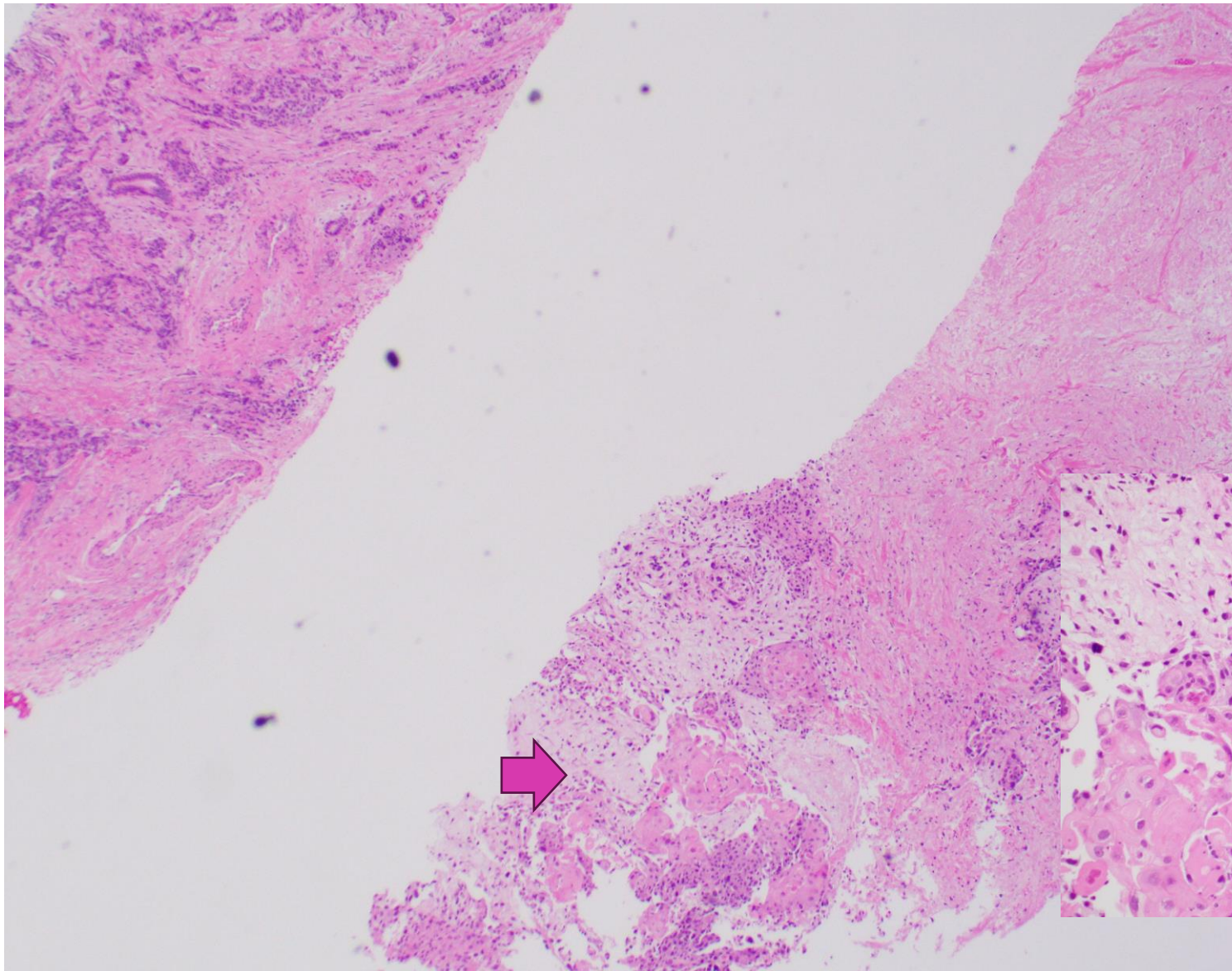
Publication	Presentation	Risk factors	Diagnosis	IHC and molecular work-up	Therapy	Outcome
Sofos et al. 2013	34-year-old female with scaly rash on the right nipple areola complex	Unknown	Moderately differentiated squamous cell carcinoma	Unknown	WLE Modified radical mastectomy with axillary tail dissection (MC in 1 of 11 LN)	DF x12 months
Upasham et al. 2014	87-year-old female with fungating mass	Unknown	Well differentiated squamous cell carcinoma	Unknown		DF x 5 years
Loveland-Jones et al. 2010	66-year-old female with non healing ulcer of the right nipple	DCIS, XRT	Invasive squamous cell carcinoma	Positive CK903, CK5/6, p63 and calponin Negative ER, PR and Her-2/ neu	WLE	Unkown
Pendse et al. 2015	29-year-old female with nipple nodule	Pregnant	Invasive squamous cell carcinoma	Positive p16 and p53 Negative HR HPVish	WLE and reginal LN dissection	DF x15 months
Hosaka et al. 2011	67-year-old female with exophytic mass	Unknown	Invasive poorly differentiated squamous cell carcinoma with neuroendocrine differentiation	Positive AE1/AE3, CK–HWM, EMA Negative for CK7, CK20, CEA, Ber-EP4, GCDFP-15, ER, PR, HPV, NF, CD15, CD56 Focally positive for chromogranin A, synaptophysin, NSE	Mastectomy, ALND	DF x5 years
King et al. 2012	62-year-old male with scaly rash	Sun exposure	Well differentiated squamous cell carcinoma	Positive CK904 Negative S100 and CEA and CAM5.2	WLE	Unkown
Rebielak et al. 2022	61-year-old female with bloody discharge from the left nipple associated with scaling	Asthma, hypertension, hyperlipidemia and osteoarthritis	Invasive moderately differentiated squamous cell carcinoma and squamous cell carcinoma in situ	Positive p63, CK5/6, and AE1/AE3 Negative S100 and CEA Ki67 showed marked proliferative activity	WLE	DF x6 months
Zaesim et al. 2018	49-year-old female with 1 year history of growing right nipple erythematous lesion	HPV L1	Microinvasive squamous cell carcinoma and squamous cell carcinoma in situ	Positive HPV L1 capsid protein	WLE	Unknown

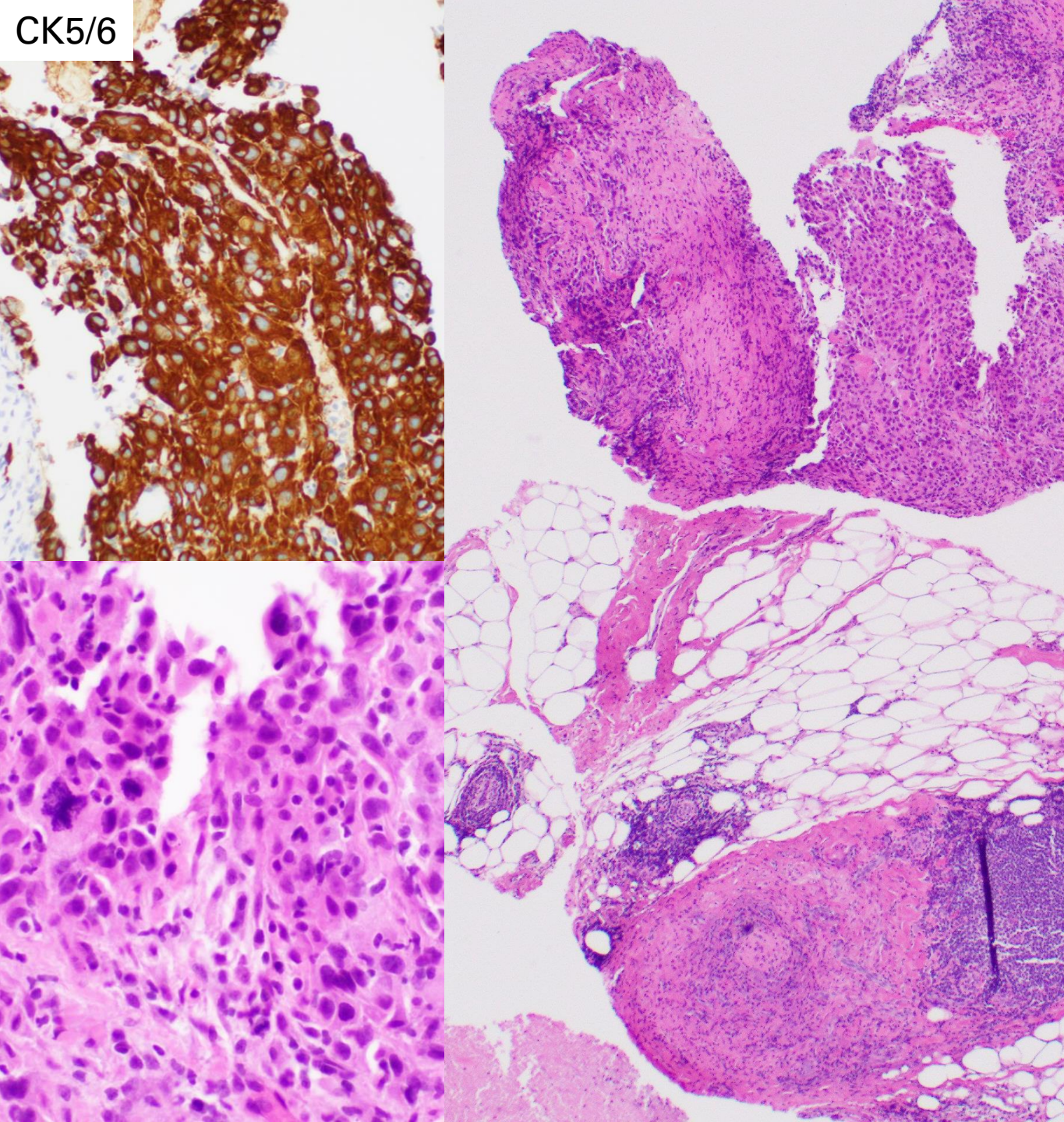


Cutaneous squamous cell carcinoma

- Mass was medial to the nipple without definitive nipple involvement
- There was a prior biopsy site related change forming dermal scar (pink star)
- The tumor was moderately to poorly differentiated and had depth of 1.2 cm

Invasive carcinoma with squamous differentiation (metaplastic)





METASTATIC SQUAMOUS CELL CARCINOMA

- Axillary biopsy
- Positive p40 and negative GATA3
- History of squamous cell carcinoma of his back
- Must be distinguished from benign squamous inclusions

Summary

- Invasive squamous cell carcinoma of the nipple is a very rare diagnosis with the differential including cutaneous squamous cell carcinoma, metastatic squamous cell carcinoma and metaplastic breast carcinoma
 - Clinical approach is different for cutaneous squamous cell carcinoma and metaplastic breast cancer [Burton et al. 2016, Karia et al. 2012, Pirot et al. 2020]
- Finding a precursor lesion may be helpful in establishing the diagnosis
- The differential of Paget's disease is Bowen's disease and in-situ melanoma
- The diagnosis of squamous cell carcinoma requires clinical and radiographic correlation, especially if the sample is limited

Take home message

- Squamous metaplasia of lactiferous ducts is on the differential with epidermal inclusion cyst in nipple biopsy
- Squamous metaplasia may occur in benign breast tissue, after prior procedures, in sclerosing lesions or in papilloma(s)
- Primary breast squamous cell carcinomas are rare, and most are metaplastic breast cancers
- Metaplastic (squamous) breast carcinoma looks identical to cutaneous squamous cell carcinoma or metastases from other sites, but prognosis varies
 - Identifying precursor lesion may help in favoring the primary site of origin
- Squamous nests, cellular stroma or lymphoid aggregates in a radial sclerosing lesion should prompt assessment for low-grade adenosquamous carcinoma

QUESTIONS?



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- Dr. Alexander Kikuchi

Thank you for your attention



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