Immunohistochemistry for problem solving (and causing problems)

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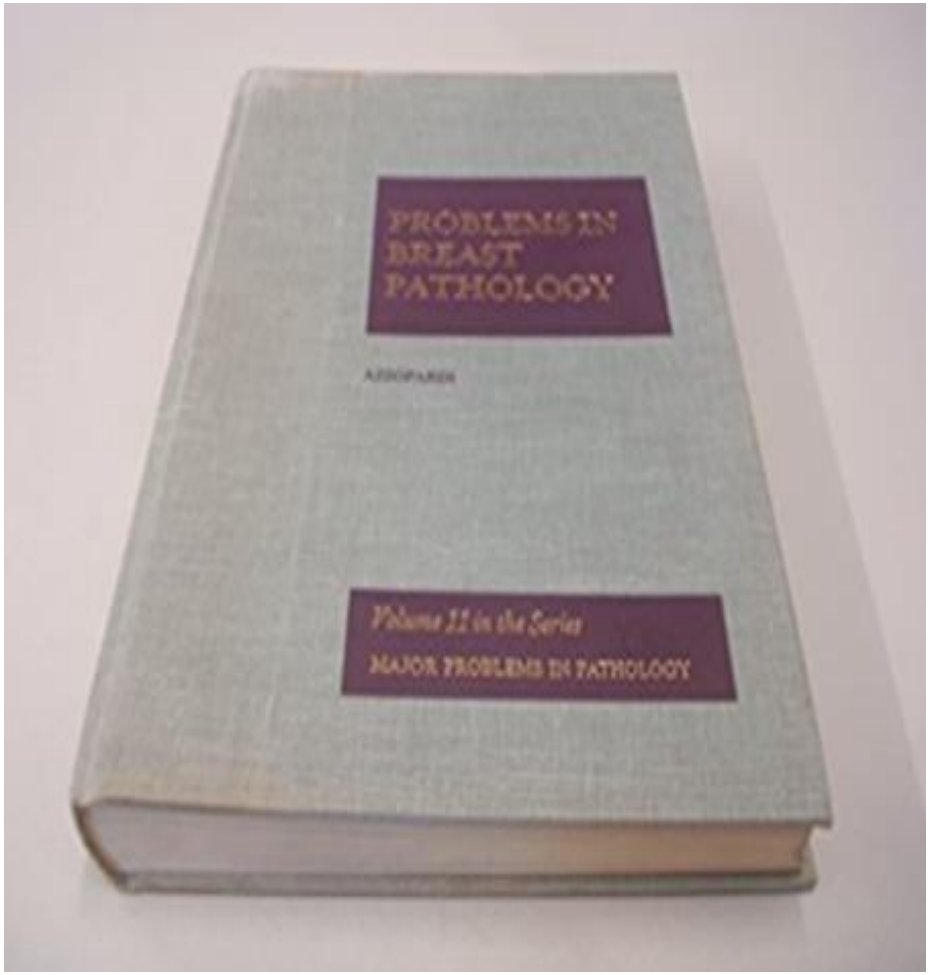


INVASIVE TUMOUR TYPE

LVI or DCIS with retraction ?

***IN SITU* or INVASIVE**

IHC for DIAGNOSIS

PRIMARY or OTHER

UDH or ADH / DCIS ?

SPINDLE CELL LESIONS

GLANDULAR & PAPILLARY LESIONS

EVALUATION OF METASTASES

Antibodies for diagnosis

- Myoepithelial cell markers

  p63, SMM-HC, Calponin, SM actin
- Cytokeratin family

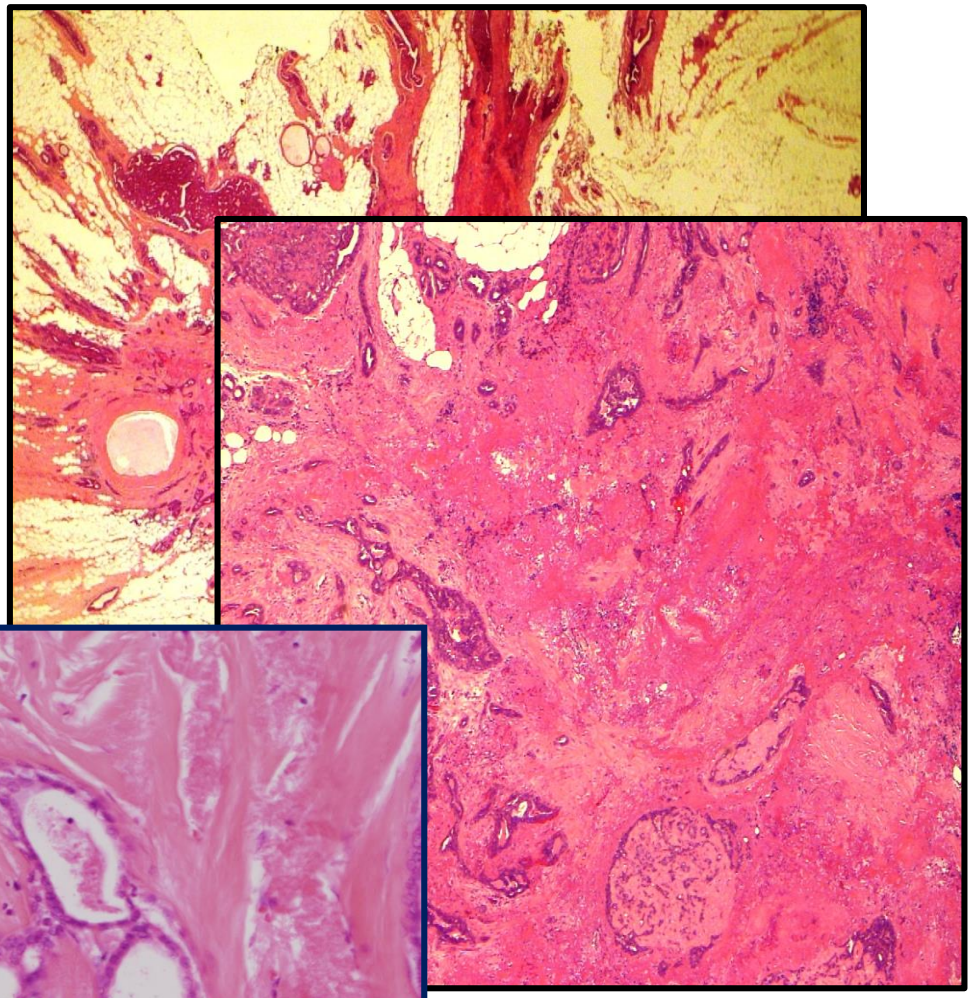
  AE1/3, Cam 5.2, CK5/6, CK7, CK20 etc
- E-cadherin
- Breast specific antibdies

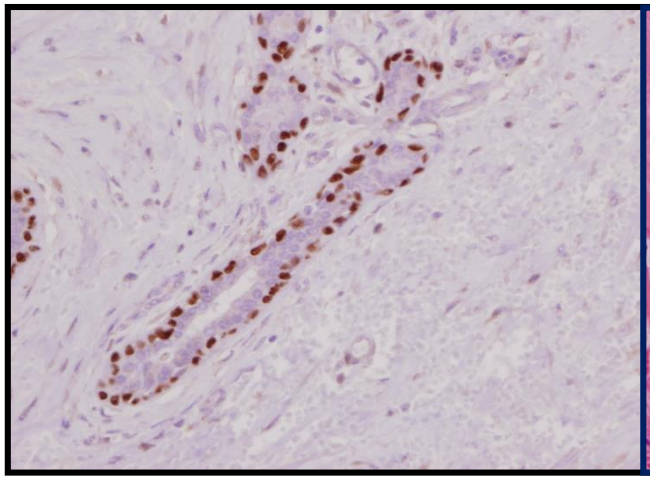
  ER, PR, Gata 3, GCDFP-15, mammoglobin
- Others

  B-catenin, CD34 etc

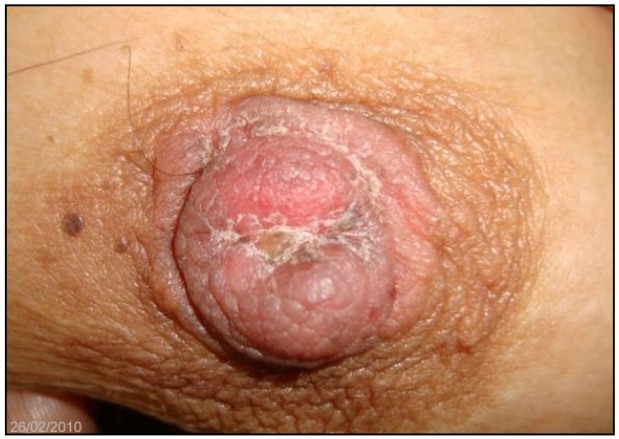

Benign vs malignant
glandular lesions

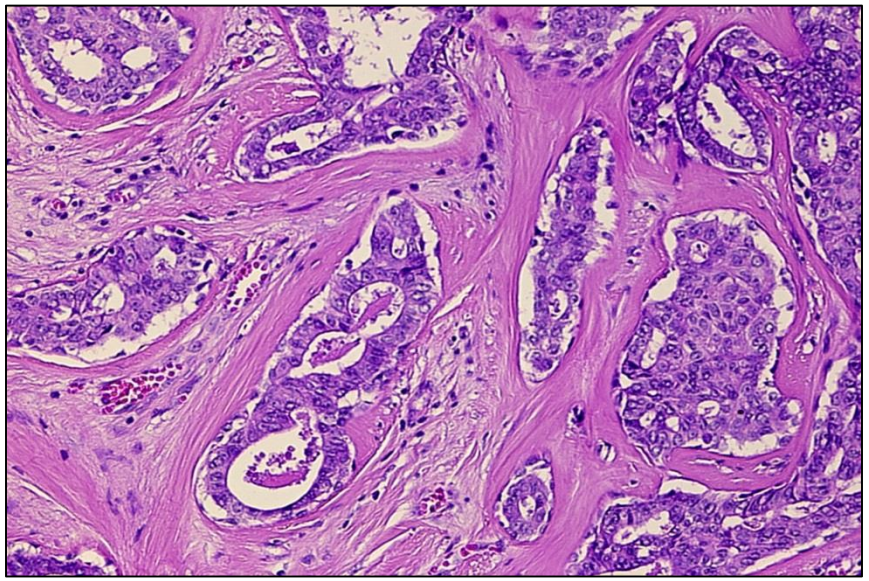
Radial scar





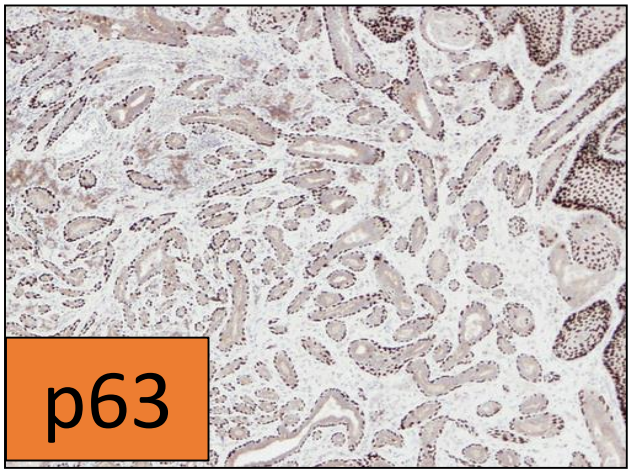
Nipple duct adenoma



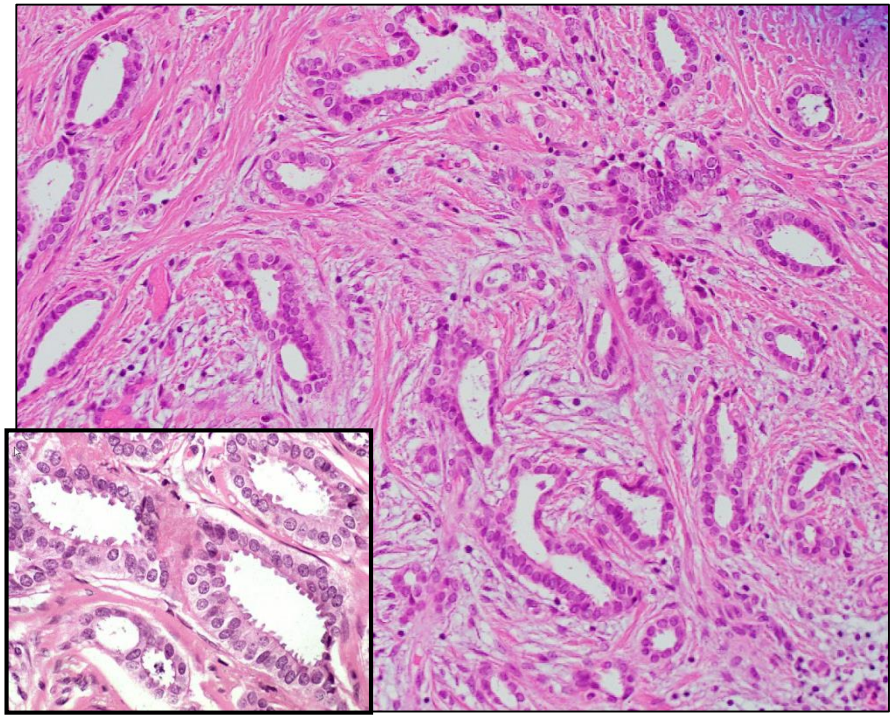


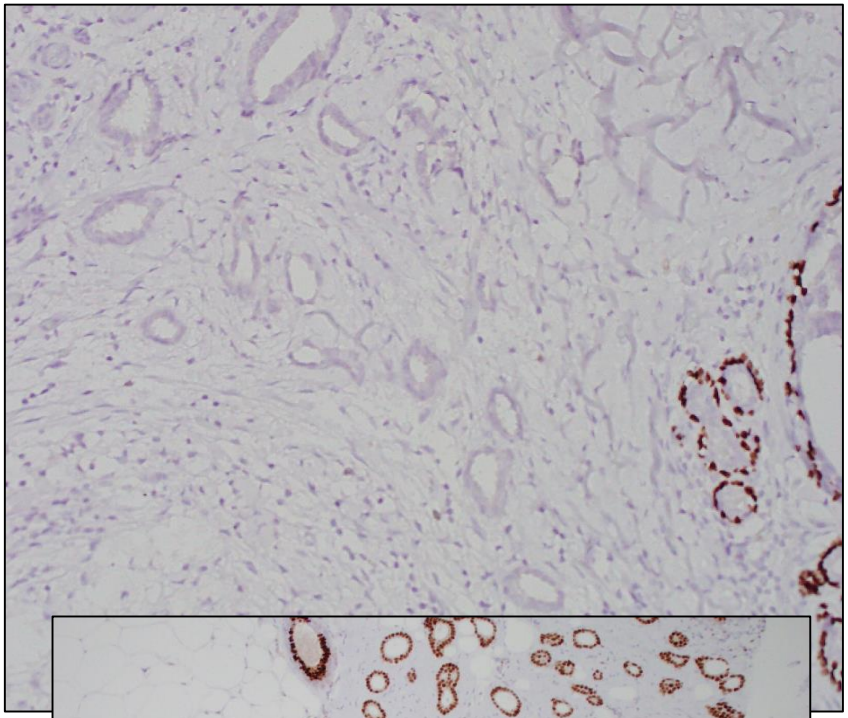
Mimics carcinoma

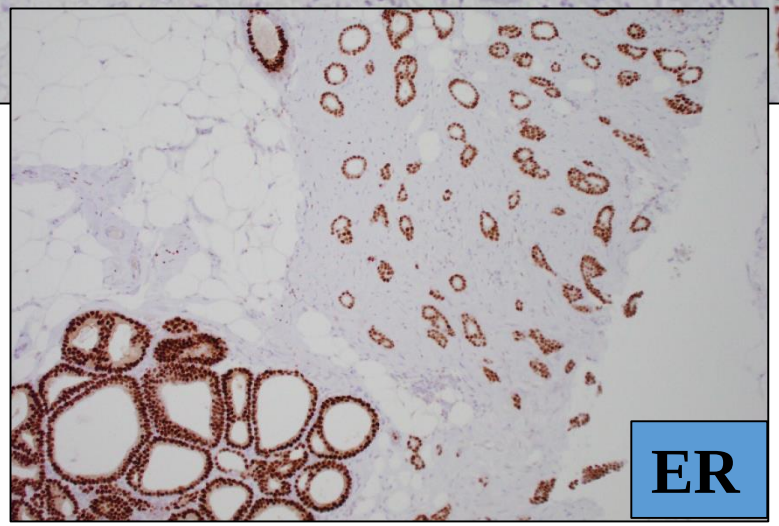
- **Ulcerated nipple clinically**
- **Infiltrative lesion microscopically**



Tubular carcinoma

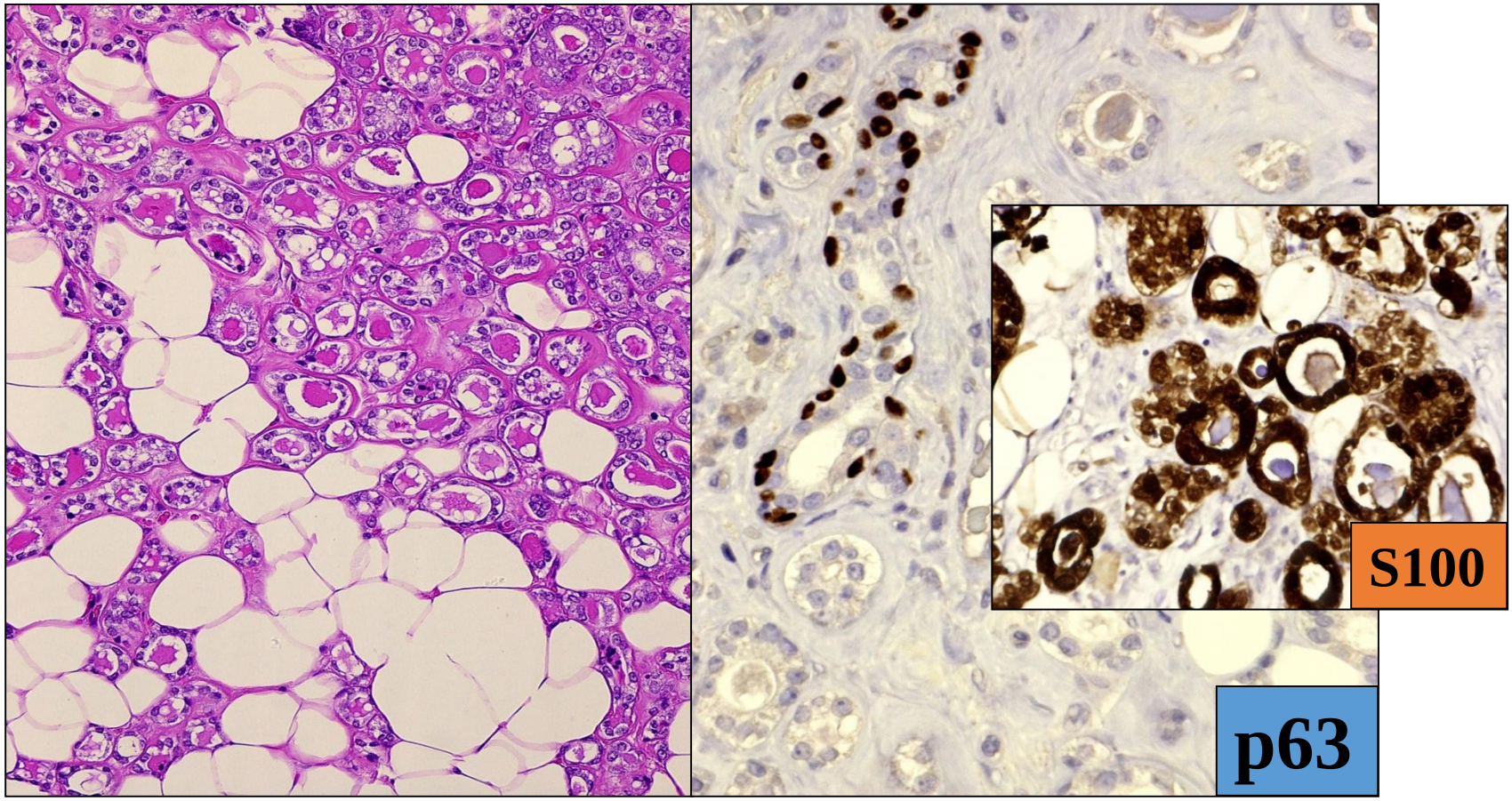






- Open tubules
- Single cell layer
- Apical snouts
- Extend into fat

Microglandular adenosis



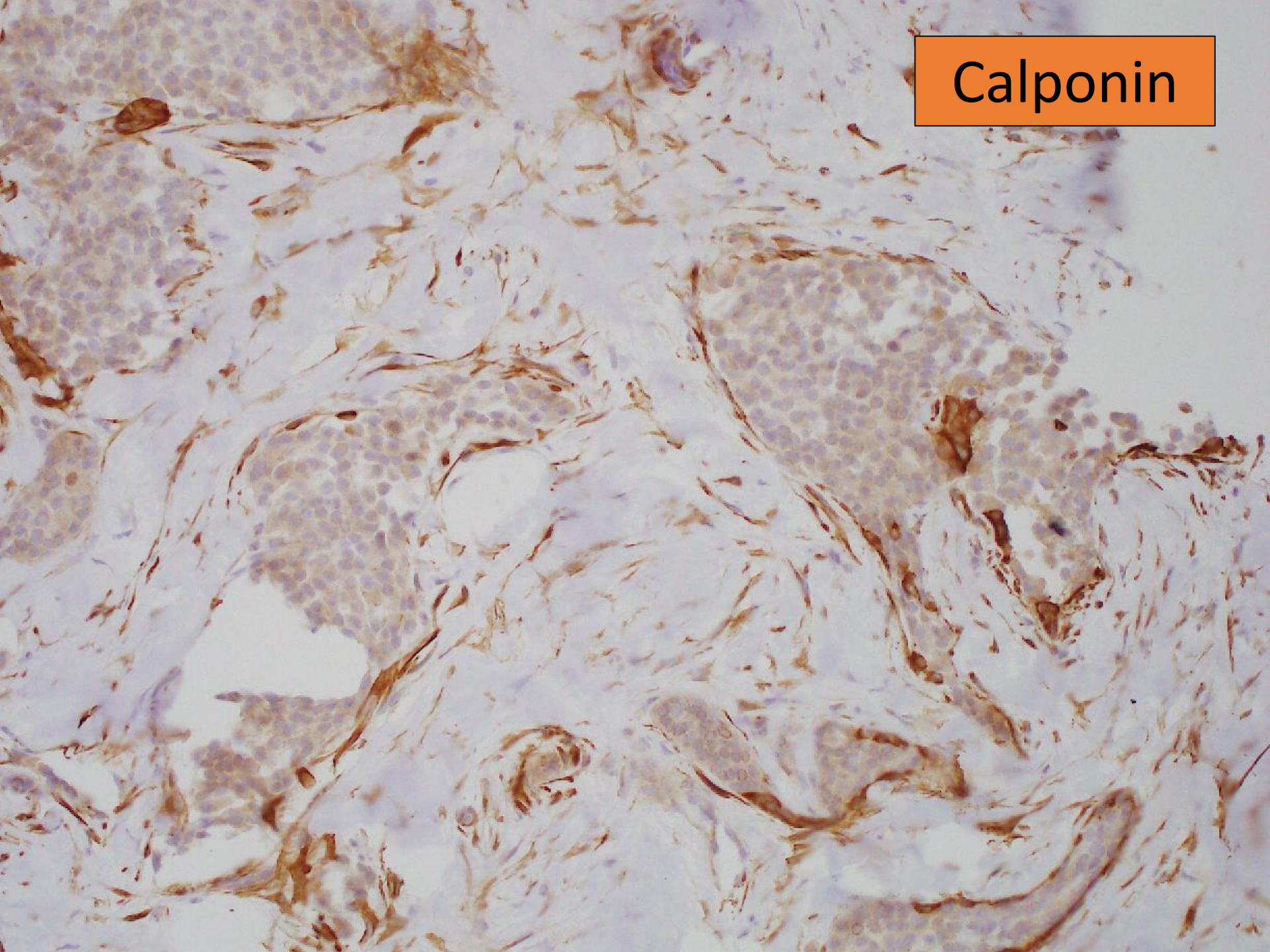
MGA = low grade triple negative tumour with potential to progess

Myoepithelial cell markers

Marker	Sensitivity	Specificity
p63*	Excellent	Excellent
SM actin**	Good	Poor
Calponin**	Excellent	Poor
SM myosin**	Good	Excellent

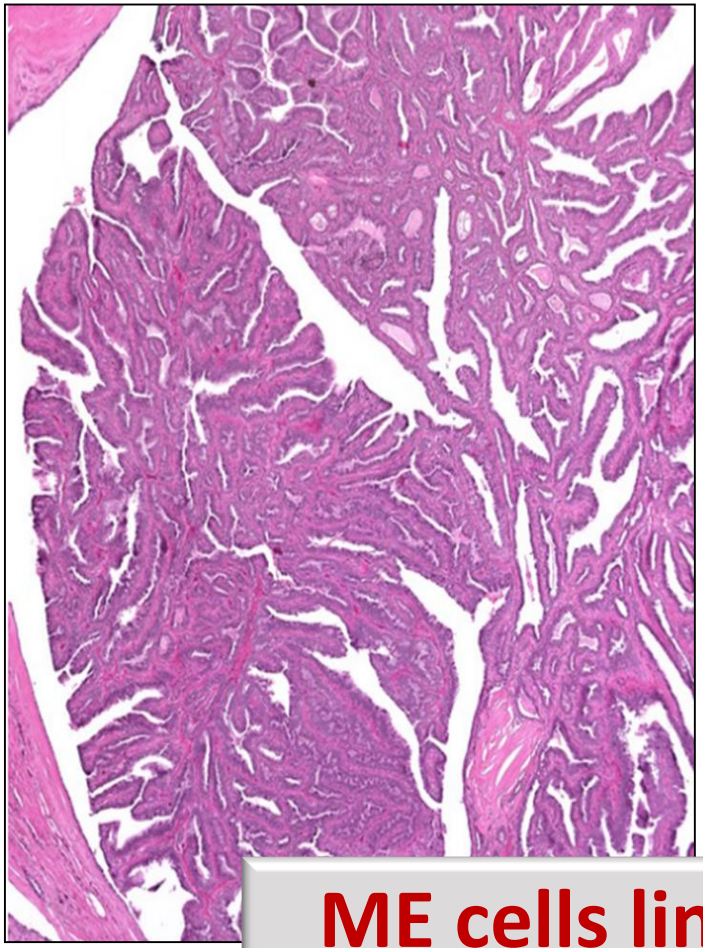
*** May be difficult to see due to me cell attenuation around enlarged ducts**

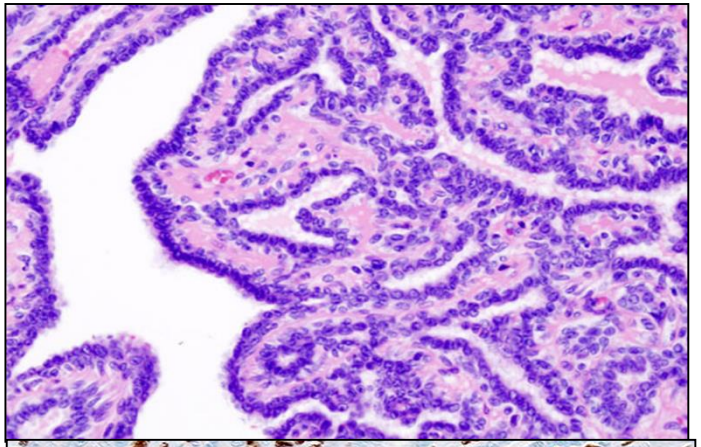
**** Myofibroblast staining**

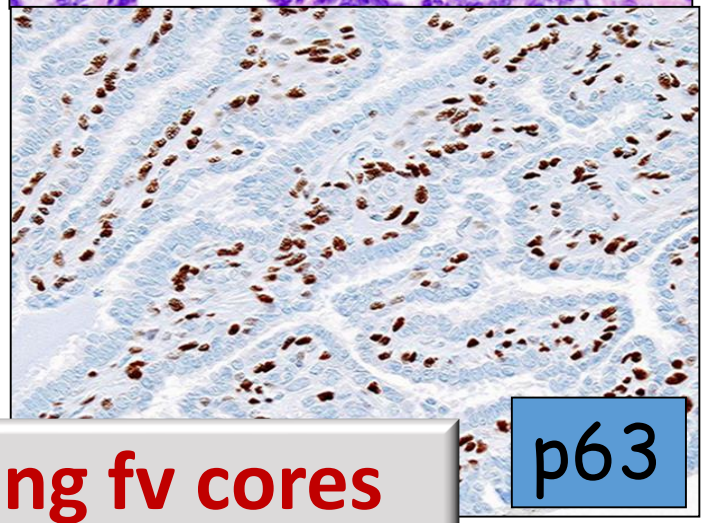

Calponin


Papillary lesions

Intraduct papilloma

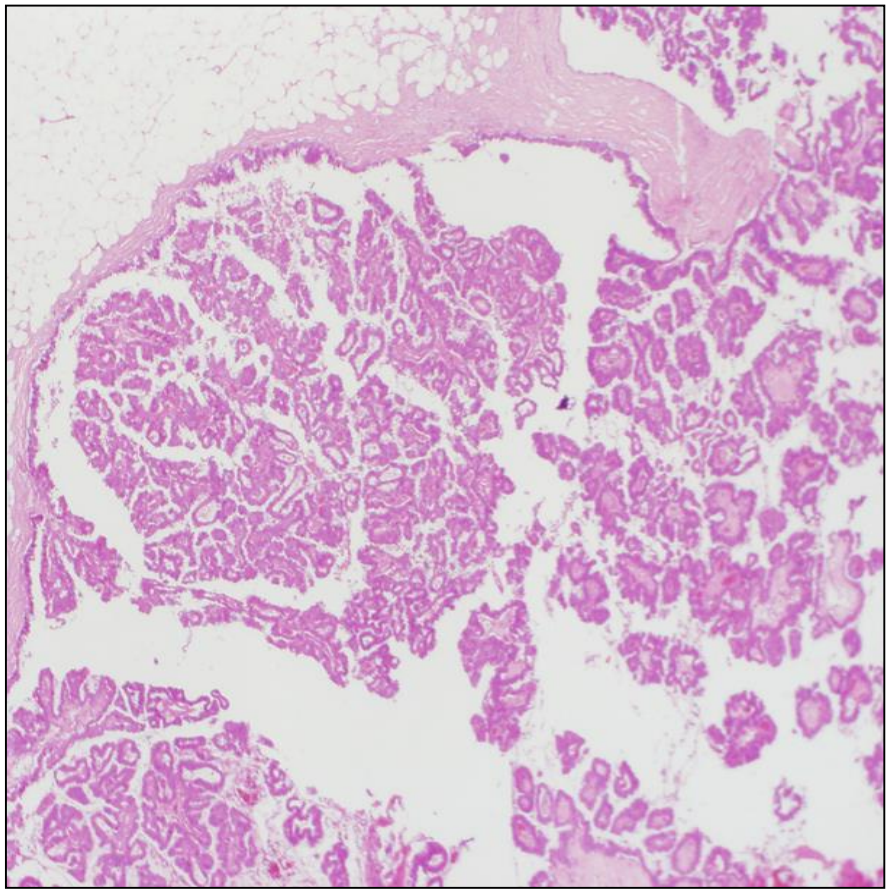


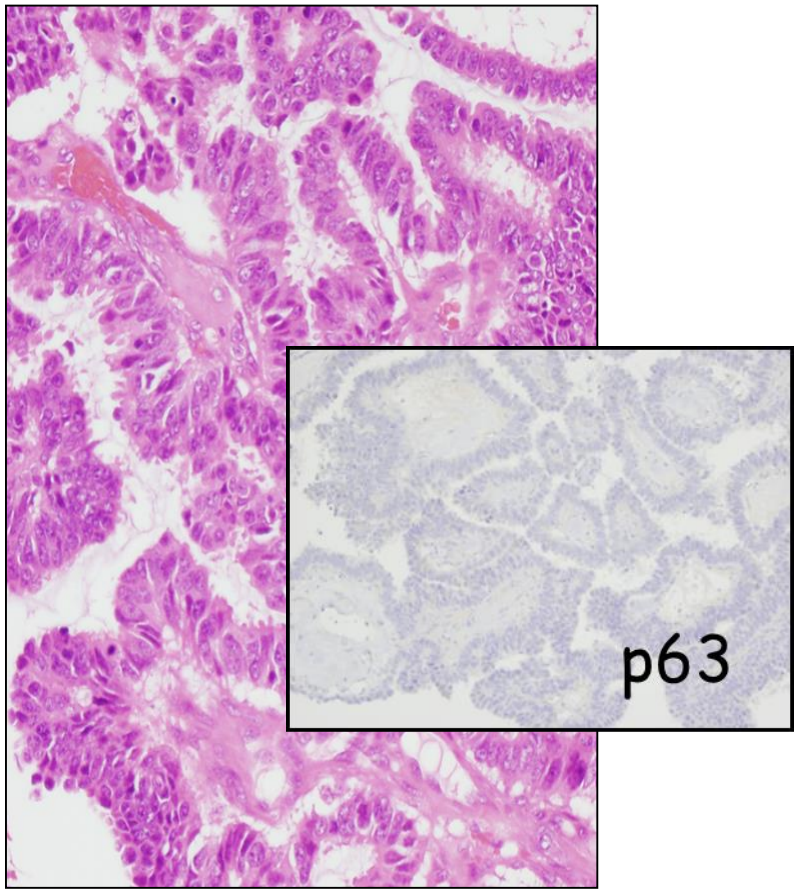




ME cells lining fv cores and at periphery

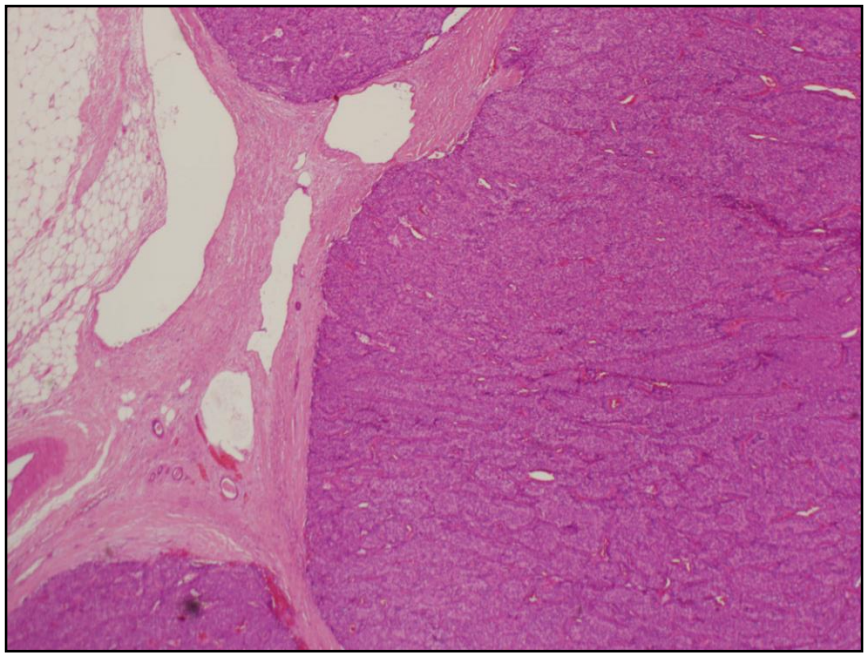
Encapsulated papillary carcinoma

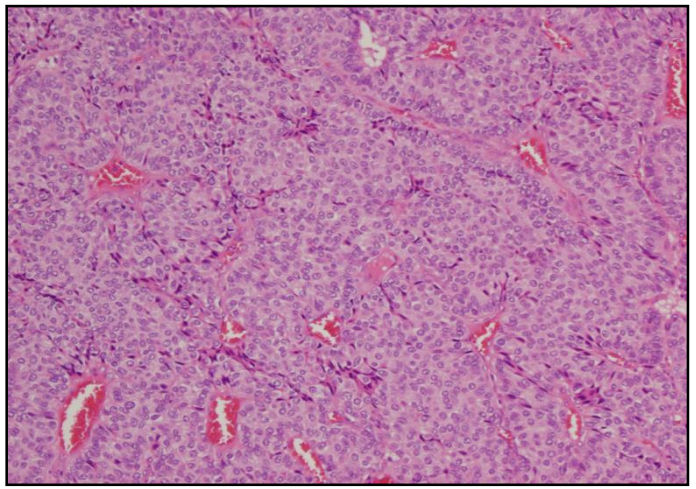


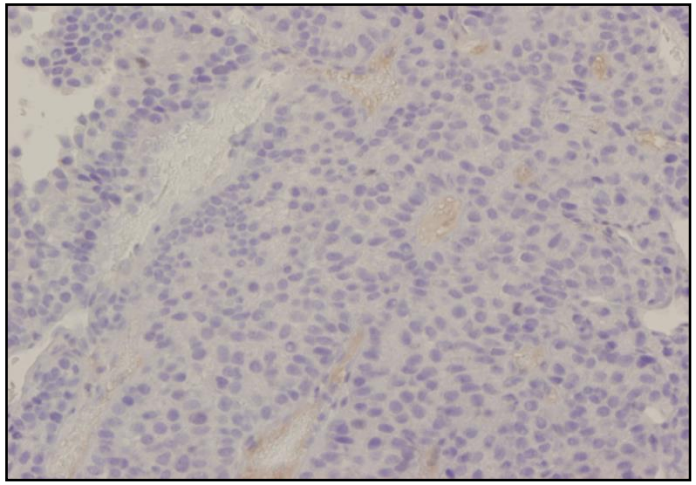


No ME cells lining fv cores
+/- at periphery

Solid papillary carcinoma



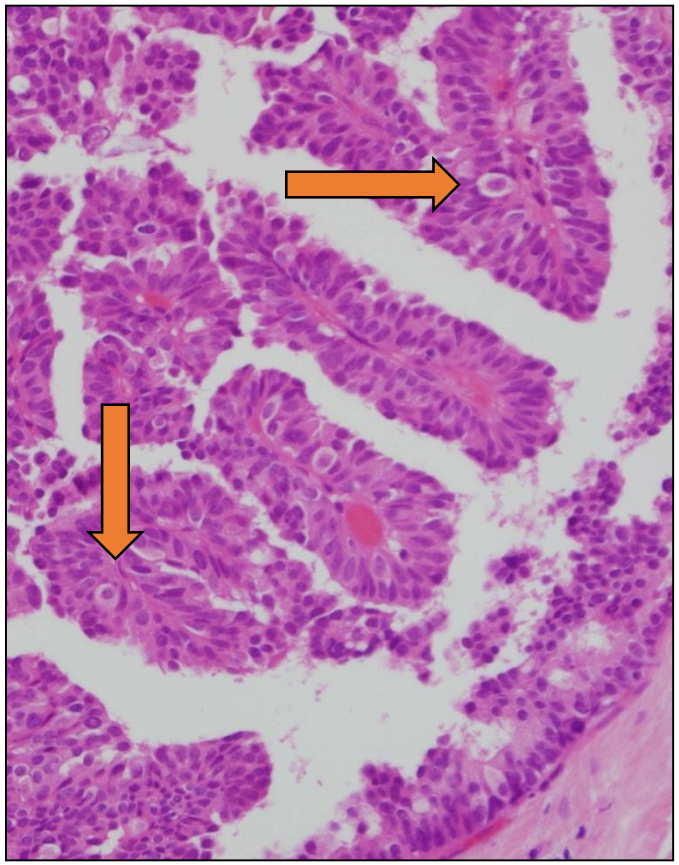




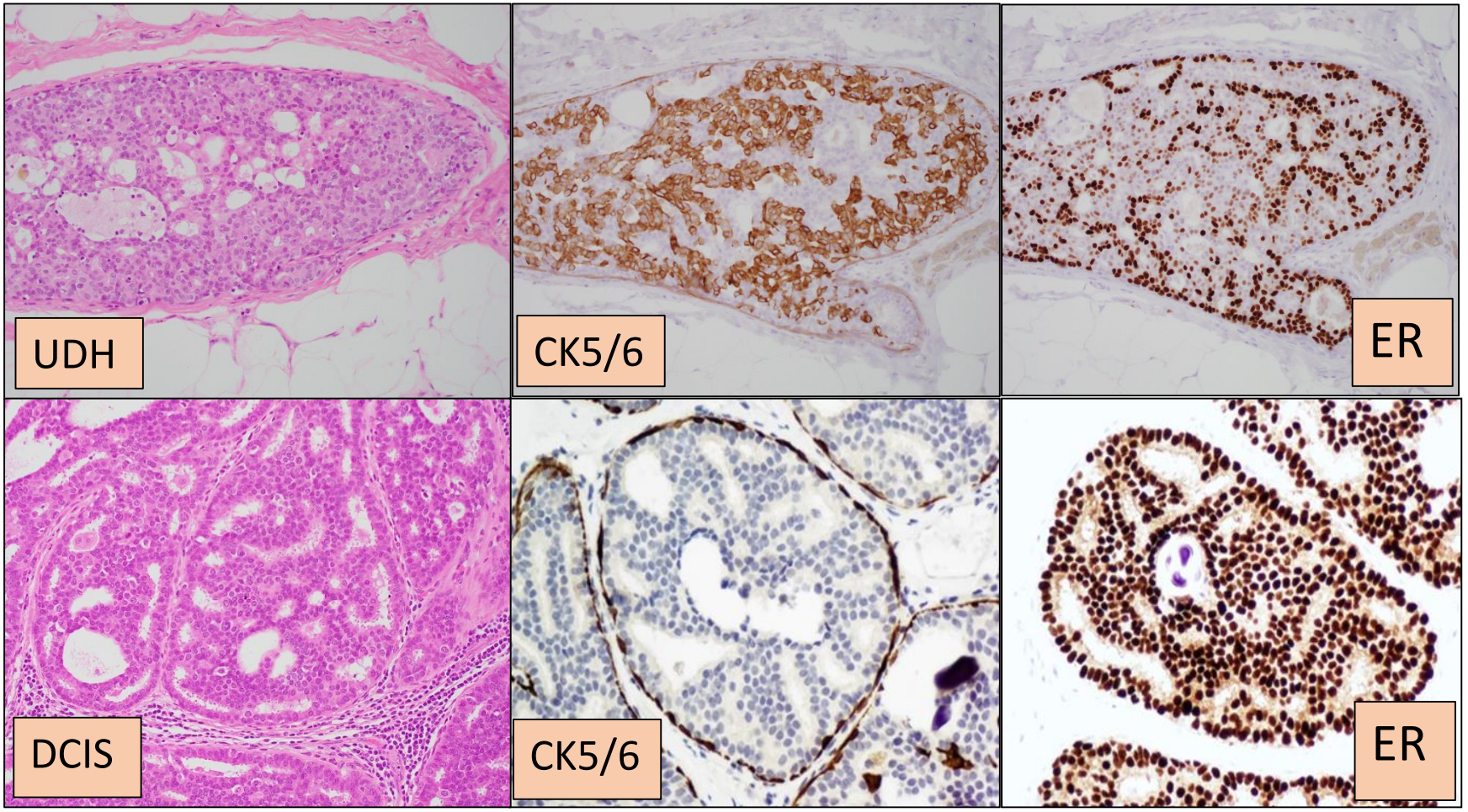
No ME cells within lesion
+/- at periphery

Encapsulated papillary carcinoma
Dimorphic variant

- Epithelial cells in direct contact with fibrovascular cores morphologically different - ‘globoid’
- May mimic ME cells
- Erroneous diagnosis of benign papilloma
- ME marker negative

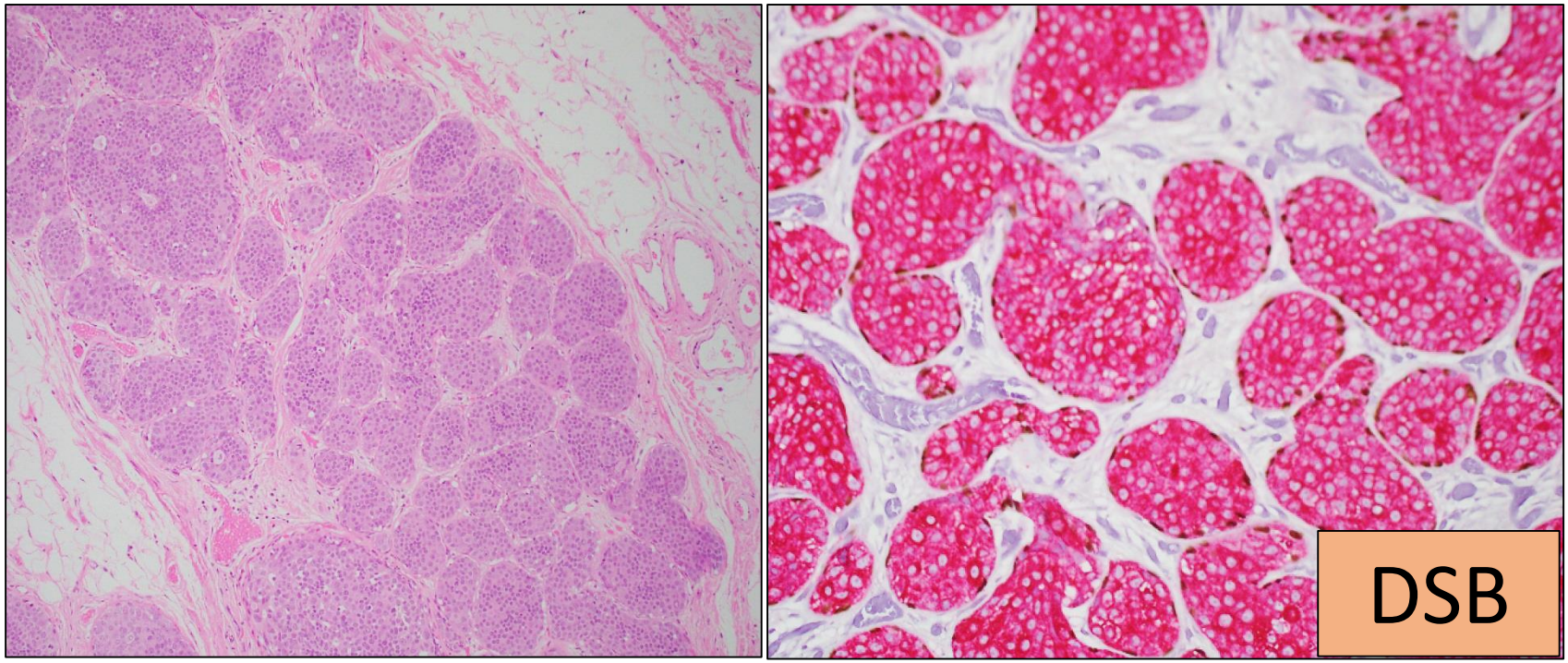


UDH versus ADH/DCIS

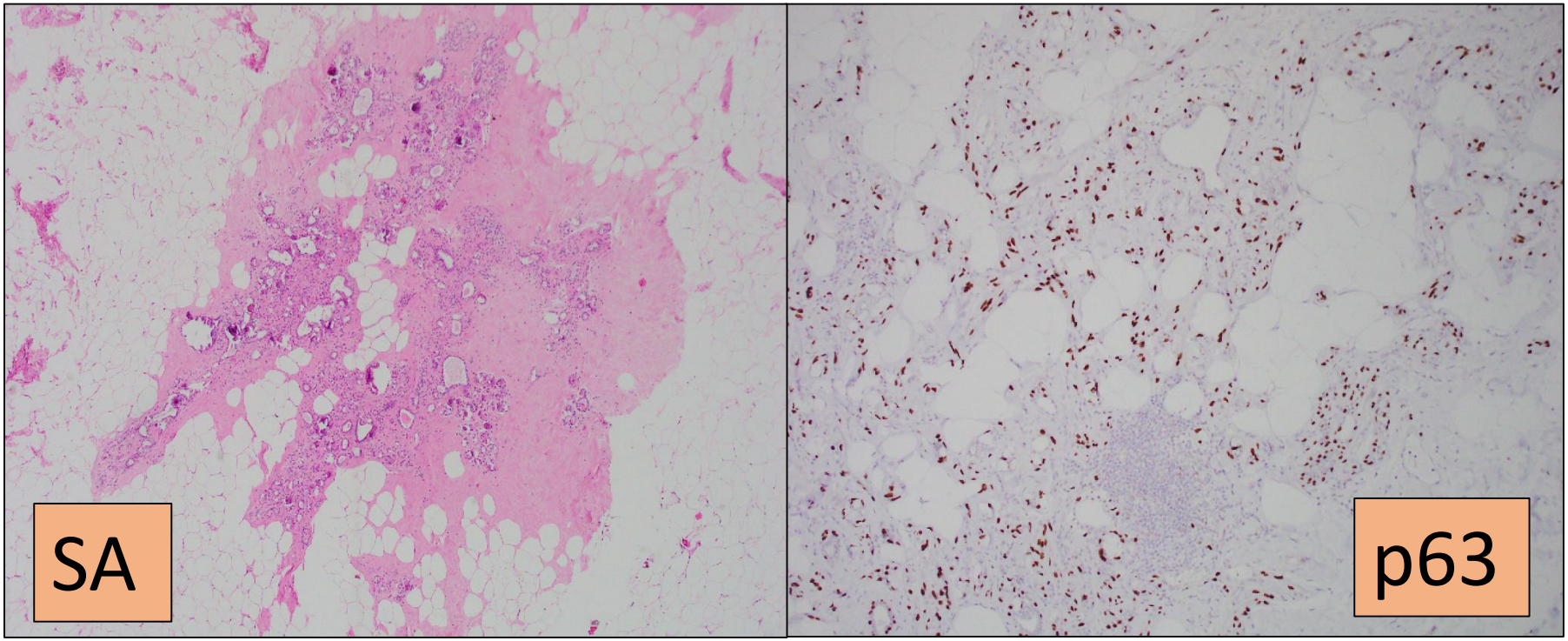


The distinction between ADH and DCIS relies on morphology and not on IHC

DCIS in TDLU

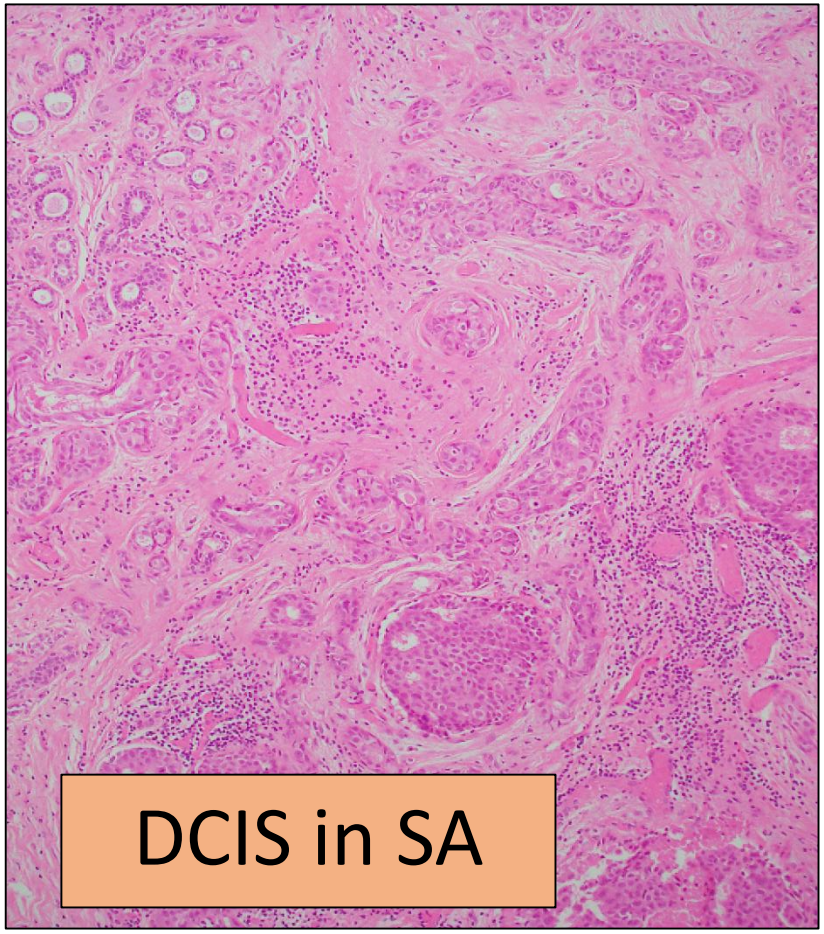


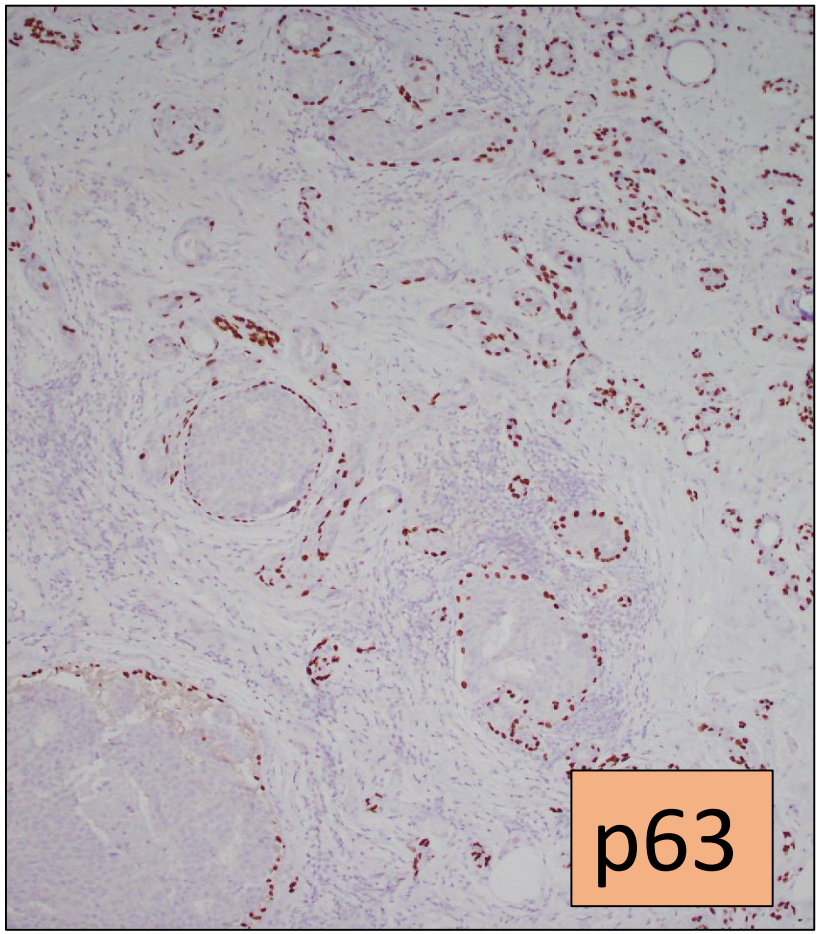
Sclerosing adenosis *vs* invasive carcinoma



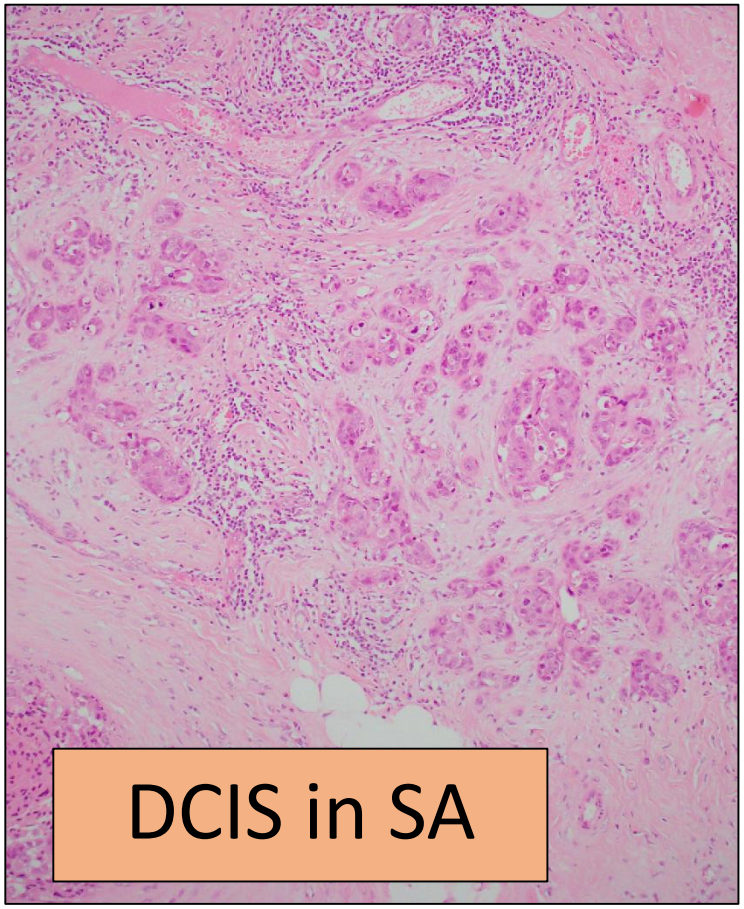
Nodular arrangement at low power

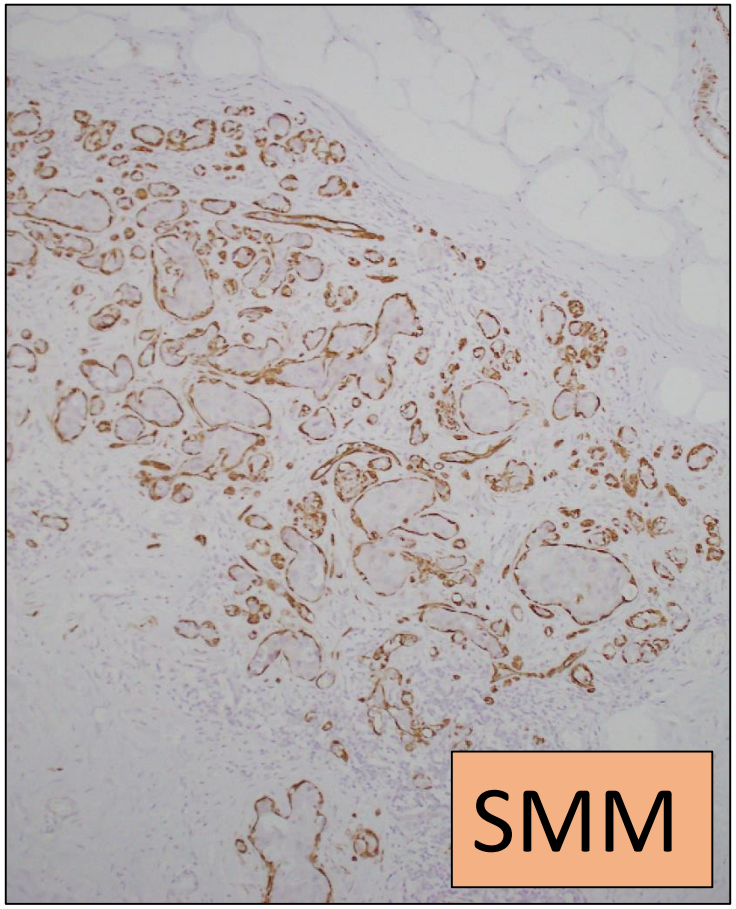
DCIS in sclerosing adenosis *vs* invasive carcinoma



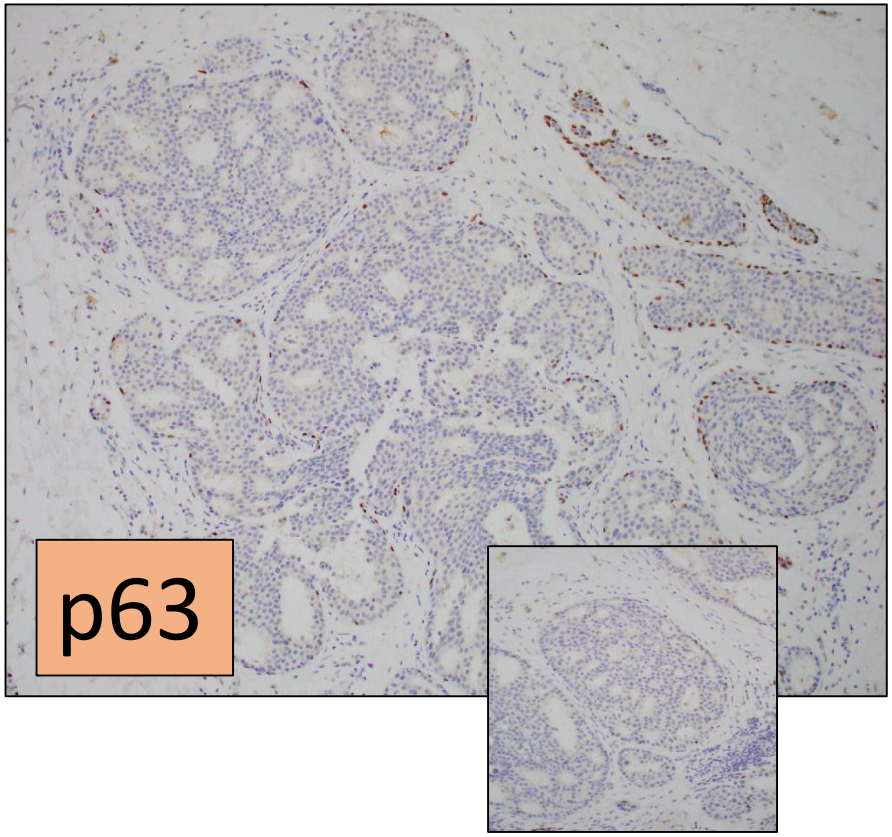


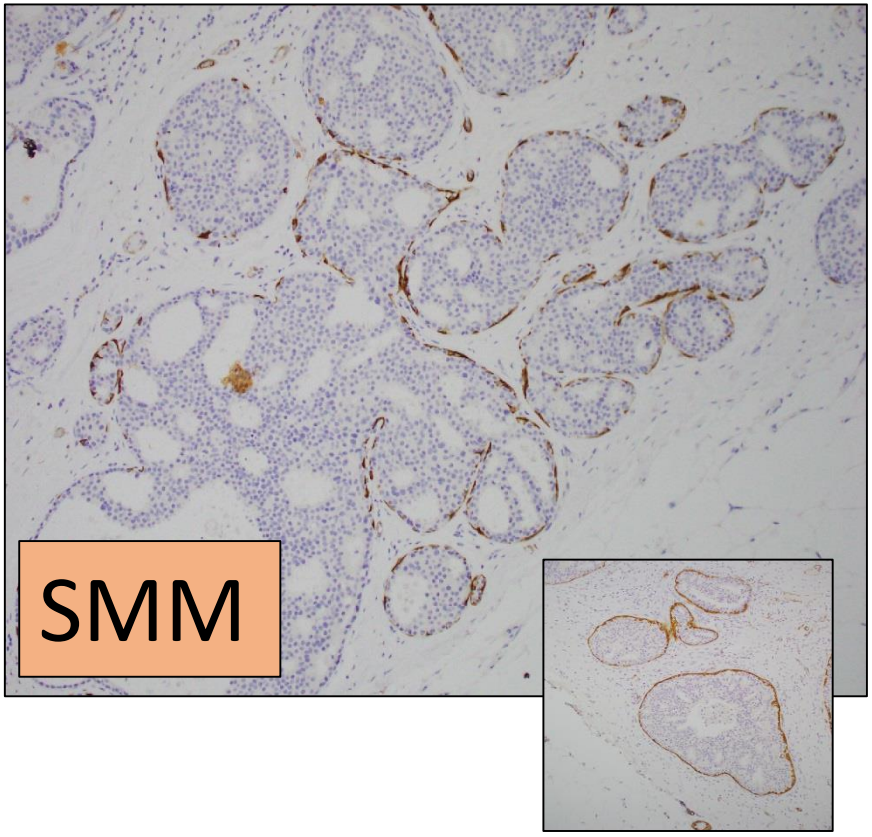
DCIS in sclerosing adenosis *vs* invasive carcinoma





DCIS
vs invasive carcinoma





Reduced expression of DCIS associated MEC vs normal MEC

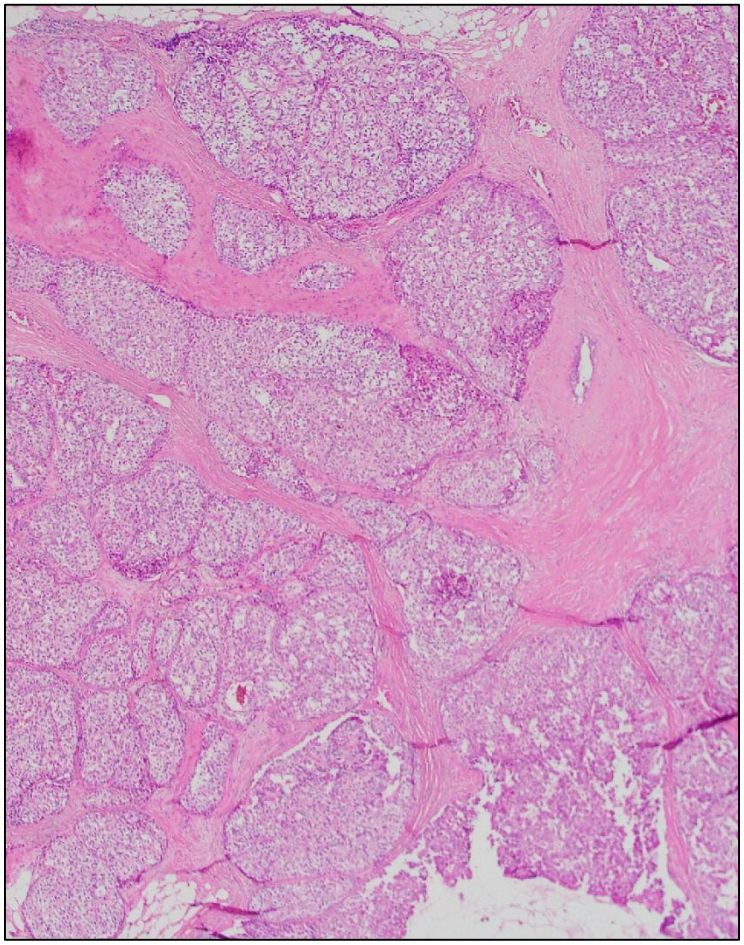
Myoepithelial cell marker	% DCIS cases with reduced expression (n = 56)
Smooth muscle actin	0%
Calponin	16%
SMM HC	76%
p63	10%

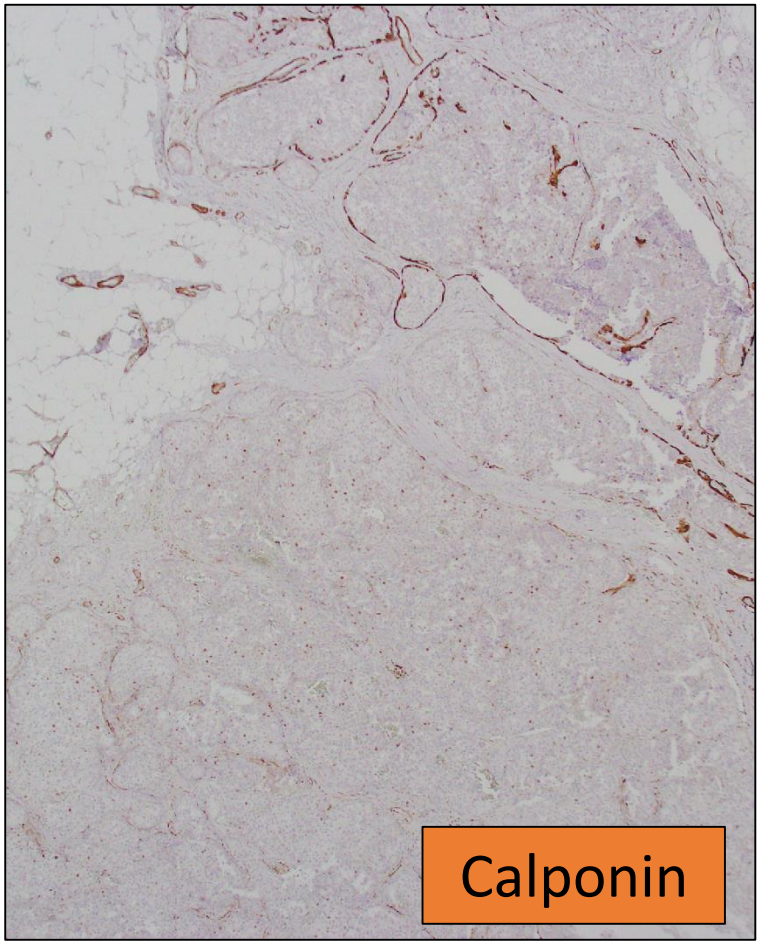
Phenotypic Alterations in Ductal Carcinoma In Situ-associated Myoepithelial Cells: Biologic and Diagnostic Implications

Justin B. Hilson; Stuart J. Schnitt; Laura C. Collins

Am J Surg Pathol 2009

% DCIS *vs* % invasive carcinoma





Quality Assurance in Breast Pathology

Lessons Learned From a Review of Amended Reports

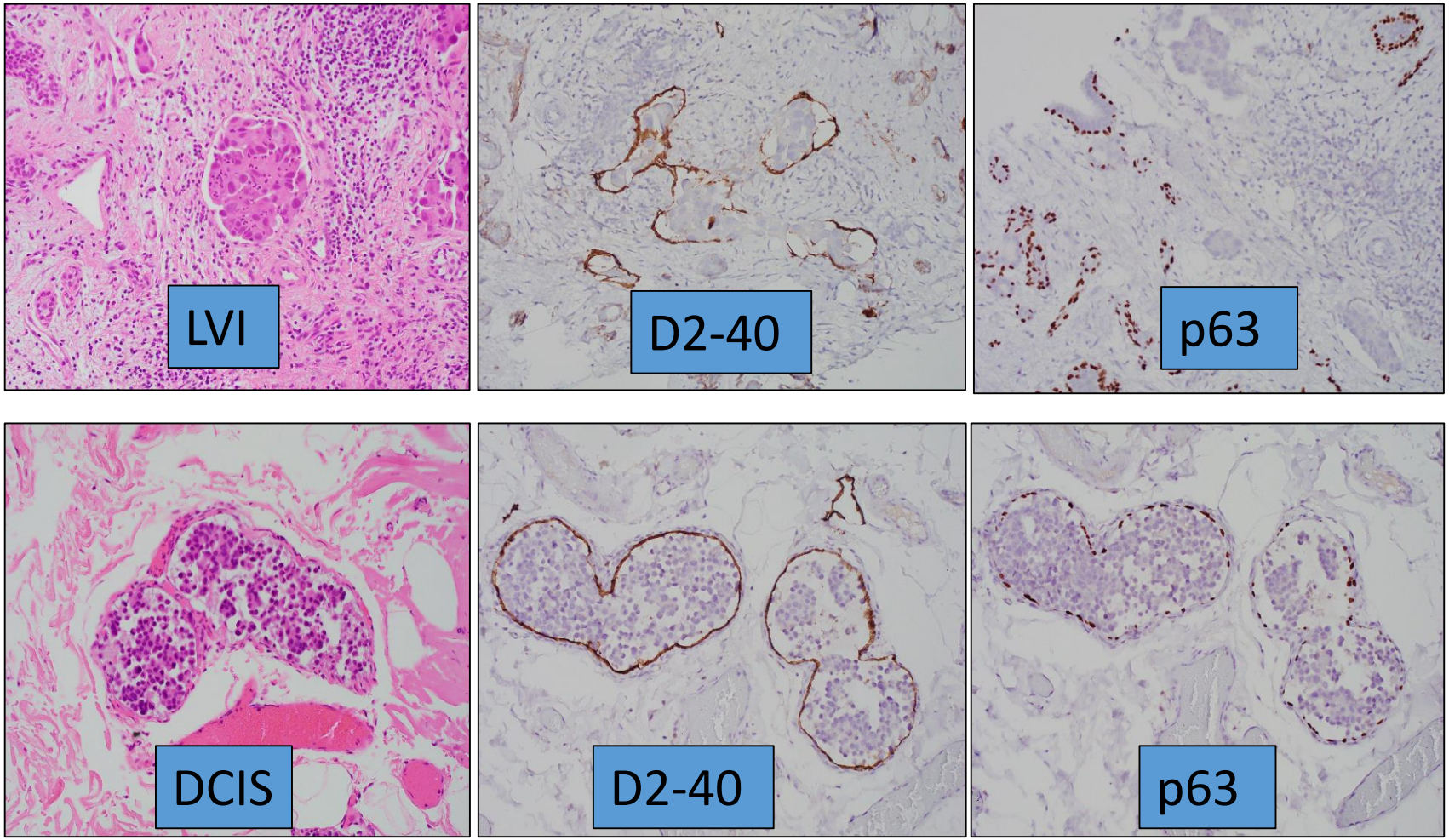
Table 2. Major Diagnostic Changes During a 5-Year Period

Case No.	Specimen	Original Diagnosis	Amended Diagnosis	Discoverer	Mechanism of Discovery	Time to Discovery, d
Downgraded diagnoses						
1	Core biopsy	IDC, DCIS	DCIS in sclerosing adenosis	Pathologist	Surgical excision	35.1
2[a]	Core biopsy	IDC	DCIS in sclerosing adenosis	Pathologist	Surgical excision	78.9
3	Excision	IDC	DCIS in sclerosing adenosis	Pathologist	Predictive factor reporting	6.2
Upgraded diagnoses						
4	Core biopsy	DCIS	IDC	Pathologist	Predictive factor reporting	4.1
5	Core biopsy	DCIS	IDC, DCIS	Pathologist	Predictive factor reporting	4
6	Mastectomy	DCIS	IDC, DCIS	Pathologist	Predictive factor reporting	3
7	Excision	DCIS	DCIS with microinvasion	Pathologist	Predictive factor reporting	2.1
8	Core biopsy	LCIS	Microinvasive lobular carcinoma	Pathologist	Predictive factor reporting	2
9	Excision	DCIS with microinvasion	IDC, DCIS	Pathologist	Predictive factor reporting	16.8
10	Mastectomy SLNB	No lymph node metastases	Micrometastatic carcinoma	Pathologist	Other ancillary studies	0.3
Changed diagnoses						
11	Excision	DCIS in complex sclerosing lesion	ADH in complex sclerosing lesion	Pathologist	Predictive factor reporting	13
12	Re-excision	DCIS	Severe ADH	Pathologist	Predictive factor reporting	3
13	Core biopsy	IDC	DLBCL	Pathologist	Surgical excision	19.9
14	Core biopsy	Fibroadenoma, fat necrosis	Amyloidoma	Pathologist	Intradepartmental consultation	5

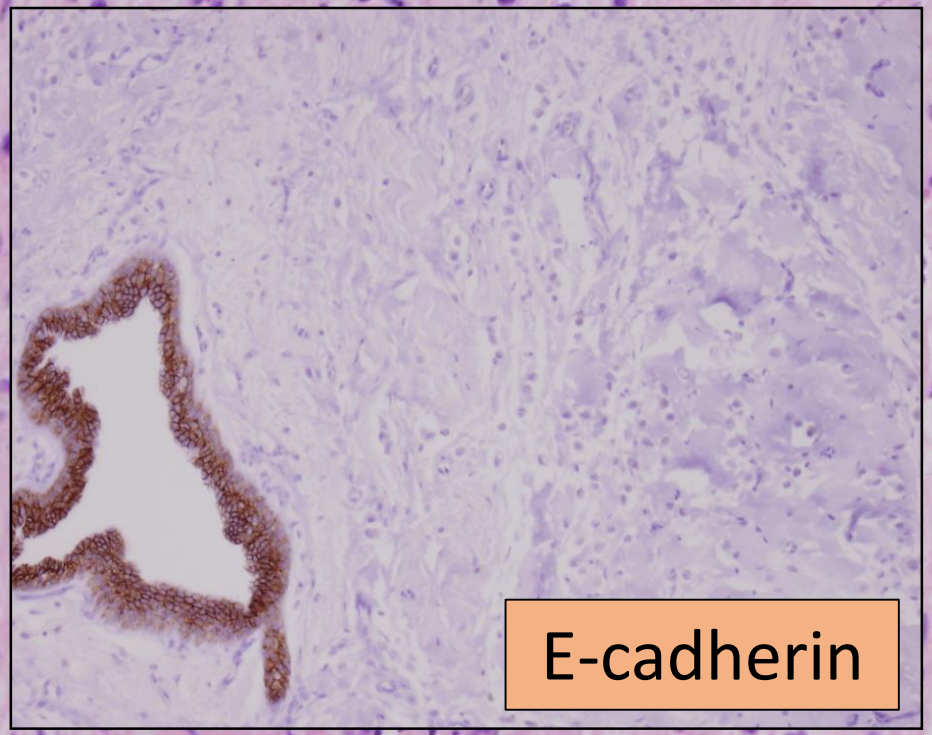
Abbreviations: ADH, atypical ductal hyperplasia; DCIS, ductal carcinoma in situ; DLBCL, diffuse, large B-cell lymphoma; IDC, invasive ductal carcinoma; LCIS, lobular carcinoma in situ; SLNB, sentinel lymph node biopsy.

[a] Cases 2 and 3 represent a core biopsy and a subsequent excision of the same lesion.

Lymphovascular invasion or DCIS with retraction?



Invasive lobular carcinoma

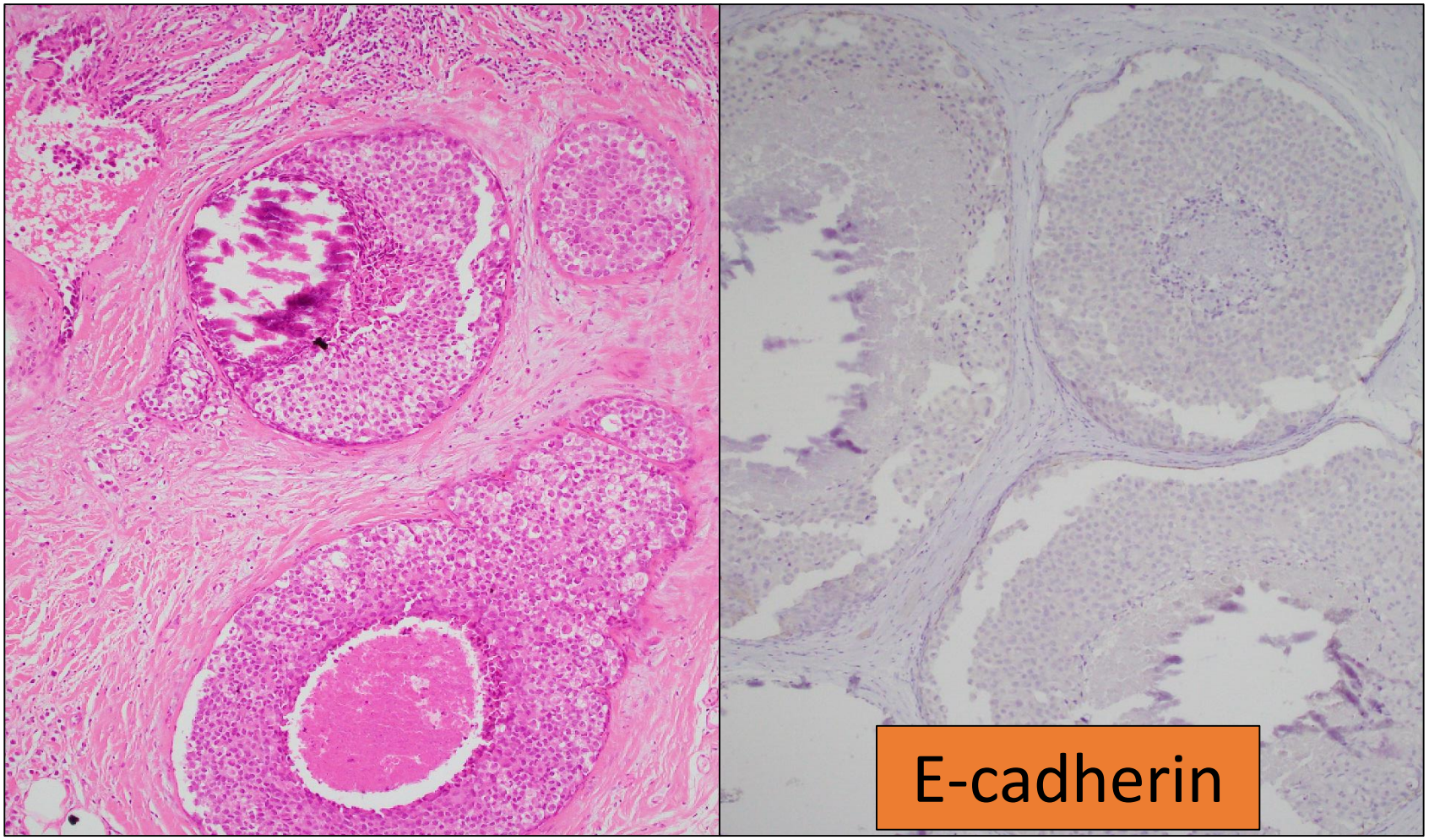


E-cadherin

- Cell adhesion molecule
- Regulated by CDH1 gene
- **Loss of expression observed in 85% ILC**
- Characteristic dyscohesive cell arrangement

- **15% ILC e-cadherin positive**
- **Do not change diagnosis!**
- Other catenin complex proteins lost
- p120 catenin – cytoplasmic staining

Pleomorphic LCIS



Alternatives to primary breast carcinoma

Metastases

Lymphoma

CLUES

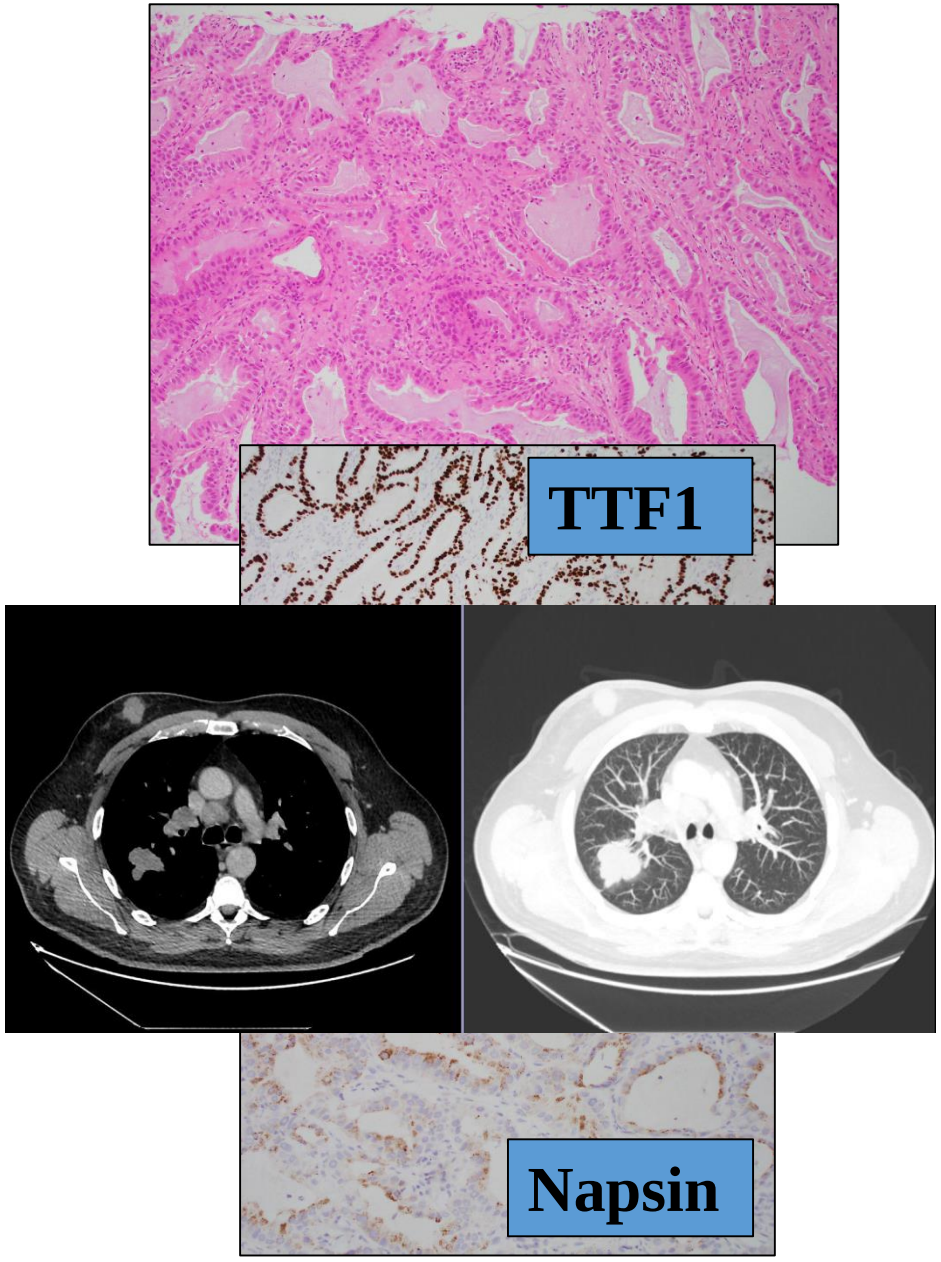
- ❖ Multiple lesions
- ❖ Circumscribed outline
- ❖ Unusual morphology
- ❖ No DCIS
- ❖ Triple negative
- ❖ Significant history

Metastases

- Melanoma
- Lung
- Ovary
- Sarcoma
- Prostate
- Kidney
- Stomach

Lymphoma

- Primary
- Secondary



Histopathology

Histopathology 2016, **68**, 33–44. DOI: 10.1111/his.12865

REVIEW

An approach to the diagnosis of spindle cell lesions of the breast

Emad A Rakha, Mohammed A Aleskandarany, Andrew H S Lee & Ian O Ellis

Department of Histopathology, Nottingham University Hospitals NHS Trust and the University of Nottingham, Nottingham City Hospital, Nottingham, UK

Rakha E A, Aleskandarany M A, Lee A H S & Ellis I O

(2016) *Histopathology* **68**, 33–44. DOI: 10.1111/his.12865

An approach to the diagnosis of spindle cell lesions of the breast

Although most breast spindle cell lesions (BSCLs) are rare, they constitute a wide spectrum of diseases, ranging from reactive processes to aggressive malignant tumours. Despite their varied histogenesis and behaviour, some lesions show an overlap of morphological features, making accurate diagnosis a challenging task, particularly in needle core biopsies. Clinical history and immunohistochemistry can help in making a correct diagnosis in morphologically challenging cases. To make an accurate diagnosis, it is important to maintain a wide differential diagnosis and be familiar with the diverse morphological appearances of these different entities. BSCLs can generally be classified into bland-looking and malignant-looking categories. In the former, the commonest diagnosis is scarring. However, it is important to distinguish low-grade spindle cell metaplastic breast carcinoma from other benign entities, as the management is clearly different. In the malignant category, it is important to differentiate metaplastic carcinoma from other malignant primary and metastatic malignant spindle cell tumours of the breast, such as malignant phyllodes tumour, angiosarcoma, and melanoma. This review focuses on the classification and histological and molecular diagnosis of various BSCLs, with an emphasis on the diagnostic approach, including in core biopsies.

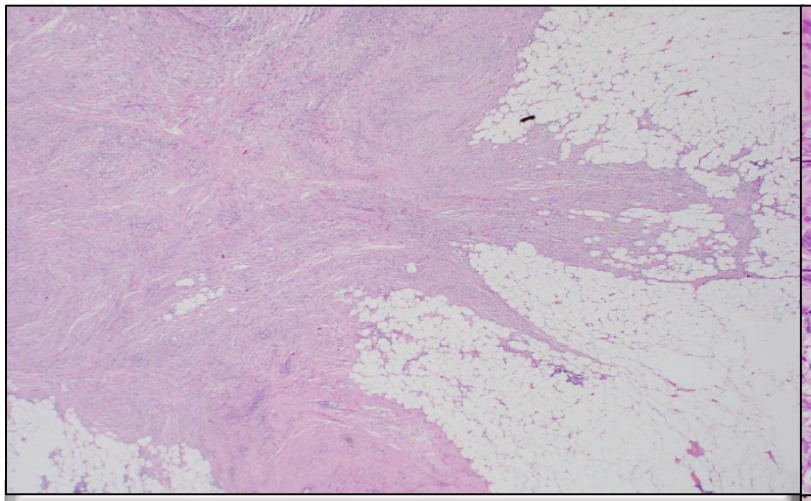
Keywords: breast, core biopsy, diagnosis, immunohistochemistry, spindle cell lesions, update

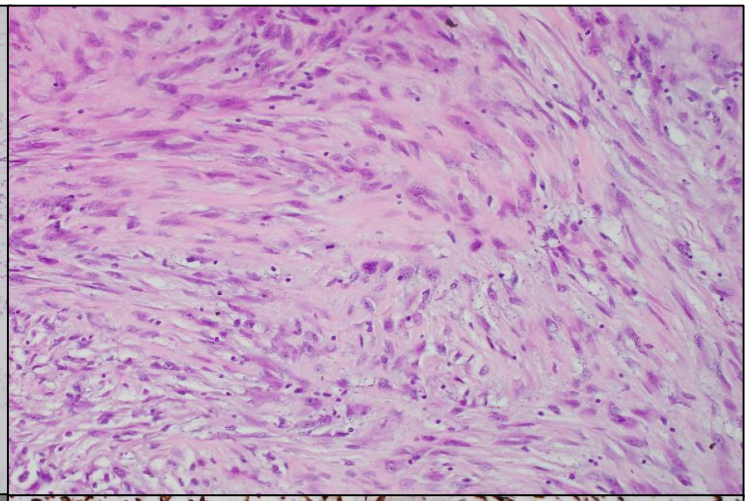
Immunohistochemistry

- Use a panel of antibodies
- Interpret in the light of morphology and clinical context
- Beware of the pitfalls

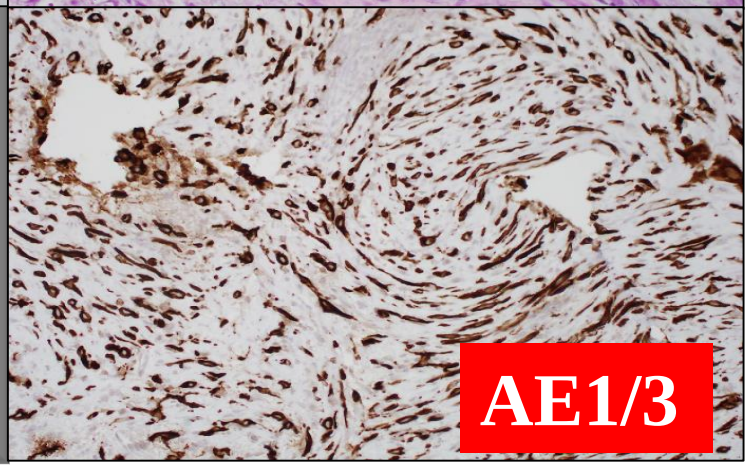
Bland looking pure SCLs

- **Fibromatosis – like MBC**



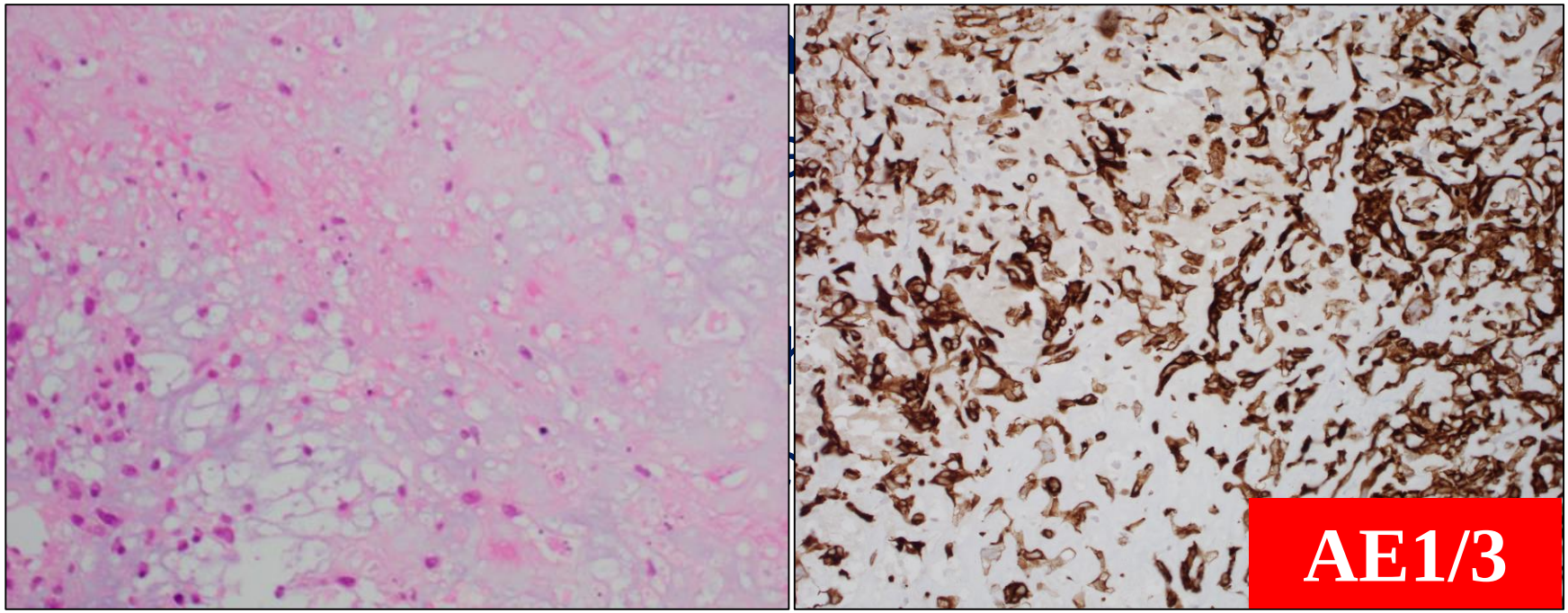


Cytokeratin +
p63 positive +/-
SMA frequently +
***CD34 -**
ER, PR and Her2 -



Malignant looking pure SCLs

- **Metaplastic spindle cell carcinoma**



Cytokeratin (CK)

- **Firstline** IHC if considering MBC
- Use a **panel** of antibodies

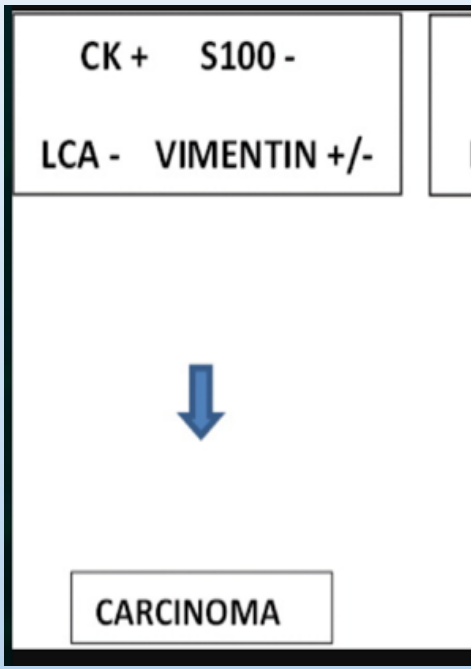
- Staining may be **focal** or **absent** in **mbc**
  p63 useful especially if CK negative
  Repeat on excision if CK negative on NCB
- MBC may co-express mesenchymal markers

- **Focal CK positivity** possible in **PT stroma** and in **leiomyosarcoma**

Arch Pathol Lab Med. 2017 Aug;141(8):1014-1032. doi: 10.5858/arpa.2016-0518-RA.

Application of Immunohistochemistry in Undifferentiated Neoplasms: A Practical Approach.

Kandukuri SR, Lin F, Gui L, Gong Y, Fa



	CK20⁻	CK20⁺
CK7⁺	• Lung • Breast • Upper GI ADC • Pancreatic/biliary ADC • Endometrial/ endocervical ADC • Thyroid • Thymic CA • Salivary gland duct CA • Hepatocellular CA, fibrolamellar type • Ovarian serous CA • Anal duct CA • Mesothelioma	• Urothelial CA • Esophagus ADC • Gastric ADC • Small bowel ADC • Mucinous ADC of lung • Ovarian mucinous CA • Pancreaticobiliary ADC • Cholangiocarcinoma
CK7⁻	• Hepatocellular CA • Clear cell renal cell carcinoma • Adrenal cortical CA • Prostate ADC • Small cell carcinoma • Squamous cell CA • Germ cell tumors • Neuroendocrine neoplasm • Medullary CA of the colon	• Colorectal ADC • Small bowel ADC • Merkel cell carcinoma • Mucinous ADC of lung • Squamous cell carcinoma, type II

Abbreviations: ADC, adenocarcinoma; CA, carcinoma; CK, cytokeratin; GI, gastrointestinal.

- **Check out history**
- **Review any previous pathology**

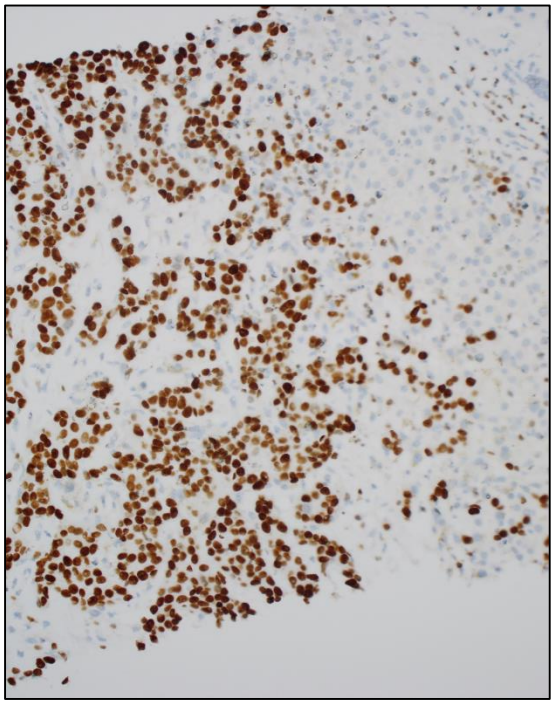
BREAST

- Gata 3
- ER & PR
- GCDFP-15
- Mammoglobin

Gata -3

- **Transcription factor in luminal epithelial cells**
- **Expressed in 90% breast tumours**

- **Also present in**
  - *Range of normal tissues*
  - *Other tumours*
    - *Urothelial*
    - *Renal*
    - *Mesothelioma*
    - *Paraganglioma*

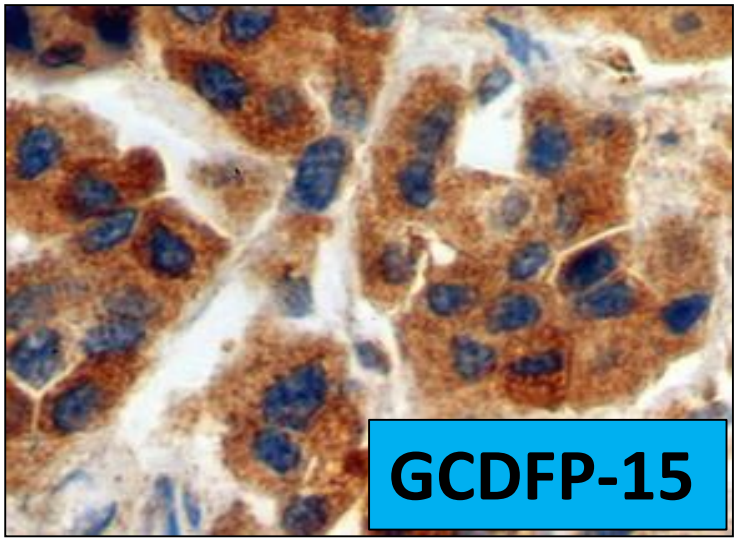


GCDFP-15

- **15 kDa glycoprotein**
- **Expressed in 50 -70% breast tumours**

- **Also expressed in**

Skin appendage tumours
Salivary gland tumours
Some lung tumours
Some prostate tumours



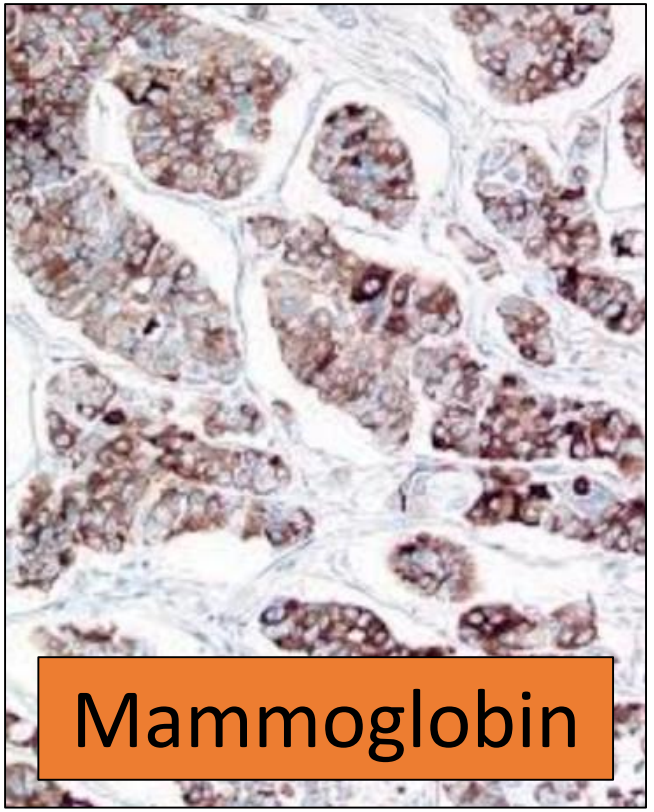
- **Expression linked to hormone receptors**
- **Positivity rate higher in luminal & HER2+ tumours compared with triple negative**

Mammoglobin

- **10.5 kDa secretory protein**
- **Expressed in 50-70% breast tumours**

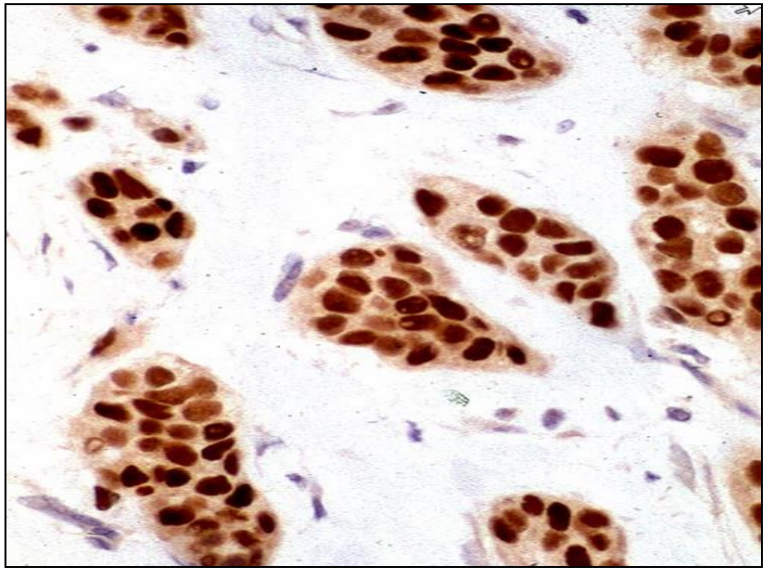
- **Also expressed in**

Skin appendage tumours
Salivary gland tumours
Some GYN tumours
Some melanomas



ER & PR

- **Nuclear transcription factors**
- **Regulate normal breast development**
- **ER - expressed in 80% breast tumours**
- **PR – expressed in 65%**
- **Also expressed in**
  - Other tumours
    - Ovary
    - Endometrium
    - Stomach
    - Lung
    - Thyroid
    - Neuroendocrine tumours



Antibodies in breast carcinoma

Frequently positive	Sometimes Positive	Usually negative
Cytokeratin 7		Cytokeratin 20
ER, PR	S100	HMB45, Melan A
Gata 3	WT1	PAX 8
GCDFP-15	TTF1	Napsin
Mammoglobin		LCA
		PSA

Conclusions

- Immunohistochemistry is very helpful in the diagnosis of breast pathology
- Always begin by carefully evaluating the H&E appearances
- Beware of the IHC pitfalls