Invasive or not?

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CONFLICT OF INTEREST: NONE
AIMS

• To show how MEC and BM markers can help in making the diagnosis of benign vs malignant and show exceptions to the rule
Normal breast (myoepithelium)
Normal breast (basement membrane)

- PAS
- Collagen IV
- Laminin
- Orcein
MECs and BM...

• ...are not only part of the normal epithelial structures of the breast, but they are typical features of benign lesions and in situ carcinomas;

• one well-known exception is microglandular adenosis (MGA):
  MEC- BM+
Myoepithelial (ME) markers 1

- Cytoplasmic staining:
  - Contractile proteins: SMA, MSA, SMMHC, calponin
  - Cytokeratins (High Molecular Weight): CK5, CK14, 34β-E12
  - S100
  - (P-cadherin, p75, maspin)

- Nuclear staining: p63, S100, maspin

- Membranous staining: CD10, cytokeratins, (p75)

Myoepithelial markers 2

• None of the markers is 100% specific or sensitive.

• The review recommends: SMMHC, Calponin, p75, p63, P-cadherin, basal cytokeratins, maspin and CD10.

• Varying cross-reactivity patterns and variably reduced expression in DCIS.

• Choice based on several factors, but more than 1 marker may be required.

• Utilizing antibodies to type IV collagen and laminin aids in both understanding the pathophysiology of the invasive process and the recognition of its presence in tissue sections.

Sclerosing lesions/tubular carcinoma:

„Immunohistochemical staining to demonstrate the presence of an intact myoepithelial cell layer or basement membrane is indicated in cases of doubt.”
Complex sclerosing lesion / radial scar:

“The main differential diagnosis is carcinoma of tubular or low grade ‘ductal’ type. The major distinguishing features are the presence of myoepithelium and basement membrane around the tubules of the sclerosing lesions. Immunocytochemical studies for basement membrane proteins and myoepithelial cells are useful.”

Royal College of Pathology

Pathology reporting of breast disease in surgical excision specimens incorporating the dataset for histological reporting of breast cancer – June 2016
Complex sclerosing lesion vs TUBULAR carcinoma

CSL

TUBULAR CA
Invasive or in situ? x100 (E28)
Invasive or in situ? x100
Invasive or in situ? x400
In situ – **calponin** x40: Lobular cancerisation of sclerosing adenosis
In situ – calponin x100
2.4 In situ – **calponin** x400 (E28)
The use of IHC markedly improves the consistency of identifying microinvasion. This corroborates previous recommendations to use IHC for myoepithelial markers to clarify cases where uncertainty exists about the presence of microinvasion.
„Aberrant” phenomena

Unknown source, circulated on Facebook…
At least 1 ME marker with decreased staining: 23/48 (48%); 2 or more ME markers with decreased staining: 11/48 (23%).
Most commonly reduced staining with CK5/6: 14/44 (32%) reduced staining, and 7/44 (16%) no staining at all;
Other IHC stains showing reduced staining included SMMHC (in 21%), CD10 (in 15%), p63 (in 9%) and calponin (in 6%); complete lack of staining in only 1/46 with CD10.
SMA and p75 not reduced in any of the cases tested.

Lack of 1 ME marker positivity ≠ lack of ME.
The authors use a triple IHC consisting of SMMHC, p63 & calponin – none of these were completely negative in the above study and a similar study on ME cells around DCIS.

Phenotypic Alterations in Myoepithelial Cells Associated With Benign Sclerosing Lesions of the Breast

Justin B. Hilson, MD, Stuart J. Schnitt, MD, and Laura C. Collins, MD
Invasive vs in situ?

- Reduced expression of markers around ME cells of DCIS:
  - SMMHC 77%
  - CD10 34%
  - CK 5/6 30%
  - Calponin 17%
  - p63 13%
  - p75 4%
  - SMA 1%

p40 & p63 in DCIS: * scattered positive cells in DCIS; no positive cells around DCIS: bottom left
CASE REPORT

Benign apocrine papillary lesions of the breast lacking or virtually lacking myoepithelial cells—potential pitfalls in diagnosing malignancy

GÁBOR CSERNI
p63: No staining in this area, positive control in the non-apocrine periphery of the lesion
p63: No staining in this area, no cells at ME position
CD10: No staining in this area, no cells at ME position
SMA: Complete thin cytoplasmic staining at ME position everywhere in the lesion
S100: Complete thin cytoplasmic & nuclear staining at ME position everywhere
Diagnosis

• Sclerosing papilloma with apocrine epithelium virtually missing myoepithelial cells
• Negative areas on HE(!), p63, and CD10 but not on SMA, Calponin and S100
Conclusions (1)

• Lack of 1 ME marker positivity ≠ lack of ME. (More than 1 marker may be necessary to prove the presence of MECs)
CNB: Infiltrative pattern without MECs
Same slides from CNB (non-digital)
SMA

<table>
<thead>
<tr>
<th></th>
<th>MGA</th>
<th>ApoA</th>
<th>TubCa</th>
</tr>
</thead>
<tbody>
<tr>
<td>ME cells</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>BM</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>GCDFP-15</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>EMA</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

This case

- ME cells: No
- BM: Yes
- GCDFP-15: Not done
- EMA: Yes
CNB Diagnosis

- B4: Suspicious for malignancy; complete excision required
  - Infiltrative growth pattern
  - Small glands
  - Lack of ME

  *****

- Pro microglandular adenosis: the above & presence of BM
- Pro carcinoma: the above & EMA+/S100-; ER+PR+, lack of characteristic secretion
Collagen IV
Different infiltrative patterns
Collagen IV

E-cadherin also positive (not shown)
ER+ & PR+
Diagnosis

Vincenzo Eusebi 2nd opinion:

„I fully agree, it is invasive duct carcinoma grade 1/2. Basal lamina present in MGA, but no ME cells. EMA is distinctively negative.”

Later discussion:

EMA may be positive with novel techniques of antigen retrieval and novel antibodies.
Diagnosis

Well differentiated ductal carcinoma

(„microglandular or microglandular adenosis like carcinoma”)

Tubulolobular ca (B5)
Basement membrane and malignancy – an understated phenomenon

Carcinomas (the WD ones) may have an incomplete (or nearly complete) rim of BM material as demonstrated by collagen IV IHC (laminin is more often negative).


• 3/4 G1 carcinomas had BM by IHC
• 0/14 G2/G3 carcinomas had BM by IHC

Conclusions (2)

• Lack of 1 ME marker positivity ≠ lack of ME. (More than 1 marker may be necessary to prove the presence of MECs)

• A BM is a sign of a benign lesion in general, but besides MGA, some carcinomas (especially well differentiated ones) may maintain a BM staining.
„Aberrant” entities
(HU: Iron rings made of wood)

Elliott Ewritt: Retrospective (2017)
Managua, Nicaragua 1957
Encapsulated papillary carcinoma

- Older age
- Nipple discharge or subareolar mass
- One or more nodule(s) of papillary carcinoma with thick fibrous capsule
- Delicate papillae with monotonous ... epithelial cells of L or I nuclear grade
- Papillary, cribriform and solid patterns may be seen
- ME cells absent both within and surrounding the papillary nodules
- May represent form of LG invasive cancer with expansile growth pattern rather than an in situ lesion - pTis
- Foci of frankly invasive carcinoma (most often invasive ductal carcinoma) may be seen - >pTis; pT1-4

Schnitt SJ, Collins LC. Biopsy interpretation of the breast.
Apocrine EPC

- Resemblance of this lesion to EPC
- 5 cases reported so far
- Composed of apocrine cells without significant cellular atypia
- A papillary tumor without ME consistent with a papillary carcinoma (either in situ or invasive)
- Lack of ME cells at the periphery of the cyst wall.
- EPC may present with nipple discharge and may have small foci with preserved ME cells at the periphery, in the “cyst” wall.

- Uncertain malignant potential: good prognosis of the five previously reported cases.

Solid papillary carcinoma

- A single large expansile mass or multiple solid, closely apposed cellular nodules
- Containing inconspicuous delicate fibrovascular cores
- At low power giving the impression of a solid growth pattern
- NE differentiation, spindle cell morphology & mucin production are frequent
SPC

• MECs are present around: DCIS (pTis)
• Rounded nodular masses without MECs: consider as DCIS (pTis)
• Irregularly shaped islands with jagged contours without MECs around, arranged in a jigsaw pattern, with a desmoplastic reaction: invasive SPC (pT1 to 4)

Textbook data:

- Benign lesions are characterised by the presence of both myoepithelium and a basement membrane.
- Invasive carcinomas lack myoepithelial cells.
- The well known exception is the rare microglandular adenosis (MGA)…
MGA

- BM+ / MEC-
- ER- / PR- / HER2-
- S100+
- (EMA-)

A case from the John Azzopardi heritage;

Courtesy of Profs. MP Foschini & V. Eusebi
A hamartoma with fibroepithelial (phyllodes-like) areas &
benign apocrine glandular structures devoid of myoepithelial cells different from MGA
Calponin
Another focus – S100; attenuated ME on the left
Collagen IV
Another focus – another slide
Organoid structure, no ME cells are present.
Cystic, organoid lobule without ME cells
Transition within a cyst between ME – & ME + parts
In summary

- Organoid, lobular structures; lack of an invasive pattern
- Multifocality
- BM partially present
- Transition between lacking ME and ME present

Benign apocrine glands without ME
Conclusions (3)

• Lack of 1 ME marker positivity ≠ lack of ME. (More than 1 marker may be necessary to prove the presence of MECs)
• A BM is a sign of a benign lesion in general, but besides MGA, some carcinomas (especially well differentiated ones) may maintain a BM staining.
• The lack of ME in apocrine glands doesn’t necessarily imply malignancy.
Figure 2. No ME cells on HE, p63 and Calponin
Editorial comment on my MS

- Histopathology:
  Associate Editor: 1
  Comments to the Author:
  This is an interesting case which raises an important issue regarding myoepithelium around apocrine glands in the breast. It is a question I have come across on several occasions in cases sent for opinion recently!
45-mm-long nearly cylindrical ductectomy specimen had a diameter between 5 to 12 mm.
A ruptured and compressed, crescent like cystic apocrine lesion in the 3 last slices (away from the nipple) identified by microscopy.
SMA
Somewhat deeper: next transverse slice
Orcein stain: cyst

A duct

Not a duct

Collagen IV
Summary

• No ME cells in the central papillary proliferation (HE, p63, CK14, SMA, Calponin, S100)

• Focal (minimal) presence / predominant absence of ME cells at the periphery
Half full vs half empty
Partially present vs partially absent

http://api.ning.com/files/x8Fo.../Glass.jpg
Encapsulated apocrine papillary carcinoma of the breast—a tumour of uncertain malignant potential: report of five cases

Melanie Seal · Christine Wilson · Gregory J. Naus · Stephen Chia · Terry C. Bainbridge · Malcolm M. Hayes

Virchows Arch 2009; 455:477-483

Fig. 8 Immunostain for p63 to show absence of myoepithelial cells at the periphery of the cyst and normal adjacent lobules (×200)
• P63: 21/59 (36%) fewer ME cells, enlarged interME cell gaps (not correlating with atypia or distension)
• 6 cases with evident gaps on both p63 and calponin:
  – 2 complete lack no atypia (1 had also CD10 stain - negative & collagen IV stain - positive),
  – 1 papillary case had no ME cells at the periphery, no ME cells in the papillary part but had collagen IV in both areas: interpreted as ID papilloma and not as ICPC/EPC
Figure 2. Apocrine papilloma without atypia; no ME cells on HE, p63 and Calponin
<table>
<thead>
<tr>
<th>Condition</th>
<th>ME cells in papillae</th>
<th>ME cells at periphery</th>
<th>Other features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apocrine EPC</td>
<td>No</td>
<td>No (but focal presence allowed)</td>
<td>Thick fibrous capsule (cystic – orcein)</td>
</tr>
<tr>
<td>Apocrine papillary DCIS</td>
<td>No</td>
<td>Yes (but it is mainly absent)</td>
<td>Apocrine lesions may lack ME</td>
</tr>
<tr>
<td>Apocrine papilloma</td>
<td>Yes</td>
<td>Yes (but it is mainly absent)</td>
<td>Apocrine lesions may lack ME</td>
</tr>
<tr>
<td>Apocrine cyst with papillary hyperplasia</td>
<td>Yes</td>
<td>Yes (but it is mainly absent)</td>
<td>-Apocrine lesions may lack ME</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-Intracystic</td>
</tr>
</tbody>
</table>
Summary of the case

- Cystic lesion with predominant lack of ME at the periphery
- Transition between ME- and ME+ area in the same cyst wall – allowable in EPC
- Elastic stain suggesting cystic origin - unstudied
- Partial presence of a BM (collagen IV) – unstudied
- Papillary intracystic growth without ME cells
- Apocrine (lack of ME may not mean the same thing)
- No thick fibrous capsule
A semantic problem

- Signed out as cyst partially lacking ME.
- On the basis of the best match of the key features it could be Apocrine EPC or more precisely Apocrine Intracystic PC… but its apocrine nature casts some doubts. (Would favour the bottom two benign options)
- Expected good prognosis – reflected by

Follow-up:
The patient had no further treatment and was without evidence of disease 30 months after the removal of the lesion.
Apocrine EPC exists and can be associated with invasive cancer.

Apocrine Encapsulated Papillary Carcinoma of the Breast: The First Reported Case with an Infiltrative Component

Bence Kövári¹, Katalin Ormáni², Zsolt Simonka⁴, András Vörös¹, Gábor Cserni¹, ⁵
Conclusions (4)

• Lack of 1 ME marker positivity ≠ lack of ME. (More than 1 marker may be necessary to prove the presence of MECs)

• A BM is a sign of a benign lesion in general, but besides MGA, some carcinomas (especially well differentiated ones) may maintain a BM staining.

• The lack of ME in apocrine glands doesn’t necessarily imply malignancy.

• Some apocrine lesions defy classification on the basis of ME and BM IHC
Cribriform DCIS vs invasive cribriform carcinoma

Cribriform DCIS: MEC+ BM+

Invasive cribriform carcinoma: MEC- (BM?)

DCIS?
Minor focus with MECs (CK5 x2)
All areas with BM (coll. IV)  
i.e.: DCIS without ME / with BM
MEC+ malignancies
LG ASC
HE x140 & dPAS x20 (+*)
CAM5.2 & p63
MECs+ LG ASC
SMA
LG ASC BM + or -?
Collagen IV x60 & x50
Canine AME („benign”)

BM
Adenomyoepithelioma (AME) - has some malignant potential: epithelial & myoepithelial

- Generally benign, requiring excision
- Any component (or both) can become malignant

**Signs of malignancy** in AME (malignant AME) - AFIP:
- Infiltrative pattern
- Myoepithelial overgrowth
- $>3$ mitoses / 10 HPF
- Cellular atypia

Case shared by Malcolm Hayes:
2007 primary as WHO "benign" AME
2009 recurrence
2011 recurrence
2019 lung metastasis: looking as low grade, identical to the initial and recurrent tumours.
Conclusions (5)

- Lack of 1 ME marker positivity ≠ lack of ME. (More than 1 marker may be necessary to prove the presence of MECs)
- A BM is a sign of a benign lesion in general, but besides MGA, some carcinomas (especially well differentiated ones) may maintain a BM staining.
- The lack of ME in apocrine glands doesn’t necessarily imply malignancy.
- Some apocrine lesions defy classification on the basis of ME and BM IHC
- Some lesions are malignant (potentially malignant) even in the presence of ME… (and BM)
"Note that myoepithelial staining may be discontinuous, therefore absence of staining does not always imply invasion and peripheral myoepithelial positivity does not imply \textit{in situ} in, for example, adenoid cystic and adenosquamous carcinomas."
MECs and BM…

• …are not only part of the normal epithelial structures of the breast, but they are typical features of benign lesions and in situ carcinomas; their lack reflects an invasive process.

• …although one well-known exception is microglandular adenosis: MEC- BM+, there are other RARE exceptions to the rule:
  – MEC- BM(+) benign apocrine glands / cysts
  – MEC- BM+ DCIS and invasive carcinoma
  – MEC+ BM+-/ - malignancies
  – Pseudo MEC- (altered MEC phenotype)
A final theoretical question…

• MECs are generally made responsible for making the BM.
• What makes the BM (material) in MEC-BM+ lesions?

• Which cell makes the BM in the breast?
• Prof. V. Eusebi: „Both” (the epithelial and ME cells)