Special Types of Invasive Breast Carcinoma

Farnaz Hasteh, MD
Associate Professor of Pathology
Disclosure

- I do not have any financial or other relationships that create a conflict related to this educational course.
Course Objectives

- Clarify and discuss diagnostic criteria for classification of special type of breast carcinoma
- Identify potential diagnostic pitfalls in diagnosis from the benign entity
- Describe the clinical implications associated with these diagnoses
- Discuss the importance of clear pathology reporting on cases with mixed component of invasive breast carcinoma of no special type
- Discuss the possibilities of immunohistochemical, molecular, and other ancillary studies in proper diagnosis
### WHO classification of tumours of the breast

#### EPITHELIAL TUMOURS

**Microinvasive carcinoma**

**Invasive breast carcinoma**

- Invasive carcinoma of no special type (NST) 8500/3
  - Pleomorphic carcinoma 8022/3
  - Carcinoma with osteoclast-like stromal giant cells 8035/3
  - Carcinoma with choriocarcinomatous features 8035/3
  - Carcinoma with melanotic features 8035/3
- Invasive lobular carcinoma 8520/3
  - Classic lobular carcinoma
  - Solid lobular carcinoma
  - Alveolar lobular carcinoma
  - Pleomorphic lobular carcinoma
  - Tubulolobular carcinoma
  - Mixed lobular carcinoma
- Tubular carcinoma 8211/3
- Cribriform carcinoma 8201/3
- Mucinous carcinoma 8480/3

**Carcinoma with medullary features**

- Medullary carcinoma 8510/3
- Atypical medullary carcinoma 8513/3
- Invasive carcinoma NST with medullary features 8500/3

**Carcinoma with apocrine differentiation**

**Carcinoma with signet-ring-cell differentiation**

**Invasive micropapillary carcinoma** 8507/3

**Metaplastic carcinoma of no special type** 8575/3

- Low-grade adenosquamous carcinoma 8570/3
- Fibromatosis-like metaplastic carcinoma 8572/3
- Squamous cell carcinoma 8070/3
- Spindle cell carcinoma 8032/3

**Metaplastic carcinoma with mesenchymal differentiation**

- Chondroid differentiation 8571/3
- Osseous differentiation 8571/3
- Other types of mesenchymal differentiation 8575/3
- Mixed metaplastic carcinoma 8575/3

**Invasive papillary carcinoma** 8503/3

**Acinic cell carcinoma** 8550/3

**Mucoepidermoid carcinoma** 8430/3

**Polymorphous carcinoma** 8525/3

**Oncocytic carcinoma** 8290/3

**Lipid-rich carcinoma** 8314/3

**Glycogen-rich clear cell carcinoma** 8315/3

**Sebaceous carcinoma** 8410/3

**Salivary gland/skin adnexal type tumours**

- Cylindroma 8200/0
- Clear cell hidradenoma 8402/0*

#### Epithelial–myoepithelial tumours

**Pleomorphic adenoma** 8940/0

**Adenomyoepithelioma** 8983/0

**Adenomyoepithelioma with carcinoma** 8983/3*

**Adenoid cystic carcinoma** 8200/3

#### Precursor lesions

**Ductal carcinoma in situ** 8500/2

**Lobular neoplasia**

- Lobular carcinoma in situ
- Classic lobular carcinoma in situ 8520/2
- Pleomorphic lobular carcinoma in situ 8519/2*
- Atypical lobular hyperplasia

#### Intraductal proliferative lesions

**Usual ductal hyperplasia**

**Columnar cell lesions including flat epithelial atypia**

**Atypical ductal hyperplasia**

#### Papillary lesions

**Intraductal papilloma** 8503/0

**Intraductal papilloma with atypical hyperplasia** 8503/0

**Intraductal papilloma with ductal carcinoma in situ** 8503/2*

**Intraductal papilloma with lobular carcinoma in situ** 8520/2

**Intraductal papilloma carcinoma** 8503/2

**Eccrine ductal with papillomatosis** 8504/0
Case 4 History

• A 73 year old female with a breast mass found by mammogram underwent percutaneous ultrasound-guided core biopsy
Tubular carcinoma
Tubular carcinoma

• It has been defined as a distinctive type of breast ca for more than a century (Cornil 1869)

• Specific type of well differentiated (mBR I) invasive breast carcinoma

• *It should not be diagnosed as just well-differentiated Invca*

• Excellent Prognosis

• Long term prognosis in some studies is similar to the healthy women without breast ca
Tubular carcinoma
Clinical Presentation

• Incidence of pure form: ~2%
  – ~8% in breast carcinomas < 1 cm
• More common in older patients (range: 24-92)
• More cases diagnosed by new techniques
• Easily detectable
• Incidental findings
  – Stellate mass lesion
  – Like radial scar or sclerosing papillary lesion
• Small size (0.2 – 2 cm)
• Firm and hard mass, ill defined, stellate lesion
Tubular carcinoma
Histopathology

- Irregular margins
- Haphazard invasive glands
- Well defined tubules
- Round to oval shape glands
- Open lumen with sharply angulated contour
- Minority of glands can show more complex growth (layering of epithelium)
Tubular ca
Tubular carcinoma (20x)
Tubular carcinoma
Histopathology

- Single cell layer (cuboidal or columnar)
- Nuclear grade I
- No mitosis or rare one
- Inconspicuous nucleoli
- Cytoplasmic snouting
- Abundant desmoplasia/ elastosis in stroma
- ER and PR always positive
- EM: no basal lamina or discontinuous one
Tubular carcinoma
+ ER, +PR
immunostains
Tubular carcinoma
Histopathology

- Flat epithelial atypia
- Columnar cell hyperplasia with atypia
- Low grade DCIS
  - Cribriform
  - Micropapillary
- LCIS especially with tubulolobular carcinoma
- Mixed with cribriform carcinoma
- Mixed with lobular carcinoma (tubulolobular carcinoma)
Tubular ca

Low grade DCIS
Flat Epithelial Atypia
When should we call it tubular carcinoma?

- Majority of the tumor should be tubular carcinoma

- WHO recommends $\geq 90\%$
Mixed Carcinomas

• It is usually seen with cribriform carcinoma
  – Invasive tubular/cribriform carcinoma
  – Excellent prognosis

• It can be seen with classic lobular carcinoma
  – Invasive tubulolobular carcinoma
  – Prognosis is still good!
  – More multifocal

• When more than 10% of tumor is Inv, NST
  – Mixed ductal, NST and tubular carcinoma
  – Prognosis depends on the ductal component
Differential Diagnosis

• Benign mimics
  – Sclerosing adenosis
  – Microglandular adenosis
  – Radial scar (sclerosing papillary lesion)
  – Duct adenoma

• Panel of myoepithelial markers (p63, CD10, calponin, SMM)

• Special stain for basement membrane (reticulin and PAS)
Sclerosing adenosis
Sclerosing adenosis
Microglandular adenosis + reticulin Stain
ER and PR negative
Radial scar or sclerosing papillary lesion
Small glands of radial scar + calponin
Tubular carcinoma
Negative staining for p63 and calponin
Smooth muscle myosin: NEG
Differential diagnosis
Tubular carcinoma

• Other carcinomas
  – Mixed ductal and tubular carcinoma
  – Invasive tubulolobular ca
  – Invasive well differentiated ductal carcinoma, NST, mBR grade I
Mixed ductal and tubular
Tubular Mixed ductal and tubular ca
Mixed ductal, tubular and lobular
Tubular
Tubulolobular ca
ductal, NST

mitosis

tubular
ductal

tubular
Prognosis
Tubular carcinoma

• Excellent
• Long term prognosis in some studies is similar to the healthy women without breast ca
• Overall survival rates: 93.1-99.1% and 99-100%
• Review of seven studies
  – 341 women with pure tubular carcinoma
    • ~4% had recurrence (12)
      – 6 in the same breast after simple excision
      – 6 after mastectomy
Prognosis
Tubular carcinoma

- Axillary metastasis is uncommon in patients with single pure small tubular carcinoma (< or = 1 cm)
- Level I axillary node metastasis is seen in patients with
  - Size > 1 cm
  - Multifocal tumors
- Multifocality is seen (~20%)
- The reported range of axillary node metastasis is from 6-30% (average 10%)
Prognosis
Mixed ductal and tubular carcinoma

• Prognosis is worse in patients with mixed tubular and ductal

• Axillary node metastasis: 34% (Berger et al. The Breast J 1996;2:204-208)

• Recurrence in up to 32% of patients
  – 6-28% died of disease
Treatment

- Breast conservation therapy for unifocal tumors
- No additional treatment
- Low axillary node dissection
  - Mixed tubular/cribriform
  - Size >1cm
  - Multifocal tumors
- Radiation therapy with recurrence

- ?Chemotherapy even in rare cases with axillary metastasis
  - Or if there is cancer in the other breast
Summary

- Special type of breast carcinoma
- Strict histological criteria
- Pure form (>90 %)
- When more than 10% of tumor is InvDC, NST - Mixed tubular and ductal or ductal with tubular features
- Excellent prognosis in pure form or mixed tubular/cribriform
- ER and PR positive
• Breast, right side, biopsy
  – *Invasive ductal carcinoma with predominant tubular features* (*mBR grade I*).
  – *Low grade ductal carcinoma in-situ, see comment.*

Comment: The final classification of the carcinoma will depend on the findings in an excisional biopsy.

• Breast, right side, lumpectomy
  – *Tubular carcinoma (mBR grade I), see synoptic report.*
  – *Low grade ductal carcinoma in-situ, see comment.*
  – *Surgical margins free.*
  – *pT1bN0*
- Invasive tumor type: tubular
- Invasive tumor size: 1.0 cm
- Invasive tumor grade (modified Bloom-Richardson): 1
- Nuclear grade: 1
- Mitotic grade & mf count: 1
- Tubule/papilla formation: 1
- Total mBR score: 3
- Lymphatic-vascular invasion: absent
- Blood vascular invasion: absent
- Resection margins for invasive tumor: widely clear
- Duct carcinoma in situ type: solid and cribriform
- Duct carcinoma in situ size: 0.3 cm around the invasive tumor
- Duct carcinoma in situ grade: low grade
- Microcalcifications: present
- Resection margins for carcinoma in situ: widely clear [> 1 cm]
- Lymph nodes positive /total lymph nodes sampled: negative (0/3)
- AJCC/UICC stage: pT1bN0
- Her2/neu status: negative (0 ASCO/CAP)
- Hormone receptor status (ER/PR): Both positive (3+, 100%)
- Additional comments: biopsy site changes present
Cribriform carcinoma

- Special type of well differentiated breast carcinoma (mBR I)
- It should be recognized as distinct entity
- Excellent prognosis
- Morphologically similar to cribriform DCIS
- Often mixed with <50% of tubular carcinoma component (invasive tubular/cribriform ca)
- Closely related tumors
Cribriform carcinoma
Clinical presentation

• Age range: 19-86, mean age: 53-58
• Incidence: 0.3-4% of breast ca (WHO Classification)
  ~ 6% of breast ca
• Present as a mass or an incidental finding
• Spiculated mass with microcalcification by imaging
Cribriform carcinoma
Histopathology

- Pure form shows >90% of cribriform architecture
- Invasive **irregular cribriform** growth of tumor cells
- Similar to low grade cribriform DCIS
- Desmoplastic stroma
- Tumor cells have low grade nuclei
- Rare or no mitosis
- Often mixed with <50% tubular ca
Cribriform ca
Cribriform ca
Lumpectomy biopsy site and residual ca
Cribiform ca
Lumpectomy specimen
Mixed cribriform & tubular
Mixed cribriform & tubular
Cribriform carcinoma
Prognosis

- Venable et al. reported a disease-free survival of 100% for 45 patients with classic pure carcinoma
- No deaths in one study with 34 patients with 10-21 year follow-up
  - One patient died from metastasis from other breast ca
- Some reports of high frequency metastasis to lymph node (14.3% to ~40% in one series)
Cribriform carcinoma
Treatment

- Breast conservation therapy for unifocal lesions
- Sentinel node biopsy
- Multifocality increases the chance of axillary node metastasis
- Systemic therapy for patients with axillary metastases or other type of carcinoma in the other breast
Cribriform carcinoma
Differential diagnosis

- Cribriform DCIS
  - +Myoepithelial cells
  - Rounded even contour
  - Absence of mucin positive material

- Carcinoid tumor

- Adenoid cystic carcinoma
Cribriform DCIS

Cribriform invasive ca
Cribriform Carcinoma
Summary

- An invasive special type of breast carcinoma with excellent prognosis
- Usually associated with <50% tubular carcinoma
- Cases with component of another carcinoma: Mixed type of carcinoma
- Exclude the possibility of extensive DCIS
- ER and PR always positive
Breast, left, needle core biopsy

- Invasive cribriform carcinoma (nuclear grade I), see comment.

Synoptic Report

- Invasive tumor type: invasive cribriform ca
- Invasive tumor size: 0.7 cm
- Invasive tumor grade (modified Bloom-Richardson): 1
- Nuclear grade: 1
- Mitotic grade & mf count: 1
- Tubule/papilla formation: 1
- Total mBR score: 3
- Lymphatic-vascular invasion: not seen
- Duct carcinoma in situ type: solid
- Duct carcinoma in situ size: minimal (0.1 cm)
- Duct carcinoma in situ grade: low-grade
- -Her2/neu status: negative (0 ASCO/CAP)
- -Hormone receptor status (ER/PR): positive 3+, 100%
Case 5

• 57 year old woman with palpable breast mass
• Patient was participating in some breast cancer awareness month function when she examined her own breasts and noticed the left breast mass.
• Mammogram found 2 cm suspicious mass at 5 o'clock position of the left breast
Case 5
Mucinous Carcinoma
Mucinous carcinoma

- Large amount of extracellular mucin (>50%)
- Mucin is grossly and microscopically seen
- We call it when it is pure form of mucinous carcinoma

- Otherwise diagnosis should be:
  - Mixed invasive ca, NST (mBR grade II) and mucinous ca
  - Invasive carcinoma, NST (mBR grade I) with marked mucinous differentiation
Clinicopathological features
Mucinous Carcinoma

• 2% of all breast cancer (WHO classification)
  – ~1% in younger than 35
  – ~7% in women >75

• Usually older age (>60 year old)

• Present as palpable mass with short duration

• No calcification by imaging

• Gross: gelatinous mass with pushing margins

• Size: 1 cm to >20 cm
Histopathology
Mucinous Carcinoma

- Proliferation of clusters of uniform tumor cells, floating in lake of mucin
- Low cellular atypia, rare mitosis
- Absent microcalcification
- Any amount of invasive ductal component (>1% of tumor is non-mucinous or if the non-mucinous component is poorly diff)
  - Mixed subtypes
  - Usually more high grade tumors
Histopathology
Mucinous Carcinoma

- Mucin is PAS positive
- Intracellular mucin is rare
- Signet ring cell may suggest lobular carcinoma
  - Aggressive ca
  - Carcinomas with signet-ring-cell differentiation (WHO 2012)

- DCIS present in 75% of cases
  - Any pattern of DCIS
  - Like intracystic papillary ca
  - Mucinous differentiation is seen in DCIS
Histopathology
Mucinous Carcinoma

- Epithelial cells have different pattern
  - Strands, alveolar nests, cribriform sheets
  - Papillary clusters
  - Micropapillary clusters
  - Large sheets

- Nuclear grade I or II (mBR grade I)

- Typically ER and PR positive
Mucinous ca
Mucinous ca
Mucinous ca
Mucinous Carcinoma
Mixed mucinous and ductal carcinoma
Mixed mucinous and ductal carcinoma
Prognosis
Mucinous Carcinoma

• Pure form has favorable prognosis
• Pure forms are smaller than the mixed ones
• Negative axillary nodes in patients with pure form range from 71 to 97%
• Positive lymph nodes have been reported in pure mucinous carcinoma especially in cases with micropapillary pattern and in younger age
Prognosis
Mucinous carcinoma

• Komaki et al.
  – 10 year survival for pure tumor: 90%
  – Versus 60% for mixed ductal and mucinous

• Periera et al.
  – 10 year survival for all pure tumor: 81%
    • 86% for mBR grade I
    • 75% for mBR grade II

• 5 year survival after mastectomy from 84-100%
Treatment

- Breast conservation and radiation therapy
- Late metastasis and recurrence of 25-30 years have been reported
Differential Diagnosis

• DCIS with extravasated mucin
  – No epithelial component is present in mucin
  – Prior FNA and biopsy might have caused displacement of epithelial cells!

• Benign mucocele-like tumor
  – Extravasated mucin with multiple dilated cysts lined by flat bland epithelium
  – No tumor floater or rare cells (+ myoepithelial cells)
  – Large, granular calcification

• Cystic hypersecretory hyperplasia
  – Ectatic ducts filled by eosinophilic, colloid like secretion
Benign mucocele like lesion of breast
Mucocele like lesion of breast and ADH with calcification
Mucocele like lesions

• It is prudent to excise all benign mucocele-like lesions diagnosed on core needle biopsy because of sampling phenomena, intralesional heterogeneity, and associated atypia or malignancy

Incipient mucocele-like lesion
Cystic hypersecretory hyperplasia
59 year old with breast mass
Summary

Mucinous carcinoma

- Distinct entity and specific type of breast carcinoma
- Pools of mucin with floating tumor cells
- Favorable prognosis in pure form (low stage)
- Additional sampling in high grade tumors
- Mixed mucinous and ductal with presence of any amount of invasive ca, NST
- ER and PR positive
- Important benign lesions in the DDx
Pearl of Pathology

- Breast, left, core biopsy
  - Invasive ductal carcinoma with mucinous features, nuclear grade 2.

- Breast, right side, lumpectomy
  - Invasive pure mucinous carcinoma, mBR 1, pT2N0, see Synoptic Report

- Breast, left calcifications, core biopsy
  - Benign proliferative fibrocystic changes with focal mucinous extravasations and calcifications, see comment.
Case #6

- 29 year old female found a breast lump with palpation around her nipple.
- Mammogram found a 2 cm suspicious mass under the nipple.
- Needle core biopsy:
Secretory Carcinoma
Secretory carcinoma
Clinicopathological features

• Rare breast ca (0.15%)
• Located near the areola in 50% of cases
• “Juvenile carcinoma “
• Range age: 3-73 years old
• Male breast
• Rosen et al:
  – 37% <20 y, 31% 20-30 y and 30% >30 y
• Excellent prognosis
Secretory carcinoma
Clinicopathological features

• Reported in a 9 year old boy
• Female breast (average age: 25 y)
• Gross finding:
  – Well-defined, white or brown
  – Size: 0.6 -12 cm
Secretory carcinoma
Histopathology

- Large amount of extra- and intracellular secretions, pale pink with vacuolated or bubbly appearance
- PAS+
- Mucicarmine positive
- Tumor cells: granular, clear to signet ring or vacuolated cytoplasm
- Negative for GCDFP-15
- Positive for S100, pCEA
Secretory carcinoma
Histopathology

- Secretory microacini, solid areas, foci of cystic papillary formations with abundant secretion
- Fibrous stroma
- Monotonous and bland nuclei
- Rare or absent mitosis
- +/- DCIS (papillary, cribriform and solid)
- ER: most cases are negative
- PR: +/-
- Triple negative
- Other IHC: EMA, alpha lactalbumin and S100
Secretory ca
Secretory ca
Secretory ca
Secretory ca
- ER immunostain
Prognosis
Secretory carcinoma

• Excellent in children
• Slightly more aggressive in adults
• Risk of lymph node involvement is similar in both children and adults (usually 4 nodes at most)
• Tumors with smaller size better prognosis
• Recurrence after 20 years have been reported
Differential diagnosis

• Should not be confused with InvC, NST with apocrine features

• Apocrine adenoma (ductal hyperplasia with apocrine metaplasia or sclerosing adenosis with apocrine changes)
Tubular adenoma with apocrine changes
# Summary

## Secretory carcinoma

- Special type of breast carcinoma
- Younger patients
- Around nipple
- Excellent prognosis in children and young adults
- ER is usually negative
Pearls

- Left breast, lumpectomy
- *Secretory carcinoma, mBR grade 1, pT1cN0, stage I,
  See synoptic report.*

- Invasive tumor type: *Secretory*
- Invasive tumor size: *1.7 cm*
- Invasive tumor grade (modified Bloom-Richardson (mBR): *1*
- Nuclear grade: *2*
- Mitotic grade & mf count: *1mf/10hpf*
- Tubule/papilla formation: *1*
- Total mBR score: *4*
- -Lymph nodes positive /total lymph nodes sampled: *0/10*
- -Duct carcinoma in situ type: *None identified*
- -Her2/neu status: *Negative, 0 on DAKO scale*
- -Hormone receptor status (ER/PR): *Negative*
Thank you for participating!
New case

• 60 year old woman with newly identified breast mass
• Mammogram found 1.5 cm suspicious mass at 12 o'clock position of the left breast
Carcinoma with Apocrine Features
(Apocrine Carcinoma)
Carcinomas with apocrine differentiation

- Focal apocrine differentiation is common in invasive ca, NST
- Apocrine differentiation in special type of breast ca
  - Lobular ca
- Extensive apocrine differentiation (~100%):
  - Rare (4% of cases)
- Tumor cells
  - Abundant granular eosinophilic cytoplasm (PAS positive)
  - Abundant foamy cytoplasm
  - Can be seen with many lymphocytes
Carcinomas with apocrine differentiation

- Immunoprofile:
  - BCL2 -
  - BRST +
  - ER and PR are usually –
  - Her2neu +
  - Androgen receptor +
Carcinomas with apocrine differentiation

• Differential diagnosis:
  – Granular cell tumor
  – Inflammatory process
  – Misdiagnosed as lymph-node with metastasis

• Prognosis
  – Same clinical outcome as Invasive Ca, NST
    • Grade and stage

• Rare study: better prognosis
Apocrine ca
Summery

• 2012 WHO classification:
  – Inv ca with apocrine features
• Focal; rarely diffuse
• ER and PR: negative
• Her2neu positive
• Same clinical outcome as Invasive Ca, NST
  – Grade and stage
New Case

• 42 year old female with 2 hypoechoic irregular masses in US
• The mass was also palpated on physical examination
• Needle care biopsy of the largest mass
Invasive Micropapillary Carcinoma
Invasive Micropapillary Carcinoma

- Pure form (~75% micropapillary): 0.9-2%
- Micropapillary areas are found in 7.4% of all invasive ca (mixed types)
- Age range: 25-89
- Pure from tend to be older patients
- Usually present as palpating mass
Invasive Micropapillary Carcinoma

• Presence of hollow or morula-like clusters
• No fibrovascular cores
• Reverse polarity
  – Inside-out pattern
• Empty stromal spaces
  – No endothelial lining
  – Fixation artifact
  – Mucin
  – Myxoid material
Micropapillary ca
MUC1 immunostain in InvMPCa vs. Inca

Modern Pathology (2004) 17, 1045–1050

Micropapillary ca

• Inv ca, NST
Invasive Micropapillary Carcinoma

- Usually larger tumor
- Higher grade (mBR grade II or III)
- Eosinophilic or granular cytoplasm
  - Apocrine diff is common
- Most of them are ER+, PR+
- Her2neu + / -
  - More commonly Her2+
LVI in micropapillary ca
Mixed MPC and lobular ca
Invasive Micropapillary Carcinoma

• Prognosis:
  – LVI incidence: high >50% cases
  – More lymph node involvement
  – ER, PR and Her2neu more commonly +

• Differential diagnosis:
  – Mucinous ca
  – Metastatic serous papillary carcinoma
Metastatic serous papillary ca to breast
Summery

• Special type of invasive carcinoma
• Characteristic pattern
  – Reverse polarity
  – Retraction artifact
• Pure form and mixed types
• mBR grade II or III
• ER, PR and Her2neu are usually positive
• Higher rate of LVI and lymph node metastasis
Thank you for participating!