Evaluation of Invasion in Papillary Lesions

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Professor

"We have struggled with this differential diagnosis (benign from malignant papillary lesions) in our laboratory of surgical pathology for many years, and we still find it to be probably the most difficult diagnostic problem that we face with breast neoplasms.....And we check the accuracy of our diagnosis by very long-term follow-up of the patients."

--Dr. Cushman D. Haagensen, 1986

Outline of Talk

- Overview of papillary lesions
- Benign alterations in papilloma mimicking invasion
- Invasion arising in papillary DCIS
- What is “invasive papillary carcinoma”? • Intracystic/encapsulated papillary carcinoma • Solid papillary carcinoma

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Classification of papillary lesions

- Papilloma
  - Involved by non-atypical proliferative changes
  - Involved by atypical hyperplasia (atypical papilloma)
  - Involved by DCIS (DCIS arising in a papilloma)

- Papillary DCIS

- Intracystic/encapsulated papillary carcinoma

- Solid papillary carcinoma

- Invasive papillary carcinoma

Useful IHC markers for papillary lesions--
p63, SMM and CK5/6

Predominantly papillary

Predominantly solid

Benign papilloma retains a continuous layer of ME cells along the fibrovascular cores

P63 stain
Papillary carcinoma lacks or has a paucity of ME cells along the fibrovascular cores

Solid papillary DCIS vs papilloma with florid UDH

Solid papillary DCIS vs papilloma with florid UDH

CK5/6 stain

Solid papillary DCIS    Papilloma with florid hyperplasia

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Benign alterations in papilloma

Potential diagnostic pitfalls

- Sclerosis
- Infarct / Necrosis
- Epithelial Displacement
- Squamous metaplasia

Mimic Invasive Cancer

Sclerosis in papilloma/sclerosed papilloma

Pitfall: mimic invasive carcinoma, esp in core biopsy

Myoepithelial markers confirm benign

P63 stain
Sclerosed papilloma

Pitfalls: Mask the papillary process, mimic invasion

Caution: ME markers may be reduced or focally absent in sclerosed papilloma

Infarct / necrosis in papilloma
Infarct / necrosis in papilloma

Pitfall: mimic invasive cancer, esp in a core biopsy

Pseudo-invasive growth in papilloma

Settings:
- After infarct
- After duct rupture
- After biopsy (epithelial displacement)

Diagnostic clues favoring benign nature:
- Granulation tissue
- Hemosiderin
- Cholesterol cleft
- Squamous metaplasia
- Myoepithelium

Squamous metaplasia in papilloma with pseudo-invasive growth

Pitfall:
- Mimic metaplastic carcinoma
- ME markers | or - in squamous metaplasia

Pseudo-invasive growth in papilloma

- Myoepithelium is not always present

- Caution advised in evaluating epithelium entrapped within inflamed granulation tissue

- Caution advised in core biopsies
  Excision may be needed to exclude cancer
“In practice, if a papillary tumour in the ductal lumen is judged to be benign, a nubbin of apparent infiltration of the wall can safely be disregarded, and is usually the result of the process described (pseudo-infiltration)”

-- Professor John G. Azzopardi, 1979

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Invasion arising from papillary DCIS

- When papillary intraductal carcinomas invade, they generally assume the pattern of infiltrating ductal carcinoma and lack a papillary architecture
- Papillary DCIS with sclerosis: mimic invasion
- ME marker may be attenuated in papillary DCIS
  
  Avoid overDx of invasion

DCIS involving sclerosed papilloma or sclerosis in papillary DCIS may mimic invasion
**Outline of Talk**

- Overview of papillary lesions
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- Invasion arising in papillary DCIS

**Invasive papillary carcinoma (IPC)**

- Definition: An invasive carcinoma with predominantly papillary morphology
- What are the pathologic features of IPC?
- Is papillary carcinoma that lacks a peripheral layer of ME cells an IPC?

**Sclerosis in papillary DCIS may mimic invasion**

*ME markers rule out invasion*

**IDC arising in association with papillary DCIS**

*Note the patchy loss of ME marker in papillary DCIS*
Pathologic Findings from the National Surgical Adjuvant Breast Project (Protocol No. 4)

VI. Invasive Papillary Cancer

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Incidence: 2.2 % (35/1603)

Pathologic

- Circumscribed (2/3 cases)
- Intermediate histologic grade
- Associated papillary DCIS

Clinical

- Non-Caucasian
- Post-menopausal women
- Lower incidence of + LN (32%)
- Better survival, prognosis similar to pure tubular and mucinous ca

"Unique histologic type of invasive mammary cancer with a favorable prognosis"

"stromal non-intraductal component was self-evident"

Examples of invasive papillary carcinoma from NSABP B04

Examples of invasive micropapillary carcinoma from NSABP B04
Intracystic papillary carcinoma

- Synonyms:
  - Encysted papillary carcinoma
  - Encapsulated papillary carcinoma

- Definition:
  - Papillary carcinoma in a large cystic space
  - Well circumscribed, surrounded by a fibrous wall
  - Special type of DCIS (WHO 2003)
  - Histology of papillary DCIS, except:
    - Lacks peripheral myoepithelium

Intracystic/encapsulated papillary carcinoma

SMM
Is intracystic papillary carcinoma invasive?

Compressed Myoepithelium

Invaded Past Myoepithelium

In-situ

Invasive

Controversial!

Encapsulated PC showing skeletal muscle invasion

Encapsulated PC showing vascular invasion

(case contributed by Dr. K. Che Prasad)
Mammary papillary carcinoma metastatic to lung
(h/o DCIS 10 years ago, s/p mastectomy)

(case contributed by Dr. Jeffrey A. McDavit)

Intracystic/encapsulated papillary carcinoma:
an invasive tumor with circumscribed growth and excellent prognosis

Synonyms:
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Clinical:
- 6th-7th decades
- Adjacent conventional in situ or invasive ca may be present
  - If pure: Behavior mostly similar to DCIS, with rare cases of nodal metastases, local recurrence, and skeletal muscle invasion
Encapsulated papillary ca with adjacent IDC, NOS

Solid papillary carcinoma

**Definition:**
- Papillary carcinoma with a solid growth pattern
- Well-circumscribed, single or multiple nodules
- Special histologic and IHC features
- Heterogeneous: Myoepithelium may be + or -

Solid papillary carcinoma

(courtesy of Dr. Dean Fong)
Histologic features of solid papillary carcinoma

Plasmacytoid

Spindle cells
Pseudo-rosette around cores

Histologic features of solid papillary carcinoma

Mucinous production

Neuroendocrine differentiation

Chromogranin stain

Some solid papillary carcinomas
have intact myoepithelial layer

In situ SPC

calponin

Some solid papillary carcinomas
lack peripheral myoepithelium

p63 stain
SPC as one single large nodule

SPC: one single large nodule, no ME layer

SPC with multiple nodules, no ME layer

Features suggestive of invasion in SPC

- Large tumor size
- Complex, irregular, coalescent papillary nodules/nests
- Irregular tumor-stromal interface
- Encircling large blood vessels
- Entrapment of benign ducts and lobules
SPC-- large tumor size

3.5 cm, well-circumscribed mass

SPC--complex, irregular, coalescent papillary nests

SPC--irregular tumor-stromal interface

Tumor-stromal interface in papillary carcinoma

Invasive PC

Adjacent papillary DCIS

Irregular vs smooth

p63 stain
SPC encircling large blood vessels

PC showing entrapment of normal ducts and lobules

Features suggestive of invasion in SPC

- Large tumor size
- Complex, irregular, coalescent papillary nodules/nests
- Irregular tumor-stromal interface
- Encircling large blood vessels
- Entrapment of benign ducts and lobules
- Invading stroma/fat or skeletal muscle

SPC showing stromal invasion
Features suggestive of invasion in SPC

- Large tumor size
- Complex, irregular, coalescent papillary nodules/nests
- Irregular tumor-stromal interface
- Encircling large blood vessels
- Entrapment of benign ducts and lobules
- Invading stroma/fat and skeletal muscle
- Metastatic disease with same solid papillary growth

SPC showing LN metastasis

Metastatic ca in LN with SPC pattern

Definition:

- Papillary carcinoma with a solid growth pattern
- Well-circumscribed, single or multiple nodules
- Special histologic and IHC features
- Heterogeneous: Myoepithelium may be + or -

Clinical:

- 6th-7th decades
- Adjacent conventional invasive ca may be present often mucinous or neuroendocrine-like
- If pure and lack myoepithelium
  Indolent behavior
  Low rate of LN metastasis
**Approach for evaluating papillary carcinoma**

- Tumor with fibrovascular cores lined by epithelial cells
- IHC markers (p63, SMM, ± CK5/6): evaluate malignancy and invasion
  - Exclude benign papillary lesions
  - ++ ME cells along papillae, + CK5/6
  - In situ papillary ca
    - ME cells along papillae, - CK5/6
    - ME cells at periphery of space
  - Circumscribed papillary ca
    - Circumscribed nodule of PC in a dilated cystic space, with a thick fibrous capsule
  - Encapsulated/circumscribed papillary ca
    - Circumscribed nodule of PC in a dilated cystic space, with a thick fibrous capsule

**UCSF approach for evaluating papillary carcinoma**

- Tumor with fibrovascular cores lined by epithelial cells
  - IHC markers (p63, SMM, ± CK5/6): evaluate malignancy and invasion
  - Exclude benign papillary lesions
  - ++ ME cells along papillae, + CK5/6
- In situ papillary ca
  - ME cells along papillae, - CK5/6
  - ME cells at periphery of space
- Circumscribed Solid papillary ca
  - Circumscribed nodule of PC with a solid papillary growth pattern and a smooth tumor-stromal interface

**Dx:** Encapsulated/circumscribed PC or SPC; see comment.

Comment: The tumor has a well-circumscribed border, but lacks a peripheral myoepithelial layer. These lesions likely represent a very low-grade invasive tumor with an expansile growth pattern and an excellent prognosis. The incidence of local recurrence or nodal metastasis is low and incidence of distant metastasis or cancer-related death is extremely low.

**UCSF approach for evaluating papillary carcinoma**

- Tumor with fibrovascular cores lined by epithelial cells
  - IHC markers (p63, SMM, ± CK5/6): evaluate malignancy and invasion
  - Exclude benign papillary lesions
  - ++ ME cells along papillae, + CK5/6
- In situ papillary ca
  - ME cells along papillae, - CK5/6
  - ME cells at periphery of space
- Invasive papillary ca
  - Carcinoma with predominantly papillary morphology with features of stromal invasion
Dx: Invasive PC; see comment.

Comment: Invasive papillary carcinoma is a special type of invasive carcinoma with a favorable prognosis. These tumors are associated with a low risk of LN metastasis and infrequent development of distant recurrence.

ME-negative papillary ca (EPC, SPC and IPC)

- Older women
- ER +, PR +, HER2 –
- Favorable prognosis, low rate of LN metastasis
- Less genomic changes than ER & grade-matched IDC
- Genomic profile remarkably similar in the 3 morphologic subtypes of PC

UCSF approach for evaluating papillary carcinoma

- Tumor with fibrovascular cores lined by epithelial cells
- IHC markers (p63, SMM, ± CK5/6): evaluate malignancy and invasion
- Exclude benign papillary lesions
  - + ME cells along papillae, + CK5/6
  - - ME cells, - CK5/6
- In situ papillary ca
  - ME cells along papillae, - CK5/6
  - ME cells at periphery of space

Encapsulated/circumscribed papillary ca:
- Circumscribed nodule of PC in a dilated cystic space, with a thick fibrous capsule
- Involved stromal reaction
- Idiopathic papillary stromal cells

Circumscribed solid papillary ca:
- Circumscribed nodule of PC with a solid papillary growth pattern and a smooth tumor-stromal interface

Invasive papillary ca:
- Carcinoma with predominantly papillary morphology with features of stromal invasion
- Idiopathic papillary stromal cells

ME-negative papillary ca (EPC, SPC and IPC)

- DUPREZ R et al: J Pathol 2012

When encapsulated/circumscribed PC associated with conventional invasive ca

- Dx:
  1. IDC, 0.7 cm; see comment
  2. Encapsulated papillary ca, 2.1 cm
  3. pT1b

- Tumor type and stage based on nonpapillary invasive component
- Report: associated with EPC, size, for clinical and imaging correlation
Pure encapsulated/circumscribed PC without conventional invasive ca

- No consensus in staging
- UCSF: Tx or Tis with a comment
- Avoid overtreatment, but understand potential low rate of recurrence and metastasis

Invasive papillary carcinoma

- Use the size of the lesion for pT
- Comment about special type of invasive carcinoma with a favorable prognosis

Management for pure ME-negative papillary ca (I)

- Matter of debate
- Avoid overtreatment
- Overall, manage similar to DCIS
- Adequate local control: appropriate treatment

Management for pure ME-negative papillary ca (II)

- ? SLN sampling
  - appropriate for those with frankly invasive growth pattern
- ? Hormonal therapy (probably yes)
- ? Radiation therapy
- Chemotherapy not appropriate
Take home message

- Alterations in benign papilloma may mimic invasion
- ME markers may be in various benign papillary lesions and in papillary DCIS
- Avoid overdiagnosis of invasion, especially with a benign papilloma background and in CNB
- ME-negative “intracystic” papillary carcinoma and solid papillary carcinoma are likely low-grade invasive tumors
- Conservative management for ME-negative papillary carcinoma

Acknowledgement

- UCSF residents/fellows: beautiful gross photos
- Contributing pathologists: challenging cases and wonderful gross photos

Selected references