



American Society for  
Clinical Pathology

**33 Special Types of Invasive Breast Carcinoma: Diagnostic Criteria  
with Prognostic and Therapeutic Signs**

**Farnaz Haste MD  
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**2011 Annual Meeting – Las Vegas, NV**

**AMERICAN SOCIETY FOR CLINICAL PATHOLOGY  
33 W. Monroe, Ste. 1600  
Chicago, IL 60603**

### 33 Special Types of Invasive Breast Carcinoma: Diagnostic Criteria with Prognostic and Therapeutic Signs

Up to 35% of invasive breast carcinomas can be considered of "special" type (e.g., tubular, lobular, medullary, metaplastic, colloid and adenoid cystic carcinoma). Since many of these invasive breast carcinomas have a relatively favorable prognosis, correct diagnosis is important especially for patient management and appropriate therapeutic procedures. This session will present current nomenclature, diagnostic criteria, differential diagnosis, and clinicopathologic significance for special types of invasive breast carcinoma.

- Clarify and discuss the diagnostic criteria for classification of special types of invasive breast carcinoma.
- Identify potential diagnostic pitfalls in diagnosis from the benign entity.
- Describe the clinical implications associated with these diagnoses.

#### FACULTY:

Farnaz Hasteh MD  
Noel Weidner MD

Practicing Pathologists  
Surgical Pathology  
Surgical Pathology (Derm, Gyn, Etc.)  
2.0 CME/CMLE Credits

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**Special Types of Invasive Breast Carcinoma**

**Noel Weidner, MD  
Farnaz Hasteh, MD**

 American Society for Clinical Pathology  UNIVERSITY of CALIFORNIA, SAN DIEGO MEDICAL CENTER

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**Disclosure Statement**

- The speakers (Noel Weidner, MD and Farnaz Hasteh, MD) do not have any financial or other relationships that create a conflict related to this educational course.

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**Learning 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

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**Course Outline:**

- Noel Weidner, MD
  - » Introduction
  - » Case 1:
  - » Case 2:
- Farnaz Hasteh, MD
  - » Case 3
  - » Case 4:
- Noel Weidner, MD
  - » Case 5:
- Farnaz Hasteh, MD
  - » Unknown cases

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**INTRODUCTION:  
SPECIAL TYPES OF INVASIVE BREAST  
CARCINOMA**

- ~35% invasive breast carcinomas special type (IC,ST).
- Most IC,ST have favorable prognosis – **IMPORTANT!**
- ST tumors must be ~ 90% or more special pattern.
- Those not meeting criteria of a special type called:  
Invasive duct carcinoma - IDC,NOS or IDC,NST.
- But, mixed patterns common, ~33% of invasive breast carcinomas.

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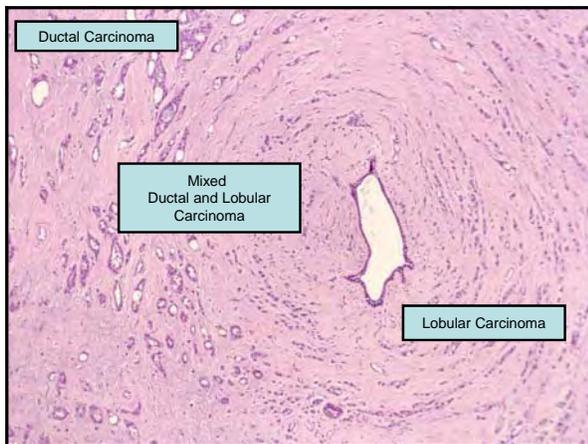
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**INVASIVE BREAST CARCINOMAS CONSIDERED TO HAVE A RELATIVELY GOOD PROGNOSIS**

1. Tubular Carcinoma
2. Cribriform Carcinoma
3. Pure Mucinous (Colloid) Carcinoma
4. Adenoid Cystic Carcinoma
5. Secretory Carcinoma
6. Low-Grade Adenosquamous Carcinoma
7. ? Classical Lobular Ca
8. ? Medullary Carcinoma.
9. ? Tubulolobular Carcinoma
- 10.? Invasive Papillary Ca

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- IDCs,NST having 10 to 90% of ST of carcinoma diagnosed as mixed DC & ST carcinomas.
- IDCs,NST can have less than 10% of ST carcinoma and be "pure" type IDC,NST.
- Grade all histologic types of invasive carcinoma.
- Grade + tumor type together more accurately predict prognosis.
- Grade transcends disagreements in subtype diagnosis.
- Clinicians often more easily accept grade designation than subtype.

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**10-YEAR SURVIVAL BY INVASIVE TUMOR TYPE AND MODIFIED BLOOM-RICHARDSON GRADE (mBR)**  
(Periera et al. Histopathol 1995;27:219-226)

Type (~100% total):	Overall	Grade 1	Grade 2	Grade 3
Ductal (NST) (50%)	46	76	55	39
Lobular (Classic) (6%)	53	71	55	38
Mixed Ductal + Lobular (5%)	41	88	52	31
Tubular (2.4%)	90	90	none	none
Tubulo-lobular (1%)	91	91	none	none
Mixed Tubular + Ductal (15%)	64	86	63	18
Mucinous (1%)	81	86	75	none
Mixed Ductal+Special type (2.5%)	64	81	59	55
Medullary (3%)	51	none	none	51
Atypical Medullary (5%)	63	none	none	63
Invasive Papillary (0.3%)	60	to few	to few	to few
Invasive Cribriform (0.8%)	90	90	none	none
Solid Lobular (1.4%)	33	none	63	18
Alveolar Lobular (0.6%)	77	none	77	none
Mixed Lobular (6.4%)	48	71	52	43

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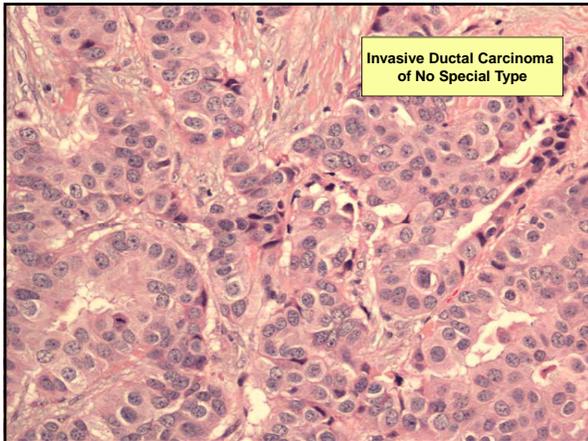
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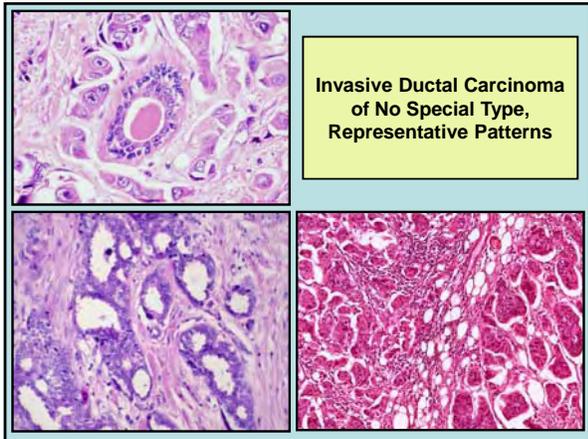
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**Basal-Like & Triple-Negative Breast Cancers**

- Within IDC,NST group there are different outcomes.
- Caused by tumor- & patient-specific characteristics.
- Gene expression microarray taxonomy for breast cancer:
  - 1) Luminal A
  - 2) Luminal B
  - 3) Normal breast-like
  - 4) HER2 over-expressing
  - 5) Basal-like
  - Identifies subgroups already known to some extent.
  - Stability and/or utility questioned.
  - Not being used by UCSD oncologists.
  - Yet, the basal-like group has generated interest.
  - No clear-cut histologically defined basal-cell in breast.

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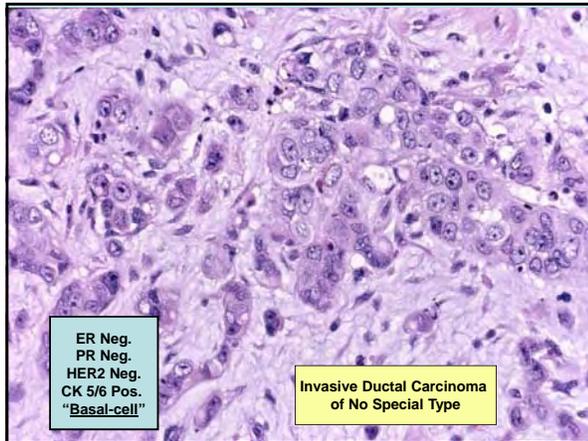
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• **No internationally accepted definition of basal-like breast cancer.**

• **Some use microarray profiling, others IHC markers.**

• **Proposed IHC panels defining basal-like breast cancers include:**

(1) Lack ER, PR, & HER2 expression (i.e., any "triple-negative" immunophenotype).

(2) Expression of one or more HMW basal CKs (CK5/6, CK14, CK17).

(3) Lack ER & HER2 in conjunction with CK5/6 and/or EGFR.

(4) Lack ER, PR, & HER2 in conjunction with CK5/6 and/or EGFR.

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**Basal-like Breast Cancers**

- Heterogeneous group, up to 15% of all breast carcinomas.
- Younger patients, more prevalent in African-Americans.
- Often present as interval cancers.
- Majority classify as IDC,NST type.
- High histological grade, high mitotic index.
- Often central necrotic or fibrotic zones & pushing borders.
- Have conspicuous lymphocytic infiltrate.

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**Basal-like Breast Cancers**

- Often display medullary-like features.
- Usually express low levels of ER/PR & lack HER2 over expression or amplification.
- Resemble the myoepithelial-cell phenotype.
- Minority harbor EGFR gene amplification or aneusomy.
- p53 expression or TP53 mutations in up to 85%.
- ~30% of basal-like cancers are pRB-/p16+/p53+.
- Carcinomas in BRCA1 germ-line mutation carriers are basal-like.

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- Some high-grade DCIS lack ER, PR, HER2.
- These DCIS cases express 'basal' markers.
- Triple-negative and basal-like cancers often lack in situ component.
- Less frequently disseminate to LNs & bones.
- Favor hematogenous spread, with a proclivity for metastatic deposits to the brain and lungs.
- **At present, use of the term "basal-like breast cancer" in diagnostic surgical pathology reports does not appear to be justified, as it does not lead to any direct clinical action.**

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Other basal-like phenotype cancers are...

- Medullary & atypical medullary carcinoma.
- Metaplastic carcinomas.
- Myoepithelial carcinoma ("metaplastic").
- Secretory carcinoma.
- Adenoid cystic carcinomas.

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**Triple-negative Breast Carcinomas**

- By definition, all lack ER,PR,HER2.
- Up to 17% of breast carcinomas.
- Lack of tailored therapies (i.e., for now).
- Much overlap with “basal-like” cancers.  
*-75% of triple-negative cancers are basal-like.*  
*-75% of molecular basal-like tumors are triple-negative.*
- Frequently affect younger patients.
- More prevalent in African-Americans.

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**Triple-negative Breast Carcinomas**

- Often present as interval cancers.
- Shorter survival following first metastatic event.
- Vast majority moderate to poorly differentiated.
- Maybe ~10% of triple negative tumors are grade 1 of 3 (others disagree & report all as Gr. 2 or 3).
- Favor hematogenous spread, with a peculiar proclivity to develop metastatic deposits in the brain and lungs.
- Some apocrine & pleomorphic ILCs are triple negative.

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**INTERESTING CASE**

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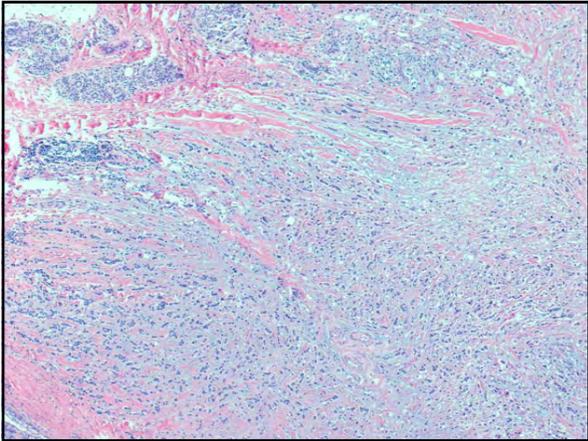
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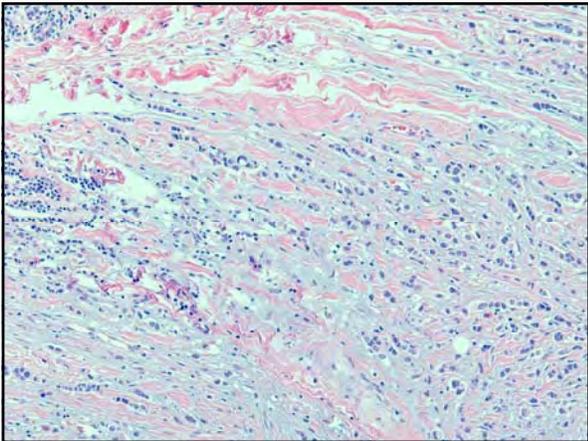
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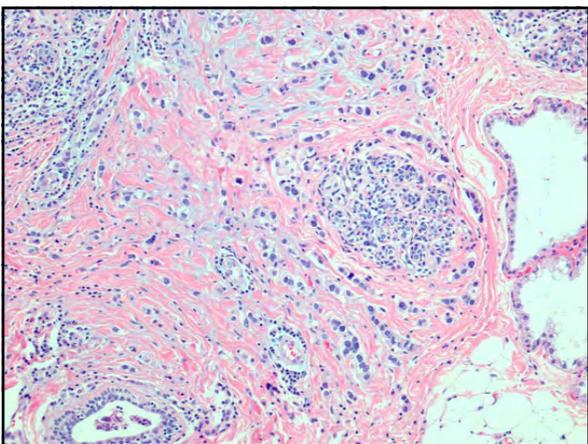
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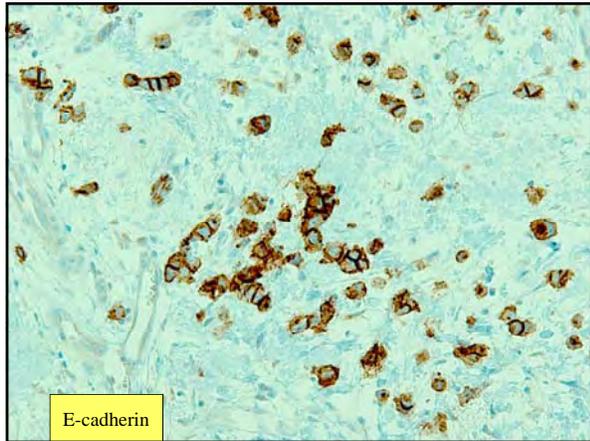
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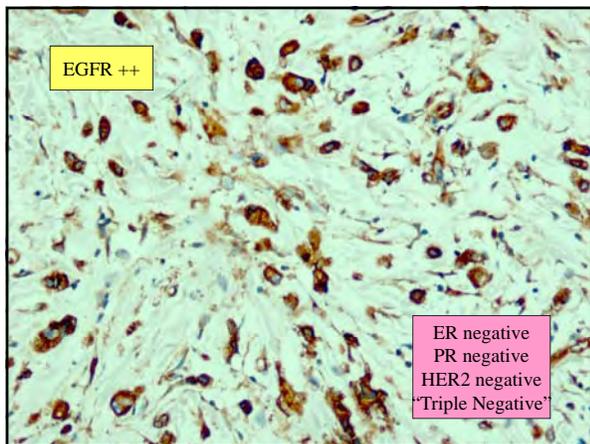
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Case 1:

- History: 65 y/o female with 2.5 cm poorly defined left breast mass with firm, tan cut surfaces.

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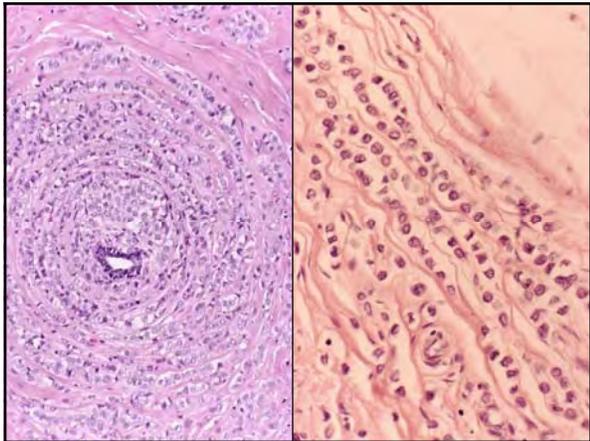
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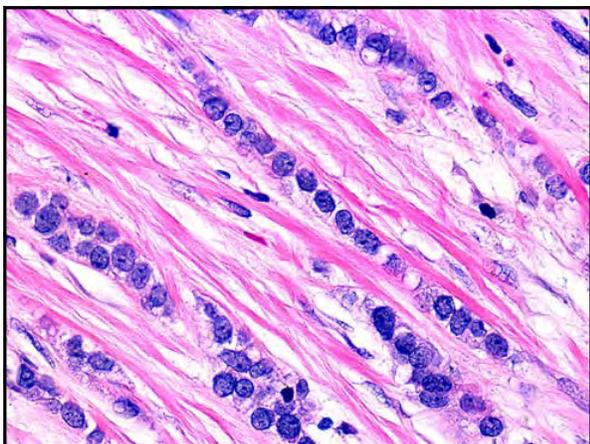
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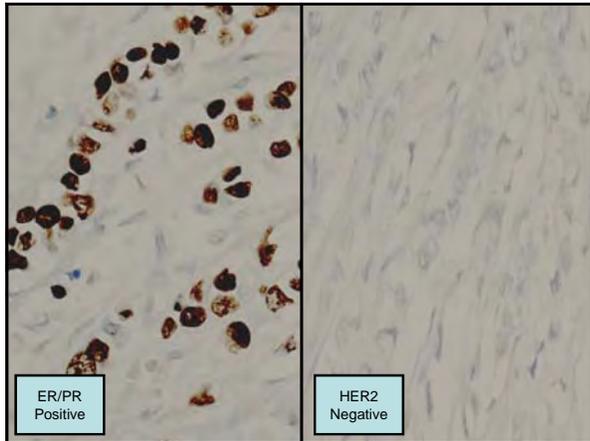
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**INVASIVE LOBULAR CARCINOMA (ILC)**

- ILC, classic type, is well-recognized.
- Other less well-known forms include:
  - **Pleomorphic (often "apocrine")\***
  - **Solid\***
  - **Signet-ring\***
  - **Tubulolobular\*\***
  - **Alveolar\*\*\***
  - **Histiocytoid\*\*\***  
(aka., "lipid" or "myoblastomatoid" or "granular-cell")

\* Worse prognosis  
\*\* Better prognosis  
\*\*\* Incompletely studied

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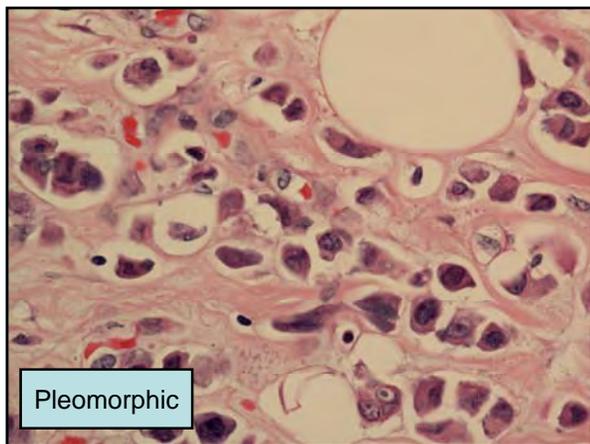
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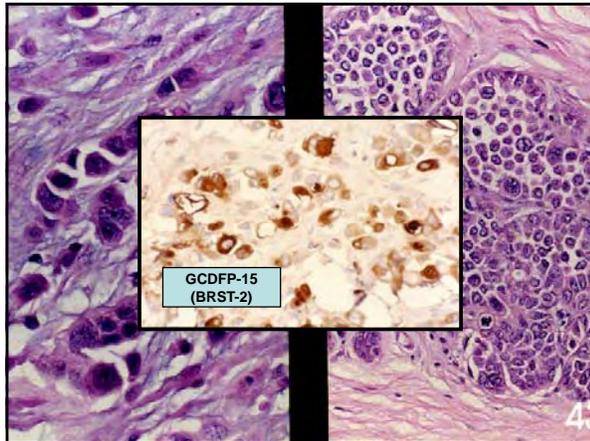
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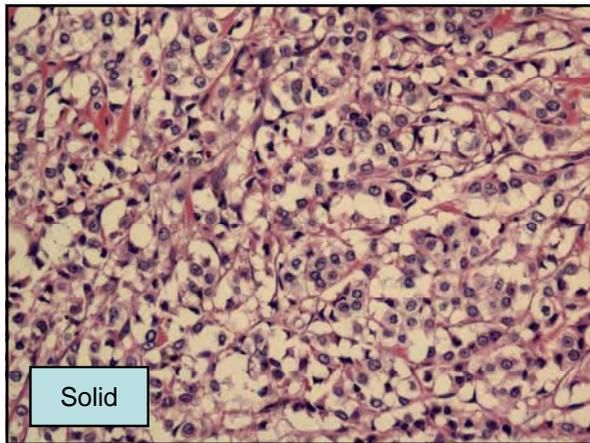
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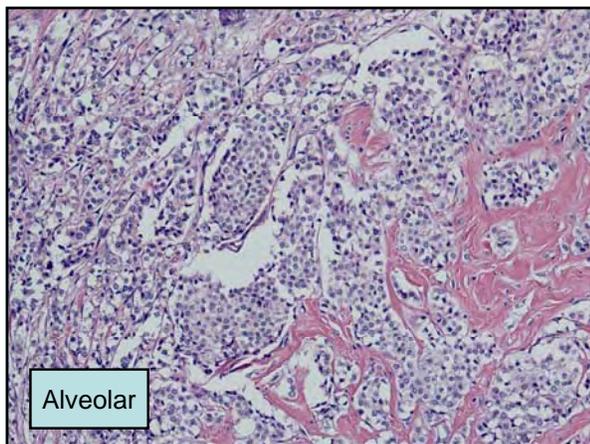
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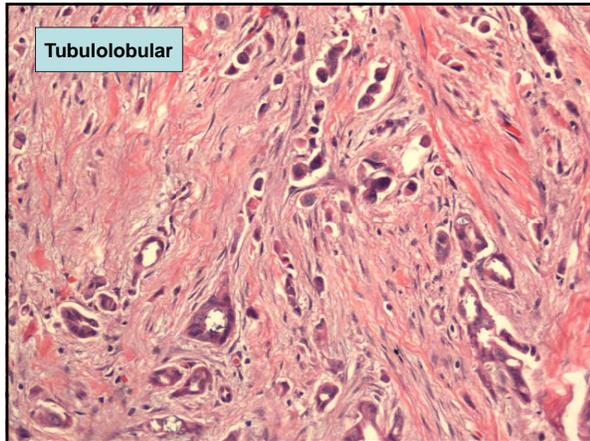
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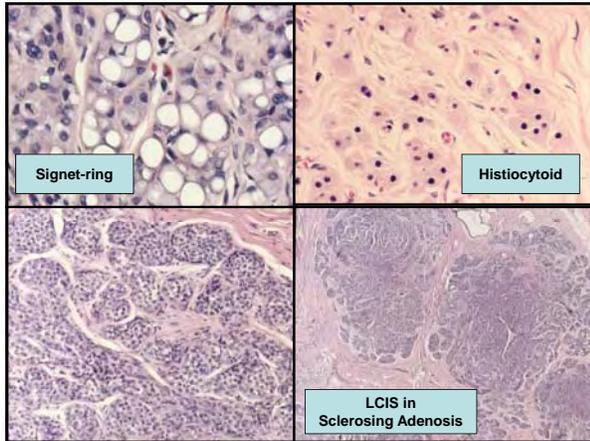
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- ILCs ~14% of breast carcinomas.
- Age range like other carcinomas.
- Some data suggest ILC more frequently bilateral, than IDC,NST.
- From occult focal lesions to diffusely involving the entire breast.
- Can be firm, but often fails to form a discrete mass (delayed diagnosis of breast carcinoma).

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- ILCs often show multifocal invasive “skip” lesions and more diffuse growth patterns within the breast, when compared to IDC.
- Hence, ILC would seem less amenable local surgical excision than IDC.
- But, direct comparison of the effectiveness of lumpectomy+radiation between ILC vs. IDC have shown no differences in outcome (*Eur J Cancer* 28:660-666, 1992).

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- ILC can be difficult to visualize by X-ray.
- May feel doughy & mimic benign breast.
- FS dx & margin evaluation treacherous.
- FNA samples usually sparsely cellular, containing bland small cells with scanty, inconspicuous cytoplasm dispersed singly or in small groups.
- ILCs not prone to form calcifications.
- Classical ILC positive for ER/PR.
- Lymph node mets can be hard to spot.

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- ILC metastatic patterns: proclivity for GI tract, GYN system, peritoneum & retroperitoneum.
- CNS mets occur as carcinomatous meningitis.
- Mets to the stomach may mimic linitis plastica.
- Cause Krukenberg tumors.
- E-cadherin absent or weakly expressed.
- Also loss of  $\alpha$ -,  $\beta$ -, &  $\gamma$  catenin in ILC.
- Most ductal carcinomas express E-CD.
- ILCs commonly express Bcl-2.
- Bcl2 correlates with ER and PR positivity.

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**Illustrative Example:**

61 y/o female presents with antral thickening and h/o metastatic breast carcinoma. Gastric lesion, rule out metastatic breast carcinoma.

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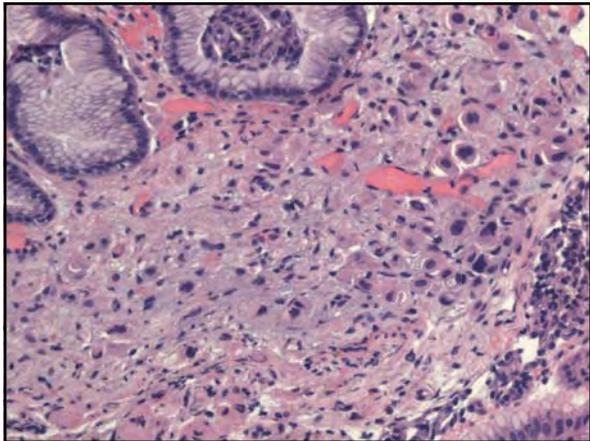
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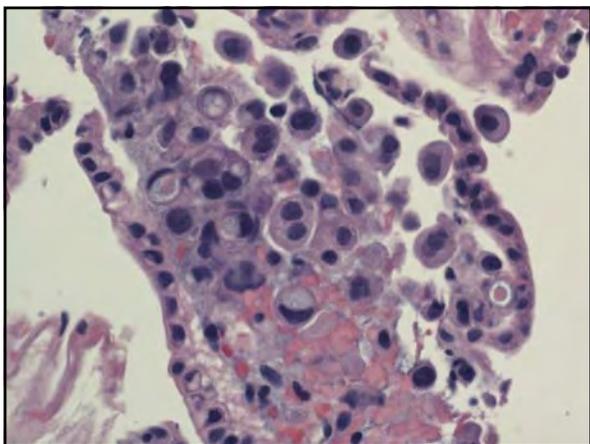
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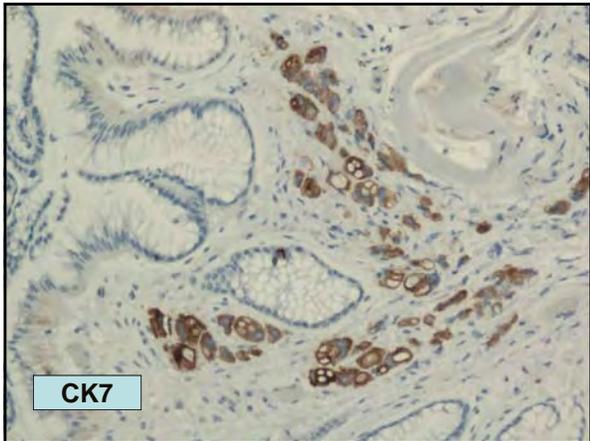
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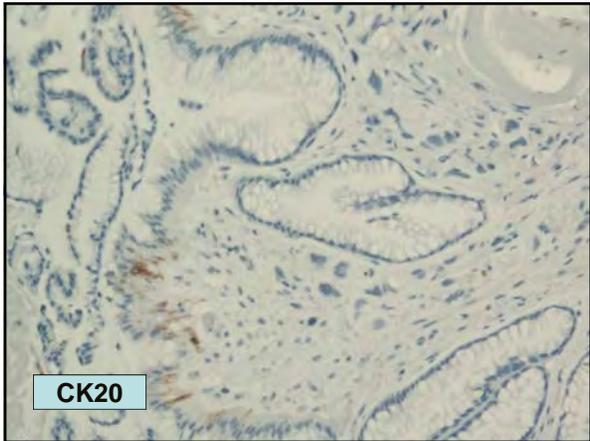
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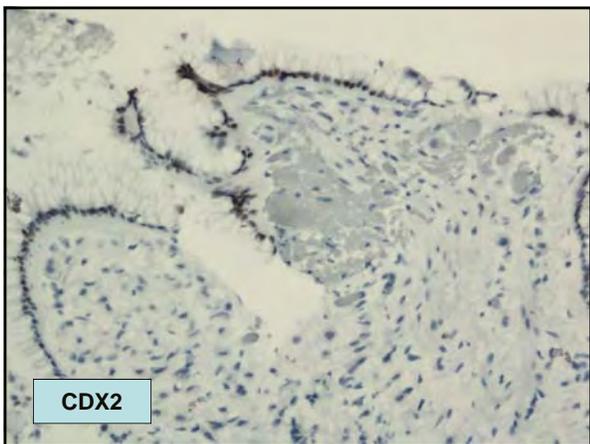
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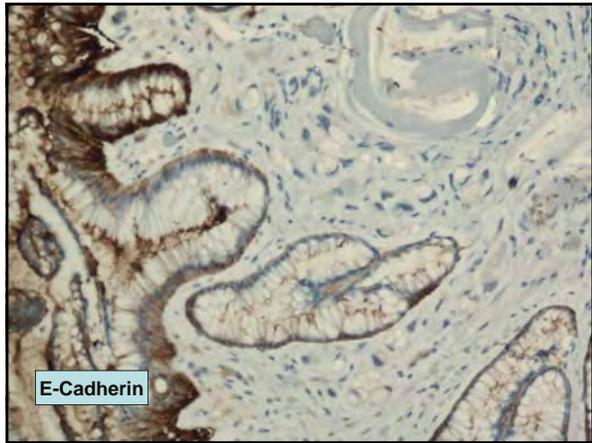
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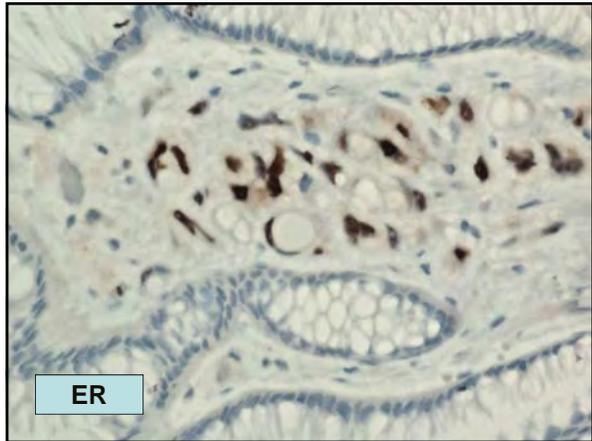
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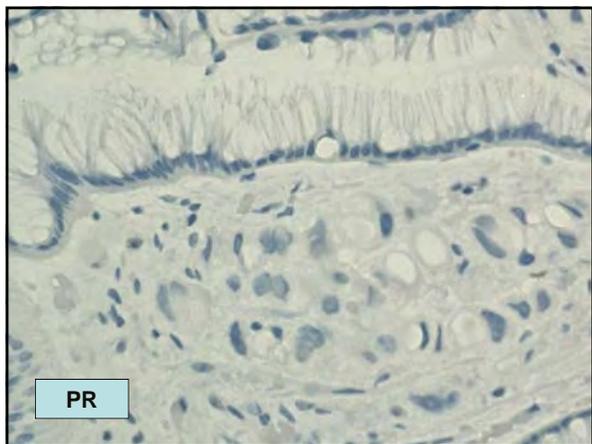
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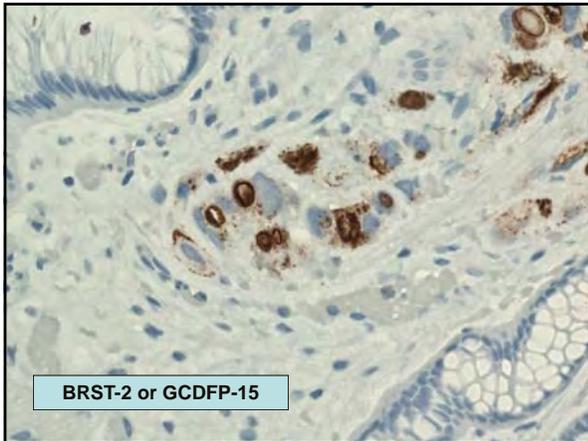
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Diagnosis:

Metastatic lobular breast carcinoma

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**Hereditary diffuse gastric cancer: association with lobular breast cancer**

Kasmintan A. Schrader · Serena Masciari · Niki Boyd · Sara Wyrick · Pardeep Kaurah · Janine Senz · Wylie Burke · Henry T. Lynch · Judy E. Garber · David G. Huntsman

Fam Cancer 2008;7:73-82

Published online: 29 November 2007  
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**Abstract** Hereditary diffuse gastric cancer (HDGC) has been shown to be caused by germline mutations in the gene *CDH1* located at 16q22.1, which encodes the cell-cell adhesion molecule, E-cadherin. Not only does loss of expression of E-cadherin account for the morphologic differences between intestinal and diffuse gastric cancer (DGC) variants, but it also appears to lead to distinct cellular features which appear to be common amongst related cancers that have been seen in the syndrome. As in most hereditary cancer syndromes, multiple organ sites may be commonly affected by cancer, in HDGC, lobular carcinoma of the breast (LBC) and possibly other organ sites

have been shown to be associated with the familial cancer syndrome. Given the complexity of HDGC, not only with regard to the management of the DGC risk, but also with regard to the risk for other related cancers, such as LBC, a multi-disciplinary approach is needed for the management of individuals with known *CDH1* mutations.

**Keywords** Hereditary diffuse gastric cancer (HDGC) · Diffuse gastric cancer · E-cadherin mutation · *CDH1* mutation · Lobular breast cancer · Screening · Prophylactic total gastrectomy

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LCIS vs DCIS

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- Patients with lobular ca have ↑ risk for bilateral disease (~1/3<sup>rd</sup> of cases [9-69%]).
- Yet, pts with ductal carcinoma ALSO have ↑ risk of bilateral disease (~1/6<sup>th</sup> of cases [1-25%]).
- A related issue - ipsilateral multicentricity:  
Reported in ~2/3<sup>rd</sup>s for LCIS [42-86%].  
Reported in ~1/3<sup>rd</sup> for DCIS [23-46%].
- DCIS currently considered amenable to local-regional therapies - LCIS is not, because of the latter's greater risk of multicentricity & bilaterality.

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- Ottesen reported follow-up study of 69 patients with pure LCIS and 19 patients with LCIS + DCIS treated with excision only (*AJSP 17:14-21,1993*).
- Some (i.e., LCIS + DCIS cells) were found close and merging, with individual CIS cells indistinguishable in junctional zone.
- Thus, "LCIS occurring with DCIS (22%) makes a theory of coincidence unlikely, but rather indicates a relation between the two."
- Of LCIS cases, 20% had both small (type A) and large (type B) nuclei (i.e., large or type B cells are DCIS-like).

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- 17% recurred with recurrence rates equal in both pure LCIS and LCIS+DCIS cases.
- All recurrences were IPSILATERAL.
- 50% of recurrences invasive carcinomas.
- Recurrence related to extent and cell type.
- Recurrence Rate Among LCIS Types:  
(<10 lobules LCIS + small nuclei) = 7%  
(>10 lobules LCIS + large nuclei) = 41%

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- I believe, CIS having mixed ductal & lobular features, should be (at least in part) called DCIS - this encourages complete excision.
- YET, I mention the concomitant LCIS pattern to emphasize somewhat greater risk of bilateral carcinoma (e.g., "mixed ductal & lobular CIS").
- This encourages adequate follow-up studies of the contra-lateral breast.

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WHO 2003

"The current recommended management for lobular neoplasia is life long follow-up with or without tamoxifen rx. Re-excision should be considered in cases of massive acinar distention, and when pleomorphic, signet ring, or necrotic variants are identified at or close to the margin."

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Examples of  
E-cadherin staining  
in Breast Carcinomas  
- Classic and Otherwise -

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CASE A

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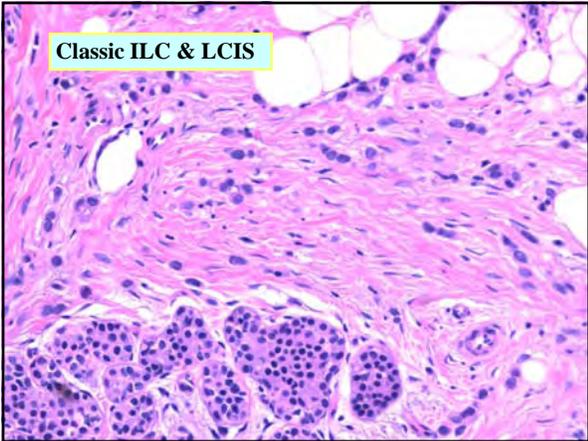
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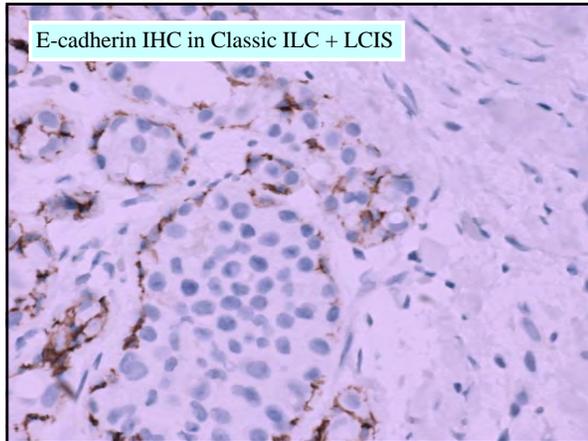
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**CASE B**

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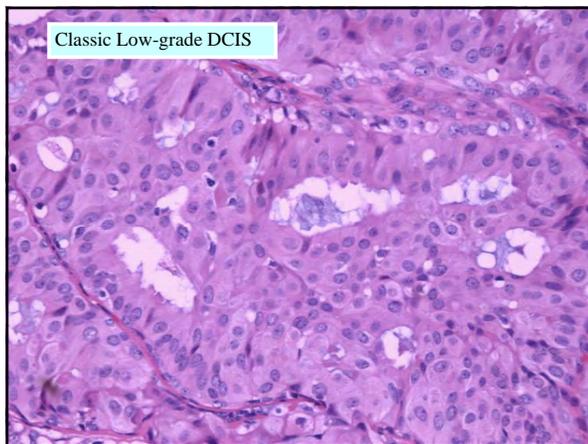
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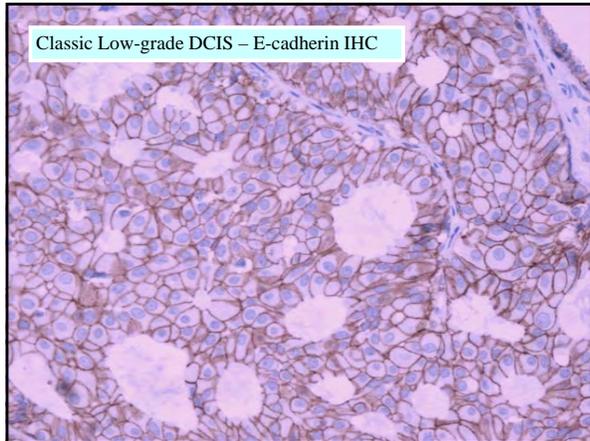
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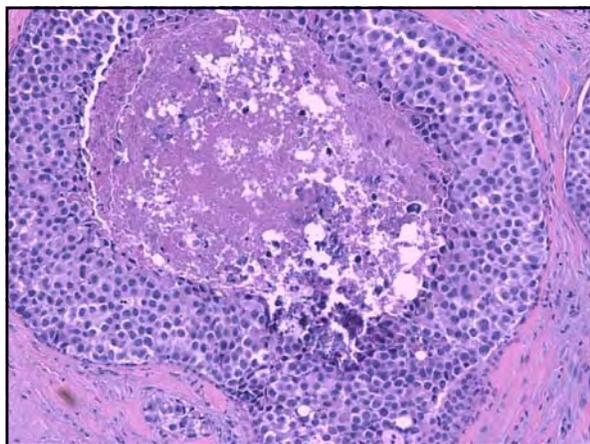
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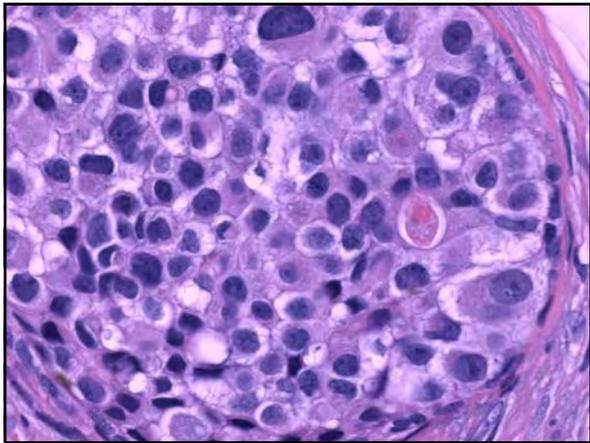
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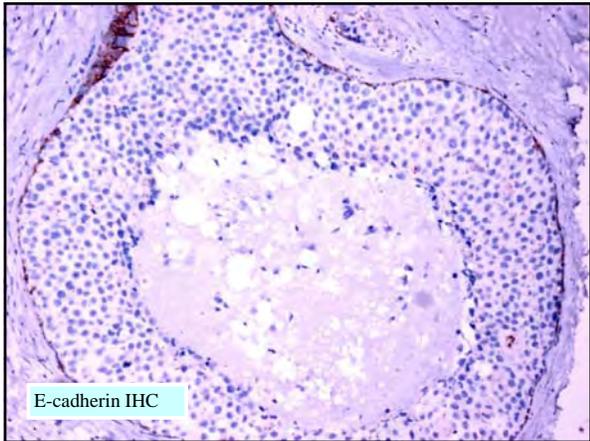
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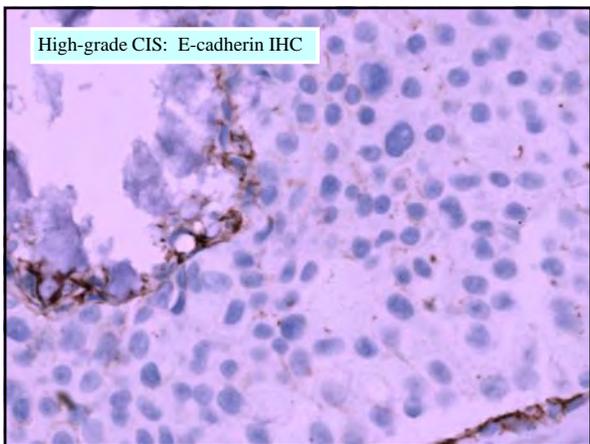
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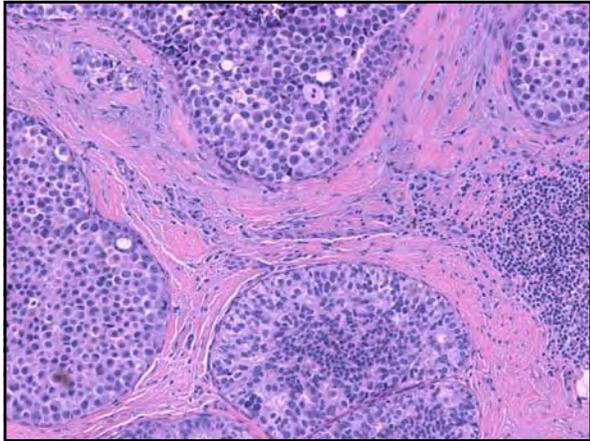
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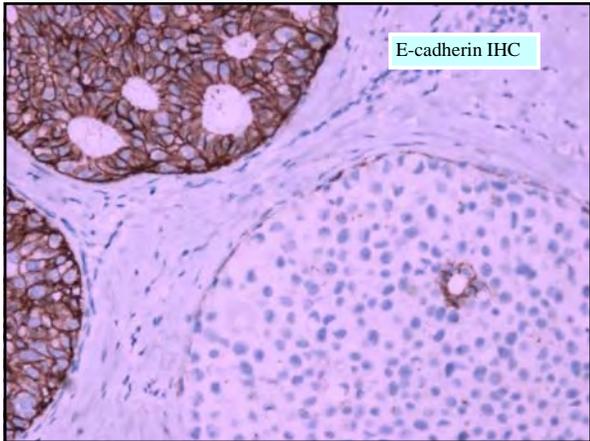
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**CASE D**

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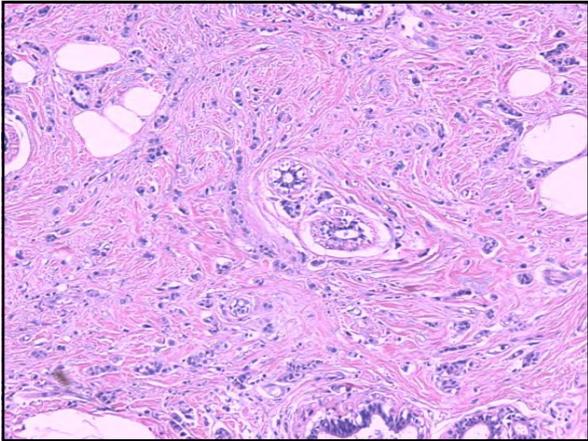
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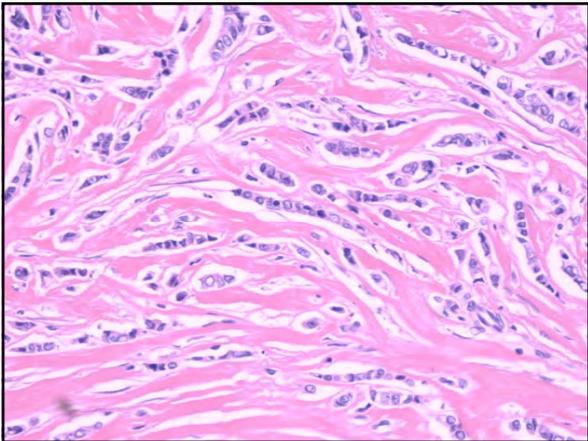
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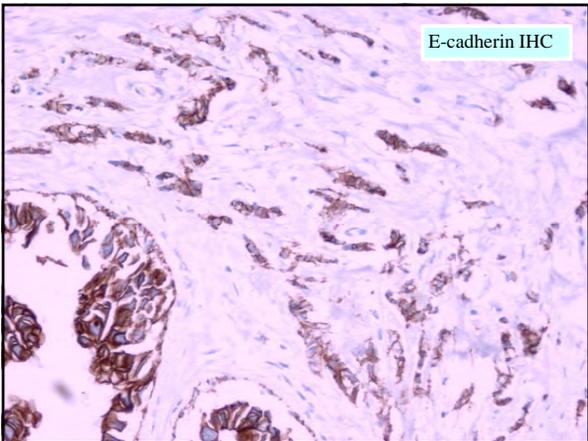
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E-cadherin IHC

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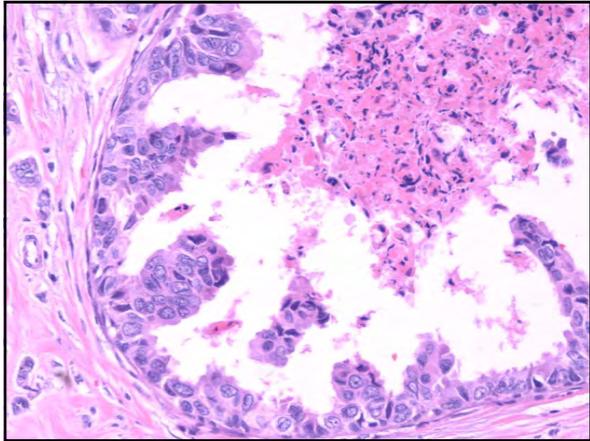
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**CASE E**

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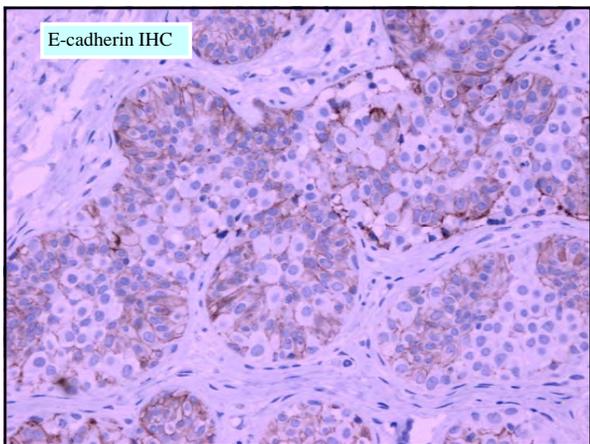
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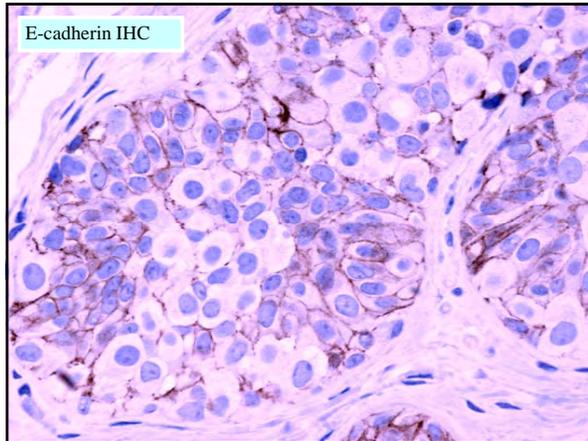
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CASE F

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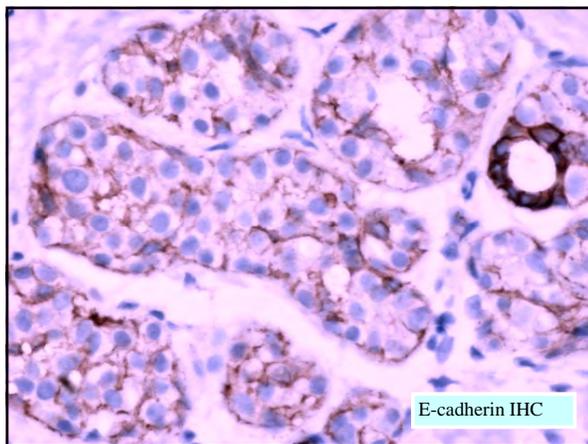
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**Literature Summary:  
Correlation of E-cadherin  
Expression as a Prognostic Factor**

- 5 papers report lack of expression as a predictor of poor outcome.
- 7 papers report no significance.
- 4 papers report expression as a predictor of poor outcome prognosticator.

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E-cadherin status in breast cancer correlates with histologic type but does not correlate with established prognostic parameters.

*Am J Clin Pathol (United States), Mar 2006, 125(3) p377-85*

- "Statistically a correlation of EC loss with a positive diagnosis of ILC was found but there was no correlation with any prognostic tumor variables."
- "EC is helpful in classifying cases with indeterminate histologic features. EC loss is uncommon in non-lobular carcinomas with no correlation to currently established prognostic variables."

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Location of our sign-out  
microscopes in surgical pathology  
in San Diego

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Case 2:

- History: 60 y/o male with 3.1 cm partially cystic right breast mass with soft, tan cut surfaces.

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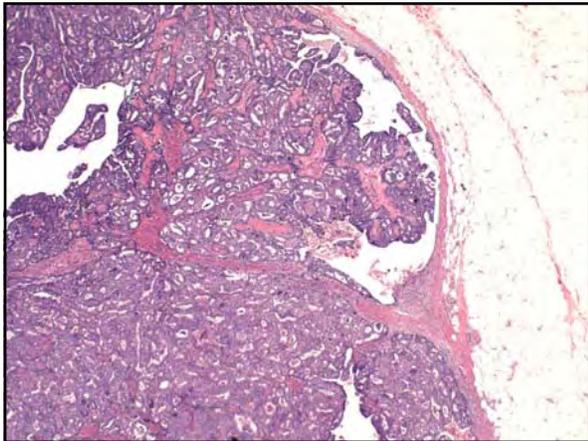
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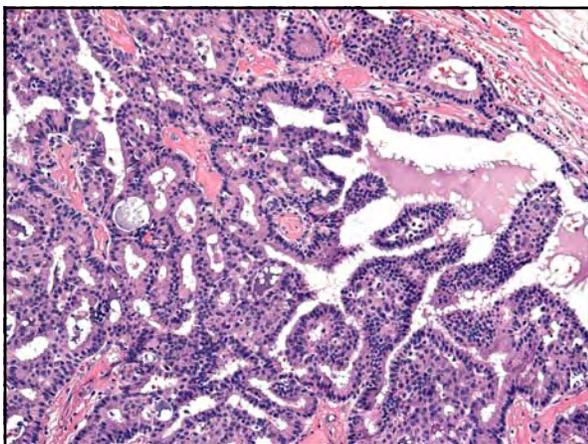
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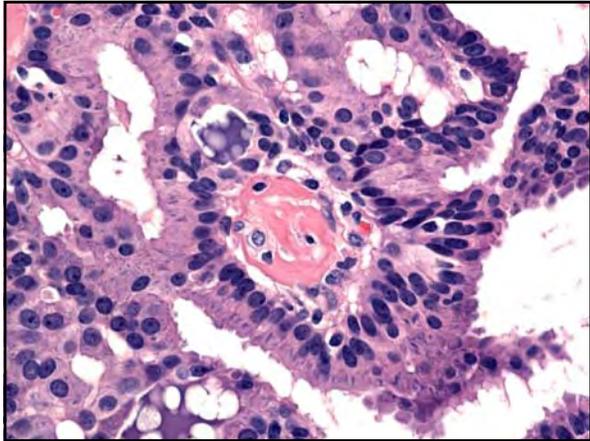
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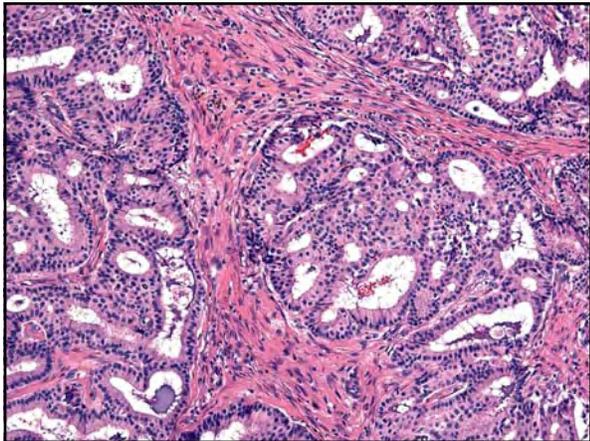
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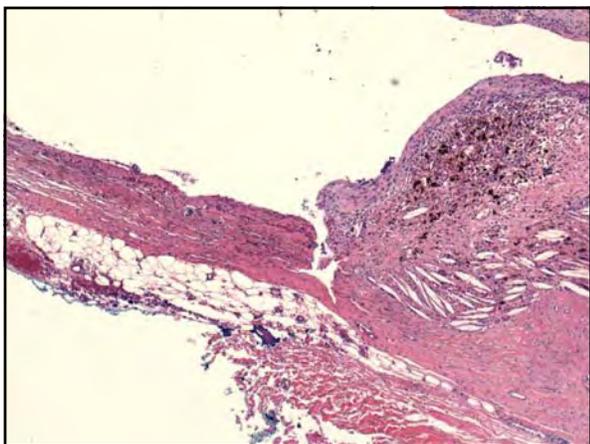
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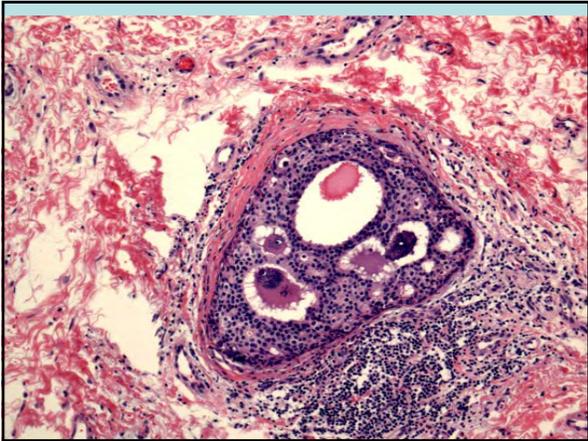
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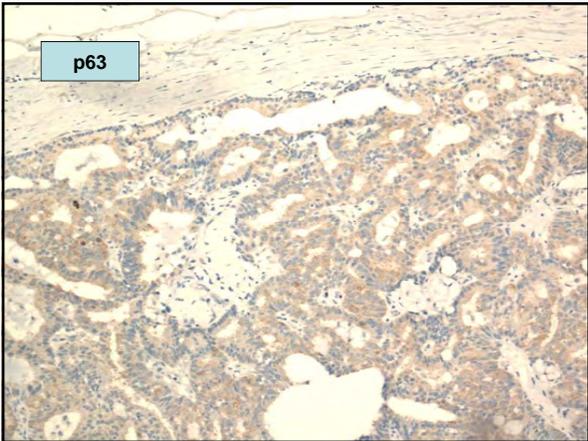
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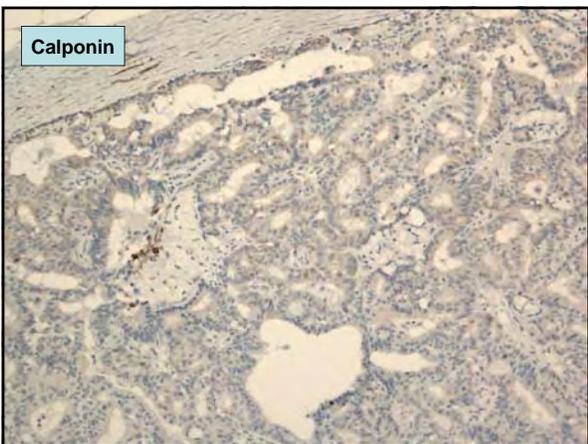
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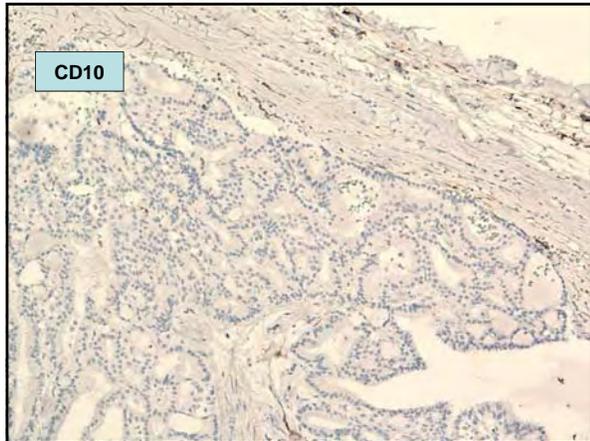
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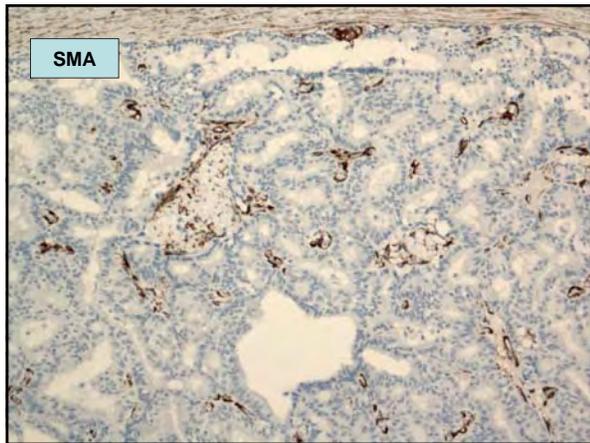
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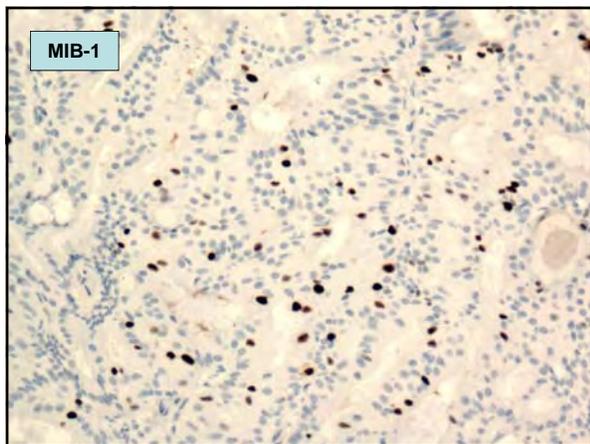
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**CASE 2 - Diagnosis:**

Intracystic Papillary Carcinoma  
with Adjacent Low-grade DCIS.  
(Encapsulated Papillary Carcinoma)

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**Intracystic Papillary Carcinoma**

- IPC "uncommon" breast tumor.
- Elderly patients (median ~70 yrs, range 27 to 99);
- Discrete, circumscribed solitary masses (usually central & subareolar)
- At least 1 cm diameter (Carter defined).
- ~3.5% of IPC cases occur in men.

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**Carter et al. *Cancer* 1977 & 1983**

- Carter et al. among first to report this tumor.
- 41 cases, mean age 63 yrs (range 42-87).
- Mean size 3.5 cm (range 1-14 cm).
- Cystic & encapsulated; none infiltrating.
- Adenocarcinoma projected into cystic cavity.
- Bound by fibrosis, often recent or old hemorrhage, chronic inflammation.
- Wall may or may not have epithelium.

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**Carter et al. Cancer 1977 & 1983**

- All had papillary pattern.
- 56% had a cribriform pattern.
- 37% had solid areas.
- Cribriform + solid areas may predominate.
- Low-grade nuclei in 1/3<sup>rd</sup>.
- Spindle cells in 1/4<sup>th</sup>.
- Necrosis in 32%.

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- DCIS extended beyond cyst in 46% & considered IPC with DCIS.
- Pts with pure IPC had no LN mets or recurrences.
- ~50% with adjacent DCIS recurred.
- 15 separate pts, who had IPC & truly invasive carcinoma, had ~73% incidence of DCIS & 2 had positive axillary LNs & eventually DOD.

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**Solorzano et al. Am J Surg. 2002;184:364-8.**

- Identified 3 patient groups:
  - IPC alone (n=14),
  - IPC with ductal carcinoma in situ (DCIS)(n=13),
  - IPC with invasion with or without DCIS (n=13).
- Recurrence-free or overall survival of IPC did not differ between the 3 groups regardless of therapy!
- Disease-specific survival was 100%.

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**Grabowski et al. Cancer 2008**

- 917 IPC cases (California Tumor Registry), 47% only "CIS".
- 53% had invasion.
- 90% of invasive cases localized.
- At 10 yrs, pts with "CIS" & invasive disease had same survival (96.8% and 94.4%; P = 0.18).
- No significant difference in long-term survival of pts in the 2 subgroups of IPC.
- Thus, excellent prognosis for IPC whether diagnosed as in situ or invasive.
- The usual absence of axillary involvement and low recurrence rate after local excision suggests that wide local excision without axillary dissection is currently the treatment of choice for pure IPC.

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**IPC in Males**

- Up to 7.5% of all breast cancers in males.
- Presentation & pathology same as females.
- Japanese men, mean age in males is 68 yrs.
- Regardless of in situ or invasive status, excellent prognosis with adequate local therapy alone.
- Thus, manage pts with IPCs as currently managed (i.e., like pts with DCIS) and avoid categorization of such lesions as frankly invasive papillary carcinomas.

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**Collins et al. AJSP 2006**

- Studied 22 IPCs.
- 15 benign intraductal papillomas.
- IHC for 5 MEC markers.
- Smooth muscle myosin heavy chain, calponin, p63, CD10, & cytokeratin 5/6.
- All IPCs showed complete absence of MEC
- MEC layer detected around DCIS adjacent to IPC.
- Intraductal papillomas showed a MEC layer.
- Possibly, MEC layer attenuated by compression or encapsulated nodules of invasive papillary carcinoma.
- Authors favored "encapsulated papillary carcinoma (EPC)" over "intraductal papillary carcinoma"

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**Differential Diagnosis:**

1. Invasive papillary carcinoma, grade 1 of 3.
2. Infiltrating duct carcinoma, micropapillary type
3. Solid papillary carcinoma.
4. Intraductal papilloma.
5. Sclerosing papillary lesions:
  - scleroelastotic lesion simulating malignancy.
  - nonencapsulated sclerosing lesion.
  - indurative mastopathy.
  - complex sclerosing lesion.
  - invasive epitheliosis.
  - radial scar.
  - duct adenoma (within sclerosing papillary lesion spectrum).

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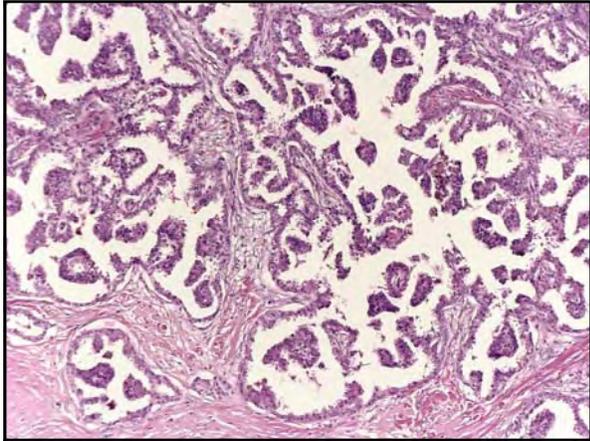
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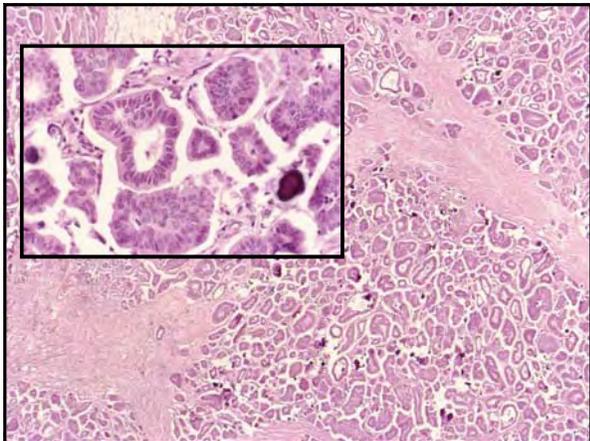
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Illustrative Example:

66 y/o female presents with a central fairly discrete breast mass.

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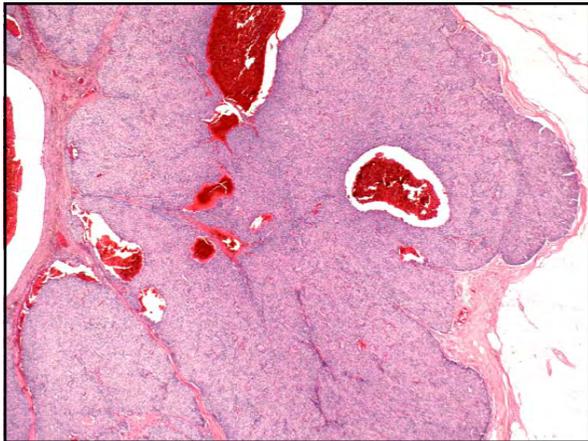
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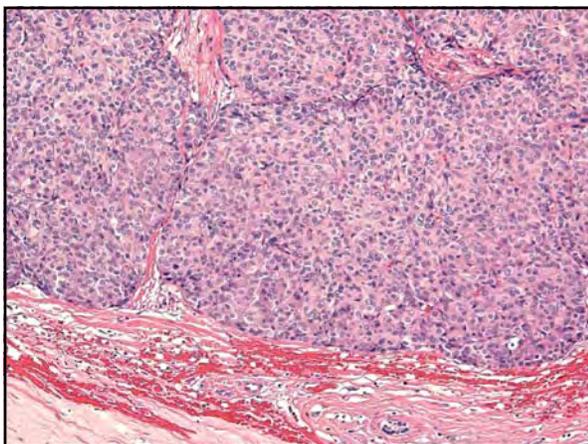
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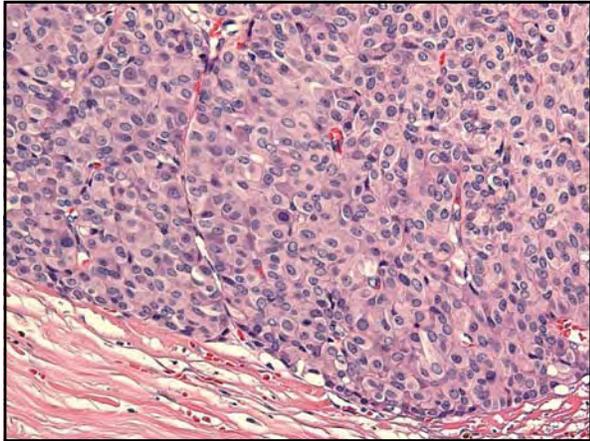
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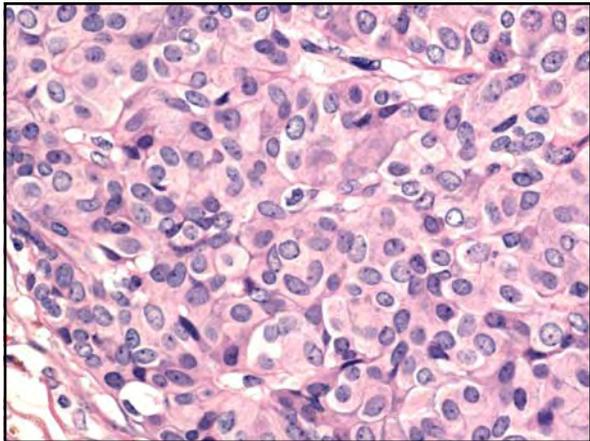
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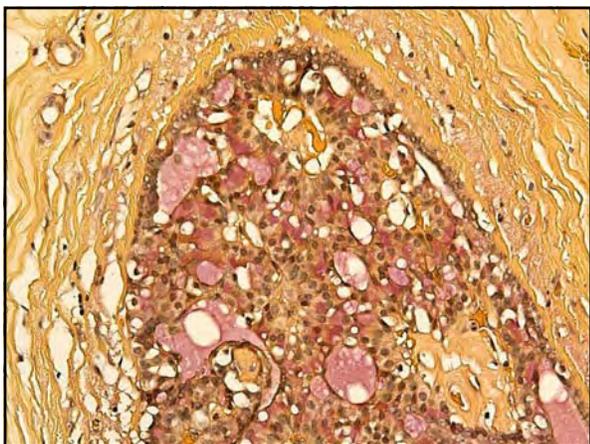
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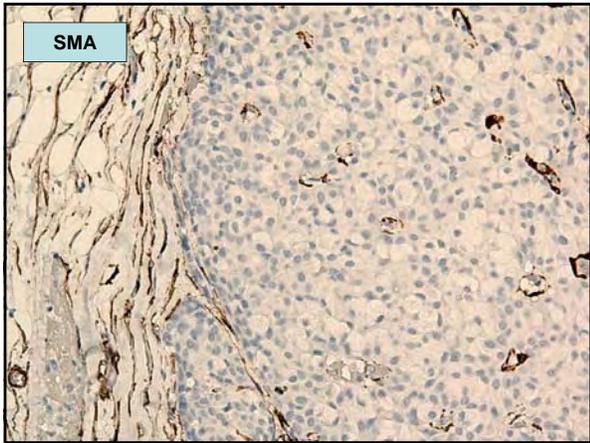
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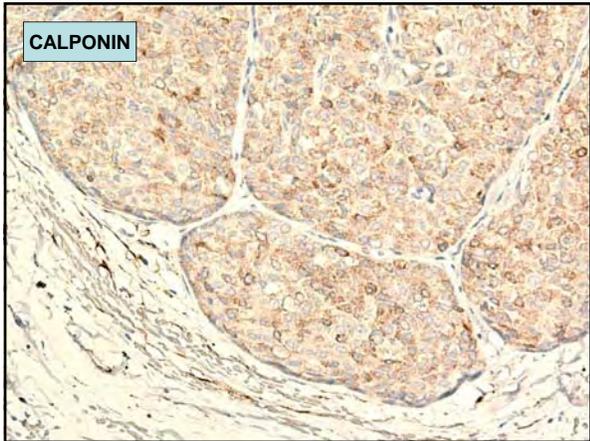
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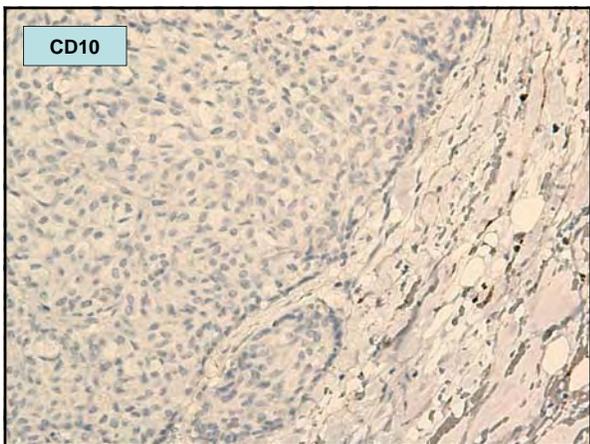
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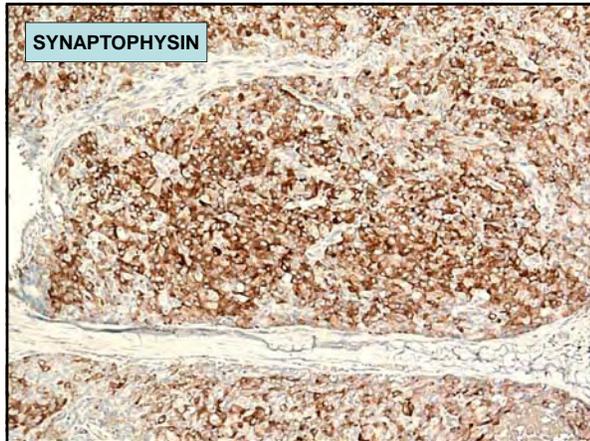
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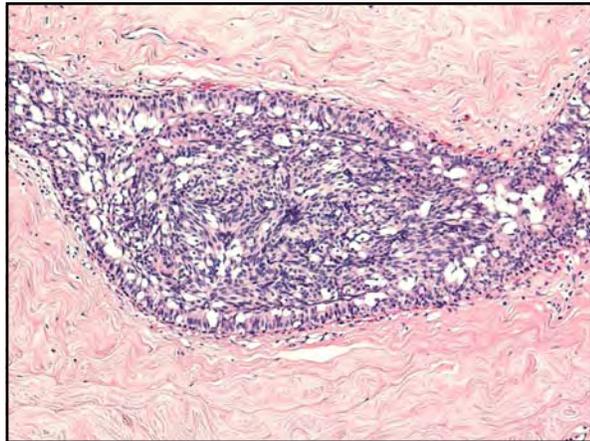
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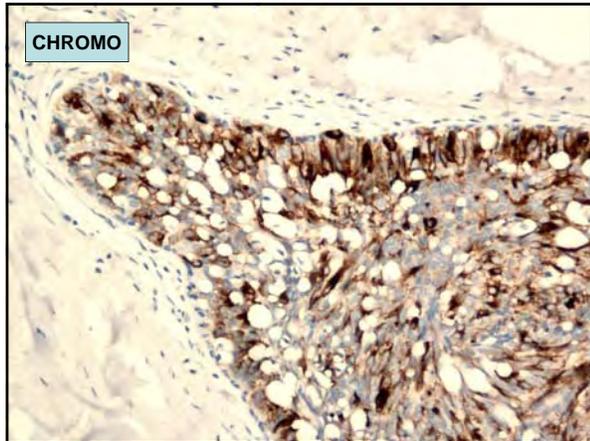
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**Solid Papillary Carcinoma (SPC)**

- Sometimes the “intracystic” proliferation is so dense that the basic papillary or cribriform patterns is obscured (i.e., becomes solid).
- Such tumors may be so-called solid papillary carcinomas (SPCs).
- SPCs uncommon, circumscribed, large cellular nodules separated by bands of fibrosis.
- Sometimes neuroendocrine differentiation
- Often mucin secretion (focal to marked), may be extravasated mucin or mucinous carcinoma.
- Can have other types of invasive carcinoma.

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**Nassar et al. (AJSP 2006;30:501-7.)**

- 58 with SPC component (SPCs), mean f/u, 9.4 yrs.
- Mean age 72 years, tumor sizes 0.3 to 15 cm.
- Carcinomas divided into 3 groups:
  - 1) SPC only (~33%),
  - 2) SPC with extravasated mucin (~10%),
  - 3) SPC with invasive components (~60%)
    - neuroendocrine-like (~30%),
    - colloid (~25%),
    - ductal, not otherwise specified (~15%),
    - lobular (~3%),
    - tubular (~3%),
    - mixed (~25%).
- All estrogen receptor positive and ~90% grade 1.
- Axillary LNs positive in 13% (all had invasive tumor).

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Nassar et al. (AJSP 2006;30:501-7.)

- Local recurrence in 5 pts, all with invasive carcinoma.
- ~12% died of tumor in 1 to 4 yrs (mean, 2.3 yrs).
- None died of noninvasive SPC.
- 5 of 6 patients who DOD had invasive components.
- Sixth pt died with "metastatic signet-ring cell carcinoma" at 10 years had SPC with extravasated mucin, but the SPC lesion had signet-ring cells.
- **Conclusion: SPCs heterogeneous, arise in older pts, & have indolent behavior. LN & distant mets uncommon & limited to SPCs with (conventional) invasive components.**

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Differential Diagnosis:

4. Intraductal papilloma.
5. Sclerosing papillary lesions or proliferations:
  - scleroelastotic lesion simulating malignancy.
  - nonencapsulated sclerosing lesion.
  - indurative mastopathy.
  - complex sclerosing lesion.
  - invasive epitheliosis.
  - radial scar.
  - duct adenoma (? spectrum of sclerosing papillary lesions).

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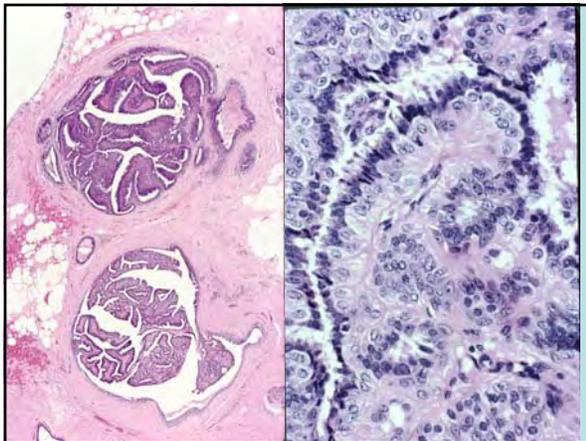
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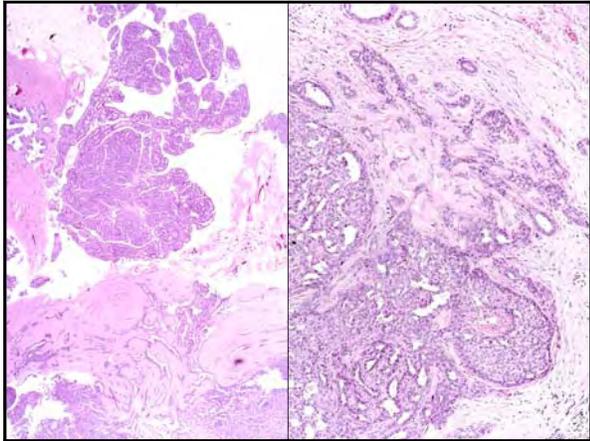
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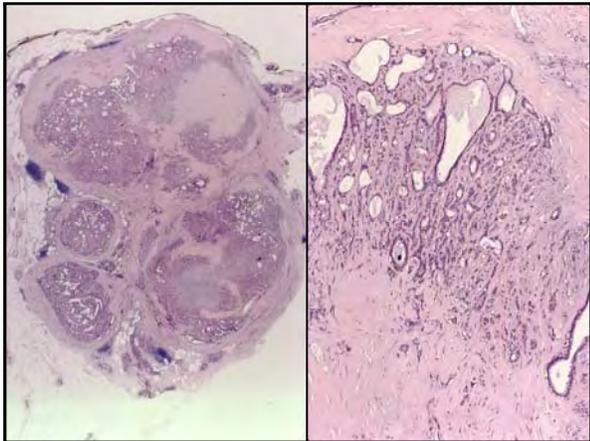
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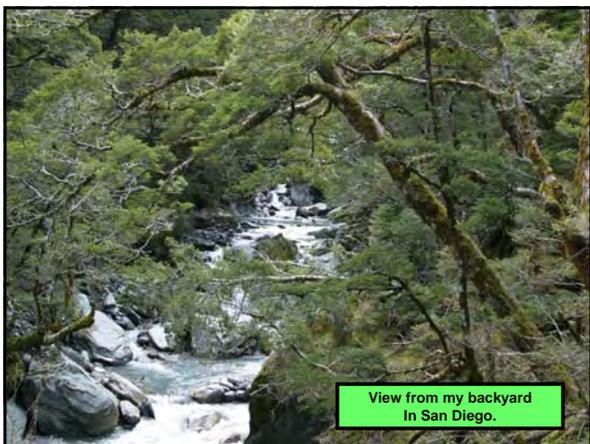
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## Special Types of Invasive Breast Carcinoma

Farnaz Hasteh, MD



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### Case 3 History

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

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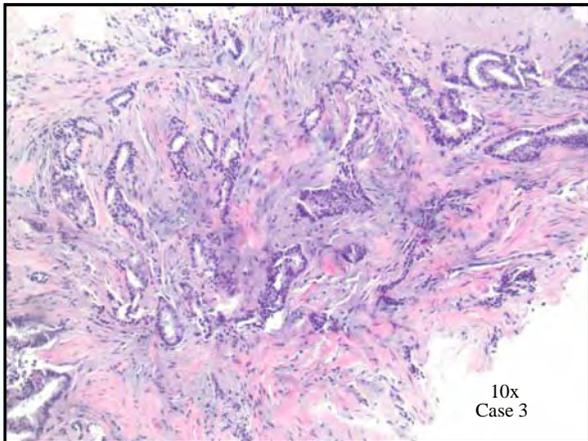
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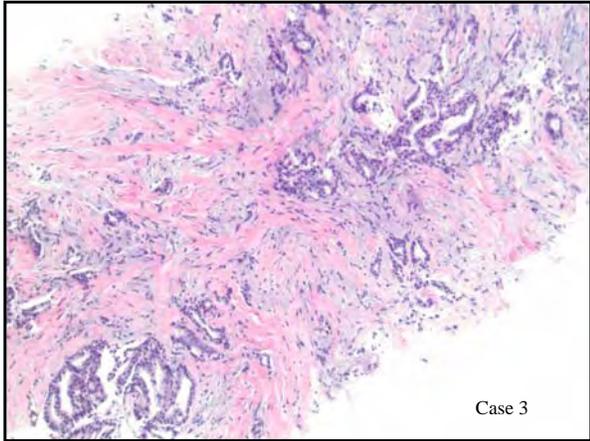
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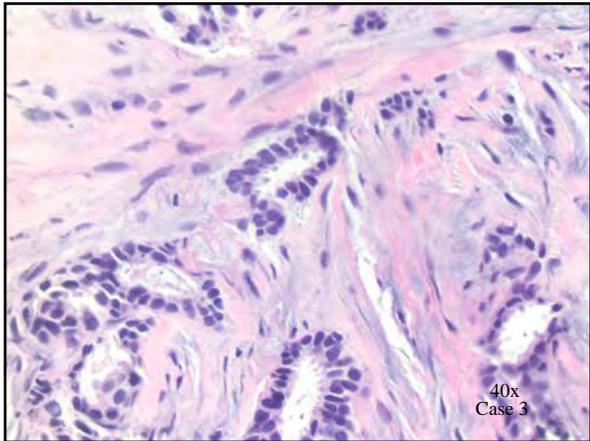
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**Tubular Carcinoma**

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### 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

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### 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

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### 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)

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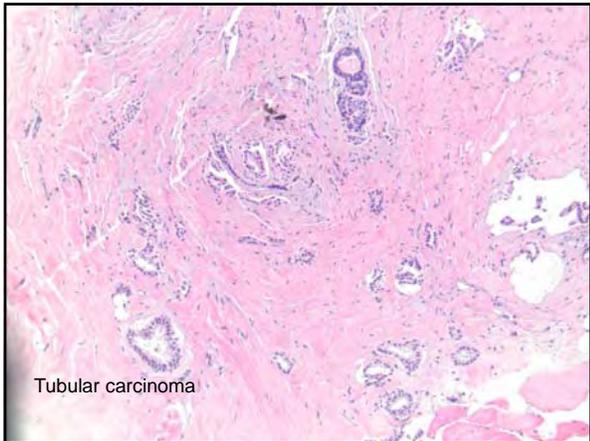
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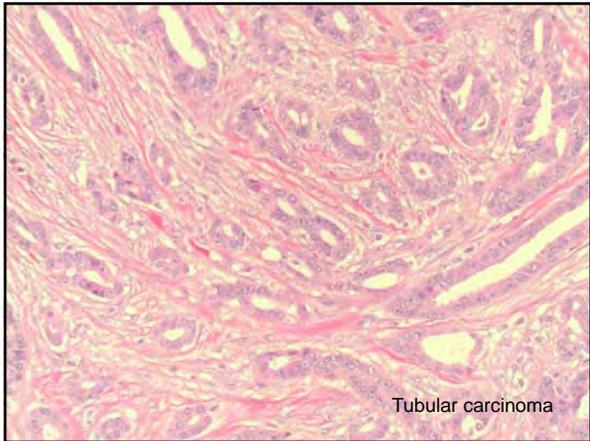
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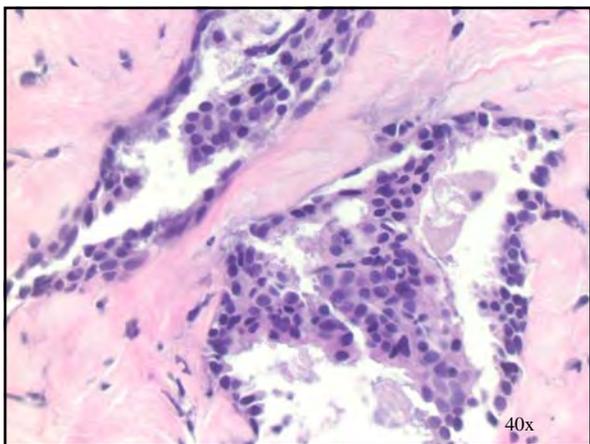
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### Tubular carcinoma Histopathology

- Single cell layer (cuboidal or columnar)
- Nuclear grade I
- No mitosis or rare one
- Inconspicuous nucleoli
- Cytoplasmic snouting
- Abundant desmoplasia stroma
- ER and PR always positive
- EM: no basal lamina or discontinuous one

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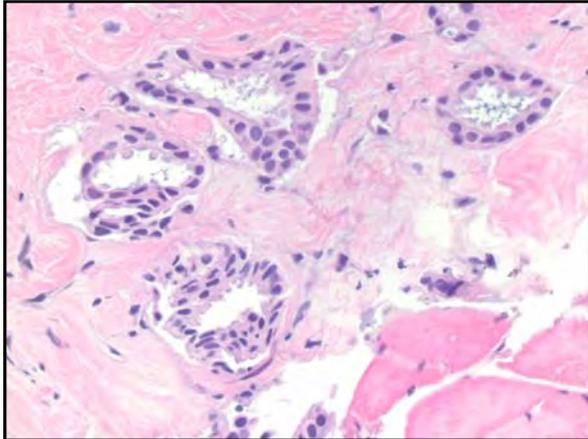
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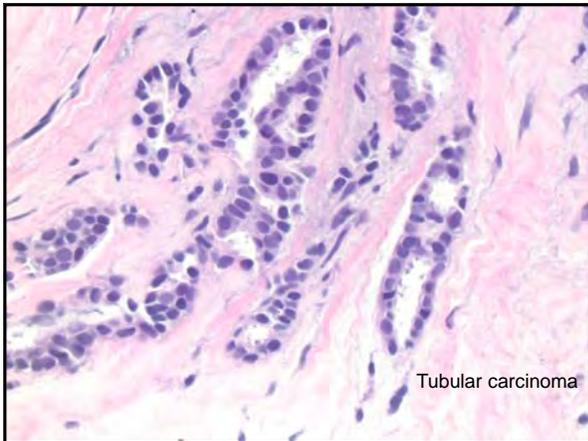
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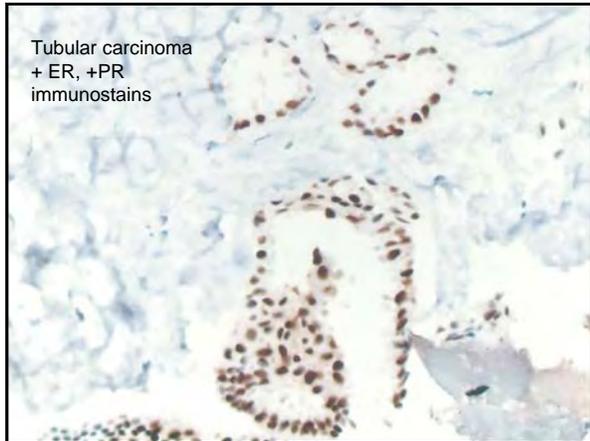
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### Tubular carcinoma Histopathology

- 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)

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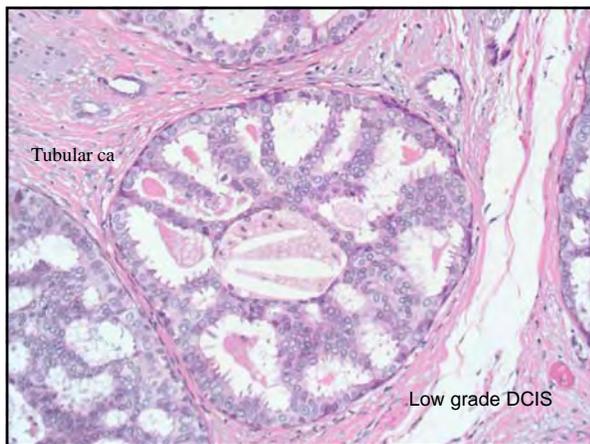
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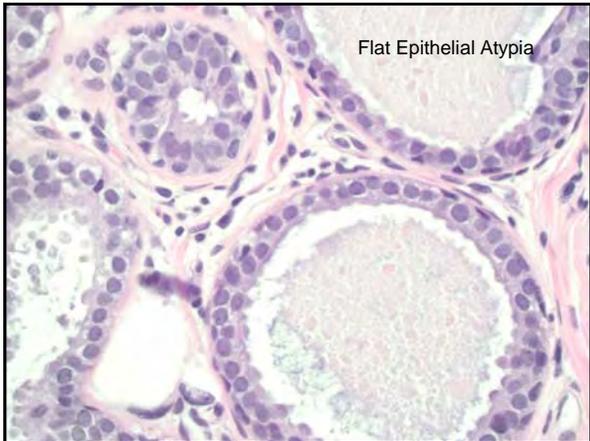
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### When should we call it tubular carcinoma?

- Majority of the tumor should be tubular carcinoma
- WHO recommends  $\geq 90\%$

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### Mixed Carcinomas

- It is usually seen with cribriform carcinoma
  - Invasive tubular/cribriform carcinoma
  - Excellent prognosis
- When more than 10% of tumor is Inv,NST
  - Mixed ductal and tubular carcinoma
  - Prognosis depends on the ductal component
- It can be seen with classic lobular carcinoma
  - Invasive tubulolobular carcinoma
  - Prognosis is still good!
  - More multifocal

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### Differential Diagnosis

- Benign mimics
  - Sclerosing adenosis
  - Microglandular adenosis
  - Radial scar (sclerosing papillary lesion)
  - Duct adenoma
- Panel of myoepithelial markers (p63, CD10, calponin, SMA)
- Special stain for basement membrane (reticulin and PAS)

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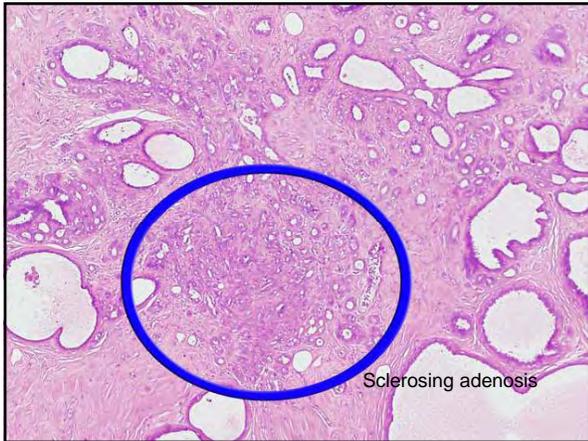
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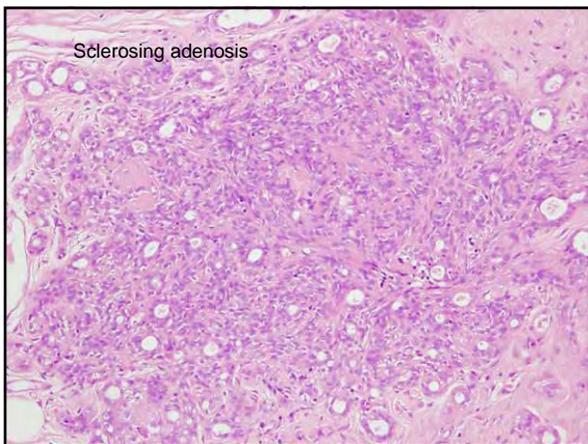
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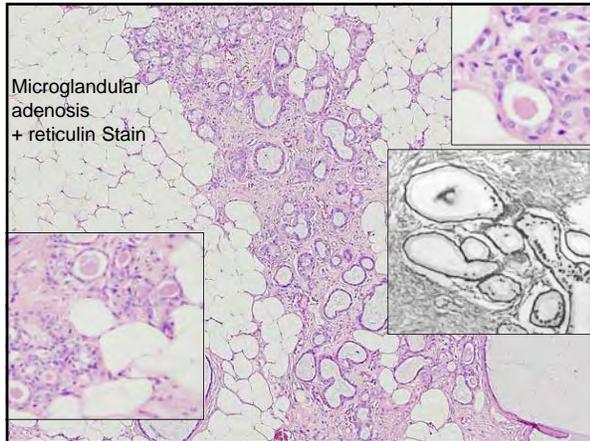
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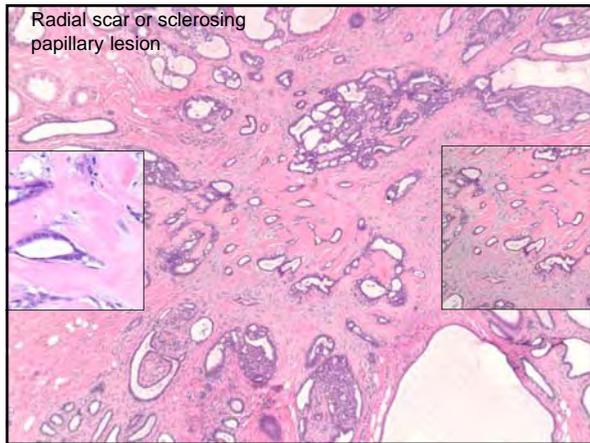
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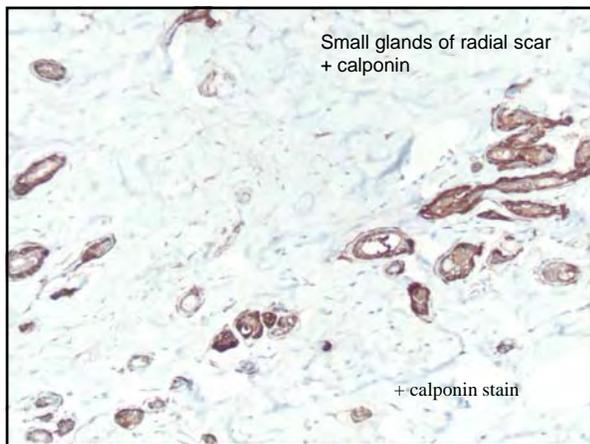
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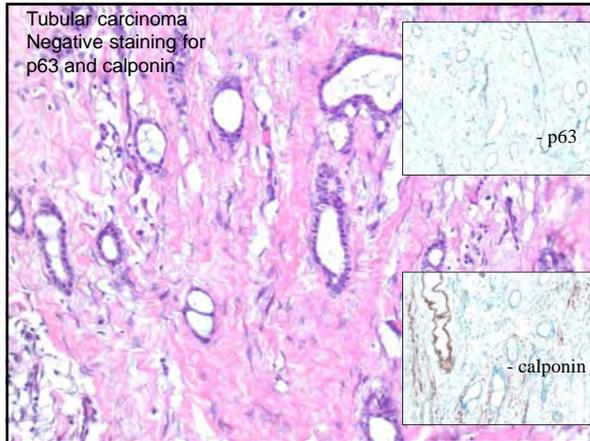
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### Differential diagnosis Tubular carcinoma

- Other carcinomas
  - Mixed ductal and tubular carcinoma
  - Invasive tubulolobular ca
  - Invasive well differentiated ductal carcinoma, NST, mBR grade I

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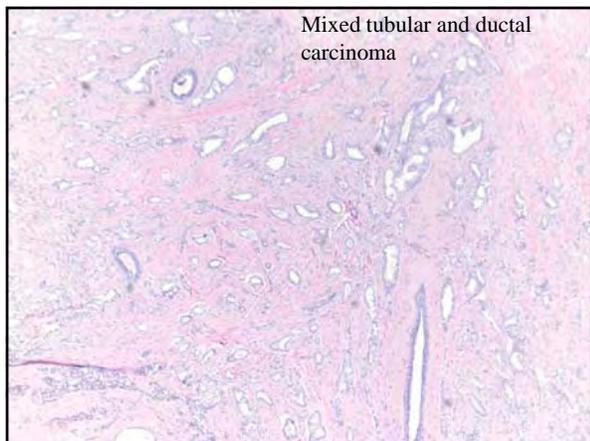
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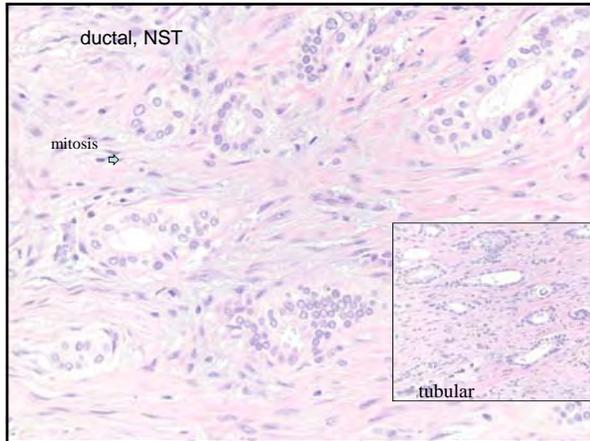
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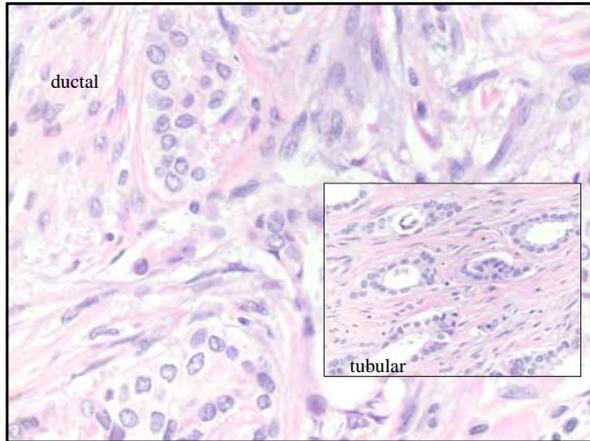
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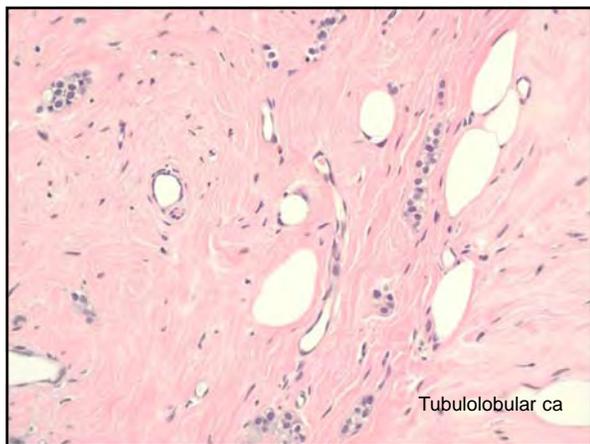
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**Prognosis  
Tubular carcinoma**

- Excellent
- Long term prognosis in some studies is similar to the healthy women without breast ca
- 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

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**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 9%)

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**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

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### 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 possibly in rare cases with axillary metastasis or if there is cancer in the other breast

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### Summary

- Special type of breast carcinoma
- Strict histological criteria
- Pure form (>90 % or close to 100%)
- 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

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### Pearls of Pathology

- Breast, right side, biopsy
  - Tubular carcinoma (mBR grade I).
  - Low grade ductal carcinoma in-situ, see comment.
- Breast, right side, lumpectomy
  - Tubular carcinoma (mBR grade I), see synoptic report.
  - Low grade ductal carcinoma in-situ, see comment.
  - Surgical margins free.
  - C/w pT1cN0

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### Breast Synoptic Report

- **-Invasive tumor type:** tubular
- **-Invasive tumor size:** 1.1 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 [ $>$  1cm]
- **-Lymph nodes positive /total lymph nodes sampled:** negative (0/3)
- **-AJCC/UICC stage:** pT1cN0
- **-Her2/neu status:** negative
- **-Hormone receptor status (ER/PR):** positive (3+, 100%)
- **-Additional comments:** biopsy site changes present

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### 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

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### Cribriform carcinoma Clinical presentation

- Age range: 19-86 year
- Incidence: 0.8-3.5% of breast ca (WHO Classification)
  - » ~ 6% of breast ca
- Present as a mass or an incidental finding
- Spiculated mass with microcalcification by imaging

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### 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
- Mucin positive secretion
- Often mixed with <50% tubular ca

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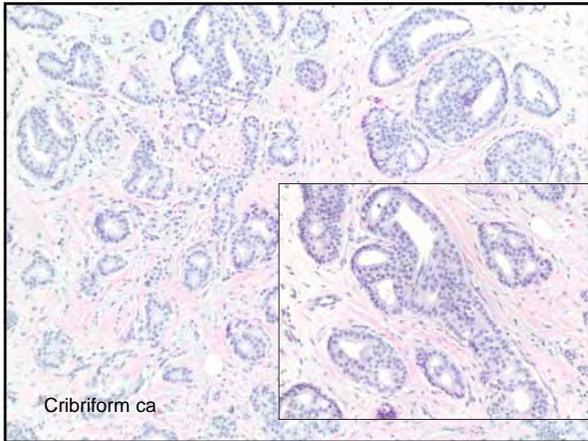
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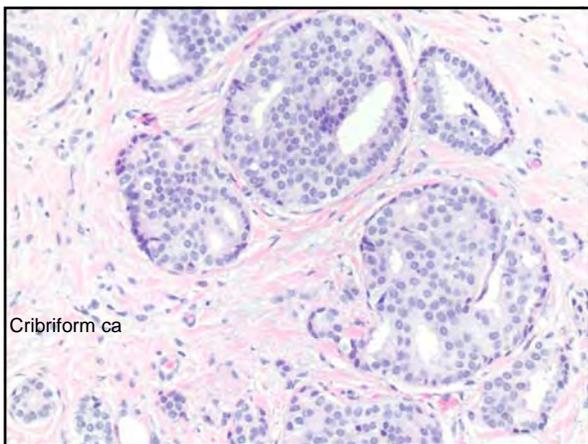
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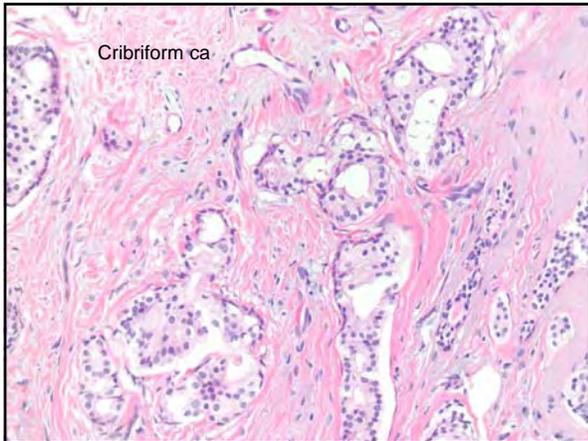
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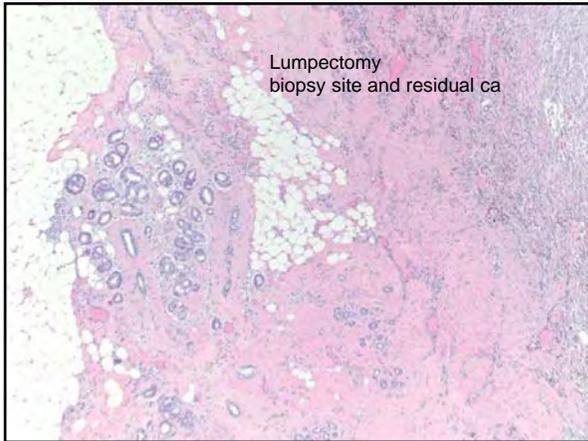
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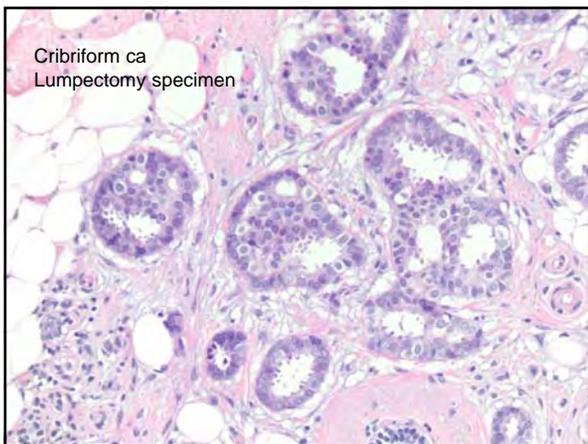
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### Cribriform carcinoma Prognosis

- 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)

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### 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

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### Cribriform carcinoma Differential diagnosis

- Cribriform DCIS
  - +Myoepithelial cells
  - Rounded even contour
  - Absence of mucin positive material
- Carcinoid tumor
- Adenoid cystic carcinoma

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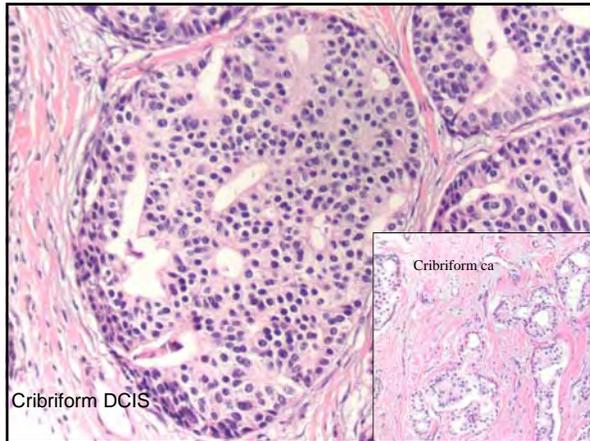
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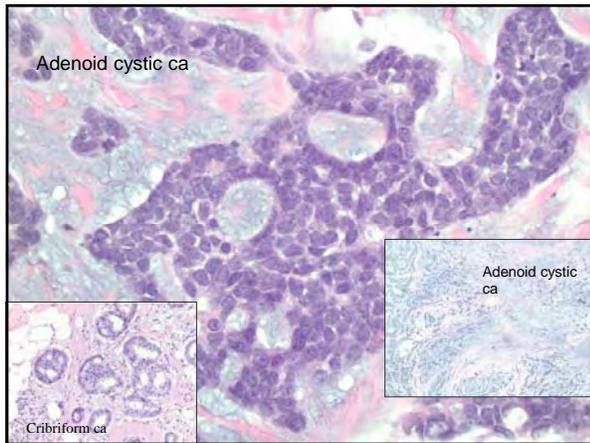
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### Cribriform Carcinoma Summary

- An invasive special type of breast carcinoma with excellent prognosis
- Usually associated with tubular carcinoma
- Cases with component of another carcinoma: Mixed type of carcinoma
- Exclude the possibility of extensive DCIS
- ER and PR always positive

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## Cribriform Carcinoma Pearls of Pathology

- Breast, left, needle core biopsy
  - Invasive cribriform carcinoma (nuclear grade I), see comment.
  - Synoptic Report
    - Invasive tumor type: invasive cribriform
    - 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
    - -Hormone receptor status (ER/PR): positive 3+, 100%

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## Case 4

- 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

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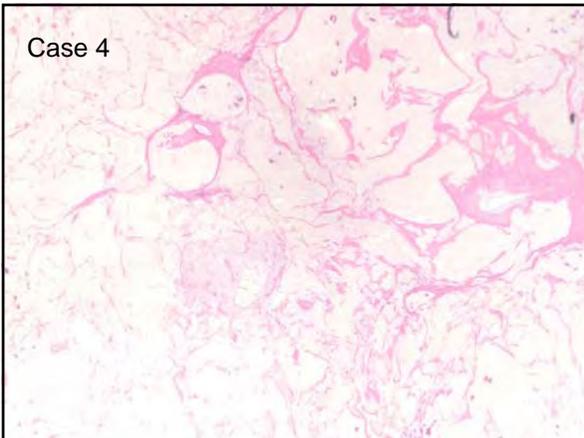
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Case 4



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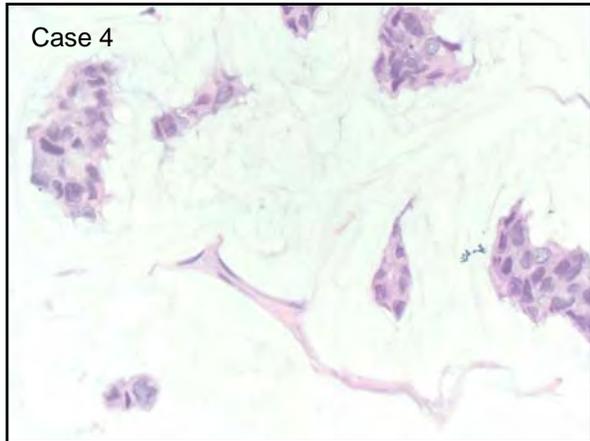
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## Mucinous Carcinoma

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- ### Mucinous carcinoma
- Large amount of extracellular mucin (>1/2)
  - Mucin is grossly and microscopically seen
  - We call it when it is pure form of mucinous carcinoma
  - Otherwise diagnosis should be:
    - Mixed ductal (NST) (?mBR) and mucinous ca
    - Invasive ductal carcinoma (NST) (? mBR) with marked mucinous differentiation

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### Clinicopathological features Mucinous carcinoma

- 2% of all breast ca (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

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### 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 (>10% of tumor is non-mucinous or if the non-mucinous component is poorly diff)
  - Mixed subtypes
  - Usually more high grade tumors

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### Histopathology Mucinous carcinoma

- Mucin is PAS positive
- Intracellular mucin is rare
- Signet ring cell may suggest lobular carcinoma
  - Aggressive ca
- DCIS present in 75% of cases
  - Any pattern of DCIS
  - Like intracystic papillary ca
  - Mucinous differentiation is seen in DCIS

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**Histopathology**  
**Mucinous carcinoma**

- Pure mucinous carcinoma
  - Cellular
  - Hypocellular
- 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

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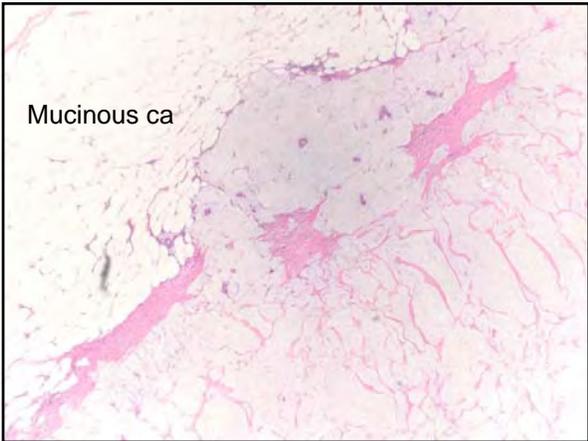
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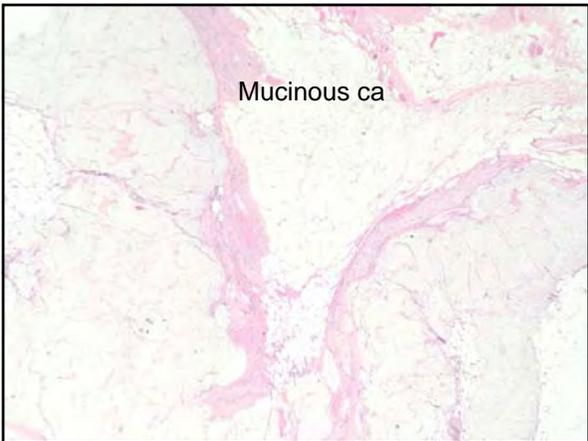
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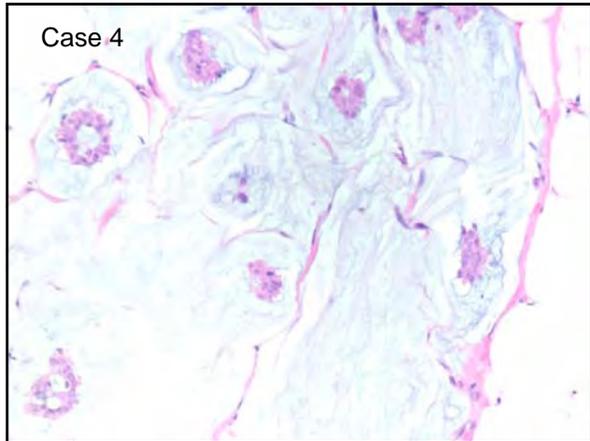
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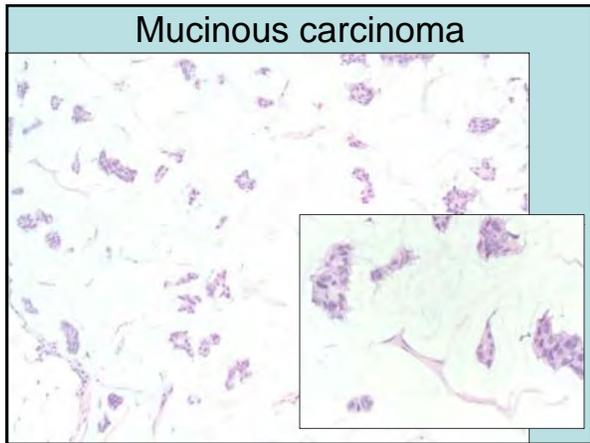
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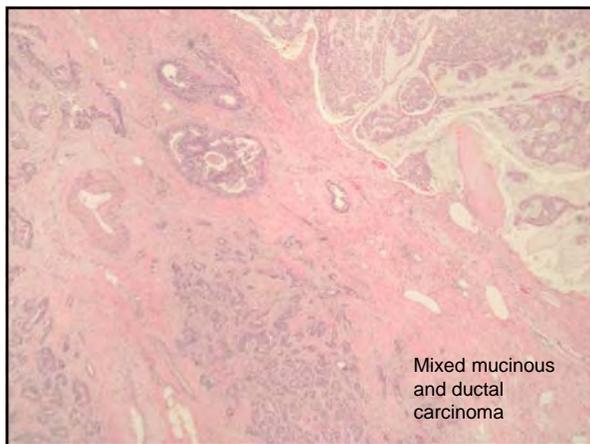
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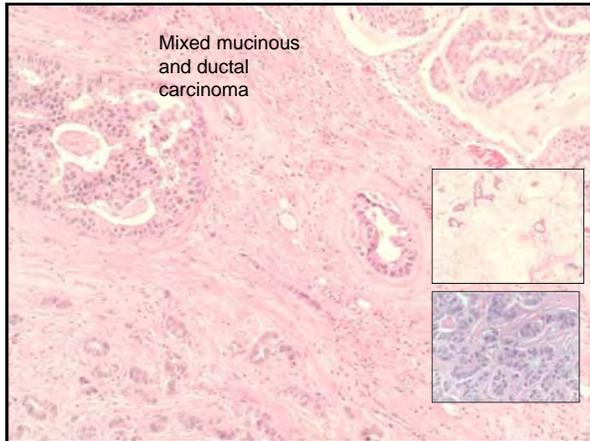
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### Prognosis Mucinous carcinoma

- Pure form has favorable prognosis
- Pure forms are smaller than the mixed ones
- Negative axillary node metastasis 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

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### 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%

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### Treatment

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

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### Differential Diagnosis

- DCIS with extravasated mucin
  - No epithelial component is present in mucin
  - Prior FNA and biopsy!
- 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

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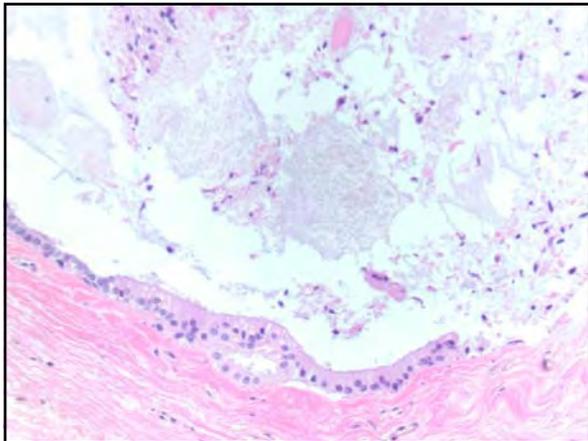
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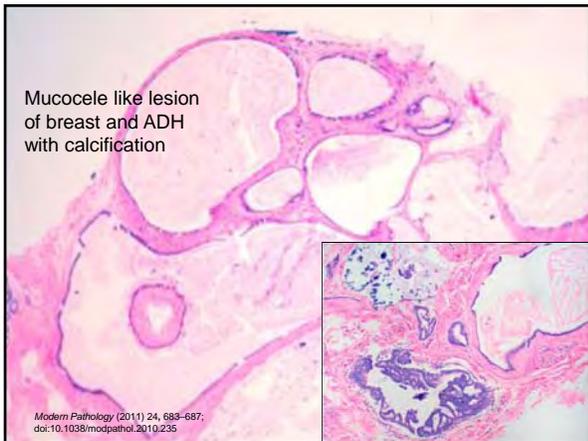
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### Mucocele like lesions

- 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

• Modern Pathology (2011) 24, 683–687; doi:10.1038/modpathol.2010.235

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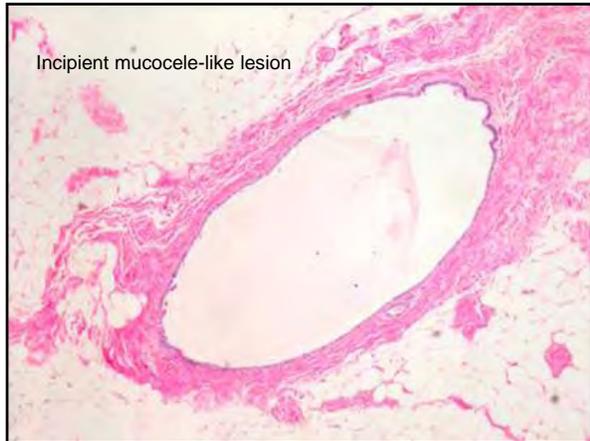
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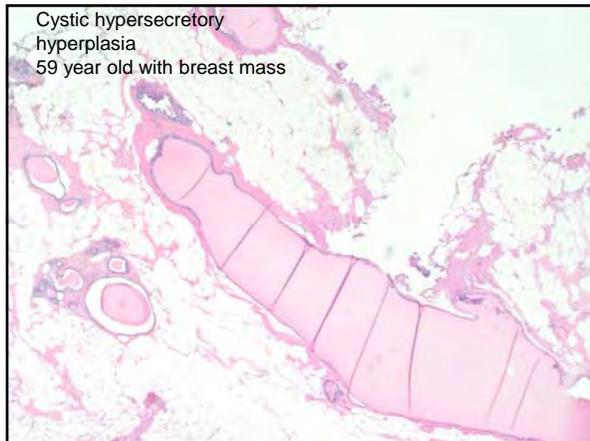
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**Summary**  
**Mucinous carcinoma**

- Distinct entity and specific type of breast carcinoma
- Pools of mucin with floating tumor cells
- Favorable prognosis in pure form (low stage)
- Mixed mucinous and ductal with presence of any amount of invasive ductal (NOS)
- ER and PR positive
- Important benign lesions in the DDx

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### 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 with calcifications, see comment.*

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Thank you for participating!



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### Case 5

Case History:

A 50 y/o female with round firm breast mass.

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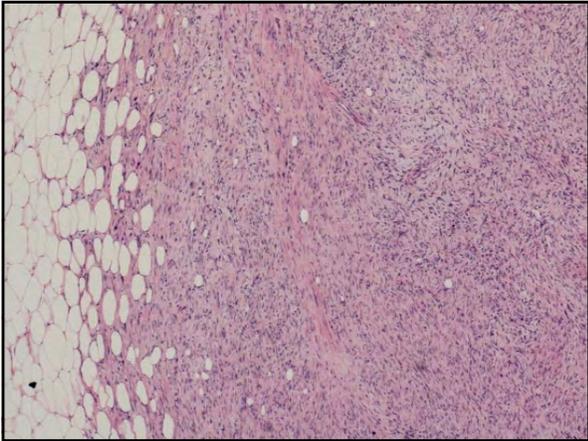
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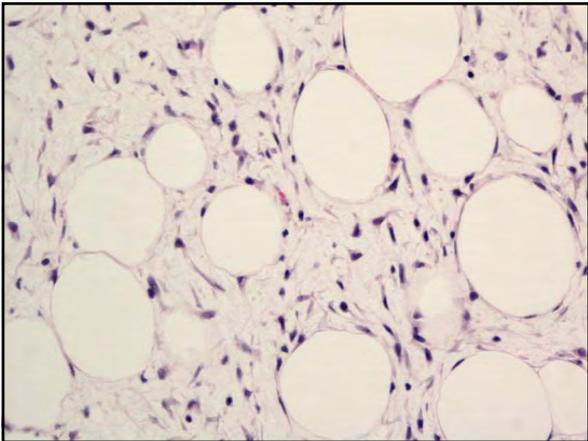
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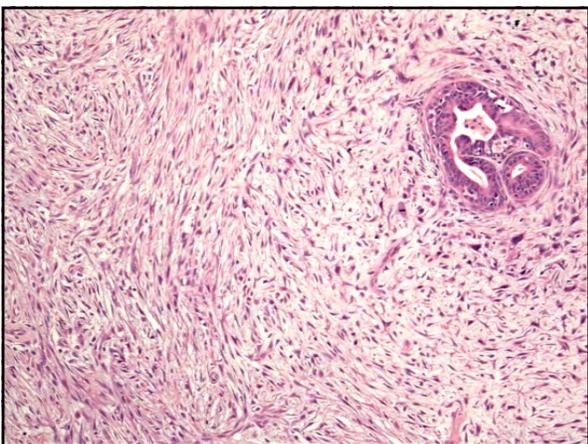
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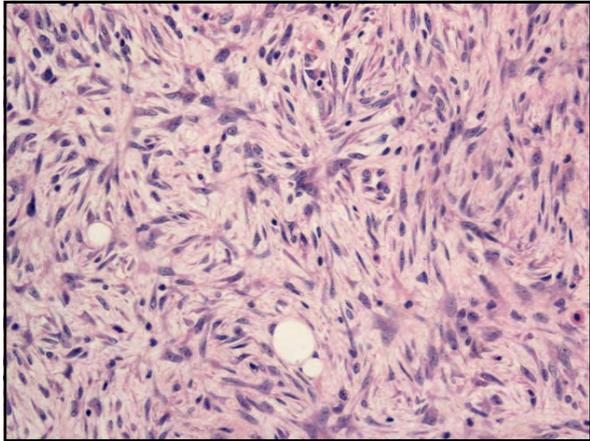
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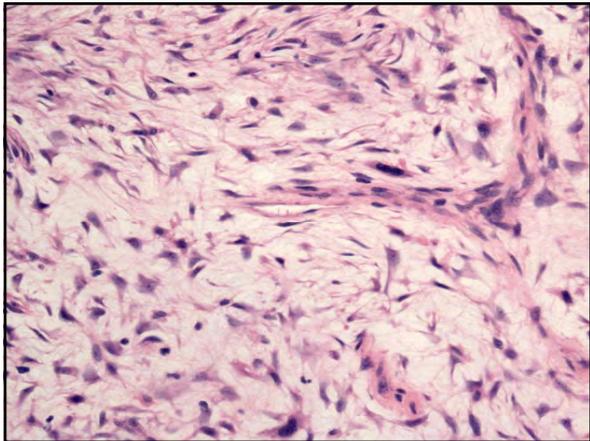
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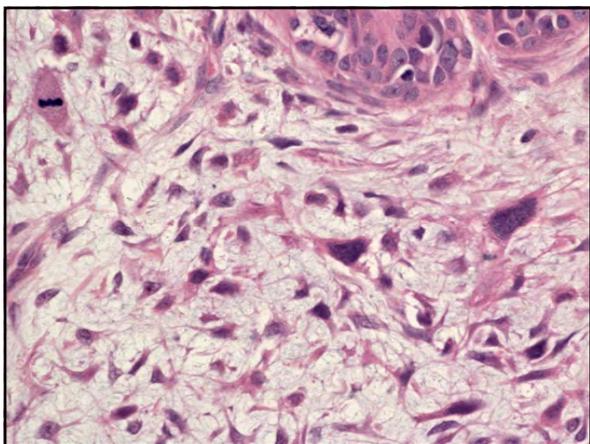
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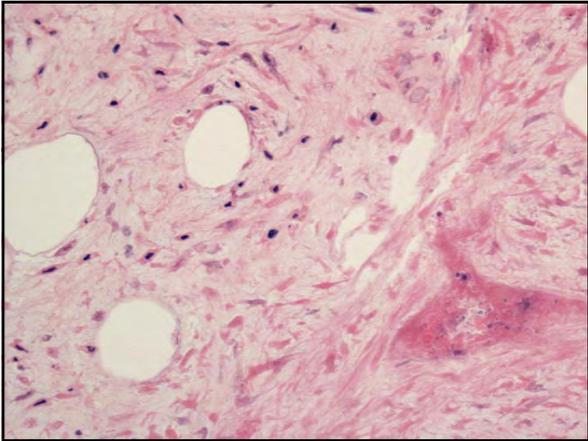
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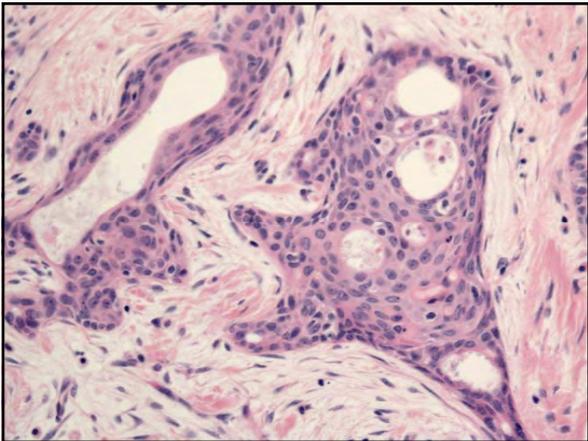
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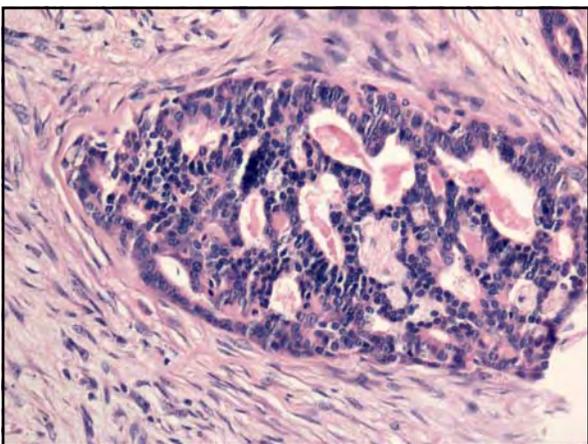
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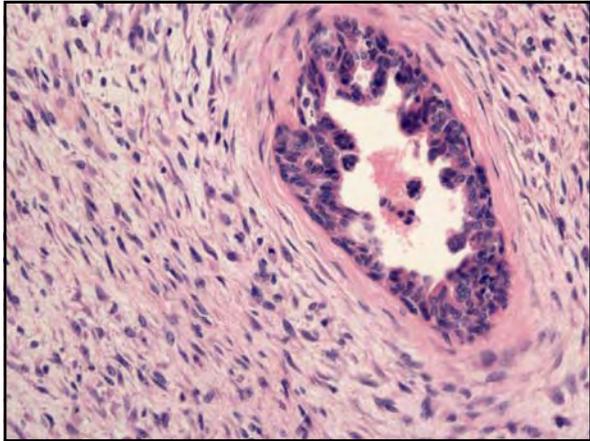
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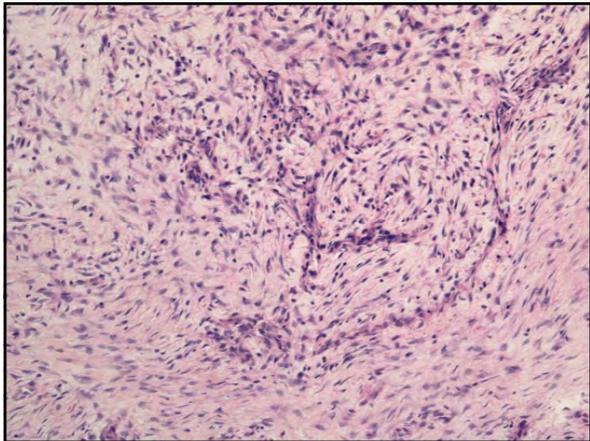
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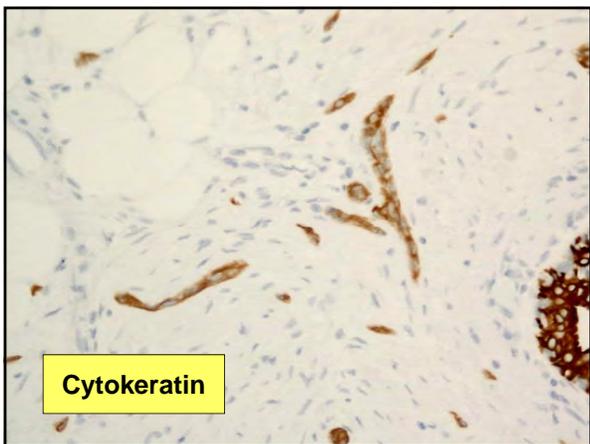
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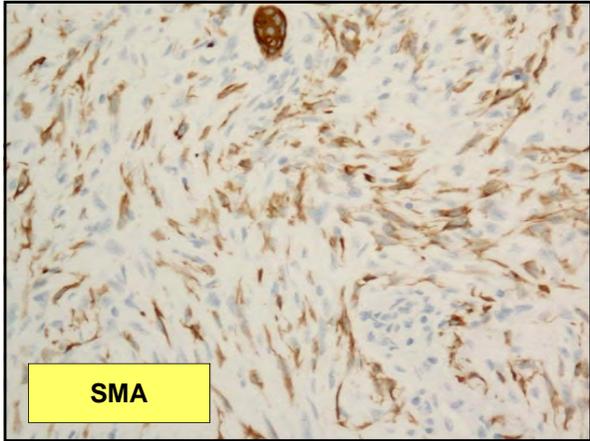
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**Dx:  
Spindle-cell  
Breast Carcinoma  
(Fasciitis-like)**

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**Metaplastic  
Breast  
Carcinoma**

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**WHO Classification of Metaplastic Carcinomas**

**Pure Epithelial Carcinoma**

- Squamous Carcinoma.
  - Large-cell type
  - With spindle-cell metaplasia (with or without acantholysis)
- Adenocarcinoma with spindle-cell metaplasia.
- Adenosquamous ("Mucoepidermoid") Carcinoma.

**Mixed Epithelial and Mesenchymal Carcinoma (Carcinosarcoma)**

- Carcinoma with chondroid differentiation.
- Carcinoma with osseous differentiation.
- Carcinoma with rhabdomyosarcomatous differentiation.

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- *Pathol Int.* 2009 Sep;59(9):676-80.
- **Metaplastic breast carcinoma with melanocytic differentiation.** [Bendic A, et al.](#)
  - Only seven cases reported so far in World literature.
  - Initial Dx: "Collision Tumor Of Invasive Ductal Carcinoma And Metastatic Melanoma."
  - 6 years follow up: pt alive and healthy, without local recurrence or metastases.
  - Final Dx: Metaplastic Carcinoma With Melanocytic Differentiation.

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**Illustrative Case #1**

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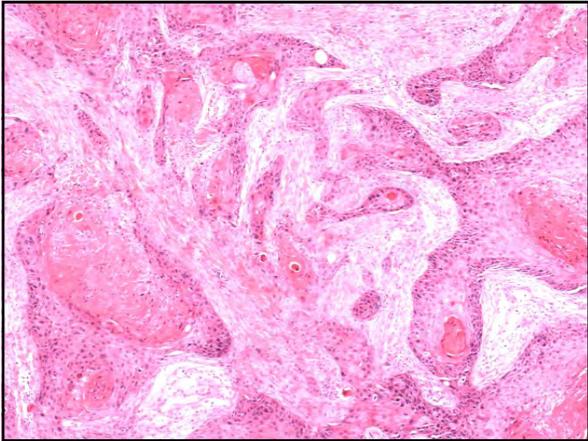
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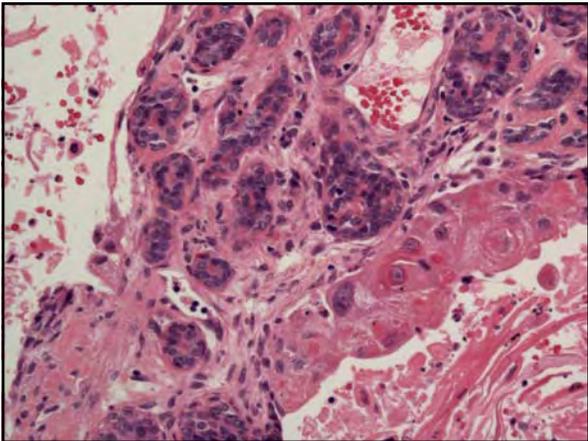
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**Dx:  
Pure  
Squamous  
Carcinoma**

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**Illustrative  
Case #2**

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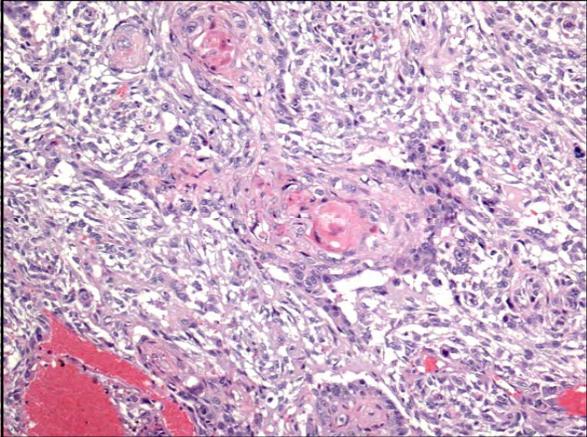
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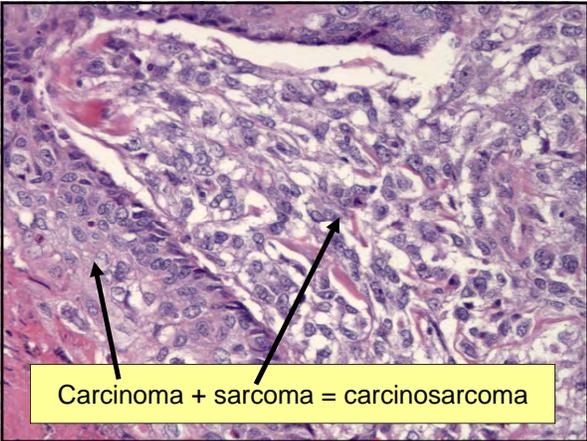
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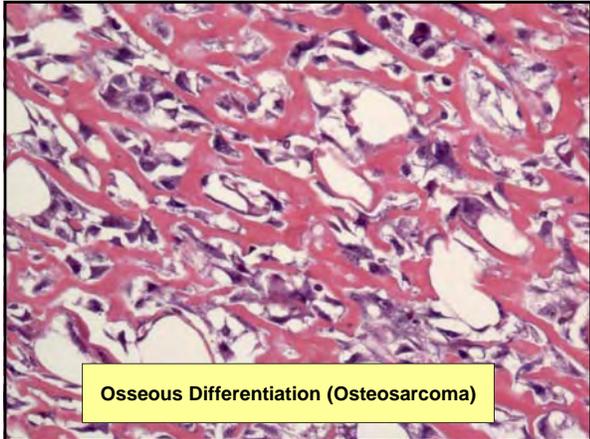
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**Dx:**  
**Carcinosarcoma**  
**with**  
**Osseous Differentiation**  
**(Osteogenic Sarcoma)**

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**Prognosis of Metaplastic Carcinoma**  
Rayson, et al. (Mayo Clinic). *Annals of Oncology* 10:413-419, 1999.

- 3-year DFS was 40%.
- 3-year OS was 71%.
- 87% of MBC patients were node negative.
- 10 chemo regimens used for metastatic disease - one partial response.
- No responses to tamoxifen in 4 patients with metastatic disease.
- Median survival after development of metastases was 8 mos.
- **Conclusions: Despite presenting more commonly as node-negative disease, DFS and OS in MBC is decreased compared to typical adeno-carcinomas. Systemic therapy also appears to be less effective.**

- 5-year OS for matrix-producing carcinoma roughly 68%.
- 5-year OS for invasive breast carcinoma (all types) roughly 75%

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### Metaplastic breast carcinomas (MC)

- ER/PR/HER2 “triple negative” (TN) (80% of cases)
- 3-yr disease-free survival (DFS) 75.5%
- 3-yr overall survival (OS) 86.3%
- 3-year OS TNMC 93.4%; NTNMC 58.2% (P = 0.007)
- With respect to DFS: no survival difference
- Contrary to that for invasive ductal carcinoma
- Jpn J Clin Oncol. 2009 Nov 3. [Epub ahead of print]

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### Spindle-cell Carcinoma of the Breast

- Most metaplastic cas clearly high-grade.
- BUT, spindle-cell ca can be deceptively benign.
- Misdiagnosed as nodular fasciitis, fibromatosis, granulation tissue, or squamous metaplasia.
- Also can be misclassified as sarcoma.
- YET, these spindle-cell cas show aggressive behavior like infiltrating duct carcinomas (NST).
- 5-year survival for spindle-cell ca report at 64%.

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### Spindle-Cell (Metaplastic) Breast Carcinoma

- **A malignancy capable of causing death.**
- **Emphasized in 1981 by Gersel & Katzenstein.**
- **Confirmed by Wargotz, Sneige, & others.**
- **May appear deceptively benign – fasciitis-like.**
- **Transition from SCCa to spindle cells present.**
- **SCCa may be very, well differentiated & cystic.**
- **Capillary-like tracery (angioid areas).**
- **Tracery & spindle cells positive for keratin.**

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**Spindle-cell Carcinoma of the Breast  
(Metaplastic Carcinoma Variant)**

- Most metaplastic carcinomas are high-grade.
- BUT, spindle-cell ca can be deceptively benign.
- Misdiagnosed as nodular fasciitis, fibromatosis, granulation tissue, or squamous metaplasia.
- Also can be misclassified as sarcoma.
- YET, these spindle-cell cas can show aggressive behavior like infiltrating duct carcinomas (NST).
- 5-year survival for spindle-cell ca reported at 64%.

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**Dx:  
High-grade  
Sarcomatoid  
Carcinoma**

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**Illustrative  
Case**

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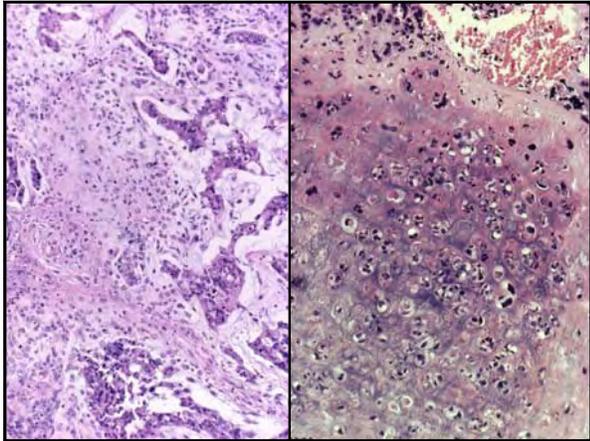
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**Dx:**

**Matrix Forming  
Metaplastic Carcinoma**

*Matrix-producing Carcinoma of the Breast.  
An Aggressive Subtype of Metaplastic Carcinoma*  
*Am J Surg Pathol 2009;33:534-541*

*"MPC is an aggressive...carcinoma with a worse  
clinical outcome than invasive ductal carcinoma."*

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**Spindle-cells in Many Breast Lesions**  
*Remember a core biopsy may only sample spindled areas*

**Malignant lesions:**

- **Metaplastic Breast Carcinoma**  
(esp. Spindle-Cell Variant).
- **Phyllodes Tumor.**
- **Periductal Stromal Sarcoma.**
- **Primary Breast Sarcomas ("Stromal Sarcoma").**
- **Spindle-cell Duct Carcinoma in situ.**

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**Phyllodes Tumors**

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**Illustrative  
Case**

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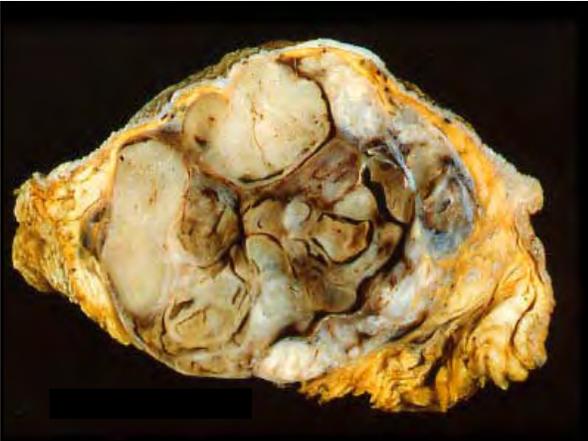
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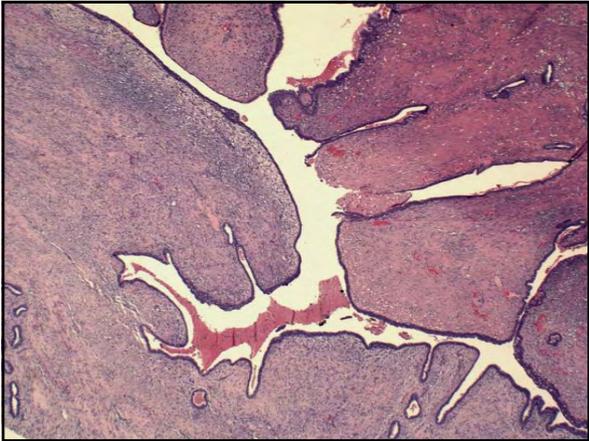
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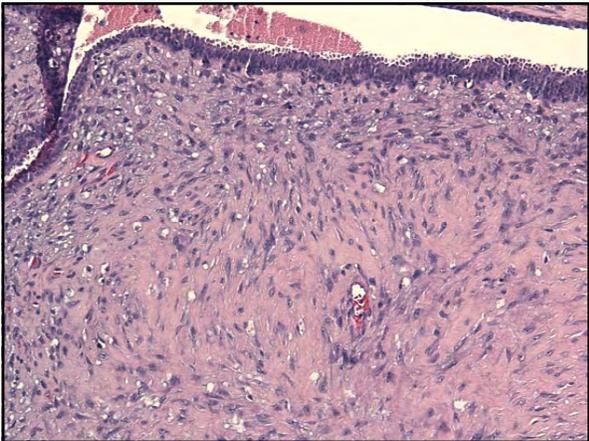
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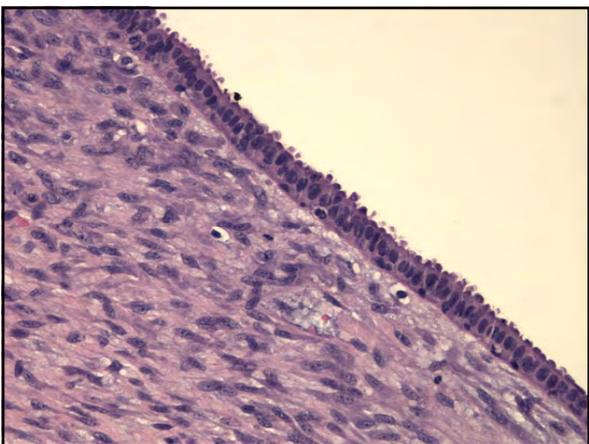
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**Diagnosis:**

**Benign**  
**(Low-grade)**  
**Phyllodes Tumor**

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**Illustrative  
Case**

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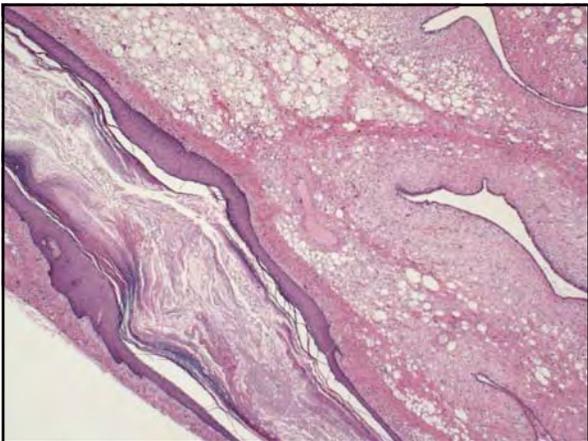
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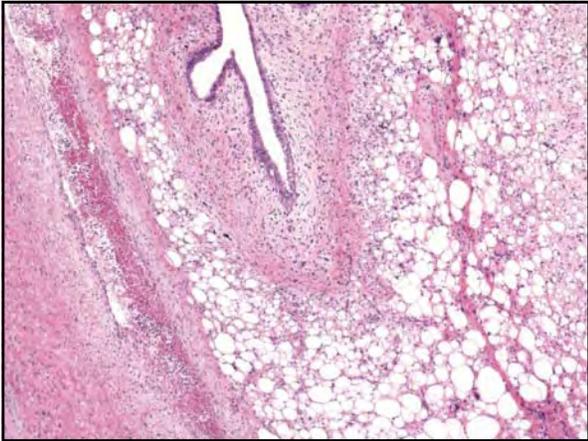
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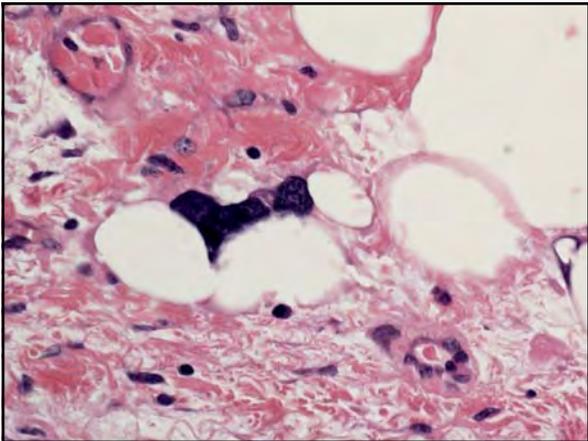
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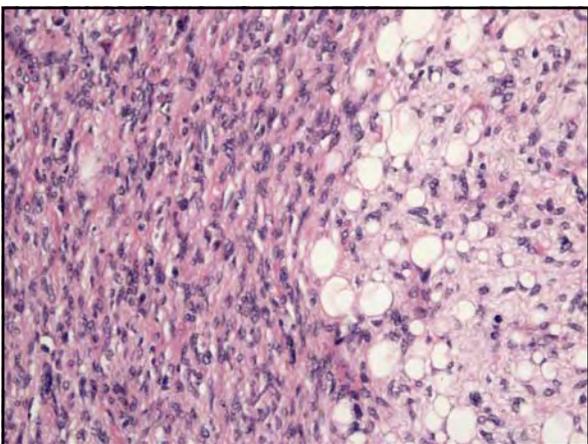
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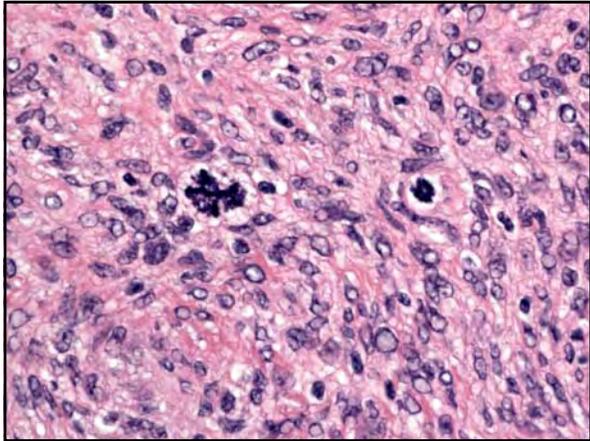
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**Diagnosis:**

**Malignant**  
**(High-grade)**  
**Phyllodes Tumor**  
**with**  
**Pleomorphic**  
**Liposarcoma**

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**Illustrative**  
**Case**

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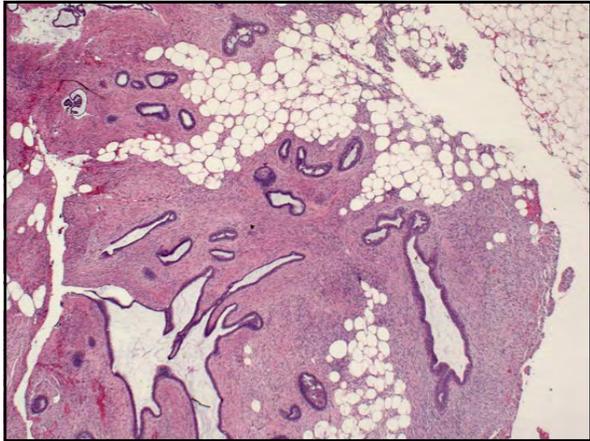
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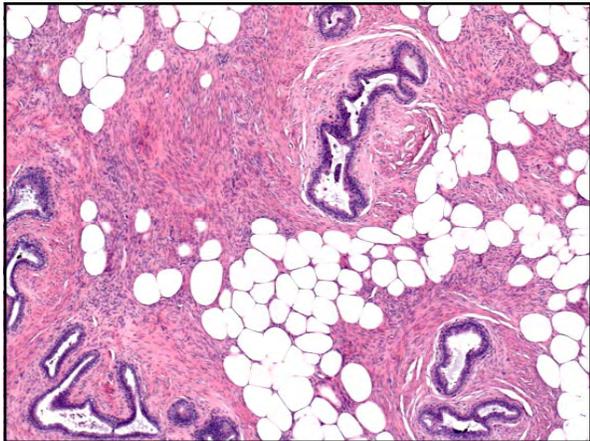
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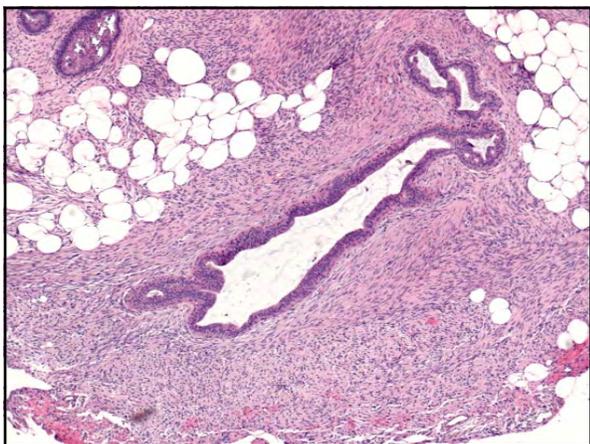
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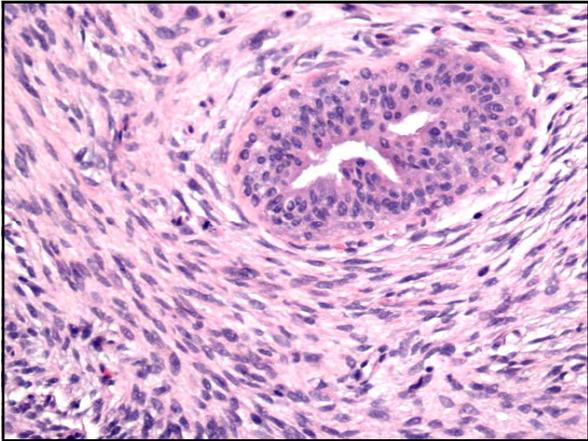
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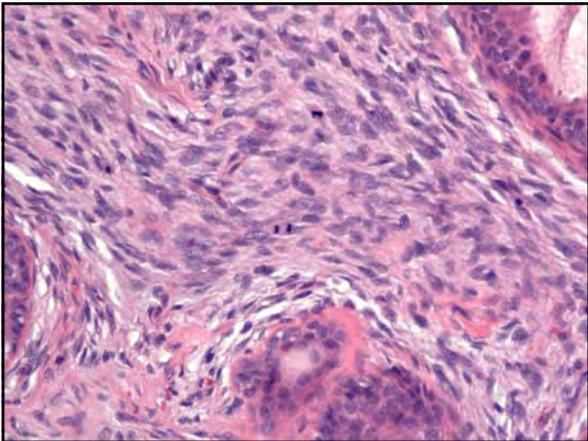
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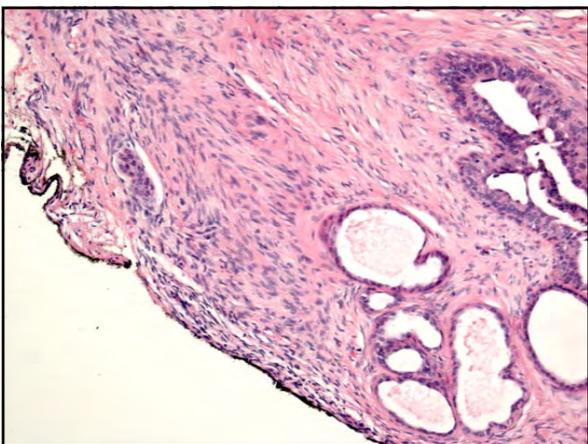
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**Dx: Periductal Stromal Sarcoma**

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- Soft-Tissue Sarcoma of the Breast**
- Any soft-tissue sarcoma possible in the breast.
  - R/O Sarcomatoid Carcinoma.
  - R/O Stromal Overgrowth of Phyllodes Tumor.
  - Does it matter? – for now, yes.

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**Illustrative Case**

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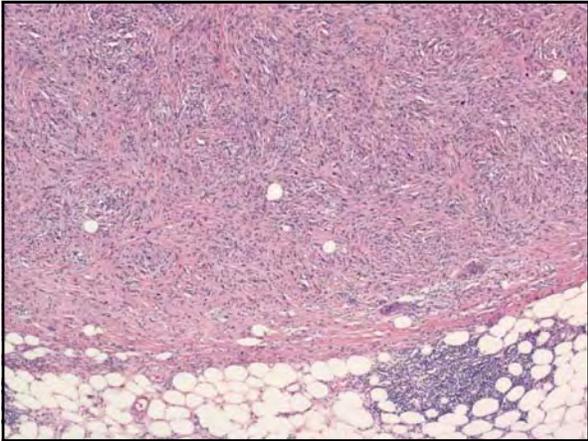
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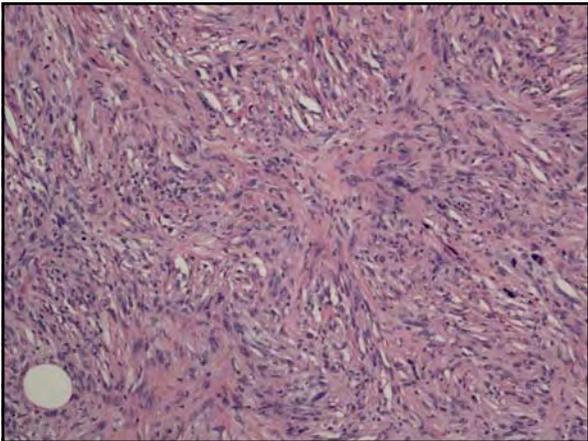
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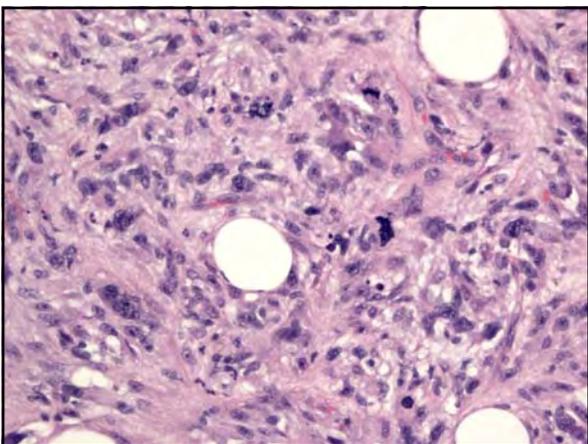
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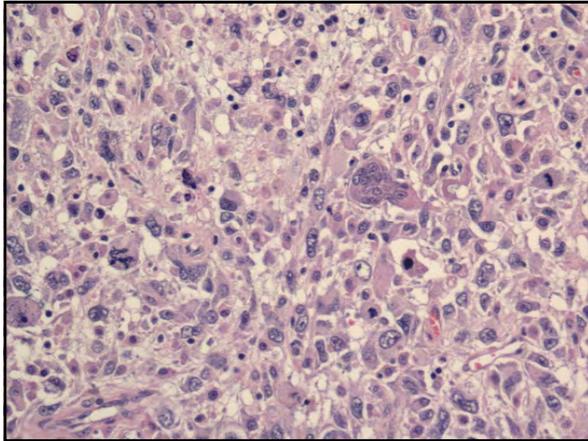
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**Diagnosis:**

Pleomorphic Malignant  
Fibrous Histiocytoma/  
Undifferentiated  
Pleomorphic Sarcoma

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**Spindle-cell DCIS**

Farshid et al. **Spindle cell ductal carcinoma in situ. An unusual variant of ductal intra-epithelial neoplasia that simulates ductal hyperplasia or a myoepithelial proliferation.** *Virchows Arch.* 2001 Jul;439(1):70-7.

Tan et al. **Ductal carcinoma in situ with spindle cells: a potential diagnostic pitfall in the evaluation of breast lesions.** *Histopathology.* 2004 Oct;45(4):343-51.

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**Illustrative  
Case**

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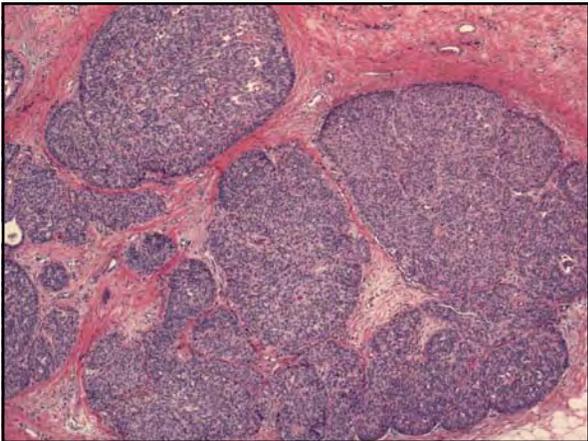
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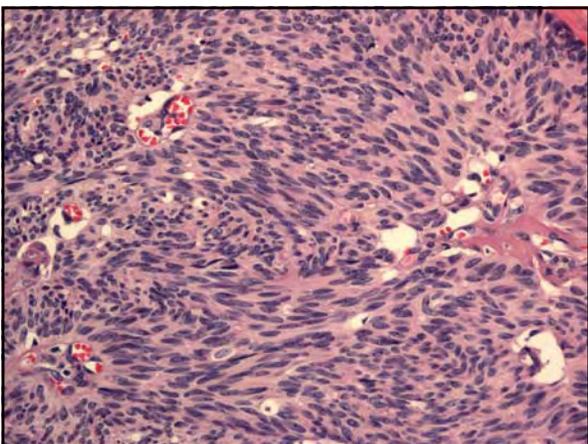
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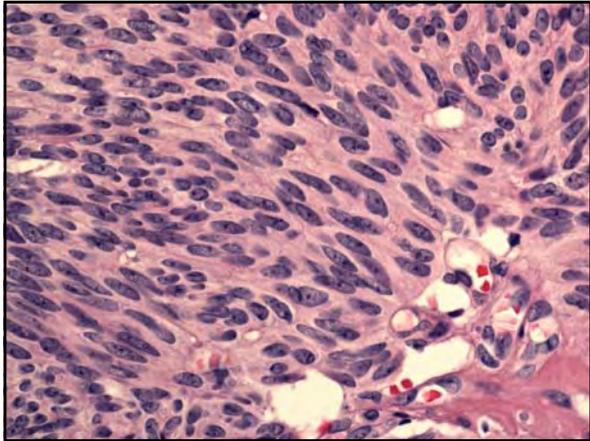
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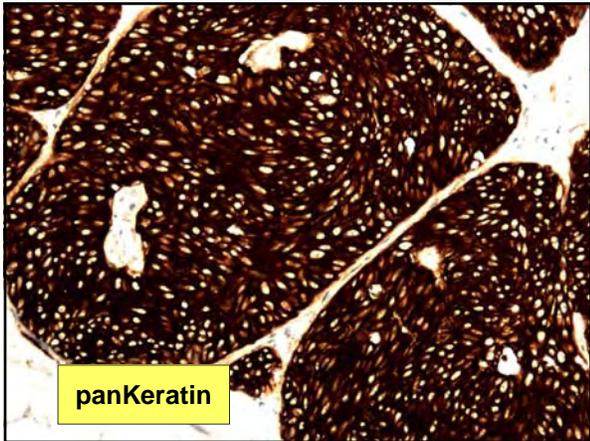
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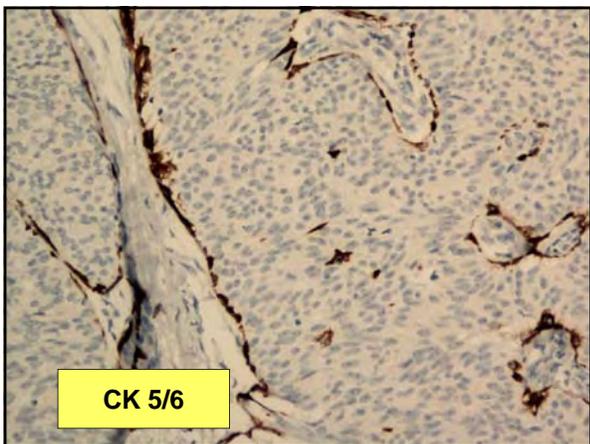
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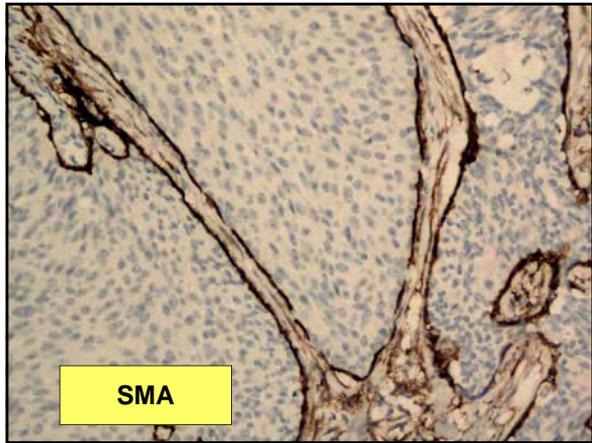
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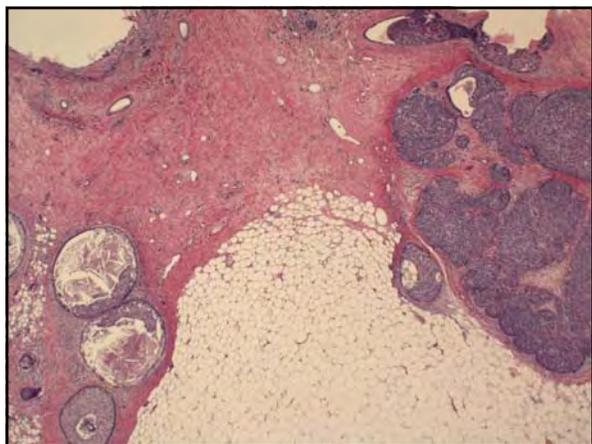
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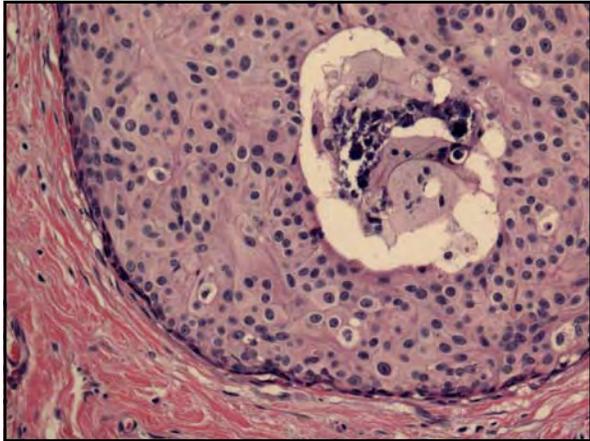
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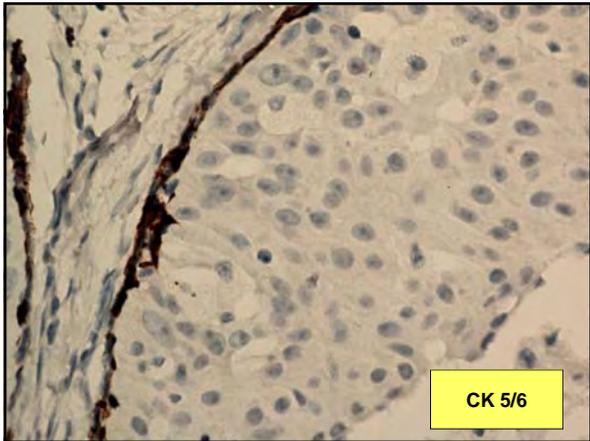
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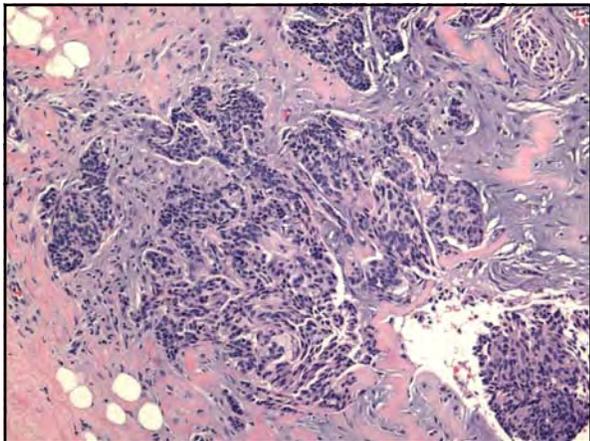
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**Dx:  
Mixed Spindle-cell  
&  
Classic DCIS  
&  
Invasive Duct Carcinoma**

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**Spindle-cells in Many Breast Lesions  
Core biopsy may only sample only spindled areas**

**Benign lesions:**

- Sclerosing Lymphocytic Lobulitis (Diabetic Mastopathy)
- Fibroadenoma
- Sclerosing Adenosis
- Adenomyoepithelioma (Spindle-Cell)
- Inflammatory Myofibroblastic Tumor
- Myofibroblastoma
- Leiomyoma (Usually Nipple)
- Fibromatosis
- Spindle-Cell Lipoma
- Repair Reaction (i.e., at Prior Bx Site or Fat Necrosis).
- Pseudoangiomatous Stromal Hyperplasia (PASH)
- Cellular Angiolipoma

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**Adenomyoepithelioma**

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### Adenomyoepithelioma of the Breast

- Adenomyoepitheliomas well documented.
- Breast masses (2 to 3 cm), same pt. ages as Inv. Duct Ca.
- Firm to rubbery, can mimic carcinoma grossly.
- **Biphasic:** luminal epithelial cells + myoepithelial cells.
- Myoepithelial cells may predominate, necrosis may be present, mitotic activity can be brisk.
- Majority benign (Rosen), but can recur locally.
- BUT, occasional malignant examples causing death.
- Malignant: high mitotic rates and cytoatypia.

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### Illustrative Case

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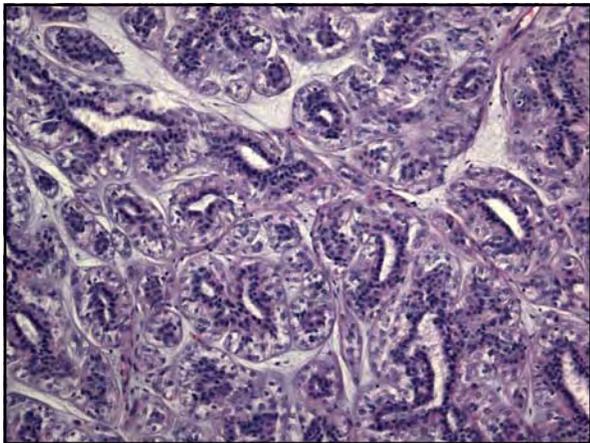
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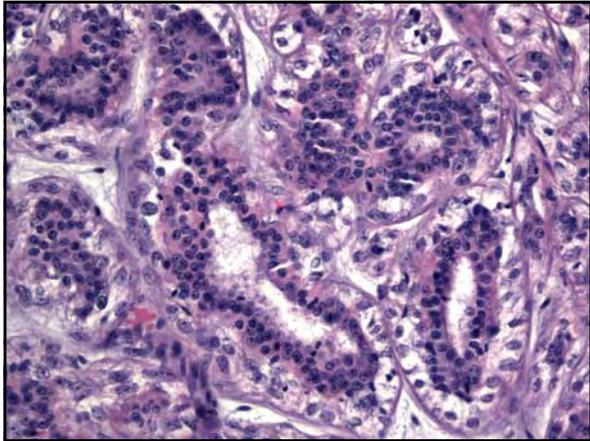
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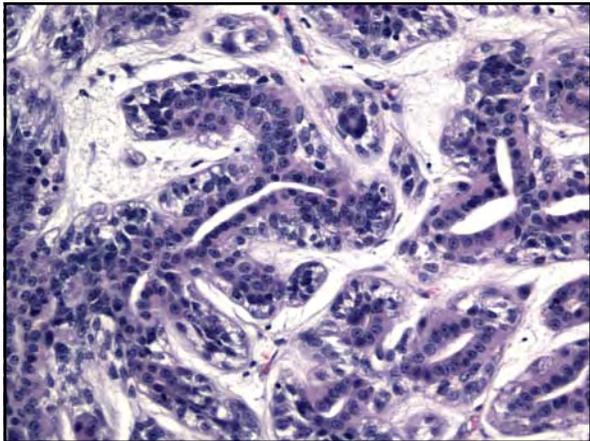
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Dx:  
Adenomyoepithelioma,  
Epithelioid Variant

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**Illustrative  
Case**

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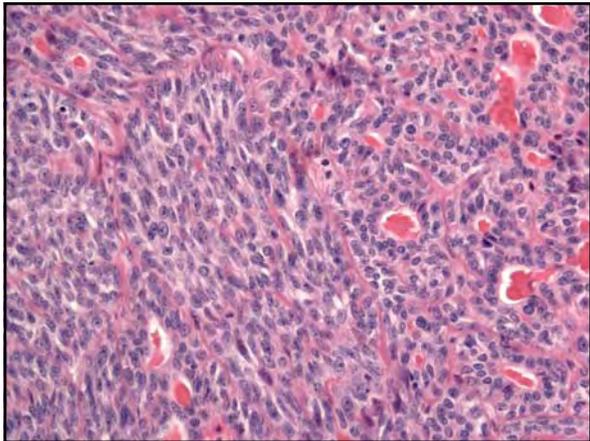
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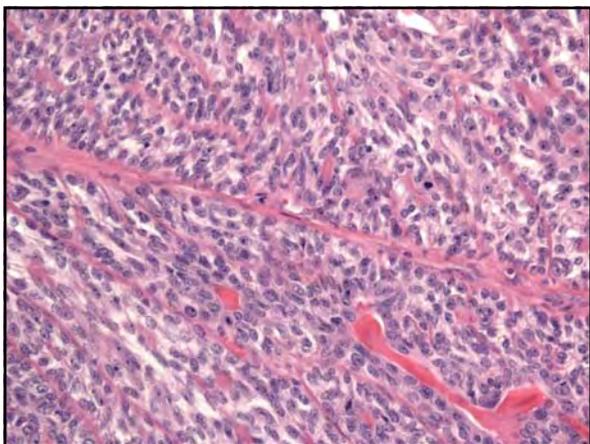
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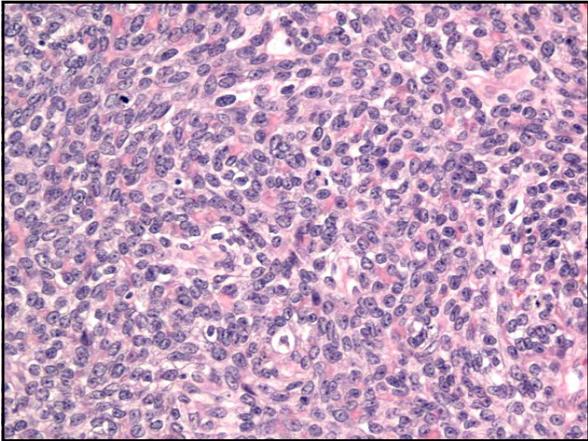
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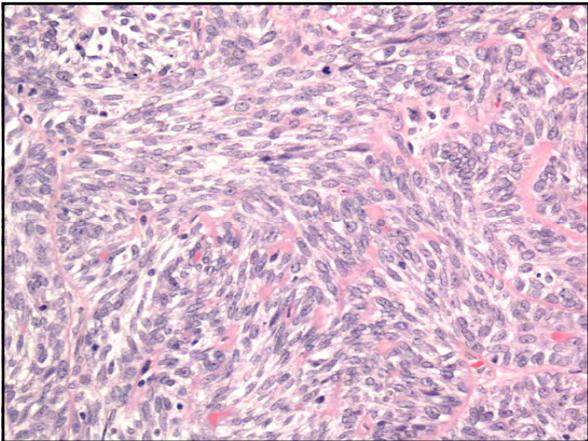
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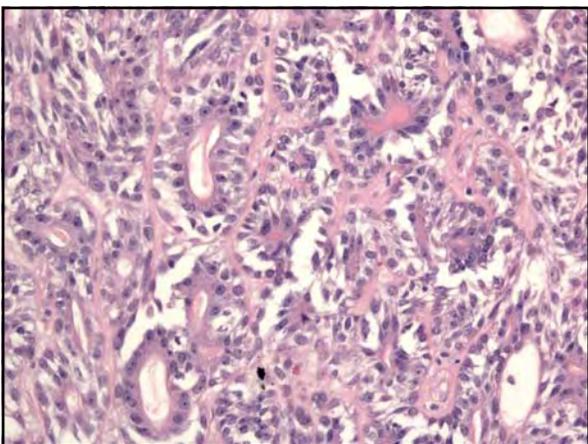
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**Dx: Adenomyoepithelioma,  
Predominantly  
Spindle-cell Variant**

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**Illustrative  
Case**

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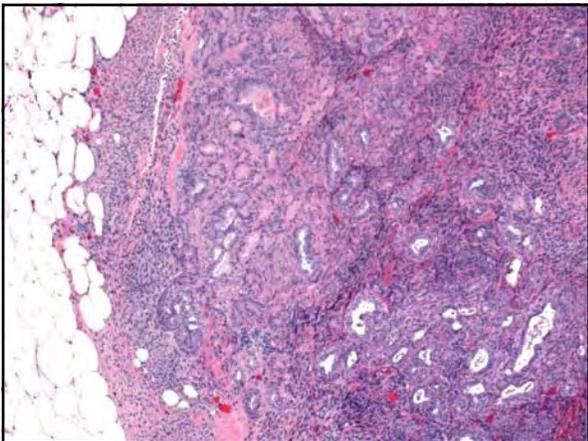
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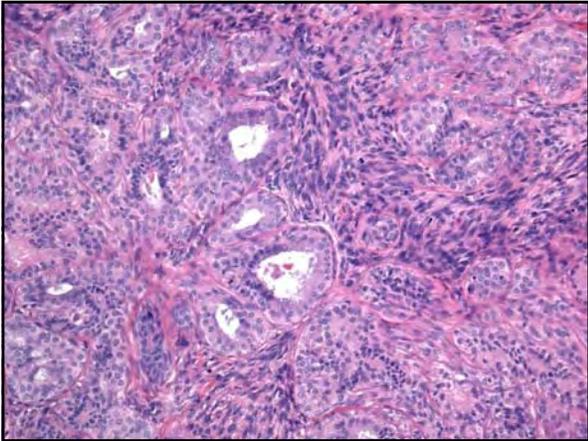
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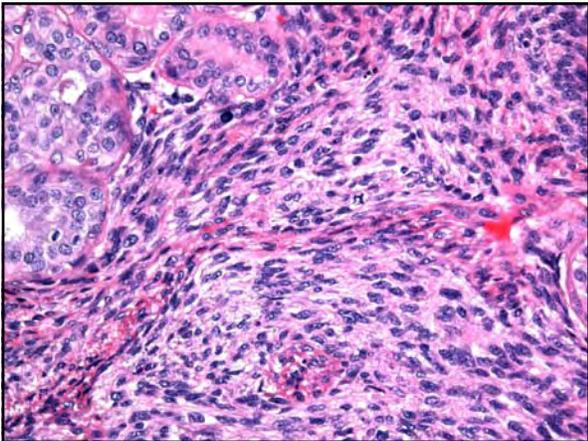
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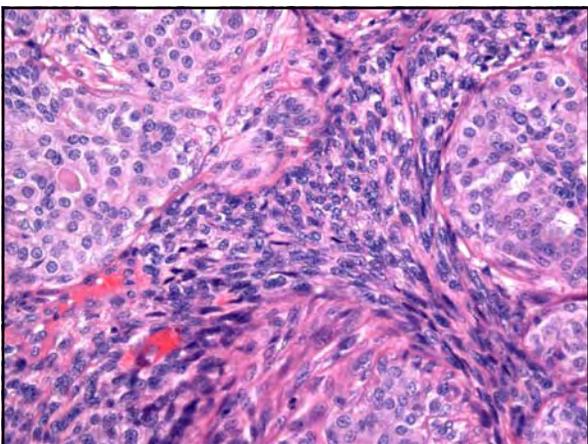
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Dx: Adenomyoepithelioma,  
Possibly Malignant  
("Myoepithelial Carcinoma")

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**The End**

**Thank You  
For Your Time**

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**Special Types of Breast  
Carcinoma  
Unknown Cases**

Farnaz HasteH, MD

 American Society for  
Clinical Pathology  UNIVERSITY of CALIFORNIA, SAN DIEGO  
MEDICAL CENTER

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### Case 1

- 40 year old female
- Breast mass found by palpation
- Imaging showed a suspicious mass with calcification

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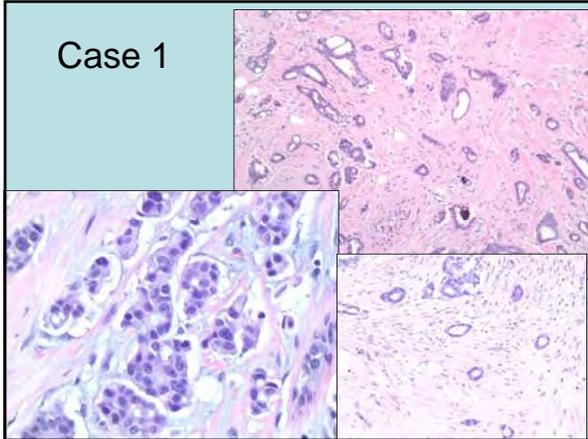
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### Case 1



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### What is your diagnosis?

1. Invasive ductal ca, NST
2. Invasive tubular ca
3. Invasive mixed tubular and ductal ca
4. Invasive tubulolobular ca

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### Case 2

- 64 year old patient found to have a 0.8 cm mass on MRI

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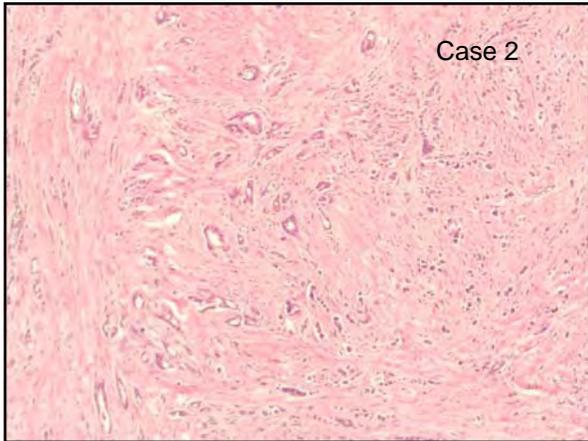
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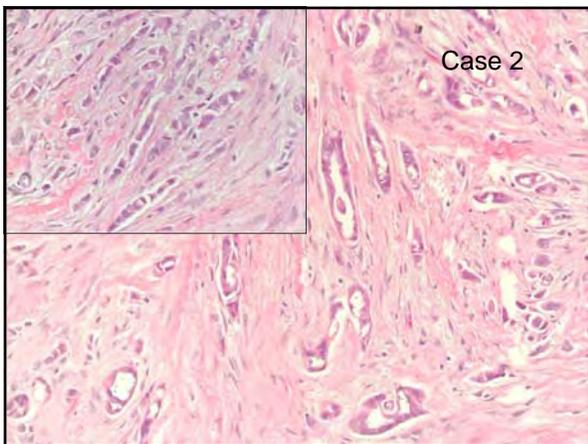
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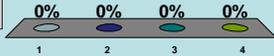
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### What is your diagnosis?

- 1. Invasive ductal ca (NST)
- 2. Invasive tubulobular ca
- 3. Invasive lobular ca
- 4. Invasive tubular ca



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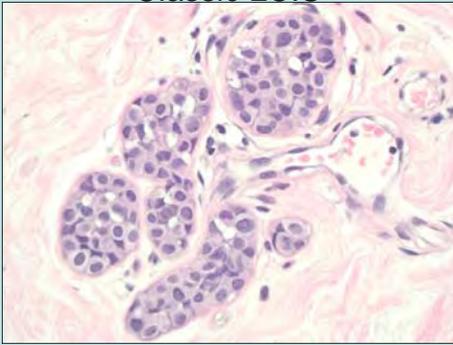
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### Case 2 Classic LCIS



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### Case 2 Flat Epithelial Atypia



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### Case 3

- 48 year old female with 1.5 cm highly suspicious breast mass

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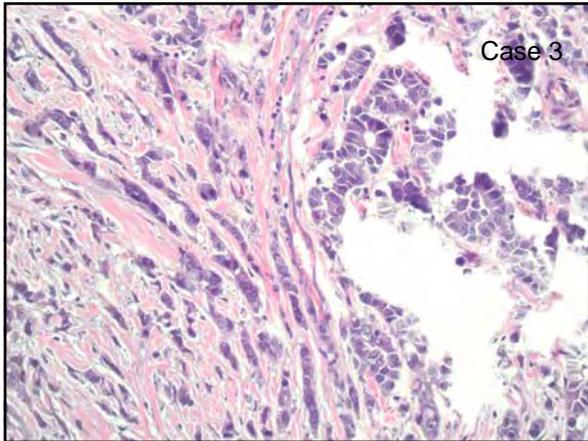
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### What is your diagnosis?

1. Invasive ductal ca, NST
2. Invasive lobular ca
3. Invasive mixed ductal and lobular ca
4. Invasive tubulolobular ca



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### Case 4

- Irregular large breast mass in 65 year old female.

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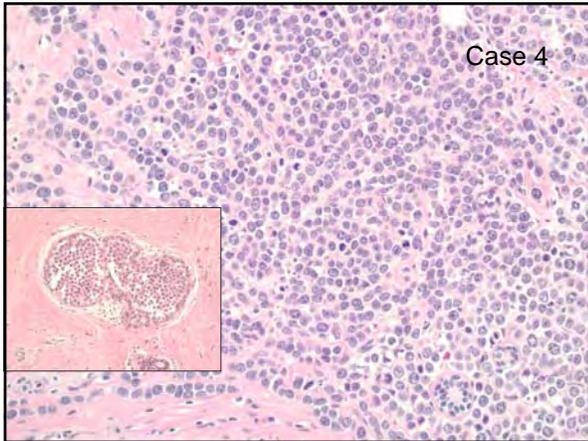
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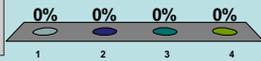
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What is your best diagnosis?

1. Invasive ductal ca, NST
2. Invasive pleomorphic lobular ca
3. Invasive classic lobular ca
4. Invasive mixed ductal and lobular ca



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### Case 5

- Biopsy of a non tender firm mass in a 75 Y old woman with recent history of below knee amputation

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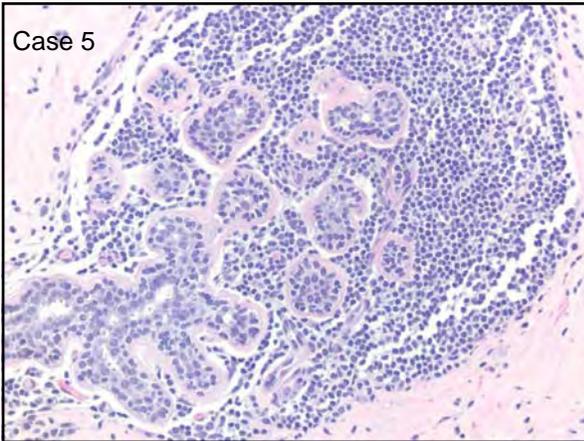
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Case 5



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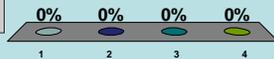
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What is your best interpretation?

1. Atypical lymphoid proliferation
2. Lymphocytic lobulitis
3. Invasive Lobular ca
4. Multiple myeloma



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### Case 6

- Needle core biopsy of a breast mass in a 45 year old female

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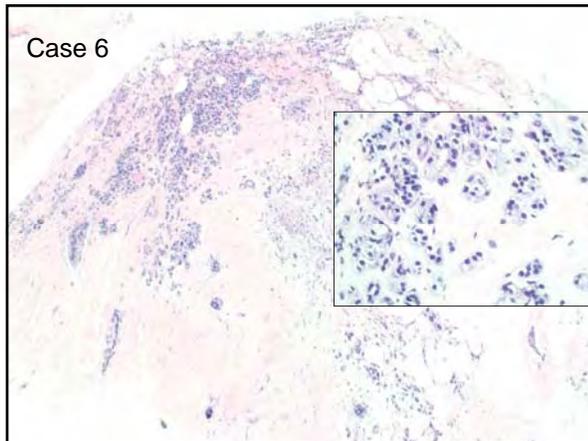
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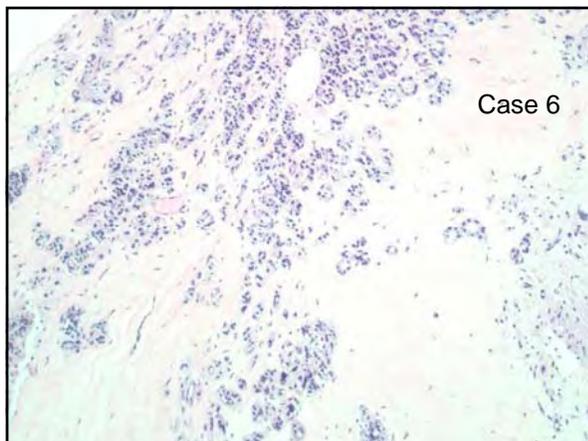
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What is your diagnosis?

1. Radial scar
2. Invasive tubular carcinoma
3. Invasive ductal carcinoma, NST
4. Sclerosing adenosis

0% 0% 0% 0%

1 2 3 4

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Case 7

- Breast biopsy for calcification in a 70 year old female is shown here:

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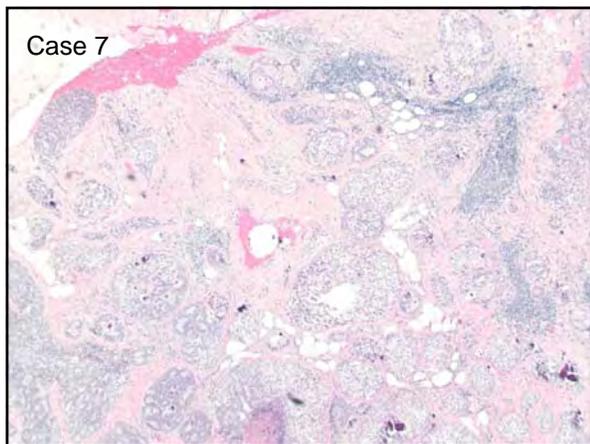
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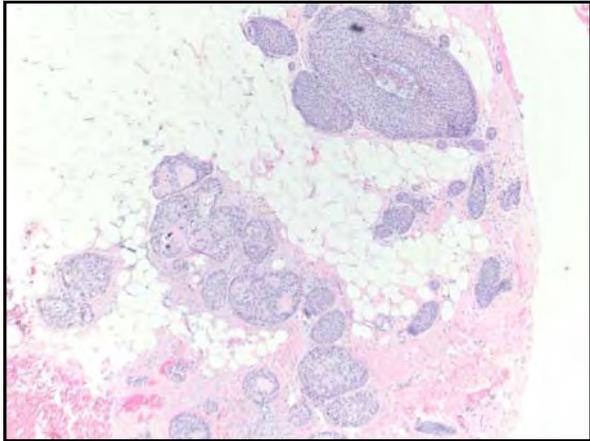
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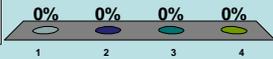
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What is your best diagnosis?

1. Invasive ductal carcinoma, NST
2. Invasive cribriform carcinoma
3. Cancerization of lobules involving radial scar
4. Proliferative FCC with atypia



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### Case 8

- A 0.8 cm spiculated mass with microcalcification on routine mammography
- Needle core biopsy

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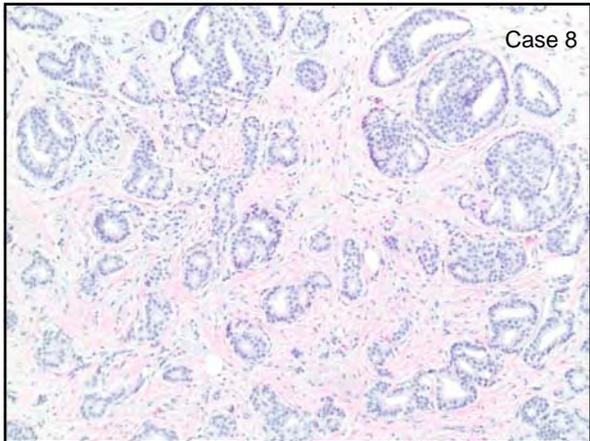
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What is your best diagnosis?

1. Invasive ductal carcinoma, NST
2. Ductal carcinoma in-situ
3. Invasive cribriform /tubular carcinoma
4. Adenoid cystic carcinoma

0% 0% 0% 0%

1 2 3 4

A poll interface with four options and corresponding colored buttons (white, blue, green, yellow) and a 0% vote count for each.

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Case 9

- 79 year old female with well defined mass found by palpation

A text box containing the clinical history for Case 9.

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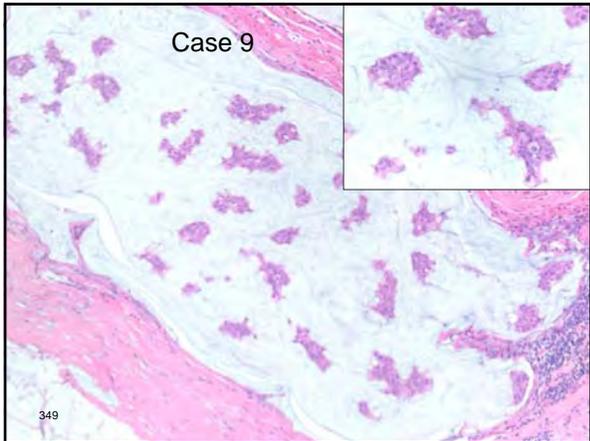
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What is your diagnosis?

- 1. Mucinous carcinoma
- 2. Mucocele like lesion of breast
- 3. Invasive ductal carcinoma mixed with mucinous carcinoma
- 4. Invasive lobular

0% 0% 0% 0%

1 2 3 4

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Case 10

- Representative section of a breast mass in a lumpectomy specimen from a 52 year old female

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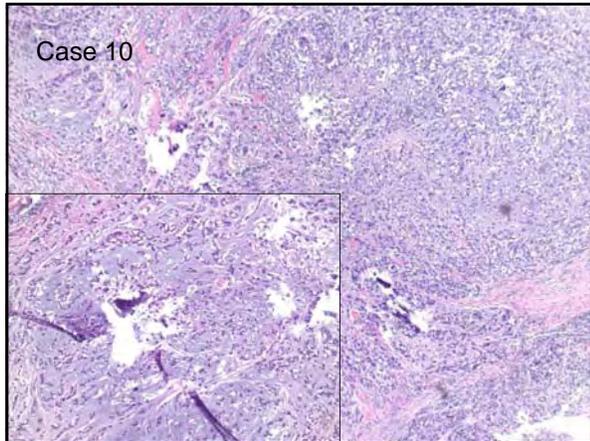
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What is your diagnosis?

1. Mixed tumor
2. Adenoid cystic carcinoma
3. High grade sarcoma
4. Metaplastic carcinoma

0% 0% 0% 0%

1 2 3 4

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Case 11

- Mastectomy specimen in a 78 year old female
- Representative sections of a 1.4 cm mass

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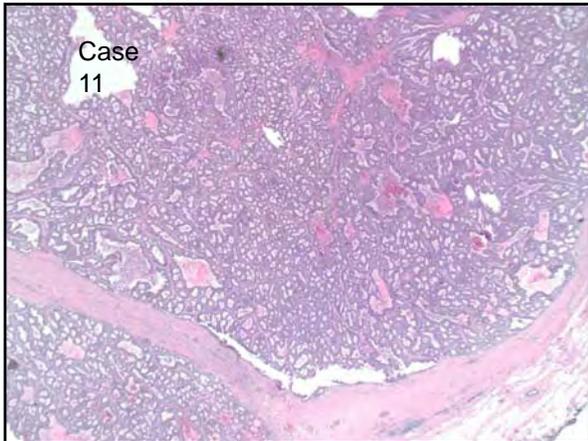
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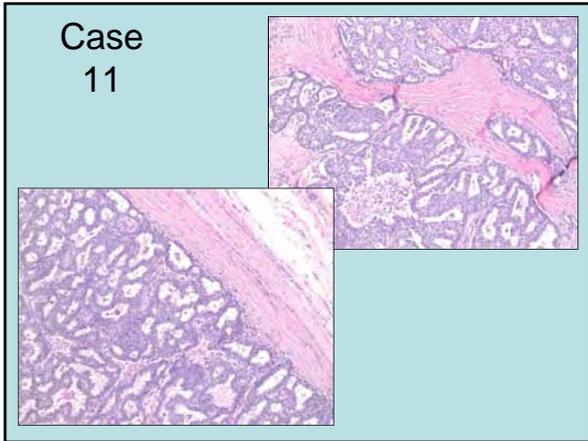
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Case 12

- A 68 year old woman with history of hysterectomy and salpingo-oophorectomy for malignancy 3 years ago. Patient has found to have a 2 cm breast mass by imaging. Needle core biopsy of the mass shows:

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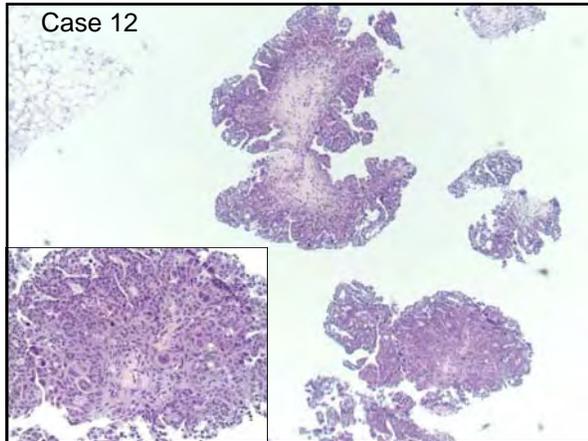
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What is your best diagnosis?

- 1. Intraductal papilloma
- 2. Invasive papillary carcinoma
- 3. Metastatic serous papillary carcinoma
- 4. DCIS, micropapillary type

0% 0% 0% 0%

1 2 3 4

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What is your diagnosis?

- 1- Intraductal papilloma with atypia
- 2- Invasive ductal carcinoma, papillary subtype
- 3- Intracystic papillary carcinoma
- 4- Cribriform DCIS

0% 0% 0% 0%

1 2 3 4

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### Case 13

- Needle core biopsy of a breast mass in a 56 year old patient who was scheduled for total hysterectomy for recent diagnosis of FIGO grade I endometrial adenocarcinoma is shown in the next slide (RUSH specimen).

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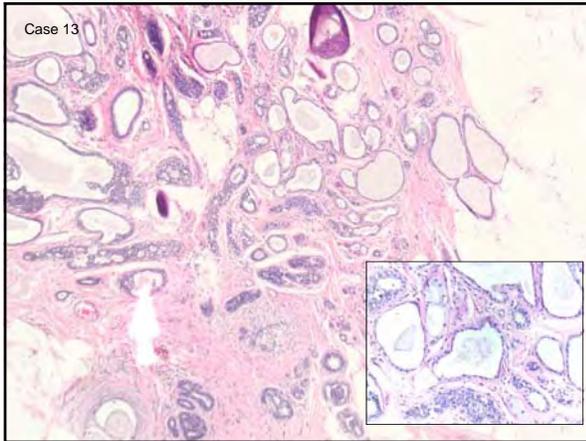
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What is your best diagnosis?

1. Tubular carcinoma
2. Sclerosing adenosis
3. Radial scar
4. Tubular adenoma



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### Case 14

- Biopsy of a well circumscribed mass around nipple in a 73 year old woman

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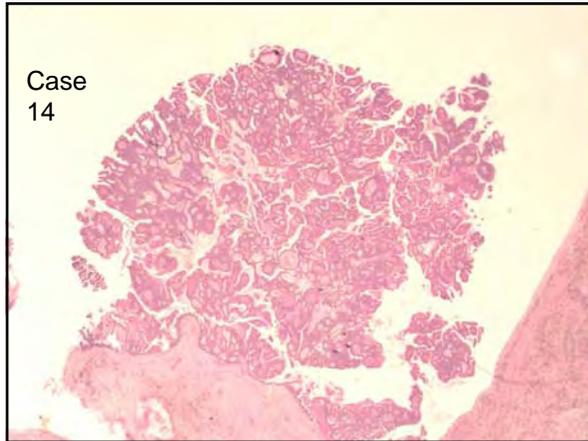
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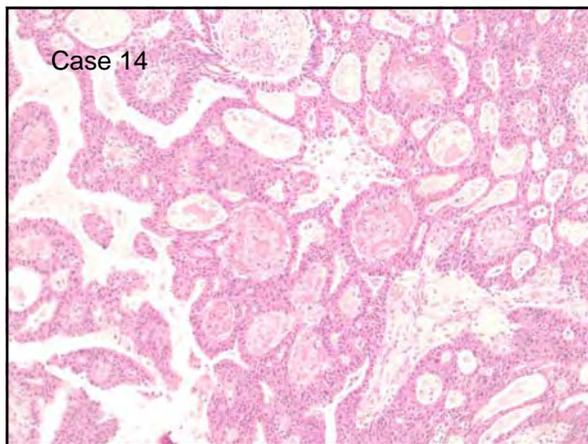
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What is your diagnosis?

- 1. Intracystic papillary carcinoma
- 2. Intraductal papilloma
- 3. Sclerosing papillary lesion
- 4. Invasive papillary carcinoma



Option	Percentage
1	0%
2	0%
3	0%
4	0%

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Case 15

- A 40 year old woman with painless, firm palpable mass
- Tumor cells are negative for pancytokeratin and S100

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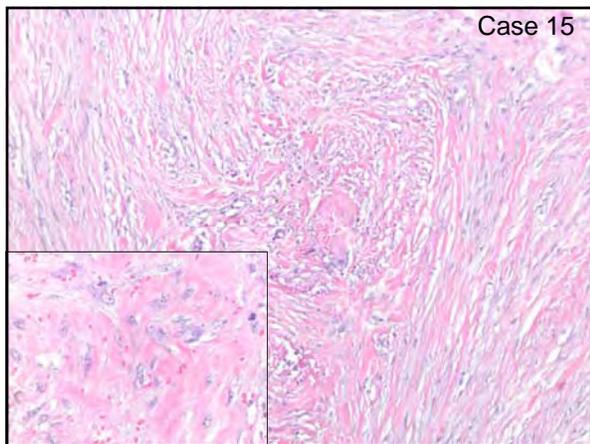
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What is your best diagnosis?

1. Metaplastic carcinoma
2. Myoepithelial carcinoma
3. Fibromatosis
4. Fat necrosis



Option	Percentage
1	0%
2	0%
3	0%
4	0%

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Case 16

- 85 year old with a 1.3 cm breast mass

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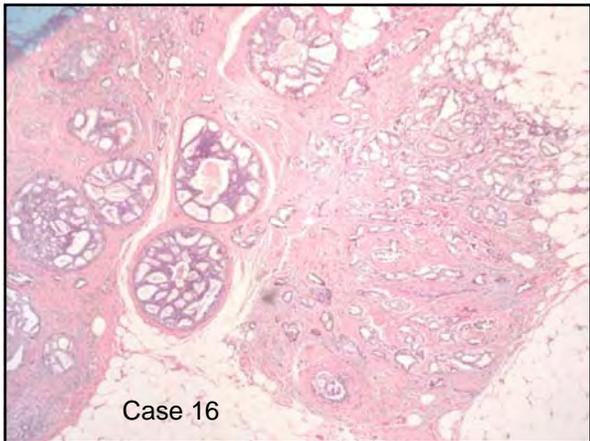
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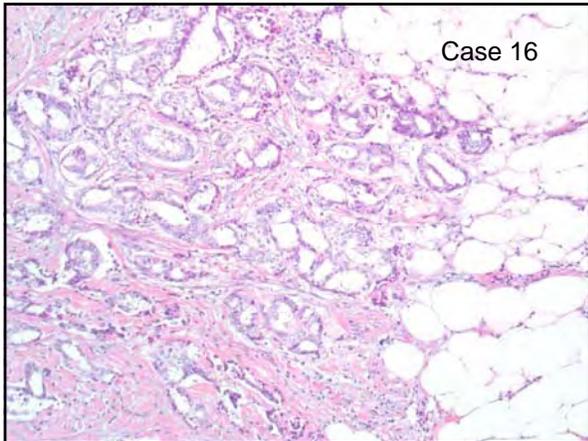
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What is your best interpretation?

1. Invasive ductal ca, NST, mBR I
2. Invasive mixed tubular and cribriform ca, mBR I
3. Cribriform DCIS
4. Invasive mixed ductal and cribriform ca,

0% 0% 0% 0%

1 2 3 4

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Case 17

- Breast mass in 54 year old
- Needle core biopsy

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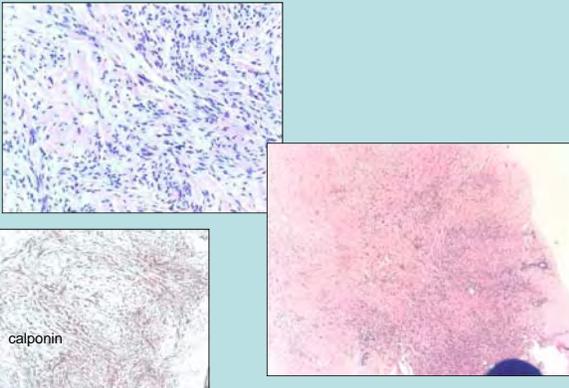
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### Case 17



calponin

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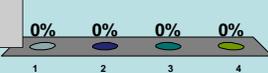
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### What is your diagnosis?

1. Adenomyoepithelioma
2. Metaplastic ca
3. Invasive lobular ca
4. Sclerosing papillary lesion



Option	Percentage
1	0%
2	0%
3	0%
4	0%

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### Case 18

- Breast mass in 75 year old woman
- Needle core biopsy

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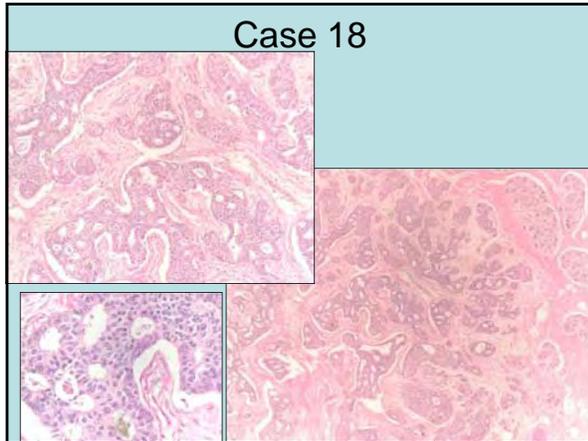
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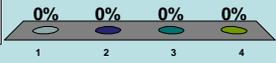
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What is your best interpretation

1. Invasive ductal ca, NST
2. Ductal carcinoma in-situ
3. Invasive cribriform ca
4. Invasive mixed tubular and cribriform ca



Option	Percentage
1	0%
2	0%
3	0%
4	0%

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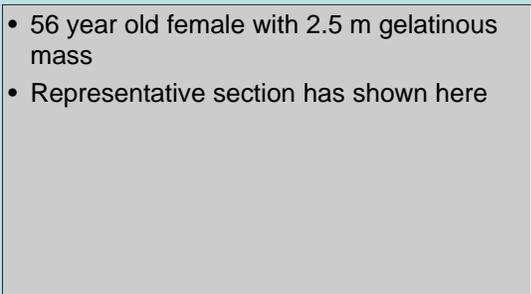
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Case 19

- 56 year old female with 2.5 m gelatinous mass
- Representative section has shown here



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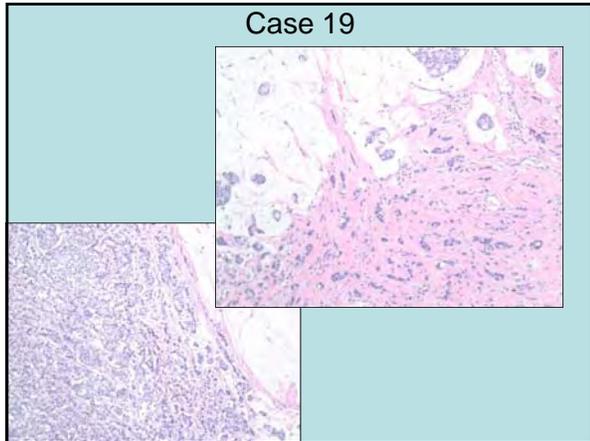
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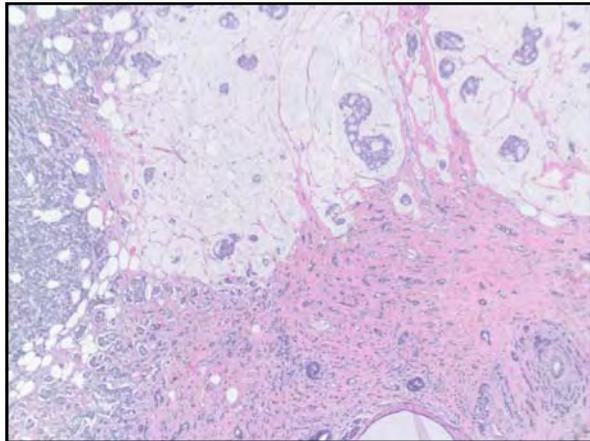
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What is your best interpretation?

1. Invasive mucinous ca
2. Invasive mixed mucinous, lobular and ductal ca
3. Invasive ductal ca, with focal mucinous differentiation, NST
4. Invasive micropapillary ca

0%	0%	0%	0%
1	2	3	4

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### Case 20

- 35 year old female with 4 cm breast mass
- Needle core biopsy

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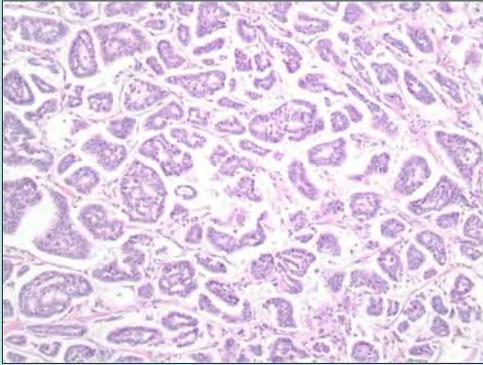
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### Case 20



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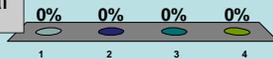
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### What is your best interpretation

1. Invasive ductal ca, NST
2. Invasive micropapillary ca
3. Invasive papillary ca
4. Invasive mixed papillary and ductal ca



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### Case 21

- A 22 year old female with right breast mass
- The mass is located under the nipple
- Imaging: 3 cm round mass

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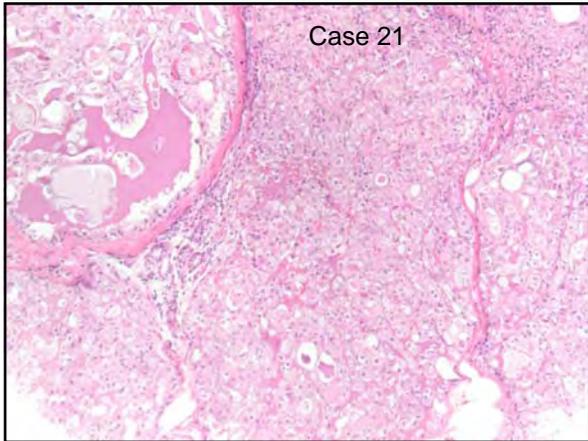
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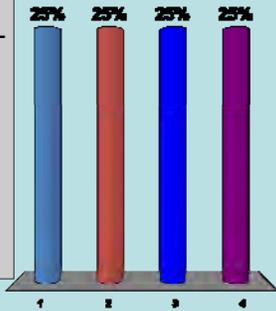
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### What is your diagnosis

- 1. Secretory ca
- 2. Ductal carcinoma in-situ
- 3. Apocrine ca
- 4. Neuroendocrine ca



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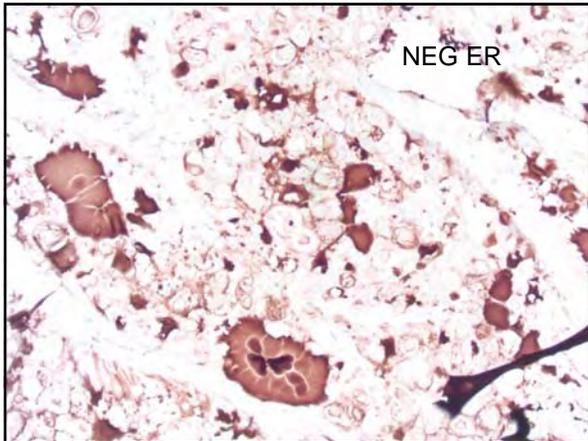
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**Case 22**

- 76 year old female with a periareolar painful breast mass

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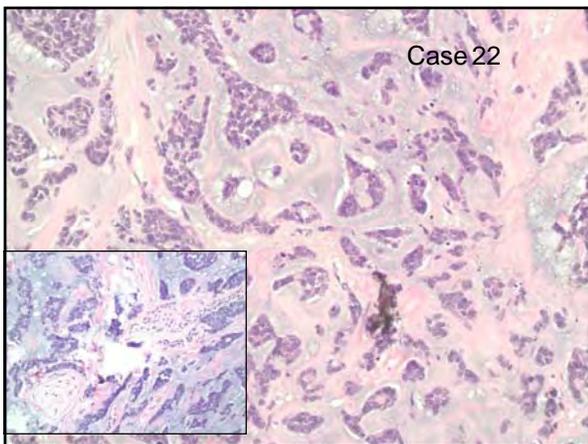
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### What is your diagnosis?

1. Pleomorphic adenoma
2. Adenoid cystic ca
3. Metaplastic ca
4. Invasive ductal ca, NST



Option	Percentage
1	0%
2	0%
3	0%
4	0%

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### Case 23

- Representative sections of a round soft mass in a 49 year old woman
- Tumor is triple negative

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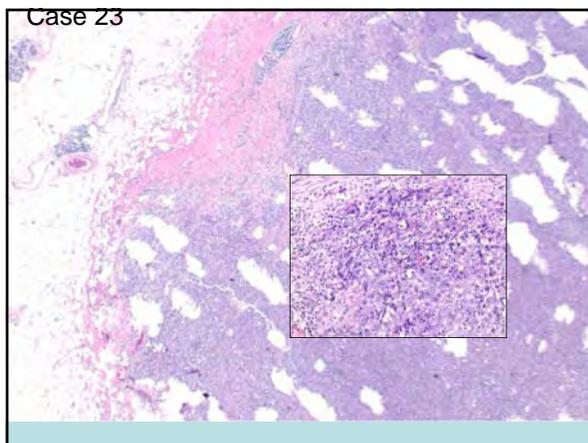
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**What is your best interpretation?**

1. Invasive ductal ca NST , mBR III
2. Invasive modullary ca, mBR III
3. Invasive squamous ca, mBR III
4. Metastatic ca into lymph node



Option	Percentage
1	0%
2	0%
3	0%
4	0%

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**Case 24**

- 65 year old woman with breast mass
- Needle core biopsy

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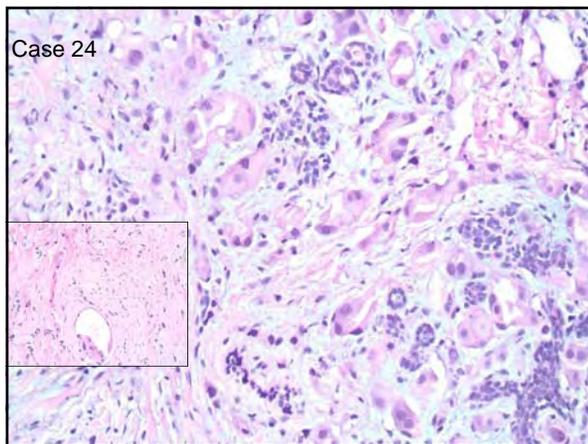
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What is your diagnosis?

1. Mucinous ca
2. Invasive ductal ca, NST
3. Secretory ca
4. Apocrine ca



Option	Percentage
1	0%
2	0%
3	0%
4	0%

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Case 25

- Breast mass in a 45 year old
- Needle core biopsy

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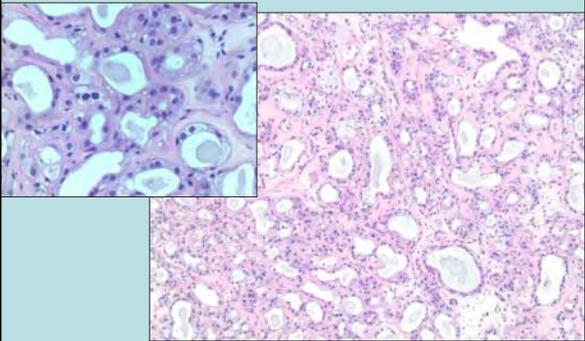
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Case 25



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### What is your diagnosis?

- 1. Secretory carcinoma
- 2. Apocrine carcinoma
- 3. Tubular adenoma with apocrine changes
- 4. Microglandular adenosis

Option	Percentage
1	0%
2	0%
3	0%
4	0%

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### Questions and Answers

Thank you for participating.

American Society for  
Clinical Pathology

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## **American Society of Clinical Pathology 2011**

### **Special Types of Invasive Breast Carcinoma: Diagnostic Criteria with Prognostic and Therapeutic Significance**

#### **Disclosure Statement**

Speakers (Noel Weidner, MD and Farnaz Hasteh, MD) do not have any financial or other relationships that create a conflict related to this educational course.

#### **Learning 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

## **American Society of Clinical Pathology 2011**

### **Special Types of Invasive Breast Carcinoma: Diagnostic Criteria with Prognostic and Therapeutic Significance**

Noel Weidner, MD, Farnaz Hasteh, MD

Oct 21, 2011 10:00 AM - 11:50 AM

Introduction and basal-like and triple-negative breast cancers      Noel Weidner, MD

Case 1:      Noel Weidner, MD

History: A 65 y/o female with 2.5 cm ill-defined left breast mass with firm, tan cut surfaces.

Submitted diagnosis: Invasive lobular carcinoma

Case 2:      Noel Weidner, MD

History: 60 y/o male with 3.1 cm partially cystic right breast mass with soft, tan cut surfaces.

Submitted Case Diagnosis: Intracystic papillary carcinoma

Case 3:      Farnaz Hasteh, MD

History: A 73 y/o female with history of breast mass found by mammogram underwent percutaneous ultrasound-guided core biopsy of the left breast mass.

Submitted diagnosis: Invasive tubular carcinoma (well-differentiated invasive breast carcinoma, overall mBR grade 1; nuclear grade 1, tubular grade 1, mitotic grade)

Case 4:      Farnaz Hasteh, MD

History: 57 y/o female with palpable breast mass. Patient was participating in the 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.

Submitted diagnosis: Invasive mucinous carcinoma, "pure" (well-differentiated invasive breast carcinoma, overall mBR grade 1; nuclear grade 1, tubular grade "1",

mitotic grade 1).

Case 5: Farnaz Hasteh, MD  
History: 29 year old female with a breast lump who was felt by patient. Mammogram found a 2 cm suspicious mass under the nipple  
Submitted diagnosis: Invasive secretory carcinoma (well-differentiated invasive breast carcinoma, overall mBR grade 1; nuclear grade 2, tubule grade 2, mitotic grade 1).

Case 6: Noel Weidner, MD  
History: 66 year old female with 2.5 cm cystic-solid left breast mass with soft, tan cut surfaces.  
Submitted diagnosis: Adenoid Cystic Carcinoma

Case 7: Noel Weidner, MD  
History: A 57 year old female with 3.4 cm well defined breast mass with firm, solid white cut surfaces.  
Submitted diagnosis: Metaplastic carcinoma, spindle-cell carcinoma variant (poorly differentiated invasive breast carcinoma, overall mBR grade 2; nuclear grade 3, tubule/papillary grade 3, mitotic grade 2).

Case 8: Noel Weidner, MD  
History: A 50 year old female with round firm breast mass.  
Submitted diagnosis: Medullary Carcinoma (poorly differentiated invasive breast carcinoma, overall mBR grade 3; nuclear grade 3, tubular grade 3, mitotic grade 3).

Unknown cases Farnaz Hasteh, MD

## SPECIAL TYPES OF INVASIVE BREAST CARCINOMA

### INTRODUCTION

Depending on the series cited, up to 35% of invasive breast carcinomas can be considered of “special” type (1,2). Invasive breast carcinomas not meeting the criteria of “special” type are usually designated by the generic term “invasive duct carcinoma, not otherwise specified” (InvDC,NOS) or of no special type (InvDC,NST). This term can be useful for distinguishing these tumors from other specific forms of invasive breast carcinoma (e.g., tubular, lobular, medullary, metaplastic, colloid, adenoid cystic carcinoma, etc.). Many of the invasive breast carcinomas of special type (InvC,ST) have a relatively favorable prognosis, but this only applies to those tumors composed entirely or in very large part (i.e., 90% or more) of the special pattern (1). Also, InvDC,NOS may be used to designate tumors that express in small part, rather than purely, one or more characteristics of the specific types of breast carcinoma. More specifically, InvCa,NOS can have limited microscopic foci (i.e., less than 10%) of special types of differentiation. Examples of InvCa,NOS, containing 10 to 90% of a special type of carcinoma, can be diagnosed as “mixed ductal and special-type carcinomas” (see table below). Mixed patterns are quite common, and in one review of 1000 breast carcinomas, ~33% of invasive breast carcinoma expressed combinations of features (3). The discussion that follows focuses primarily on invasive carcinomas, although selected in situ carcinomas are also included.

Although certain types of breast cancer have a better prognosis than others, Elston et al. (4,5) and Periera et al. (6) continue to grade all histologic types of invasive carcinoma; a practice which is still encouraged. Indeed, their data on grading include grades of the various special types (6), regardless of the fact that special types of invasive breast carcinoma that have a favorable prognosis usually (but not always) fall into the SBR grade 1 category. This association suggests that, in most cases, the correlation of tumor grade with outcome can be explained by the fact that most of these special tumor types are SBR grade 1 tumors. Indeed, ~20% of breast carcinomas are grade 1 by the modified Bloom-Richardson (mBR) criteria (5,6), and some suggest that "special-type" carcinomas comprise about the same number of all invasive breast carcinomas. However, Clayton and Hopkins. (7) were able to show prognostic significance of histologic grading within the category of infiltrating ductal (no special type) carcinoma, and Pereira et al. (6) have found that histologic grade and tumor type, when used together, more accurately predict prognosis (see table below). In this latter

study of 2658 cases of primary invasive breast carcinoma patients, when histologic grade, lymph node status, and tumor size were considered, histologic grade was the most important independent factor in predicting survival. Yet, when histologic type was also considered in the multivariate analysis, it was found to be independently significant, although comparatively of less importance than histologic grade.

Furthermore, histologic grading is important, because disagreements continue to occur between pathologists as to the subclassification of breast carcinoma. This happens because criteria remain controversial (especially in diagnosing medullary carcinoma and making distinctions between infiltrating lobular and duct carcinomas), and clearly mixed and/or intermediate patterns of breast carcinoma occur that can be difficult to classify. Also, some clinicians appear to more easily accept a histologic grade designation than a vaguely understood and sometimes controversial subtype designation. Thus, it is wise to give all invasive breast carcinomas a histologic grade, including the special types like lobular, mucinous, secretory, adenoid cystic, tubular/cribriform carcinomas, etc. Often, as noted above, these types receive well differentiated or mBR grade 1 designation, an expected result given their less aggressive behavior. An exception is medullary carcinoma, for which controversy continues regarding diagnostic criteria and prognosis. Medullary carcinoma is almost always mBR grade 3. In contrast to other studies, Elston et al. (5,6,8) were unable to show an improved outcome for patients with medullary breast carcinoma, even when strict morphologic criteria were imposed. I believe medullary carcinoma can be over diagnosed, and it is a diagnosis difficult to reproduce between competent pathologists (9). The diagnosis of medullary carcinoma has become uncommon in our practice. Histologic grade (especially when using standardized criteria such as the Bloom-Richardson criteria [10-16]) helps place any invasive breast carcinoma into its proper prognostic and therapeutic category, especially when there is controversy or confusion about the proper subtype designation.

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**INVASIVE BREAST CARCINOMAS THAT ARE CONSIDERED TO HAVE  
A RELATIVELY GOOD PROGNOSIS**

- |                                      |                                    |
|--------------------------------------|------------------------------------|
| 1. Tubular Carcinoma                 | 6. Secretory Carcinoma             |
| 2. Cribriform Carcinoma              | 7. ? Tubulolobular Carcinoma       |
| 3. Pure Mucinous (Colloid) Carcinoma | 8. ? Classical Lobular Carcinoma   |
| 4. Adenoid Cystic Carcinoma          | 9. ? Medullary Carcinoma           |
| 5. Low-Grade Adenosquamous Carcinoma | 10. ? Invasive Papillary Carcinoma |

Note: We believe, as others do (17), that the defining features of special types of breast carcinoma should comprise more than 90% of the tumor, and the closer to 100% the better, especially for the mucinous subtype, which should be "pure". In the table above a "?" designates those carcinomas whose prognoses remain controversial, either because of difficulty in reproducing the diagnosis or because of contradictory reports regarding prognosis. Many papillary carcinomas are pre-invasive, a finding that explains their good prognosis in many series. Truly invasive papillary carcinomas likely have a prognosis similar to similar grade and stage InvDC,NST.

**10-YEAR SURVIVAL BY INVASIVE TUMOR TYPE  
AND MODIFIED BLOOM-RICHARDSON GRADE (mBR)  
(Periera et al. Histopathol 1995;27:219-226)**

Type (~100% total):	Overall	Grade 1	Grade 2	Grade 3
Ductal (NST) (50%)	46	76	55	39
Lobular (Classic) (6%)	53	71	55	38
Mixed Ductal + Lobular (5%)	41	88	52	31
Tubular (2.4%)	90	90	none	none
Tubulo-lobular (1%)	91	91	none	none
Mixed Tubular + Ductal (15%)	64	86	63	18
Mucinous (1%)	81	86	75	none
Mixed Ductal+Special type (2.5%)	64	81	59	55
Medullary (3%)	51	none	none	51
Atypical Medullary (5%)	63	none	none	63
Invasive Papillary (0.3%)	60	to few	to few	to few
Invasive Cribriform (0.8%)	90	90	none	none
Solid Lobular (1.4%)	33	none	63	18
Alveolar Lobular (0.6%)	77	none	77	none
Mixed Lobular (6.4%)	48	71	52	43

NOTE: (Ellis et al. [8] and Periera et al. [6] criteria): Tubular = > 90% classic low-grade tubular carcinoma. Mixed tubular = stellate mass with peripheral infiltrating border showing ductal (NST) carcinoma + some central areas showing classical tubular carcinoma. Cribriform = > 90% invasive cribriform pattern of small regular cells or > 50% classic cribriform, if remainder classic tubular carcinoma. Mucinous = small islands (10-20 cells) of uniform small cells in lakes of extracellular mucin; any amount of invasive ductal (NST) carcinoma places the lesion in the mixed ductal + mucinous type. Mixed ductal + special types or lobular = a special type or lobular tumor that also contains ductal (NST) carcinoma amounting to 10-90% of the total invasive tumor. Medullary = must show all of the following features: 1) sheets of large bizarre carcinoma cells forming syncytial network, 2) moderate to large numbers

of lymphoid cells between sheets of tumor cells, 3) sharply defined pushing margin, 4) usually little fibrous stroma, and 5) usually no DCIS or LVI. Atypical Medullary = any deviation from the criteria defined for medullary but with medullary features; usually this is either less inflammation, microscopic invasion beyond the sharply defined pushing margin, or dense areas of fibrosis.

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### Basal-like and triple-negative breast cancers

Breast cancer encompasses multiple entities with distinct morphological features and clinical behaviors – that is, diversity resulting from distinct genetic, epigenetic, and transcriptomic alterations. This is true for invasive ductal carcinomas of no special type (IDC-NST), wherein tumors of the similar histological appearance and grade may have different outcomes and responses to systemic therapy. This results from not only individual tumor characteristics, but also from patient-specific characteristics (such as immune and angiogenic response). These patient or tumor characteristics interact in poorly understood ways and determine the eventual natural history of the disease.

Using gene expression microarrays, some have proposed a new taxonomy for breast cancer based on their molecular features. This microarray approach has identified at least five molecular breast cancer subtypes: 1) luminal A, 2) luminal B, 3) normal breast-like, 4) HER2 over-expressing, and 5) basal-like. Although incompletely

studied, this taxonomy identifies subgroups of breast cancer that were to some extent already known and the stability or utility of the assigned subtypes has been questioned. Indeed, this taxonomy is not be used by UCSD oncologists. Nonetheless, the most robust distinction observed by microarray is between estrogen receptor-positive and ER-negative breast cancers, and none has generated as much interest as the basal-like group. Although there is no clear-cut histologically defined basal cell in breast epithelium, the myoepithelial cell is well defined.

So-called basal-like breast cancer has been extensively reviewed, and there remains no internationally accepted definition for basal-like breast cancer. Some use microarray-based expression profiling to define basal-like breast cancers, whereas others use immunohistochemical markers. Unfortunately, direct comparisons between the proposed immunohistochemical markers and microarray-defined molecular subtypes are scarce. Immunohistochemical marker panels that have been proposed to define basal-like breast cancers include: (1) lack of ER, PR, and HER2 expression (“triple-negative” immunophenotype); (2) expression of one or more high-molecular-weight/basal cytokeratins (CK5/6, CK14, and CK17); (3) lack of expression of ER and HER2 in conjunction with expression of CK5/6 and/or epidermal growth factor receptor (EGFR); and (4) lack of expression of ER, PR, and HER2 in conjunction with expression of CK5/6 and/or EGFR. These high-molecular-weight keratins also highlight myoepithelial cells.

Despite the different definitions for basal-like breast cancers, these tumors may have somewhat distinctive clinical presentations, histological features, response to therapy, sites of distant relapse, and outcome. Basal-like tumors are heterogeneous, account for up to 15% of all breast cancers, affect younger patients, are more prevalent in African-American women, and often present as interval cancers. The majority classify as IDC-NST type, are high histological grade, have high mitotic indices, show central necrotic or fibrotic zones, have pushing borders, have conspicuous lymphocytic infiltrate, and often display medullary-like features.

However, not all basal-like cancers are of the IDC-NST type. Indeed, the majority of medullary and atypical medullary, metaplastic, secretory, myoepithelial, and adenoid cystic carcinomas also have a basal-like phenotype. A subgroup of lobular carcinomas express high-molecular-weight cytokeratins, but may not show a basal-

like transcriptome. Most basal-like breast cancers lack or express low levels of ER/PR and lack HER2 protein overexpression or HER2 gene amplification. They often express genes and proteins usually found in myoepithelial cells of the normal breast including high-molecular-weight cytokeratins (CK5/6, CK14 and CK17), P-cadherin, caveolins 1 & 2, nestin, aB crystallin, CD109, and EGFR . In a minority of cases, they harbor EGFR gene amplification or aneusomy. p53 immunohistochemical expression or TP53 gene mutations is observed in up to 85% of cases, and alterations of the pRB and p16 G1/S cell-cycle checkpoint are prevalent in these cancers. A recent study demonstrated that approximately 30% of basal-like breast cancers concurrently show lack of pRB expression, over expression of p16 and p53 immunoreactivity (pRB-/p16+/p53+), whereas this profile was rarely seen in tumors of other molecular subtypes.

Basal-like cancers show high proliferation indices as defined by mitotic counting or by high Ki67 labeling index. Basal-like breast cancers, unlike myoepithelial cells of normal breast, almost uniformly express cytokeratins 8 and/or 18, calling into question the initial histogenetic implications of the microarray-based taxonomy of breast cancers that suggested that basal-like cancers would arise from or show differentiation like myoepithelial cells. This has been emphasized in a recent study, which suggested that at least a subgroup of basal-like breast cancers may originate from luminal progenitors rather than myoepithelial cells of the breast, and further supported by the results of conditional mouse models. In this context, it is important to note that histogenesis and differentiation are two distinct processes although often mistakenly used as synonyms.

In contrast to the controversy regarding the definition of basal-like breast cancers, there is uniform agreement that triple-negative cancers are defined as tumors that lack ER, PR, and HER2 expression. These tumors account for up to 17% of all breast carcinomas, depending on the thresholds used to define ER and PR positivity and the methods used for HER2 assessment.

The clinical interest in triple-negative tumors stems from the lack of tailored therapies for this group of breast cancer patients and the overlap with the profiles of basal like cancers, but these two terms are not synonymous and should not be used interchangeably. Nonetheless, triple-negative cancers more frequently affect younger patients (less than 50 years), are more prevalent in African-American women, often present as interval cancers, and are significantly more aggressive than tumors of other

molecular subtypes. Indeed, the peak risk of recurrence is between the first and third years and the majority of deaths occur in the first 5 years following therapy. Patients with triple-negative cancers, similar to those with basal-like cancers, have a significantly shorter survival following the first metastatic event when compared with those with non-basal-like/non-triple-negative controls.

It is true that the majority of triple negative cancers are of basal-like phenotype and the majority of tumors expressing basal-cell markers are triple-negative – that is, not all basal-like cancers determined by gene expression profiling lack ER, PR and HER2. Conversely, not all triple negative cancers show a basal-like phenotype by expression array analysis. Roughly, 75% of triple-negative cancers are of basal-like subtype by gene expression profiling and roughly 75% of molecular basal-like tumors are triple-negative. Some triple-negative cancers that do not express basal markers and are classified by gene expression profiling as normal breast-like, molecular apocrine (i.e., tumors with androgen receptor pathway activation) or claudin-low subtype (i.e., cancers with transcriptomic features suggestive of epithelial to mesenchymal transition and reported to be enriched for the so-called ‘cancer stem cells’). Triple-negative cancers also show more varied histological features. Indeed, up to 10% of triple negative tumors were reported to be of grade 1 of 3 in one study. However, other studies have failed to identify any grade 1 breast cancers with a triple-negative phenotype. Furthermore, other histological special types of breast cancer that do not show a basal-like phenotype by transcriptomic analysis have been shown to occasionally express a triple-negative phenotype, including apocrine carcinomas, pleomorphic lobular carcinomas, and some mixed duct-lobular cancers.

There is increasing evidence to suggest a link between BRCA1 pathway and basal-like breast cancers. The majority of tumors arising in BRCA1 germ-line mutation carriers, in particular those diagnosed before 50 years of age, have morphological features similar to those described in basal-like cancers and show a basal-like phenotype as defined by immunohistochemistry or expression arrays. Although they lack BRCA1 somatic mutations, sporadic basal-like cancers show similar molecular genetic profiles to tumors arising in BRCA1 mutation carriers. Indeed, BRCA1 dysfunction appears to be one of the drivers of basal-like breast cancers and of a subgroup of triple-negative tumors.

A group of high-grade DCIS lacking ER, PR and HER2, and expressing ‘basal’ markers has been identified. However, it should be noted that its prevalence is lower than that of invasive triple negative and basal-like breast cancers and that triple-negative and basal-like cancers often lack an overt in situ component. Whether this is the result of basal-like and triple-negative breast cancers progressing rapidly from DCIS to invasive cancer and/or obliterating the DCIS precursor from which they arose remains a matter of speculation. The majority of invasive cancers developing in microglandular adenosis is of triple-negative phenotype and show metaplastic elements or is of adenoid cystic morphology. It has been recently shown that microglandular adenosis may be a nonobligate precursor of triple-negative and basal like breast cancers. However, given the extreme rarity of microglandular adenosis, it is unlikely to be the precursor lesion for most triple-negative cancers.

Basal-like and triple-negative breast cancers, as defined by microarrays or immunohistochemical surrogates, have been shown to have a more aggressive clinical behavior. In fact, some studies have demonstrated that expression of basal keratins is a prognostic factor independent of tumor size, grade, and lymph node status. Yet, when compared with either ER negative non-basal-like cancers or grade-matched non-basal-like cancers, carcinomas with a basal-like phenotype are not associated with a poorer outcome in some studies, whereas a more adverse prognosis is observed in others.

The pattern of metastatic spread of tumors with a basal-like phenotype seems to be different from that of non-basal-like cancers – that is, they are reported to less frequently disseminate to axillary nodes and bones and to favor a hematogenous spread, with a peculiar proclivity to develop metastatic deposits in the brain and lungs. It should be noted that patients with triple-negative and basal-like cancers tend to develop adverse events and die due to disease within the first 5–8 years after diagnosis. After the 8-year mark, the hazard rate for patients with grade 2 or ER positive cancers is actually higher than that of patients with basal-like cancers.

Importantly, some tumors in the basal-like group have a favorable prognosis, e.g., adenoid cystic carcinomas and secretory carcinomas. This emphasizes that basal phenotype and bad behavior are not inextricably linked and serves to highlight the heterogeneous nature of basal-like carcinomas.

In summary, basal-like breast cancer is a heterogeneous group of tumors that is more prevalent in young and African-American patients and is generally associated with a poor outcome. Currently, although it is clearly important that triple-negative cancers be accurately identified in clinical practice for the purposes of management, there is no internationally accepted definition for basal-like cancers and still no clear clinical indication for the routine identification of these tumors as such. Thus, at present, use of the term “basal-like breast cancer” in diagnostic surgical pathology reports does not appear to be justified, as it does not lead to any direct clinical action. Given that basal-like breast cancers are heterogeneous regardless of the definition used, it is possible that in the next few years, markers that identify subgroups of basal-like or triple-negative cancers that respond to specific agents will become part of our diagnostic armamentarium. With the advent of massively parallel (next generation) sequencing, which allows for the genome-wide quantitative and qualitative genomic and transcriptomic characterization of cancers, and the imminent death of microarrays, it is likely that the taxonomy of breast cancers will be revisited again. At that time, it is quite possible that more homogeneous molecular subgroups, their biological drivers, and therapeutic targets will be identified. Until then, it is essential that pathologists continue to strive toward providing optimal assessment of the histological features of breast cancers (including histological grade), as well as accurate determination of ER, PR, and HER2 status according to published guidelines, since these factors remain the primary determinants of the use and type of systemic therapy for patients with invasive breast cancer.

### **References (Basal-cell and Triple-negative Breast Carcinoma)**

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## Case 1:

**History: 65 y/o female with 2.5 cm ill-defined left breast mass with firm, tan cut surfaces.**

**Submitted diagnosis: Invasive lobular carcinoma.**

## INVASIVE LOBULAR CARCINOMA

**Background:** The classical type of invasive lobular carcinoma is a well-recognized invasive breast lesion (1-9); but, other forms of this tumor, including pleomorphic, solid, alveolar, mixed, apocrine, signet-ring, tubulolobular, and histiocytoid (“myoblast-omatoid” or “granular-cell”) variants are less well known (1-20). Some studies have focused on the clinicopathologic significance of these infiltrating lobular carcinoma variants and have shown that solid, alveolar, mixed, and signet-ring forms apparently have a poorer prognosis than the classical variant (6-15 and 57). Fisher et al. (1) reported that the short-term treatment failure rates in patients with tubulolobular invasive carcinoma were intermediate between those of tubular carcinoma and infiltrating lobular carcinoma, suggesting that this variant had a better overall prognosis than some others. Similar findings were reported by Ellis et al. (2) who found that the classical, tubulolobular, and lobular mixed types were associated with a better prognosis than ductal carcinomas (no special type [NST]), but this was not true for the solid variant of infiltrating lobular carcinoma, which showed a prognosis similar to ductal NST. Too few cases of the histiocytoid and/or apocrine variants of infiltrating lobular carcinoma have been reported to make firm conclusions as to their behavior relative to other variants of infiltrating lobular carcinoma (11,12); however, recent work suggests that the apocrine variant displays aggressive behavior (16). It is important to know about these variants to avoid under diagnosing them as benign lesions such as reactive benign histiocytes, fibrohistiocytic lesions, or granular-cell tumors. Keratin immunostaining of carcinoma cells can be used to avoid this pitfall.

Page et al. (15) described a pleomorphic variant that has the infiltrating pattern of classic infiltrating lobular carcinoma, but with more pleomorphic nuclei, and tendency for the tumor cells to aggregate. Dixon et al. (6-8) listed this pleomorphic variant in their mixed category, which also included infiltrating lobular carcinomas that display various combinations of classical, solid, and/or alveolar patterns. Also, DiCostanzo et al. (9) studied the mixed variant of infiltrating lobular carcinoma, but their study only included cases of infiltrating lobular carcinoma with classical cytologic features (small and uniform cells), and thus excluded breast carcinomas with pleomorphic nuclei.

Eusebi et al. (16) presented a series of 10 patients with pleomorphic infiltrating lobular carcinoma with prominent apocrine differentiation. Six of these patients died of their disease within 42 months of diagnosis. Three other patients developed distant metastases or suffered recurrences of their cancers within a short period of time. In contrast, only two of 22 control patients with classic infiltrating lobular carcinoma died of their disease after 48 months of follow up. The authors concluded that pleomorphic infiltrating lobular carcinoma was a very aggressive variant of infiltrating lobular carcinoma. All of their cases of pleomorphic infiltrating lobular carcinoma had the linear, single-file, and targetoid invasive pattern of classic infiltrating lobular carcinoma; but, the cytologic features were considered pleomorphic to a degree that contrasted with classic infiltrating lobular carcinoma and highlighted the difficulty of distinguishing pleomorphic infiltrating lobular carcinoma from infiltrating duct carcinoma. Furthermore, the tumor cells in their 10 cases often had eosinophilic, slightly granular, and/or foamy cytoplasm, and all immunoreacted with gross cystic disease fluid protein-15 (GCDFP-15), a known apocrine marker (16). In this same study, 22 classic infiltrating lobular carcinomas failed to react with GCDFP-15.

Weidner et al. & Cha et. al. (18,21) showed that pleomorphic infiltrating lobular carcinoma had a significantly shorter relapse-free survival rate than classical infiltrating lobular carcinoma ( $p \leq 0.05$ , when followed for  $>30$  months). Patients with pleomorphic infiltrating lobular carcinoma and no lymph node involvement were four times more likely to experience recurrence than node-negative patients with classical infiltrating lobular carcinoma. Likewise, those with positive lymph nodes and pleomorphic histology were 30 times more likely to experience recurrence. Although there appeared to be a trend toward decreased overall survival for those patients with

pleomorphic infiltrating lobular carcinoma compared to those with classical infiltrating lobular carcinoma, this difference was not statistically significant.

Invasive lobular carcinoma, like InvDC,NST, can be treated conservatively with partial mastectomy or only lumpectomy followed by whole breast irradiation (22). Recurrence rates appear to be no higher than with InvDC,NST treated in the same manner (61).

**Clinicopathologic features:** When using the criteria of Foote and Stewart, invasive lobular carcinoma constitutes ~5% of the invasive carcinomas in most series (23-25), but with less restrictive diagnostic criteria, the disease frequency increases up to ~14% of invasive carcinomas (5,6,14,15). Invasive lobular carcinoma occurs throughout the age range of most breast carcinomas in adult women (28 to 86 years, median age 45 to 56 years)(6,9,24-26,27,28). It appears more common in women over 75 years (~11%) than in women under 35 years (29). Some data suggest that invasive lobular carcinoma is more frequently bilateral than other invasive breast carcinomas (1-21). Tumor size ranges from occult, focal lesions of microscopic dimension to tumors that diffusely involve the entire breast. The median and average sizes of measurable tumors are not significantly different from the dimensions of invasive duct carcinomas. The gross presentation of infiltrating lobular carcinoma can be firm, like InvDC,NST; but frequently, it may be difficult to detect when it fails to form a discrete mass. In these cases, lesions of infiltrating lobular carcinoma can be difficult to visualize mammographically. They may feel doughy when palpated and may closely mimic benign breast disease (22). This gross presentation, coupled with its often bland cytologic features, makes the frozen-section diagnosis and evaluation of resection margins of infiltrating lobular carcinoma very treacherous. Recognition on fine needle aspiration samples may also be difficult. The diagnosis of invasive lobular carcinoma may be suspected in a fine-needle aspirate (30). FNA samples are usually sparsely cellular, containing small cells with scanty, inconspicuous cytoplasm dispersed singly or in small groups on the slide. Signet-ring cells may be found and linear arrays of tumor cells are helpful characteristic features. Invasive lobular carcinomas are not prone to form calcifications, but calcifications may be present coincidentally in adjacent benign proliferative lesions. The detection of these tumors by mammography depends largely on the recognition of a mass, but the latter does not have a specific or characteristic mammographic appearance.

The classical pattern of infiltrating lobular carcinoma is that of diffuse and/or multifocal (i.e., discontinuous) infiltration of small, round, regular tumor cells arranged in single file between collagen bundles, which sometimes encircle ducts in a targetoid or onionskin fashion. Occasional lesions form foci of small tubules, referred to as the “tubulolobular variant of infiltrating lobular carcinoma.” DiCostanzo et al. (9) detected LCIS associated with 65% of 176 classic infiltrating lobular carcinomas and 57% of 54 variant tumors. In my experience, when studied with immunoperoxidase techniques, classical invasive lobular carcinoma has always been positive for hormone receptors. This may not be true for the more poorly differentiated variant forms.

Pleomorphic infiltrating lobular carcinoma has a pattern of infiltration similar to that of the classical variant (best appreciated at low magnification); however, the nuclei are more pleomorphic and they display varying degrees of contour irregularity, more prominent nucleoli, greater hyperchromaticity, increased chromatin clumping and mitotic activity, and/or greater nuclear size (grade 2 or 3 nuclei) than do the nuclei of the classical variant. The degree of nuclear atypia can approach that found in infiltrating duct carcinomas, but, the invasive pattern characteristic of the classical lobular variant is always well maintained.

To be considered pleomorphic infiltrating lobular carcinoma, Weidner et al. (18,21) insisted that pleomorphic nuclei be present in at least half of the tumor cells composing the lesion. Also, if portions of the tumor (more than one low magnification field, 40x) showed alveolar and/or solid areas of invasion, the tumor could not be considered invasive pleomorphic lobular carcinoma.

The alveolar variant of infiltrating lobular carcinoma consists of cells of the same uniform appearance as the classical type but they are clustered in small aggregates of 20 or more cells. In the solid variant, the cells are of uniform lobular type but infiltrate in diffuse sheets with little or no intervening stroma. The tubulolobular variant is composed of cords of small lobular carcinoma-like cells in collagenous stroma. But, the cells in some cords form distinct microtubules. These tubules are smaller than those in tubular carcinoma and the invasive pattern is that of classical invasive lobular carcinoma. In tubulolobular carcinoma elastosis is often present as are foci of

low-grade (small-cell-type) duct carcinoma in situ (DCIS), which has a micropapillary, clinging, and/or cribriform pattern. Necrosis and inflammatory infiltrates are rare. For a tumor to be considered tubulolobular (and thus have a very favorable prognosis) Ellis et al. (2) insisted that the tumor display the characteristic pattern in over 90% of its area.

Invasive carcinomas showing combinations of the various "lobular" patterns are classified as mixed variant lobular carcinomas. Ellis et al. (2) insisted that a second pattern had to compose greater than 20% of the tumor to be considered mixed. Also, like Dixon et al. (6-8), Ellis et al. included in the mixed category those invasive lobular carcinomas that displayed the classical lobular morphology, but also had areas of greater cellular atypia and pleomorphism (or features overlapping with ductal NST). Ellis et al. did not consider a pleomorphic variant of invasive carcinoma, but instead chose to place "biphasic" tumors, containing less than 90% invasive lobular carcinoma and greater than 10% ductal NST, into a category of mixed ductal (NST) and lobular (apparently the remainder were considered as mixed lobular, although it is not entirely clear from the Ellis et al. paper).

When invasive lobular carcinomas metastasize to lymph nodes, the carcinoma cells may be distributed largely in sinusoids, sparing lymphoid areas. When lymph node involvement is sparse, the distinction between tumor cells and histiocytes may be difficult and reactive changes in histiocytes in the sinusoids of lymph nodes may resemble metastatic lobular carcinoma. Moreover, the metastatic patterns may mimic lymphoma. I have seen examples of invasive lobular carcinoma of the breast associated with a prominent lymphoid component that obscures the "true" diagnosis. Cytokeratin immunoperoxidase stains usually resolve these problem cases.

The metastatic patterns of lobular carcinoma are different from those of InvDC, NST, with GI tract, gynecologic system, and peritoneum-retroperitoneum metastases markedly more prevalent in lobular carcinoma (31). Central nervous system metastases usually occur as carcinomatous meningitis in the form of diffuse leptomeningeal infiltration (32,33). Intra-abdominal metastases tend to involve the serosal surfaces, retroperitoneum (32,34), or ovaries (35). Metastases to the stomach may closely mimic linitis plastica (36). Diffuse spread to the uterus and ovaries with ovarian enlargement creates the features of Krukenberg tumor with clinical and

pathologic findings indistinguishable from those of metastatic gastric carcinoma (32,34,37,38). A positive immunohistochemical stain for hormone receptors suggests metastatic breast carcinoma, but it is not specific. A better stain is GCDFP-15, which is more specific for breast carcinoma, especially if signet-ring cells are present (36).

Invasive lobular carcinomas commonly express Bcl-2, a protein that plays a pivotal role in overriding programmed cell death (apoptosis) and, thus, favors a prolonged survival of normal and neoplastic cells. Doglioni et al. (39) recently investigated the expression of Bcl-2 in 212 breast carcinomas using the monoclonal antibody 124 and correlated it with the estrogen (ER), progesterone (PR) and epidermal growth factor receptor (EGFR) status, and with other clinicopathological variables, including tumor type, grade, stage, growth fraction (as evaluated by Ki-67 immunostaining and p53 accumulation). Of the 212 carcinomas, 173 (81.6%) exhibited Bcl-2 immunoreactivity in more than 25% of the neoplastic cells. Bcl-2 immunoreactivity was strongly correlated with ER and PR expression (P 0.00001), with lobular variant (P = 0.012) and with better differentiated neoplasms (P = 0.00003), whereas it inversely correlated with EGFR (P 0.00001), p53 (P = 0.0004) and Ki-67 (P = 0.0002) immunoreactivities. No association was found with tumor stage (T and N categories). They concluded that Bcl-2 expression in breast cancers is related to the estrogen-dependent transcription pathway. Also, Bcl-2 is expressed more commonly in well-differentiated breast carcinomas (40).

The cell-cell adhesion molecular E-cadherin (E-CD) has been implicated as a suppressor substance for invasiveness, and it appears to be weakly expressed or absent in invasive lobular carcinoma. There is also loss of  $\alpha$ -,  $\beta$ -, and  $\gamma$  catenins in invasive lobular carcinoma (60).

Gamallo et al. (41) studied intensity and extension of E-CD immunoreactivity in 61 breast carcinomas and correlated these findings with their histological type and grade, nodal involvement, and hormonal receptor status. Histological types were infiltrating ductal carcinoma of no special type (n = 54) and infiltrating lobular carcinoma (n = 7). All infiltrating ductal carcinomas of no special type, except two grade 3 carcinomas, had varying degrees of positive immunoreactivity. Grade 1 breast carcinomas (n = 10) showed greater immunoreactivity than grade 2 (n = 25) and grade 3 (n = 19) carcinomas. E-CD immunoreactivity correlated positively with the degree of tubule formation and inversely with the number of mitoses. In this study, none of the

infiltrating lobular carcinomas expressed E-CD in their infiltrating cells, whereas they showed only weak immunostains in areas of atypical lobular hyperplasia and lobular carcinoma in situ.

However, the pathologists should keep in mind that in the some recent studies, a low percentage of invasive lobular carcinomas have been shown to express E-cadherin (58, 59). Therefore, E-cadherin positivity or negativity cannot be reliable factor by itself for the classification of lobular and ductal carcinomas.

Of additional interest, p53 is rarely expressed in lobular carcinoma. Domagala et al. (42) found striking differences between different histological types of breast cancer when 263 invasive breast carcinomas were tested for nuclear p53 accumulation in formaldehyde-fixed paraffin sections. Nuclear p53 accumulation was found in at least 10% of the tumor cells in 61% of the medullary carcinomas (22/36), 37% of grade 3 ductal not otherwise specified carcinomas (32/86), 4% of lobular carcinomas (2/47), and 0% (0/7) of mucinous carcinomas. Strong cytoplasmic p53 staining was noted in 32% of lobular carcinomas. Medullary and high-grade ductal breast carcinomas accumulated nuclear p53 in high percentages, but these tumors have favorable and poor prognoses, respectively. Thus, while nuclear p53 accumulation can be associated in these tumors with high morphological malignancy grades in general and with tumor cell proliferation in particular; p53 accumulation is not necessarily correlated with biological aggressiveness.

**Differential Diagnosis:** The diagnosis of the classical form of infiltrating lobular carcinoma is seldom difficult, and experienced diagnostic pathologists concur in the vast majority of cases. Yet, some invasive breast carcinomas contain features of both infiltrating lobular carcinoma and infiltrating duct carcinoma, and (so far as this author is concerned) those invasive tumors that maintain the invasive pattern of infiltrating lobular carcinoma, yet have nuclear features approaching that of duct carcinoma, represent the pleomorphic variant of lobular carcinoma. Infiltrating duct carcinomas have a more solidly cohesive invasive pattern without the diffuse, single file, multifocal, and periductal targetoid pattern of infiltrating lobular carcinoma. Obviously, the distinction between mixed ductal and lobular carcinoma and the pleomorphic variant of invasive lobular carcinoma could become quite subjective and observer dependent. In an attempt to overcome the subjectivity in subclassifying

breast carcinomas with overlapping features, this author always provides a histologic grade for all invasive breast carcinomas (regardless of subtype) according to the criteria adapted from those of Bloom and Richardson (3). Remember, occasional cases of infiltrating lobular carcinoma contain considerable foamy, histiocytoid, granular, and/or "lipid-rich" cytoplasm. The malignant cells resemble foamy histiocytes, but they can be distinguished from that cell-type by their positive cytokeratin immunostaining, concomitant lobular carcinoma in situ, and/or positive mucicarmine staining. Also, some poorly differentiated carcinomas, especially from the stomach, or medullary carcinoma from the thyroid, can metastasize to breast and mimic primary invasive lobular carcinoma.

A benign lesion that can be over diagnosed as invasive lobular carcinoma is lymphocytic lobulitis with prominent epithelioid fibroblasts (aka, "diabetic mastopathy"). Taniere et al. (43) have reported two such cases. The patients presented with rapidly enlarging masses wherein the prominent epithelioid fibroblasts were misinterpreted as malignant cells of an invasive lobular carcinoma. Although initially described in patients with longstanding insulin-dependent diabetes, more recent reports have reported cases in patients with autoimmune disorders, such as SLE and hypothyroidism.

## **LOBULAR CARCINOMA IN SITU**

Background: Lobular carcinoma in situ (LCIS) is usually an incidental finding in biopsies taken for other reasons, usually for fibrocystic changes (1,44-51). Although most common in pre- and perimenopausal women, LCIS can also occur in postmenopausal women. LCIS is a multicentric, bilateral lesion that has a well-established association with the subsequent development of invasive carcinoma (44, 46,50), and both breasts are at risk. (In a review article, Elston et al. [45] reported a 10- to 11-fold increased risk for the subsequent development of invasive breast carcinoma with a 25% absolute risk in 10 years. But, it is very important to add that absolute risk is highly dependent on patient age at the time of the initial diagnosis because the incidence of invasive breast carcinoma varies considerably with age [46]).

The distinction of LCIS from atypical lobular hyperplasia (ALH) is quantitative since individual cells of both lesions are essentially identical (48,50). Indeed, LCIS and ALH have been collectively referred to as lobular neoplasia (48, 50). ALH has a

reported 4- to 5-fold increased risk for the subsequent development of invasive breast carcinoma with a 10% absolute risk in 10 years (48, 50). ALH with duct involvement has a 7-fold increased risk, and ALH and a positive family history of breast carcinoma in a first degree relative increase the risk to 8- to 11-fold (44-46, 50).

Clinicopathologic features: LCIS has no distinctive gross appearance nor does it have a specific microcalcification pattern. Indeed, when calcospherites are present they are usually in adjacent benign structures or are apparently "overrun" by an ingrowth of LCIS cells (47). Classical LCIS is characterized by a group of acini and/or ductules filled by a monotonous (often noncohesive) population of small cells with regular nuclei, evenly dispersed chromatin, and inconspicuous nucleoli. The cytoplasm is scant and finely granular to clear; mitotic figures are rare.

As Page and Anderson state, "consistency in diagnosis of LCIS is fostered by requiring that each of the following criteria be fulfilled: 1. the characteristic and uniform cells must comprise the entire population of cells in a lobular unit, 2. there must be filling of all the acini (no interspersed, intercellular lumens), and 3. There must be expansion and/or distortion of at least one-half the acini in the lobular unit...Lesser degrees of involvement are diagnosed as ALH, a diagnosis carrying a lesser risk of subsequent carcinoma" (48). Extension of the cells characteristic of ALH/LCIS (lobular neoplasia) into segmental ducts does not allow the diagnosis of LCIS, unless the above stated criteria are met in at least one lobular unit (48). Yet, ALH with duct involvement should lead to the initiation of a careful search for LCIS by ordering level sections, submitting additional tissue, and/or slide reexamination.

**Differential diagnosis:** Variant patterns of LCIS that can be mistaken for ductal carcinoma in situ (DCIS) occur. In the most common variant pattern, the entire population of LCIS cells are not small and uniform (type A cells), but rather, are an admixture of tumor cells with more abundant cytoplasm and larger, more pleomorphic nuclei sometimes containing nucleoli (type B cells)(17). The large-cell variant can develop apocrine differentiation (11) or form signet-ring cells of varying sizes (15,16). In these instances DCIS enters into the differential diagnosis. The diagnostic problem is further complicated by well-documented examples of DCIS plus LCIS occurring within the same biopsy and even the same duct (49). Moreover, occasional microacini may form in ducts involved by cells with all the cytologic features of classical LCIS. Indeed, Page et al. (50) presented a photograph they designated as depicting the "gold

standard" LCIS (their figure 2), which contained some of these tiny microacini. Also, Fechner described both cribriform and papillary patterns of duct extension of LCIS (28). It is difficult for this author to accept that a few tiny microacini in an otherwise solid area of LCIS totally alters the biologic characteristics of the lesion to render it DCIS.

Recent data reported by Ottesen et al. (52) provide additional insight into the significance of these variant patterns of LCIS. They reported results of a follow-up study (median follow-up 61 months) of 69 patients with LCIS and 19 patients with LCIS + DCIS that had been treated with excision only. Of the pure LCIS cases, 20% showed cellular heterogeneity with a component of both small and large nuclei. The DCIS lesions showed clinging, solid, cribriform, and/or papilliferous types. This mixture prompted the authors to state that "the demonstration of LCIS in combination with DCIS in 19 of the 88 original lesions (22%) makes a theory of coincidence unlikely, but rather seems to indicate a relation between the two. Supporting this view, the components in several cases were found close together, sometimes merging, with the individual cells being hardly distinguishable in the junctional zone..." Seventeen percent (13 in the LCIS group and 2 in the LCIS + DCIS group) recurred (refinding of LCIS was not considered recurrence), and all recurrences were ipsilateral. In fact, the distribution of the recurrences within the breast among the LCIS and LCIS + DCIS groups were not significantly different. Roughly, 50% of the recurrences were invasive carcinomas. Furthermore, the frequency of recurrence was significantly associated with the number of lobules involved by LCIS and the nuclear size of the LCIS cells. LCIS lesions with less than 10 lobules involved by LCIS and small nuclear size had a 7% recurrence rate, whereas, there was a 41% recurrence rate when more than 10 lobules were involved by LCIS and the lesion contained large nuclei. Cases of LCIS with mixtures of small and large nuclei were included among those with large nuclei only. The authors illustrated LCIS with and without large cells, although they did not provide strict definitions or actual dimensions for separating small-cell from large-cell examples of LCIS.

Nonetheless, this author believes that in cases where CIS displays features of ductal and lobular types, a diagnosis of DCIS should be favored to encourage adequate local excision of the lesion. Also, mention should be made of the concomitant LCIS patterns to emphasize the possible greater risk of bilateral breast carcinoma. This will encourage adequate follow-up studies of the contralateral breast. That intermediate forms of CIS exist is no surprise, especially if Wellings is correct that the terminal

duct lobular unit complex (lobule) is the site of origin not only of LCIS but also the bulk of DCIS (53).

Cancerization of lobules by duct carcinoma may have features that overlap with the large-cell, apocrine type, and/or pleomorphic variants of LCIS. Admittedly, it would be very difficult to distinguish cancerization of lobules by DCIS from these variants of LCIS, especially if there were no "classical" areas of LCIS present in the biopsy. Furthermore, how could one rule out the concomitant presence of LCIS and DCIS? Cancerization of lobules by high-grade DCIS is usually quite easy to recognize. The lesion contains large pleomorphic cells, areas of necrosis, and mitotic figures; lumens are also often present. Yet, distinguishing LCIS from cancerization of lobules by a low-grade, non-comedo, or small-cell DCIS could be problematic. Such distinctions are not easy, likely arbitrary, and of uncertain clinicopathologic significance since the two disease processes may be more alike than different. When in doubt, it is best to favor low-grade DCIS and mention the LCIS patterns, so as to optimize both surgery and patient follow-up.

Benign lesions that may be confused with LCIS (especially the signet-ring form) are lactational changes and so-called clear-cell metaplasia of lobules. Clear-cell metaplasia can also be confused with clear-cell variants of duct carcinoma (54,55). The cause of focal lactational changes and clear cell metaplasia remains unclear, but the cytologic features are benign, and once understood should not cause diagnostic confusion (55).

When considering the diagnosis of recurrent in situ breast carcinoma in patients with prior radiation therapy, radiation-induced atypia should be considered (56). The most characteristic radiation effects produce atypical epithelial cells in the lobules associated with lobular sclerosis and atrophy. Epithelial atypia in larger ducts, stromal changes, and vascular changes were less frequent but are always accompanied by prominent lobular changes. Mitotic figures in radiation-induced atypia are rarely, if ever, seen. A final area of potential confusion is over diagnosing reactive foamy histiocytes when present either adjacent to areas of duct ectasia or when insinuating themselves between epithelial cells. These patterns mimic infiltrating histiocytoid and/or lipid-cell carcinoma or pagetoid spread of lobular neoplasia into segmental ducts.

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## Case 2:

**History: 60 y/o male with 3.1 cm partially cystic right breast mass with soft, tan cut surfaces.**

**Submitted Case Diagnosis: Intracystic papillary carcinoma**

## PAPILLARY CARCINOMA OF THE BREAST

**Background:** Among papillary breast carcinomas truly invasive tumors are rare (i.e., <2% of breast carcinomas) – that is, those whose invasive pattern is predominantly in the form of papillary structures (1-5). Among breast carcinomas, papillary patterns appear to be relatively more common in males than females, where they comprise ~17% of cases (6). Papillary carcinoma has been associated with a relatively favorable prognosis in many studies, even in women with axillary node metastases (3); but, this may reflect inclusion of many pre-invasive and/or intracystic papillary carcinomas in the various series. Recurrences often become clinically apparent more than 5 years after diagnosis. The low frequency of axillary lymph node metastases is consistent with the actual sizes of the invasive elements as well as the histologically low-grade character of most of the carcinomas (1,3). When axillary node metastases occur, they tend to involve no more than three lymph nodes (3). The papillary pattern of the primary tumor is often in the metastases.

But, some patterns of truly invasive papillary carcinoma – that is, the micropapillary invasive subtype - may not have a better prognosis when compared to similar stage and grade invasive duct carcinomas of no special type (InvDC,NST)(7,8). Indeed,

invasive micropapillary carcinoma may be highly aggressive (8). In any event, it is important that, whether cystic and/or solid, papillary carcinoma without invasion can be considered a form of “intraductal” carcinoma (1,9,10), and patients with noninvasive papillary carcinoma are essentially cured by mastectomy (1). But, recurrences can occur with pre-invasive examples, and they can be either in situ and/or invasive diseases.

**Clinicopathologic features:** Papillary carcinomas occur in an older age group (mean ages from 63 to 67 years) than InvDC,NST (11). They tend to occur centrally, and nipple discharge and/or bleeding develops in ~33% of patients (1,4). Invasive papillary carcinomas can be large tumors, due to the bulky, cystic component frequently present. The average size is 2 to 3 cm, and, as their often low histologic grade would predict, papillary carcinomas are hormone receptor-positive in the majority of cases (12,13). Papillary carcinomas are usually circumscribed, as are fibroadenomas, benign cystic lesions, and medullary or mucinous carcinomas (14,15). Invasion is suggested by an irregular contour (14). Cut surfaces are brown or hemorrhagic, but usually they are tan or grey.

Although variable, the arborescent fronds of papillary carcinoma are usually composed of very delicate fibrovascular cores; indeed, the fibrous component may be inconspicuous. The lining epithelial cells are of a single type, showing high nuclear to cytoplasmic ratios, increased mitotic activity, and usually uniform, hyperchromatic nuclei. Furthermore, the tumor cells may show stratification and resemble adenomatous polyps of the colon. Mitotic figures are variably present and more numerous in lesions that exhibit the most severe cytologic atypia. Myoepithelial cells, distributed relatively uniformly and proportionately within the epithelium in benign papillary lesions, are largely overgrown in papillary carcinomas; but, they may not be entirely absent from a papillary carcinoma. The finding of myoepithelial cells in some parts of a papillary lesion is not inconsistent with a diagnosis of carcinoma (16-18).

“Intracystic papillary carcinomas” (IPC) is an uncommon breast tumor usually developing in elderly patients (median age ~70, range 27 to 99); and, they present as discrete, circumscribed solitary masses (usually subareolar), which are present within ducts of at least 1 cm in diameter by definition (1,9). 3.5% occur in men (19). They often contain dark brown, partly clotted blood and detached degenerated papillary fragments of the tumor. Mural nodules of residual tumor can usually be found on the inner or luminal surface or in the cyst wall. Presenting as a discrete cystic mass, “intracystic papillary carcinoma” has been considered a special form of preinvasive or

intraductal breast carcinoma by some (20) or as an “encapsulated papillary carcinoma,” the latter implying a variant of circumscribed invasive carcinoma.

Carter et al. (1,9) were among the first to highlight this tumor type. In a series of 41 cases the average age was 63 years (range 42-87) and average size was 3.5 cm (range 1-14 cm). They were all cystic and encapsulated and none had infiltrating margins either by gross or microscopic examination. Adenocarcinoma projected into the cystic cavity. All had papillary patterns; 56% also had a cribriform pattern and 37% had solid areas, and sometimes the cribriform and/or solid patterns were predominate. Low-grade nuclei occurred in at least 1/3rd, spindle cell components were found in 1/4th, and a dimorphic malignant-cell population occurred in another 1/4th, which can be confused with myoepithelial cells (20). Necrosis was noted in 32%. Many intracystic lesions were bounded by zones of fibrosis, recent or old hemorrhage, and/or chronic inflammation. The fibrous wall may or may not be lined by epithelium (21).

It has been debated whether IPC are truly in situ carcinomas or circumscribed (encapsulated) nodules of invasive papillary carcinoma. Given that the demonstration of a myoepithelial cell (MEC) layer around nests of carcinoma cells is a useful means to distinguish in situ from invasive carcinomas of the breast in problematic cases, assessment of the presence or absence of a MEC layer at the periphery of the nodules that comprise these lesions could help resolve this issue. Collins et al. (22) studied the presence and distribution of MEC at the periphery of the nodules of 22 IPC and, for comparison, 15 benign intraductal papillomas using immunostaining for 5 highly sensitive markers that recognize various MEC components: smooth muscle myosin heavy chain, calponin, p63, CD10, and cytokeratin 5/6. All 22 lesions categorized as IPC showed complete absence of MEC at the periphery of the nodules with all 5 markers. In contrast, a MEC layer was detected around foci of conventional DCIS present adjacent to the nodules of IPC. Furthermore, all benign intraductal papillomas, including those of sizes comparable to those of IPC, showed a MEC layer around virtually the entire periphery of the lesion with all 5 MEC markers. In conclusion, the authors could not detect a MEC layer at the periphery of the nodules of any of 22 lesions categorized histologically as IPC. One possible explanation for this observation is that these are in situ lesions in which the delimiting MEC layer has become markedly attenuated or altered with regard to expression of these antigens, perhaps due to their compression by the expansile growth of these lesions within a cystically dilated duct. Alternatively, it may be that at least some lesions that have been categorized as IPC using conventional histologic criteria actually represent circumscribed, encapsulated nodules of invasive papillary carcinoma. Regardless of

whether these lesions are in situ or invasive carcinomas, available outcome data indicate that they seem to have an excellent prognosis with adequate local therapy alone. Therefore, we believe it is most prudent to continue to manage patients with these lesions as they are currently managed (ie, similar to patients with DCIS) and to avoid categorization of such lesions as frankly invasive papillary carcinomas. Given these observations these authors favored the term "encapsulated papillary carcinoma (EPC)" over "intracystic papillary carcinoma" for circumscribed nodules of papillary carcinoma surrounded by a fibrous capsule in which a peripheral layer of MEC is not identifiable. In another study, Esposito and coworkers (22a) used collagen type IV immunohistochemical procedure to assess "invasion" in 21 cases of pure EPC and 6 EPCs with adjacent invasive ductal carcinoma (IDC) and compared these results with those for papilloma, DCIS, and IDC. Moderate to intense collagen type IV expression was seen in all EPCs and was absent or decreased in all IDCs. All patients with pure EPC had negative axillary nodes with the exception of 1 who had a micrometastasis, and all were alive with no evidence of disease at follow-up (mean, 40.4 months). The authors concluded that EPCs are in situ carcinomas with an excellent prognosis and can be managed with local therapy with or without sentinel lymph node biopsy.

In the 41 cases reported by Carter et al. (1,9), extension of ductal carcinoma in situ (DCIS) beyond the cyst into the small and medium sized ducts occurred in 46%, and these cases were considered intracystic papillary carcinoma with DCIS. Patients with pure intracystic papillary carcinoma did not have axillary nodal metastases or recurrences, but about half of the cases with DCIS recurred, although the number of cases was small. Fifteen separately identified patients who presented with intracystic papillary lesions and truly invasive carcinoma (usually ductal type) had a ~73% incidence of DCIS and two had positive axillary lymph nodes and eventually died from breast carcinoma.

But, the association of aggressive or sometimes fatal behavior, in IPCs complicated by adjacent DCIS or invasive carcinoma has not been observed by all. For example, Solorzano et al. (23) identified three patient groups: IPC alone, IPC with associated ductal carcinoma in situ (DCIS), and IPC with associated invasion with or without DCIS. Forty patients were treated for IPC during the study period. Fourteen had pure IPC, 13 had IPC with DCIS, and 13 had IPC with invasion. The incidence of recurrence and the likelihood of dying of IPC did not differ between the three groups regardless of the type of surgery (mastectomy or segmental mastectomy) performed and whether radiation therapy was administered. The disease-specific survival rate was 100%.

Likewise, in a second large follow-up study of 917 cases, Grabowski et al. (19) found

that 47% of cases (n = 427) were “in situ” lesions (CIS), whereas 53% of had invasion (n = 490). The majority of the invasive cases were localized at the time of diagnosis (89.6%; n = 439). At 10 years, patients with “CIS” and invasive disease had a similar relative cumulative survival (96.8% and 94.4%; P = .18). There was no significant difference in the long-term survival of patients in the 2 histologically derived subgroups of IPC. Thus, there is an excellent prognosis for patients diagnosed with IPC regardless of whether the tumor is diagnosed as in situ or invasive.

The usual absence of axillary involvement and low recurrence rate after local excision suggests that wide local excision without axillary dissection is currently the treatment of choice for pure IPC. The role of sentinel lymph node biopsy has not been evaluated in this disease, but it may be an excellent alternative to full axillary dissection in patients with IPC associated with invasive carcinoma. The role of radiation therapy in these patients remains undefined. IPC associated with DCIS or invasive cancer or both and should be treated on the basis of this associated pathology. Prognosis of pure IPC is usually excellent because the malignant potential and the proliferative activity of the cancer is low. Clinicians should keep this in mind when planning surgical and adjuvant treatments, although these findings suggest that wide, local excision with sentinel node biopsy is currently the treatment of choice and that the prognosis is very favorable.

Tsuda et al. (24) reported that loss of heterozygosity (LOH) on chromosome 16q was a useful marker for the intracystic papillary carcinoma, since intraductal papilloma showed no LOH. Using the polymerase chain reaction, the malignant potential of intracystic papillary lesions may be more clearly determined

Intracystic breast carcinoma is uncommon in females and rare in males with only a handful of case reports in the literature (25-27). It accounts for 5–7.5% of all breast cancers in males. As in females, it is a localized, non-invasive breast cancer with papillary, cribriform, or solid proliferations arising within or on the wall of a large cyst. It commonly presents as a benign-appearing, well-localized lump due to its underlying cystic nature. In Japanese men, Tochika et al. (27) reported the mean age of intracystic carcinoma in males as 68.2 years. Most of the patients presented with a palpable lump. In addition to abnormalities felt on palpation, a few patients presented with mild pain, bloody nipple discharge and pruritus. Radiological studies are helpful. Ultrasonography of these lesions typically reveals a hypo-echoic area (representing the cyst) with soft tissue echoes projecting from wall of the cyst (intracystic tumour). Intracystic papillary carcinoma tends to be well-defined on mammography; an

irregular margin suggests the presence of invasion.

Some papillary carcinomas contain Grimelius and chromogranin-positive cells (neuroendocrine differentiation), which have not been found in papillomas (28). In some parts of the tumor the cell proliferation becomes so dense that basic papillary properties are obscured. Such a tumor is described as having a solid papillary pattern (28,29). Moreover, there is a broad range of mucin secretion, which can be marked in some cases; this feature is highly associated with concomitant neuroendocrine differentiation and, sometimes, invasive mucinous carcinoma. These solid papillary carcinomas have been recently reviewed (30). The authors reported that solid papillary carcinomas (SPCs) are uncommon tumors composed of circumscribed large cellular nodules separated by bands of dense fibrosis. Fifty-eight SPCs were analyzed (mean follow-up, 9.4 years). Cases were divided into three groups: 1) SPC only (32.7%), 2) SPC with extravasated mucin (8.6%), and 3) SPC with invasive components (58.7%) consisting of neuroendocrine-like (29.5%), colloid (23.5%), ductal not otherwise specified (14.5%), lobular (3%), tubular (3%) or mixed (26.5%). The mean age was 72 years. All were estrogen receptor positive and 86% were histologic grade 1. The total size of the tumor measured 0.3 to 15 cm. In the group with invasive carcinoma, the size of the invasion was 0.1 to 4 cm. Axillary nodes were involved in 13% of the cases and all of these had an invasive component in the primary tumor. Local recurrence was seen in 5 patients, all from the group with invasive carcinoma. Overall, 11.7% died of their tumor, 1 to 4 years after diagnosis (mean, 2.3 years); none of them belong to the group of noninvasive SPC. Five of the 6 patients who died of tumor had invasive components. The sixth patient who died with “metastatic signet-ring cell carcinoma” at 10 years was in the group of patients with SPC with extravasated mucin where the SPC lesion had prominent signet-ring cell features. In conclusion, SPCs are heterogeneous lesions that arise in older women and have an indolent behavior. Lymph node and distant metastases are uncommon and generally limited to cases with (conventional) invasive components

Clearly identifying invasive papillary carcinoma can be difficult in some cases. Entrapped papillary or glandular clusters of epithelial cells found in sclerotic areas with evidence of prior hemorrhage represent a diagnostic problem. Because the same pattern of pseudoinvasion occurs in sclerotic portions of benign papillary lesions, these foci are not evidence of invasion. The best evidence of invasion is clear-cut extension of tumor into stroma beyond the zone of reactive changes. Invasive micropapillary carcinoma is defined by the presence of myriads of small solid or tubular neoplastic cell groups lying within individual connective tissue “cells” formed from a spongiform-appearing desmoplastic collagenous matrix. Neoplastic cells

display the reverse polarity typical of the papillary phenotype. This is revealed by the detection of acid mucinous rims, lineal deposits of epithelial membrane antigen, and microvilli in a peripheral position, even in areas where the micropapillae resemble tubules. Most invasive micropapillary carcinomas are admixed with InvDC,NOS and/or invasive mucinous carcinoma. Lymphatic vascular invasion is seen in 2/3rds of cases, and the majority present with positive lymph nodes (8).

**Differential diagnosis:** Sclerosing papillary proliferations can be mistaken for invasive papillary carcinoma. Fibrocystic changes containing florid intraductal hyperplasia may undergo sclerosis, distortion, and entrapment of distorted ducts. This benign lesion has been variously referred to as sclerosing papillary proliferation (31), scleroelastotic lesion simulating malignancy (32), nonencapsulated sclerosing lesion (33), indurative mastopathy (29), complex sclerosing lesion (34), invasive epitheliosis (35), and radial scar (36,37). Duct adenomas also likely lie within the spectrum of sclerosing papillary lesions (38-40). They are common lesions that can be mistaken for invasive carcinoma, not only by mammogram, but also by gross appearance and light microscopy. Indeed, Fenoglio et al. (31) state in their classic report that "unfortunately, radical or modified mastectomies are still occasionally performed because a distorted sclerosed benign papillary proliferation was misinterpreted as a carcinoma, especially on frozen section."

In one series of 32 patients with sclerosing papillary proliferations (36), patients' ages at diagnosis ranged from 30 to 57 years (mean, 43 years). After being observed from 15 to 24.5 years (mean, 19.5 years), only one of the 32 patients developed breast carcinoma, a rate comparable to a control population. Furthermore, an autopsy study failed to show a higher malignant potential for sclerosing papillary proliferations (other than that expected in patients having fibrocystic changes). The investigators suggested that only those sclerosing papillary proliferations containing high-risk epithelial changes such as atypical hyperplasia and carcinoma in situ are associated with increased risk of subsequent breast cancer development (37). Fibrocystic changes and/or duct ectasia were also present in 88% of patients with sclerosing papillary proliferations; in only 9% did sclerosing papillary proliferations occur as a single lesion without fibrocystic changes (36). Multicentricity of sclerosing papillary proliferations has been noted in 44% of cases (36). On mammogram, these lesions can have an irregular stellate appearance and by gross exam, the lesions are gray-white to yellow, stellate, firm densities, and sometimes have spiculated margins, features easily confused with scirrhous carcinoma. Sclerosing papillary proliferations display a central, relatively hypocellular core composed of dense, hyalinized connective tissue

rich in elastic fibers. The connective-tissue fibers seem to radiate toward the periphery, where fibrocystic changes are arranged circumferentially and are characterized by varying combinations of duct hyperplasia, cyst formation, sclerosing adenosis, and apocrine metaplasia. The central scleroelastotic core may contain small epithelial nests and glands, which appear distorted and entrapped within the connective tissue, resulting in a pattern simulating invasive carcinoma ("pseudoinvasion").

Intraductal papillomas are benign, yet clonal, fibroepithelial lesions (21). Most occur in large ducts where they are usually single, but they also arise in peripheral smaller ducts where they are multiple in about 10% of cases (41-44). In two large series, approximately 10% of the benign papillomas had been misdiagnosed as malignant, sometimes resulting in inappropriate radical surgery (41,42). In the report of Kraus and Neubecker (42), patients with benign papilloma ranged in age from 16 to 71 years (average, 39 years). In contrast, patients with papillary carcinoma tended to be slightly older, with ages at diagnosis ranging from 29 to 78 years (average, 50 years).

Benign papillomas, like papillary carcinomas, present as masses, often near the nipple, and are sometimes associated with a bloody nipple discharge. These lesions are soft, friable tumors, usually found within dilated cysts (ectatic ducts). In one series they measured from 0.5 to 8.0 cm (mean, 2.3 cm) (42). Grossly, papillary carcinomas can appear similar to intraductal papillomas (42,45). The cysts contain fluid, which may be bloody or yellow-brown. Microscopically, intraductal papillomas show a prominent arborescent, fibrovascular core lined by a double layer of epithelial cells (which is at least focally present in all papillomas). Typically, the core has a prominent collagenous and/or spindled myoepithelial component. The lining epithelial cells have normochromatic nuclei and may have areas of apocrine metaplasia and/or typical duct hyperplasia. Adjacent ducts often have these same features, as well as areas of sclerosing adenosis. Rarely, focal comedo-like necrosis can occur; indeed, it is important to know that comedo necrosis is not an absolute indicator of malignancy. In my experience, among benign lesions, so-called subareolar sclerosing duct hyperplasia is most prone to contain some comedo necrosis.

Solitary subareolar intraductal papillomas uncommonly display adjacent duct hyperplasia, atypical duct hyperplasia, and/or carcinoma in situ (43,44); whereas, papillomas that are peripheral and multifocal are more frequently associated with duct hyperplasia, and are sometimes atypical and/or carcinomatous (43,44). In fact, some investigators feel strongly that peripheral duct papillomas are highly susceptible to

cancerous change (43-47). To some extent, this reflects a tendency in some studies to include orderly papillary carcinomas in the group of papillomas. Yet in some cases, carcinoma and a papilloma are in such close proximity that they must be regarded as parts of a single lesion. Usually, the carcinomatous component is in situ. It is important that in a detailed 3-D reconstruction study of intraductal papillomas, Ohuchi et al. (44) "accidentally" discovered that 6 of 16 patients (37%) with peripheral duct papillomas had carcinomas in "close anatomic continuity" to the benign papillomas, whereas none of the 9 patients with central duct papillomas had cancers. Thus, these observations suggest that multiple peripheral duct papillomas may be a form of "benign" breast disease deserving of complete, yet conservative, local excision, especially, when palpable and/or cytoarchitectural atypia is present. Haagensen (45) advised that "when local excision of the lesion is carried out, the surgeon must take great care to try to remove all of the grossly evident disease."

Standard histologic criteria for atypia and/or malignancy should be used in evaluating areas of duct hyperplasia that occur in conjunction with intraductal papilloma. Finally, it is important to add that in and around the bases of papillomas there may be considerable fibrosis and epithelial entrapment, resulting in a pseudoinvasive pattern. When the glands in these pseudoinvasive areas have a double cell layer cytologically identical to those found in the papilloma, their benign nature is secure. Over diagnosing the pseudoinvasive areas as invasive carcinoma (especially on frozen sections) must be avoided. But please remember that true invasive papillary carcinoma (48) and invasive micropapillary carcinoma (49) should not be underdiagnosed as benign. If there is any doubt, defer the final diagnosis until permanent sections are available, when special studies can be performed, and/or when consultation can be obtained from a trusted colleague and/or an expert in breast pathology.

Although the above criteria may seem straightforward, controversial and/or borderline cases do arise. In some cases, the double cell layer may be inconspicuous. To delineate the double-cell layer, Papottie et al (50) were among the first to propose using immunohistochemical staining with carcinoembryonic antigen (CEA) to highlight carcinoma cells and actin to highlight myoepithelial cells. Benign papillomas have a basal layer of actin-rich, myoepithelial cells, and the cytoplasm of the benign luminal epithelial cells are CEA-negative. Papillary carcinomas, including intracystic papillary carcinoma, lack the myoepithelial layer. CEA was detected in 85% of the papillary carcinomas in Papottie's study. Two of their cases of "suspected" carcinoma lacked myoepithelial cells and were interpreted as carcinomas. Other immunohistochemical studies of papillomas and papillary carcinomas have found that antibodies to muscle actin (HHF-35) were reliable markers for myoepithelial cells

(i.e., much better than an antibody to high molecular weight keratin [34BE12] and antiserum to S-100 protein). Subsequently, many reports have documented that smooth-muscle myosin, calponin, p63, and CD10 are also reliable markers for myoepithelial cells. I often employ multiple myoepithelial markers in difficult cases. Furthermore, these studies show that the presence of a few myoepithelial cells alone does not exclude a malignant diagnosis in papillary lesions such as micropapillary duct carcinoma in situ and peripheral papillomas with cancerization from adjacent DCIS. The distinction between a papilloma and noninvasive intraductal papillary carcinoma is determined by the cytology and microscopic structure of the lesion. There are no simple rules and in many cases the diagnosis is a judgment reached after assessing all the important features. When in doubt, obtain consultation. Finally, CK5/6 can be useful in highlighting benign luminal cells, CK5/6 is negative in atypical duct hyperplasia and DCIS involving an otherwise benign papillary duct lesion. But, keep in mind that CK5/6 is negative in apocrine metaplasia and columnar-cell change.

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### Case 3:

**History:** A 73 year old female with history of breast mass found by mammogram underwent percutaneous ultrasound-guided core biopsy of the left breast mass

**Submitted diagnosis:** Invasive tubular carcinoma (well-differentiated invasive breast carcinoma, overall mBR grade 1; nuclear grade 1, tubular grade 1, mitotic grade 1).

## TUBULAR AND CRIBRIFORM CARCINOMA

**Background:** Tubular carcinoma is a well-differentiated (mBR grade 1) invasive carcinoma with regular cells arranged in well-defined tubules typically one layer thick and surrounded by an abundant fibrous stroma. Tubular carcinoma should not be confused with invasive ductal carcinomas with gland-like structures whose cells are less well differentiated (1,2). Pure tubular carcinomas constitute at least 2% of all breast carcinomas (3-5) and they are being seen with increasing frequency as a result of screening mammography. Likewise, cribriform carcinoma is a well-differentiated (mBR grade 1) variant of invasive breast carcinoma, in which the majority of the invasive component grows in an irregular cribriform pattern, often admixed with features of well-differentiated tubular carcinoma. Approximately 6% of invasive mammary carcinomas have a cribriform element with nearly equal proportions of "pure" and "mixed" lesions (6,7). When the tubular component is less than 50%, some advocate use of the term "invasive cribriform carcinoma;" when over 50%, then "invasive tubular carcinoma" is suggested as more appropriate (6-8). But, because of

the often close morphologic overlap and similar prognosis, it might be more expedient to refer to these mixed lesions as “invasive tubular/cribriform carcinomas,” rather than attempt to apply such an arbitrary cutoff point. Tubular and cribriform carcinomas are likely very closely related, and probably represent different points in the morphologic spectrum of a single form of well-differentiated invasive breast carcinoma. Although tubular carcinoma can be diagnosed by FNA (9, 41), excisional biopsy is usually necessary to clearly establish the diagnosis.

The prognosis for both of these well-differentiated breast carcinomas is equivalent. A review of seven studies, including 341 women with pure tubular carcinoma, found that ~3.5% had recurrences (10); 6 in the same breast after simple excision and 6 after mastectomy. Three had axillary node metastasis, two patients had local recurrence, 3 had systemic metastases, and one patient had persistent carcinoma. Death due to pure tubular carcinoma is rare (11), but more dire outcomes occur in patients with mixed tubular and ductal carcinoma (i.e., recurrences have been reported in up to 32% of patients with mixed tubular and ductal carcinoma and 6% to 28% of these patients died)(4,5).

Two studies concluded that patients with classic cribriform carcinoma are less likely to develop axillary lymph node metastases than women with mixed cribriform (6) or ordinary invasive duct carcinoma (7). No deaths due to classic cribriform carcinoma occurred in one study of 34 patients with a 10 to 21 year follow-up (6); however, one patient had recurrence and another died of metastases from a different contralateral carcinoma. Venable et al. (7) reported a disease-free survival of 100% for 45 patients with classic cribriform carcinoma who were followed for 1 to 5 years.

Patients with unifocal pure tubular/cribriform carcinoma are candidates for breast conservation therapy and, possibly, radiation for possible recurrence. Most experts agree that low axillary dissection should be performed on patients with a tubular/cribriform carcinoma larger than 1 cm, when invasive lesions are multifocal, or if there are other indications to suggest axillary node metastases. The average frequency of axillary lymph node metastases resulting from such lesions is from 9% to 12%, but the reported range is from 6% to 30% (5,11,12). Multifocality, which occurs in ~20% of patients with pure tubular carcinoma, appears to increase the incidence of axillary metastases (13). Affected lymph nodes are usually in the low axilla (level I) and only rarely are more than three involved (11). When present, metastases in lymph nodes tend to have a tubular growth pattern. Axillary metastases are uncommon in patients with “pure” tubular carcinoma tumors 1.0 cm or less in diameter. This led Berger et al. (13) to advise against axillary dissections in such

cases. In this small tubular carcinoma group there were no axillary metastases in 14 patients; “pure” tubular carcinoma was defined as exclusively tubular differentiation with or without concomitant DCIS. But, this practice remains controversial; and, in contrast, Elson et al. (14) found metastatic tubular carcinoma in axillary lymph nodes in 4 (29%) of 14 patients who had had axillary dissections, three of whom had a primary tumor 1.0 cm or less in diameter. But in the latter series the tubular carcinoma had to have 75% or more of the classic tubular pattern to qualify. In another study of 50 patients with tubular carcinoma, Winchester et al. (15) noted a 20% incidence of axillary nodal metastases that could not be predicted by any features displayed by the primary tumors.

The average frequency of axillary lymph node metastases in patients with “mixed” tubular and ductal carcinomas is 34% (12). Because of these reports, I believe it is best to require that 90% or more of the tumor be of the classic invasive tubular pattern before a diagnosis of “pure” tubular carcinoma can be made, and the closer to 100% the better. Invasive cribriform carcinoma, even of “pure” variety, appears to metastasize more frequently to axillary lymph nodes (i.e., ~40% in one series)(7).

In view of the extremely favorable prognosis of tubular/cribriform carcinoma, there is little evidence that systemic adjuvant therapy would prove beneficial, except possibly for women with axillary metastases or if there is also a less well-differentiated carcinoma in the ipsilateral or contralateral breast. Patients with mixed tubular/ductal or mixed cribriform/ductal carcinomas should receive treatment appropriate for an infiltrating duct carcinoma of the grade of the non-tubular component as determined by tumor size and stage.

**Clinicopathologic features:** Tubular carcinomas are either incidental findings or discovered as small, stellate mass lesions. The gross appearance is similar to that of benign lesions such as sclerosing papillary lesions (aka, "radial scar") (16). Invasive cribriform carcinomas can present in a similar fashion, but more often form firm mass lesions with no distinctive features. Both tumor types, including the mixed forms, may be multifocal in a significant number of patients (i.e., ~20%) (13). About 8% of invasive carcinomas 1 cm or less in diameter are tubular carcinomas (17). Most tubular carcinomas are 2 cm or less in diameter, but some as large as 4 cm have been reported (5,11,18). This tumor is more common in older patients but the age at diagnosis is ranging from 24 to 92 years (11,18,19). For invasive cribriform carcinoma, at least one male and 113 female patients (ranging in age from 19 to 86 years) have been described (6,7,20). In my experience, when studied by immunohistochemistry, both tubular and cribriform carcinomas have always been hormone

receptor-positive (21).

Microscopically, tubular carcinomas have stellate irregular margins of haphazard invasive glands separated by abundant desmoplastic stroma (22,23). The glands have open lumina with irregular, sharply angulated contours, and are composed of a single layer of neoplastic epithelial cells (2). Some minority of glands can have more complex growth (42) Much less commonly, the glands are round or oval and of relatively uniform caliber, However, when faced with a population of rounded glands, microglandular adenosis should be a diagnostic consideration, especially if the lumens contain eosinophilic or colloid-like secretion. The cells in tubular carcinoma are homogeneous with cuboidal or columnar shapes and round or oval hyperchromatic nuclei that tend to be basally oriented and about the size of the nuclei in the adjacent benign breast epithelium (i.e., nuclear grade 1). Nucleoli are inconspicuous or inapparent, and mitoses are rarely seen. Cytoplasmic snouting is commonly present at the luminal cell border. The cytoplasm is usually amphophilic. EM shows an absent or, more commonly, a discontinuous basal lamina. Although some suggest 75%, as indicated above, I only diagnose tubular carcinoma when over 90% of the tumor exhibits the classic tubular growth pattern. When more than 10% of the tumor consists of InvDC, NST, I make the diagnosis of mixed ductal and tubular carcinoma. Nonetheless, there are studies suggesting that 75% is an appropriate cut point, because the prognosis is reported as favorable when tumors consist of at least 75% tubular elements (3,5,11,18,22).

The invasive component of cribriform carcinoma has a sieve-like or irregular cribriform growth pattern very similar to low-grade cribriform intraductal carcinomas. The round and angular masses of uniform, well-differentiated tumor cells are embedded in desmoplastic stroma. In some areas it may be difficult to distinguish between the intraductal and invasive components of the lesion. Yet, the invasive cribriform clusters are usually irregular in outline, which is in contrast to the rounded even contours of intraductal carcinoma. When present, myoepithelial cells serve as a clue to intraductal carcinoma. Mucin-positive secretion is present in varying amounts within these lumens. As previously mentioned, tubular carcinoma is often admixed (8). When present, nodal metastases from classic tumors usually also have a cribriform structure while those derived from mixed tumors are more likely to have a less well-differentiated noncribriform pattern (6,7).

Calcifications are reportedly found microscopically in at least 50% of tubular carcinomas. They may be distributed in the neoplastic glands or in the stroma but are most often found in the intraductal carcinoma component, which has been described in 60% to 84% of tubular carcinomas (4,11,18,19). It is possible to find intraductal

carcinoma in almost all tubular carcinomas. It is typically a peculiar low-grade in situ carcinoma with a clinging or micropapillary pattern, yet cribriform patterns or mixtures of the two occur as well (11,23). Coexistent lobular carcinoma in situ has been found in from 1% to 23% of patients with tubular carcinoma (14,11,18). LCIS is more common in cases of tubulolobular carcinoma (42). Foci of atypical lobular hyperplasia are also not unusual. Tubular/cribriform carcinoma does not elicit a marked lymphocytic reaction, and lymphatic-vascular invasion is extremely rare.

**Differential diagnosis:** Because of the extremely good prognosis of tubular carcinoma, one could debate the utility of separating it from benign mimics. Nonetheless, the distinction between tubular carcinoma and sclerosing adenosis can be a challenging diagnostic problem. The proliferative pattern of sclerosing adenosis is lobulocentric, and at low magnification it is almost always possible to perceive individual altered lobules in the lesion. Tubular/cribriform carcinomas do not have a lobulocentric configuration, although it can be multifocal. Individual foci of sclerosing adenosis are composed of elongated and largely compressed glands with interlacing spindled myoepithelial cells. Varying numbers of more dispersed round, oval, or angular glands are present in some cases, which have been described as tubular adenosis. Proliferation of myoepithelial cells is a regular feature of sclerosing adenosis while these cells are absent in tubular carcinoma. Both lesions may be present in fat. Cribriform areas may also be found in adenoid cystic carcinomas when gland formation is more prominent than cylindromatous elements. They are part of the spectrum of adenoid cystic carcinoma (24).

Microglandular adenosis resembles normal breast or an ill-defined, indurated area of gray-white, fibrofatty breast (essentially identical to that of fibrocystic changes, not otherwise specified). Most lesions are 3 to 4 cm in diameter, but can range from an incidental microscopic focus to 20-cm lesions (23,30-33). Microglandular adenosis can mimic invasive, well-differentiated (tubular) carcinoma (23,25-29). Microglandular adenosis is a proliferation of small uniform glands, which grow in a haphazard and diffuse fashion in the breast parenchyma (23, 30-33, 42). Although currently considered benign in most instances, some investigators believe that microglandular adenosis may be a precancerous lesion (30,33). This lesion has features of both benign sclerosing adenosis and invasive well-differentiated (tubular) carcinoma, with which it might be confused (23,30-33). In one series of 11 patients with microglandular adenosis, two patients were inappropriately treated with mastectomy (32). Typical microglandular adenosis is treatable with excision biopsy, since no metastasis of microglandular adenosis has yet been documented (32).

Microscopically, microglandular adenosis is characterized by a haphazard proliferation of fairly uniform, small, round glands in either fibrous connective tissue or fat. The growth pattern is distinctly not lobulocentric and without an intervening spindle-cell component, as observed with sclerosing adenosis. The glands are lined by a single layer of monotonous, cuboidal cells with clear (vacuolated) to eosinophilic cytoplasm. Nuclei are bland and nucleoli are small and indistinct; mitotic figures are uncommon. Gland lumens often contain deeply eosinophilic (colloid-like) secretions. Like tubular carcinoma, the myoepithelial cells are lacking (negative staining for myoepithelial markers like p63, CD10, CK5 and calponin) (42) and a basement membrane around the glands is not easily recognizable by light microscopy. However, with the help of special stain like reticulin and PAS, the basement membrane can be seen (42). Apical "snouts," like those frequently seen in tubular carcinoma, are not present.

The features most helpful in distinguishing microglandular adenosis from tubular carcinoma are a) the distribution of glands in microglandular adenosis at low magnification appears random rather than stellate (as in tubular carcinoma); b) the glands in microglandular adenosis appear uniform and round rather than having angular protrusions, which seem to dissect desmoplastic stroma; c) the epithelium in microglandular adenosis is flatter and without apocrine snouts; and d) cribriform or micropapillary intraductal carcinoma frequently accompanies tubular carcinoma but not microglandular adenosis (2325-29). Indeed, when the cribriform growth pattern comprises the majority of the infiltrating component (tubular component less than 50%), the neoplasm is called invasive cribriform carcinoma.

Recently, James et al. (33) reported on 14 patients with microglandular adenosis who also developed peculiar, yet "distinctive" invasive carcinomas in association with the adenosis (23% of cases in the authors' files). These carcinomas were associated not only with typical microglandular adenosis, but also with a form of atypical microglandular adenosis that suggested transitions from microglandular adenosis to invasive carcinoma (33). Atypical microglandular adenosis is a more pleomorphic form of microglandular adenosis that is characterized by its more complex architecture, formation of trabecular bridges in glandular lumina, cellular expansion and crowding of these lumina, and the presence of vesicular nuclei. Although more clinical follow-up is necessary to characterize these distinctive invasive carcinomas, all patients had a favorable outcome in spite of the fact that each carcinoma had a high-grade component. Atypical microglandular adenosis should be widely excised and followed as a form of atypical hyperplasia.

Sclerosing papillary proliferations (aka, radial scars) are most frequently confused with invasive, well-differentiated (tubular) carcinomas. Invasive tubular carcinomas can (23), but usually do not display the zonal character of sclerosing papillary proliferation (central hypocellular core surrounded by proliferative fibrocystic changes in a radial fashion). In addition, the pseudoinvasive glands of sclerosing papillary proliferations may display a double row of cells (myoepithelial cell layer adjacent to luminal epithelial cells) encased in a hyalinized, elastic tissue-rich stroma. Glands of invasive tubular carcinoma are composed of a single row of atypical cells encircled by relatively loose, desmoplastic stroma. Furthermore, the pseudoinvasion of sclerosing papillary proliferations is limited to the immediate periductal zone; involvement of the interlobular fat would suggest a true carcinoma. Both microglandular adenosis and sclerosing adenosis can involve fat (34-36,23). Finally, sclerosing papillary proliferations (like other forms of fibrocystic changes) can occur concomitantly with atypical hyperplasia, carcinoma in situ, and invasive carcinoma. A recent study (37) reported that atypical hyperplasia and/or carcinoma rarely associated with sclerosing papillary lesions less than 6 cm in size in women under 40 years of age. Usual histologic criteria for atypia and carcinoma should be applied in making the diagnoses.

Duct adenoma of the breast, which is likely a variant or within the spectrum of sclerosing papillary lesions, is a benign lesion that should be considered in the differential diagnosis of invasive tubular carcinoma (38,39). Lammie and Millis (39) concluded that ductal adenomas evolved by sclerosis of benign intraductal papillary lesions, although sclerosing adenosis and duct ectasia showed similarities. Azzopardi (38) noted similarities between papilloma and salivary-type adenoma. Duct adenomas are adenomatous nodules occurring in small to medium-sized ducts surrounded by densely fibrous walls. These lesions have a circumscribed, variably lobated outline, often with a central scar. Fibrous distortion leads to pseudoinvasion of central or adjacent tissues. Worrisome atypia can also occur, especially when apocrine metaplasia is present. But, demonstrating the well-circumscribed outline and the biphasic epithelial-myoepithelial differentiation are reliable criteria for recognizing this lesion as benign (38,39). Core needle biopsies of these tumors can be especially treacherous, when the lobulocentric character of duct adenoma cannot be readily appreciated.

Finally, tubular carcinoma needs to be differentiated from invasive lobular carcinoma, tubulolobular variant (40). This should not be difficult, since the invasive components of the latter neoplasm form not only small tubules, but also cords of cells more characteristic of invasive lobular carcinoma. Tubulolobular carcinoma has been

considered to have a prognosis essentially identical to pure tubular carcinoma, but this view is not held by all. Green et al. (13) noted that tubulolobular carcinomas were more frequently associated with positive axillary lymph nodes (i.e., ~43%) and multifocality (i.e., ~29%), compared to pure tubular carcinoma. They concluded that the distribution of prognostic factors suggested that tubulolobular carcinoma was a higher-grade lesion than pure tubular carcinoma.

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#### Case 4:

**History:** 57 y/o female with palpable breast mass. Patient was participating in the 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

**Submitted diagnosis:** Invasive mucinous carcinoma, "pure" (well-differentiated invasive breast carcinoma, overall mBR grade 1; nuclear grade 1, tubular grade "1", mitotic grade 1).

### MUCINOUS CARCINOMA

**Background:** Mucinous carcinoma contains large amounts of extracellular epithelial mucin, sufficient to be visible grossly, and recognizable microscopically surrounding and, sometimes, within tumor cells. These tumors have blunt, rather irregular borders. Mucin can be found in most carcinomas of the breast, but the term mucinous

carcinoma should be restricted to those tumors containing large amounts of extracellular mucin (1). “Large amounts” of extracellular mucus has been arbitrarily defined as more than 1/3rd of the tumor volume made up of extracellular mucin (2-4). Some have insisted on a 50% or more mucinous growth pattern before the diagnosis of mucinous breast carcinoma can be made; others require that at least 75% of the tumor have the distinctive mucinous pattern (3,5). I find these arbitrary percentages difficult to apply and even unrealistic. Do these definitions include the in situ component, which may be prominent and sometimes difficult to separate from the earliest phases of stromal invasion? Should we apply automated image analysis routinely? How many tumor sections should we examine? I insist on a pure pattern of classical invasive mucinous carcinoma before making the diagnosis.

Examples composed in part of areas more c/w InvDC,NOS are best diagnosed as “mixed ductal (NOS) and mucinous carcinoma” or “invasive ductal carcinoma (NOS) with marked mucinous differentiation,” and I histologically grade the tumor using either a mBR or SBR grading scheme. The admixture of InvDC,NOS with classical mucinous carcinoma worsens the prognosis and requires the designation “mixed ductal (NOS) and mucinous carcinoma.” “InvDC,NOS with marked mucinous differentiation” features marked extracellular mucin deposition, but nowhere in the invasive tumor does the volume of mucin comprise more than 1/3rd of the tumor volume. It, too, has a worse prognosis than pure mucinous carcinoma.

Pure mucinous carcinoma has been shown to have a favorable prognosis in many studies (6-11). Pure mucinous carcinomas tend to be smaller than tumors that have mixed mucinous and ductal patterns, and patients with these tumors have a lower frequency of axillary lymph node metastases (2,3,6,8,9,12). Negative axillary lymph nodes in patients with pure mucinous carcinoma range from 71% to 97% compared to 50% for patients with mixed mucinous carcinomas. Positive lymph nodes have been reported in pure mucinous carcinoma especially in cases with micropapillary pattern and in younger age (39). Therefore, sentinel lymph node biopsy and staging is recommended even for pure variants (39).

Five-year disease-free survivals, after the treatment of pure mucinous carcinoma by mastectomy, are from 84-100% (3,6,8). Patients with mixed mucinous and ductal histologies do more poorly. Komaki et al. (12) reported a 90% 10-year overall survival for pure mucinous carcinoma versus 60% for those with mixed ductal/mucinous carcinoma. Toikkanen et al. (9) reported that the 15-year disease-free survival was 85% and 63% for pure mucinous and mixed mucinous/ductal carcinoma patients, respectively. Nonetheless, late systemic recurrences can occur with pure

mucinous carcinoma (7,11,12,14). Intervals to recurrence of 25 (15) and 30 years (14) have been reported, and up to (or at least) ~27% of patients with pure mucinous carcinoma may eventually die of breast carcinoma, with ~42% of the those deaths occurring 12 years or more after diagnosis (7). These patients can be treated effectively with breast conservation and radiation therapy (16).

**Clinicopathologic features:** The mean age of women with pure mucinous carcinoma is greater than those with non-mucinous carcinoma (7-9). These carcinomas comprise ~7 percent of carcinomas in women 75 years or older and only ~1 percent in those younger than 35 years (17). They typically present as mass lesions of relatively short duration (i.e., 3 months or less) in elderly patients and are usually circumscribed masses without calcifications located mostly in upper outer quadrant (41). Irregularities and/or calcifications suggest the presence of non-mucinous components (8). They may measure from <1 cm to over 20 cm in diameter with a size distribution similar to that of breast carcinomas in general (3,9). When stroma is sparse, the tumor feels soft and gelatinous, but the cut surface is moist and glistening, even in relatively fibrotic tumors.

Pure mucinous carcinoma shows accumulation of abundant extracellular mucin around invasive tumor cells and they can be cellular or hypoceullar based on the number of tumor cells (1). The relative amounts of mucin and tumor epithelium vary from one case to another, but the distribution in any one tumor tends to be constant; and, as mentioned above, the extracellular mucin should account for 1/3rd or more of the tumor volume in all areas. In one study, the proportion of extracellular mucin relative to carcinomatous epithelium varied from ~40% to 99.8%, with a mean of 83.5% (12). Tumor cells may be sparse and difficult to detect in selected cases. The extracellular mucin is positive for mucicamin but the intracytoplasmic mucin is rarely present (1).

The amount of intracellular mucin in mucinous carcinomas is variable. Usually, only a small proportion of the tumor cells can be shown to contain mucin by histochemical procedures, but intracellular mucin can be found easily by electron microscopy (18-20). Abundant intracellular mucin, producing many signet-ring cells, suggests invasive lobular carcinoma. Careful review of additional sections may disclose the invasive lobular component. Rarely, signet-ring breast carcinomas and lobular carcinoma with over 1/3rd extracellular mucin by volume throughout the tumor have been reported (40). The proper classification and behavior of these tumors remain to be determined, but until we know with certainty, I believe they should be considered

potentially aggressive carcinomas and treated appropriately.

Ductal carcinoma in situ is present in 75% of cases. Occasionally, mucinous differentiation is evident in the intraductal component, but any pattern of DCIS can be found. One pattern is an intracystic papillary carcinoma (21), in which multiple cysts are distended with mucin and lined by papillary carcinoma. "Mucin leakage" into the stroma surrounding cysts resembles the mucin extravasation seen in mucocele-like tumors.

In invasive mucinous carcinoma, tumor cells are arranged in a variety of patterns, including strands, alveolar nests, papillary clusters, and micropapillary growth (39), as well as larger sheets that may have cribriform areas or focal necrosis. Nuclei are usually grade 1, but examples with grade 2 nuclei occur. Periera et al. (22) have defined mucinous breast carcinoma as a tumor composed of small islands (10-20 cells) of uniform small cells in lakes of extracellular mucin; any amount of invasive ductal (NOS) carcinoma places the lesion in the mixed ductal and mucinous type. They reported that the 10-year overall survival for all pure mucinous carcinomas was 81%; but, it was 86% for those examples that were mBR grade 1 and 75% for those mBR grade 2. They had no cases of mBR grade 3 tumors. I have seen occasional grade 2 pure mucinous carcinomas and even rarer examples that some pathologists might consider grade 3, and I believe additional long-term follow-up studies are needed to determine the behavior of these higher grade examples of pure mucinous carcinoma. Often, when extensively sampled, these higher grade examples of "pure" mucinous carcinoma are found to contain areas of InvDC, NOS, thus making them mixed mucinous and ductal tumors. As expected, pure mucinous carcinomas are almost always diploid (~96%)(10), but only ~40% of mixed mucinous and ductal carcinomas are diploid, with most being aneuploid.

Argyrophilic granules have been detected in 25% to 50% of mucinous carcinomas (3,4,9,14); these occur more frequently in elderly women and the tumor cells often grow in clumps, sheets, or trabeculae sometimes suggesting an endocrine growth pattern. The granules can contain immunohistochemically detectable serotonin, somatostatin, and gastrin (23). The presence of argyrophilic granules has not been prognostically significant in pure mucinous tumors or in infiltrating duct carcinomas with focal mucinous differentiation (3,24). Maluf et al. (25) have recently described a low-grade form of DCIS that shows both endocrine and mucinous differentiation. They postulated that these lesions are the pre-invasive counterpart of mucinous carcinoma with endocrine differentiation. Tsang et al. (26) have described a very similar lesion with both endocrine differentiation and mucinous carcinoma in 80% of those with an invasive component. The fine-needle aspirate from mucinous carcinoma reveals isolated cells and small clusters in a background of mucin. Occasionally, myxoid material from an edematous fibroadenoma results in an aspirate that resembles

mucinous carcinoma. A fine-needle aspiration sample, however, is not reliable for distinguishing between mucocele-like tumor, pure mucinous carcinoma, and infiltrating duct carcinoma with a mucinous component (27).

**Differential diagnosis:** Mucinous carcinoma should be distinguished from the benign mucocele-like tumor of the breast, as well as cystic hypersecretory hyperplasia and cystic hypersecretory duct carcinoma. Rosen initially described mucocele-like tumor of the breast as a benign condition characterized by extravasated mucin in the mammary stroma (a constant feature) accompanied by multiple cysts filled with mucin and lined by flat or cuboidal columnar epithelium devoid of significant papillary or other proliferative features (28). The epithelium in the typical mucocele-like tumor is largely flat or cuboidal, but columnar and focal papillary elements may be present. Large, granular calcification are also seen in the mucin in these benign lesions. Detached epithelial cells are not found in the secretion within cysts or when it is discharged into the stroma. The resultant picture resembles the mucocele of salivary gland origin commonly found in the oral cavity. (Apparently, true connective-tissue myxomas can arise in the breast (29), and these myxomas are distinct from mucocele-like tumors.)

Subsequently, it was shown that the typical mucinous cysts can be lined with hyperplastic ducts and could contain foci of low-grade papillary carcinoma (30-32). Mucocele-like tumors appear to represent a morphologic continuum from benign lesions to carcinoma in situ with abundant mucus production to invasive mucinous or colloid carcinoma (33,34). Benign mucocele-like lesion is characterized by extracellular mucin extravasation but without epithelial elements. The ducts associated with benign mucocele-like lesions are dilated and lined by bland epithelium without stratification. Ro et al. (35) described a group of mucocele-like tumors with foci of more extensive epithelial proliferation, including atypical hyperplasia, intraductal carcinoma, and focal invasive mucinous carcinoma. The secretion in various mucocele-like tumors and mucinous carcinomas had similar immunohistochemical properties and the authors proposed that mucocele-like tumor and mucinous carcinoma may be two extremes of a spectrum of lesions. Clearly, these mucocele-like lesions must be carefully and completely examined, and the patients followed because these patients may already have or develop low-grade papillary and mucinous carcinomas (30-34). While available evidence suggests that some mucinous carcinomas resemble and may arise from mucocele-like tumors, the majority appear to arise from conventional forms of intraductal carcinoma.

Cystic hypersecretory hyperplasia is characterized by ectatic ducts filled with eosinophilic, colloid-like secretion. The colloid-like secretion does not extravasate into adjacent stroma (36-38). The cysts of hypersecretory carcinoma are lined by

highly atypical malignant cells that form micropapillary projections, whereas hypersecretory hyperplastic cysts are lined by cytologically benign cells composed of cysts lined by cuboidal and columnar cytologically benign epithelium and extravasated mucin that does not contain neoplastic cells (36-38). The finding of areas with typical features of cystic hypersecretory hyperplasia, sometimes with atypia, in association with cystic hypersecretory carcinoma, suggests that these processes are related. Invasive cystic hypersecretory carcinoma consists of cystic hypersecretory intraductal carcinoma accompanied by an invasive component. These invasive carcinomas have all been poorly differentiated duct carcinomas with a solid growth pattern. Metastatic foci in the axillary lymph nodes of one patient had small cystic foci that contained eosinophilic secretions (39-40).

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#### Case 5:

**History:** 29 year old female with a breast lump who was felt by patient. Mammogram found a 2 cm suspicious mass under the nipple  
**Submitted diagnosis:** Invasive secretory carcinoma (well-differentiated invasive breast carcinoma, overall mBR grade 1; nuclear grade 2, tubule grade 2, mitotic grade 1).

## SECRETORY CARCINOMA

**Background:** A rare tumor, with a frequency of less than 0.15% of all breast carcinoma. The tumor is located near the areola in about 1/2 of cases. Although initially described in young patients and called juvenile carcinoma, secretory carcinoma may not only be found in children under 10 years of age, but also in adults as old as 73 years of age (1-6). Indeed, the majority of cases in later studies have been reported in

adults and, thus, the term “secretory” is preferable to “juvenile”. The microscopic appearance of the lesion is the same regardless of patient age. No clinical hormonal abnormality has been found to explain the secretory activity of the tumor and there is no association with pregnancy.

Secretory carcinoma has an excellent prognosis. Although secretory carcinomas have been reported to be more aggressive in adults, Rosen et al. (3) failed to find any clinicopathologic difference with age, except for a greater delay in diagnosis in younger patients. Axillary metastases occur, but they rarely involve more than three lymph nodes (6-11); and, the risk of nodal involvement is as great in children as it is in adults. Local excision is usually the initial treatment in children, and consideration should be given to retaining the breast bud in prepubertal patients. In postmenarchal children, wide local excision is adequate for small lesions, but quadrantectomy may be needed for negative margins around larger tumors. Axillary dissection is indicated, if clinical examination suggests nodal metastases. The value of radiation and/or chemotherapy remain unclear (10,11). Clearly, secretory carcinoma should not be confused with more common and more aggressive breast carcinomas such as InvDC,NST with apocrine features. Familiarity with its histologic features should allow its easy recognition.

**Clinicopathologic features:** In a review, Rosen et al. (3) found that 37% of patients were less than 20 years old, 31% were in their twenties, and the remainders were over 30. The median age of 19 patients studied at the Armed Forces Institute of Pathology (4) was 25 years (range 9 to 69 years); 14 were older than 20 years while one was a 9-year-old boy. Affected boys are usually under 10 years of age, although it was reported in a 24-year-old man (10). Secretory carcinoma is uncommon in perimenarchal girls 10 to 15 years of age. Secretory carcinomas are usually well circumscribed, white or brown, and measure from 0.6 to 12 cm. The tumor is characterized by large amounts of extra- and intracellular secretions, which are strongly PAS and mucicarmine positive. The abundant secretion is usually pale pink or amphophilic, often with a vacuolated or bubbly appearance. Tumor cells have granular, clear, signet-ring, and/or vacuolated cytoplasm, sometimes with an apocrine appearance. Indeed, secretory carcinomas are negative for gross cystic disease-fluid protein-15 [GCDFP-15], an apocrine marker (3,4). But, Lamovec et al. (12) report that two of four cases they studied were GCDFP-15 positive. All four cases were strongly positive for S100 protein and alpha-lactalbumin; two of the four were negative for CEA. These groups of tumors were diploid or near diploid and all had low S-phase fractions by flow cytometry. A control group of 13 InvDC,NSTs, which showed

considerable secretion and/or morphologic overlap with secretory carcinoma, had much less frequent S100 and alpha-lactalbumin staining.

Histologic patterns for secretory carcinoma include varying proportions of secretory microacini, solid areas, and foci of cystic papillary formations containing abundant secretion. The secretions are usually pink or amphophilic on H&E stain and the tumor cells show cytoplasmic vacuolization. Fibrous stroma may be focally prominent (especially centrally) and contain irregular tubules or ducts, simulating microglandular adenosis or tubular carcinoma (5,6). Nuclei are monotonous and cytologically bland; mitotic figures are uncommon; and DCIS may be present in adjacent breast. Secretory carcinoma can have an in situ component, consisting of papillary or cribriform, solid foci; comedo necrosis can rarely be found as well. Estrogen receptors were negative in nine tumors and positive in one; three tumors were positive and four were negative for progesterone receptors (13,14). Coexistence of juvenile papillomatosis and secretory carcinoma has been described in four patients, three of whom had the lesions concurrently in the same breast (3,13).

**Differential diagnosis:** Of the various invasive breast carcinomas, InvDC, NST with apocrine differentiation (i.e., “apocrine carcinoma”) could be easily confused with secretory carcinoma. Florid, usual ductal, hyperplasia with apocrine metaplasia or so-called apocrine adenoma could also be easily mistaken for secretory carcinoma. Distinction from the latter is confounded by the fact that apocrine metaplasia in sclerosing adenosis and radial scars, which may be identified by mammography, can be atypical (15). Observing typical areas of sclerosing adenosis, complex sclerosing lesion (i.e., radial scar), and/or usual ductal hyperplasia in adjacent breast tissues or sections should lead to the correct diagnosis.

Apocrine glands are part of the odoriferous or accessory sex gland system. They are normally present in the skin, the ears (ceruminous glands), and eyelids (Moll glands). The breasts develop from the anlage that gives rise to apocrine glands but apocrine glands are not a constituent of the normal microscopic anatomy of the mammary gland. Mammary apocrine metaplasia is seen most frequently in the epithelium of simple cysts and hyperplastic ducts but can also be found in sclerosing adenosis, fibroadenomas, papillomas, and other benign proliferative abnormalities. When studied by histochemistry or by electron microscopy, metaplastic apocrine cells formed by metaplasia are similar to the cells of normal apocrine glands (16-21). Apocrine change may occur focally in mammary carcinomas, but the diagnosis of apocrine carcinoma should be reserved for tumors in which all or nearly all of the epithelium is distinctly apocrine. Apocrine carcinomas have the same structure as other mammary carcinomas, differing only in the cytologic appearance of the cells (19,22-25). The architecture of apocrine intraductal carcinoma is similar to that

commonly found in nonapocrine intraductal carcinomas, including comedo, micropapillary, solid, and cribriform patterns. Apocrine carcinomas have nuclei that are enlarged and pleomorphic when compared to the nuclei of benign apocrine cells. Typically, nucleoli are large, prominent, and usually eosinophilic, although they occasionally exhibit basophilia. Some examples have pleomorphic, deeply basophilic nuclei in which little or no internal structure can be discerned. In these cells, nucleoli are usually not evident. In most cases the cytoplasm exhibits eosinophilia that may be homogeneous or granular, but cytoplasmic vacuolization or clearing occur and are features associated with atypical apocrine proliferations and are most prominent in apocrine carcinomas.

The tumor cells contain diastase-resistant, PAS-positive granules, which also stain with toluidine blue and are red with the trichrome stain. Cytoplasmic iron granules, a feature of benign apocrine cells, are variably present. Occasional cells may contain mucicarmine-positive secretions, but most tumors are negative for mucin and alpha-lactalbumin (26,27). Benign and malignant apocrine cells are strongly immunoreactive for GCDFP-15. This marker was positive in 55% of carcinomas, including 75% of those with apocrine histologic features, 70% of intraductal carcinomas, and 90% of infiltrating lobular carcinomas that had signet ring cell features (19,24,25). Positive staining was found in only 23% of carcinomas that did not have apocrine features and in 5% of medullary carcinomas. Staining for GCDFP-15 has not been a useful predictor of prognosis (25). Apocrine carcinoma cells contain abundant organelles, including many variably sized mitochondria (20) that often have incomplete cristae, and varying numbers of osmiophilic secretory granules (19,24,28,29). Many tumor cells also contain empty vesicles of about the same size as the osmiophilic granules. The prognosis of apocrine carcinoma, whether intraductal or invasive, is determined mainly by conventional prognostic factors such as grade, tumor size, and nodal status (22,30-32). Apocrine differentiation should be mentioned as a descriptive feature of the lesion, but it does not have prognostic or therapeutic implications.

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**Case 6:**

**History:** 66 year old female with 2.5 cm cystic-solid left breast mass with soft, tan cut surfaces.

**Submitted diagnosis:** Adenoid Cystic Carcinoma

**Background:** A variety of breast lesions exhibit myoepithelial differentiation, both benign and malignant. This should cause no surprise, since typical breast ducts are composed of a duct luminal epithelial-cell layer encircled by myoepithelial cells; and,

at least some lesions developing from these ducts should show both myoepithelial and duct luminal epithelial-cell differentiation. The most commonly encountered benign myoepithelial lesion of the breast is sclerosing adenosis, and its variants, but myoepithelial features are also expected in sclerosing papillary lesions, which have protean histologic presentations and monikers (e.g., radial scar, complex sclerosing lesion, indurative mastopathy, etc.). True neoplasms expected to show myoepithelial differentiation are many and the list continues to grow. Included in this latter category are adenomyoepithelioma and variants, salivary gland-like tumors primary in the breast, metaplastic breast carcinoma (a.k.a., “myoepithelial carcinoma”), adenoid cystic carcinoma, low-grade adenosquamous carcinoma, and breast carcinoma, “basal-cell” variant, the latter of which is thought to show, at least in some cases, myoepithelial-like differentiation.

**Clinicopathological features:** Of the malignant breast tumor showing myoepithelial differentiation adenoid cystic carcinoma deserves extensive discussion. Adenoid cystic carcinoma of the breast closely resembles adenoid cystic carcinoma of salivary gland origin, but it is much rarer in the breast, accounting for only ~ 0.1% of all breast carcinomas (1-6). Electron microscopic studies have revealed the same diverse cell types in mammary adenoid cystic carcinoma that are encountered in adenoid cystic carcinoma arising in the salivary glands. This likely reflects the common ectodermal “sweat gland” origin of both breast and salivary gland; and, it seems that there should be even more overlap in the patterns of tumors arising in both locations, but this is not usually the case. Other salivary gland-like tumors arising within the breast are very uncommon.

Indeed, breast glands and salivary glands are tubulo-acinar exocrine glands that can manifest as tumours with similar morphological features, but that differ in incidence and clinical behavior depending on whether they are primary in breast or salivary glands. Salivary gland-like tumours of the breast are of two types: tumours with myoepithelial differentiation and those devoid of myoepithelial differentiation. The first and more numerous group comprises a spectrum of lesions ranging from "bona fide" benign, such as benign adenomyoepithelioma and pleomorphic adenoma, to low grade malignant, such as adenoid cystic carcinoma, low grade adenosquamous carcinoma, and adenomyoepithelioma, to high grade malignant lesions such as metaplastic breast carcinoma (a.k.a., “malignant myoepithelioma”). A second group comprises lesions that have only recently been recognized, such as acinic-cell carcinoma, oncocytic carcinoma of the breast, and the rare mucoepidermoid carcinoma (7).

Adenoid cystic carcinoma (AdCC) is clearly a tumour with adenomyoepithelial differentiation and characterized by the presence of a dual population of basaloid and luminal cells arranged in specific growth patterns. These adenomyoepithelial features are unscored by Van Dorpe and coworkers who reported a case of adenoid cystic carcinoma arising in a tubular adenomyoepithelioma (8).

AdCCs, regardless of the anatomical site, are characterized by expression of the proto-oncogene and therapeutic target c-KIT, and seem to harbor a specific chromosomal translocation t(6;9) leading to the fusion gene MYB-NFIB and overexpression of the oncogene MYB. However, as already noted the clinical behavior of salivary gland and breast AdCC differs; while salivary gland lesions have a relatively high proclivity to metastasize, patients with breast AdCCs have an excellent outcome (9).

Mastectomy has been curative in the vast majority of cases (1, 3-6, 10-14); but, chest wall recurrence has been reported after simple mastectomy (14). Moreover, there can be isolated systemic metastases, which occur in ~10% of cases (2, 10, 15-18). This contrasts with a ~43% distant metastasis rate for salivary gland adenoid cystic carcinoma (18). In a review of ~100 cases of adenoid cystic carcinoma of the breast, there were only 12 with distant metastases. Pulmonary metastases are by far the most common site, and metastases may be detected 6 to 12 years (10, 15, 16, 19) after finding the primary breast tumor. Other metastatic sites include bone, liver, kidney, brain, thigh, pleura, mediastinal lymph node, supraclavicular lymph node, and inferior vena cava (2, 20). Many patients with systemic metastases will have negative axillary lymph nodes, but axillary metastases may occur (1, 17, 21). In fact, only three cases of axillary lymph nodal metastases had occurred in ~100 cases reviewed (2). Those with axillary metastases usually develop pulmonary metastases, and two such cases were considered to have died of metastatic mammary adenoid cystic carcinoma, but the diagnosis was not well established in one of the cases (17). This metastatic pattern clearly suggests that hematogenous spread is most common and that the clinical course is very slow with symptoms developing years after primary diagnosis. Moreover, surgical resection of these metachronous metastases has been successful in maintaining disease control (2, 18).

Adenoid cystic carcinoma occurs in adult women of the same age group as for mammary carcinoma (i.e., mean ages 50 to 63 years; range 25 to 80 years of age) (2, 3, 5, 6, 10-12, 22). Adenoid cystic carcinoma usually presents as discrete, firm masses. Uncommonly, they are detected by mammography (12). They can present “acutely” but some have been present for 10 years or more (11). Most are hormone receptor negative (12, 22, 23). Sizes vary from 0.2 to 12 cm with most between 1 and

3 cm (3, 10, 12). They are usually circumscribed, but cystic areas occur (12). They are grey, pale yellow, tan, and pink; and, they are invasive tumors composed of proliferating glands

(adenoid component) as well as stromal or basement membrane elements ("pseudoglandular" or cylindromatous component). Typically, in adenoid cystic carcinoma, the stroma is infiltrated by cell clusters containing features of smaller epithelium-lined spaces and larger myoepithelium lined cystic spaces. Adenoid cystic carcinoma has intercellular cystic spaces lined by basement membrane material and biphasic cellularity with myoepithelial cells intermixed with duct luminal epithelial cells. The tumor cells do not form apical snouts, but have low-grade nuclei, and often form delicate arches.

The adenoid parts cause resemblance to cribriform carcinoma; whereas, abundant stroma mimic scirrhous carcinoma (1, 12, 24). Growth patterns include cribriform, solid, glandular (tubular), reticular (trabecular), and basaloid areas. Adenomyoepitheliomatous and syringomatous areas occur (12), and sebaceous differentiation may be present in ~15% (25). Adenosquamous differentiation is common as a focal finding (25). Similar to grading of salivary gland adenoid cystic carcinoma, Ro et al. (1) proposed stratifying adenoid cystic carcinomas into three grades on the basis of the proportion of solid growth within the lesion (I - no solid elements; II - less than 30% solid; III - more than 30 percent solid). They found that tumors with a solid component (grades II and III) tended to be larger than those without a solid element (grade I) and were more likely to have recurrences. The only patient who developed metastatic adenoid cystic carcinoma had a grade III lesion. But, others have not observed this correlation with grade and outcome. Kleeer and coworkers (26) assessed whether histologic features and proliferative activity could identify aggressive neoplasms. They studied 31 cases of adenoid cystic carcinoma (age range of patients, 33 to 74 years). Three histologic grades were defined: grade I: completely glandular; grade II: < 30% solid areas, and grade III: > or = 30% solid pattern. In 19 of 31 cases, immunohistochemical stains for estrogen receptor were available. Twelve of 31 cases were immunohistochemically stained for Ki-67 antigen using MIB1 antibody. Ten of 20 tumors were subareolar. All tumors were grossly circumscribed; however, 12 of 20 (60%) had focal infiltration peripherally. Five of 19 tumors were estrogen receptor positive. They found no statistical correlation between MIB1 score and histologic grade, nuclear grade, infiltration of the adjacent fat or breast parenchyma, or estrogen receptor status. All patients were alive with no evidence of disease after a median follow-up of 7 years. Neither histologic or nuclear grading nor proliferative activity was useful prognosticators. None of the tumors had lymph node metastases. Thus, axillary lymph node dissection may not be necessary.

Because more than half of adenoid cystic carcinomas are infiltrative focally, the most important therapeutic goal is complete tumor removal with uninvolved margins of excision.

Pastolero et al. (27) have recently studied proliferative activity and p53 expression in four cases of adenoid carcinoma of the breast. The pathologic features examined included light microscopy; electron microscopy; immunohistochemistry using antibodies to keratin, vimentin, S100 protein, actin, estrogen, and progesterone receptors, and proliferation marker MiB-1, and p53 suppressor protein; image cytometric analysis for measurement of DNA ploidy; and molecular analysis using polymerase chain reaction single strand conformation polymorphism to assess point mutation of the p53 gene. All of the cases had a low nuclear grade, were negative for estrogen and progesterone receptors, and were DNA diploid. Three of the cases showed no evidence of metastases and had small primary tumors with low proliferative activity and absence of p53 protein expression. In contrast, one of the cases showed axillary lymph node metastases and in this case the primary tumor was large with a higher proliferative activity and expression of p53 protein, suggesting that these factors might play a role in the biological behavior of adenoid cystic carcinoma. These data suggest that detailed molecular analysis may identify a group of aggressive adenoid cystic carcinomas. We have recently studied adenoid cystic carcinomas of salivary glands and showed relatively high MIB-1 staining and frequently strong expression of Bcl-2, the apoptosis suppressor protein (28).

Some conventional, less favorable forms of mammary carcinoma may be incorrectly diagnosed as adenoid cystic carcinoma (1, 2, 13); ~50% of the cases of adenoid cystic breast carcinoma recorded by the Connecticut Tumor Registry were misclassified (13). Most of the errors resulted from including invasive duct and even multifocal intraductal carcinomas with a prominent cribriform component. Problems also occur in distinguishing adenoid cystic from papillary and mucinous carcinomas.

**Differential diagnosis:** Although many varieties of cutaneous adnexal tumors can arise in the skin and subcutis overlying the breast, some of these lesions deserve special mention because of their propensity for occurring within the breast (29-40). These are the infiltrating syringomatous adenoma of the nipple and mixed salivary-type (pleomorphic) adenoma of the breast (29-38). Given the common embryologic origin of the sweat, salivary, and mammary glands, finding similar

tumors is not surprising.

Infiltrating syringomatous adenoma is closely related to tumors described in other locations such as microcystic adnexal carcinoma, sclerosing sweat duct (syringomatous) carcinoma, and syringomatous tumor of minor salivary gland (29-31). Although locally recurrent in 50% of cases, infiltrating syringomatous adenoma should be recognized as a "benign," yet locally aggressive tumor. When infiltrating syringomatous adenoma occurs outside the nipple and within the breast parenchyma, it has been described as low-grade adenosquamous carcinoma (32). Infiltrating syringomatous adenoma presents as a firm mass in the nipple or subareolar region (1-3 cm diameter). The patient population covers a wide age group, from 11 to 76 years. (mean about 40 years). This neoplasm is composed of small ducts two cell layers thick, solid epithelial strands, and small keratin cysts that extend into smooth muscle, dermis, perineural spaces, and underlying breast parenchyma. Local excision with clear margins is the preferred curative therapy; although recurrences have occurred in up to 50% of cases. The term "infiltrating syringomatous adenoma" is preferred over "carcinoma," to avoid excessive surgery and patient anxiety. Yet, adequate treatment may require nipple resection (29-31). But, please know that Foschini et al. (41) reported six cases of invasive breast carcinoma with unusual morphological features. The ages of the female patients ranged from 46 to 79 years (mean 60.5). All tumours had areas typical of an adenomyoepithelioma. In three cases adenomyoepithelioma gradually merged with low-grade adenosquamous carcinoma. In the other three patients a sarcomatoid carcinoma was associated with adenomyoepithelial areas. A common origin was proposed for these neoplasms, which extends the morphological spectrum of adenomyoepithelial cell tumours.

Salivary gland-type neoplasms of the breast are uncommon and comprise numerous entities analogous to that more commonly seen in salivary glands. The clinicopathologic spectrum ranges from benign to malignant but there are important differences as compared with those of their salivary counterpart. In the breast, benign adenomyoepithelioma is recognized in addition to malignant one, whereas in the salivary gland a histologically similar tumor is designated as epithelial-myoepithelial carcinoma without a separate benign subgroup. Mammary adenoid cystic carcinoma is a low-grade neoplasm compared with its salivary equivalent. It is also important to appreciate that in contrast to "triple negative" conventional breast carcinomas with aggressive course, most salivary-type malignant breast neoplasms behave in a low-grade manner. Most of these tumors are capable of differentiating along both epithelial and myoepithelial lines, but the amount of each lineage-component varies from case to case, contributing to diagnostic difficulties. Well established examples of this group include pleomorphic adenoma, adenomyoepithelioma, and adenoid cystic carcinoma.

Another family of salivary gland-type mammary epithelial neoplasms is devoid of myoepithelial cells. Key examples include mucoepidermoid carcinoma and acinic cell carcinoma. The number of cases of salivary gland-type mammary neoplasms in the published data is constantly increasing but some of the rarest subtypes like polymorphous low-grade adenocarcinoma and oncocytic carcinoma are "struggling" to become clinically relevant entities in line with those occurring more frequently in salivary glands (42).

Pleomorphic adenoma of the breast occurs rarely, but it closely resembles its counterparts in salivary glands and skin, where it is also known as chondroid syringoma. Other authors consider pleomorphic adenomas of breast to be variants of intraductal papilloma with myxomatous osteocartilaginous stromal metaplasia (33). Recognition of pleomorphic adenoma in breast is important because it can be over diagnosed as malignant and result in inappropriate surgery. Indeed, Chen (34) recently reported two new cases and reviewed 24 previously reported ones. He found that inappropriate mastectomy was performed in 42% of cases of pleomorphic adenoma of the breast. Appropriate therapy is local excision with a rim of uninvolved breast. Pleomorphic adenomas of breast show little tendency to recur and even lesser tendency to metastasize.

The clinicopathologic features of pleomorphic adenomas of the breast have been nicely reviewed by Ballance et al. (37). Patients developing pleomorphic adenomas of breast have ranged from 19 - 78 years, with most tumors ranging from 0.8 - 4.5 cm (mean, 2 cm). Yet, one pleomorphic adenoma that was present for 30 years grew to 17 cm. Although pleomorphic adenomas can occur anywhere within the breast, they have a predilection to develop near the areola. Most are well-circumscribed, but can show multifocal growth or satellite lesions. Histologically, pleomorphic adenomas are composed of two cell types: duct epithelial cells and myoepithelial cells. The epithelial cells produce hyperplastic nests with focal duct differentiation (squamous metaplasia can also occur) that merges and displays varying degrees of osteocartilaginous metaplasia. Cytologic atypia, mitotic activity, and invasive growth pattern are minimal. Surrounding breast tissue can appear relatively normal or show features of proliferative fibrocystic change, including intraductal papillomas, or non-continuous invasive carcinoma. The histologic and immunohistochemical features suggest that pleomorphic adenomas arise from a single cell type capable of divergent differentiation (38). That is, cytokeratin, vimentin, glial fibrillary acidic protein, muscle-specific actin, S100 protein, epithelial membrane antigen, and GCDFP-15 expression are all variably conserved within the bimorphic population of cells found in pleomorphic adenomas (37). Pleomorphic adenoma of breast may be over

diagnosed as metaplastic breast carcinomas. Most metaplastic breast carcinomas, however, are high-grade malignancies with invasive margins, marked cytologic atypia, increased mitotic activity, regional necrosis, and an associated ductal carcinoma (in situ and/or invasive). Other pleomorphic adenomas of breast have been mistaken for adenoid cystic carcinoma, malignant phyllodes tumor, or primary breast sarcoma (38). Over diagnosis of pleomorphic adenomas based on recognition of suspicious clinical findings, a malignant frozen section appearance, or over interpretation of FNA biopsy as cystosarcoma phyllodes have resulted in unnecessary mastectomies. Recognition of the characteristic invasive patterns and significant cytologic atypia, when present, should lead to the proper diagnosis of these malignancies.

Adenomyoepithelioma has been considered in the differential diagnosis, but this distinction may be somewhat arbitrary, since pleomorphic adenomas of breast, including those arising in skin or salivary gland, can be conceptualized as "adenomyoepitheliomas with osteocartilaginous metaplasia." Obviously, the latter distinction is not quite as critical as the distinction of pleomorphic adenoma from the malignant tumors mentioned above. Clear-cell hidradenoma and eccrine spiradenoma-like tumors, all known to occur rarely in the breast, should be considered in the differential diagnosis of pleomorphic adenoma (39, 40). More recently, cylindroma of the breast has been described. Albores-Saavedra and coworkers (43) studied 4 breast cylindromas with 50 dermal cylindromas and 8 adenoid cystic breast carcinomas. Except for a modest increase in the number of eccrine ducts and reactive Langerhans cells in dermal cylindromas, breast and dermal cylindromas showed identical histologic and immunohistochemical features. Both were characterized by epithelial islands containing central basaloid cells and peripheral myoepithelial cells surrounded by a thickened, continuous, periodic acid-Schiff-positive basement membrane that was immunoreactive for collagen IV. Clusters of sebaceous cells and a few eccrine ducts are described in breast cylindromas. Cytokeratin 7 labeled predominantly the central basaloid cells, and smooth muscle actin stained peripheral myoepithelial cells in breast and dermal cylindromas. Eccrine ducts were highlighted by epithelial membrane antigen and carcinoembryonic antigen. S-100 protein and CD1a showed a variable number of dendritic Langerhans cells. Cylindromas of the breast and skin did not express cytokeratin 20, gross cystic disease fluid protein 15, or estrogen or progesterone receptor. Breast cylindroma might be confused with the solid variant of adenoid cystic carcinoma, especially in needle core biopsy specimens, because they share nodular and trabecular patterns, basaloid cells, myoepithelial cells, eccrine ducts, and hyaline globules of basement membrane material. However, adenoid cystic carcinoma displays an infiltrative growth pattern, cytologic atypia, and mitotic figures and lacks the continuous, thickened basement membrane.

Collagenous spherulosis is a recently-described benign breast lesion composed of a proliferation of duct Luminal cells and myoepithelial cells, which make abundant basement membrane material (44, 45). That collagenous spherulosis can be over diagnosed as a malignant neoplasm was demonstrated by Clement et al. (44) who reported that one of their initial 15 cases of collagenous spherulosis had been inappropriately called adenoid cystic carcinoma and three others, intraductal signet-ring carcinoma. Typically, to date, patients with collagenous spherulosis are women of from 39 to 55 years of age (mean, 41 years), who have had a breast biopsy or simple mastectomy because of the presence of a palpable mass, abnormal mammogram, or both. Collagenous spherulosis is an incidental microscopic finding, which can be unifocal or multifocal. The lesions occur in duct lumens and consist of intraductal hyperplastic cells containing focal aggregates of well-circumscribed, acellular spherules ranging in size from 20 to 100  $\mu\text{m}$ . At low power, collagenous spherulosis resembles a form of cribriform intraductal carcinoma. The spherules are usually discrete but can coalesce and range from a few to up to 50 within any given focus. The spherules stain pink-red and appear fibrillar with hematoxylin and eosin (H&E); many have a pale center and more darkly staining periphery. The fibrillar components are arranged in a concentric laminated pattern, or radiate in a star-shaped configuration, or both. Outlining the spherules in all cases seen are cells (actually myoepithelial cells) that appear to be stretched or flattened around them in some areas. Epithelial cells identical to those found in typical duct hyperplasia can also be seen (45). Adjacent breast tissue frequently contains fibrocystic changes with duct hyperplasia, sclerosing adenosis, and/or intraductal papilloma.

Intraductal signet-ring carcinoma (1, 46) should be considered in the differential diagnosis. Intraductal signet-ring carcinoma is a rare lesion composed of large, malignant cells that are vacuolated (46). The vacuoles are periodic acid-Schiff (PAS) positive (as are the spherules of collagenous spherulosis) but, in contrast to collagenous spherulosis, they are negative with collagen stains. A clear understanding of collagenous spherulosis may make it possible to distinguish it from intraductal signet-ring carcinoma.

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the breast associated with low-grade adenosquamous and sarcomatoid carcinomas. Virchows Arch (Germany), 1995, 427(3) p243-50.

### Case 7

**History: A 57 year old female with 3.4 cm well defined breast mass with firm, solid white cut surfaces.**

**Submitted diagnosis: Metaplastic carcinoma, spindle-cell carcinoma variant (poorly differentiated invasive breast carcinoma, overall mBR grade 2; nuclear grade 3, tubule/papillary grade 3, mitotic grade 2).**

### Metaplastic Breast Carcinoma

**Background:** Metaplastic breast carcinomas are a heterogeneous group that can display adenocarcinoma, squamous, spindle-cell, and/or heterologous mesenchymal growth patterns, often in various combinations (1-8). These combinations have suggested monikers such as, matrix-producing carcinoma, carcinosarcoma, spindle-cell carcinoma, and carcinoma with pseudosarcomatous metaplasia (1-8). The carcinomatous component may be minimal, hard to find, and present only as carcinoma in situ.

Metaplastic carcinomas as defined here account for less than 1% of all invasive mammary carcinomas, but up to 5% of mammary carcinomas may undergo some metaplastic change into a nonglandular growth pattern. The extent of metaplasia varies from a few microscopic foci in an otherwise typical mammary carcinoma to complete replacement of glandular growth by the metaplastic tumor pattern. Breast carcinomas with metaplasia are usually derived from poorly differentiated duct carcinomas (8), but metaplasia can occur in well differentiated tumors and, less commonly, in breast carcinomas of special type (8-10).

The average age at presentation is 55 years, and the clinical presentation is like infiltrating duct carcinoma of no special type (i.e., as a palpable breast mass usually in the 1 to 2 cm range, but occasionally as large tumors in the 20 cm range). Most metaplastic carcinomas appear as well delineated mass densities. Microcalcifications are not a common feature, but may be present and usually within a precursor carcinoma in situ component. Ossification, suggesting osteosarcomatous differentiation, appears on mammography or as gritty areas on macroscopic examination. Grossly most are firm, well delineated, and solid on cut surface. Squamous or chondroid differentiation is reflected as pearly white to firm glistening areas on the cut surface. Cystic change suggests squamous differentiation or areas of liquefactive cavitated coagulation tumor necrosis. From the biomarker perspective most metaplastic breast carcinomas are “triple negative” for ER/PR/HER2, especially in the sarcomatous components (11) and, when ER/PR/HER2 are expressed, it’s usually in the ductal adenocarcinoma component.

Some early reports indicated that metaplastic breast carcinomas had a poor survival, possibly in the range of 35% at 5 years follow-up; and, this poor survival occurred even though metaplastic breast carcinomas metastasize to lymph nodes less frequently than would be expected with invasive duct carcinomas of no special type and of similar size and grade (12). But, more recent survival studies have found that comparison with matched typical breast cancer cases there is no major difference in treatment patterns, recurrence, or survival (13). Indeed, one study suggested that their overall survival rate was 60% at 5 years and more favorable than a control group of patients with infiltrating duct carcinoma after adjustment for nodal status and tumor

size (14).

Metaplastic breast carcinomas showing mesenchymal differentiation with or without heterologous elements originate from carcinomas that undergo sarcomatous neometaplasia as a result of further genetic instability or mutations (15, 16).

Abundant ultrastructural and immunohistochemical studies have indicated that the spindle-cell components show variable myoepithelial differentiation, akin to that in mixed tumors (pleomorphic adenomas) of the salivary glands (17). It is fascinating that some myoepithelial-like differentiation has been found in so-called basal-like breast carcinoma. Thus, it is interesting that Sarrio and coworkers (18) studied metaplastic breast carcinomas and found that the epithelial-mesenchymal transition (EMT), as defined by the loss of epithelial characteristics and the acquisition of a mesenchymal phenotype, can be associated with increased aggressiveness, and invasive and metastatic potential.

**Classification:** It had been customary to separate metaplastic breast carcinomas into squamous, heterologous (i.e., cartilage, bone, and myoid differentiation), and pseudosarcomatous types. These morphologic distinctions are somewhat arbitrary because some metaplastic tumors exhibit multiple types of growth; thus, some authors have found little reason to make these distinctions. These adherents referred to all mixed carcinomas of the breast as metaplastic carcinomas, regardless of whether the metaplastic element is epithelial or mesenchymal (19, 20).

The WHO (2003) has classified metaplastic breast carcinomas into two basic types, each with subcategories. The two basic types are pure epithelial carcinoma and mixed epithelial and mesenchymal carcinoma. The pure epithelial group includes: 1) squamous carcinoma (large-cell type with or without spindle-cell metaplasia or acantholysis), 2) adenocarcinoma with spindle-cell metaplasia, 3) adenosquamous (“mucoepidermoid”) carcinoma, and 4) low-grade adenosquamous carcinoma. The mixed epithelial and mesenchymal carcinoma (carcinosarcoma) group includes: 1) carcinoma with chondroid differentiation, 2) carcinoma with osseous differentiation, and 3) carcinoma with rhabdomyosarcomatous differentiation. This discussion will follow the recommendations of the WHO classification of tumors (2003).

A common metaplastic pattern is squamous metaplasia in an otherwise typical invasive duct carcinoma, and the metaplastic component usually constitutes less than 10% of the tumor, but may comprise the entire pattern. A spectrum of squamous differentiation may be found ranging from mature keratinizing epithelium to poorly differentiated carcinoma with spindle-cell, acantholytic, or sarcomatous areas, including various combinations of these features. Yet, the specific diagnosis of

squamous carcinoma of the breast is a subtype of metaplastic carcinoma and is reserved for tumors composed entirely of keratinizing or non-keratinizing squamous carcinoma cells (3-10, 15, 21-25). It is important to rule out adjacent cutaneous or metastatic squamous carcinoma to the breast from a distant site before making the diagnosis of primary disease. Like other metaplastic breast carcinomas, squamous cell carcinomas are negative for ER/PR/HER2. The squamous differentiation is retained in metastatic foci. Squamous cell carcinoma can be graded based mainly on nuclear features and, to a lesser degree, cytoplasmic differentiation.

Spindle-cell transformation of squamous carcinoma is common but usually focal and inconspicuous. Acantholytic or pseudoangiomatous change has been reported as well and may lead to a mistaken diagnosis of angiosarcoma, and when present, acantholytic squamous carcinoma may follow a very aggressive clinical course (26). Similar aggressive behavior has been noted in primary cutaneous and oral acantholytic squamous carcinomas (27, 28). The most bland appearing and well differentiated cells often line cystic spaces; as the tumour cells emanate out to infiltrate the surrounding stroma, they become spindle shaped and lose their squamous features. A pronounced stromal reaction is often admixed with the spindled squamous carcinoma. The spindle-cell and acantholytic variants require confirmation of their epithelial nature, which are positive high molecular weight cytokeratins (CK5, CK5/6, CK14, and CK34betaE12) but negative for vascular endothelial markers. Squamous tumor cells immunostain for keratin, especially for high molecular weight keratins such as CK5/6 and for p63, which is good marker for myoepithelium, basal cells, reserve cells, and squamous cells.

Adenosquamous carcinoma of the breast is very rare invasive carcinoma with areas of well developed tubule/gland formation intimately admixed with often solid nests of squamous differentiation (WHO 2003). Since focal squamous differentiation can occur in typical infiltrating duct carcinomas of no special type (i.e., in up to 5% of cases), there should be a prominent admixture of invasive ductal and squamous carcinoma before the term adenosquamous carcinoma is used. Unlike other metaplastic breast carcinomas, the adenomatous component may be ER/PR/HER2 positive and prognosis is roughly proportional to size and grade of the tumor.

A very rare variant has been reported as low-grade mucoepidermoid carcinoma of the breast, which is similar to those occurring in the salivary glands (WHO 2003). They behave as low-grade carcinomas. Furthermore, a second rare variant has been reported as low-grade adenosquamous carcinoma or syringomatous squamous tumour – that is, a metaplastic breast carcinoma morphologically similar to adenosquamous carcinoma of the skin. The same lesion has been interpreted as an infiltrating syringomatous

adenoma by others who prefer to avoid carcinoma for a group of lesions that mainly recur after local excision (28a). Both glandular and squamous differentiation coexists in this very low-grade carcinoma, and a highly infiltrative growth pattern is responsible for the high local recurrence rate. They are cytologically bland and do not metastasize to distant sites and some examples have reached 8 cm in diameter. Lymph node metastatic spread is extremely rare and noted in a single case. Their stroma is typically "fibromatosis-like" being cellular and composed of bland spindle cells, but can be collagenous, hyalinized or variably cellular. Some low-grade adenosquamous carcinomas occur in association with a central sclerosing papillary lesion or sclerosing adenosis. Low-grade adenosquamous carcinoma lack hormone receptors.

Adenocarcinoma with spindle-cell metaplasia is an unusual invasive duct adenocarcinoma with abundant spindle cell transformation, and the spindle cells are glandular in nature. The spindle cells immunoreact with epithelial markers including CK7, but not with CK5/6 or other markers of squamous/myoepithelial differentiation. Electron microscopy reveals glandular lumens in the spindle cells. Prognosis is determined by the size and degree of differentiation, as well as pathologic stage. Most occur in postmenopausal women, presenting as discrete masses.

Matrix-producing metaplastic carcinoma is a carcinoma with direct transition to a cartilaginous or osseous stromal matrix without an intervening spindle cell zone or osteoclastic cells (1). More commonly, the heterologous areas develop from a spindle-cell component. Metaplastic cells in the osseous and cartilaginous matrix stain for S-100 protein and vimentin, with variable and sometimes negative reactivity for keratin and epithelial membrane antigen. Metastases derived from a metaplastic carcinoma may be entirely adenocarcinoma, entirely metaplastic, or a mixture of both. A minority of axillary metastases actually contain heterologous components, but they are found more commonly in local recurrences on the chest wall and in visceral metastases (8, 19). Davis and coworkers (29) studied 22 patients with metaplastic carcinoma of the breast with pure or almost pure sarcomatoid morphology. Patients were included in the study if their tumors had sarcomatoid morphology and: 1) an invasive carcinomatous component identifiable on hematoxylin and eosin stains comprising less than 5% of the invasive tumor; or 2) associated ductal carcinoma in situ; or 3) immunohistochemical expression of keratin in the sarcomatoid areas. Axillary lymph node dissection or limited axillary node excision was performed in 17 patients, including 1 patient who had a sentinel lymph node biopsy. Lymph node involvement occurred in only 1 patient and consisted of a single 3.5-mm metastasis. Clinical follow-up was available for 21 patients and ranged from 4 months to 155 months (median follow-up, 35 months). Ten patients experienced local relapse, including 7 of 11 patients treated with breast-conserving surgery, and 9 developed

distant metastases, most frequently to the lungs. These findings suggested to these authors that metaplastic sarcomatoid carcinomas that lack or have only a minimal overt invasive carcinomatous component have a biologic behavior similar to that of sarcomas. In addition to systemic treatment, early aggressive local therapy is recommended, as these patients have a high rate of local relapse.

It seems prudent to conclude that patients with high-grade metaplastic tumors are likely to have a relatively poor prognosis, and should be treated like patients having poorly differentiated (modified Bloom-Richardson grade 3) invasive duct carcinoma, not otherwise specified. These are usually of the mixed epithelial and mesenchymal carcinoma (carcinosarcoma) group as defined by the WHO (2003) includes: 1) carcinoma with chondroid differentiation, 2) carcinoma with osseous differentiation, and 3) carcinoma with rhabdomyosarcomatous differentiation. When a diagnosis is made the heterologous components should be clearly listed. Grading is based on nuclear features and, to a lesser degree, cytoplasmic differentiation. The spindle-cell elements may show positive reactivity for cytokeratins, albeit focally, and in some cases keratin reactivity is lost entirely. Chondroid elements are S-100 positive and may coexpress cytokeratins, but are negative for actin. As discussed, many of these tumors are negative for ER and PR both in the adenocarcinoma and the mesenchymal areas, but the adenocarcinoma component may be ER and PR positive if well to moderately differentiated.

Thus far, most patients have been treated by mastectomy and axillary dissection, but local recurrences were reported in two of three patients after initial treatment by local excision for heterologous metaplastic carcinoma (8). The frequency of positive axillary nodes associated with heterologous metaplastic carcinoma, including so-called matrix-producing tumors, ranges from 6% to 25%, and disease-free survivals, after 5 years or more of follow-up, have ranged from 38% to 65% (1, 3, 8, 19). Clearly, stage is important in predicting prognosis.

As noted above many metaplastic carcinomas are clearly high-grade tumors and easily recognizable as malignant; however, some varieties of so-called spindle-cell carcinoma of the breast can appear deceptively benign (2, 6, 20). These tumors are often misdiagnosed as nodular fasciitis, fibromatosis, granulation tissue reaction, or squamous metaplasia. They can also be misclassified as low-grade sarcoma or fibrosarcoma. Yet spindle-cell carcinomas appear to have the same aggressive behavior as that of infiltrating duct carcinomas. The cumulative 5-year survival for spindle-cell carcinoma of the breast has been reported at 64%, which is a better

survival rate than is usually reported for cytologically high-grade metaplastic breast carcinomas (2). Although large tumors are more likely to recur, other histologic features such as grade, cellularity, mitotic activity, differentiation of the carcinoma, presence of squamous epithelium, and degree of inflammation do not correlate with outcome (2). More specifically, Wargotz and Norris reported that "seven (41%) of the 17 neoplasms that lacked intraductal carcinoma or overt infiltrating ductal carcinoma had been diagnosed originally as fasciitis, fibromatosis, or low-grade mesenchymal tumor and had received excisional biopsy. Five (71%) of these "low-grade" appearing tumors recurred locally and more extensive surgical therapy was performed, but two of the patients subsequently died from tumor. It is important that four of the other ten patients in this group also eventually died from tumor. Twelve patients died of causes unrelated to their breast cancer. The cumulative 5-year survival rate for 100 patients with spindle-cell carcinoma, adjusting for patients who died from other causes, was 64%." Also, more recent studies of spindle-cell (sarcomatoid) carcinoma of the breast have found them to be highly aggressive neoplasms with a high rate of extranodal metastases (including the cytologically bland fasciitis-like variant) – although they may have a significantly lower rate of nodal metastases than conventional ductal and lobular carcinomas (30).

In contrast, some have suggested that the cytologically bland fasciitis or fibromatosis-like spindle cell carcinomas are more likely to follow a more favorable course with local recurrence and rare distant metastases. However, before this can be concluded, caution is advised. I believe we should be careful about implying they are locally recurrent-only tumors. Indeed, a recent publication underscores the need for caution before concluding that the bland spindle-cell breasts are not aggressive. Carter and coworkers (30) studied spindle cell (sarcomatoid) carcinoma of the breast, a rare variant of breast cancer that has been classified under the broad rubric of metaplastic carcinoma. Based on this series, spindle-cell/sarcomatoid carcinoma of the breast is a highly aggressive neoplasm with a high rate of extranodal metastases. Purely spindled/sarcomatoid tumors have a significantly lower rate of nodal metastases than conventional ductal and lobular breast carcinomas. Not surprisingly, large tumors with high nuclear grade and frequent mitoses were generally (but not always) aggressive. They also found somewhat surprisingly that even low-grade tumors were capable of aggressive behavior with metastases and subsequent mortality. Of the 6 low-grade tumors with follow-up information, 33% (2 of 6) died of metastatic disease, 1 patient was alive with widespread metastases, and 1 patient was alive with chest wall involvement and metastases to the axilla. The further observed that this group of tumors appeared to be more aggressive than conventional ductal carcinomas of similar size, with an apparent tendency for somewhat earlier systemic metastasis, and that

there appear to be no histologic features that reliably predict good prognosis in this group of tumors.

**Differential diagnosis:** Not all squamous lesions in the breast are malignant, as shown by reports of post-traumatic lobular squamous metaplasia (31), mixed squamousmucous cysts (32), squamous metaplasia in gynecomastia (33), infarction with squamous metaplasia of intraductal papilloma, Zuska's disease (squamous metaplasia of lactiferous ducts) (34-36), and squamous metaplasia in phyllodes tumors and fibroadenomas (37). Finally, given the myoepithelial nature of many metaplastic breast carcinomas, so-called adenomyoepithelioma of breast should be considered in the differential diagnosis. Due to the marked differences in tumor aggressiveness and therapy, typical adenomyoepithelioma should be clearly distinguished from the spindle-cell variant of metaplastic breast carcinoma. Examples of "malignant myoepithelioma" or "myoepithelial carcinoma" or "adenomyoepithelioma with undifferentiated carcinoma" are scattered throughout the literature (38-42).

A significant spindle-cell component can be found in many breast lesions, both benign and malignant. Even though these lesions may not be entirely spindle-celled (e.g., phyllodes tumor) sampling error caused by a core biopsy may sample predominantly spindled areas without the other identifying components being present. Benign lesions that can have a significant spindle-cell component include: desmoid fibromatosis, fibroadenoma, some examples of sclerosing adenosis, inflammatory myofibroblastic tumor (a.k.a., inflammatory pseudotumor), myofibroblastoma, leiomyoma, spindle-cell lipoma, cellular angiolipoma, pseudoangiomatous stromal hyperplasia, and repair reaction to a prior biopsy site or traumatic fat necrosis (43). Malignant breast lesions that can have a significant spindle-cell component include: phyllodes tumor, periductal stromal sarcoma, CD10 positive stromal sarcoma, primary breast sarcomas (a.k.a., stromal sarcoma), and angiosarcoma. We will begin our discussion with benign lesions.

**A. Benign Spindle-cell Breast Lesions:** Desmoid or aggressive fibromatosis of the breast is a rare benign mesenchymal transformation of connective tissue origin, usually associated with the fascia of the pectoral muscles or the Cooper ligaments (44-49). Occasional cases are associated clinically with Gardner's syndrome or familial multicentric fibromatosis (44). Only histologic examination can lead to the final diagnosis. In the breast, desmoid or aggressive fibromatosis behaves the same as when

it arises in other soft tissue sites: an aggressive infiltrative lesion with a proclivity for local recurrence after inadequate excision but without potential for distant metastases (44-50). The therapy of choice is excision with margins clear of the fibromatosis (44-50). Mastectomy is not necessarily indicated, but inadequate excision can lead to multiple recurrences, chest wall invasion, and eventual death due to pulmonary complications (46).

Of interest, Pettinato and colleagues (51) reported two cases of a peculiar "fibromatosis" of the breast characterized by a proliferation of spindle cells containing intracytoplasmic, spherical, eosinophilic inclusion bodies. Both patients were free of disease 16 and 18 months after surgery described as "simple excision" and "excision biopsy." They also often immunoreact with antibodies to muscle actins and desmin, but they are negative with antikeratin antibodies (51).

Sclerosing lymphocytic lobulitis is an inflammatory breast lesion that can mimic carcinoma. It is of probable autoimmune cause (52, 53). Moreover, many reports emphasized the association of sclerosing lymphocytic lobulitis with diabetes, especially type 1, less commonly type 2 (a.k.a., diabetic mastopathy) (54-56). But, essentially identical lesions occur in nondiabetic patients, often with other evidence of autoimmune disease (e.g., Hashimoto's thyroiditis or circulating autoantibodies) (52, 57). The masses show lymphocytic lobulitis (i.e., mature lymphocytes and plasma cells surrounding acini and invading across basement membranes), "lymphocytic vasculitis" (mature lymphocytes surrounding small venules), and dense keloidlike fibrosis, which in 75% of cases contains peculiar epithelioid cells embedded in the dense fibrous tissue (56). According to some reports (56), the lobulitis and vasculitis can be found in nondiabetic patients, but the epithelioid fibroblasts appear to be much better developed, possibly unique, in the diabetic condition. However, others question the specificity of this feature, because of identical findings in patients with type 2 diabetes and nondiabetic patients (58). What is important in this discussion is that the epithelioid stromal cells in sclerosing lymphocytic lobulitis can sometimes be so prominent and abundant that the possibility of an infiltrating carcinoma or granular cell tumor can be

seriously considered (59). These epithelioid stromal cells are fibroblastic in nature. Breast fibroadenoma is among the most common benign, mass-forming lesions of the breast. Roughly 7% of women seeking evaluation of a breast lump will have fibroadenoma. They are likely neoplastic; indeed, cytogenetic analysis of fibroadenomas has revealed clonal chromosome aberrations of the stromal cells in about half, supporting a neoplastic origin in some cases (60). Most fibroadenomas are sharply demarcated, firm masses, usually no more than 3 cm in diameter. They are

solid, grayish white, and bulging, with a whorl-like pattern and slitlike spaces; necrosis is rare.

Morphologic variations found in fibroadenoma include the following:

1. Stromal hyalinization, calcification, or ossification, especially with aging,
2. Focal stromal multinucleated giant cells,
3. Areas of stromal mature fat, smooth muscle, myxoid change, or cartilage (61-64),
5. Areas of squamous metaplasia, but phyllodes tumor should be ruled out,
6. Focal lactational changes, not necessarily associated with pregnancy or nursing,
7. Focal infarction, which is rare but usually associated with pregnancy,
8. Irregular or ill-defined margins that blend or admix with surrounding fibrocystic breast tissues, suggesting multifocality (this form has been designated fibroadenomatosis or fibroadenomatoid hyperplasia, and may explain some recurrences),
9. Areas of apocrine metaplasia,
10. Areas of sclerosing adenosis (i.e., mixed fibroadenoma–sclerosing adenosis tumor),
11. "Complex" fibroadenoma change, which has been used when fibroadenomas have cysts, sclerosing adenosis, calcifications, or papillary apocrine changes.

So-called juvenile fibroadenoma is associated with young age, large size, and hypercellularity (64-74). The juvenile fibroadenoma occurs in adolescents (often in blacks and sometimes involving both breasts), reaches a large size (even up to 10 cm), and shows hypercellularity of glands or stroma. These attributes can be found independently of each other, but there is clearly a link between them. Various names have been applied to these lesions, including juvenile fibroadenoma (63, 72, 73), giant or massive fibroadenoma, cellular fibroadenoma (73, 74) and fibroadenomas with atypical epithelial hyperplasia (72). Distinguishing cellular fibroadenoma from benign phyllodes tumor may be more of an academic exercise than a practical one, since both are easily managed by conservative local therapy, even with recurrence (64-74).

Malignant change in fibroadenomas is found in approximately 0.1% of the cases (75, 76) and involves the epithelial component in more than 90% (75-79). Carcinoma in situ within fibroadenoma can be of the lobular or the ductal type; both occur with nearly equal frequency (75). I and others (69) have seen benign fibroadenoma develop into osteosarcoma.

Sclerosing adenosis has a broad spectrum of presentations that can mimic may be associated with a 1.7-fold increased risk for the development of invasive breast cancer. These authors included sclerosing adenosis in the group of histopathologically defined lesions termed proliferative breast disease (or changes) without atypia, which

implies a relative risk for development of invasive cancer of 1.5- to 2.0-fold above that of the general population (80).

Although most examples of sclerosing adenosis are easily diagnosed, this lesion is misinterpreted as invasive carcinoma more than any other benign breast lesion (80, 81). Sclerosing adenosis occurs most commonly in the childbearing ages and perimenopausal years (80-83).

Sclerosing adenosis is composed of a cellular proliferation of both duct luminal cells that form acini and spindled myoepithelial cells that impart a sclerotic quality. An important diagnostic feature is that sclerosing adenosis grows within and expands lobules (often in multiple adjacent foci to form an aggregate) while maintaining the circumscribed, lobulocentric pattern of benign breast lobules. This lobulocentric growth has a whorled and pseudoinvasive quality. Like invasive carcinoma, sclerosing adenosis may show perineural "invasion" and involve vessel walls (84).

Foci of sclerosing adenosis can occasionally merge with areas consistent with microglandular adenosis, a related lesion that shows a more haphazard proliferation of benign glands (85). Both sclerosing adenosis and microglandular adenosis maintain a well-developed basal lamina around glands, a feature that can be highlighted by immunohistochemical stains for type IV collagen or laminin (86). Moreover, in sclerosing adenosis, duct luminal cells are surrounded by myoepithelial cells, which bind with antibodies to smooth muscle actin (86).

When sclerosing adenosis is involved by carcinoma in situ (most commonly LCIS, but it may be DCIS), the pattern mimics invasive carcinoma (87). Antibodies reactive for smooth muscle actin, calponin, and/or p63 can be used to demonstrate the intact myoepithelial cells to assist in distinguishing carcinoma in situ within sclerosing adenosis from invasive carcinoma (88).

Myoepithelial cells are known to be components of both benign and malignant tumors of sweat, salivary, and mammary gland origin (38-41, 89-108). In these tumors, myoepithelial cells can demonstrate squamous, chondromyxoid, plasmacytoid, clear cell, and myoid spindle-cell differentiation (38-41, 89-108). Pure myoepithelial cell tumors are called myoepitheliomas, and those also containing glandular elements are called adenomyoepitheliomas (89).

Adenomyoepitheliomas of the breast have been well documented in the English-language literature (109). Some of these tumors are described as either myoepithelioma or leiomyosarcoma (89, 110). Yet the bulk of the English-language literature indicates that adenomyoepitheliomas present as breast masses (on average, 2 to 3 cm) in the same age range as for patients with breast carcinoma. They are firm to

rubbery, and can mimic carcinoma grossly. They have a biphasic cytoarchitecture composed of tubular structures lined by duct luminal epithelial cells surrounded by myoepithelial cells that have spindle cell or polygonal cell shapes (often with clear cytoplasm). The myoepithelial cells may predominate, necrosis may be present, and mitotic activity can be brisk, measuring up to 10 mitotic figures per 10 high-power fields. Because of the marked differences in tumor aggressiveness and therapy, typical adenomyoepithelioma should be clearly distinguished from the spindle cell variant of metaplastic breast carcinoma. Moreover, closely related examples of "malignant myoepithelioma" or "myoepithelial carcinoma" or "adenomyoepithelioma with undifferentiated carcinoma" are scattered throughout the literature (38-42). A peculiar DCIS variant has been described that is characterized by the intraductal growth of carcinoma cells having clear cell and spindle cell myoepithelial differentiation (111). Myofibroblastoma of breast, a tumor showing myofibroblastic differentiation without epithelial features, simulates spindle cell adenomyoepithelioma and other spindle tumors of the breast (112). Myofibroblastomas have a predilection for occurring in men, but they are benign tumors in either sex. Immunoreactivity for S-100 protein and cytokeratin was absent in the 10 tumors examined, but desmin immunoreactivity was focally present in three lesions. Others have reported examples of myofibroblastoma that have been vascular and/or having infiltrating borders. Cellular examples of the angiolipoma of the breast could also simulate the spindle-cell carcinoma and even angiosarcoma (113); and don't forget, spindle-cell and atypical lipomas can occur in the breast rarely simulate other spindle-cell tumors.

Pseudoangiomatous hyperplasia (PASH) of mammary stroma is a benign proliferation of keloidlike fibrosis within which there are slitlike pseudovascular spaces. Its main importance is in its similarity to low-grade angiosarcoma (114, 115). The importance of distinguishing PASH from angiosarcoma may have become even greater because there are recent reports of the development of secondary angiosarcoma after tylectomy and postoperative radiation therapy and after segmental mastectomy complicated by lymphedema (116, 117).

The criteria for breast hamartoma remain somewhat unclear, but its recognition currently depends on the combination of clinical, radiologic, and pathologic criteria. It represents growth malformation of normal breast tissues in a dysmorphic or abnormal configuration. It presents as a breast mass and exhibits diverse appearances, which include an admixture of epithelial and stromal elements. Stromal elements may show extensive PASH changes. The stroma usually includes mature fat (118-121). A reproducible morphologic distinction of this process from circumscribed fibrocystic disease and fibroadenoma has yet to be achieved. Myoid hamartoma is a form of

sclerosing adenosis wherein the stroma shows extensive myoid metaplasia. Chondrolipoma are benign lesions composed of an admixture of fat, cartilage, and sometimes bone (122-124).

Leiomyoma usually involves the nipple but is occasionally seen within the breast substance. Some have been reported to have epithelioid features and granular changes (125). Benign peripheral nerve tumors of both schwannoma (126) and neurofibroma types occur in the breast.

Another benign spindle-cell lesion that can occur in the breast is inflammatory myofibroblastic tumor, a lesion distinct from post-operative myofibroblastic repair reaction and traumatic fat necrosis, although the latter two can be mistaken for spindle-cell carcinoma. My colleagues and I (127) recently encountered three patients who developed firm, mobile, non-tender masses in their breasts. Two were discovered by the patients and one following mammography. Macroscopically, the nodules were firm, circumscribed, yellow on cut sections, and composed of interlacing cytologically bland; spindle cells admixed with chronic inflammatory cells, (the latter predominantly of lymphocytes and plasma cells). Immunohistochemistry yielded strong, smooth-muscle actin (SMA) reactivity within the spindle cells; two lesions were negative for pankeratin, one was focally and weakly positive. No lesions were positive for anaplastic lymphoma kinase (ALK-1), desmin, S100, CD34, CD21, or CD35. In each case, a diagnosis of inflammatory myofibroblastic tumor was made (a.k.a., inflammatory pseudotumor). Following conservative excision with apparently negative margins, there has been only been a single recurrence in one patient after three months. The latter recurrence was managed successfully with a second excision (127).

**B. Malignant Spindle-cell Lesions of the Breast:** Phyllodes tumors (cystosarcoma phyllodes) are rare breast neoplasms (0.3% of all tumors) that represent up to 2.5% of all fibroadenomatous breast lesions (128). Phyllodes tumor is composed of mixed epithelial and stromal elements, which makes it difficult to clearly distinguish it from typical fibroadenoma at one end of the spectrum and soft tissue sarcomas at the other. Phyllodes tumors of the breast present as circumscribed, slow-growing masses ranging widely from 1 to 30 cm or more. Reported average sizes vary from 4 to 8 cm, with malignant forms being larger (129). In one series, the age of patients ranged from 9 to 88 years (a mean of 44 years with 80% between 31 and 60 years) (128). They are rare in patients younger than 20 years (64-71). Moreover, like fibroadenoma, phyllodes tumors occur only rarely in men (130, 131).

In macroscopic appearance, phyllodes tumors are more or less circumscribed and are composed of connective tissue and ductal epithelium, as are fibroadenomas; however, in phyllodes tumors, the connective tissue shows greater cellularity. They are fleshy tumors with spaces filled with leaflike (phyllodes) projections leaving residual cleftlike spaces. The connective tissue component can contain foci of myxoid, adipose, osseous, chondroid, and even rhabdomyomatous cells (132, 133). The increased cellularity is often noted immediately adjacent to the cleftlike spaces lined by epithelium, but this area of stromal condensation may be somewhat separated from the epithelium by a grenz zone (134).

Although prediction of biologic behavior by histologic criteria is difficult with phyllodes tumors, the World Health Organization considers it useful to separate cases into three categories (benign, borderline, and malignant), which are based on the extent of mitotic figures, infiltrative margins, cellular atypia, and cellularity. Local recurrences are much more frequent than distant metastases. In a review of 187 cases, Grimes reported an overall local recurrence rate of 28%, which was independent of the degree of malignancy (benign 27%, borderline 32%, malignant 26%). No morphologic features predicted recurrence. In this series, distant metastases occurred in 8 of 100 cases with follow-up (2 borderline and 6 malignant). Stromal overgrowth, mitotic rate greater than 15 mitotic figures per 50 high-power fields, and cytologically atypical cells characterized seven of the eight metastasizing tumors. The high local recurrence rate of phyllodes tumors suggests multifocal growth as reported by Salm. Similar, multifocal fibroadenomas can occur in women and men; when florid, they are referred to as fibroadenomatoid hyperplasia (135).

In a review of 26 cases, Ward and Evans studied a number of clinicopathologic features (tumor size, stromal overgrowth, tumor necrosis, mitotic rate, stromal cellularity, nuclear size, nuclear pleomorphism, specialized stroma, and initial therapy) and correlated their ability to predict local recurrence, uncontrolled local recurrence, and distant metastases. Of the 26 tumors, 7 caused death (5 from metastases and 2 from extensive local recurrence), and 6 of the 7 had stromal overgrowth, defined as mesenchymal proliferation with complete absence of a ductal epithelial element in an area greater than one low-power (x40) field (excluding occasional broad stromal portions of epithelium-lined papillary structures that could, by carefully selecting a given field, fulfill this criterion). With the exception of tumor necrosis (not infarct), which appeared dependent on stromal overgrowth, all the other studied factors were not significantly related to clinical behavior. Likewise, Hart and colleagues stressed the importance of stromal overgrowth in predicting metastasis. Some tumors may have to be extensively sampled to find the focal area of stromal

overgrowth (136).

While acknowledging that there were no consistently reliable morphologic landmarks for predicting outcome, Azzopardi stated that features favoring benign behavior are 1) pushing or well-demarcated tumor border at the microscopic level 2) even distribution of epithelial tissues within the tumor, and 3) less than 3 mitotic figures per 10 high-power fields, and 4) bland cytologic features with low cellularity. In contrast, features favoring malignant behavior are 1) infiltrating tumor margin, 2) connective tissue growth outstripping epithelium-lined structures, and 3) more than 3 mitotic figures per 10 high-power fields, and 4) pronounced cellular atypia with high cellularity.

When phyllodes tumors occur in women younger than 20 years, they are almost always benign, despite clinical and histologic features of malignancy (137, 138). Flow ploidy or S phase fraction determinations do not appear to reliably predict behavior (74).

Proper initial therapy (wide local excision) is helpful in controlling local recurrence but appears irrelevant in preventing distant metastases (129). Simple mastectomy should be reserved for large tumors, which for all practical purposes preclude breast conservation, and also for cases with multiple recurrences because some recurrent tumors may progress to higher grade tumors or cause death by invasion of the chest wall. Axillary metastases are rare.

Distinguishing cellular fibroadenoma from benign phyllodes tumor may be more of an academic exercise than a practical one because both are easily managed by conservative local therapy, even with recurrence (73, 74). However, borderline and malignant phyllodes tumors can develop uncontrolled local recurrence or distant metastases and should be distinguished from cellular fibroadenoma. Careful application of the criteria outlined before should avoid a misdiagnosis. Also worth noting is that, like the mammary stroma (139), fibroadenomas may contain multinucleated stromal giant cells, which can be mistaken for malignant cells (62). Some fibroadenomas have also been mistaken for phyllodes tumors because they show prominent smooth muscle differentiation (61), fatty tissue metaplasia (62), or carcinomatous transformation (77). Hiraoka and associates have described a phyllodes tumor of the breast containing intracytoplasmic inclusion bodies identical with infantile digital fibromatosis.

Whereas extensive tumor sampling may be necessary to reveal stromal overgrowth in a phyllodes tumor, extensive sampling may also be necessary to find the epithelial

component amid that stromal overgrowth. Although most recurrent phyllodes tumors have both epithelial and stromal elements, some may recur entirely as stromal sarcomas. Nonetheless, so-called stromal sarcoma of the breast should be differentiated from malignant phyllodes tumor. Indeed, the term stromal sarcoma of the breast ought to be discarded and primary sarcomas designated by their pattern of differentiation (fibrosarcoma, undifferentiated sarcoma/malignant fibrous histiocytoma, osteosarcoma, liposarcoma, etc.). Jones and colleagues have reviewed 32 cases of fibrosarcoma and malignant fibrous histiocytoma of the breast. They were able to separate them into low- and high-grade tumors. Whereas none of the low-grade tumors metastasized, 25% of the high-grade tumors spread to distant sites (a rate higher than for malignant phyllodes tumors). Breast sarcomas with giant cells and osteoid (osteogenic sarcoma) are also reported to cause death in most patients with these high-grade sarcomas (140).

Some authors have used the term “cellular periductal stromal tumor” as an alternative for cystosarcoma phyllodes; but Dr. Tavassoli (65) uses the term periductal stromal sarcoma for an even rarer biphasic breast tumor, characterized by a cellular sarcomatous spindle-cell proliferation oriented around breast ducts that retain lumens without the leaf-like (“phyllodes”) processes. A relative new entity has now been added to the mix. Leibl and Moinfar (141) have reported 7 mammary sarcomas that did not fit into any specific soft tissue sarcoma category. Histologically, they were composed of spindle cells with highly pleomorphic nuclei and abundant mitoses. Whereas CKs, CD34, desmin, and h-caldesmon were not expressed, all tumors were positive for CD10 and vimentin. CD29 and SMA were observed in 3 cases each (43%), and p63 and calponin in 2 cases each (29%). Other myoepithelial markers and steroid receptors were absent, except androgen receptors, which were expressed in one sarcoma. Five sarcomas showed positivity for EGFR. The distinction of specific, histogenetically defined sarcoma entities (such as leiomyosarcoma, angiosarcoma, liposarcoma) from NOS-type sarcoma with CD10 expression is usually clear-cut because the former exhibit a characteristic histomorphology and immunoprofile. Phyllodes tumors with stromal overgrowth or recurrent phyllodes tumors lacking epithelial structures as well as periductal stromal sarcomas can be ruled out by their frequent expression of CD34 and negativity for myoepithelial markers. The most important differential diagnosis is sarcomatoid metaplastic carcinoma, because its treatment includes axillary lymphadenectomy. But, distinction from sarcomatoid carcinoma can be extremely difficult and requires extensive immunohistochemical evaluation for CKs and myoepithelial markers. The immunophenotype of NOS-type sarcomas with CD10 expression suggests that these neoplasms represent a mammary sarcoma variant with myoepithelial features.

As noted above, any soft-tissue sarcoma or soft-tissue tumor can arise from breast connective tissue, but a relatively rare malignant stromal tumor (sarcoma) showing endothelial-cell differentiation deserves special consideration. This is known as primary breast angiosarcoma, which can occur de novo within the breast parenchyma or be secondary in patients following radiation therapy or long after radical mastectomy complicated by chronic lymphedema (Stewart Treves Syndrome). Conservative approaches to surgical therapy have largely eliminated Stewart Treves Syndrome.

Angiosarcoma of the breast may be difficult to palpate and to find in mammograms, but in some cases, a palpable mass may be discernible (142-146). Usually, breast angiosarcomas produce soft, spongy, and hemorrhagic areas. Tumor cells form irregular, invasive, anastomosing vascular channels that are lined by atypical (hyperchromatic) endothelial cells, but the cytologic features may vary, ranging from a highly undifferentiated solid tumor to one that is very bland cytologically and difficult to distinguish from benign vessels (142-146). Malignant vessels of angiosarcoma invade breast parenchyma diffusely and show no "respect" for normal breast structures. Some authors have observed the prognosis of breast angiosarcoma to correlate nicely with histologic grade, although traditionally breast angiosarcoma has been considered to have a universally poor prognosis (144-146). In fact, Rosen and coworkers report that the overall survival of patients with breast angiosarcoma is roughly 33% at 5 years, but the majority of patients with well-differentiated tumors will survive 5 years (144, 145). Tumor cells are positive for endothelial markers such as factor VIII-related antigen (vWF), CD31, and CD34. Some high-grade epithelioid tumors may mimic carcinoma, but the majority show immunoreactivity for the aforementioned endothelial markers. The differential diagnosis of breast angiosarcoma includes poorly differentiated breast carcinoma, metaplastic carcinoma, acantholytic squamous carcinoma, various benign hemangiomas (hemangiomatoses), hemangiopericytoma, cystic hygroma, cellular angioliipoma, and pseudoangiomatous stromal hyperplasia (113, 142-156). Cellular angioliipoma may be particularly troublesome, but it shows hyaline thrombi within cytologically bland capillaries and is often well circumscribed. In this spectrum of vascular lesions, atypical vascular lesions, lymphangioma-like nodules, and overt angiosarcomas of breast and/or overlying skin have been reported following segmental resection with edema and after radiation therapy (116, 117, 157-161). The latter phenomenon is somewhat reminiscent of so-called lymphangiosarcoma of the upper extremities as a result of long-standing postmastectomy lymphedema (Stewart-Treves syndrome) (142-146).

These atypical vascular lesions have, thus far, proven to follow a benign course.

Finally, I would like to point out that unusual cases of ductal carcinoma in situ have a large population of spindle cells that is 10% to 80% of the in-situ tumour cell population in one report (162). Although this would not cause a diagnostic problem in an excision biopsy, it could cause trouble in a limited needle biopsy or fine needle aspiration biopsy, where the spindle cells could be confused with other spindle-cell lesions. Almost all DCIS lesions with spindle cells disclose neuroendocrine differentiation. Although the distinction from benign florid usual hyperplasia may pose a diagnostic histological problem in an excision biopsy specimen, the presence of diffuse neuroendocrine expression, in conjunction with the pattern of high molecular weight keratin profile (CK5/6 negative) on immunohistochemistry, supports an in-situ neoplastic process. The absence of smooth-muscle actin immunostaining, in conjunction with negative reactivity for cytokeratins 5/6 and 14, makes the possibility of a myoepithelial proliferation unlikely.

#### **Reference (Metaplastic carcinoma)**

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## Case 8

**Case history: A 50 year old female with round firm breast mass.  
Submitted diagnosis: Medullary Carcinoma (poorly differentiated invasive breast carcinoma, overall mBR grade 3; nuclear grade 3, tubular grade 3, mitotic grade 3).**

### MEDULLARY CARCINOMA

**Background:** Medullary carcinoma is defined in the WHO classification of breast tumors (1) as a “well circumscribed carcinoma composed of poorly differentiated cells with scant stroma, no glangular component and prominent lymphoid infiltration.” The diagnosis of “true” medullary carcinomas requires strict application of diagnostic criteria; and, when done properly, some report that it constitutes ~5% of breast carcinomas (2-5). Like others, I believe those tumors with atypical features are best considered within the group of InvDC,NST (until additional studies indicate otherwise)(6,7) or invasvie ductal carcinoma with medullary features (42).

Successful treatment by lumpectomy and primary radiotherapy has been reported (8), and many (but not all) studies indicate an improved prognosis over InvDC,NST, when compared stage for stage with InvDC,NST (2-4,9-12). For example, Moore and Foote (9) reported that 11.5% of their patients with medullary carcinoma died of tumor within five years, despite the fact that 42% of patients had axillary node metastases. Richardson (4) reported that the 5-year disease-free survival of their 99 patients was 78%, with death due to disease in only 10%. There was 95% 20-year disease free survival for stage I patients in this series and 61% for stage II patients (2). Patients with medullary carcinoma tend to have a lower frequency of axillary node metastases than patients with atypical medullary or InvDC,NST (3,11,10); and, when present, nodal metastases are usually found in three or fewer nodes (3,10). Stage II medullary carcinoma patients have a more favorable prognosis than comparable patients with non-medullary carcinoma. But, patients with tumors larger than 3 cm or with four or more positive nodes have high recurrence rates that are not appreciably different from the recurrence rates of patients with infiltrating duct carcinoma.

Ellis et al. (13) and Periera et al. (14) do not report a significantly different survival for all patients with medullary carcinoma, compared to patients with InvDC,NST (i.e., 51% vs. 46%, respectively, at 10 years follow up). They emphasize that this holds even when strict criteria are applied for the diagnosis. However, review of their data show that the 10-year survival for mBR grade 3 InvDC,NST is 39%, whereas it is 51% for medullary carcinoma. All medullary carcinomas were mBR grade 3 in their series. Possibly, this group will accept some improved survival for patients with

medullary carcinoma, when compared to matched patients with grade 3 InvDC,NST.

**Clinicopathologic features:** The mean age at presentation in several series has ranged from 46 to 54 years (10,16,16). Medullary carcinomas have circumscribed margins, a soft to moderately firm consistency, and are often mistaken for fibroadenomas, especially in young women. Bilateral carcinomas and multicentricity may occur (3,11,16,17).

(“Multicentricity” is defined here as microscopic foci of carcinoma outside the primary quadrant, and it implies the presence of multiple clonally distinct tumors. Synchronous multicentric tumors are uncommon in my experience. “Multifocal” tumors are much more common, and “multifocal” refers to separate, satellite foci of one invasive tumor clone. This feature is often observed in invasive lobular carcinoma. It likely results from “skip” invasive tumor, resulting from lymphatic-vascular spread and/or relatively synchronous invasion from multiple separate points along the breast duct system by one carcinoma clone that has previously spread through the breast along the duct system.)

In patients with medullary carcinoma, ipsilateral axillary lymph nodes are often enlarged, even when there are no nodal metastases, due to reactive lymphoid and histiocytic hyperplasia. The median size of the primary tumors is 2 to 3 cm. Peripheral fibrosis may suggest encapsulation, and some small tumors appear less well circumscribed due to an intense lymphoplasmacytic reaction that extends into adjacent breast tissue (10). InvDC,NST may also be well-circumscribed. Cut surfaces reveal a round or lobulated, pale brown to grey tumor, which is softer than the usual breast carcinoma. Hemorrhage, necrosis, and cystic changes may be present, especially in larger lesions.

Those who believe medullary carcinoma is a tumor with a favorable prognosis agree that it is necessary to adhere to strict morphologic criteria for the diagnosis (3,11,10,18). As described by Foote and Stewart (19), the definitive features must include 1) a prominent lymphoplasmacytic reaction, 2) circumscription, 3) a syncytial growth pattern (i.e., broad anastomosing sheets of tumor cells with indistinct cell borders), 4) poorly differentiated nuclear grade, and 5) high mitotic rate. The lymphoplasmacytic reaction must be intense enough to be "graded" at least as “intermediate” or “moderate” in amount (i.e., the mononuclear infiltrate involves at least 75% of the periphery and is present diffusely in the substance of the tumor). According to Rosen et al. (15) the lymphoplasmacytic reaction commonly encompasses ducts and lobules in the surrounding breast occupied by carcinoma in situ as well as nearby benign ducts and lobules not containing carcinoma. He believes expansile growth of in situ carcinoma in ducts and lobules leads to the formation of

secondary peripheral tumor nodules responsible for the grossly nodular appearance of medullary carcinomas. The inflammatory infiltrate may be almost entirely of lymphocytes or plasma cells, but usually there is a mixture. IgG-bearing plasma cells and peripheral T-lymphocytes predominate in both medullary carcinomas and in InvDC,NST (20-22,23,24). When plasma cells predominant, the tumor is more likely to be medullary carcinoma (42).

Circumscription is defined by the border of the infiltrating carcinoma, not by the periphery of the surrounding lymphoplasmacytic reaction. The tumor cell edges should have a smooth, rounded contour that pushes aside, rather than infiltrates, the breast. Consequently, glandular and/or fatty breast tissue should not be found within the invasive portion of the tumor. If most of the tumor growth (i.e., 75% or more) is arranged in broad irregular sheets or islands, the pattern is considered “syncytial” and resembles a poorly differentiated squamous carcinoma. Some have reported that overall and relapse-free survivals are related to the size of the syncytial component, with a poorer prognosis associated with a less than 75% syncytial pattern (25). According to Rosen et al. (26), a tumor that is otherwise characteristic may be accepted as a medullary carcinoma, even if it has minor components of trabecular, glandular, alveolar, or papillary growth. Focal metaplastic changes occur in a minority of medullary carcinomas. Squamous metaplasia, often with necrosis, has been found in 16%, (10), while osseous, cartilaginous, and spindle cell metaplasia are much less common. Atypical epithelial giant cells are sometimes seen in the tumor, which also could be a representative of metaplasia or degenerative changes (42).

Criteria for diagnosing “atypical medullary carcinoma” also seem to vary. Indeed, the diagnosis may be even more difficult to reproduce between pathologists. According the Rosen et al. (26) structural variations that characterize atypical medullary carcinoma include focal invasive growth at the periphery of the tumor, diminished lymphoplasmacytic reaction, well-differentiated nuclear cytology, few mitoses, conspicuous glandular or papillary growth, and a less than 75% syncytial growth pattern. He even suggest calling these tumors as invasive duct carcinoma with medullary features (42). Tumors with more than two of these aberrant features are best classified as infiltrating duct carcinomas (26,10,11). The outcome for patients with atypical medullary carcinoma may be slightly better than for those with infiltrating duct carcinoma, but the difference is often not statistically significant. It is also interesting that in comparison to poorly differentiated duct carcinoma of no special type, invasive duct carcinoma with medullary features show the basal-like immunophenotype more commonly (62.9% vs. 18.9%) (43)

Recently, Jensen et al. (6) compared three different schemes for diagnosing medullary carcinoma and found the Ridolfi et al. (10) criteria to be the best at stratifying a group of patients with a markedly improved prognosis. The Ridolfi criteria included 1) at least 75% of the tumor area composed of a syncytial pattern, 2) completely circumscribed with pushing margins, 3) moderate to marked mononuclear infiltrate in surrounding and supporting stroma, 4) nuclear grade 2 to 3, 5) no intraductal component, and 6) no microglandular differentiation. The presence of fibrosis, necrosis, cystic and/or papillary changes, squamous metaplasia, bizarre cells, and multifocal growth were recorded; but, these features did not exclude the diagnosis. Tumors with a maximum of two of the following features were classified as atypical medullary carcinoma: infiltrative margins, sparse or only peripheral mononuclear infiltrate, grade 1 nuclei, microglands, or an intraductal component. InvDC,NST was diagnosed when the syncytial growth pattern was less than 75% and/or three or more above atypical features were present. These investigators found that the prognosis for atypical medullary carcinoma was essentially the same as for InvDC,NST; and, thus, they found no reason to maintain the category of atypical medullary carcinoma. Of interest, both Tavassoli and Fisher et al. (7) believe that dense fibrosis and/or cord-like structures disqualify the lesion as a typical medullary carcinoma.

Ellis et al. (13) defined medullary carcinoma as a breast tumor having all the following features: 1) sheets of large bizarre carcinoma cells forming a syncytial network, 2) moderate to large numbers of lymphoid cells between sheets of tumor cells, 3) a sharply defined pushing margin, 4) usually little fibrous stroma, and 5) usually no carcinoma in situ or lymphatic-vascular invasion. For them, atypical medullary carcinoma was a tumor that deviated from the criteria defined for typical medullary carcinoma but that had medullary features; usually this was either less prominent inflammation, microscopic invasion beyond the sharply defined pushing margin, or dense areas of fibrosis. This group was unable to show an improved outcome for patients with medullary breast carcinoma, even when strict morphologic criteria were imposed. Indeed, in my experience, medullary carcinoma is often overdiagnosed and difficult to reproduce between pathologists. Published studies have documented the problems encountered in the diagnosis of typical medullary carcinoma in a routine clinical context and shown high levels of diagnostic variation between pathologists (26,27,28).

Finally, over 90% of medullary carcinomas are estrogen and progesterone receptor-negative by any technique (29-31), and these high histologic grade tumors are highly proliferative (32) and typically aneuploid or polyploid (33).

Definitive diagnosis of medullary carcinoma on the needle core biopsy cannot be made. It is wise to suggest the possibility of this diagnosis and defer the definitive diagnosis to complete excision of the mass (42).

Lumpectomy and radiation is a therapy for patients with true medullary carcinoma, especially for tumors 3 cm or smaller. Sentinel lymph node biopsy is also recommended for staging. Chemotherapy is usually given to the patients with larger tumor, positive nodes and tumor with lymphovascular emboli (42).

**Differential diagnosis:** Obviously, the main differential diagnostic problem is distinguishing between circumscribed and/or “inflamed” examples of InvDC,NST (i.e., “atypical medullary carcinoma”) from “true” medullary carcinoma. This has already been discussed above. Other differential considerations include metastatic tumor to the breast. A metastasis to the breast can be the first sign of a clinically occult tumor, and its proper diagnosis will lead to a search for the primary and the avoidance of unnecessary breast surgery. Besides hematolymphoid malignancies (e.g., anaplastic large-cell lymphoma), and excluding a metastasis from contralateral breast carcinoma, most series show that metastatic melanoma and lung carcinoma account for most cases (greater than 50%) of metastatic disease in the breast (34). Ovarian, gastric, renal, and pancreatic carcinomas comprise most of the remaining tumor types. In men, prostate carcinoma has a predilection for metastasizing to the breast (35). Although it is not likely to be confused with medullary carcinoma, diffuse-type (signet-ring cell) gastric carcinoma can spread to the breast and mimic invasive lobular carcinoma (34); likewise, as mentioned above invasive lobular carcinoma can spread to the stomach and produce linitis plastica (36). Obviously, the distinction would be very difficult, but immunostaining with GCDFP-15 can help since, like S100, GCDFP-15 is positive in about 60% of breast carcinomas. (GCDFP-15 and S100 are also positive in salivary and sweat gland carcinomas, and the melanoma marker HMB-45 has now been reported to be immunoreactive with breast carcinomas [37].) Worth to mentioning is that occult breast carcinoma can be diffusely metastatic to the spleen and present as "idiopathic thrombocytopenic purpura" (38), and that extra-mammary carcinoid can initially present as a breast mass, simulating primary breast carcinoma with neuroendocrine differentiation (39). The absence of an in situ component in the breast should always raise the possibility of a metastatic tumor, but the presence of an in situ component does not always indicate a breast primary. Ovarian carcinomas metastatic to the breast can simulate DCIS by growing within the ducts and lobules and producing microcalcifications mimicking primary carcinoma on mammogram (40,41). Obtaining a complete clinical history and judicious application of immunohistochemistry should aid in the proper identification of metastasis to the breast, thus avoiding unnecessary surgery. Theoretically, rare examples of high-grade

pleomorphic sarcoma might be confused with a medullary carcinoma, but this seems unlikely for an experienced pathologist.

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## MISCELLANEOUS TYPES OF SPECIAL BREAST CARCINOMA

- Lipid-cell carcinoma and variants in breast (1).
- Breast carcinoma with sebaceous differentiation (2).
- Small-cell carcinoma of the breast (3).
- Invasive carcinoma with granulomatous reaction (4,5).
- Neural invasion in intraductal carcinoma of breast (6).
- Carcinoma with "choriocarcinomatous" features (7)
- Glycogen-rich, clear-cell carcinoma of breast (8).
- Oncocytic carcinoma of breast (9).
- Giant-cell tumor of male breast with myoepithelial & myofibroblastic features(10).
- Mammary carcinoma with osteoclast-like giant cells (11,12).
- Neuroendocrine differentiation in breast carcinoma (13).
- Anaplastic variant of Paget's disease (14).

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