Papillary Lesions of the Breast
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The Plan
• Provide an overview of diagnostic challenges associated with papillary lesions of the breast
• Discuss clinical, imaging, morphologic and immunostaining features of the spectrum of papillary lesions
• Suggest optimal follow up management strategy for each entity

The Spectrum of Diagnostic Challenges Associated with Papillary Lesions of the Breast
• Differentiation between benign intraductal papilloma with florid hyperplasia and atypical papilloma
• Distinction between atypical papilloma versus low-grade ductal carcinoma in situ arising within an intraductal papilloma
The Spectrum of Diagnostic Challenges Associated with Papillary Lesions of the Breast

- Recognition of intraductal papilloma with extensive ductal carcinoma in situ versus papillary ductal carcinoma in situ
- Understanding of the differences among variants of papillary carcinoma
- Differentiation between pseudo-invasion versus frank invasive carcinoma

Papillary Lesions of the Breast

- Comprises a collection of breast lesions that span from benign to malignant
  - Commonality among papillary lesions is the architectural pattern of epithelial proliferations with presence of fibrovascular cores
  - Subclassification of papillary lesions can often be challenging due to overlapping features

Spectrum of Papillary Lesions
Anatomy of Breast

Central vs Peripheral Intraductal Papilloma

**Central Papillomas**
- Generally same architectural pattern

**Peripheral papillomas**
- Coexisting radial scar, sclerosing adenosis, atypical hyperplasia (usual and atypical), and in situ carcinoma

Most common clinical presentation of intraductal breast lesions?

Bloody nipple discharge
Histologic Features of Intraductal Papilloma

- Varying amounts of epithelium with branch-like/ arborizing pattern
- Characteristic fibrovascular stalk
- Presence of myoepithelial cells
- Can become sclerotic
- Metaplastic changes may occur
Intraductal Papillomas

- Benign entities with excellent prognosis
- No established connection between intraductal papillomas progressing to carcinomas
- Usually managed by local excision vs surveillance

Management of Intraductal Papilloma

- In retrospective analysis of 511 cases of intraductal papilloma diagnosed by core needle biopsy, 383 cases had undergone follow up surgical excision
- The results indicated that the rate of upgrading to malignancy and high risk lesions after excision was 0.8% and 4.4% respectively

Management of Intraductal Papilloma (continued)

- The presence of concurrent contralateral breast cancer, clinical symptoms and multifocality were factors significantly associated with upgrading to malignancy
- The rate of upgrading to malignancy for a single intraductal papilloma is very low suggesting that close clinical and radiologic observation may be an optimal management strategy


Atypical Papilloma

- Basic lesion is a papilloma
- Morphologic features of atypia/low nuclear grade DCIS
  - Tavassoli Criteria
    - Atypia in <33% of the papilloma
    - Atypia in 33-90% of the papilloma = Carcinoma arising in papilloma
  - Page Criteria
    - ADH focus involving <3 mm/Atypical papilloma
    - Atypical focus involving >3 mm = Minor DCIS lesion

Atypical Papilloma

- Reserved for papillomas that demonstrate monotonous population of epithelial cells
- Atypical cells may present with solid pattern
- Do not meet the criteria for ductal carcinoma in situ
Histology of Atypical Papilloma with Immunostain P63

Intraductal Papilloma with DCIS

Area of DCIS involving papilloma

Classic intraductal papilloma

Papillary DCIS

- Variant of carcinoma in situ with papillary growth pattern
- Involvement of several ducts, similar to other types of DCIS
- Immunostains demonstrate absence of staining for myoepithelial cells within the papillae with retention of myoepithelial cells at the periphery of the ducts
- Management consistent with treatment for other types of DCIS
Papillary DCIS

Proliferation of monotonous epithelial cells with abundant cytoplasm. The neoplastic cells palisade around prominent fibrovascular cores [yellow arrows]

Underestimation of the Presence of Breast Carcinoma in Papillary Lesions Initially Diagnosed by Core Needle Biopsy:

- Intraductal Papilloma
  - 3% association with malignancy
  - Follow up is reasonable
- Atypical Papilloma
  - 67% association with malignancy
  - Prompt excision is required


Invasive Papillary Carcinoma

- Rare entity
- Greater than 90% of invasive tumor has papillary architecture
- May have multinodular growth pattern
Fibrovascular Cores

Invasive Component

Immunostaining for P63

The absence of myoepithelial cells

• Prognosis is favorable even in cases with nodal metastases
• Data collected from California Cancer Registry failed to show any difference in survival among cases of non-invasive vs. invasive papillary carcinoma
• Five year survival rates were greater than 90%
Radiologic Findings of an Invasive Papillary Carcinoma

Complex cystic lesion
BIRADS 4

Ultrasound Finding of an Invasive Papillary Carcinoma

70 year old woman with an 11 x 8 x 8 mm lobulated hypoechoic mass within the left breast. It was located at the 12:30 position, 5 cm from the nipple.
Designated BIRADS 4

Cytomorphology of an Invasive Papillary Carcinoma
Clinical History: 80 y/o woman with palpable right breast lump. BIRADS 5 on ultrasound; FNAB performed:

Clusters of epithelial cells with papillary features, suggestive of papillary carcinoma; recommend excision with rim of normal breast tissue.
**Encapsulated Papillary Carcinoma**

- Presents as solitary mass with a surrounding fibrous capsule
- Appears similar to papilloma with DCIS or papillary DCIS but differs in size (larger) and atypical cells comprise the entire lesion
- Absence of staining of myoepithelial cells in both the periphery and papillae
- ER+, PR+ and have good overall prognosis; treated as DCIS lesions; studies have shown low incidences of recurrence and metastasis

**Encapsulated/Non-Invasive Papillary Carcinoma**

- Absence of p63 staining of myoepithelial cells at the periphery and within papillae
Solid Papillary Carcinoma

- Circumscribed mass composed of hypercellular nodules
- Papillae still present but due to extensive epithelial overgrowth, fibrovascular cores may be difficult to discern
- Cytologically, tumor cells can range from low grade, similar to usual ductal hyperplasia to high grade, with neuroendocrine appearance and frequent mitotic figures
- Generally good prognosis but not at the level of cystic/encapsulated papillary carcinomas - higher rate of axillary and systemic metastases.
- No clear consensus for definitive treatment; ranges from local excision to modified radical mastectomy
Micropapillary Carcinoma

- Rare papillary entity of breast comprised of clusters of cells within stromal spaces giving the appearance of retraction artifact
- Lacks classic fibrovascular cores
- Morphologically similar to micropapillary tumor of other organs
- Predominant patient population are older women

Micropapillary Carcinoma

- Patients present with a later stage disease and experience poor outcome
- Aggressive tumor with high rate of nodal metastasis at the time of diagnosis
- Mastectomy with axillary dissection or breast conservation surgery with whole breast radiation therapy are the current treatment options

Micropapillary Carcinoma

- It is hypothesized that the “inside-out growth” pattern resulting in reverse polarization of tumor cells facilitates secretion of molecules responsible for stromal and vascular invasion
- The above mentioned molecules namely metalloproteinase permits easier dissemination of the neoplastic cell clusters
Micropapillary Carcinoma

- The majority of micropapillary carcinoma are mixed with other types of breast cancer including tubular, papillary, mucinous or lobular carcinoma
- Ductal carcinoma in situ is present in up to 80% of cases
- The presence of ductal carcinoma in situ is critically important to exclude the possibility of metastasis from a serous papillary carcinoma of the ovary or other primary sites

Majority of micropapillary carcinoma are hormone receptor and HER-2/neu oncogene positive
- High expression of P53 protein is reported in at least 50% of cases of micropapillary carcinoma
- Comparative genomic hybridization has demonstrated genetic loss involving chromosome 8 that may be responsible for its aggressive behavior

A rare entity that was called “breast tumor resembling the tall cell variant of papillary thyroid carcinoma"
- Molecular and immunohistochemical studies have shown no evidence to support any association between this entity and papillary thyroid carcinoma

Masood S, Davis C, Kubik M: Changing the Term “Breast Tumor Resembling the Tall Cell Variant of Papillary Thyroid Carcinoma” to “Tall Cell Variant of Papillary Breast Carcinoma" Adv Anat Pathol. 2012;19(2):108-10
Diagnostic mammogram and targeted ultrasound of the left breast demonstrates a well-circumscribed nodule (A), hypoechoic structure with mixed posterior shadowing and acoustic enhancement in the left upper breast (B).

Tall Cell Variant of Papillary Breast Carcinoma

Papillary architecture with delicate fibrovascular cores and numerous psammoma bodies. Epithelial cells with tall columnar configuration, granular eosinophilic cytoplasm, nuclear clearing, nuclear grooving, prominent mitoses, and stratification with palisading orientation along the basal pole of the cells. Negative TTF-1 and thyroglobulin immunostaining.

• Positive expression of estrogen and progesterone receptor
• Negative for HER-2/neu oncogene
• Negative for TTF-1 and Thyroglobulin
• Negative for BRAF Mutations and RET rearrangements

Based on the available molecular findings, no association between this entity and thyroid carcinoma was found.

We proposed to delete the words “Thyroid carcinoma” from the terminology of this tumor and consider it as a primary breast carcinoma.