Fibroepithelial lesions of the breast

Fibroepithelial breast lesions are biphasic tumors composed of both epithelial and stromal components, and include the common fibroadenoma and the rarer phylloides tumor.

Scope

- **Fibroadenoma:**
  - Core biopsy diagnosis.
  - Insights into tumorigenesis.
  - Relationship with phylloides tumor.
- **Phyllodes tumor:**
  - Grading, prediction of biological behavior.
  - Molecular highlights.
Fibroadenoma

- Common benign biphasic tumor.
- Circumscribed breast neoplasm arising from the terminal-duct lobular unit (TDLU).
- Features a proliferation of both epithelial and stromal elements.
- Occurs most frequently in women of childbearing age, especially those aged < 30 years, although it may be encountered at any age.
- Estimated 10% of women have fibroadenomas.

Gross anatomy of fibroadenoma
- Bosselated outlines
- Myxoid surface
- Fibrous homogenous appearance
- Lobulated cut surface
- Ossified fibroadenoma
- Giant fibroadenoma

Microscopic anatomy of fibroadenoma
- Intracanalicular pattern
- Pericanalicular pattern
- Simple fibroadenoma
- Complex fibroadenoma
Core biopsy diagnosis of fibroadenoma

- Core biopsies represent the standard of care in preoperative diagnosis of breast lesions discovered clinically & radiologically.
- No further treatment is needed for a diagnosis of fibroadenoma, vs excision biopsy for a conclusion of phyllodes tumor on core biopsy.
- How reliable is a core biopsy diagnosis of unambiguous fibroadenoma?
- Do we need to be concerned about underdiagnosing a phyllodes tumor?

Phyllodes Tumor Subsequent to a Diagnosis of Fibroadenoma on Breast Core Needle Biopsy: Frequency and Characteristics

Timothy W Jacobs1, Yunn-Yi Chen1, Donald G Guinee1, Peter R Eby1, Aye Aye Thike1, Poonam Vohra2, Puay Hoon Tan3
1. Virginia Mason Medical Center, Seattle, WA
2. UCSF, San Francisco, CA
3. Singapore General Hospital, Singapore

Conclusions

- The incidence of PT subsequent to a diagnosis of FA on CNB is extremely low (0.38%, 16 out of 4163 cases).
- Most PT were categorized as benign (14 benign, 2 borderline).
- PT heterogeneity (e.g. FA-like areas) likely contributed to CNB-excision discrepancies.
- No pathologic features on CNB appeared to be prospectively predictive of PT at excision.
- Suspicious imaging features at time of CNB or on follow-up should prompt consideration for surgical excision.
- Diagnosing FA on CNB is reliable and safe, provided there is adequate imaging correlation and follow-up.
Core biopsy diagnosis of cellular fibroepithelial lesions – prediction of phyllodes tumor

<table>
<thead>
<tr>
<th>Author</th>
<th>Reference</th>
<th>Key findings predicting phyllodes tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al</td>
<td>Histopathology 2007; 51: 336-344</td>
<td>Stromal cellularity ≥ 50% stroma, stromal overgrowth, fragmentation, adipose within stroma</td>
</tr>
<tr>
<td>Resetkova et al</td>
<td>Breast J 2010; 16:573-80.</td>
<td>No predictive value of clinical, radiologic or pathologic data</td>
</tr>
<tr>
<td>Jara-Lazaro et al</td>
<td>Histopathology 2010; 57: 220-232</td>
<td>Marked stromal cellularity/atrophy, stromal overgrowth, mitoses ≥ 2 per 10 hpf, ill-defined lesional borders, Ki67 &amp; topoisomerase II α indices ≥ 5%, reduced CD34 staining</td>
</tr>
</tbody>
</table>

Molecular genetics of fibroadenomas

- Cytogenetic abnormalities in 20% to 30% of fibroadenomas, usually translocations.
- No consistent pattern of specific chromosomal alterations.
- Both epithelial and stromal components are polyclonal. (Noguchi et al. Cancer Res 1993; 53: 4071-4072)
- Possible evolution into phyllodes tumors. (Noguchi et al. Cancer 1995; 76: 1779-1785)
- Low levels of LOH (0% to 1.5%). (Wang et al. Breast Cancer Res Treat 2006; 97: 301-309)

Exome sequencing identifies highly recurrent MED12 somatic mutations in breast fibroadenoma

Wong Khong Lim1,2,3, Choon Kiat Ong4,5,6, Jeng Tan2,3,4,5, Ace Aye Thike5,6, Cedric Choon Young Ng1,2, Vikaswaran Rajasegaran2,3, See Soon Symp2,3, Sanjana Nagaratnam3,5, Nuri Othman Me Nasir5, John B McPherson2, Jenoi Cattancha6, Gregory Pears6, Se Ting Tan2, Wei Sheng Ong7, Terence Kock-Mare Tan1, Michael Hartmann8, Koon Woe Ong9, Benita K T Tan5, Steven G Rosser2, Paup Hoon Tan2, Patrick Tan2,5,6,8,9 &Bin Tun Yeo2,3,4,5

Key findings:
- Exome sequencing of 8 fibroadenomas with matching whole blood samples revealed recurrent somatic mutations solely in MED12 (encodes a Mediator complex subunit).
- Targeted sequencing of an additional 90 fibroadenomas confirmed highly frequent MED12 exon 2 mutations (58/98, 59%) that are probably somatic, with 71% of mutations occurring in codon 44.
- Using laser capture microdissection, it was confirmed that MED12 fibroadenoma mutations are present in stromal but not epithelial mammary cells.

MED12 mutations in breast fibroadenoma

- MED12 is located on the X chromosome.
- Frequent MED12 exon 2 somatic mutations have been found previously only in uterine leiomyoma (UL).
- MED12 mutation spectrum observed in fibroadenomas was nearly identical to that of UL in both exon location and variant codon preference.
- Possibility that MED12 exon 2 mutations could be associated with hormonal expression.
- MED12 in phyllodes tumors.

Phyllodes tumor
Phyllodes tumor

- Uncommon fibroepithelial neoplasm with proliferation of both epithelial and stromal components.
- "Phyllodes"
  - Derived from the Greek word “phyllon” meaning leaf, and “eidos” meaning form.

Phyllodes tumor: fibroepithelial neoplasm resembling intracanalicular fibroadenoma, but with exaggerated fronded pattern and stromal hypercellularity

- 0.3-1% of all primary breast tumors.
- Affects middle aged women (40-50 years).
- Higher incidence in Asian women.
- Graded according to histological characteristics.
- Tendency to recur if incompletely excised.

Benign phyllodes tumor

Large tumor stretching skin

Circumscribed bulging mass, mucoid, fleshy, whorled
### Historical perspectives

1838
- **Cystosarcoma phyllodes**
  - Johannes Müller

1960
- **Tumor phyllodes**
  - (Lomonaco, Tumori)

1774
- Ochme described a rapidly benign-growing tumor (about 4kg) of a young woman

1960
- Numerous terms and descriptions devoted to the same tumor, e.g., intracanalicular fibroma, pseudosarcoma, serocystic tumor etc.

1941
- Owens & Adams - term cystosarcoma should be avoided as the lesion is usually not sarcomatous. Proposed 'giant intracanalicular fibroadenoma of the breast'

1839-1930
- Numerous terms and descriptions devoted to the same tumor, e.g., intracanalicular fibroma, pseudosarcoma, serocystic tumor etc.

1867
- Virchow, opined its 'limited malignancy, but capacity to metastasize'

### Evolving concepts on classification

**“...the disease is perfectly innocent” Müller (1838)**

- Benign

**Lee and Pack (1931)** reported 5 recurrences in 91 cases with available clinical outcome

**White (1940)** reported recurrence and subsequent metastasis of a case

**Cooper and Ackerman (1943)** proposed

- Benign
  - Malignant

**Treves and Sunderland (1951)** reported 18 of 77 tumours could not fit in other category

**Treves and Sunderland (1951)** proposed

- Benign
  - Borderline
  - Malignant
Histological assessment

<table>
<thead>
<tr>
<th>Norris and Taylor (1967) – 94 cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proposed criteria:</td>
</tr>
<tr>
<td>1) Contours (margins) and size of tumor</td>
</tr>
<tr>
<td>2) Degree of mitotic activity</td>
</tr>
<tr>
<td>3) Cellular atypism</td>
</tr>
</tbody>
</table>

| Oberman; Hart et al (1965;1978)    |
| Suggested stromal overgrowth as an additional adverse prognostic factor |

| Ward and Evans (1985)               |
| Specified objective for stromal overgrowth; assessment of cellularity and atypia in semi-quantitative way |

| Tan et al (2011)                     |
| Quantitative weightage of risk based on stromal atypia, mitotic rate, overgrowth and surgical margins |

Phyllodes tumor


<table>
<thead>
<tr>
<th>Table 15.28 Histological features of breast lesions: borderline and malignant phyllodes tumours</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO classification of breast tumours 2012</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Histological feature</th>
<th>Fibroadenoma</th>
<th>Benign</th>
<th>Borderline</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour border</td>
<td>Well-defined</td>
<td>Well-defined</td>
<td>Well-defined, may be partly permeating</td>
<td>Permeating</td>
</tr>
<tr>
<td>Stromal composition</td>
<td>Variable, acinar or predominantly collagenous, usually uniform</td>
<td>Cellular, usually mild, may be nodule in or diffuse</td>
<td>Cellular, usually moderate, may be nodule in or diffuse</td>
<td>Cellular, usually necrotic and fibrous</td>
</tr>
<tr>
<td>Stromal atypia</td>
<td>None</td>
<td>Mild or none</td>
<td>Mild or moderate</td>
<td>Marked</td>
</tr>
<tr>
<td>Mitotic activity</td>
<td>Usually low, rarely high</td>
<td>Usually low (5-50 per 10 HPF)</td>
<td>Usually frequent (&gt;10 per 10 HPF)</td>
<td>Usually frequent (&gt;10 per 10 HPF)</td>
</tr>
<tr>
<td>Stromal oedema</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent, or very focally</td>
<td>Absent, or very focally</td>
</tr>
<tr>
<td>Malignant heterologous elements</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Stromal reactions to all breast tumours</td>
<td>Common</td>
<td>Uncommon</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td>Relative proportion of all phyllodes tumours</td>
<td>—</td>
<td>60-75%</td>
<td>15-25%</td>
<td>15-25%</td>
</tr>
</tbody>
</table>

HPF: high-power fields.

Note: Borderline tumours are often deemed in borderline. They may all exhibit similar characteristics. Presence of a malignant heterologous element indicates a malignant phyllodes tumour, without regard for other histological criteria.
Tumor borders

circumscribed  permeative

Stromal cellularity

mild  moderate  marked

Stromal atypia

mild  moderate  marked
Mitotic activity

Benign
< 5 mitoses/10hpf

Borderline
5 to 9 mitoses/10hpf

Malignant
≥ 10 mitoses/10hpf

Rosen’s Breast Pathology 4th edition 2014 classifies phyllodes tumors with >2 mitoses/10 hpf as borderline, page 237

Stromal overgrowth

Absent

Present

Phyllodes tumors

- Histologic features have been helpful to some extent in predicting biologic behavior.
- Specific parameters that can define the likelihood for recurrence are not universally accepted.
  - **Benign**: local recurrence.
  - **Borderline**: local recurrence, and rarely metastases.
  - **Malignant**: local recurrence and metastases.
Phyllodes tumors

- Limitations of morphologic classification:
  - Subjectivity
  - Continuum of microscopic features
  - Five histological parameters
  - Each parameter with 2 to 3 categories
    ≈ 108 permutations
  - Certainty at extreme ends of classification.
  - Ambiguity in between.

Phyllodes tumors: predicting clinical behavior

Phyllodes tumors: prediction of biological behavior

- Grade correlates with behavior.
- Grade assignment is imperfect:
  - Stromal hypercellularity, atypia, mitoses, overgrowth, borders.
- Questions:
  - Does each histological parameter have equal importance?
  - Can we determine if some parameters have a greater weightage in predicting behavior?
  - Is there an objective scoring system that can define behavior?
Phyllodes tumors: prediction of biological behavior

- 605 women with phyllodes tumors diagnosed at SGH Pathology between 1992 and 2010.
- Histological parameters assessed.
- Clinical follow-up to determine recurrent disease.
- Statistical model focusing on parameters with impact on recurrence.


Phyllodes tumors: 605 cases

- Benign 440 (72.7%)
- Borderline 111 (18.4%)
- Malignant 54 (8.9%)

- Median follow-up 56.9 months; range 3.3 to 229.2 months.

Table 1: Histopathological features of 605 cases of phyllodes tumors stratified according to histological grade

<table>
<thead>
<tr>
<th>Histological Features</th>
<th>Benign</th>
<th>Borderline</th>
<th>Malignant</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &amp; Age * Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor Size (cm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor Size &amp; Age * Sex</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Tumor Size &amp; Sex</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Tumor Size &amp; Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor Size &amp; Age * Sex</td>
<td></td>
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</tr>
</tbody>
</table>

04/04/2016
Recurrences

Mean and median times to recurrence 29.8 and 24.6 months respectively.

Phyllodes tumors: prediction of biologic behavior

- Statistical method:
  - Reverse step modelling.
  - Assessment of multiple variables and their inter-relationship.
  - Derivation of a set of variables with least overlap.
  - Nomogram tested with bootstrapped sample set.
Validation of the SGH nomogram

- Japanese cohort of 45 patients with phyllodes tumors (2 excluded due to death from other causes), Shikoku Cancer Center, Matsuyama Japan.
- Median age 45 years; follow-up 4.7 to 309.9 months (median 129 months); median time to recurrence 113.3 months.

<table>
<thead>
<tr>
<th>Factor</th>
<th>No of events/No of patients</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitotic activity</td>
<td>6/43</td>
<td>0.89 (0.53, 1.50)</td>
<td>0.665</td>
</tr>
<tr>
<td>Stromal overgrowth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>4/38</td>
<td>Reference</td>
<td>0.115</td>
</tr>
<tr>
<td>Present</td>
<td>2/5</td>
<td>3.60 (0.66, 19.79)</td>
<td></td>
</tr>
<tr>
<td>Surgical margins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>0/25</td>
<td>Reference</td>
<td>0.0006</td>
</tr>
<tr>
<td>Positive</td>
<td>6/18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stromal atypia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>6/37</td>
<td>Reference</td>
<td>0.287</td>
</tr>
<tr>
<td>Moderate</td>
<td>0/6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Validation of the SGH nomogram

- Japanese cohort.

<table>
<thead>
<tr>
<th>Nomogram</th>
<th>HR (95% CI)</th>
<th>P-value</th>
<th>Concordance Index</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.11 (1.02, 1.20)</td>
<td>0.0005</td>
<td>0.904</td>
</tr>
</tbody>
</table>

High concordance index indicates the ability of the SGH nomogram to accurately predict the recurrence likelihood of the Japanese cohort of patients.


Phyllodes tumor: relationship with fibroadenoma

- 3 fibroadenomas progressing to phyllodes tumors.
  

- Clonality analysis of fibroadenomas:
  - One ‘simple’ fibroadenoma and one complex fibroadenoma with monoclonality of stroma.
  - Monoclonal ‘simple’ fibroadenoma was histologically described to contain a phyllodes component which also demonstrated stromal monoclonality. Kasumi et al. Breast Cancer Res Treat 1996; 50: 165-91

Relationship between fibroadenoma & phyllodes tumor (I)
Relationship between fibroadenoma & phyllodes tumor (II)

- Identical loss at the same microsatellite locus in a synchronous fibroadenoma and phyllodes tumor of the same breast, while allelic losses at TP53 and another microsatellite locus were observed in the phyllodes tumor but not in the synchronous fibroadenoma, implicating TP53 in progression of fibroadenoma to phyllodes tumor.
  

- 36 malignant phyllodes tumors:
  - 11 associated with previous fibroadenomas (which could be interpreted as progression of fibroadenoma to phyllodes tumors).
  - Better clinical outcome in malignant phyllodes tumors preceded by fibroadenomas than in those diagnosed de novo.
    
    Abe et al. Breast Cancer 2011; 18: 268-72

Relationship between fibroadenoma & phyllodes tumor (III)

- Fibroadenoma areas are seen in phyllodes tumors in variable frequency:
  - Phyllodes tumor is in close juxtaposition to a pre-existing hyalinized fibroadenoma.
  - Phyllodes tumor is arising from the fibroadenoma.
  - Fibroadenoma-like areas in phyllodes tumors reflect heterogeneity of phyllodes tumors.

Molecular genetics of phyllodes tumors: an update
Molecular classification

Two-tiered and three-tiered grading schemes

- Karyotyping (Dietrich, 1997)
  - Benign
  - Malignant

- CGH (Lae, 2007)
  - Benign
  - Borderline
  - Malignant

- LOH analysis (Wang, 2006)
  - Low/Intermediate
  - Malignant

- Array CGH (Jones, 2008)
  - Benign
  - Borderline
  - Malignant

Grading of phyllodes tumors

Molecular genetics

- Comparative genomic hybridization:
  - Higher copy number changes in malignant and borderline phyllodes tumors.
  - Commonest changes:
    - 1q gains, chromosome 13, 3p and 9p deletions.
    - 1q gain may upregulate genes important in pathogenesis.
  - Chromosome 7 and 8 gains associated with malignant than borderline tumors.

- Allelic imbalances:
  - Both stroma and epithelium demonstrate AI, suggesting neoplasia of both components.

Novel genetic aberrations in breast phyllodes tumours: comparison between prognostically distinct groups

- Twenty phyllodes tumors from prognostically distinct categories.
- DNA extracted from FFPE materials subjected to Affymetrix Onco-ScanTM FFPE Express molecular inversion probe microarray platform for analysis of copy number changes and mutational status.
- Results cross validated with Sanger sequencing, FISH and immunohistochemistry.
- Higher number of chromosomal aberrations observed in cases which recurred or metastasized, with median events of 19 compared to 3.5 in cases which did not recur/metastasize.
- High-level amplification and homozygous deletions were detected exclusively in the recurrent group.
- Regions of high-level amplification included MDM4 (1q32.1), RAF1(3p25), EGFR (7p12) and POU2F2 (5p13.3).
Genomic landscapes of breast fibroepithelial tumors

Proposed model of the genomic progression of breast fibroepithelial tumors

*MED12* mutations in breast fibroepithelial lesions
What’s the clinical relevance?

- Genomics based classification of breast fibroepithelial lesions, enhancing diagnostic accuracy.
- Discovery of candidate therapeutic targets in borderline/malignant PT:
  - PIK3CA activating mutations
  - EGFR amplifications
  - MED12 and RARA mutations linked to hormone receptor signaling.
Summary

Phyllodes tumors present distinct challenges relating to their diagnosis, classification, predicted behavior, and clinical management.

Practical recommendations I

- Grading of phyllodes tumors should aim to achieve accuracy and consistency at the benign and malignant ends of the spectrum.
- Definitive distinction between cellular fibroadenomas and benign phyllodes tumors may not be crucial, in light of similar reported recurrence rates. The term benign fibroepithelial lesion/neoplasm may be recommended for cases where clear diagnostic distinction cannot be made, although this should be used sparingly.

Practical recommendations II

- Malignant phyllodes tumors are diagnosed when there are marked stromal hypercellularity, atypia, increased mitoses of ≥10/10 HPFs, permeative tumor borders, and stromal overgrowth. The presence of a malignant heterologous component places the tumor into the malignant category regardless of other histological features.
- A conservative approach can be accorded to benign phyllodes tumors that have been initially enucleated without margins.
Practical recommendations III

- Excision with negative margins should be achieved for recurrent and malignant phyllodes tumors. Most would recommend that borderline tumors should also be completely excised. Although the literature often refers to a margin width of at least 10 mm, a robust evidence base to support this approach is lacking. Therefore an ideal margin width remains to be determined, and may need to be considered in relation to factors such as tumor size and cosmesis.

Practical recommendations IV

- From a diagnostic and management perspective, it is important to accurately recognize malignant phyllodes tumors, which should be surgically eradicated and effectively treated at diagnosis, as these tumors have a well-established but relatively infrequent risk of metastasis and death.
- The role of adjuvant radiation therapy in borderline and malignant tumors remains to be defined. Routine axillary dissection is not recommended.

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