OBJECTIVES

1. Overview of Bartholin Gland Carcinomas
2. Case presentation
3. Difficulties in diagnosing:
   • Mammary-like adenocarcinoma of the vulva
   • Invasive Paget disease of the vulva
   • Bartholin gland adenocarcinoma

SIGNS & SYMPTOMS

• Vulvar mass, slow growing, painless, bleeding
• Diagnosed at advanced stage due to late presentation
• Not to be mistaken for benign cyst / abcess
HISTOPATHOLOGICAL CRITERIA

1. The tumor involving the area of the Bartholin gland is histologically compatible with origin from the Bartholin gland
2. Transition from normal Bartholin gland elements to cancer
3. Intact overlying surface epithelium
4. There is no evidence of primary tumor elsewhere

HISTOLOGICAL TYPES

• Squamous cell and adenocarcinoma (80%)
• Adenoid cystic carcinoma (~15%)
• Others (~5%)
  • Transitional cell carc. / Adenosquamous / Undiff. carc.
  • Merkel Cell carc. / Epithelial-Myoepithelial carc.

PROGNOSIS & TREATMENT

Poor Prognostic indicators:
• Size & stage at time of diagnosis
• Larger size of nodal metastasis & extracapsular invasion

Treatment Recommendations:
• Early stage: local excision and sentinel lymphadenectomy
• Advanced stage: radical (hemi-)vulvectomy, lymphadenectomy & adjuvant postoperative chemoradiation treatment

2. Case presentation (# 4)
54 year old woman with right vulvar mass of 4.5 cm who underwent a partial vulvectomy
Diagnosis

Adenoid Cystic Carcinoma (ACC) of the vulva with perineurial invasion

Adenoid Cystic Carcinoma

- Rare tumor, arises from salivary & lachrymal glands
- Also arises in tissue containing secretory glands:
  - Skin, Breast, Upper Respiratory Tract, Cervix, Vulva
- 1% of all lower genital tract are ACC and arise from:
  - Bartholin gland or reserve cells of uterine cervix

Oncogenic mechanisms in ACC

- Vulvar ACC: complex chromosomal changes involving chromosomes 1, 4, 6, 11, 14, and 22*
- Translocation in salivary gland ACC t(6;9) (q22-23;p23-24) leading to oncogenic fusion protein MYB- NFIB**
- Cervical carcinomas with mixed differentiation including ACC are high-risk HPV related, whereas pure ACC are unrelated to high-risk HPV***


Frequent NFIB-associated Gene Rearrangement in Vulva Adenoid Cystic Carcinoma

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Tumor Site</th>
<th>Size (cm)</th>
<th>MYB (Bros)</th>
<th>NFIB (Bros)</th>
<th>MYB-NFIB (Fusion)</th>
<th>Perineural Invasion</th>
<th>Follow-up Status (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>54</td>
<td>Right vulva</td>
<td>4.5</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Present</td>
<td>Recent case</td>
</tr>
<tr>
<td>2</td>
<td>88</td>
<td>Left vulva</td>
<td>6.6</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Present</td>
<td>NA</td>
</tr>
<tr>
<td>3</td>
<td>67</td>
<td>Right vulva</td>
<td>1.5</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Present</td>
<td>NA</td>
</tr>
<tr>
<td>4</td>
<td>52</td>
<td>Vulva</td>
<td>7.5</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Present</td>
<td>Recent case</td>
</tr>
<tr>
<td>5</td>
<td>52</td>
<td>Vulva</td>
<td>NA</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Not identified</td>
<td>NA</td>
</tr>
<tr>
<td>6</td>
<td>27</td>
<td>Left vulva</td>
<td>2.1</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Present</td>
<td>NA</td>
</tr>
<tr>
<td>7</td>
<td>46</td>
<td>Vulva</td>
<td>2.1</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Present</td>
<td>Recent case</td>
</tr>
<tr>
<td>8</td>
<td>44</td>
<td>Right vulva</td>
<td>4.6</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Present</td>
<td>NA</td>
</tr>
<tr>
<td>9</td>
<td>44</td>
<td>Left vulva</td>
<td>2.2</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Present</td>
<td>NED (12)</td>
</tr>
</tbody>
</table>

Other structural aberrations in ACC

- MYBL1-NFIB fusion (11%)*
- NFIB with other partners (RIMS1, MYO6, RPS6KA2, MAP3K5)**
- Super enhancer translocations in NFIB, TGFB3, RAD51B loci act as drivers for MYB activation***


3. Difficulties in diagnosing

How to distinguish

- Mammary Like adenocarcinoma from the vulva
- Invasive Paget disease of the vulva or
- Bartholin gland adenocarcinoma

Mammary-like adenocarcinoma of the vulva (MLAV)

- Aggressive tumors with poor prognosis, 30-40 cases reported
- Initially thought to originate from supernumerary breast tissue remnants
- Currently believed mammary-like glands arise from vulvar eccrine glands
- Gene expression profiling was performed recently on two cases
- Treated similarly to breast carcinoma:
  - Two case reports successfully using hormonal therapy and trastuzumab

Molecular subtyping of MLAV and Paget Disease

<table>
<thead>
<tr>
<th>Molecular Subtype / IHC</th>
<th>MLAV n = 7</th>
<th>Invasive Paget Disease n = 7</th>
<th>In situ Paget Disease n = 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A</td>
<td>1</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Luminal B</td>
<td>3</td>
<td>3</td>
<td>3 with HER2+</td>
</tr>
<tr>
<td>HER2</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Basal-like</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
MLAV and Paget disease
- Part of a continuum of disease arising from the mammary-like glands of the vulva
- Diagnostic criteria for MLAV:
  - Invasive breast carcinoma morphology
  - The absence of extramammary Paget disease
- Less sensitive criteria would include
  - Breast carcinoma-like immunophenotype and
  - The presence of mammary-like glands adjacent to the invasive carcinoma

Mammary like adenocarcinoma versus adenocarcinoma of Bartholin gland
- No real clue!!
- Distinction would be based on non-mammary like morphology
- Immunophenotype required for diagnosis of Bartholin gland carcinoma
- In theory, adenocarcinoma of Bartholin gland could be HPV related

Bartholin Gland Carcinomas & High risk HPV infection
- 1984-2015: 15 cases, 3 ACC were exclude, stained 11 cases
- p16 ~ surrogate biomarker for High Risk HPV
- 10 poorly to well differentiated SCC and 1 adenocarcinoma
- 10 SCC: expressed p16 diffusely & 1 adeno: patchy staining
- We observed early stage and overall favorable outcome in this small study

Take Home Message
Understanding oncogenic mechanisms that underly Bartholin Gland (vulva) Carcinomas are emerging and highlight that genetic alterations can affect malignant transformation, disease progression and therapeutic susceptibility

Acknowledgments
University of British Columbia
Basile Tessier-Cloutier
Tayyebeh Nazaran
Sawa Sathoh
Nataliya Malynk
Karama Askhab-Aburaya
Julie Ho
Angela Cheng
Anna Timker
Anthony Karnezis
Torsten Nielsen
David Huntsman
Blake Gilks

Johns Hopkins University
Deyin Xing
Christina Isaacson
Brigitte Ronnett
Singleton Hospital, Swansea, UK
Varsha Shah
Belfast Health and Social Care Trust
Glenn McCluggage
Important Information Regarding CME/SAMs

The Online CME/Evaluations/SAMs claim process will only be available on the USCAP website until September 30, 2017.

No claims can be processed after that date!

After September 30, 2017 you will NOT be able to obtain any CME or SAMs credits for attending this meeting.