BAP-oma & BEYOND

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CONFLICTS

- No conflicts with the content of this lecture
BAP-oma

• Wiesner 2011: Families with multiple tan dome-shaped papules of head, neck, trunk, and extremities.

• Lesions with BAP-1 loss are termed BAP-oma or Wiesner’s nevus.

• Most Wiesner’s nevi are solitary (sporadic somatic mutation) and behave in an indolent fashion.

• Multiple Wiesner’s nevi: consider BAP-1 germline mutation especially with a family history of mesothelioma or uveal melanoma.
BAP-oma

- BAP-1 gene - chromosome 3p21
- Cell cycle regulation, differentiation, cell death, DNA damage response
- Many different types of mutations
- Immunohistochemistry is procedure of choice for detection BAP-1 mutations
BAP-oma

- Cancer syndrome involving predisposition to mesothelioma, multiple melanocytic nevi, uveal melanoma, and cutaneous melanoma.
- Concomitant BRAF mutation is frequent
- 85% of metastatic uveal melanomas have BAP-1 mutation
- Histone deacetylase inhibitors used for uveal melanoma with BAP-1 mutation
- Lack of BAP-1 expression associated with worse survival in cutaneous melanoma
BAP-oma

- Solitary or multiple
- Well circumscribed pink papule or nodule
- Often polypoid
- Frequently present since childhood
BAP-oma

- Lesions are often Spitzoid or Epithelioid

- Spitzoid cytology without epidermal hyperplasia, Kamino bodies, and clefts

- Various populations with different degrees of atypia (HETEROGENEITY)

- Contain highly cellular areas with pleomorphic melanocytes that are BAP-1 negative
What would I see on a report?

• Atypical Spitzoid tumor with BAP-1 loss

• Wiesner’s nevus is associated with BRAF EXPRESSION and typically lacks epidermal hyperplasia and Kamino bodies

• P16 - cyclin-dependant kinase inhibitor 2 (CDKN2A gene) tumor suppressor is EXPRESSED.

• Therefore, “melanocytic tumor of uncertain biological potential” is the best description
RESIDUAL NEVUS, R/O NEUROFIBROMA

COMBINED MELANOCYTIC NEVUS, INCLUDING A COMPONENT OF DESMOPLASTIC BAP-1 INACTIVATED SPITZOID NEVUS ('BAPOMA') (D48.5) (RIGHT LATERAL NECK)

NOTE: Two different specimens have been evaluated jointly as the basis for this consultation, and I understand that the second biopsy represents persistence at the site of the first biopsy. For both specimens, my differential diagnosis included a combined desmoplastic Spitz nevus on one hand and a combined melanocytic nevus with a component of BAP-1 inactivated spitzoid nevus ('BAPoma') on the other. Immunostaining for BAP-1 demonstrates loss of nuclear positivity in the large melanocytes that are present, thereby corroborating that BAP-1 genomic loss has occurred in those cells. Expression of p16 is preserved, and thus concomitant CDKN2A genomic loss has not occurred. The labeling combination discussed in the two preceding sentences is confirmatory of the diagnosis of ‘BAPoma’.

In summary, the combination of results derived from conventional microscopy coupled with immunohistochemistry is confirmatory of the diagnosis of BAP-1 inactivated spitzoid nevus ('BAPoma'). A key issue in the evaluation of a patient with a 'BAPoma' is the determination regarding whether the proliferation stems from a sporadic somatic mutation or whether instead the proliferation is a harbinger of an underlying germline mutation. Most combined 'BAPomas' stem from somatic mutations, but the overall clinical context must be used to make this distinction.
What do I do next?

• Complete excision with generous clear margins (margin of error) and look for additional lesions

• Inquire about eye tumors and mesothelioma

• Long term surveillance similar to a melanoma patient

• Referrals for multiple lesions with suspected germline mutation

• Multiple lesions followed for change in clinical appearance, radiologic studies, and genetic counseling
Summary

• Solitary or multiple

• Risk of melanoma is surprisingly low

• Melanocytic tumor of uncertain biological potential (different from Spitz nevus)

• Wiesner’s nevus

• Nevi, uveal melanoma, cutaneous melanoma, Familial mesothelioma (non-asbestos related)
NEW ORLEANS MINT

1838-1861 and 1879-1909
The one-of-a-kind $10 denomination proof gold coin, specially struck at the New Orleans Mint in 1844 and now insured for $2.5 million, has returned “home.” Louisiana coin dealer Paul Hollis hand-carried the historic coin after making arrangements with its anonymous current owner to exhibit the unique gold piece when the Louisiana State Museum - U.S. Mint re-opens on November 1, 2008. Photo courtesy of Paul Hollis.
EXTRAMAMMARY PAGET’S DISEASE

- Overview
- Presentation
- Differential Diagnosis
- Treatment
- Review
PAGET’S DISEASE

- Mammary
- Extramammary
- Bone
- Prototype (microscopic pattern)
• Sir James Paget 1874
PAGET’S DISEASE

- 1874 Sir James Paget

- Mammary skin involvement (nipple) associated with an underlying breast cancer in virtually 100% of cases.

- Poor prognostic sign
EXTRAMAMMARY PAGET’S DISEASE

- 1889 Radcliffe Crocker
- Occurs in anatomic sites rich in apocrine glands
- Frequently NOT associated with an underlying glandular carcinoma (confined to the skin).
EXTRAMAMMARY PAGET’S DISEASE

INTRAEPIDERMAL APOCRINE CARCINOMA

CYTOKERATIN 7 POSITIVE
EXTRAMAMMARY PAGET’S DISEASE

- Vulva most common
- Male genital area
- Perianal area
- Axilla
EXTRAMAMMARY PAGET’S DISEASE

- Perianal
- Sharply demarcated erythematous patch
- Pruritus and burning pain are common
- Primary vs. secondary
PERIANAL PAGET’S DISEASE

- Similar to mammary Paget’s since it is frequently associated with underlying visceral malignancy
- Frequently NOT limited to the perianal skin
- More referrals and worse prognosis
MICROSCOPIC FINDINGS

- Paget’s cells: Large mucin containing cells
- Single cells or small clusters at all levels of the epidermis - primarily lower layers
- Basal layer is frequently spared and compressed forming “eyeliner sign”
- Occasional signet ring cells and tubular structures
MICROSCOPIC FINDINGS

- Limited to epidermis
- Invasive - Depth of Invasion (4mm)
- Cell of origin - likely adnexal stem cell origin (primary)
Perianal Paget's disease: distinguishing primary and secondary lesions using immunohistochemical studies including gross cystic disease fluid protein-15 and cytokeratin 20 expression.

Nowak MA, Guerriere-Kovach P, Pathan A, Campbell TE, Deppisch LM.
PERIANAL PAGET’S DISEASE

- Primary lesions (limited to skin): CK20 negative/GCDFP-15 positive, good prognosis, high 5 year survival, intraepidermal apocrine carcinoma.

- Secondary lesions (skin and rectal involvement): CK20 positive/GCDFP-15 negative, poor prognosis, low 5 year survival, rectal carcinoma involving skin vs. invasive Paget’s involving rectum.
Signet ring cell perianal paget disease: loss of MUC2 expression and loss of signet ring cell morphology associated with invasive disease.

Grelck KW, Nowak MA, Doval M.
PERIANAL PAGET’S DISEASE

- Morphology (loss of signet ring cell features)
- Immunohistochemical (loss of Muc2 expression)
- Depth of invasion (> 4 mm): Depth of invasion associated with a worse prognosis (shift in phenotype and differentiation)
DIFFERENTIAL DIAGNOSIS

Erythematous plaque of groin
CLINICAL DIFFERENTIAL DIAGNOSIS

- Eczematous dermatitis including irritant and allergic contact dermatitis
- Tinea Cruris
- Candidiasis
- Intertrigo
- Psoriasis/Seborrhea
- Zoon’s
- Granular Parakeratosis
- Malignancy (high index of suspicion)
MICROSCOPIC DIFFERENTIAL DIAGNOSIS

- Paget’s/Extramammary Paget’s disease
- Melanoma/Melanoma in-situ
- Squamous cell carcinoma in-situ
- Sebaceous carcinoma (and other adnexal)
- Pagetoid reticulosis
- Merkel cell carcinoma (Golgi CK20 +) - Polyomavirus?
MORPHOLOGIC CLUES

- Eyeliner sign (thin vs. thick)
- Pigmentation
- Parakeratosis
- Sebaceous cells
- String of pearls
- Nuclear molding
- Dermal involvement (differentiation)
SPECIAL STAINS

• EMPD vs. SCCIS vs. MIS
• Primary vs. Secondary
• Invasion (CKNBD-56 expressed, MUC-2 lost)
• Lymphatic involvement (D2-40)
SPECIAL STAINS

- PAS +
- Mucicarmine +
- Alcian Blue +
- CK7 +
- GCDFP-15 +/- (primary/secondary EMDP)
- CK20 -/+ (primary/secondary EMDP)
SPECIAL STAINS

- S100 = MIS
- CK5/6 (LMW) = SCC
- EMA/Oil-red-O = sebaceous carcinoma
- CK7 = EMPD
- GCDFP-15 = primary
- CK20 diffuse = secondary
- CK20 perinuclear = Merkel
WORK UP

• Clinical trial with topical therapy
• Medium potency steroid and antifungal
• NR in compliant patient at 3-4 weeks
• Biopsy (4 mm punch in formalin)
• History and Physical (pelvic, rectal, breast, lymph nodes)
• Referrals and Staging (Internist, GYN, GE, surgical and medical oncology)
• Procedures (culposcopy, sigmoidoscopy, cystoscopy)
TREATMENT

- Topical chemotherapy
- Wide local excision (Stage 1 and 2A)
- AP resection (Stage 2B and Stage 3)
- Medical oncology (Stage 4)
- Radiation (Stage 4)
- Other referrals
- Long term monitoring
Approach to the patient with extramammary Paget disease (EMPD)

Perianal, perineal, inguinal, axillary red patch

- Recent
  - Trial of steroids or antifungals
    - No improvement
      - Surgical treatment (Mohs surgery vs. wide local excision)
        - Consider non-surgical treatment modalities if not a surgical candidate e.g., radiation, PDT, etc.

- Long standing
  - Biopsy
    - Special stains (CK7; CAM 5.2; mucin)
      - EMPD
        - Internal malignancy workup
          - Abdomen/pelvis imaging
          - CXR; mammogram
          - Consider PET scan to r/o lymph node involvement and metastasis
            - Colonoscopy
            - Cystoscopy
            - Pelvic exam
Table 1. Stage and management of perianal Paget’s disease

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Paget cells found perianal epidermis and adnexa without primary carcinoma</td>
<td>WLE</td>
</tr>
<tr>
<td>IIA</td>
<td>Cutaneous Paget’s disease with associated adnexal carcinoma</td>
<td>WLE</td>
</tr>
<tr>
<td>IIB</td>
<td>Cutaneous Paget’s disease with associated anorectal carcinoma</td>
<td>APR</td>
</tr>
<tr>
<td>III</td>
<td>Paget’s disease in which associated carcinoma has spread to regional nodes</td>
<td>ILND + WLE/APR</td>
</tr>
<tr>
<td>IV</td>
<td>Paget’s disease with distant metastases of associated carcinoma</td>
<td>CT + RT + LPM</td>
</tr>
</tbody>
</table>

WLE: Wide local excision, ILND: Inguinal lymph node dissection, CT: Chemotherapy, RT: Radiotherapy, LPM: Local palliative management
EXTRAMAMMARY PAGET’S DISEASE
TREATMENT RESPONSE

<table>
<thead>
<tr>
<th>Age/Sex</th>
<th>Location</th>
<th>Size (cm)</th>
<th>Treatment</th>
<th>Recurrence (months)</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>52/f</td>
<td>Vulva</td>
<td>17</td>
<td>Radiotherapy, Vulvectomy, CO₂ laser, Vulvectomy</td>
<td>4, 12, 36, 7-10</td>
<td>CR, PR, CR, PR</td>
</tr>
<tr>
<td>71/f</td>
<td>Inguino-crural</td>
<td>14</td>
<td>Radiotherapy, Mohs micrographic surgery</td>
<td>3, 84</td>
<td>CR, CR</td>
</tr>
<tr>
<td>72/m</td>
<td>Penis</td>
<td>7</td>
<td>Surgery</td>
<td>6-84</td>
<td>CR</td>
</tr>
<tr>
<td>68/m</td>
<td>Axilla</td>
<td>8</td>
<td>Imiquimod, PDT</td>
<td>0</td>
<td>PR, PR</td>
</tr>
<tr>
<td>76/M</td>
<td>Scrotum</td>
<td>5</td>
<td>PDT</td>
<td>NA</td>
<td>CR</td>
</tr>
<tr>
<td>73/F</td>
<td>Vulva</td>
<td>10</td>
<td>PDT</td>
<td>NA</td>
<td>PR</td>
</tr>
<tr>
<td>67/F</td>
<td>Vulva</td>
<td>20</td>
<td>PDT</td>
<td>NA</td>
<td>PR</td>
</tr>
</tbody>
</table>

Note: CR - complete response (100% clearance); PR - partial response (50-99% clearance); MR - minimal response (< 50% clearance); NA - not available.
Summary

- Mammary vs. Extramammary
- Primary vs. Secondary
- Clinical Differential Diagnosis
- Microscopic Differential Diagnosis
- Referrals and treatment
- Long term monitoring