Mesenchymal Tumors of the Vulva:
Old, New, Something(s) Different

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Notice of Faculty Disclosure

US Pathology Biomarker Advisory Board, Merck
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Case #1

- 44-year-old has excision of "Bartholin cyst"
Deep Aggressive Angiomyxoma

• Subcutaneous or deep soft tissue
• Typically large (> 5 cm), gelatinous or myxoid mass – may be well defined but usually poorly circumscribed with infiltrative margins
• Bland, spindle shaped cells with pale staining cytoplasm, round to oval nuclei
• Small to medium sized blood vessels which may be thick walled and hyalinized

Deep Aggressive Angiomyxoma

• Condensation of fibrillar collagenous material or bundles of smooth muscle around blood vessels
• No nuclear atypia
• Low mitotic index
• Paucicellular, but may be more densely cellular or fibrotic in recurrences
Deep Aggressive Angiomyxoma

- Desmin +/-
- Actin +/-
- CD34 +/-
- ER + (AR+ in men)
- PR +

Deregulation of HMGA2 protein, an architectural transcriptional factor, due to rearrangements on 12q13-15

HMGA2 rearrangements not specific

Role of HMGA2 in diagnosis and margin assessment needs further study
Deep Aggressive Angiomyxoma

- Reproductive age women (3rd to 5th decades) – vulvovaginal region, pelvis
- Men (6th to 7th decade) – scrotum, inguinal region, spermatic cord, perineum
- Vague symptoms, pressure effects
- Clinical impression: Bartholin gland cyst, lipoma, or hernia


Deep Aggressive Angiomyxoma

- Reported recurrence rates vary from 36 to 72%, but are probably overestimated
- Risk for recurrence depends on size, anatomical location, circumscription, and amenability to wide resection
- Most are treated by one re-excision
- Essentially non-metastasizing – 2 documented cases of lung metastases

Deep Aggressive Angiomyxoma Differential Diagnosis*

- Angiomyofibroblastoma
- Cellular angiofibroma
- Superficial angiomyxoma
- Superficial myofibroblastoma
- Fibroepithelial stromal polyp

*Specialized genital stromal tumors*
Angiomyofibroblastoma

- Reproductive age women (and men)
- Typically small (<5 cm), circumscribed, no-recurring superficial soft tissue tumor
- Spindle and plump epithelioid or plasmacytoid cells, may be multinucleate, clustered around vessels
- Alternating hypocellular and hypercellular areas

**Cellular Angiofibroma**

- Rare, small (< 5 cm), superficial soft tissue tumor in middle age women (and men)
- Resembles spindle cell lipoma with wispy (not ropy) collagen
- Uniformly cellular & mitotically active proliferation of spindle cells, may be multinucleate
- Numerous small to medium caliber vessels, often hyalinized, may have prominent lymphoid aggregates

Superficial Angiomyxoma

- Superficial, small (< 5 cm), circumscribed, with multilobulated pattern
- Neutrophilic inflammatory cells
- Epithelial or adnexal component (1/3)
- Assoc with Carney’s complex
- Significant risk for local (nondestructive) recurrence (up to 40%)

Superficial Myofibroblastoma of the Lower Female Genital Tract

- Cervix, vagina & vulva
- Wide age range: 23 to 80 years
- Size: 1 to 6.5 cm
- Well-circumscribed
- Benign
Superficial Myofibroblastoma of the Lower Female Genital Tract

- Bland ovoid to spindle-shaped cells, often with wavy nuclei set in a finely collagenous stroma
- Variety of architectural patterns
- Stromal edema or myxoid change or hyalinized areas with thick, dense collagen bundles

Superficial Myofibroblastoma of the Lower Female Genital Tract

- Positive for vimentin (100%), CD34 (50%), desmin (75%), & ER/PR (80+%).
- Negative for S100, h-caldesmon, HMB45, & CD31
- Alpha smooth muscle actin variably positive
Case #2

- Vulvar mass in 18-year-old.
Fibroepithelial Stromal Polyp

- Small, superficial exophytic or polypoid mass (may simulate condyloma) in reproductive aged women
- Vagina, vulva, cervix
- Propensity to occur during pregnancy – may be multiple

*Cancer* 1966;19:227-232
**Fibroepithelial Stromal Polyp**

- No grenz zone
- Multinucleate cells, enlarged bizarre nuclei
- May have high mitotic index (>10 MF/10 HPF)
- Pale, edematous and myxoid stroma
- Variable vascular component with thick-walled vessels in middle

**What If Tumor Doesn’t Fit?**

- Tumor size and depth (e.g., cutaneous, subcutaneous, deep soft tissue).
- Margin status (infiltrative vs circumscribed).
- Imaging studies, if performed.
- History of prior malignancy – exclude metastasis.
- Use immunohistochemistry in directed fashion, e.g., S100, CK, EMA.
- Consider “specialized genital stromal tumor”

**Differential Diagnosis: Other Clinically Benign Tumors**

- Myxoid neurofibroma
- Myxoid schwannoma
- Myxoma
- Hemangioma
- Spindle cell lipoma
Differential Diagnosis: Clinically Intermediate Tumors

- Dermatofibrosarcoma protuberans
- Pelvic fibromatosis
- Atypical lipomatous tumor
- Low grade fibromyxoid tumor
- Low grade myxofibrosarcoma

Dermatofibrosarcoma Protuberans

Differential Diagnosis: Clinically Malignant Tumors

- Embryonal rhabdomyosarcoma
- Myxoid liposarcoma
- Myxoid leiomyosarcoma
- Myxoid malignant melanoma
- Myxoid carcinoma
Case #3

- 37-year-old with vulvar mass
Reticular-Microcystic Schwanomma
- 11 to 93 years (median, 63)
- 0.4 to 23 cm (median, 4.3 cm)
- Predilection for visceral locations
- Microcystic & reticular pattern with anastomosing strands of spindle cells with eosinophilic cytoplasm
- Myxoid or collagenous/hyalinized stroma

Vulvar Nerve Sheath Tumors
- Neurofibroma
- Schwannoma
Schwannoma

- Reticular-microcystic
- Pseudoglandular elements
- Ancient change
- Plexiform (deep seated)
- Psammomatous melanotic
- Prominent lipomatous component

Virchows Arch 2010;456:411-22

Differential Diagnosis: Reactive Processes

- Nodular fasciitis
- Postoperative spindle cell nodule
- Fallopian tube prolapse
- Vulvar hypertrophy with lymphedema

Vulvar Hypertrophy with Lymphedema

Arch Pathol Lab Med 2000;124:1697-1699
Prepubertal Vulval Fibroma
(Vulvar Fibrous Hyperplasia)

• Median age: 8 years (range, 4-12)
• Unilateral
• Subcutaneous, painless, ill-defined – typically labia majora
• Patternless, bland spindle cell proliferation extends around nerves, muscle and fat
• No interface, so if incompletely excised, may recur


Case #4

• Vulvovaginal mass in 6-year-old
Genital Rhabdomyosarcoma

- Most common in children & young adults: embryonal (botryoid) type
  - Vagina in children
  - Cervix in young adult
  - May harbor cartilage
- Extraordinarily uncommon in older adults
  - Pleomorphic, alveolar types
  - Highly aggressive clinical course
  - Complicated differential diagnosis

Skeletal Muscle Markers

- Myogenin and MyoD1—skeletal muscle specificity and sensitivity
  - Negative in 2-3% of RMS [B5 fixation]
  - Expression often stronger in alveolar type
  - Myogenin>MyoD1
  - PAX7 (PNET)
- Desmin - sensitive, but not specific
  - Negative in 1% of RMS
Rhabdomyosarcoma

- Embryonal, alveolar, pleomorphic types
- Cartilage present in almost 50% of cervical rhabdomyosarcoma
- Cervical rhabdomyosarcoma assoc with DICER mutation
Female Genital Tract Rhabdomyosarcoma

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<th>Type</th>
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<th>Adult</th>
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<td>NOS</td>
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<td>Uterine corpus, ovary</td>
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Rhabdomyosarcoma

**Immunohistochemistry**

- Myogenin - expression tends to be stronger, more diffuse in alveolar rhabdomyosarcoma
- Desmin – can be negative in 1% of cases
- May also express cytokeratin, CD99, CD56, S100, WT1

* PAX3-FOX01 or PAX7-FOX01 fusion

Rhabdomyosarcoma

- Embryonal, alveolar, pleomorphic types
- Cartilage present in almost 50% of cervical rhabdomyosarcoma
- Cervical rhabdomyosarcoma assoc with DICER mutation
Case #5

- Vulvar mass in 42 year old
Differential Diagnosis

- Poorly differentiated carcinoma (primary)
- Metastatic carcinoma
- Other (sarcoma)?
Diagnosis

- Epithelioid sarcoma, proximal type

Epithelioid Sarcoma

- Distal (classic) type
- Proximal type
Epithelioid Sarcoma, Distal Type

- Young adults – 10 to 39 years
- M:F 2:1
- Flexor surfaces of fingers, hands, wrists forearm, followed by distal leg
- Slow growing, small, superficial, painless
- Recurrence 35-80%; metastases 40% (including nodes)

Epithelioid Sarcoma, Distal

- Nodules of spindled and epithelioid cells
- Central hyalinization and necrosis
- May be mistaken for granuloma or poorly differentiated carcinoma
- May exhibit inflammatory, myxoid, or pseudoglandular features
- May have calcifications
Epithelioid Sarcoma, Proximal Type

- Similar to epithelioid sarcoma proximal type, but larger, deeper
- Larger, epithelioid carcinomatous cells
- Atypical, pleomorphic rhabdoid cells
- Sheets more prominent than discrete nodules
- Large areas of geographic necrosis
- Myxoid or spindle cell morphology

Epithelioid Sarcoma, Proximal Type

- Age range 22 - 71 years (mean, 46)
- Highly aggressive
- Metastases to regional lymph nodes, lungs, and brain
- Often misdiagnosed as carcinoma

Cancer 1983;52:1462-1469
Epithelioid Sarcoma

- Vimentin positive
- Cytokeratin positive
- EMA positive
- CD34 positive (50%)
- INI loss (90%)


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SMARCB1/INI1 Loss

- Epithelioid sarcoma
- Pediatric rhabdoid tumor of kidney, CNS & soft tissue
- Renal medullary carcinoma
- Extracellular myxoid chondrosarcoma

*Adv Anat Pathol* 2014;21:394-410

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SMARCB1/INI1 Loss

- Poorly differentiated chordoma
- Myoepithelial carcinoma (subset)
- Epithelioid MPNST (subset)
- Other: gastroenteropancreatic tumors, collecting duct carcinomas, synovial sarcoma, undifferentiated pancreatic rhabdoid tumor, gastrointestinal carcinomas with MSI-H phenotype, and sinonasal carcinoma

*Adv Anat Pathol* 2014;21:394-410
**SMARCB1/INI1 Loss, Mosaic Pattern**

- Ossifying fibromyxoid tumors (74%)
- Gastrointestinal stromal tumors (70%)

*Adv Anat Pathol* 2014;21:394-410

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**SMARCB1**

- Integral component of the switch/sucrose nonfermenting (SWI/SNF) complex
- Located on chromosome 22q11.2
- Encodes a 47kDa of the SWI/SNF complex, which is involved in chromatin remodeling and transcriptional regulation.
- Ubiquitously expressed


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Diagram:
- Epithelioid Morphology
- Proximal Epithelioid Sarcoma
- Angiosarcoma
- Lymphoma
- Myoepithelial carcinoma
- Melanoma
- Smooth muscle
- PEComa
- Carcinoma, Primary vs Metastatic
Poorly Differentiated Carcinoma: Primary

- Squamous cell carcinoma
- Adenocarcinoma (Bartholin gland, adnexal)

Poorly Differentiated Carcinoma: Metastatic

- Cervix, endometrium, urethra, vagina, or ovary
- Metastatic squamous cell carcinoma usually appears as a circumscribed, subepithelial mass
- Metastatic adenocarcinoma tends to invade the surface epithelium
- SMARCB1/INI1 intact.
Poorly Differentiated Carcinoma

Myoepithelial Carcinoma

- Malignant epithelioid or rhabdoid cells similar to proximal epithelioid sarcoma
- Spindle cell morphology, stromal hyalinization & myxoid change often present.


Myoepithelial Carcinoma

- EMA-positive
- SMA-positive
- Cytokeratin & CD34 limited or absent
- SMARCB1/INI1 loss in up to 40-50% of cases
- EWSR1 rearrangement may be present on FISH

Vulvovaginal Smooth Muscle Tumors

- Premenopausal women
- Vaginal more common than vulval
- Vaginal usually benign, but recurrence seen when mitotic index >5 MF/10 HPF
- Vulval recur locally and may metastasize to lungs (<25%)
- Both types express ER/PR and may respond to hormonal therapy

Vulval Smooth Muscle Tumors: Criteria for Malignancy

- Size > 5 cm*
- Infiltrative margins*
- Moderate to severe cytologic atypia*
- Mitotic index > 5 MF/10 HPF*
- Tumor cell necrosis
- Any single feature warrants complete excision

* Tumors with 3 of these features are classified as malignant
Differential Diagnosis of Vulvovaginal Smooth Muscle Tumors

- Nerve sheath tumors
- Melanoma
- GIST (metastatic)
- Granular cell tumor
- Epithelioid sarcoma (proximal type)

Case #6

- 51-year-old with vulvar mass
Lipoblastoma-like Tumor of the Vulva

- Rare
- Indolent, but may recur after excision
- Wide age range: 17 to 46 years (median 27)
- May be large: 3.5 to 15 cm (median 5.6 cm)

Lipoblastoma-like Tumor of the Vulva

- Mature adipocytes, bland uni- and bi-vacuolated lipoblasts, & spindle cells with short stubby nuclei
- Diffuse myxoid background with prominent branching vessels
- Nuclear atypia minimal
- No necrosis
- Little or no mitotic activity


Thank you