Lesions of the Vulva

Non-Neoplastic Lesions

Lichen Sclerosus *(formerly lichen sclerosus et atrophicus)*

Most common in postmenopausal women. Autoimmune disease.

Clinically appears as white to red plaques with wrinkling and hypopigmentation resembling “tissue paper.”

Causes pruritis and pain.

*Sclerosis of papillary dermis and atrophy of overlying epithelium.*

1) Hyalinization and edema in papillary dermis (“homogenization”)
2) Some degree of vacuolar degeneration of basal keratinocytes
3) Band-like lymphocytic infiltrate beneath homogenized collagen.
4) Epidermal atrophy

Increases risk of differentiated VIN.

Lichen Simplex Chronicus

Non-specific pattern in response to *chronic rubbing/scratching.*

Can be seen in association with other disorder (e.g., Candida infection, contact dermatitis) or due to clothing or other irritation.

Clinically looks thickened, leathery, scaled (“Lichenification”)

Marked hyperkeratosis (sometimes parakeratosis)

Hypergranulosis

**Irregular epidermal hyperplasia**

Papillary dermis is thickened with vertical dense collagen between papillae

Lots of spongiosis? → consider *contact dermatitis*

Neutrophils in stratum corneum? → consider *fungal* → PAS/GMS

Bartholin’s Cyst

Vulvar cyst due to Bartholin gland duct outlet obstruction with subsequent retention of mucinous secretions (Duct → Cyst).

Located in posterior vestibule.

Unilocular with smooth inner lining of nonkeratinizing squamous, transitional, or mucinous epithelium.

Bartholin Glands (can be seen in wall of Bartholin cyst)
Tumors in the Epithelium

Seborrheic Keratosis

Benign. Clinically, “Stuck-on” look

Varying degrees of: Acanthosis, hyperkeratosis, interlacing pigmented epidermal strands, papillomatosis, and horn cysts

Hidradenoma Papilliferum

Benign. Often presents as an asymptomatic nodule.

Virtually identical to intraductal papilloma of the breast

Well-circumscribed subepithelial nodule
Papillary proliferation with tubular glands
Apocrine differentiation with apical snouts
Two cell layers (inner epithelial and outer myoepithelial) can be seen on IHC.

Squamous Intraepithelial Lesion (SIL)

Intraepithelial (in situ, non-invasive), squamous dysplasia due to HPV infection.
Clinically, can be flat or plaque-like, white to reddish-brown in color, and asymptomatic or pruritic

Low-grade Squamous Intraepithelial Lesion (LSIL)
Vulvar Intraepithelial Neoplasia grade 1 (VIN1)

Can be due to High or Low-risk HPV. Most common during reproductive age. Low risk of progression to cancer.

Proliferation of hyperchromatic basal-like cells that extends no more than 1/3 of the way up the epithelium

Cells differentiate (gain cytoplasm) in upper epithelium
Mitoses confined to lower zone. Epithelium often thickened.

Many nuclei are hyperchromatic with irregular nuclear contours (at all levels)

Koilocytes = large superficial cells with perinuclear halos and large, irregular, “Rasinoid” nuclei. Sometimes binucleated.

Often spontaneously regresses, so just observed clinically with repeat cytology

Condyloma acuminatum → grossly evident variant of LSIL. Often composed of papillary fronds.
Squamous Intraepithelial Lesion (SIL) (Continued…)

**High-grade Squamous Intraepithelial Lesion (HSIL)**

Associated with High-risk HPV (usually type 16). Higher risk of progression to invasive carcinoma if left untreated compared to LSIL, but not super high absolute risk.

Proliferation of hyperchromatic basal-like cells that extend 2/3 of the way up (VIN2) or full-thickness (VIN3/CIS) of the epithelium

Cells have **enlarged, hyperchromatic nuclei with irregular nuclear contours and increased N:C ratios**.

Little to no superficial maturation.

Mitoses common at all levels, including atypical mitoses

Nucleoli are unusual → raise the possibility of inadequately sampled invasive carcinoma (p16+) or metaplasia (p16-)

Can colonize skin appendages → **mimicking** invasion!

Treatment includes: excision, laser ablation, topical chemotherapy

**When to use P16 Immunohistochemistry**

Used as surrogate marker of High-risk HPV infection

- When the morphologic **DDX is between HSIL (P16 +) and a mimic (P16 -)**
- When you are considering a **Dx of VIN2**, which should be P16+ (vs. LSIL, which should be P16 -)
- When there is **disagreement** between pathologists
- When there is a **high-risk** for missed HSIL disease (e.g., HPV +)

**P16 Positive**

Strong, diffuse, nuclear and cytoplasmic, block staining along the basal layer going at least 1/3 of the way up

**P16 Negative**

Weak/Patchy i.e., Anything but “Block” positive

**When P16 Immunohistochemistry will NOT help**

- When the biopsy is unequivocally LSIL, HSIL, or Negative morphologically
- When the DDX is between LSIL and Negative, as both processes are P16 negative.
Differentiated-type Vulvar Intraepithelial Neoplasia

**HPV-negative** squamous dysplasia.
Predominantly in elderly women, associated with lichen planus and **lichen sclerosus**.

**Basal cell atypia with nuclear hyperchromasia.**
Anastomosing of rete ridges.
Atypical basal mitoses. Prominent nucleoli.

**Superficial terminal differentiation**
(cornification) with hyperkeratosis and dyskeratosis

IHC: **p16 negative** (non-block positive), **p53 mutant** with strong staining of all basal cells (see example), Ki67 profoundly increased.

Higher risk/quicker progression to invasive SCC than normal VIN3, so treat with excision.

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**Extramammary** Paget Disease

Intraepithelial proliferation of apocrine-like cells.
Often old Caucasian women. Often red, pruritic lesion.

**Large, round “Paget” cells with prominent pale cytoplasm and nucleoli spreading throughout epithelium.** Can be single cells or in groups/glands. Can extend down adnexal structures.

Important to rule out cutaneous pagetoid spread of urothelial or GI cancer with IHC (see below)

Treatment: Resection, but high rates of recurrence. Can progress to invasive adenocarcinoma.

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<table>
<thead>
<tr>
<th></th>
<th>CK7</th>
<th>CK20</th>
<th>GCDFP-15</th>
<th>CDX2</th>
<th>CEA</th>
<th>S100, MelanA, etc...</th>
<th>UPK III</th>
<th>HER2</th>
<th>GATA-3</th>
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<tbody>
<tr>
<td><strong>Primary Paget Disease</strong></td>
<td>+</td>
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<td><strong>Urothelial carcinoma</strong></td>
<td>+</td>
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<td><strong>Anorectal carcinoma</strong></td>
<td>+/-</td>
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<td><strong>Melanoma</strong></td>
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Squamous Cell Carcinoma

An **invasive** epithelial tumor composed of squamous cells with varying degrees of differentiation.

Derived from HSIL (HPV-related) or Differentiated VIN (not HPV-related)

Most common vulvar malignancy. Most common in elderly.

Most important factor determining outcome → Lymph node status

Most important factor determining Lymph node metastases → depth of invasion

Femoral and inguinal lymph nodes are the sites of regional spread

Sheet-like growth with infiltrating bands and single cells

**Often desmoplastic/inflammatory stroma**

**Two main morphologic types:**

<table>
<thead>
<tr>
<th>Keratinizing Squamous Carcinoma</th>
<th>Basaloid Squamous Carcinoma</th>
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</thead>
<tbody>
<tr>
<td>High-risk HPV association</td>
<td>No</td>
</tr>
<tr>
<td>Associated precursor lesion</td>
<td>Differentiated-type VIN</td>
</tr>
<tr>
<td>Association with inflammatory condition</td>
<td>Common. Often Lichen sclerosus</td>
</tr>
<tr>
<td>Morphology</td>
<td>Keratinizing</td>
</tr>
<tr>
<td>Age</td>
<td>Older females</td>
</tr>
<tr>
<td>Distribution</td>
<td>Usually unifocal</td>
</tr>
<tr>
<td>Prevalence</td>
<td>More common (approximately 80%)</td>
</tr>
<tr>
<td>IHC</td>
<td>p53: Some cases positive</td>
</tr>
<tr>
<td></td>
<td>p16: Negative</td>
</tr>
</tbody>
</table>


**Verrucous Carcinoma:** Highly-differentiated, exophytic SCC variant with prominent acanthosis, minimal nuclear atypia, superficial cells with abundant eosinophilic cytoplasm, and **broad “pushing” invasion** (non-infiltrative) with an associated inflammatory infiltrate. Lymph node metastases are very rare.

Other Tumors

**Melanocytic nevi**—Like nevi elsewhere on the skin, but remember the vulva is a “special site.” As such, there can be concerning (but benign) changes including Pagetoid spread, moderate cytologic atypia, an adnexal spread. There should be dermal maturation and no dermal mitoses.


**Basal Cell Carcinoma**—Like elsewhere on the skin. Basaloid cells with peripheral palisading.

**Bartholin Gland Carcinomas**—can be SCC, adenocarcinomas, transitional cell, etc...

**Mammary-type Adenocarcinoma**—like breast cancers in the breast, thought to arise from anogenital mammary-like glands. Notably, you can get phyllodes tumors too!

**Adenocarcinoma of Skene glands**—resembles prostate cancer. Stains with PSA
Unique Vulvar Mesenchymal Lesions

Fibroepithelial Stromal Polyp

Benign.

Polypoid growth with variably cellular central fibrovascular core covered in squamous epithelium.

Stroma contains predominantly bland spindled cells. Can see multinucleated stroma cells with degenerative-type atypia including significant pleomorphism.

Most common in reproductive age women. Can grow during pregnancy.

Massive Vulvar Edema

Also called “Vulvar hypertrophy with lymphedema” (or other, similar, names)

Reactive (non-neoplastic), likely due to lymphatic obstruction.

Associated with obesity and immobilization.

May present with generalized vulvar enlargement, papillomatous plaques, polyps, or pedunculated masses.

Dermal edema with uniformly distributed cells.

Dilated lymphatics (arrows).

Perivascular inflammation.

Aggressive Angiomyxoma

Benign (despite name!), but with a tendency to recur after incomplete recurrence.

Often presents as a “cyst” in reproductive age

Large (>5 cm), poorly-circumscribed, infiltrative. Gelatinous consistency.

Low-grade, hypocellular. Composed of small, bland spindled cells with scant cytoplasm. Numerous blood vessels of varying sizes, including thin-walled capillary-like and thick-walled arteries with radiating perivascular smooth muscle.

Invades fat and muscle. Extravasated RBCs. No mitotic activity of atypia.

IHC: (+)ER, PR, desmin. (+/-)CD34

Molecular: HMGA2 rearrangements

Treatment: Complete surgical resection. Most people treated with first surgery.
Superficial Angiomyxoma
Benign with localized recurrences.
Small (<5 cm), exophytic polypoid mass centered in skin and subcutaneous tissue ("Superficial"!!). Multilobulated.
Well-dermarcated, but unencapsulated.
Hypocellular myxoid nodules in dermis.
Bland stellate and spindled cells and inflammatory cells (classically neutrophils) and numerous delicate vessels.
Can envelope skin adnexal structures/epithelium

Cellular Angiofibroma
Benign. Usually painless superficial mass or polyp.
Small (<5 cm). Rare.
Circumscribed, but unencapsulated. Often traps fat at edges.
Composed of uniform bland spindled cells in fibrous stroma.
Small to medium-sized blood vessels with thick hyalinized walls.
Sort of resembles a spindle-cell lipoma, but with wispy collagen.

Superficial Myofibroblastoma
Benign.
Discrete, unencapsulated. Usually small (< 5 cm)
Oval to spindled cells with wavy nuclei and scant cytoplasm
Fine collagenous stroma. Varied architecture.
Thin-walled vessels, which might be dilated and “Stag-horn”
IHC: (+) Desmin, ER/PR; (+/-) CD34

Angiomyofibroblastoma
Benign. Non-recurring.
Small (<5 cm), circumscribed.
Alternating hypocellular and hypercellular areas
Spindle and plump epithelioid or plasmacytoid cells
IHC: (+) Desmin, ER/PR; (-) CD34