Lesions of the Vulva

Non-Neoplastic Lesions

Lichen Sclerosus

(formerly lichen sclerosus et atrophicus)

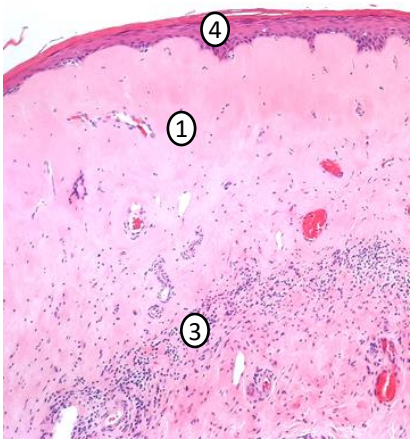
Autoimmune disease.
Most common in postmenopausal women.

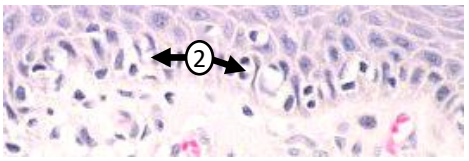
Clinically appears as white to red plaques with wrinkling and hypopigmentation resembling "tissue paper."

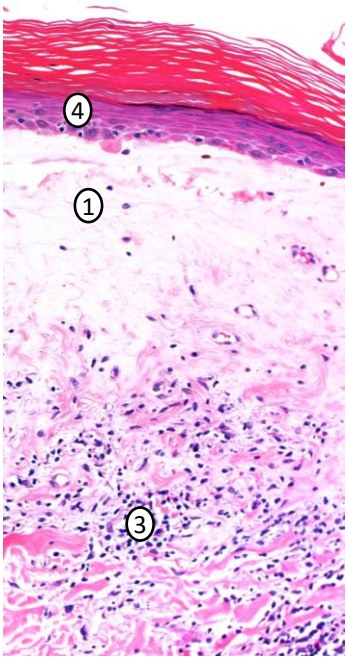
Causes pruritis and pain.

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 (dVIN).







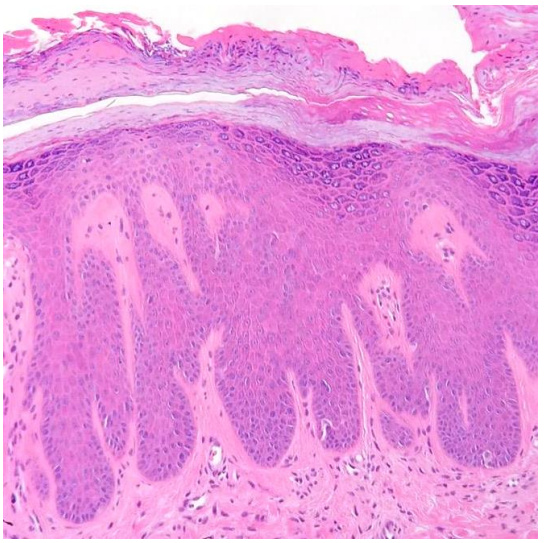
Lichen Simplex Chronicus

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 (± parakeratosis)
Hypergranulosis
Irregular epidermal hyperplasia
Papillary dermis is thickened with vertical dense collagen between papillae

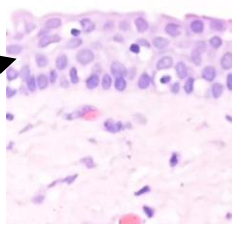
Lots of spongiosis? → consider contact dermatitis
Neutrophils in stratum corneum? → consider fungal → PAS/GMS



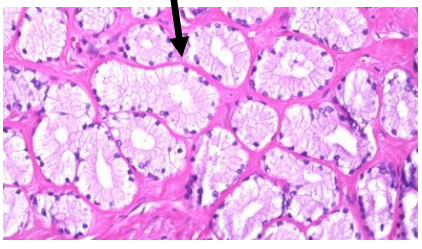
Bartholin's Gland Cyst

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

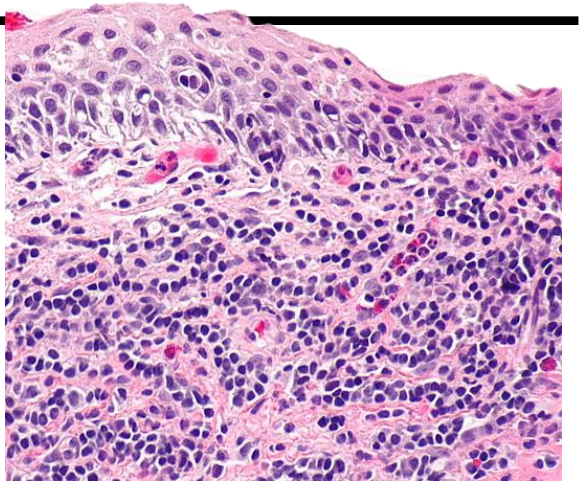
Unilocular with **smooth inner lining** of nonkeratinizing squamous, transitional, or mucinous epithelium.



Bartholin Glands
(can be seen in wall of Bartholin cyst)



Plasma Cell Vulvitis (Zoon Vulvitis)



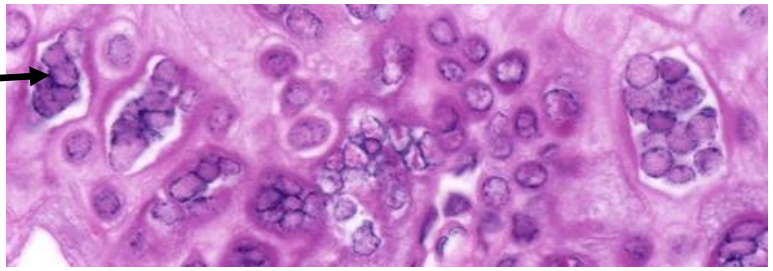
Idiopathic inflammatory dermatitis.
Well-circumscribed, erythematous plaques or patches.

Prominent lichenoid infiltrate of <u>plasma cells</u>
Thinned epidermis, with spongiosis.
"Lozenge"-shaped (diamond-like) squamous cells.

Presents with itching and/or pain
Wide age range, usually older adult.

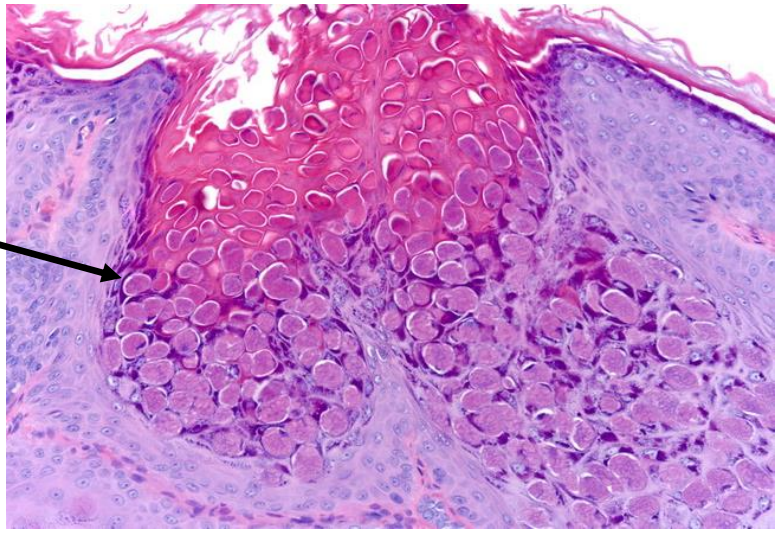
DDX: Syphilis → consider spirochete IHC!

(Non-HPV) Viral Infections



<u>Herpes Simplex Virus (HSV)</u>

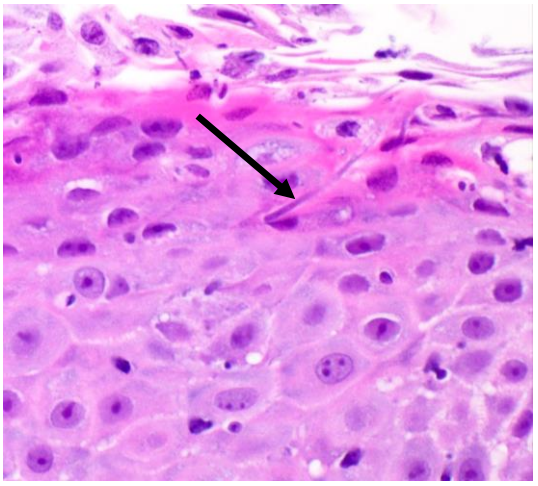
Sexually transmitted disease (STD).
Most commonly HSV-type 2
Clinically: Pustule→ Vesicle→ Ulcer
"3 M's": Molding, Multinucleation, Margination
Ground-glass nuclear inclusions
See inclusions in squamous epithelial cells.
Can use HSV IHC to confirm Dx.



<u>Molluscum contagiosum</u>

Caused by Molluscipox virus
Children: Anywhere on body through close contact
Adults: Usually on genitals only as an STD.
Clinically: small, dome-shaped smooth papule with a central punctum
Marked acanthosis with eosinophilic intracytoplasmic viral inclusions (Henderson-Patterson bodies)

Candidiasis



Candida albicans can cause chronic vulvovaginal infections.

Clinically: erythema and pruritis

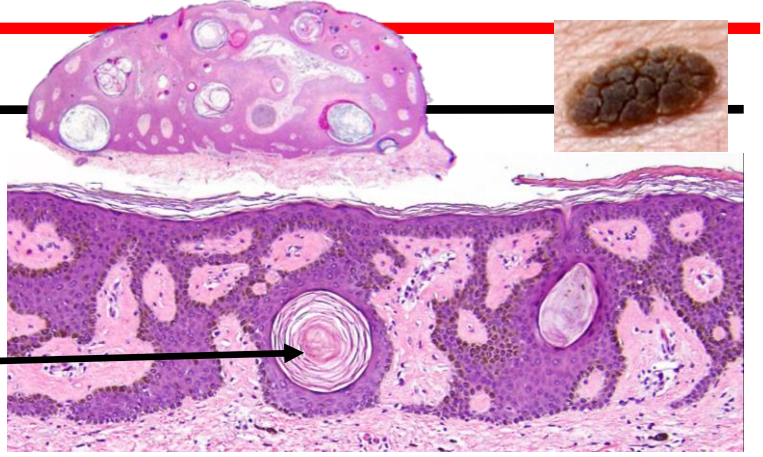
Pseudohyphae present→ can highlight with PAS and GMS

Psoriasiform hyperplasia, spongiosis with mixed dermal inflammation.

***<u>Good hint</u>:* Intracorneal neutrophils and neutrophilic aggregates within the superficial epidermis**

Tumors in the Epithelium

Seborrheic Keratosis *"SK"*

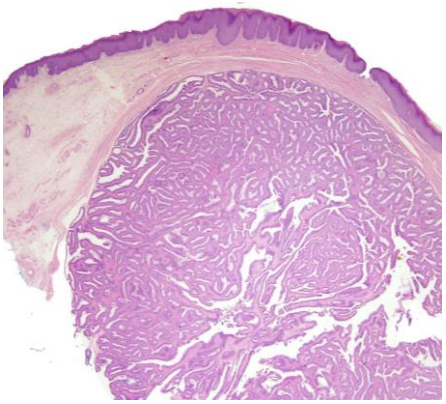


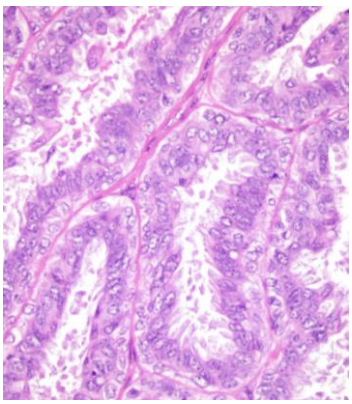
Benign. Clinically, plaque-like "Stuck-on" look

Varying degrees of: **Acanthosis**, hyperkeratosis, **<u>interlacing pigmented epidermal strands</u>**, papillomatosis, and keratin-filled **<u>horn cysts.</u>** No significant atypia.

Old women→ likely conventional skin SK
Younger women→ often HPV-positive, so better considered condyloma acuminatum

Hidradenoma Papilliferum



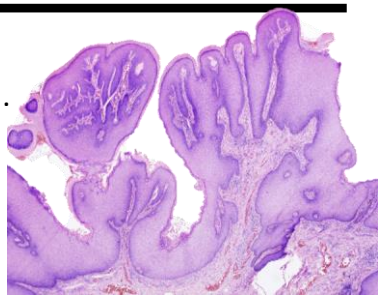


Benign. Often presents as an asymptomatic **nodule**.

<u>Virtually identical to intraductal papilloma of the breast</u>

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

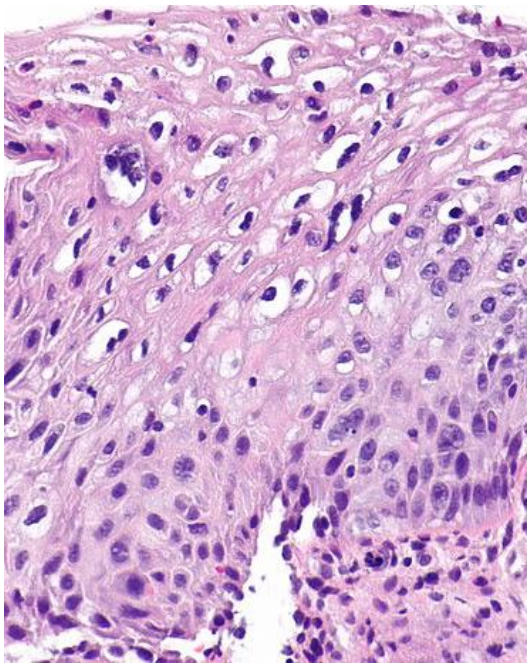
Squamous Intraepithelial Lesion (SIL)



Intraepithelial (in situ, non-invasive), squamous **dysplasia due to HPV infection**.

<u>Low-grade Squamous Intraepithelial Lesion (LSIL)</u>
Vulvar Intraepithelial Neoplasia grade 1 (VIN1)

Within the Vulva, most VIN1 is limited to Condyloma Acuminatum. (Flat LSIL in the vulva is rare.)



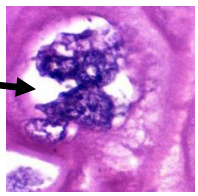
<u>Condyloma acuminatum</u>→ aka "Genital warts." Grossly evident verrucous LSIL. Composed of acanthotic papillary fronds with acanthosis, parakeratosis, and hyperkeratosis. Often multiple.

Mostly due to low-risk HPV (types 6 and 11). Most common during reproductive age. Low risk of progression to cancer.

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

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

<u>Many nuclei are **hyperchromatic** with **irregular nuclear contours**</u> (at all levels)



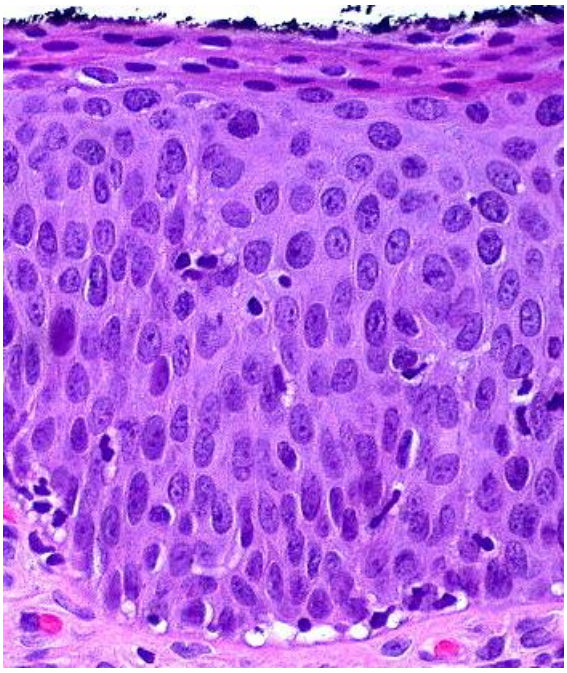
<u>Koilocytes</u> = large superficial cells with perinuclear halos and large, irregular, "Raisinoid" nuclei. Sometimes binucleated.

Often spontaneously regresses.
Can observe, or do excision, cautery, imiquimod.

Squamous Intraepithelial Lesion (SIL) *(Continued…)*

"Giant Condyloma Acuminatum" *(aka Bushke-Löwenstein tumor)*
Rare. Very large HPV-mediated condylomatous growth. Koilocytes present. Locally aggressive. Associated with immunosuppression. Potential for malignant transformation.

High-grade Squamous Intraepithelial Lesion (HSIL)



Most flat vulva SIL is 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.

Little to no superficial maturation. 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**.

Mitoses common at all levels, including atypical mitoses

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

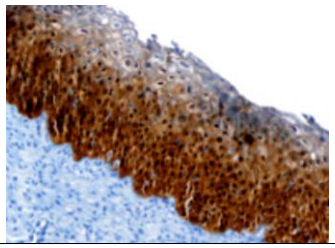
Can colonize skin appendages→ *mimicking* invasion!

Treatment includes: excision, laser ablation, topical chemotherapy

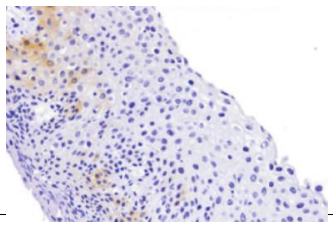
When to use P16 Immunohistochemistry

Used as surrogate marker of High-risk HPV infection

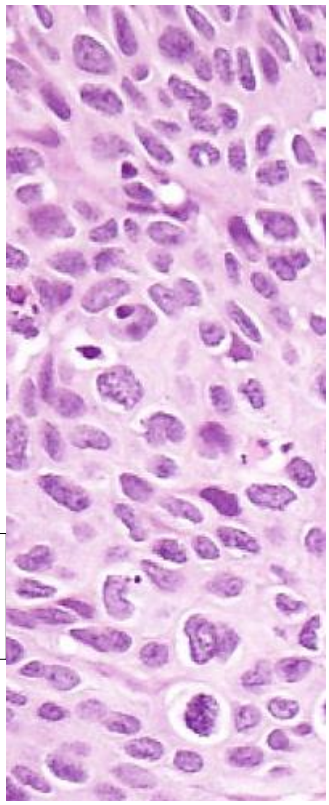
- When the morphologic **DDX is between HSIL (P16 +) and a mimic** (P16 -)
- When you are considering a **Dx of VIN2**, which should be P16+ (vs. LSIL, which should be P16 -)
- When there is **disagreement** between pathologists
- When there is a **high-risk** for missed HSIL disease (e.g., HPV +)



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 Vulvar Intraepithelial Neoplasia (dVIN)

HPV-negative (independent) squamous dysplasia.

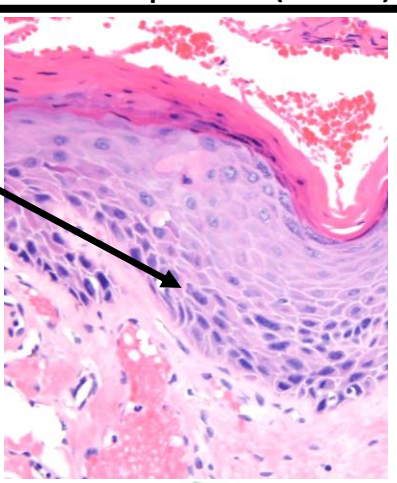
Predominantly in elderly women, associated with lichen planus and **lichen sclerosus**.

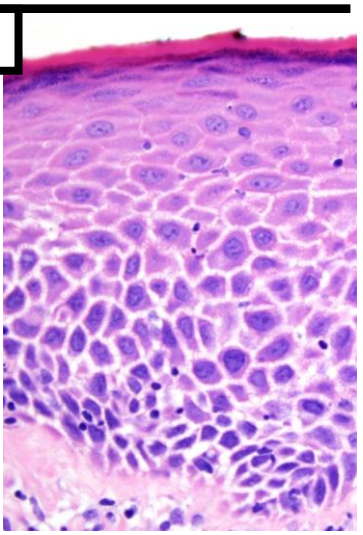
Basal cell atypia with nuclear hyperchromasia.
Anastomosing of rete ridges.
Atypical basal mitoses.

Superficial terminal differentiation (cornification) with hyperkeratosis and dyskeratosis. Abundant eosinophilic cytoplasm with prominent nucleoli.

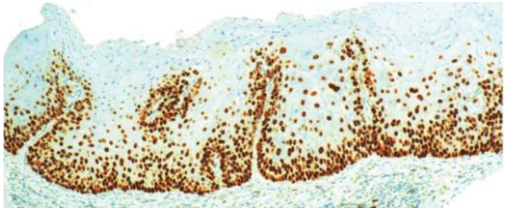
IHC: p16 negative (non-block positive),
p53 mutant with strong staining of all basal cells (see example) or null, Ki67 profoundly increased.

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





p53 IHC→



(Extramammary) Paget Disease

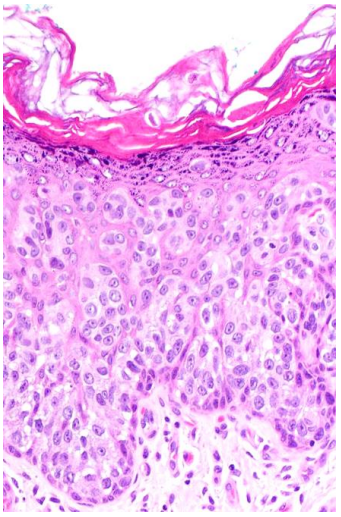
Intraepithelial proliferation of apocrine-like cells.

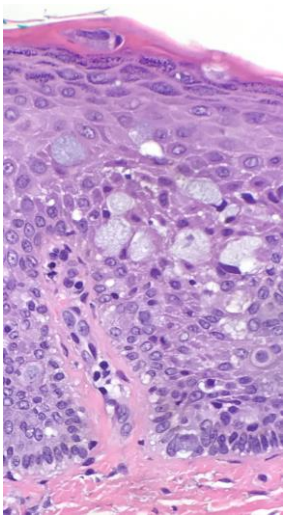
Often old Caucasian women. Often red, pruritic lesion.

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.

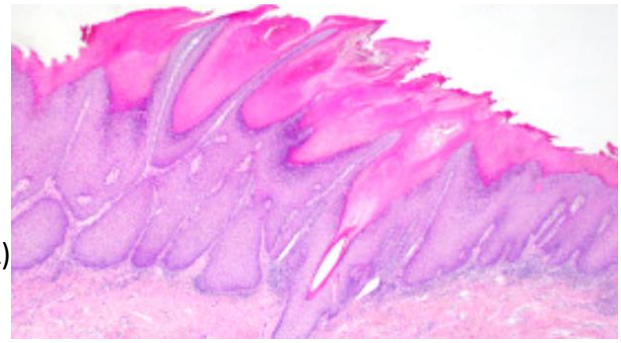




	CK7	CK20	GCDFP-15	CDX2	CEA	S100, MelanA, etc…	UPK III	HER2	GATA-3
Primary Paget Disease	+	-	+	-	+	-	-	+	+
Urothelial carcinoma	+	+	-	-	-	-	+	-	+
Anorectal carcinoma	+/-	+	-	+	+	-	-	-	-
Melanoma	-	-	-	-	-	+	-	-	-

HPV-independent, p53-wild-type Vulvar Intraepithelial Neoplasia "verruciform acanthotic Vulvar Intraepithelial Neoplasia (vaVIN)"

Emerging diagnosis
Marked acanthosis, verruciform growth and altered squamous maturation. ***No*** significant atypia.
Hyper- or hypogranulosis. Hyperkeratosis.



IHC: Negative/normal p16, p53 (by definition)

Varied names/morphology:
Differentiated Exophytic Vulvar Intraepithelial Lesion (DEVIL)
Vulvar Acanthosis with Altered Differentiation (VAAD)

Predominantly in elderly women
Clinical: Cauliflower-like plaque

Molecular: PIK3CA and HRAS mutations

Can progress to Conventional and Verrucous SCC

Comparison of VIN types:

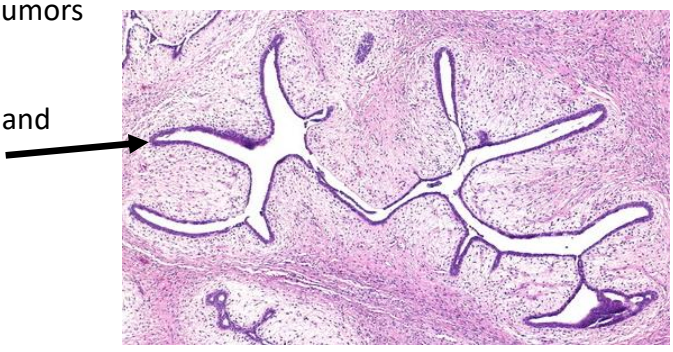
	HPV-associated VIN (HSIL)	HPV-independent, p53 mutant (dVIN)	HPV-independent, p53 wild-type (vaVIN)
Atypia	All layers Loss of polarity	Confined to basal layer	Absent
Nuclei	Hyperchromatic	Open chromatin, large	Normal
Maturation	None	Retained, but abnormal with elongated/fused rete ridges and dyskeratosis	Retained but altered with thickening and hyper/hypogranulosis
p16 IHC	Overexpressed "Block" positive	Negative/patchy	Negative/patchy
p53 IHC	Wild-type	Mutant	Wild-type

Modified from: Parra-Herran, Carlos et al. Modern Pathology, Volume 35, Issue 10, 1317 - 1326

Anogenital Mammary-gland Lesions

Anogenital mammary glands can give rise to multiple tumors resembling their breast counterparts

Fibroadenoma/Phyllodes tumors—biphasic epithelial and stromal tumors (like in the breast)



Adenocarcinoma of mammary gland type

Paget disease (see prior discussion)

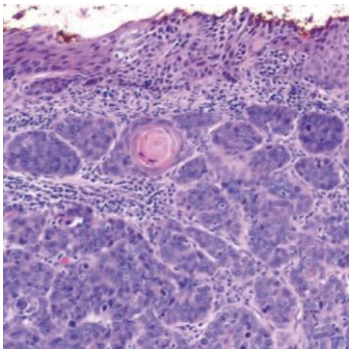
Myofibroblastoma

Squamous Cell Carcinoma

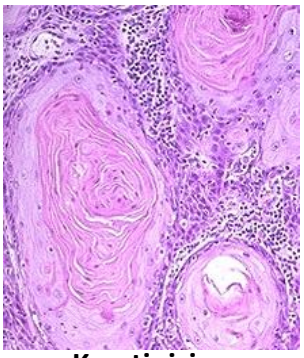
An **invasive** epithelial tumor composed of squamous cells with varying degrees of differentiation.
Derived from HSIL (HPV-associated) *or* Differentiated VIN (HPV-independent)

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



Basaloid

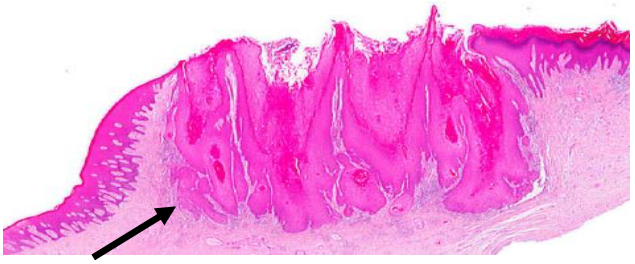


Keratinizing

Classified by HPV status:

	HPV-independent SCC	HPV-associated SCC
High-risk HPV association	No	Yes (Type 16>18)
Associated precursor lesion	Differentiated-type VIN	Classic VIN
Association with inflammatory condition	Common. Often Lichen sclerosus	Rare
Most common morphology	Keratinizing	Warty, Basaloid
Age	Older females	Younger females
Distribution	Usually unifocal	Often multifocal
Prevalence	More common (approximately 80%)	Less common (approximately 20%)
IHC	p53: Mutant p16: Negative	p53: Wild-type p16: Positive
Survival	Worse	Better

Modified from: CAP Cancer Protocol Template: Vulva. 2020.



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. HPV-negative.

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.

Melanoma—Malignant. Variable appearances (epithelioid to spindled). Large nuclei, prominent nucleoli. Absence of maturation. Lots of mitoses. Extensive pagetoid spread.

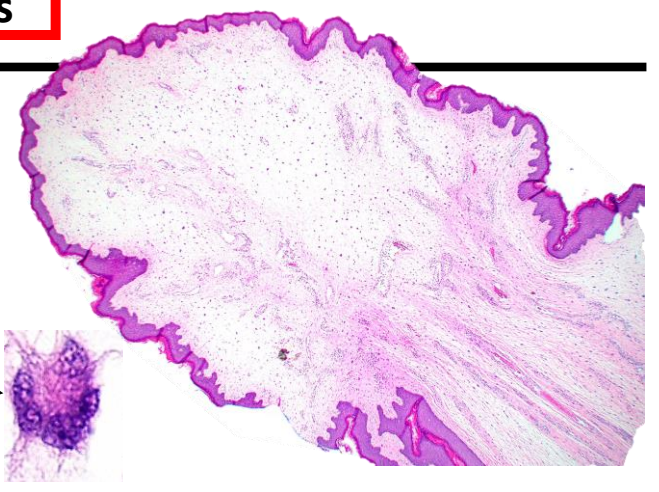
Basal Cell Carcinoma—Like elsewhere on the skin. Basaloid cells with peripheral palisading.

Bartholin Gland Carcinomas—Carcinomas arising from Bartholin gland—found in posterolateral vestibular region. Can be SCC, adenocarcinomas, transitional cell, salivary gland-like, etc…

Adenocarcinoma of Skene glands—resembles prostate cancer. Stains with PSA

Unique Vulvar Mesenchymal Lesions

Fibroepithelial Stromal Polyp



Benign.

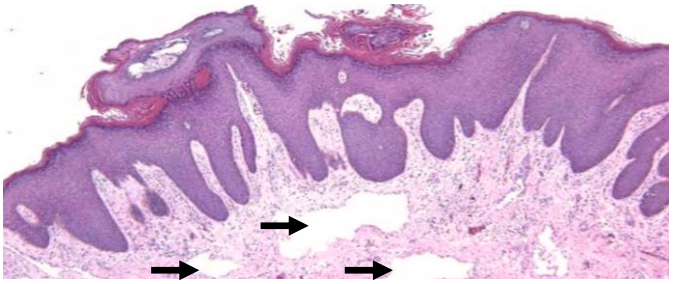
Polypoid growth with variably cellular central **fibrovascular core covered in squamous epithelium**.

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

IHC: Stromal cells (+) ER, PR, Desmin

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

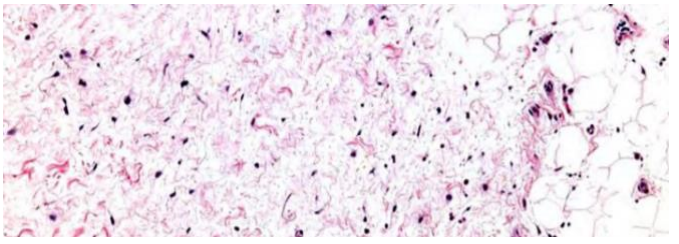
Massive Vulvar Edema



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

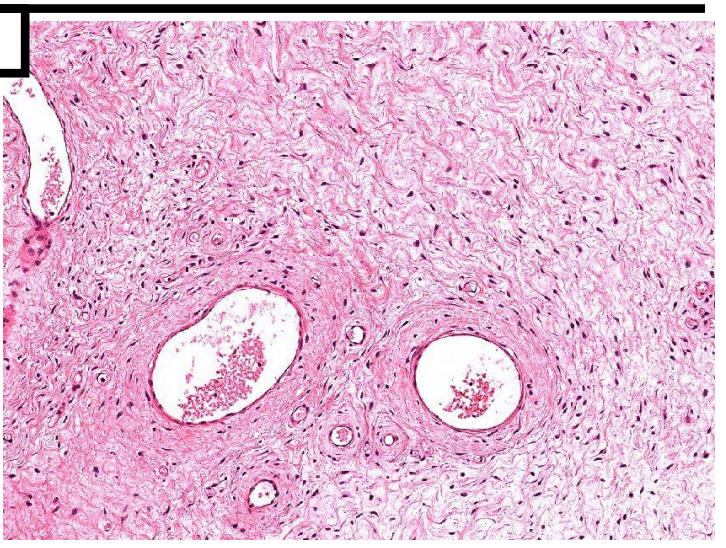
Reactive (non-neoplastic), likely due **to lymphatic obstruction.**
Associated with **obesity** and immobilization.

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



Dermal edema with uniformly distributed cells.
Dilated lymphatics (arrows).
Perivascular inflammation.

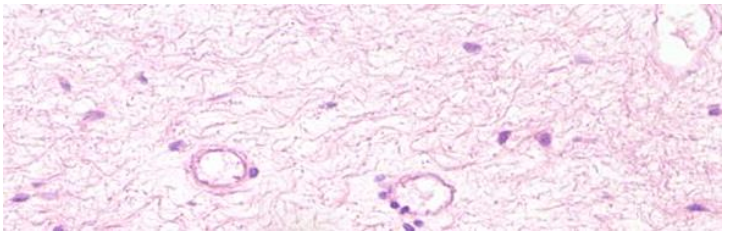
Deep (Aggressive) Angiomyxoma



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.

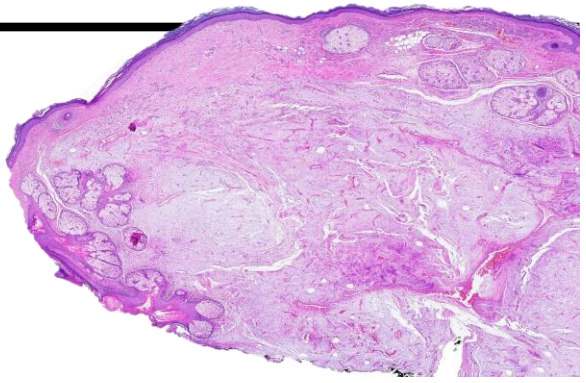


Low-grade, hypocellular. Composed of small, bland spindled cells with scant cytoplasm.
Numerous blood vessels of varying sizes, including thin-walled capillary-like and thick-walled arteries with radiating perivascular smooth muscle.
Invades fat and muscle. Extravasated RBCs.
No mitotic activity of atypia.

IHC: (+)ER, PR, desmin. (+/-)CD34
Molecular: **HMGA2 rearrangements**

Treatment: Complete surgical resection. Most people treated with first surgery.

Superficial Angiomyxoma

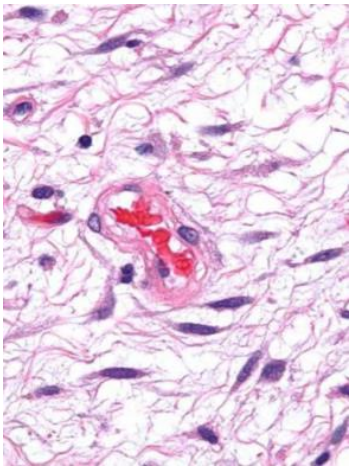


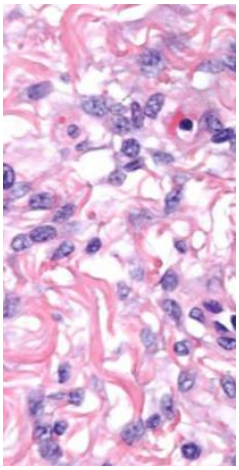
Benign with localized recurrences.

Small (<5 cm), exophytic polypoid mass **centered in skin and subcutaneous tissue** ("*Superficial*"!!). **Multilobulated**.

Well-demarcated, 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

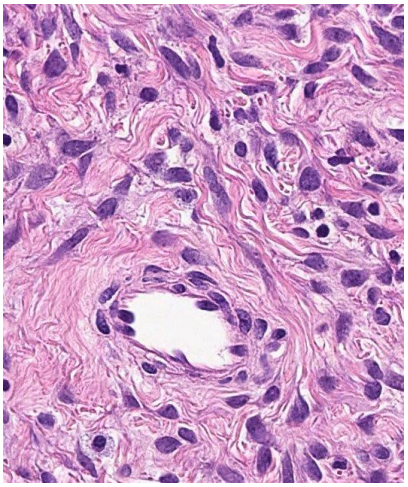


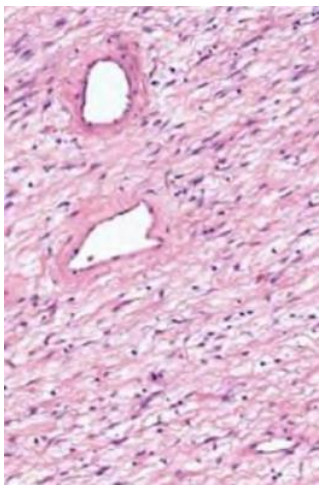


Benign. Usually painless superficial mass or polyp.
Small (<5 cm). Rare.

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



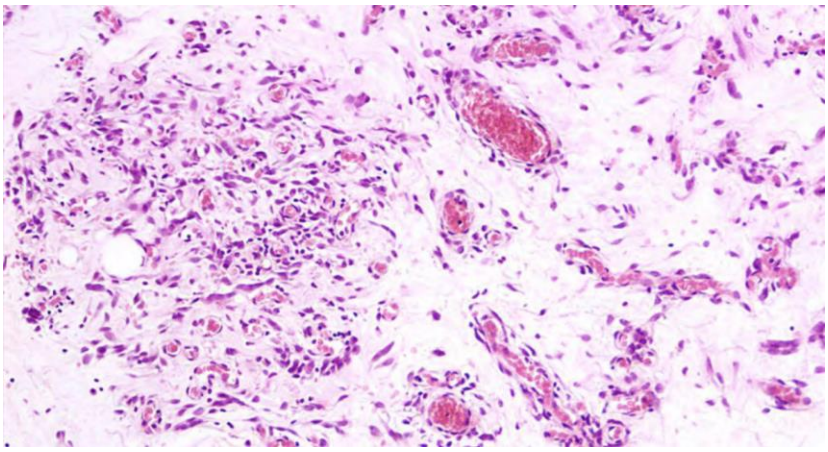


Benign.

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

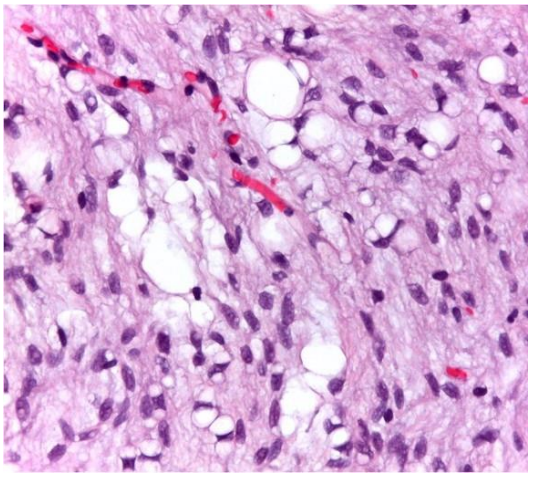


Benign. Non-recurring.

Small (<5 cm), circumscribed.
Alternating hypocellular and hypercellular areas
Spindle and plump epithelioid or plasmacytoid cells.
Prominent small to medium-sized blood vessels.

IHC: (+) Desmin, ER/PR; (-) CD34

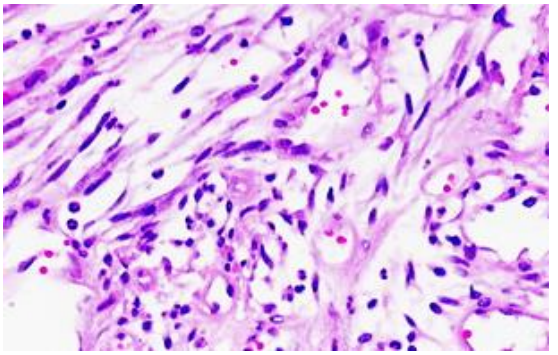
Lipoblastoma-like tumor of the vulva



Rare. May recur.
Adipocytic tumor with lobulated growth with variably sized septa.
Admixture of adipocytes, univacuolated and bivacuolated lipoblasts, and bland spindled cells.
Variably myxoid stroma with thin-walled branching vasculature.

Must rule out:
Myxoid liposarcoma (No DDIT3 rearrangements),
Lipoblastoma (No PLAG1 rearrangements),
Spindle cell lipoma (No RB1 regional gain/loss)

Postoperative Spindle Cell Nodule



Benign, presumably reactive, spindle cell proliferation.
Site of prior procedure, usually within a few weeks of surgery.
Usually poorly-defined, <3cm.
Loose, intersecting fascicles of spindle cells.
Associated chronic inflammation and edema.

	Superficial Myofibroblastoma	Cellular Angiofibroma	Angiomyofibro-blastoma	Deep (Aggressive) Angiomyxoma	Fibroepithelial polyp
Histology	Bland, ovoid to spindled cells; Often wavy nuclei within finely collagenous of myxoid matrix	Cellular with spindled cells and numerous thick-walled vessels	Alternating cellularity. Plasmacytoid stromal cells around vessels	Hypocellular with stellated to spindled cells in loose myxoid matrix with numerous large vessels	Scattered spindled to stellate cells with overlying squamous epithelium
ER/PR	+	+/-	+	+	+
Desmin	++/-	-	+	+ (focal)	+
SMA	-/+	-	-/+	+ (focal)	-/+
S100	-	-	-	-	-
CD34	+/-	+/-	-/+	+/-	+/-
Molecular	FOXO1 deletion	Loss of 13q (with FOXO1 and RB1)		HMGA2 frequent	

Modified from: Nurman, T. "Atlas of Gynecologic Pathology: A Pattern-based Approach." Wolters Kluwer, 2024.