Skin Appendage Tumors

General

Overall, appendage tumors are relatively **rare** and **diverse** with significant overlap in features (and are therefore hard to classify and master!). They derive from/differentiate toward adnexal structures, including apocrine, follicular, sebaceous, and multilineage differentiation. Some tumors show similarity to breast and/or salivary gland tumors.

Benign tumors are much more common and can occur at any age.
Malignant tumors are rarer and are most often present in older patients. For adnexal carcinomas, it is essential to exclude a cutaneous metastasis (including from a potentially occult primary).

Importantly, many tumors can be **markers of hereditary syndromes**, particularly when multiple.

Immunohistochemistry is rarely helpful is classification (with a few exceptions).

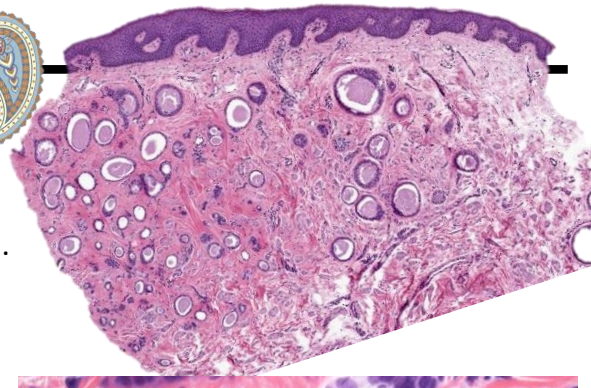
Given the overlap, it is common to experience uncertainty in diagnosing some tumors, even including whether a particular tumor is benign or malignant! In such cases, it is ok to give a descriptive diagnosis like, "Basaloid skin adnexal tumor," "Atypical skin adnexal tumor," or "Skin adnexal tumor of uncertain malignant potential," along with a differential diagnosis and a recommendation for complete excision and consideration for follow-up.

New: Because many of these diagnoses are relatively rare (and therefore lower-yield), I've marked ones designated by the American Board of Pathology on their exam content specifications as "Core/Foundational Knowledge" or "Advanced Resident" knowledge for the US Board exams with a star. For general AP boards purposes, you can likely stick to learning primarily those.

Sweat Gland Tumors

Syringoma

Think: Paisley pattern



Small, benign sweat gland tumor thought to derive from eccrine ducts.
Ducts, cords, tubules, and cysts, embedded in sclerotic stroma.
Well-circumscribed, in upper half of dermis.
Ducts have 2 cell layers and resemble "*tadpoles*."
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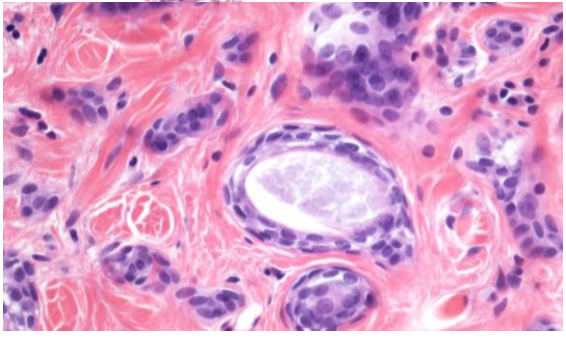
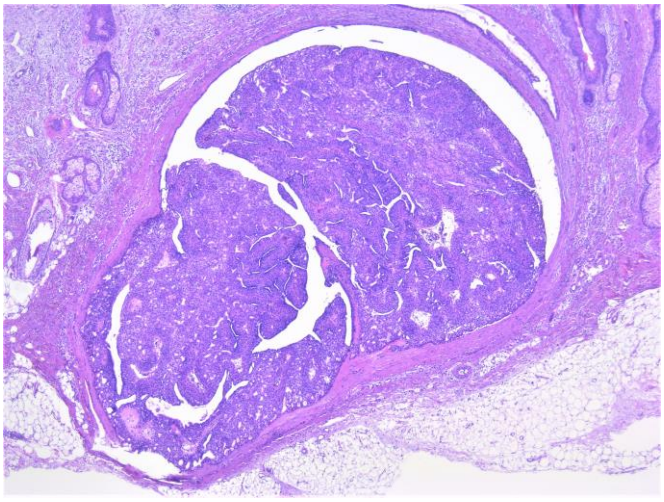


Clinical: Skin-colored or yellow smooth papule.
Most often periorbital, particularly lower eyelid.

Want to see the "bottom" of the lesion, as Microcystic Adnexal Carcinoma (MAC), columnar trichoblastoma, and sclerosing BCC can appear similar on superficial biopsies.

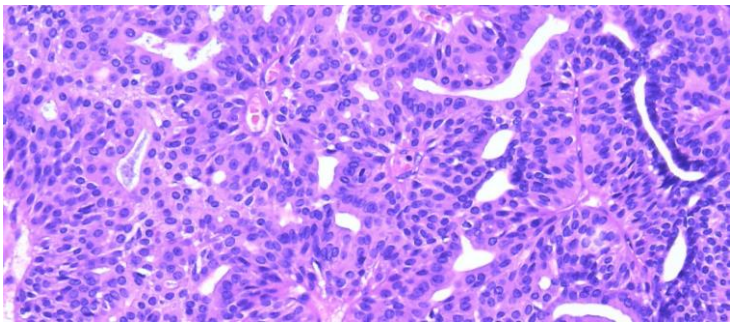
Hidradenoma

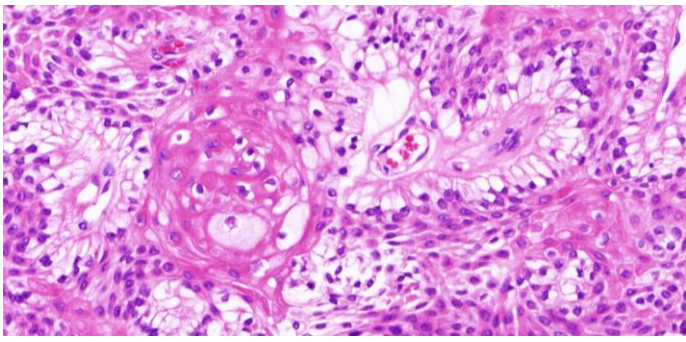


Benign solid and cystic sweat gland neoplasm with ductal and glandular differentiation.

Well-circumscribed,
Lobular and solid/cystic growth pattern
Mixture of clear cells, polygonal eosinophilic cells, mucinous cells, squamoid cells, and ductal structures.
Hyalinized stroma.

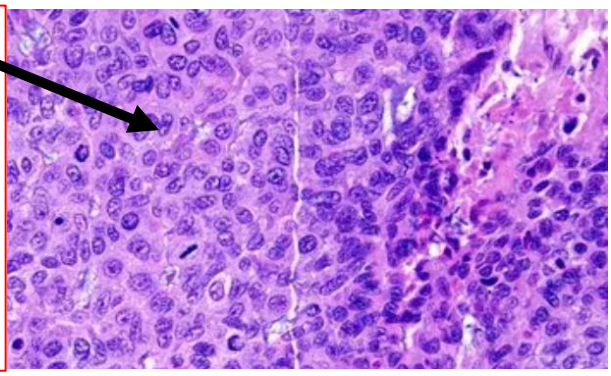
Frequent **MAML2 fusions** (usually with CRTC1)→ same as salivary gland mucoepidermoid carcinoma!
Virtual slide 2 3 4



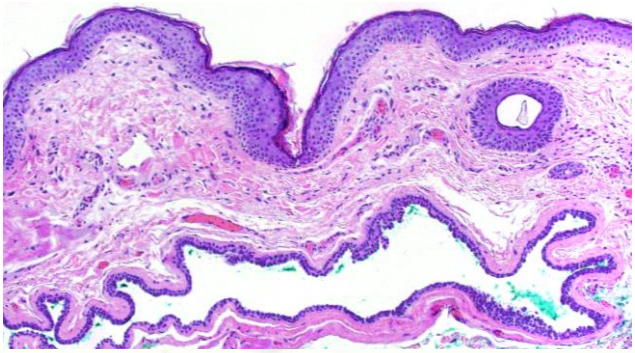


Hidradeno*carcinoma*:

Rare! An **infiltrative** tumor composed of any combination of atypical clear, eosinophilic polygonal, squamoid, oncocytic, and mucinous cells with increased mitotic activity and necrosis; Exclusion of metastasis. Ideally also see perineural and lymphovascular invasion and remnants of a benign hidradenoma.

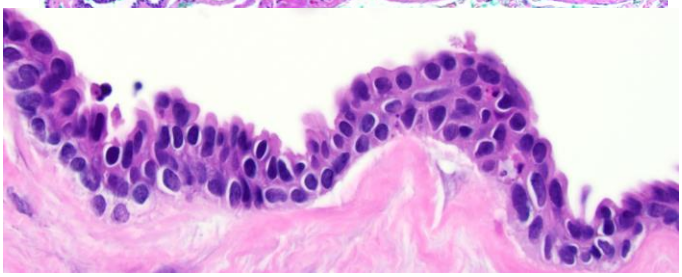


Hidrocystoma/cystadenoma



Spectrum of **benign cystic lesions** of predominantly ductal sweat gland origin, with architecture ranging from **simple cystic, unilocular (hidrocystoma)** to more complex, multilocular (cystadenoma).

Lined by columnar cells with or without decapitation secretion. **Surrounded by myoepithelial layer.**

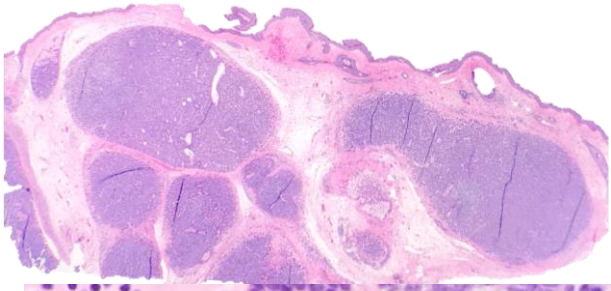


Clinically: solitary, blue-black, small papule.
Usually on face.
Most likely reactive from duct obstruction.

Virtual slide 2

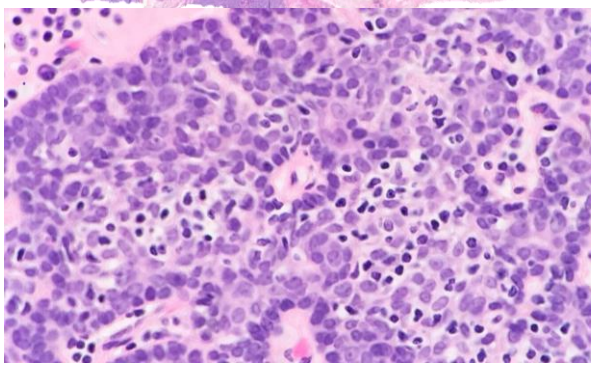
Spiradenoma

"blue cannonballs in the dermis"



Benign, (multi)nodular, solid sweat gland neoplasm.

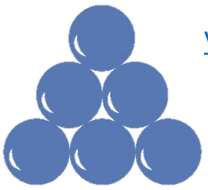
Single or several **round nodules of basaloid cells with round borders in the dermis.**
Two cells types:
1)Central clear cells, 2)Peripheral dark cells
Frequent ductular structures.
Basement membrane around outside and maybe in round deposits. Frequent **lymphocytes**.



Frequent **CYLD mutations** (germline mutations in syndromic ones: "Brook-Spiegler syndrome")

Usually on face or upper trunk. Often painful.

IHC: (+)SOX10; Some cells also express myoepithelial stains, while luminal cells express CK. (not necessary for DX!)



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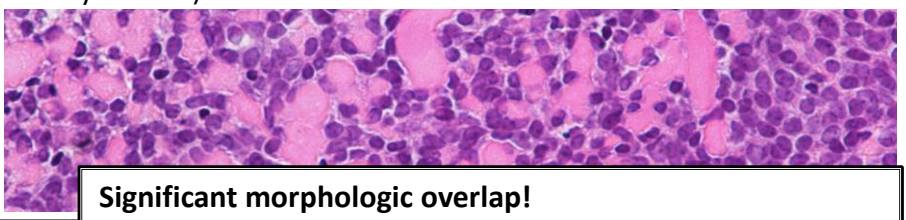
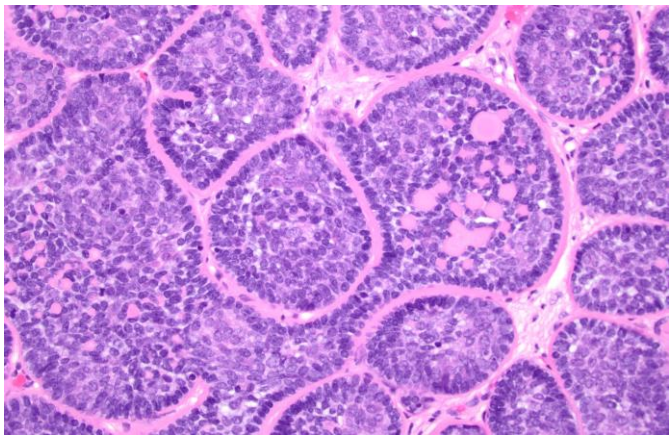


Significant morphologic overlap!
(and underlying molecular—maybe we should just consolidate?!)
Ok to diagnose as "Spiradenocylindroma"

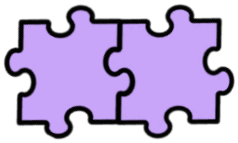
Cylindroma

"jigsaw puzzle"

Benign neoplasm with mosaic pattern.
Symmetrical, well-circumscribed.
Multiple aggregates of basaloid cells in a jigsaw-puzzle pattern. Surrounded by prominent basement membrane.



Usually on face or upper trunk.



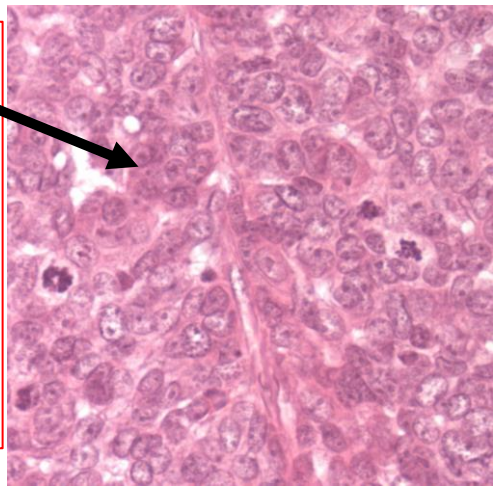
Virtual slide 2

Malignant neoplasms arising from Spiradenoma, Cylindroma, or Spiradenocylindroma:
(aka Spiradenocarcinoma, Cylindrocarcinoma, etc..)

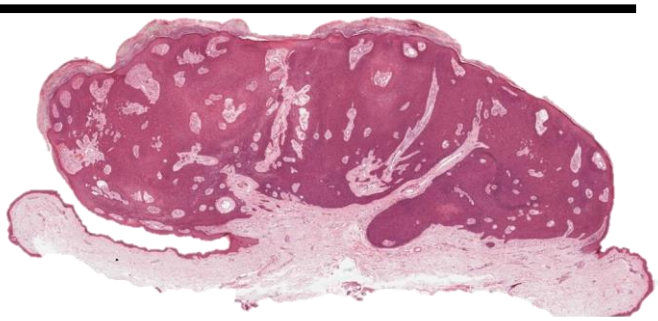
Wide morphologic spectrum, but essentially want to see a pre-existing benign tumor and a bona fide malignant proliferation.

Clues to malignancy: Cytologic atypia, increased mitotic rate, loss of two cell population, infiltrative growth

Often large (several cm), multinodular, and involve dermis and subcutis. Virtual slide



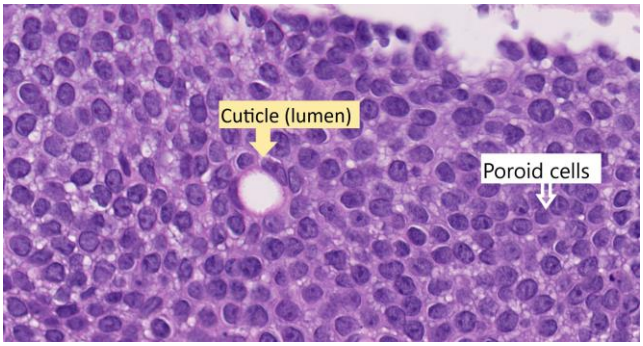
Poroma



Benign neoplasms with differentiation towards the intradermal portion of the sweat gland.

Widely connected to dermis. Well-circumscribed.
2 cell populations:
1) Poroid (smaller and darker, scant cytoplasm)
2) Cuticular (larger with eosinophilic cytoplasm)
Duct differentiation: small intracytoplasmic vacuoles and/or ducts (can highlight with EMA or CEA)

Richly vascular stroma resembling granulation tissue.



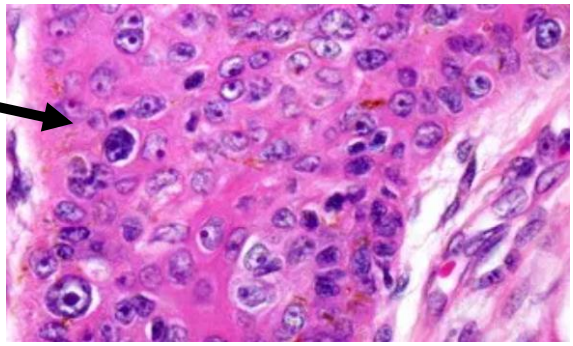
Molecular (not necessary for Dx): **YAP1 fusions**, with MAML2 or NUTM1 *(so can stain with NUT IHC!)*

Clinical: often on hands or feet.

Virtual slide 2

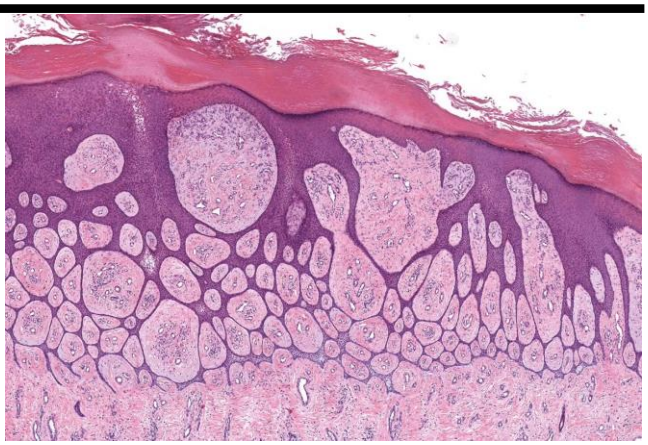
Porocarcinoma:

Malignant counterpart of poroma.
Often arises de novo (no identifiable poroma).
Infiltrative neoplasm connected to the epidermis, composed of poroid cells and displaying at least focal ductal differentiation. Atypical cytology.



Syringofibroadenoma

Proliferative lesion derived from the intraepidermal eccrine duct, characterized by a proliferation of cords and **strands of epithelial cells with ductal differentiation in loose myxoid stroma**.
"Fenestrated" pattern of interconnected, anastomosing cords perpendicular to surface.
Thought to be a **reactive**/hyperplastic process.

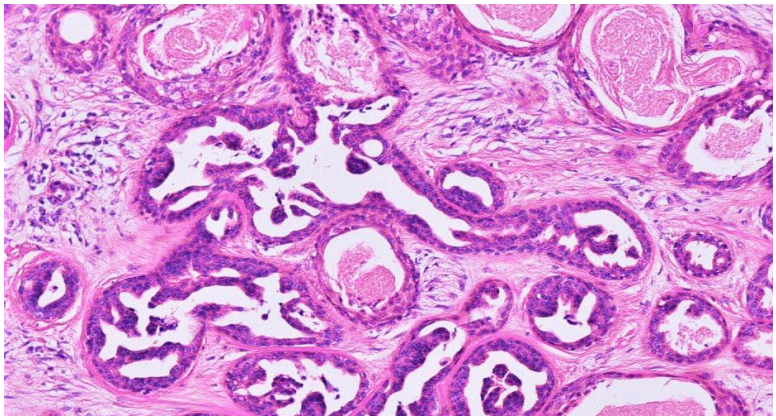


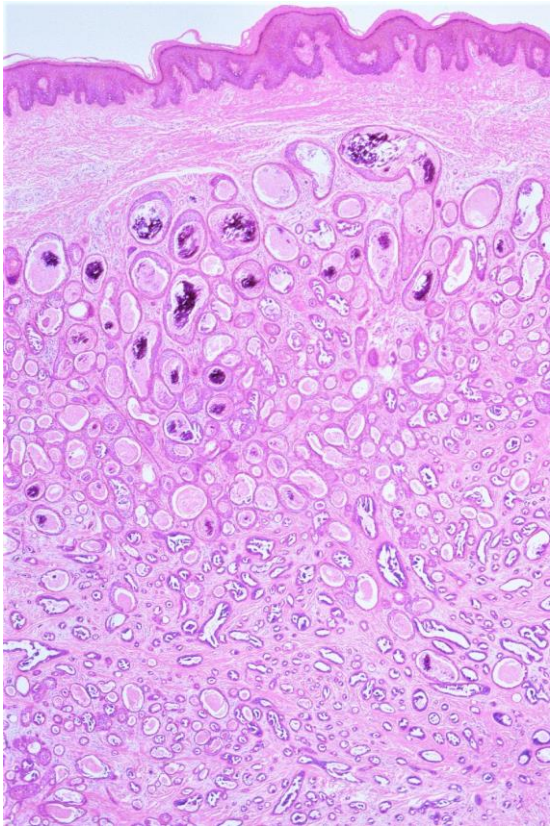
Tubular adenoma

Benign dermal neoplasm composed of tubules and glandular structures with or without papillae.

Well-circumscribed. Lobules of irregularly shaped tubules.
Dual multilayered epithelium embedded in fibrous stroma. No significant atypia or mitoses.
Intraluminal micropapillae lacking fibrovascular cores.
Overlying skin my show hyperplasia.

Most common on lower limbs of middle-aged women.





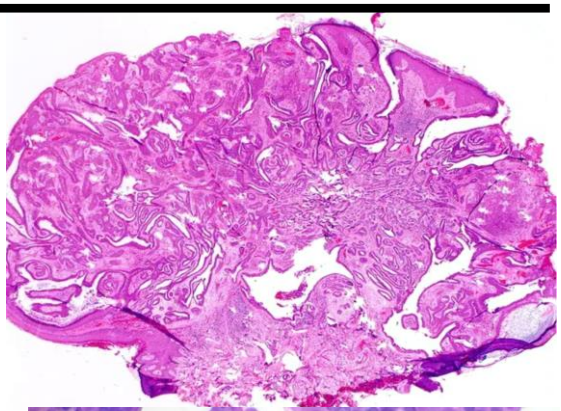
Syringocystadenoma papilliferum *"SCAP"*

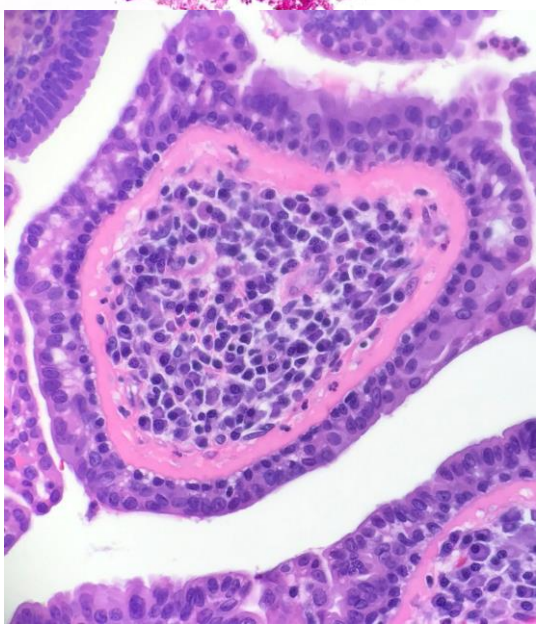
Benign apocrine neoplasm
Endophytic, crateriform intradermal tumor.
Two cell layers forming dilated **papillary and cystic** architecture. Luminal cells have rounded, basal nuclei and abundant eosinophilic cytoplasm.
Connection with the epidermis and/or hair follicle.
Plasma cell-rich stroma.

Vast majority are in **head and neck**.
Female predominance

Can arise in Nevus sebaceous (of Jadassohn).

Molecular: activating mutations in MAPK pathway, affecting RAS genes (e.g., BRAF V600E or HRAS)
Virtual slide 2 3





Syringocystadeno*carcinoma* papilliferum

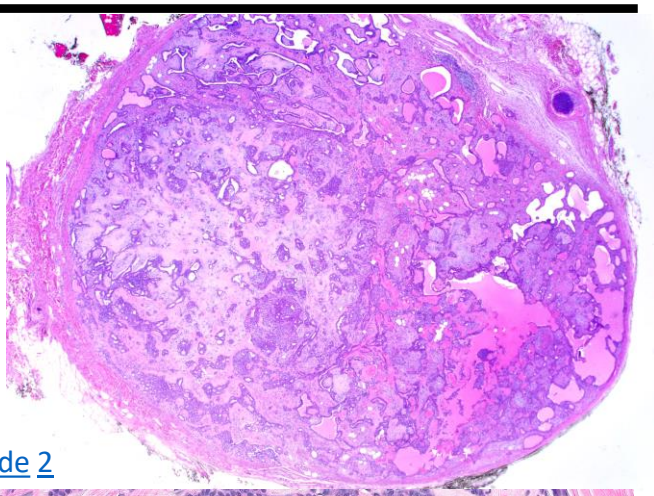
Very Rare! Malignant neoplasm evolving (in most cases) from a pre-existing SCAP, usually in the setting of Nevus Sebaceous.

Hints for malignancy: Cellular atypia, Abnormal mitoses, Loss of polarity, Disorderly proliferation.

Ideally see pre-existing SCAP.

Mixed tumor

Old name: "Chondroid syringoma"

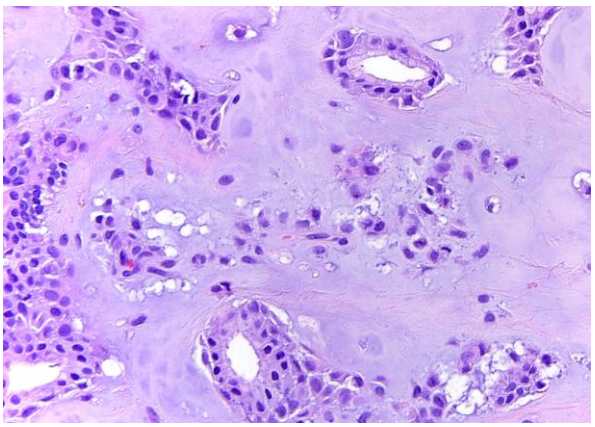


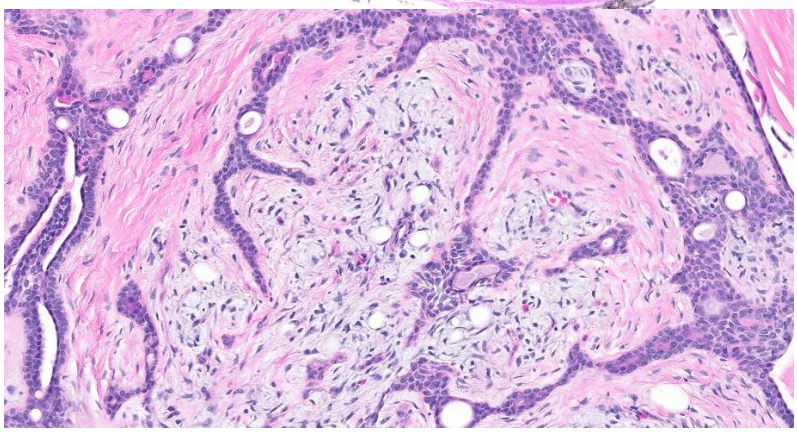
Benign.
Essentially, like a salivary gland pleomorphic adenoma.
Well-circumscribed nodule.
Three components:
1) Glandular epithelium arranged in tubes and cords
2) Mesenchymal myxohylinized or cartilaginous stroma
3) Myoepithelial cells in stroma

Follicular or sebaceous differentiation can be seen.

Molecular: PLAG1 or EWSR1 fusions

Virtual Slide 2





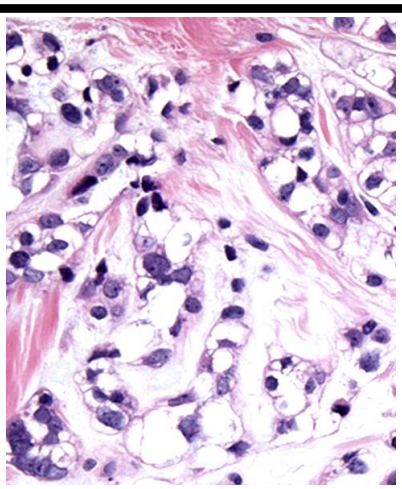
Myoepithelial tumor

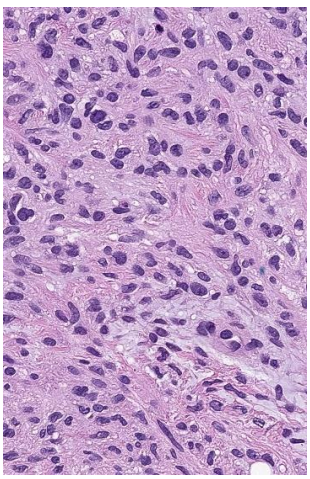
(similar to soft tissue and salivary gland)
Relatively rare.
Composed exclusively of myoepithelial cells.

Lobulated, trabecular, or nested architecture with variably epithelioid, spindled, plasmacytoid, or clear cells with myxoid to hyalinized stroma

IHC: (+) EMA, S100, (+/-) GFAP, p63, CK, SOX10

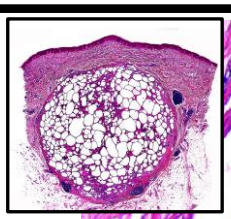
Molecular: Frequent EWR1 fusions





Cribriform tumor

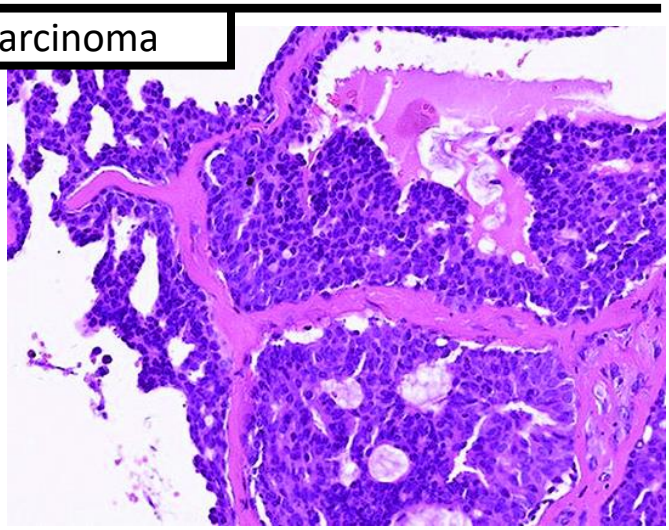
(previously called carcinoma)

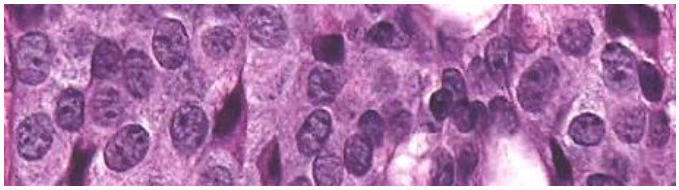


Rare. Indolent adnexal tumor.

Epithelial cells with eosinophilic cytoplasm forming interconnected solid and cribriform structures with small lumina, devoid of myoepithelial cells.
Nuclear hyperchromasia present.
Thin thread-like intraluminal bridging strands.
Usually well-circumscribed, unencapsulated.
Usually lower extremity.
Virtual slide

Endocrine mucin-producing sweat gland carcinoma





Low-grade mucin-producing neuroendocrine neoplasm of sweat gland origin.

Well-demarcated expansile nodules.
Solid, papillary, and/or cystic architecture.
Polygonal cells with bluish cytoplasm,
Low mitotic activity. Mild atypia.
Neuroendocrine nuclei.
Intracellular or extracellular mucin.

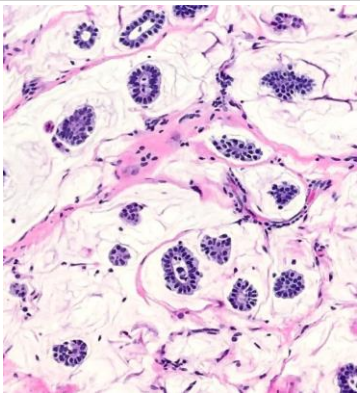
IHC: **(+)Synaptophysin,** chromogranin, **ER**, PR, CK7, GATA3, GCDFP-15. Ki67 usually <10%

Predilection for **eyelid** and periorbital skin.

(cutaneous analogue to breast solid papillary carcinoma)
Precursor to mucinous adenocarcinoma with neuroendocrine differentiation.

Progression

Mucinous carcinoma

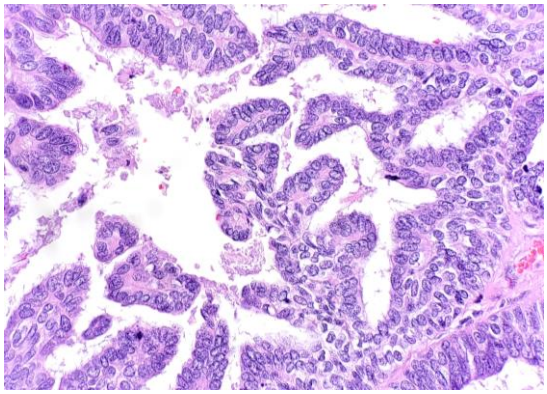


Rare adnexal tumor. Malignant, but not too aggressive.
Nests and strands of atypical epithelial cells floating in extracellular mucin.
Identical to mucinous carcinoma of the breast. Most common near eye.

IHC: (+)GATA3, GCDFP-15; Usually (+) ER/PR. (+/-)Neuroendocrine markers

Must exclude a metastasis!
A clue that it may be primary cutaneous is a similar proliferation within ducts (in situ component, which is found in most cases). Virtual slide

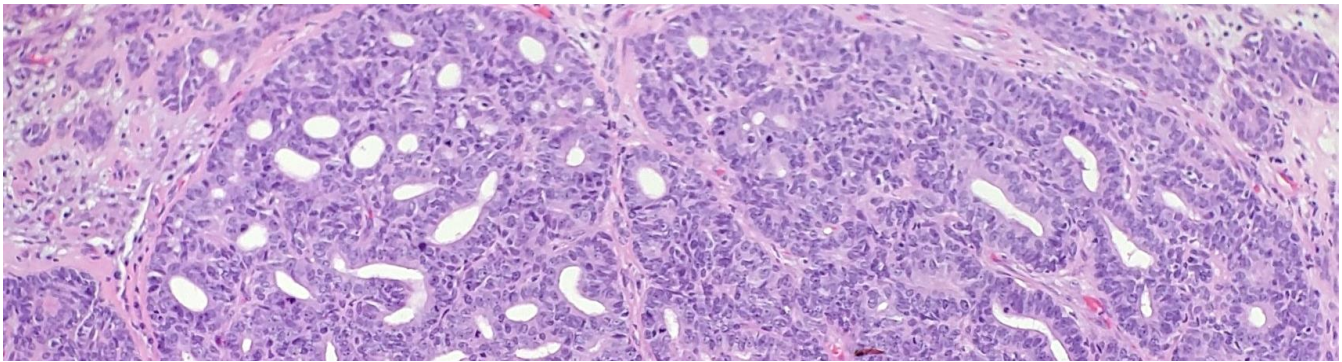
Digital papillary adenocarcinoma



Rare. Malignant and relatively aggressive.
Marked predilection for **acral sites** (esp. fingers/toes)

True papillae with fibrovascular cores. Solid and Cystic.
Fused back-to-back glands, solid lobules, and nests.
At least a focally recognizable myoepithelial cells at the periphery. Virtual slide 2

Driven by HPV type 42 (+ HPV testing)



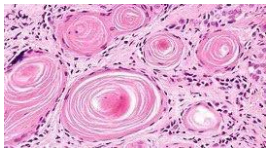
Microcystic Adnexal Carcinoma *"MAC"*

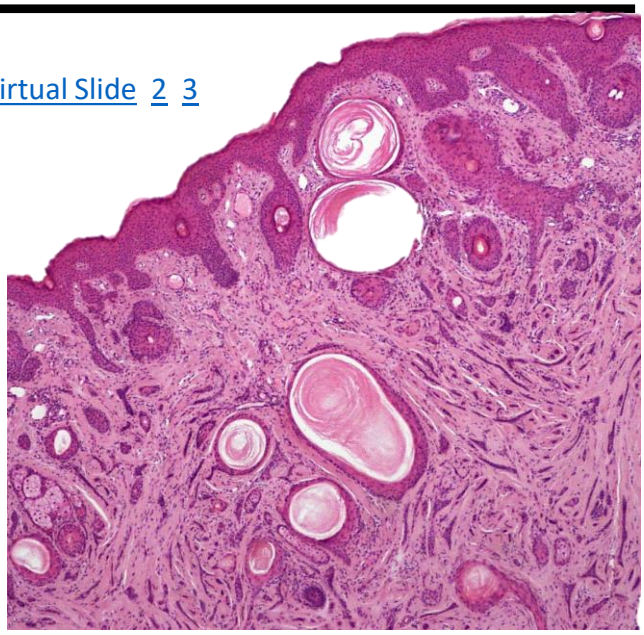
Virtual Slide 2 3

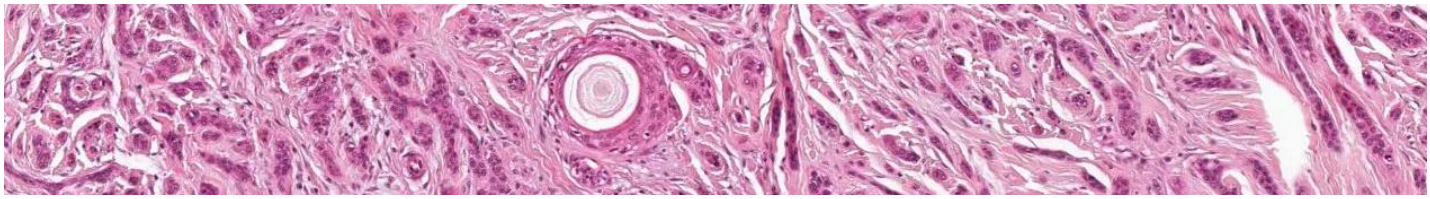
Locally aggressive.
Infiltrative adnexal carcinoma showing follicular and sweat duct differentiation and bland cytology.

Usually sclerotic plaque.
Usually central face: esp. upper lip/nasolabial fold.

Infiltrative stands and nests of bland cells with variable cyst and duct formation.
Frequent zonation with superficial cornifying cysts and deeper strands.
Desmoplastic sclerotic stroma.
No mitotic activity.
Usually perineural invasion.



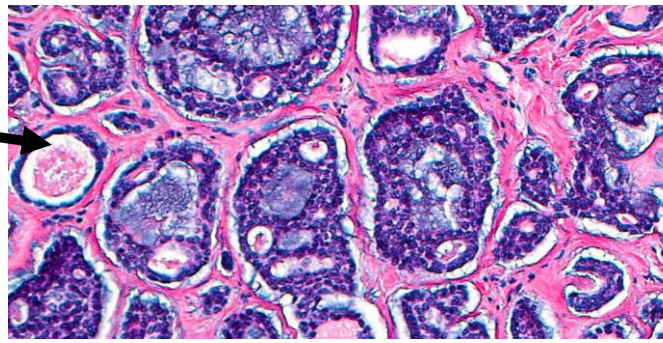




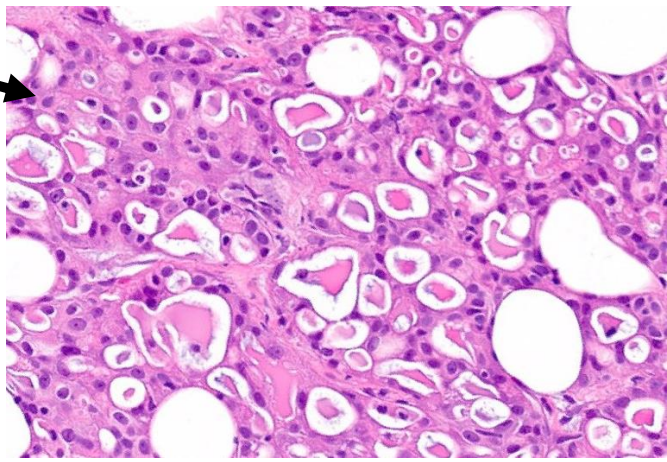
Additional Salivary gland-like carcinomas

(Relatively rare skin cancers with more common salivary gland counterparts)

Adenoid cystic carcinoma
Infiltrative nests with cribriform, tubular, and solid architecture. Multinodular. Bilayered ducts and pseudocyst containing mucous or basement membrane material. Frequent PNI.
Fusions of MYB or MYBL1.



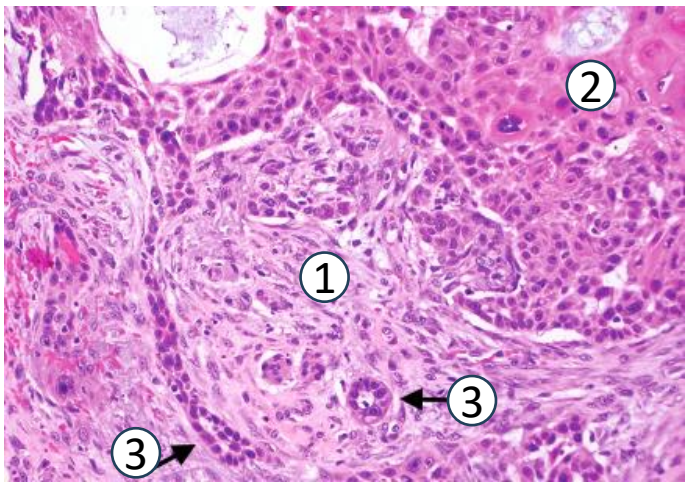
Secretory carcinoma
Characteristic abundant eosinophilic secretion within microcystic and tubular spaces.
Bland, eosinophilic tumor cells.
IHC: (+) S100, mammaglobin
Fusions of ETV6::NTRK3



Malignant mixed tumor
Very rare. Resulting from transformation of pre-existing mixed tumor *(think: carcinoma ex-pleomorphic adenoma of the salivary gland).*
Very heterogeneous malignant component (adenocarcinoma, myoepithelial carcinoma, etc…)

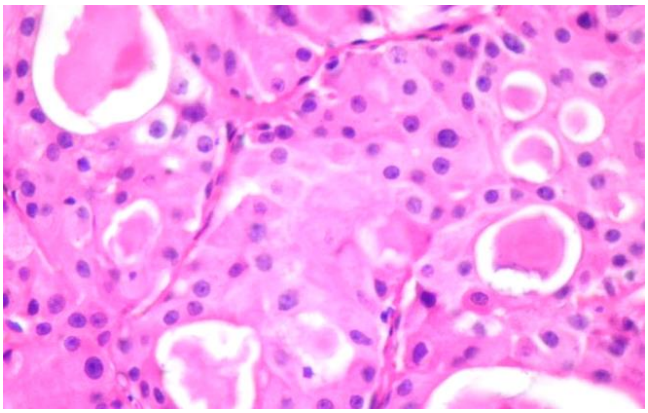
Squamoid eccrine ductal carcinoma

Rare. Usually in head and neck.
Biphasic tumor with a
1) desmoplastic stroma,
2) a component of SCC unusually superficial to mid dermis, and
3) a ductal component in the mid to deep dermis.



Apocrine carcinoma

Rare. Most often in axilla.
Apocrine secretion (abundant eosinophilic cytoplasm, sometimes granular or vacuolated. Decapitation secretion is usually not present.)
±myoepithelial cells.
Papillary, tubular, or solid
Must exclude metastatic cancer, esp. breast!
IHC: (+) CK7, GCDFP-15; (+/-)S100, ER, PR, AR.

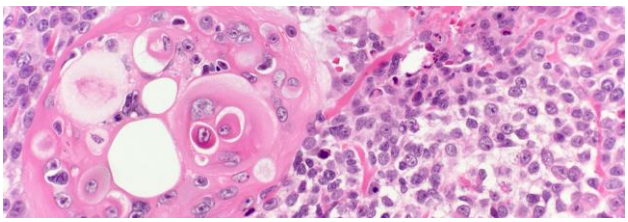


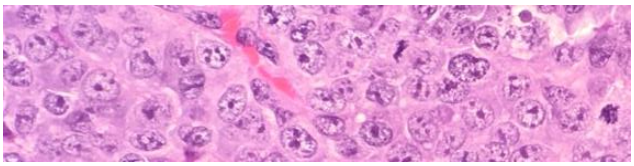
NUT carcinoma

(Similar to elsewhere in the body, but a little different)
Provisional and Rare.

Primary cutaneous carcinoma with rearrangements of BRD3 or NSD3 with a member of the NUT family.

<u>"Primitive" with monotonous tumor cells</u> displaying prominent single nucleolus with frequent formation of ducts and keratinizing foci.



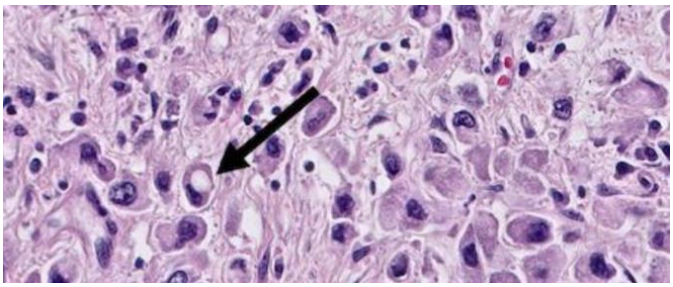


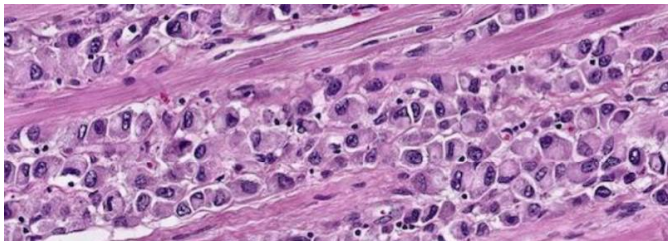
Signet-ring cell/histiocytoid carcinoma

Rare. Aggressive.
Preferentially involves **eyelid**.
Single rows of cells with eccentric nuclei displaced by vacuolated cytoplasm and/or with eosinophilic granular cytoplasm.

IHC: (+) CK7, E-cadherin, CEA, EMA, GCDFP-15

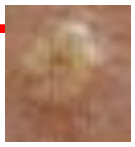
Must exclude metastatic lobular carcinoma of the breast and metastatic carcinomas with signet ring morphology.



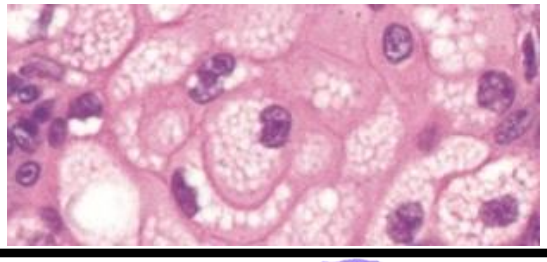


Sebaceous tumors

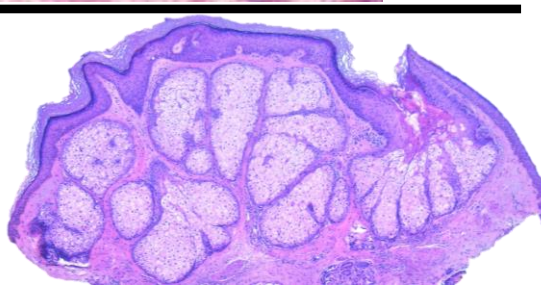
Clinically, these appear **Yellow-tan**
Ectopic sebaceous glands = Not associated with hair follicles



Sebocytes = abundant vacuolated, "bubbly" cytoplasm with a central scalloped nucleus.
IHC supporting sebaceous differentiation:
(+) Adipophilin (most sensitive/specific)
Also (nonspecific): CK, EMA, BerEP4, AR, p40, etc..

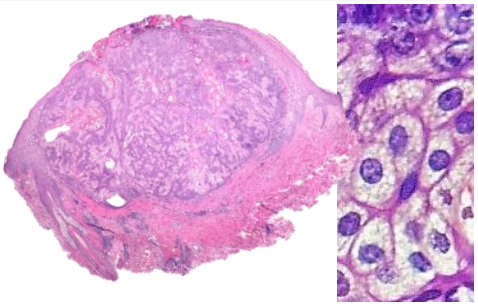


Sebaceous hyperplasia



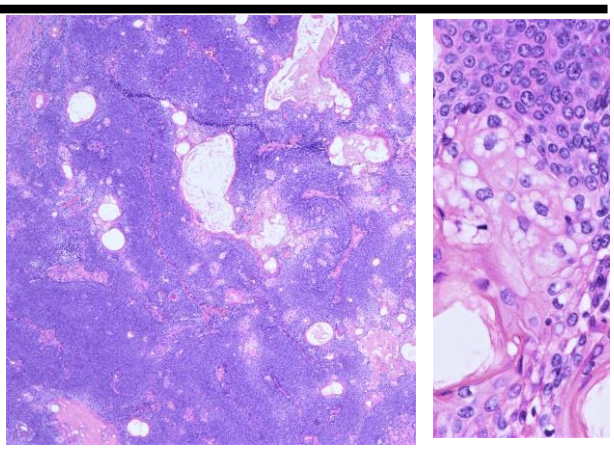
Overgrowth of Sebaceous glands.
Lobules of sebocytes arranged around infundibulum of central hair follicle. 1 layer of basaloid cells compressed at periphery of sebocytes. No cytologic atypia. Virtual slide 2

Sebaceous adenoma



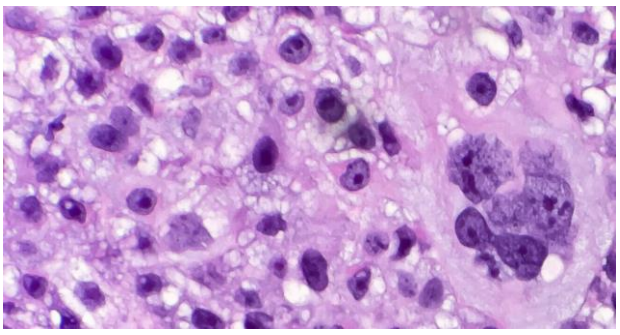
Benign. Yellow-tan nodule.
Well-circumscribed, lobular aggregates consisting of mostly mature sebocytes (> 50% cells), with a variable rim of immature, cytologically benign basaloid cells of sebocytes. Direct connection to overlying dermis, and *not* connected to hair follicle. Virtual slide 2

Sebaceoma



Benign. Mostly on face and scalp.
Well-circumscribed cellular lobules composed of mostly small, monomorphic, immature but cytologically benign basaloid cells admixed with fewer mature sebocytes (<50%), haphazardly arranged throughout the tumor. Mitoses common.
Lots of patterns (e.g., rippled, cribriform, labyrinthine)
Virtual slide 2

Sebaceous carcinoma



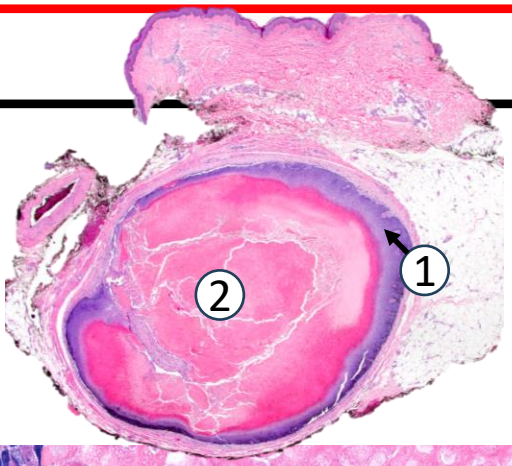
Malignant. Often periocular.

Invasive or intraepithelial tumor showing sebaceous differentiation, manifesting as multivesicular cytoplasmic clearing with nuclear scalloping.
Prominent atypia and mitoses.
Virtual slide 2 3

Muir-Torre syndrome (Autosomal Dominant) → Associated with multiple sebaceous neoplasms.
A part of Lynch Syndrome, associated with the loss of mismatch repair proteins (*MLH1*, *MSH2*, *MSH6*, *PMS2*).

Follicular tumors

Pilomatricoma



Benign. Relatively common.
Any age, but often **children** on **head**/neck.
Usually sporadic, but can be syndromic.

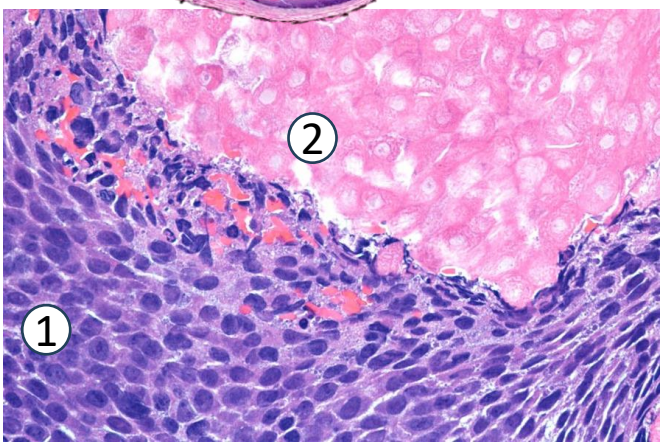
Well-circumscribed dermal nodules.

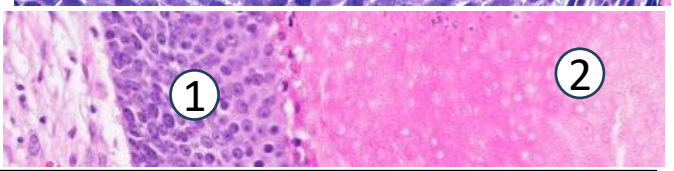
1)Peripheral cells are **monomorphic, round, small, and deeply basophilic**, and vesicular nuclei.

2) These cells keratinize toward **shadow** ("**ghost**" or mummified) cells with pink cytoplasm and cell borders and an empty nuclear cavity, in varying proportion *(older → more ghost, calcifications, ossification, etc..)*

Often mitotically active with a foreign body giant cells.

Virtual slide 2 3





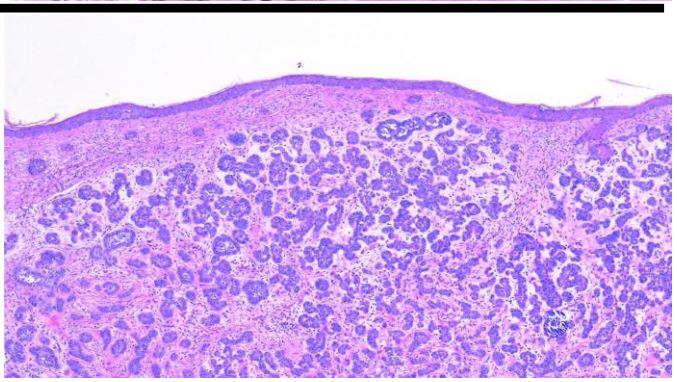
Pilomatrical *Carcinoma*

Rare! Poorly-circumscribed, infiltrative neoplasm composed of solid aggregates of matrical cells, with areas of necrosis en masse and focal aggregates of shadow cells.

Trichoblastoma

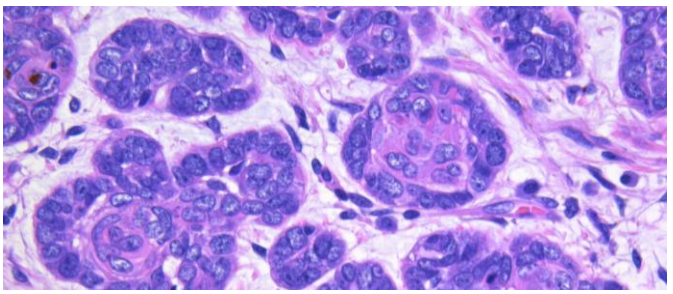
Benign. Usually head/neck, esp. Scalp.

Well-circumscribed, biphasic neoplasm composed of 1) epithelial aggregates of basaloid germinative follicular cells with *no* epithelial connection and 2) abundant, densely cellular fibrotic stroma resembling follicular papillae/follicular sheath.



Usually confined to dermis and non-ulcerated.
If multiple, could be syndromic→ Brooke-Spiegler syndrome with germline CYCLD mutations.

Many patterns! (all benign) Virtual slide 2 3

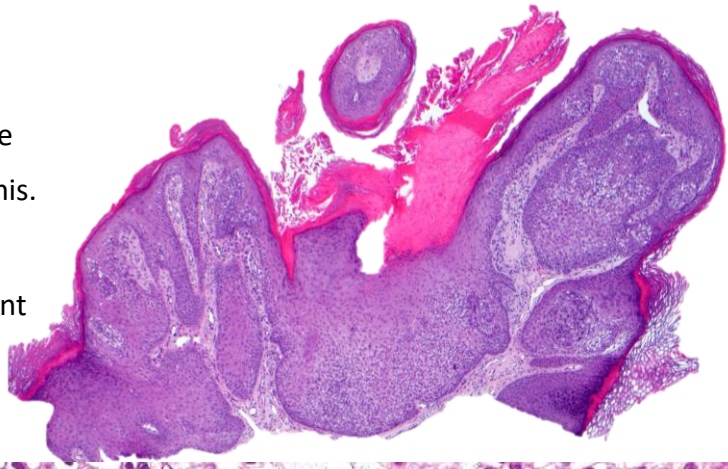


DDX: BCC→ in contrast, BCC is connected to surface, and has mucinous stroma with clefting, lots of mitoses.
IHC: (+) BerEP4

Trichoblastic *Carcinoma* *(and carcinosarcoma)*

Rare! *Invasive* tumor with similar dual differentiation toward follicular stroma and epithelium. Moderate to severe atypia.

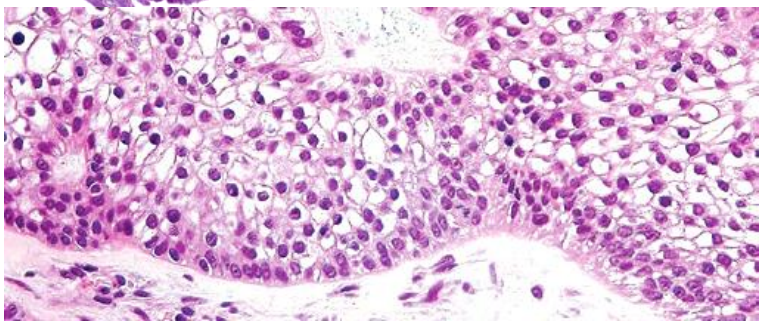
Trichilemmoma



Benign.
Most common on the head (esp. face) of middle-age

Vertically oriented. Multiple connections to epidermis.
Endophytic and exophytic components
Hair-follicle associated lobules of clear cells with peripheral palisading surrounded by a thick basement membrane.

Multiple trichilemmomas, especially in the oral mucosa, is **associated with Cowden's syndrome**.
Virtual slide 2 3



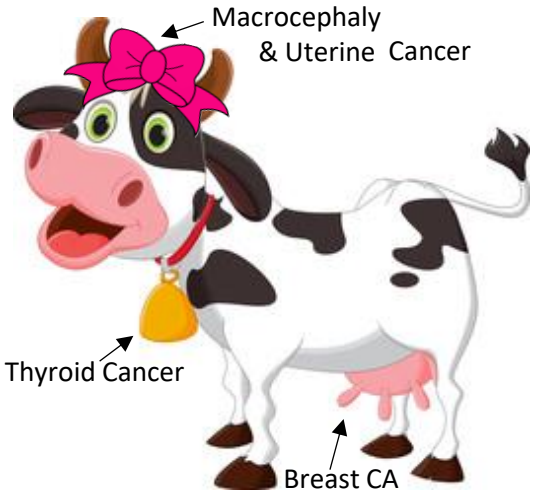
Trichilemmal ***Carcinoma***

Rare! Sun-exposed, hair-bearing site.
Lobular proliferation of atypical, glycogenated clear cells lacking mucin and palisading around a follicular unit.

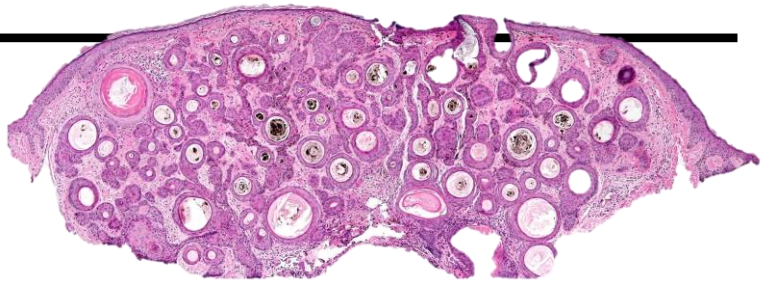
COWden's Syndrome

PTEN mutation (tumor suppressor)

Multiple hamartomas (mouth, GI tract)
Thyroid carcinoma (usually Follicular)
Breast Cancer (very high risk)
Endometrial Cancer
Macrocephaly
trichile***MMOOOO***mas



Trichoadenoma

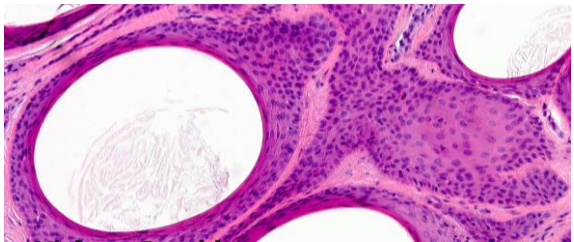


Benign. Usually on face/scalp.

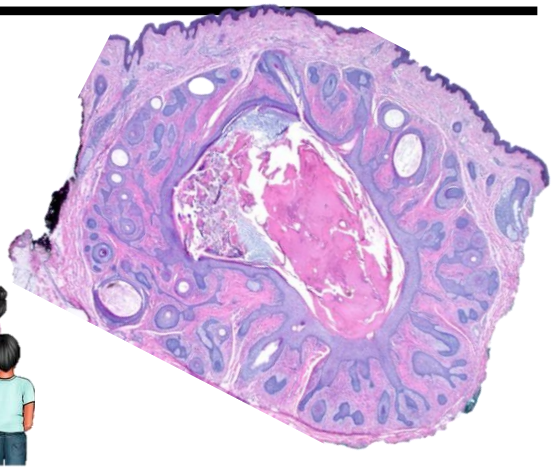
Well-circumscribed, dermal nodule.
Tiny interconnected infundibular cysts, lined by squamous epithelium.

Not connected to epithelium.

Virtual slide 2



Trichofolliculoma

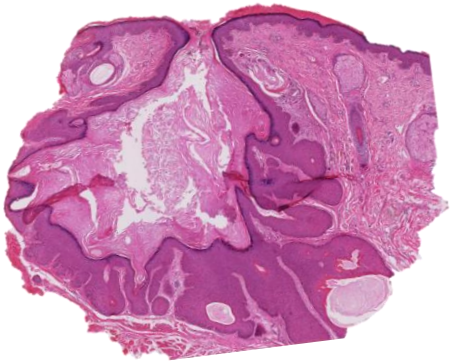


Benign. Usually on the face.
Central, cystic, dilated follicular infundibulum (in contact with surface) surrounded by radiating immature villous hair follicles at different stages of development.
Cystic space filled with keratinous debris and hair shafts.

"A mama and her babies"

Virtual slide 2 3

Pilar sheath acanthoma

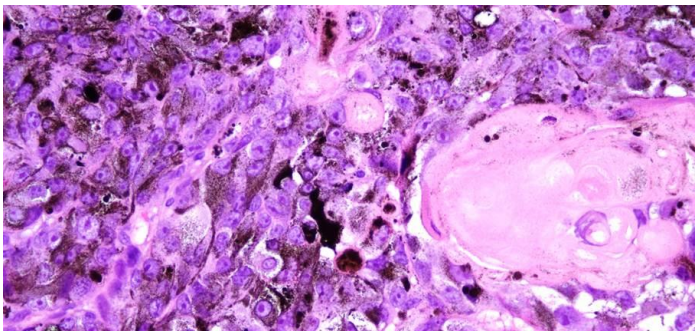


Benign. Relatively rare. Usu. Facial.

Solid lobules of isthmic epithelium around dilated infundibular structures.
Well-circumscribed. Vertically-oriented.

Virtual slide 2

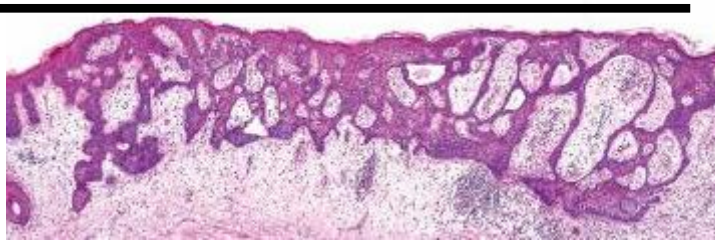
Melanocytic matricoma



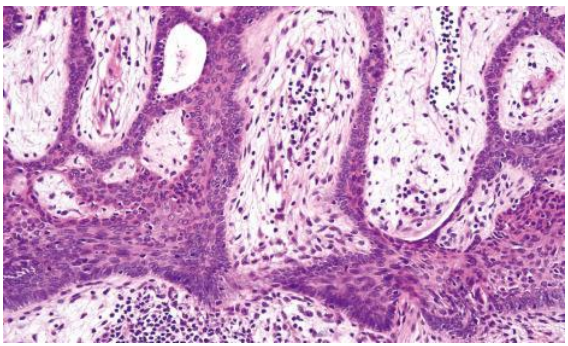
Benign. Rare. Usually on head/neck.
Recapitulates bulb of anagen hair follicle.

Well-circumscribed dermal nodule composed of solid aggregates of matrical cells with numerous scattered dendritic pigmented melanocytes and melanin deposits. +/- ghost cells.

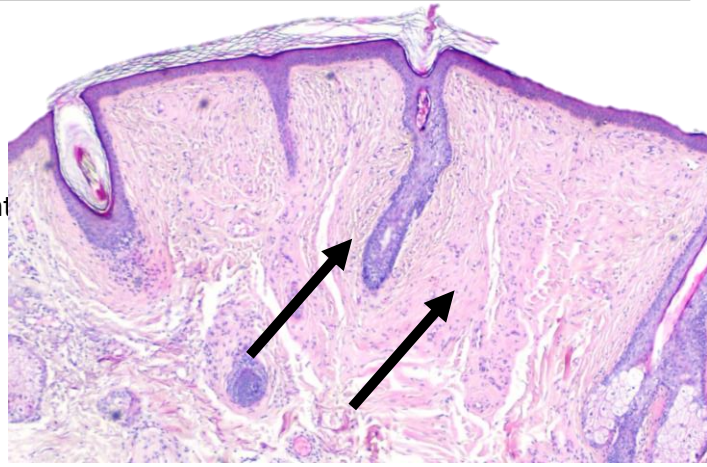
Tumor of the follicular infundibulum



Benign. Usually on the face.
Anastomosing horizontal epithelial cords, similar to the epithelium of the follicular isthmus, connected to the epidermis and involving the superficial dermis with reticulated and fenestrated pattern.
Small ductules can be present.



Trichodiscoma and Fibrofolliculoma

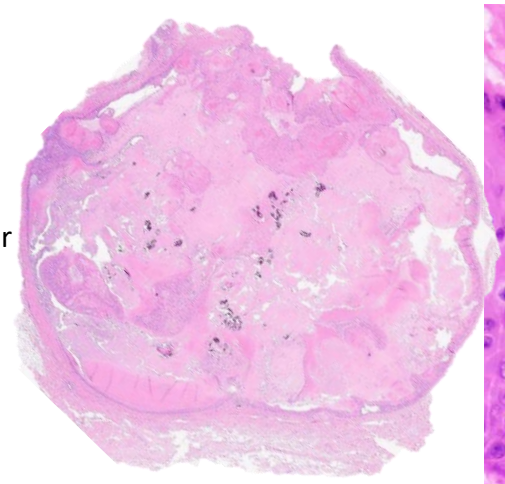


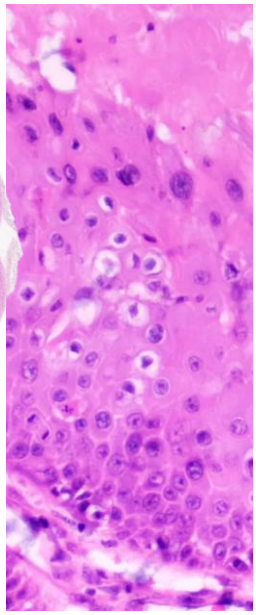
Benign. Rare. Hamartomatous lesions.
Dome-shaped papule with infundibulocentric proliferation of delicate epithelial strands and surrounding stroma (fibrofolliculoma), or predominant central stroma with lateral collarettes of mature sebaceous lobules (trichodiscoma);
Stroma is composed of fibrillary collagen bundles, mucin, and CD34-positive fibrocytes.

Multiple lesions suggests **Birt-Hogg-Dubé syndrome** (also associated with pulmonary cysts, renal tumors, and angiofibromas, etc..). Germline folliculin (FLCN) gene mutation.

Trichodiscoma Fibrofolliculoma

Proliferating trichilemmal tumor





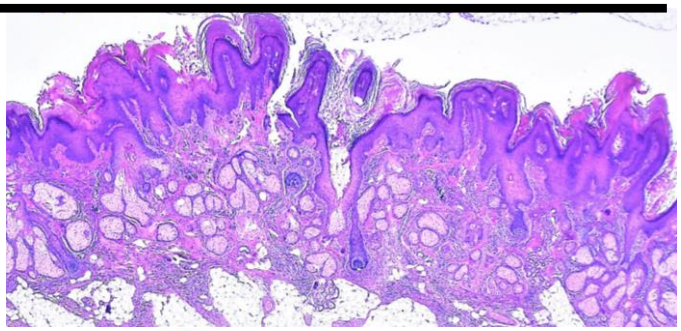
Usually benign (but malignant ones exist).
Vast majority on Scalp. Often older women.

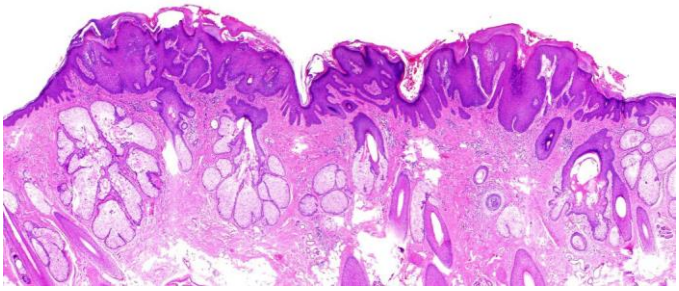
Solid-cystic neoplasm with prominent epithelial infoldings into a cystic cavity, composed of irregular aggregates of keratinocytes with trichilemmal keratinization.
Benign = well-circumscribed
Virtual slide 2 3

***Think**: Trichilemmal cyst + papillary infoldings*

Features of malignancy (can be indistinguishable from SCC): Infiltrative growth beyond cyst, severe nuclear pleomorphism, high mitotic activity.

Nevus Sebaceous





Hamartoma with abnormalities of epidermis, follicles, sebaceous glands, and apocrine glands.

Usually present in **infancy** and enlarges during puberty.
Usually on **scalp**: yellow, warty, hairless plaque

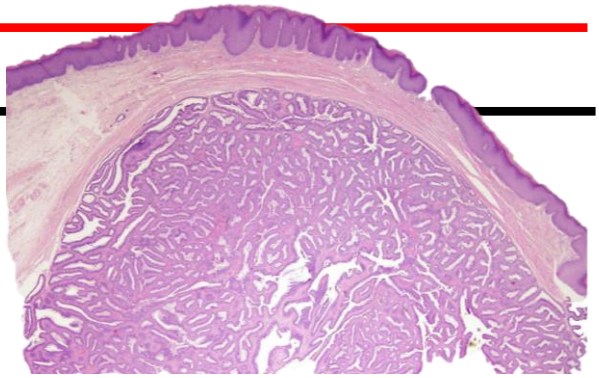
Acanthosis and papillomatosis.
Disorganized sebaceous glands: high in dermis, communicate with surface (not hair follicle).
Abnormalities of sweat glands (apocrine) **and follicles.**

Can develop superimposed tumors, including trichoblastoma.

Virtual slide 2 3

Site-specific appendage tumors

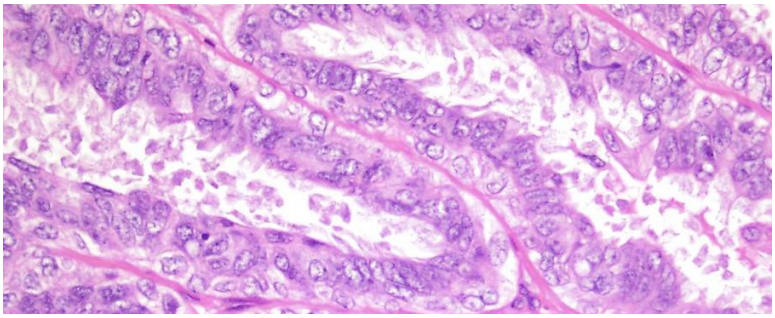
Hidradenoma papilliferum



Benign. Associated with anogenital mammary-like glands.
Solitary, asymptomatic. Often in vulva.
Complex growth of branching and anastomosing epithelial papillae and tubules with a myoepithelial layer.

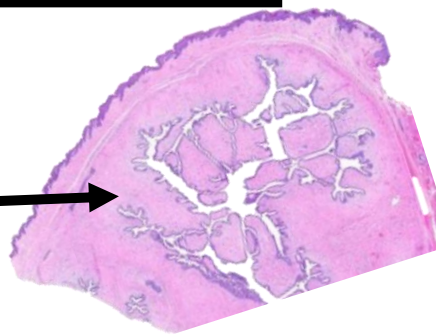
***Think*: breast intraductal papilloma**

Virtual slide 2



Fibroadenoma & phyllodes tumor of anogenital mammary-like glands

Benign (usually). Biphasic fibroepithelial tumors.
Usually vulvar or perianal.
Fibroadenoma: round or elongated, often branching and anastomosing glandular structures, surrounded by usually paucicellular stroma.
Phyllodes tumor: leaf-like projections and hypercellular stroma.

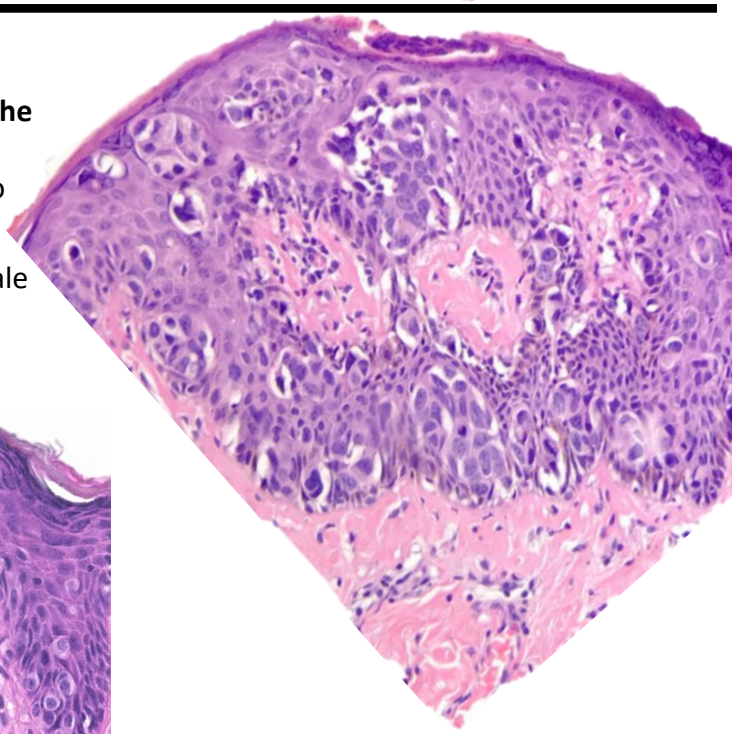


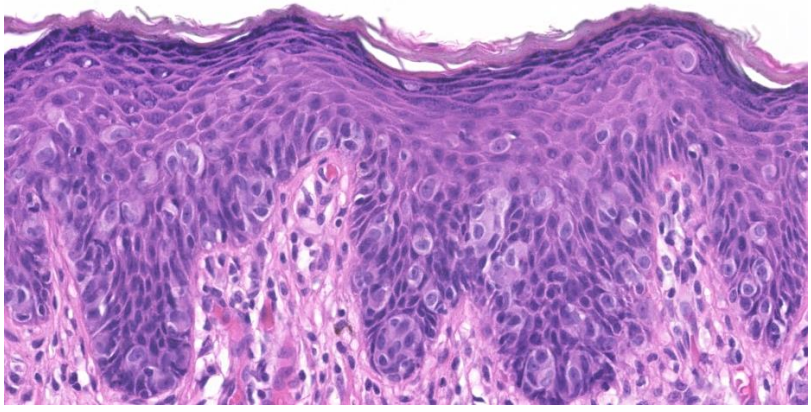
***Think*: like in the breast!**

Mammary Paget disease

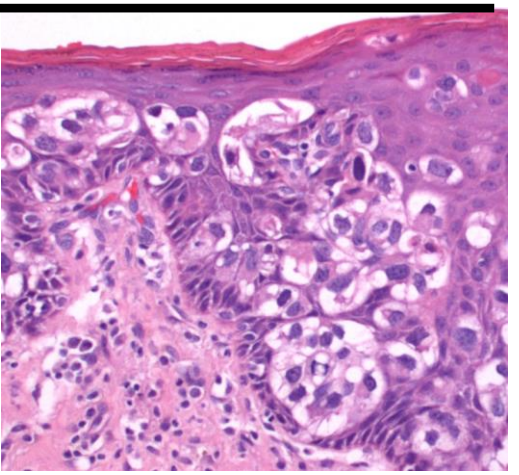
Malignant epithelial cells within the epidermis of the nipple and areola. In >95% of cases, there is an underlying breast carcinoma, which has extended to the surface through ducts.

Large intraepidermal atypical cells with abundant pale cytoplasm and large nuclei with prominent nucleoli.
Single cells or clusters.
IHC: (+) CK7, HER2





Extramammary Paget disease

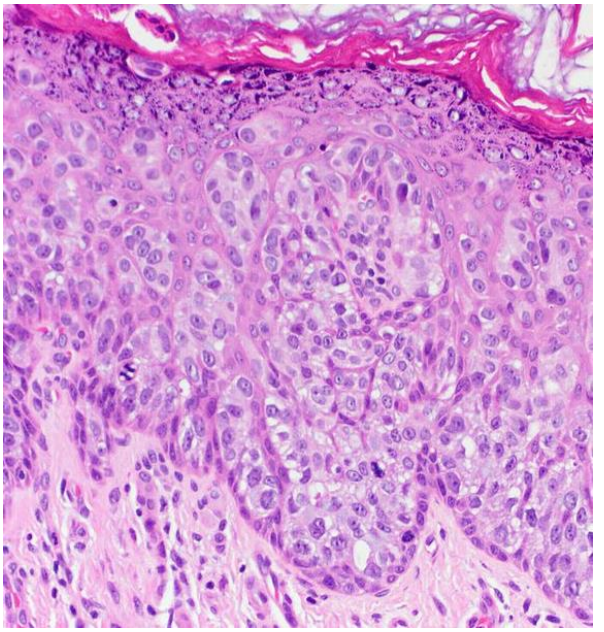


Predominant intraepithelial growth of neoplastic cells originating in the skin (primary) or representing intraepithelial spread of an underlying visceral carcinoma (secondary).

Atypical epithelial cells involving the epidermis with prominent nucleoli and abundant cytoplasm.

Most common site: **vulva**.

Important issue: helping distinguish primary from secondary EMPD.
Primary EMPD IHC (like in breast!): (+) CK7, GATA3;
Usually (+) HER2, GCDFP5

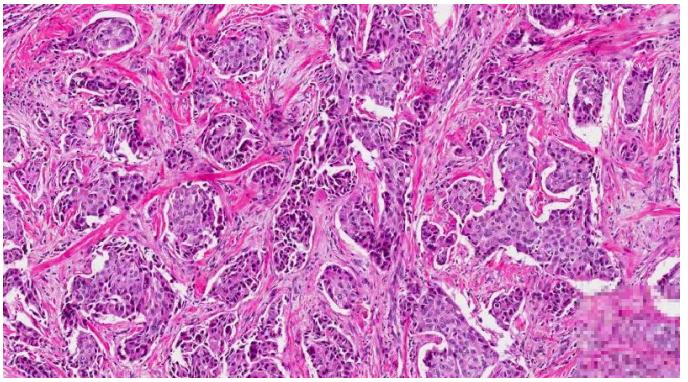


Possible secondary sites of origin:
Colorectal origin: (+) CK20, CDX2, SATB2
Urothelial origin: (+) Uroplakin-3
Prostatic origin: (+) PSA, NKX3.1
Often requires clinical and imaging evaluation to conclusively separate primary and secondary.

Also, consider Melanoma and VIN.

Virtual slide 2 3

Adenocarcinoma of mammary type



Malignant. Rare.
Primary **vulvar tumors** showing histopathological features identical to primary breast carcinoma.

Commonly express ER, PR, GATA3, HER2.