

The background is an abstract, painterly composition. It features a mix of teal, cyan, and light blue tones, with some darker, more saturated red and purple hues. The colors are blended and layered, creating a sense of depth and movement. The overall effect is reminiscent of a microscopic view of tissue or a stylized natural landscape.

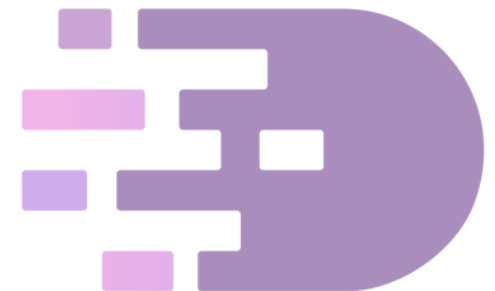
# NEOPLASMS WITH HAIR FOLLICLE DIFFERENTIATION

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Soheil S Dadras MD-PhD

# DEFINITION: HAMARTOMA VS. NEVUS VS. NEOPLASM (THEME OF THE CHAPTER)

- Hamartoma: local anatomic malformation made up of an abnormal mixture of cells and tissue  
e.g. sebaceous glands in areola (Montgomery's tubercle), lips or genitalia (Fordyce spots)
- Nevus is similar to hamartoma: melanocytic nevus
- Neoplasm: abnormal tissue mass that forms when cells grow and divide excessively and do not die when they should (Benign vs. malignant)
- Hamartomas with hair follicle differentiation, examples:
  - Hair nevi
  - Hair follicle nevus
  - Woolly hair nevus
  - Comedo nevus
  - Basaloid follicular hamartoma



# INTRODUCTION: FOLLICULAR NEOPLASMS

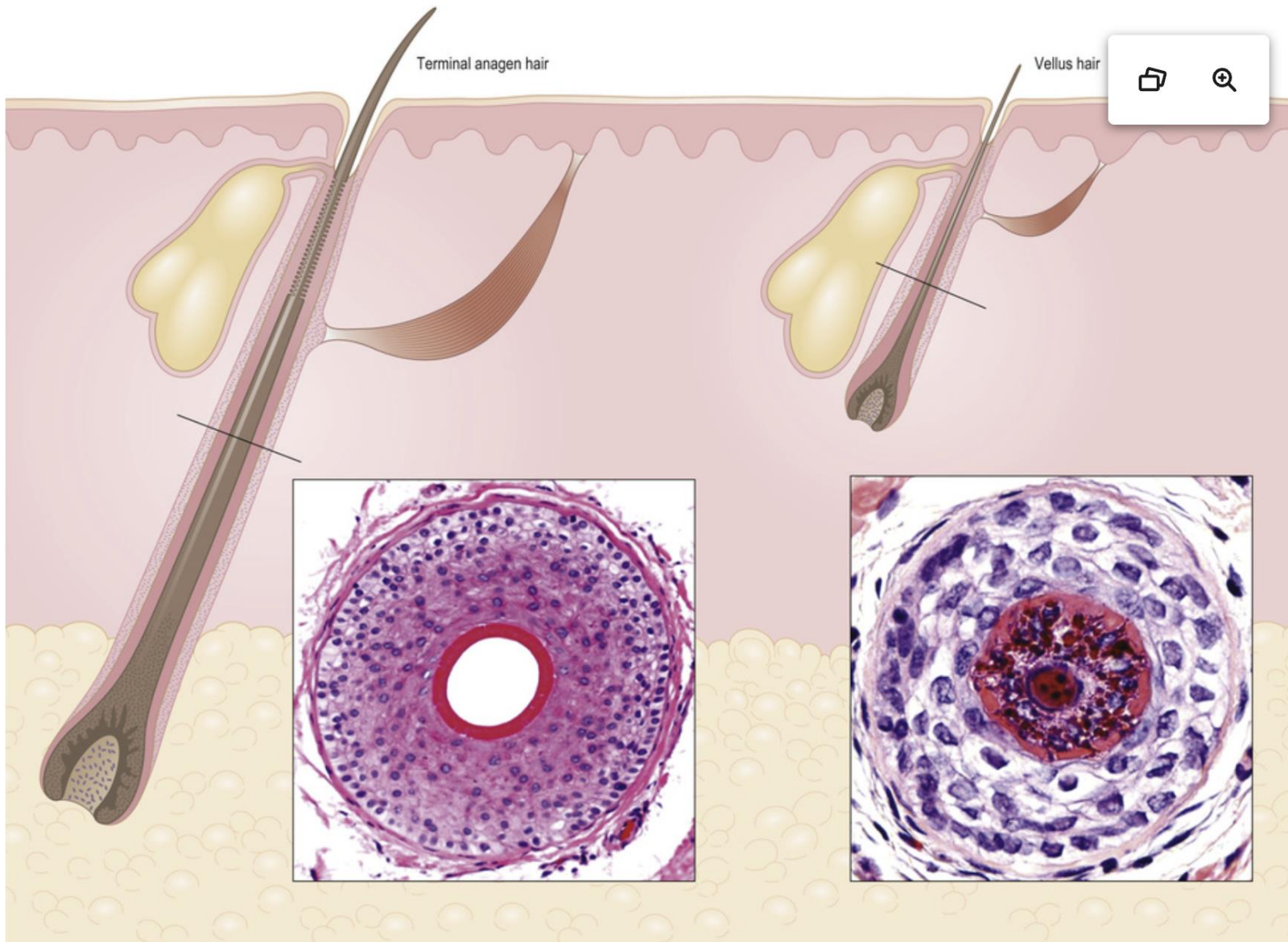
## GENERAL CONSIDERATION

- Disputed classification schema
- Exhibit a diverse range of morphology when compared to other adnexal neoplasms
- Replicate specific compartments:
  - Normal adult hair follicle
  - Developing embryo
  - Hair follicle cycle
- Lack of specific IHC and molecular diagnostic markers (not used in practice), except EMA, CEA (ductal differentiation)

### Tips:

- Learn hair follicle microanatomy, correlate with tumor name
- Recognize the various types of differentiation towards a specific hair follicle compartment
- My own experience: Pluripotency of adnexal neoplasms
- Note the interplay between epithelium and stroma
- Most are benign, malignant version exist (Look for infiltrating pattern)
- See many examples (Quiz yourself)





Vellus hair: in dermis

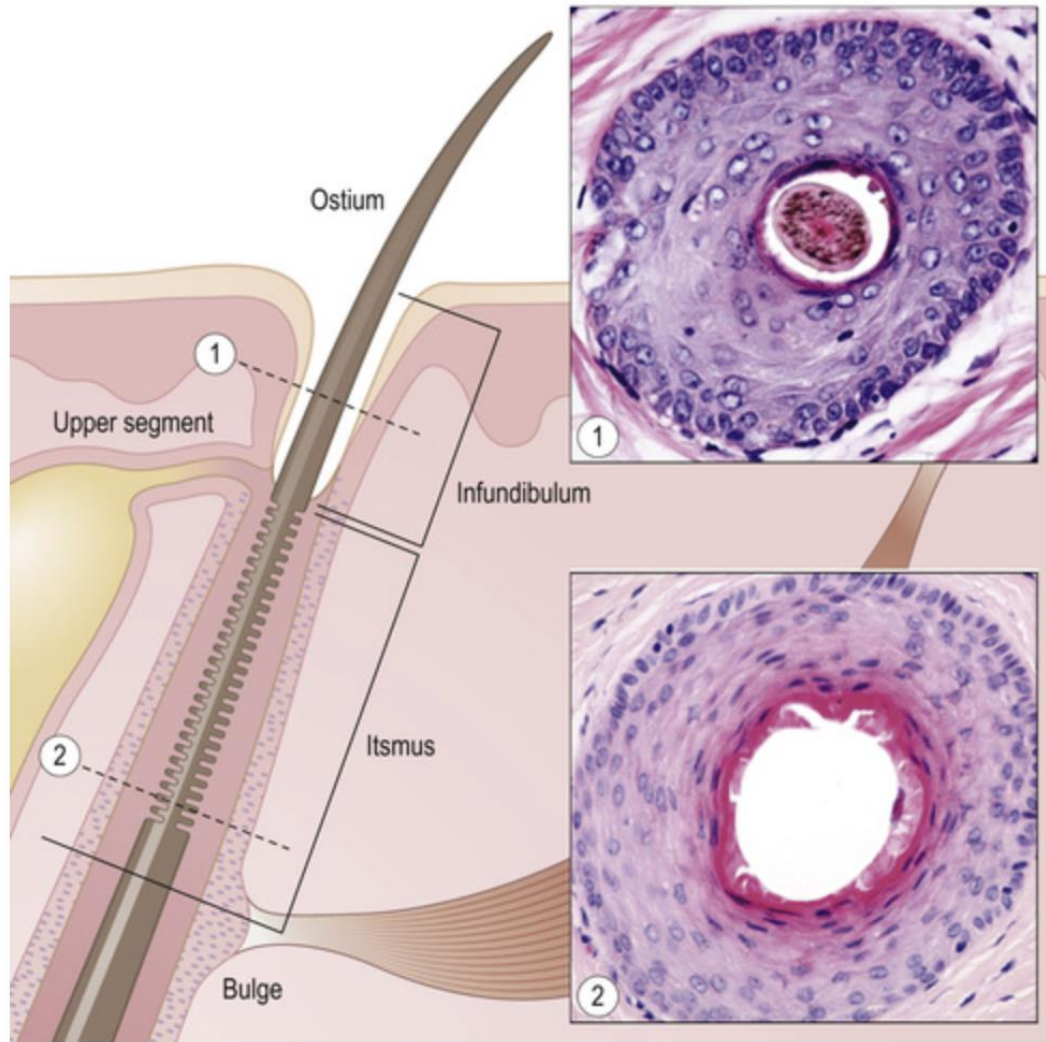
Nuclei in hair shaft & inner root sheath

Terminal anagen hair: in fat

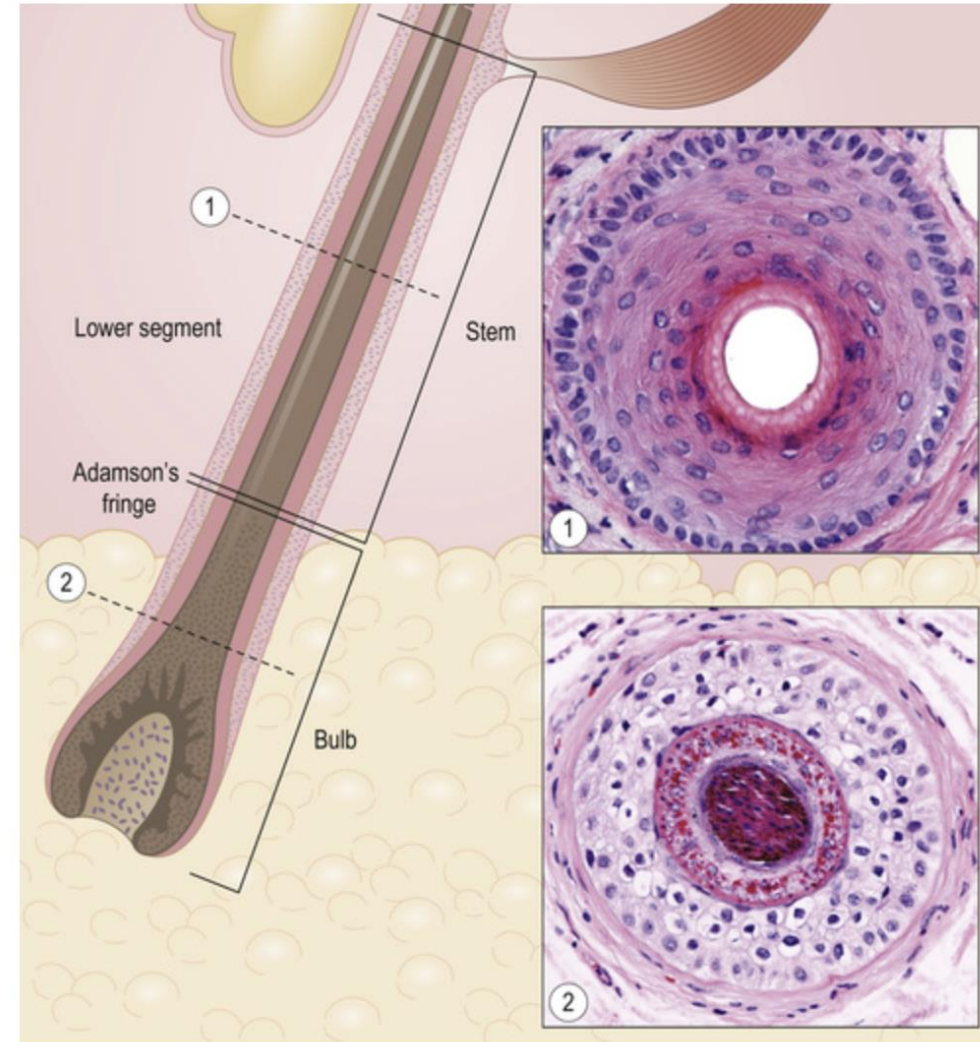
Reference: *McKee's Pathology of the Skin* by Eduardo Calonje



Squamous: ~ epidermis



Terminal anagen hair: the upper segment

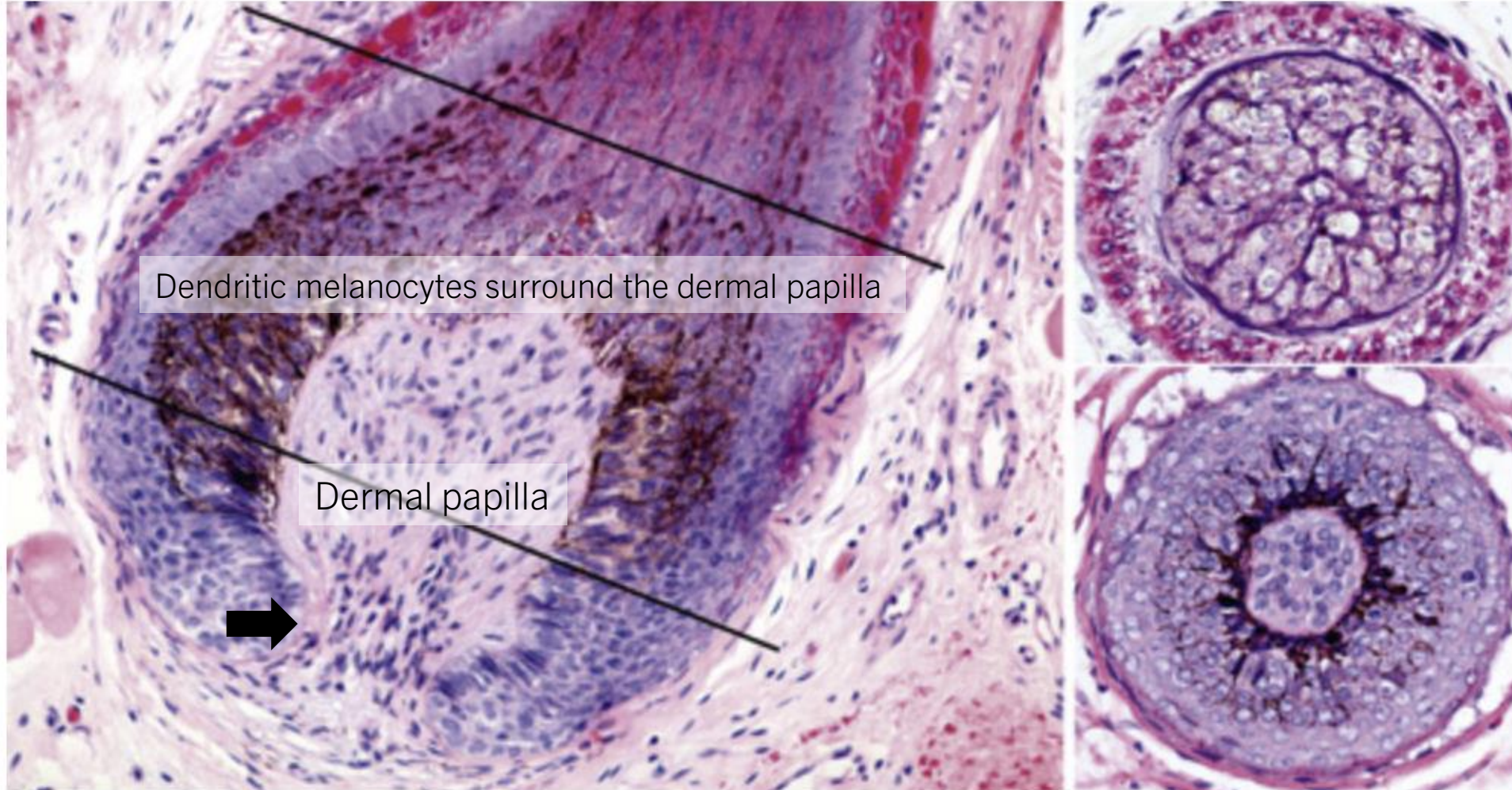


Terminal anagen hair: the lower segment

Nuclei in hair shaft & inner root sheath



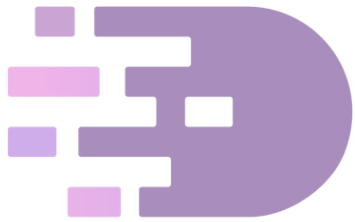
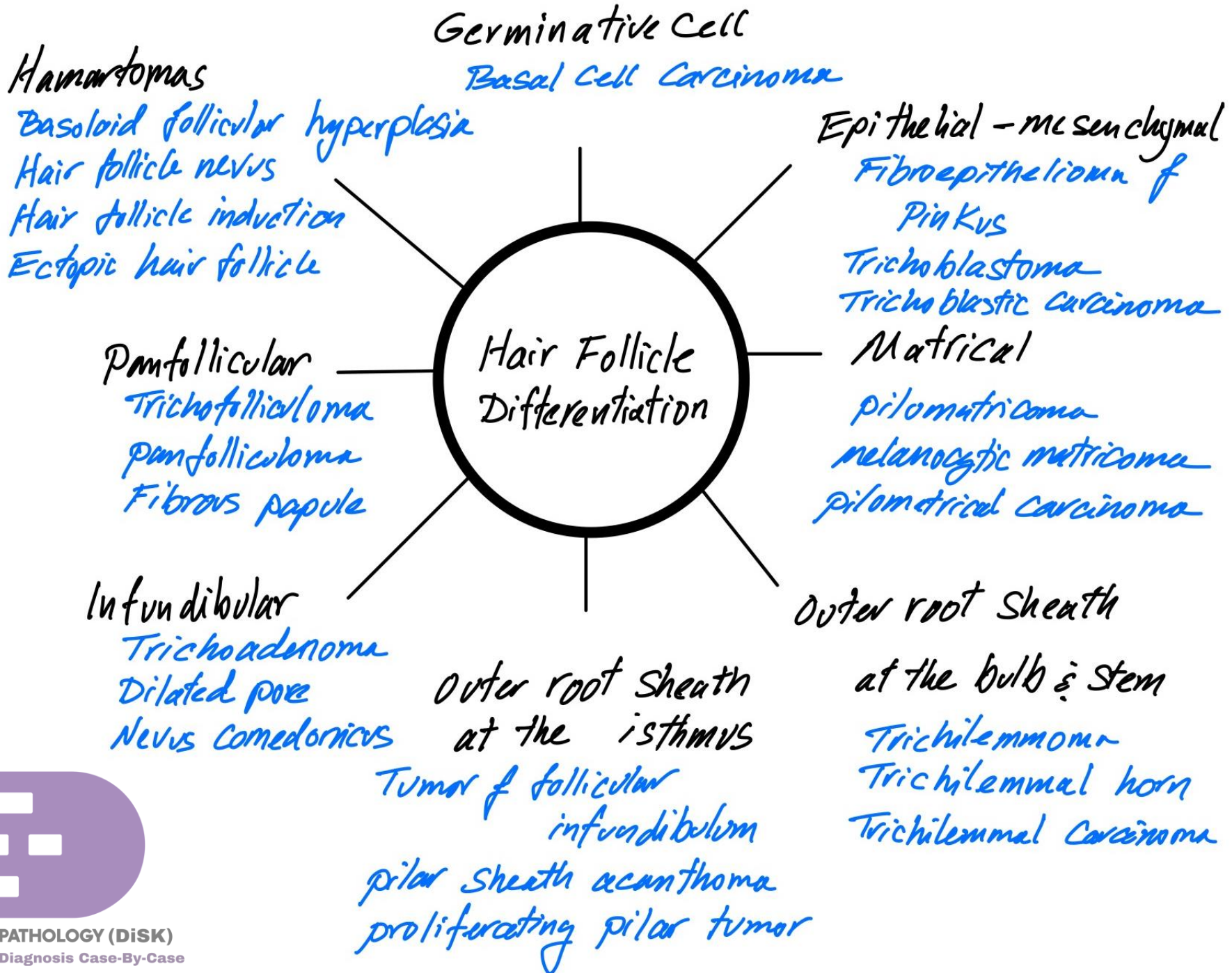
## Terminal anagen hair: Bulb and Pigmentary unit



Dermal papilla composed of connective tissue and blood vessels

Reference: *McKee's Pathology of the Skin* by Eduardo Calonje

# Outline: Neoplasms with follicular differentiation





# FOLLICULAR GERMINATIVE CELL DIFFERENTIATION: BASAL CELL CARCINOMA (BCC)

- Prevalence: The most common skin cancer
- Definition: Historically categorized as epidermal or keratinocytic, yet acknowledged for its follicular characteristics.
- Origin: Develops in skin with hair follicles, similar to follicular germinative epithelium.
- Molecular Data:
  - Backed by *sonic hedgehog* gene knockout studies.
  - Mice with a disrupted *sonic hedgehog* gene exhibit halted hair follicle development, resembling superficial BCC.

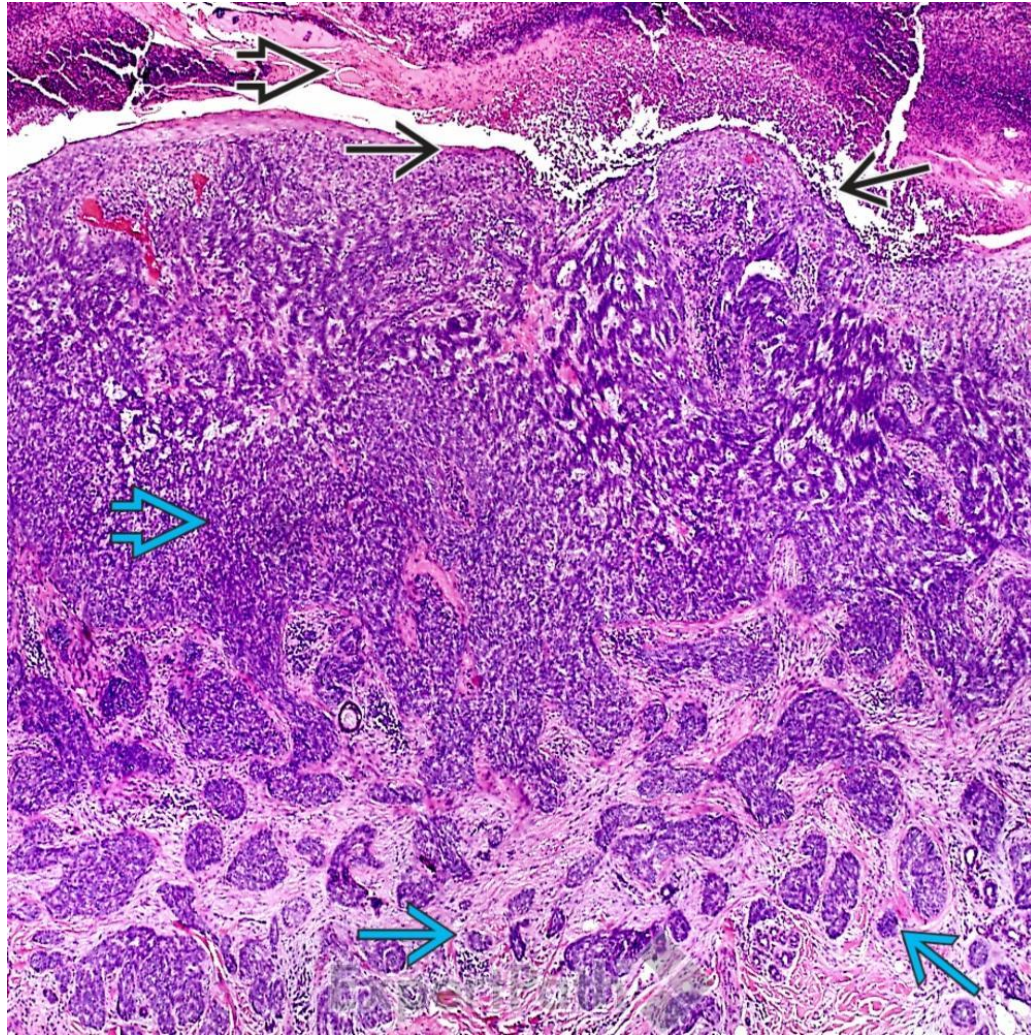
Subtypes of BCC:

- Superficial BCC
- Nodular, solid-cystic, and cystic BCC
- Micronodular BCC
- Morpheaform and infiltrative BCC
- Keratotic and metatypical (basal squamous) BCC
- Infundibulocystic BCC
- Folliculocentric BCC
- Adenoid cystic BCC
- Additional rare variants

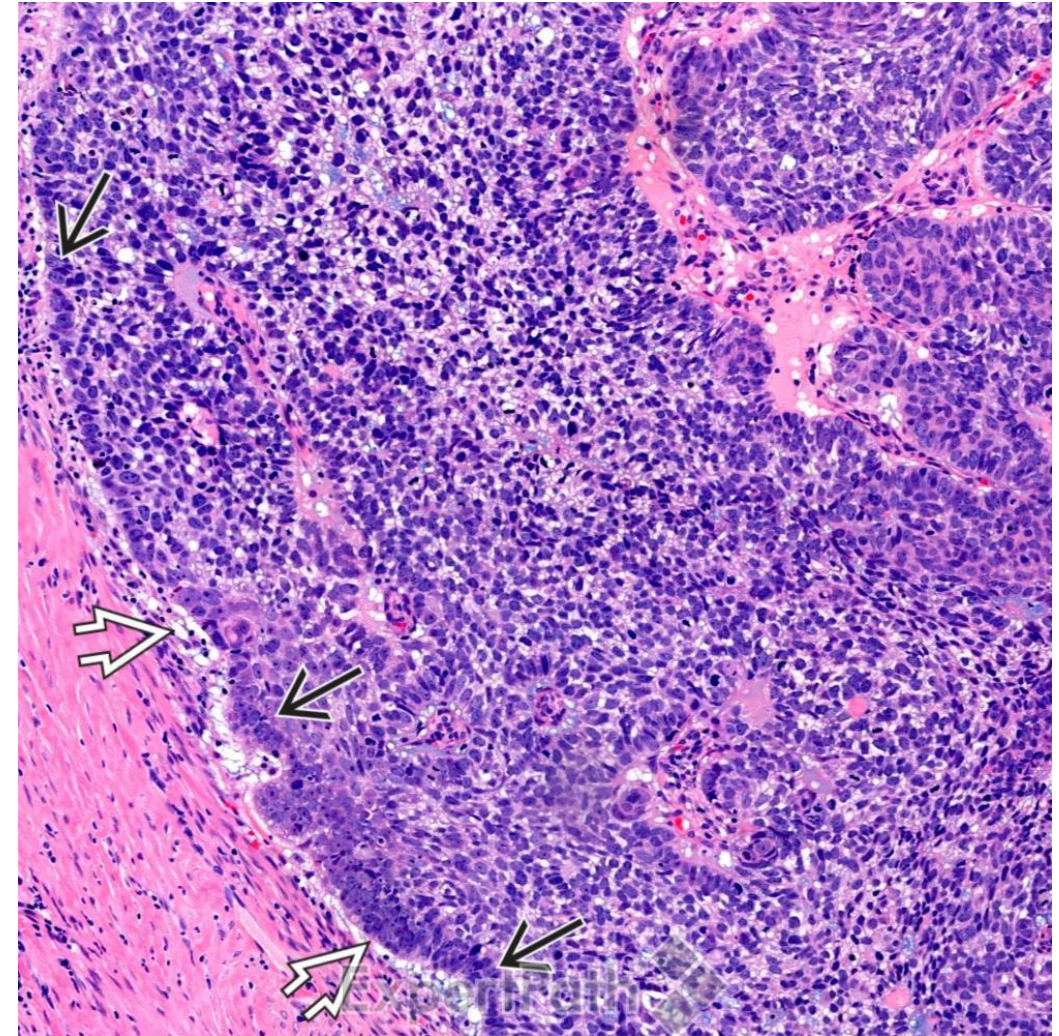
DDX: Merkel cell carcinoma, trichoblastoma



# BASAL CELL CARCINOMA

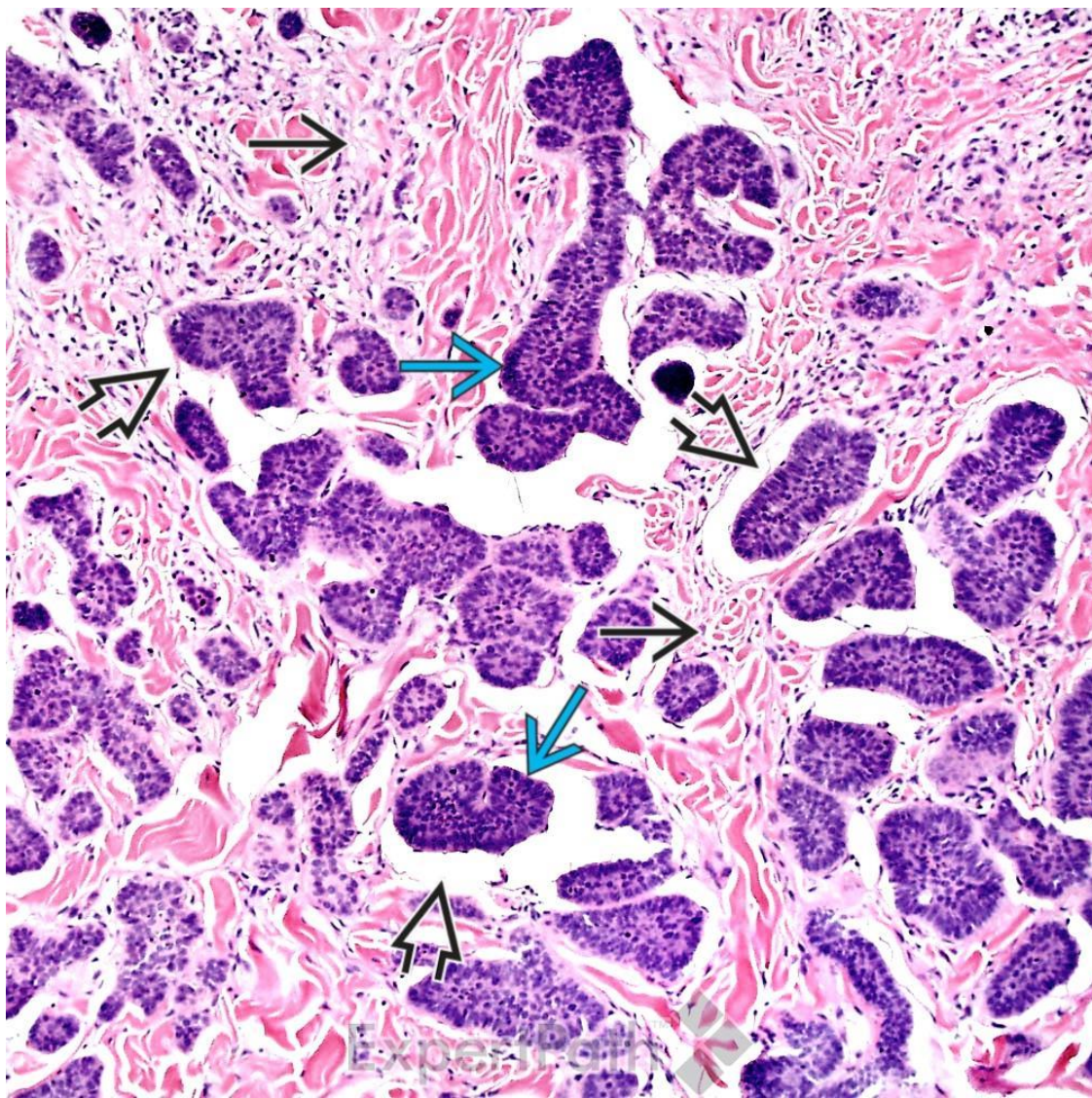


Large, micronodular (cyan solid arrow) and nodular (cyan open arrow) BCC with diffuse overlying ulceration (black solid arrow) and dense serum crust (black open arrow) containing degenerating neutrophils.

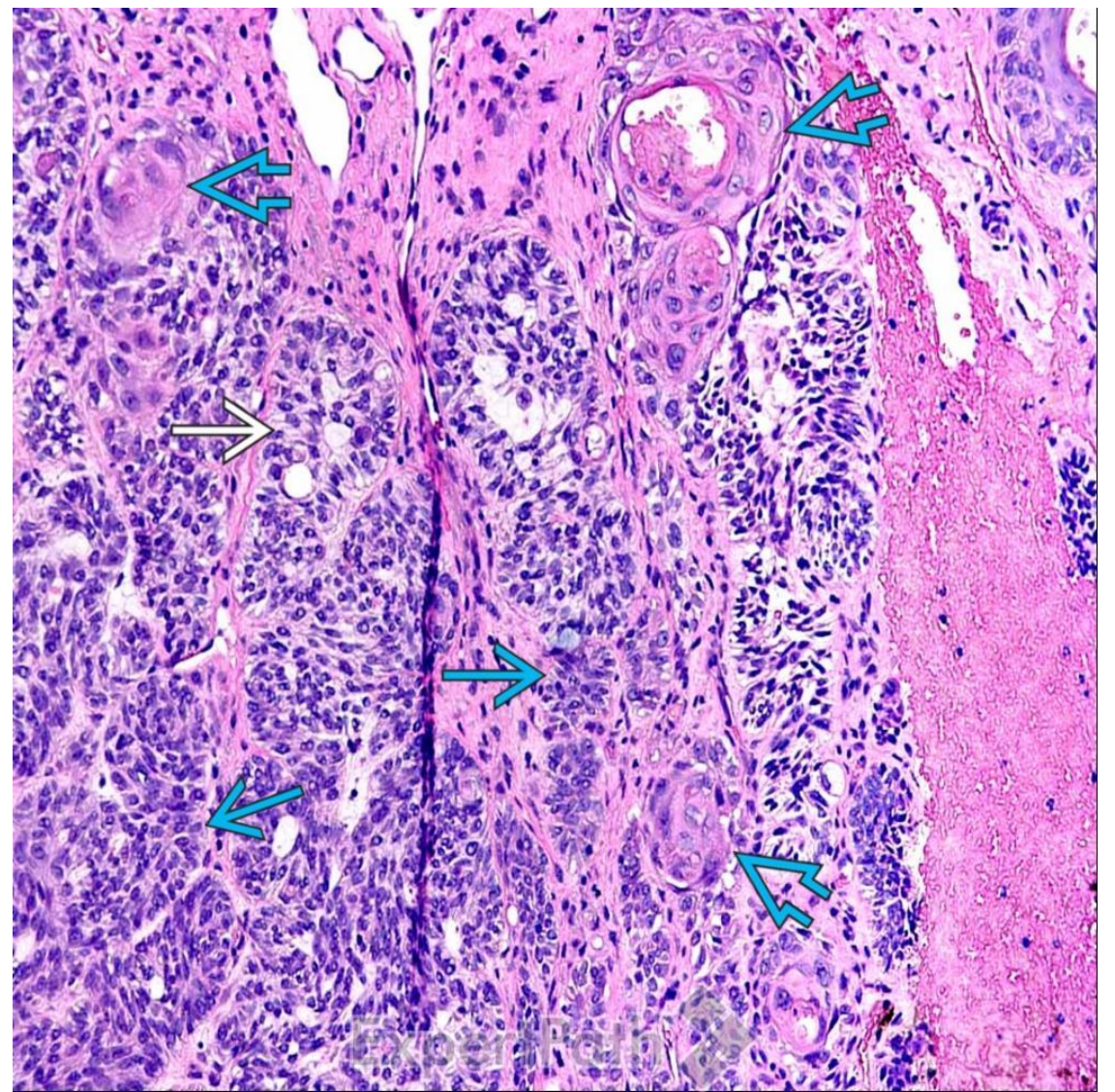


Palisading tumor cells define the peripheral border (black solid arrow). Retraction artifact is formed as the tumor cells pull away from the stroma, creating a cleft (white open arrow).



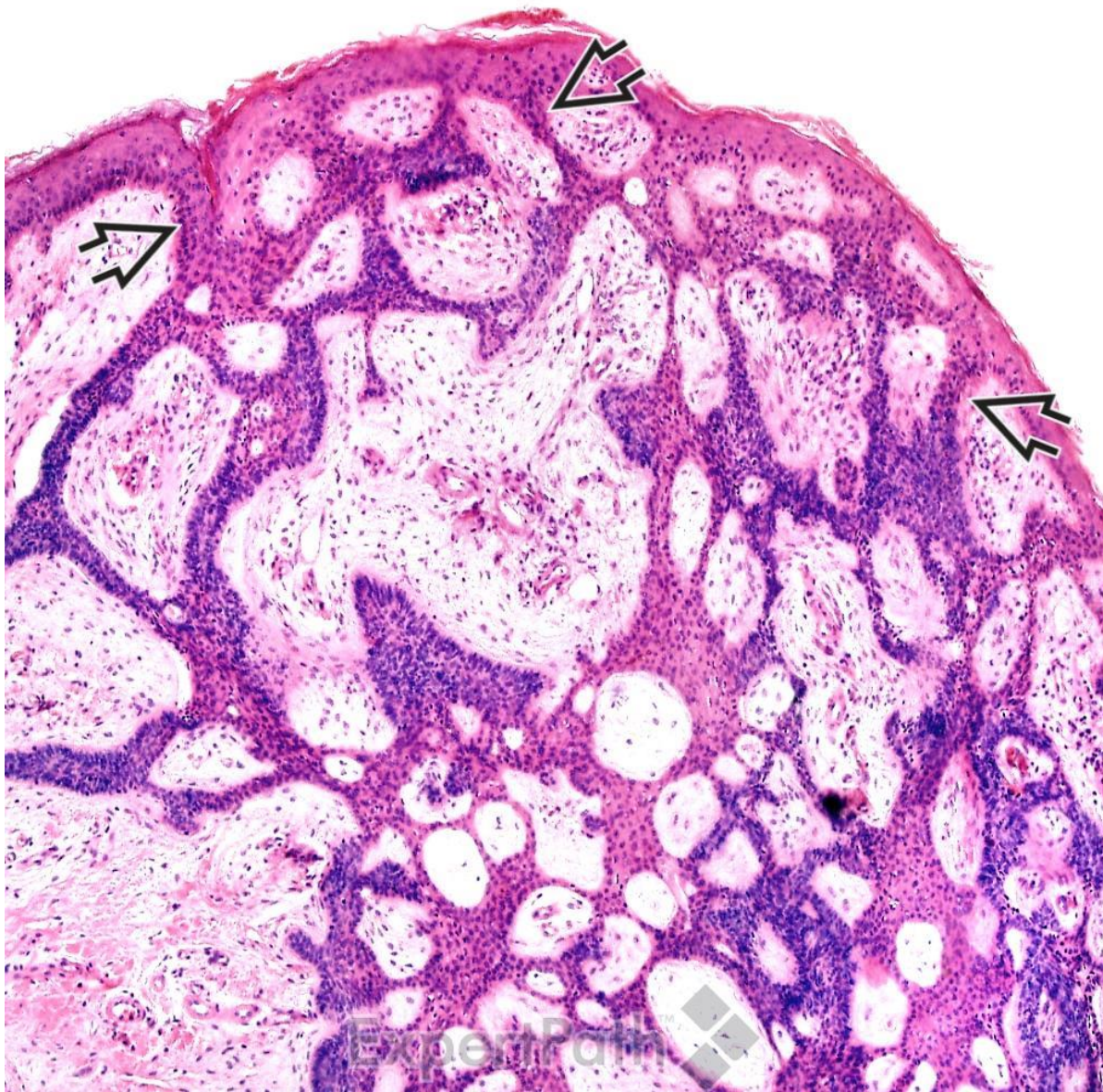


**Micronodular BCC:** a proliferation of small, round nests of basaloid cells with prominent retraction artifact (black open arrow) (washed out mucin) set in a fibromyxoid stroma (black solid arrow). Peripheral palisading of nuclei (cyan solid arrow) in these islands is evident.

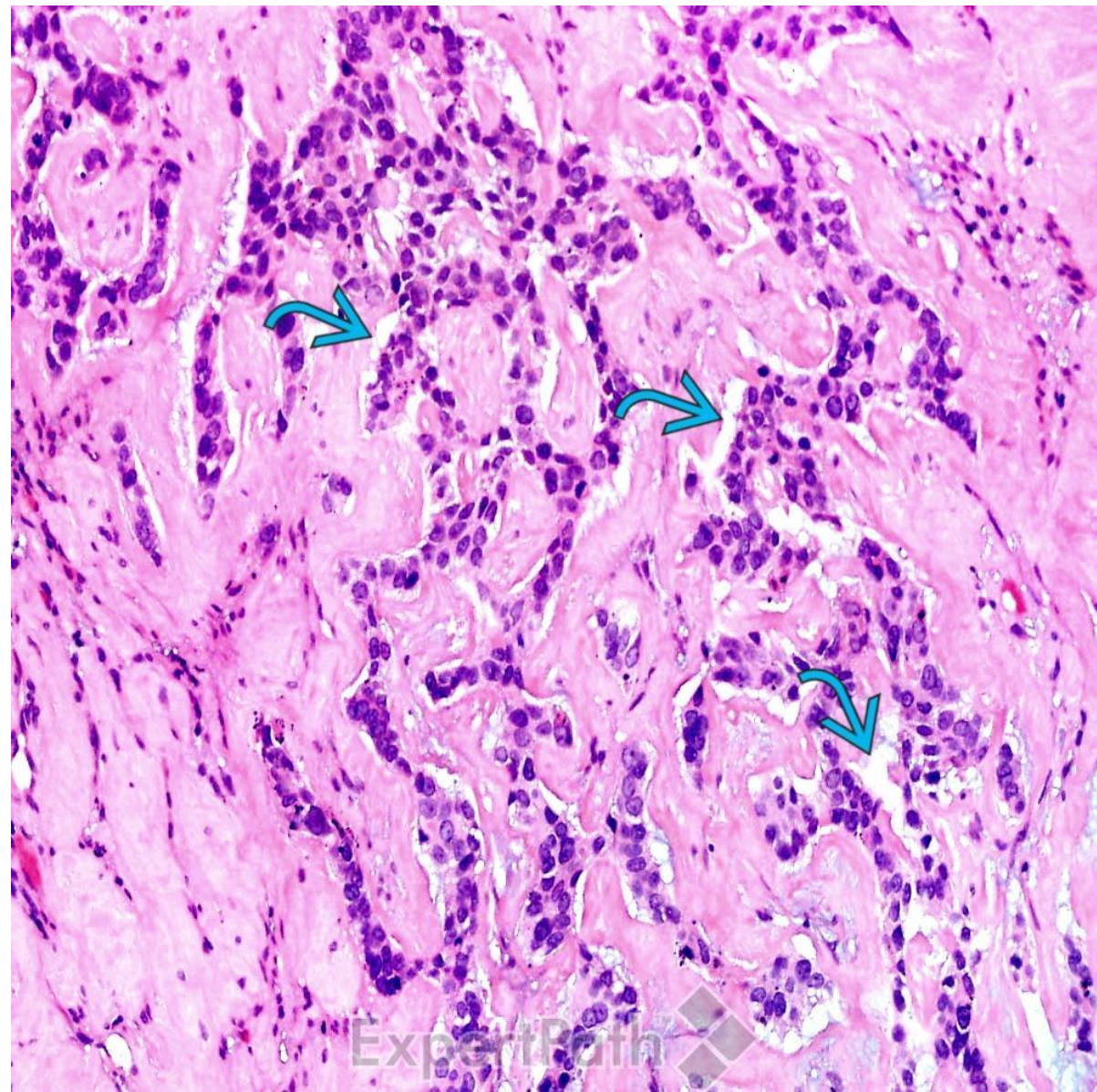


**BCC with squamous differentiation:** the majority of the tumor is composed of basaloid nests (cyan solid arrow). Amid the basaloid tumor, foci of squamous differentiation (cyan open arrow) are evident with focal, clear cell change (white solid arrow).





**Fibroepithelioma of Pinkus BCC:** numerous small, anastomosing cords of basaloid cells with multiple epidermal connections (black open arrow).



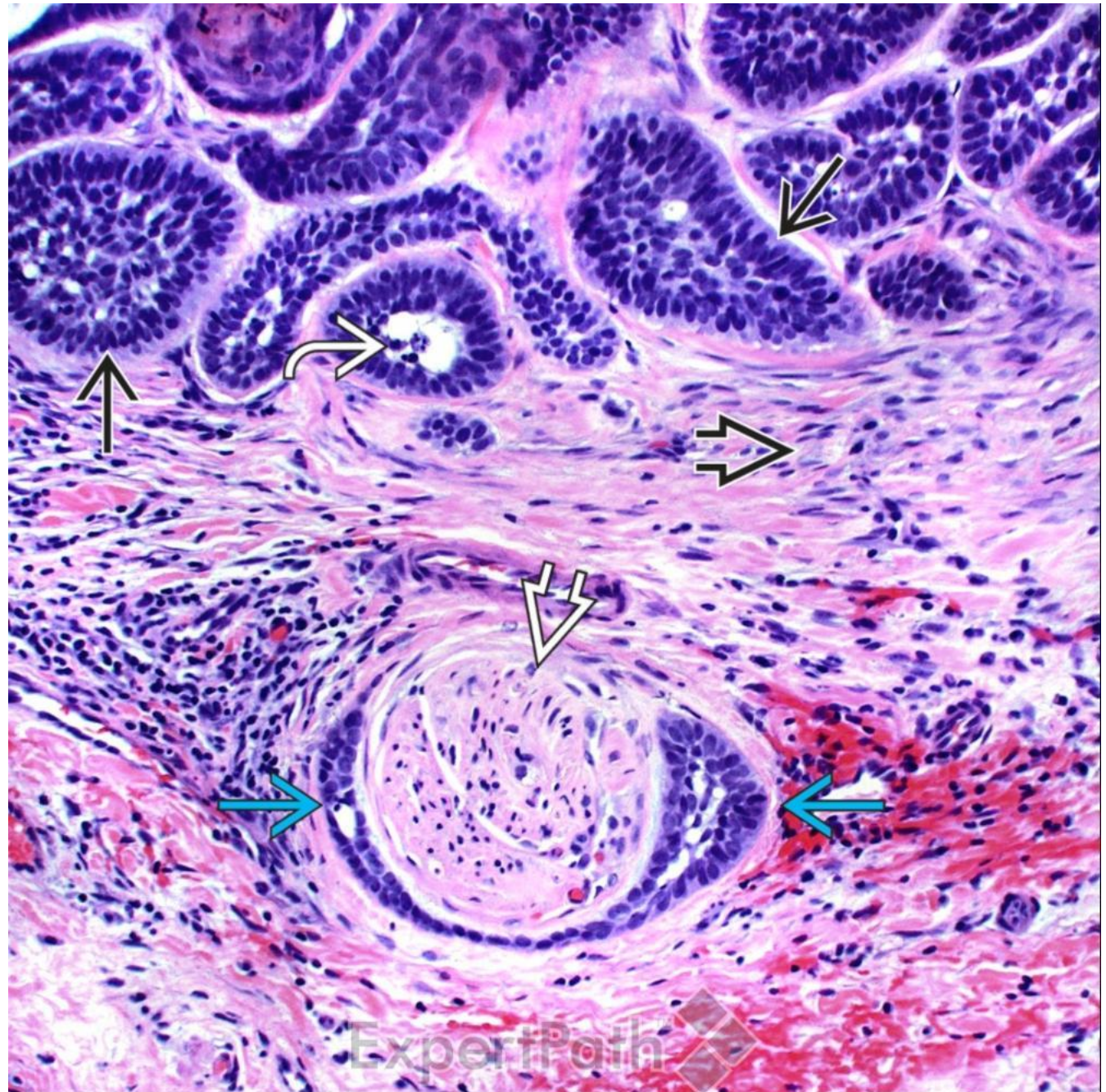
**Morpheaform (desmoplastic/sclerosing) BCC:** thin cords of atypical basaloid cells infiltrating a very dense, desmoplastic stroma. Note the retraction artifact (cyan curved arrow) present around many of the cords.



# WHAT ARE THE HIGH-RISK HISTOLOGIC SUBTYPES OF BCC?

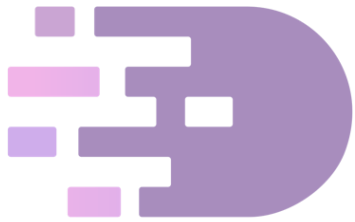
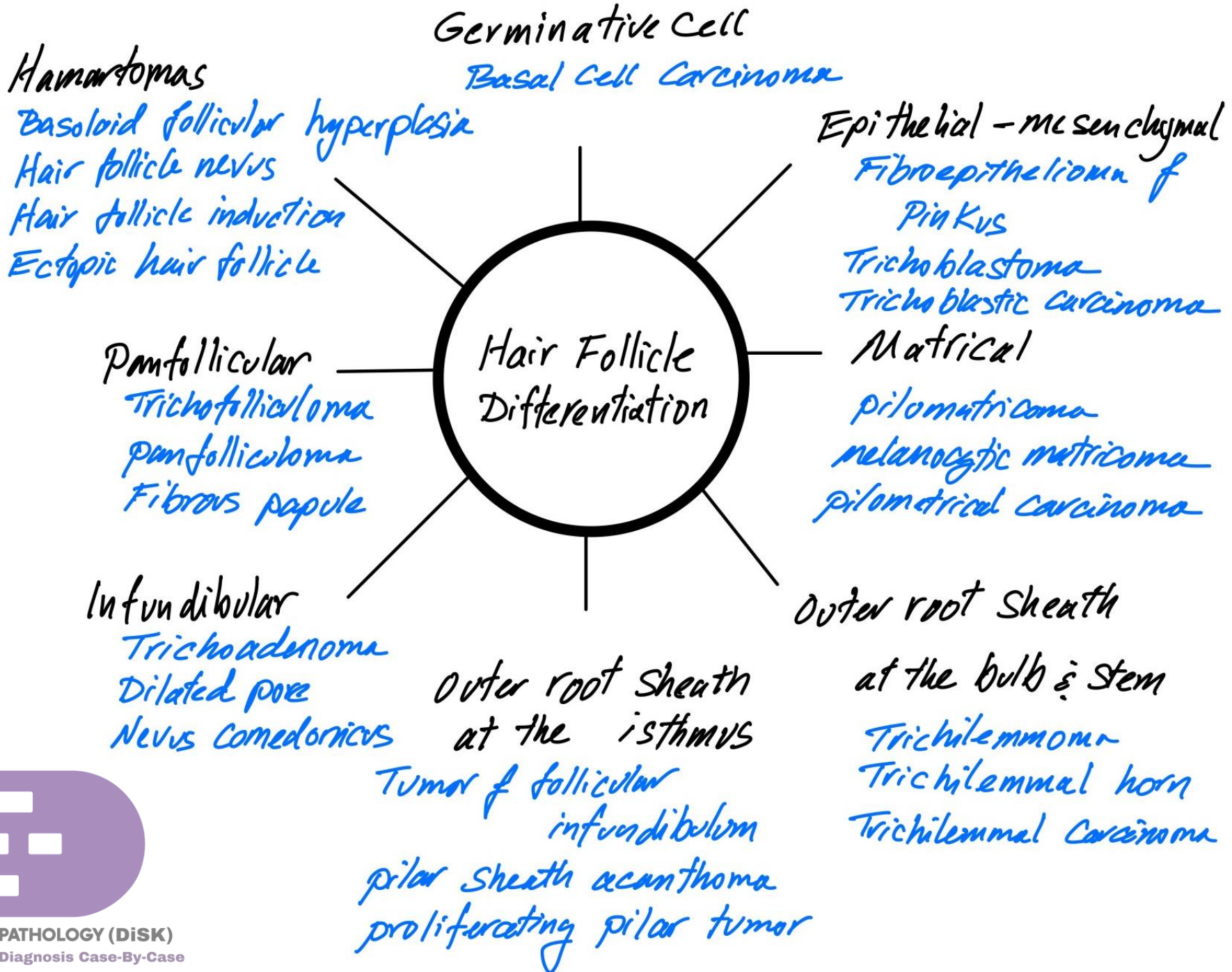
1. Infiltrative BCC
  2. Morpheaform (Sclerosing) BCC
  3. Micronodular BCC
  4. Basosquamous (Metatypical) BCC
- Can occur in any subtype, leading to local recurrence

A basaloid nest (cyan solid arrow) tightly wraps around a nerve bundle (white open arrow). Fibromyxoid stroma (black open arrow), a focal mucin pool (white curved arrow), and peripheral nuclear palisading (black solid arrow) in the tumor nests are evident.





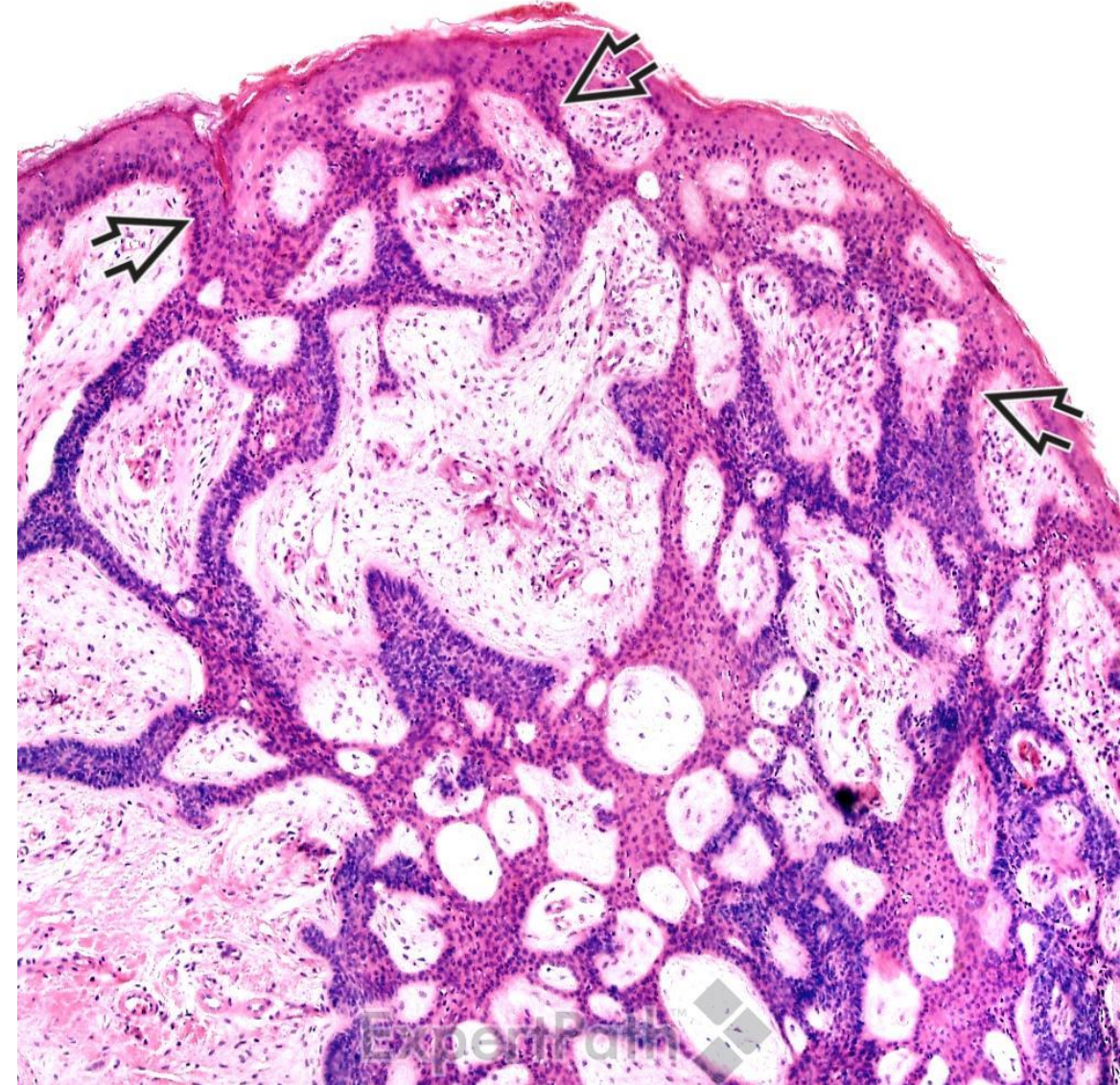
# Outline: Neoplasms with follicular differentiation





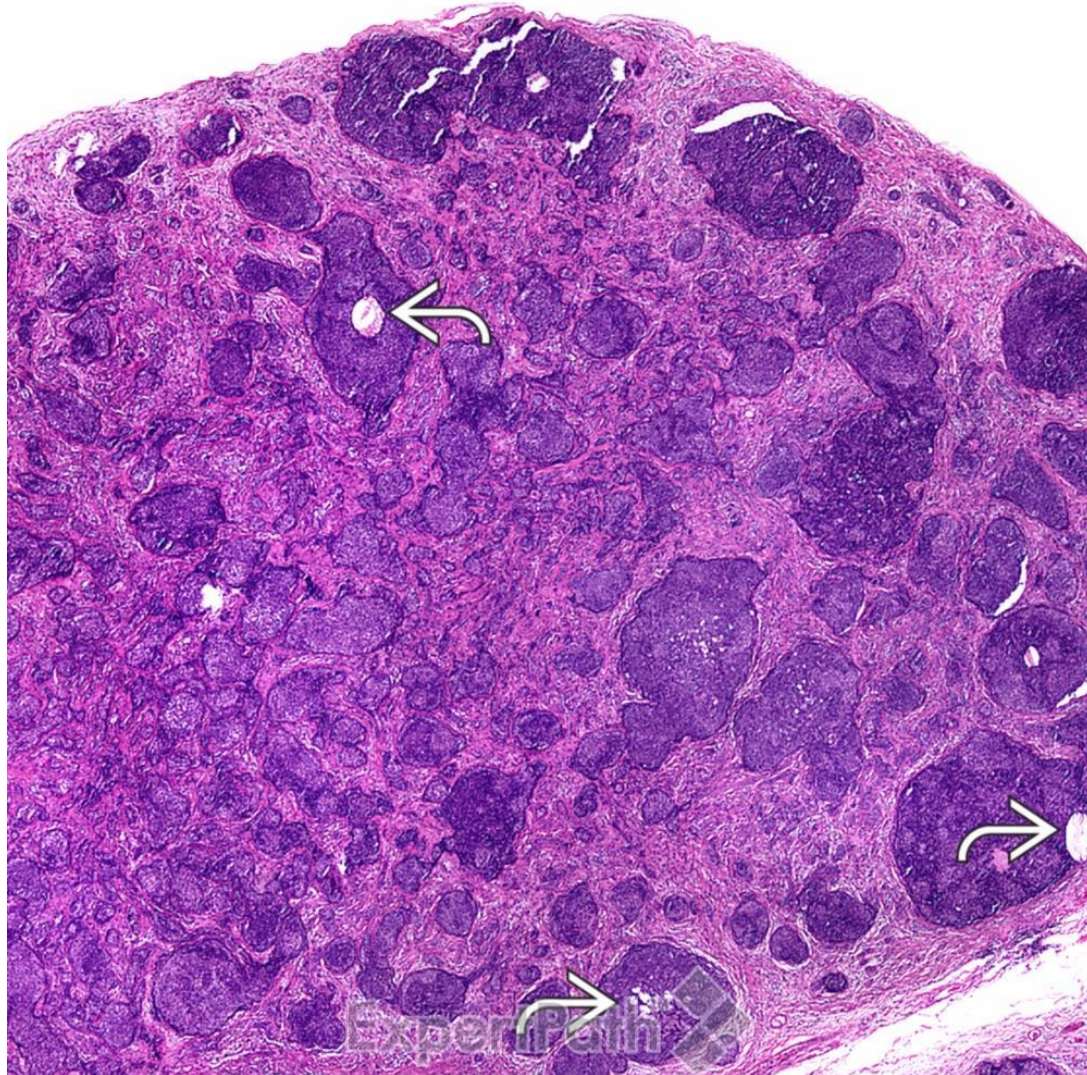
# BIPHASIC EPITHELIAL-MESENCHYMAL NEOPLASM: FIBROEPITHELIOMA OF PINKUS

- **Clinical Presentation:** Solitary, asymptomatic, soft reddish polypoid tumor.
- **Histopathologic Features:**
  - Eosinophilic cells from epidermis forming germ-like structures.
  - Surrounded by fibrotic stroma with follicular papillae differentiation.
- **Behavior and Prognosis:** No aggressive behavior or metastasis.
- **Differential Diagnosis:**
  - Basal cell carcinoma, fibroepitheliomatous variant





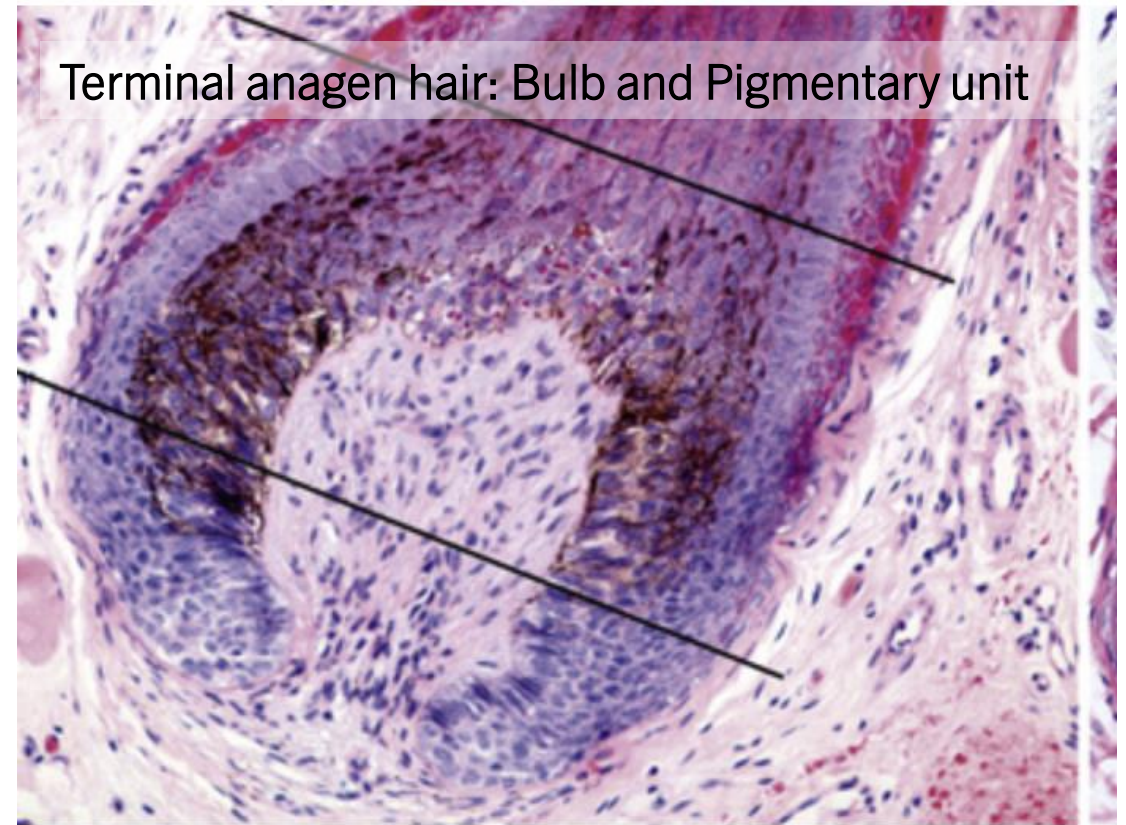
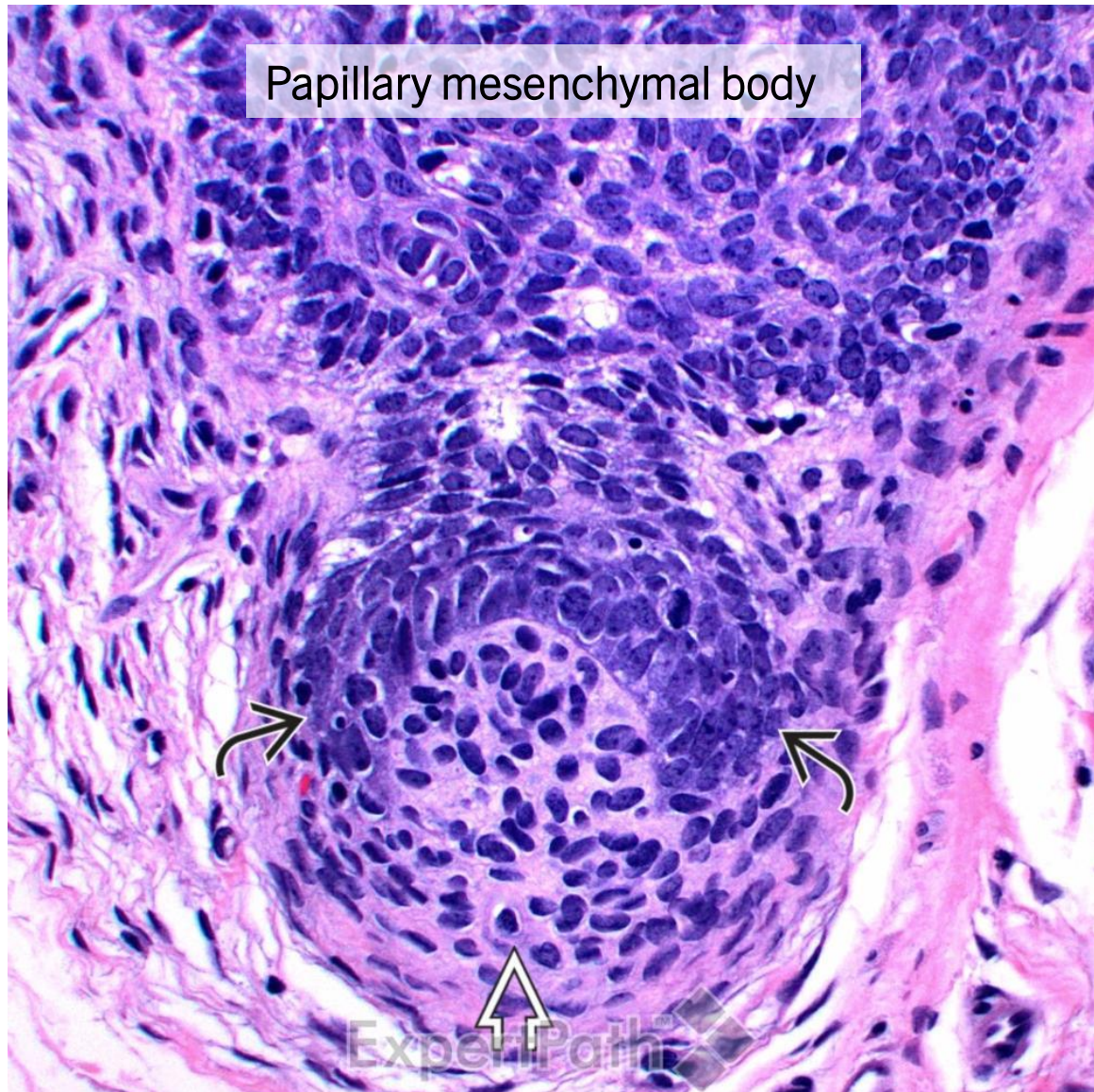
# BIPHASIC EPITHELIAL-MESENCHYMAL NEOPLASM: TRICHOBLASTOMA



- Histological Characteristics:
  - A prominent, basaloid-looking nodule located in the deep dermis, exhibiting clearly defined borders
  - Absence of connections to the epidermis
- Potentially extends into the superficial subcutis
- Accompanied by fibrotic stroma featuring a higher count of fibroblasts
- Classically includes the presence of papillary mesenchymal bodies
- Differential Diagnosis:
  - Basal cell carcinoma
  - Spiradenoma, lymphoepithelial-like carcinoma

Nodular dermal basaloid proliferation associated with a fibrotic stroma. Note the presence of scattered folliculocystic structures (white curved arrow).

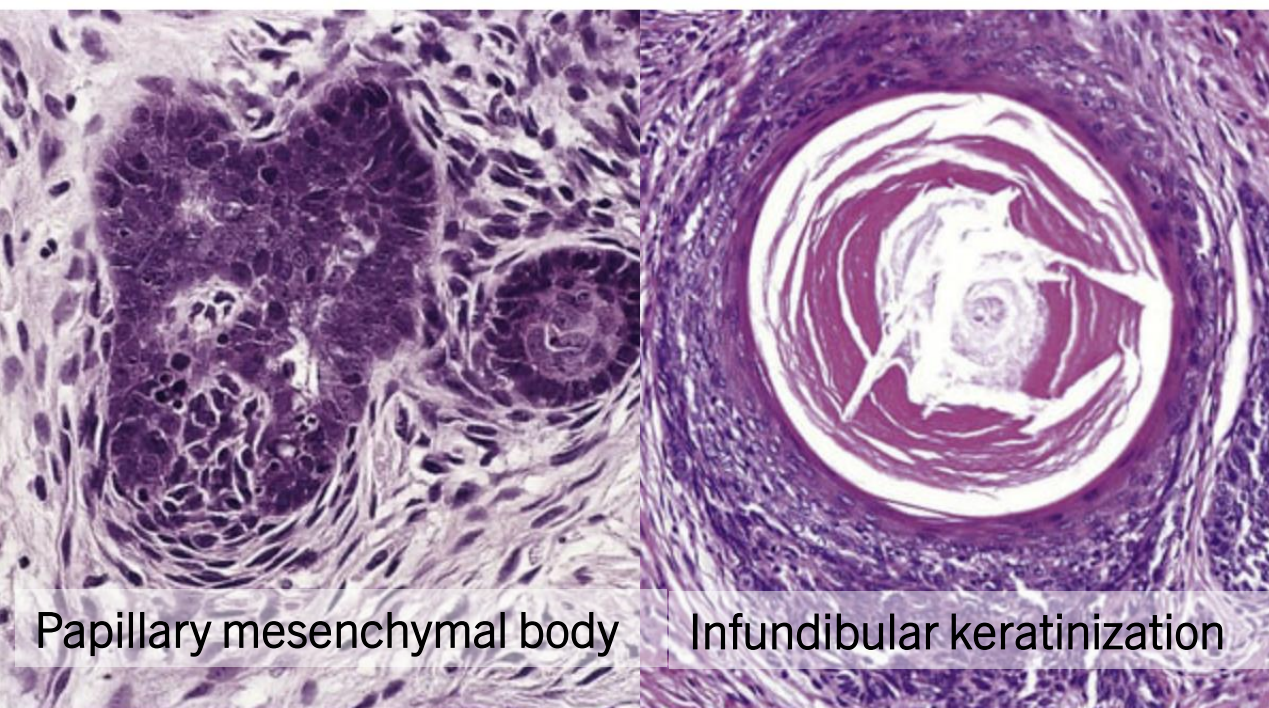




Dermal papilla composed of connective tissue and blood vessels

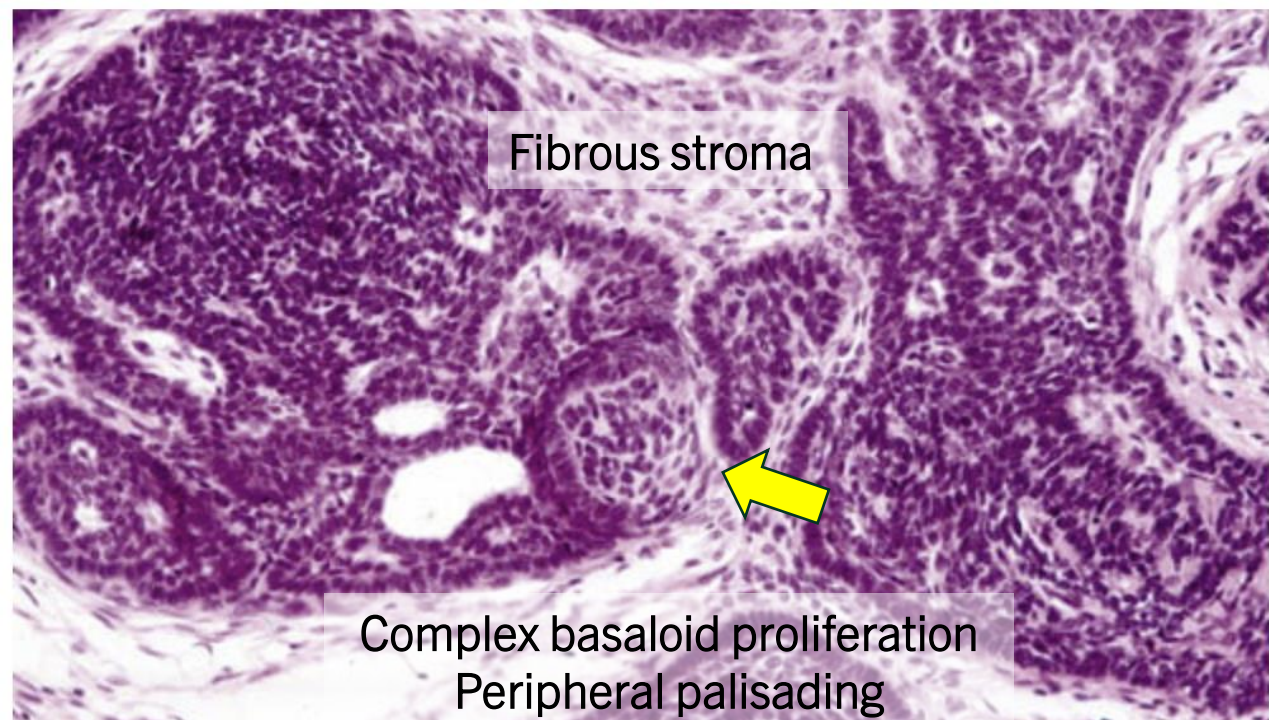
A papillary mesenchymal body shows an invagination of cellular fibroblastic stroma (white open arrow) into a peripheral bulb-like area of the tumor. These bodies are surrounded by the epithelial tumor cells (black curved arrow).





Papillary mesenchymal body

Infundibular keratinization



Fibrous stroma

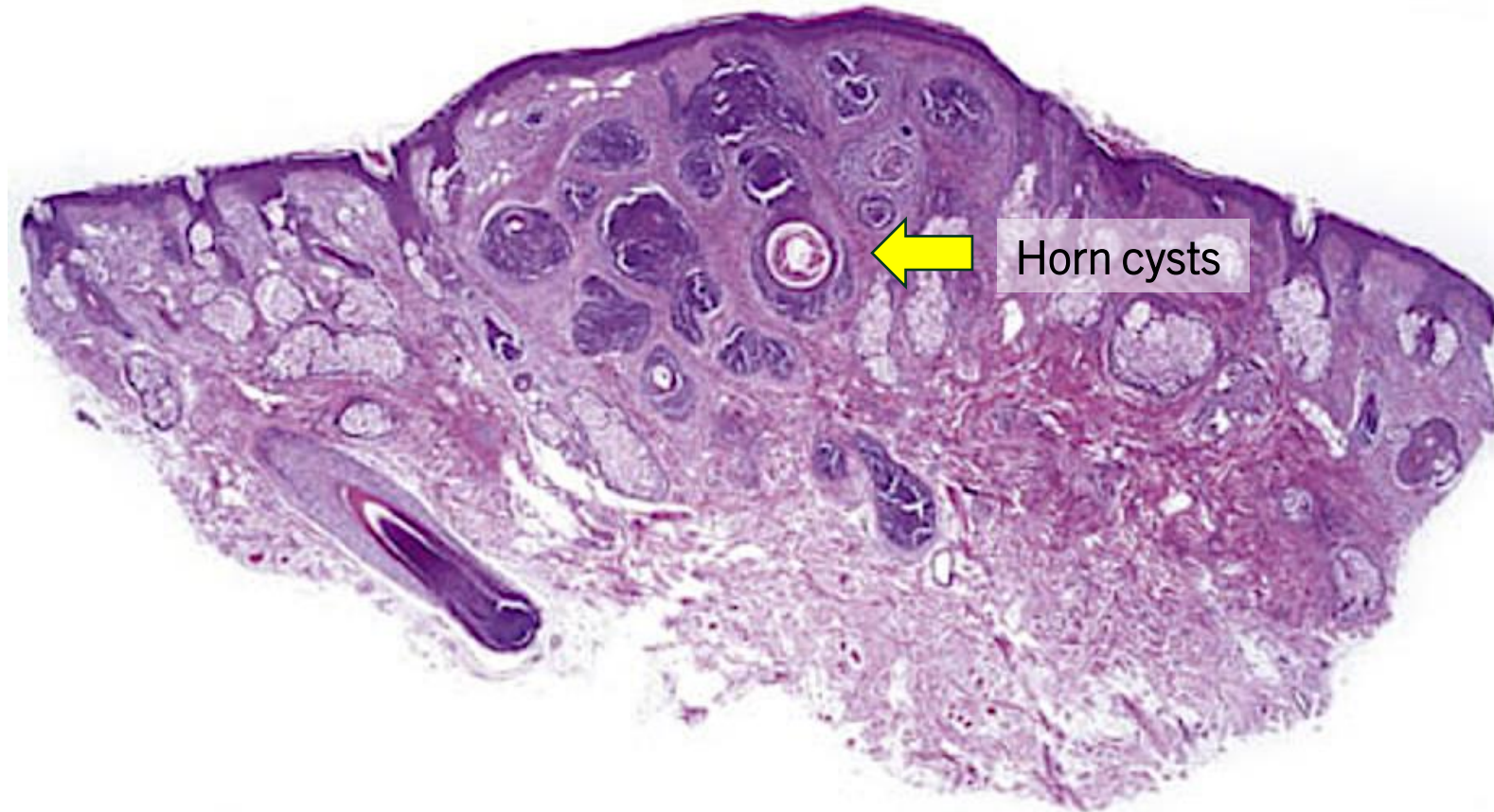
Complex basaloid proliferation  
Peripheral palisading

# TRICHOEPITHELIOMA

- Hamartoma with follicular differentiation
- Skin-colored papules, symmetrical
- Face
- *CYLD* gene mutations
- DDX: keratotic basal cell carcinoma (mucin, retraction), trichoblastoma
- IHC: trichoepithelioma CK15+  
Trichoblastoma (CK20+ Merkel cells)  
BCC (BCL-2+)  
Trichoepithelioma (CD34+ stromal cells)



# TRICHOEPITHELIOMA



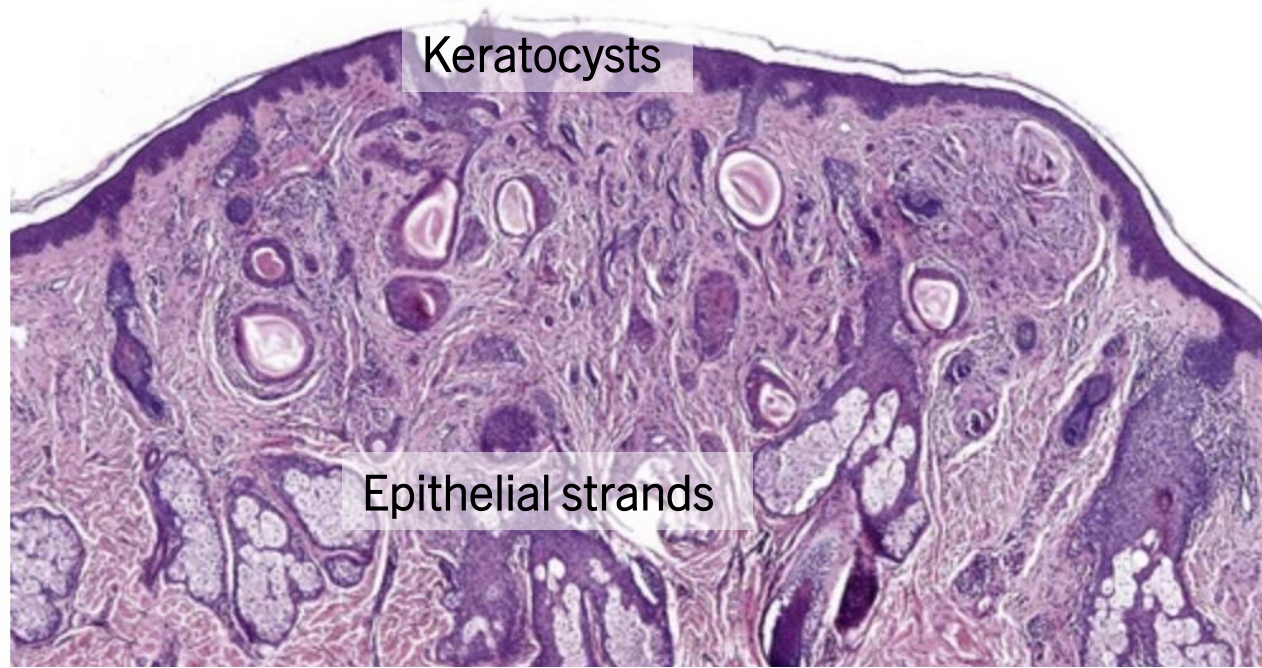
Dermal ( $\pm$ epidermal connection) tumor

Basaloid tumor nests



# DESMOPLASTIC TRICHOEPITHELIOMA

- Young adults, face (cheek, chin and forehead) or neck
- White-yellow flat papule with atrophic center
- Not syndromic or familial
- Microcalcification
- DDX: morpheaform BCC (absent CK20+ Merkel cells), Syringoma, microcystic adnexal carcinoma (ductal differentiation, EMA, CEA+)





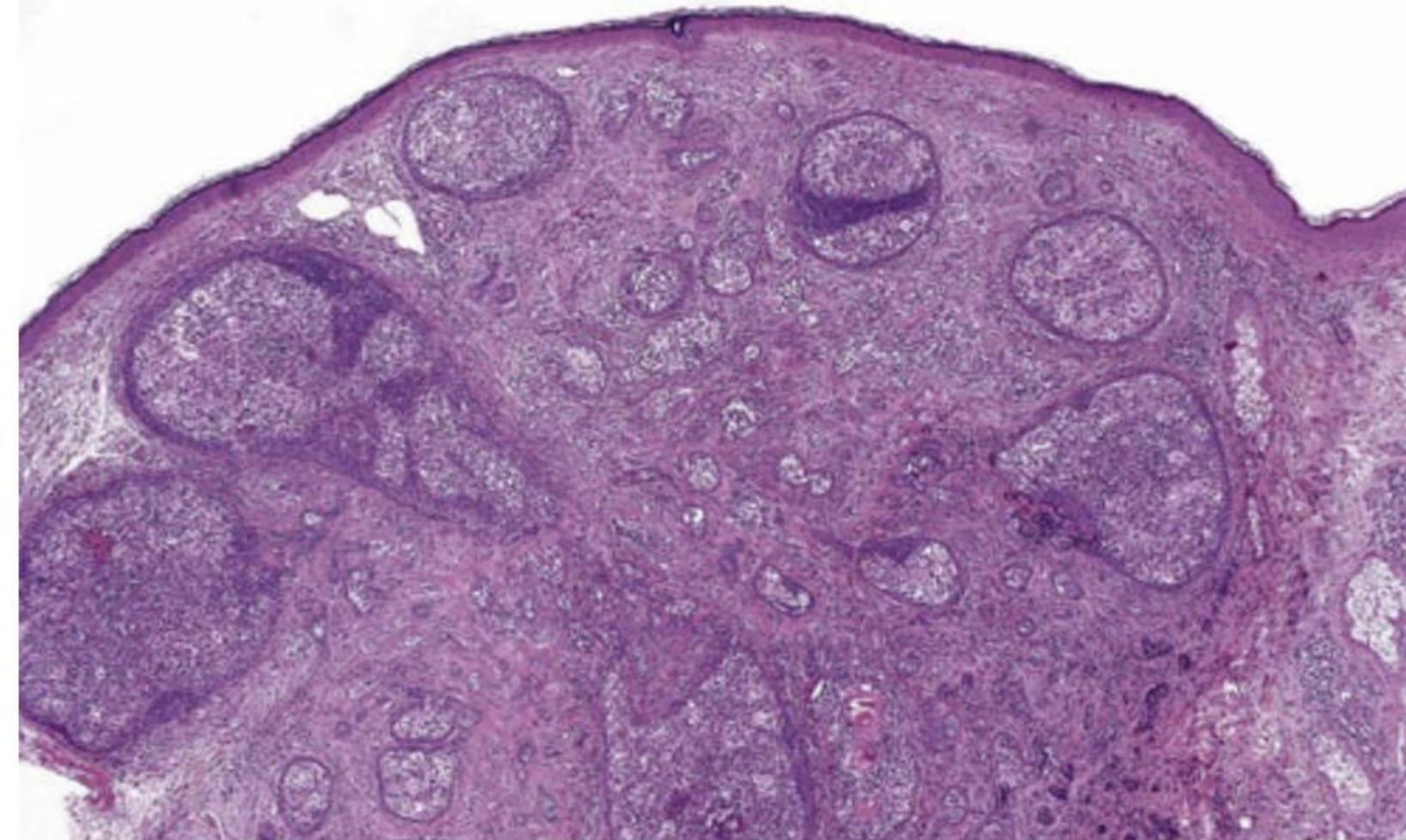
# DIFFERENTIATING BASAL CELL CARCINOMA, TRICHOBLASTOMA, AND TRICHOEPITHELIOMA BY IMMUNOHISTOCHEMICAL PROFILE

## Key Points

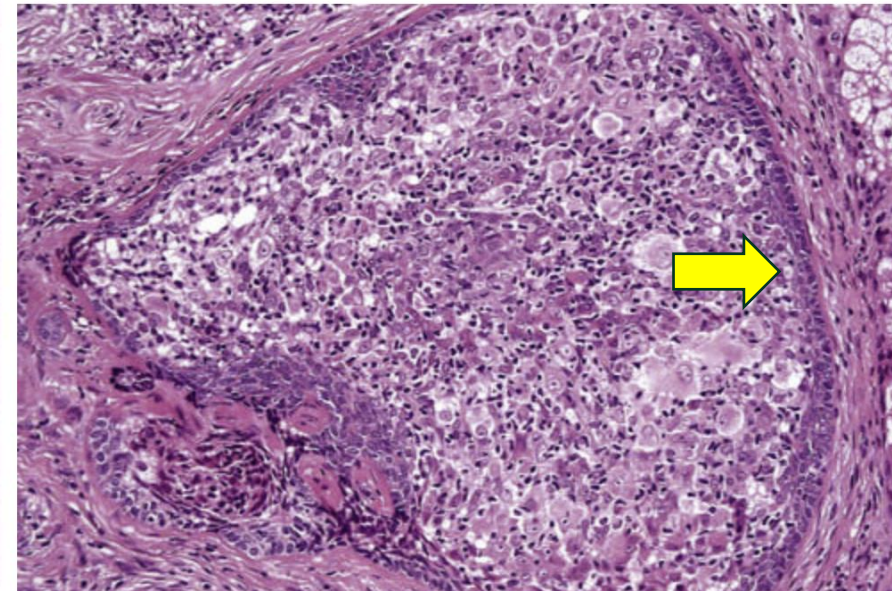
- **Basal Cell Carcinoma:** Characterized by a positive and diffuse expression of BCL2 in the epithelium. CD10 is positive in 80% of cases, while CD10 in stroma is negative, and CD34 in stroma can vary ( $\pm$ ).
- **Trichoblastoma:** Shows a peripheral and variable ( $\pm$ ) pattern of BCL2 expression in the epithelium. CD10 expression is also variable in the epithelium and positive in stroma. CD34 in the stroma is also variable ( $\pm$ ).
- **Trichoepithelioma:** Similar to trichoblastoma with peripheral and variable ( $\pm$ ) BCL2 expression. CD10 shows a similar pattern, being variable in the epithelium and positive in the stroma. CD34 is consistently positive in the stroma.



# CUTANEOUS LYMPHADENOMA



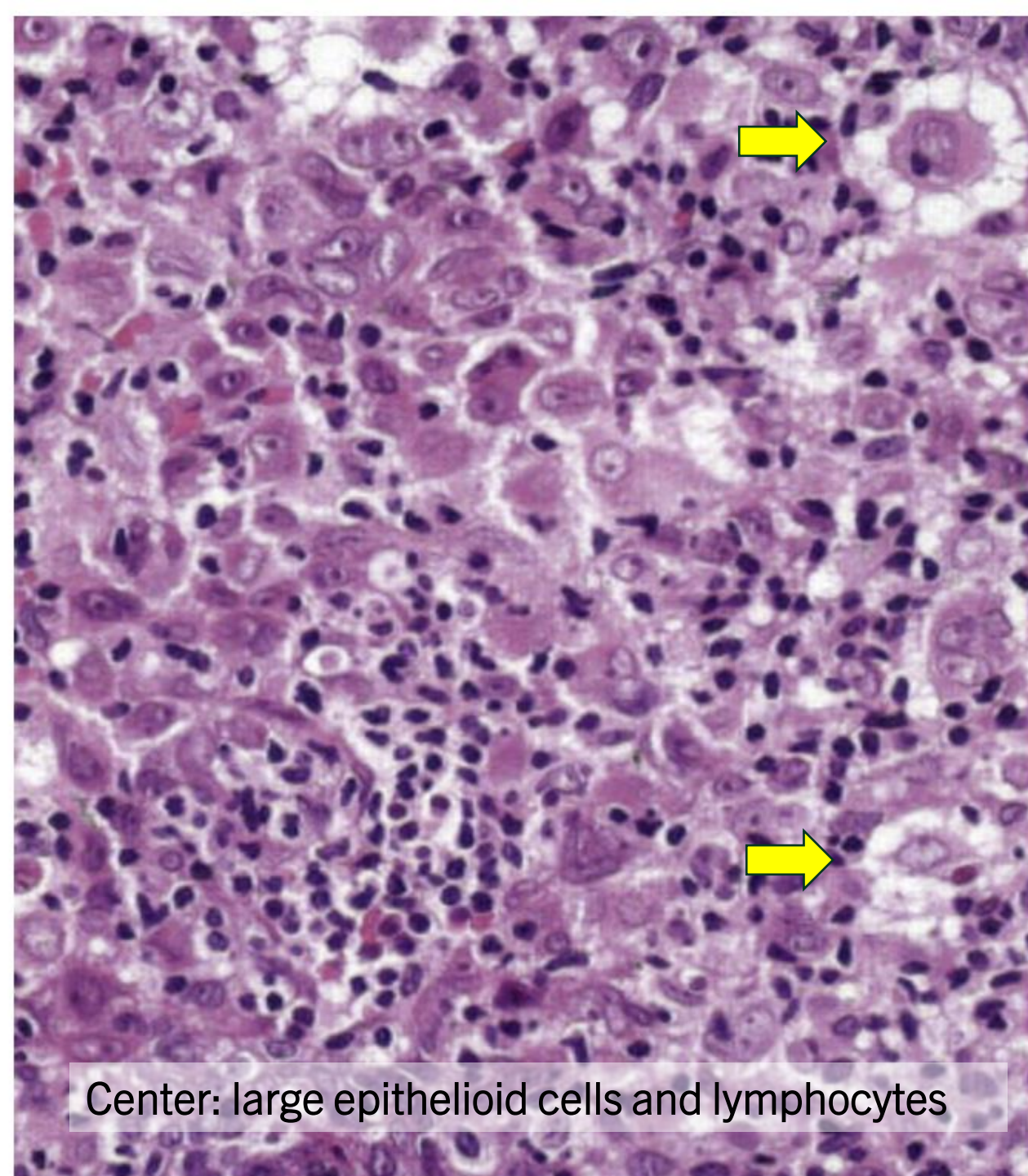
Multiple epithelial nodules  
Pale center  
Embedded within dense fibrous stroma  
Rimmed by epithelial cells





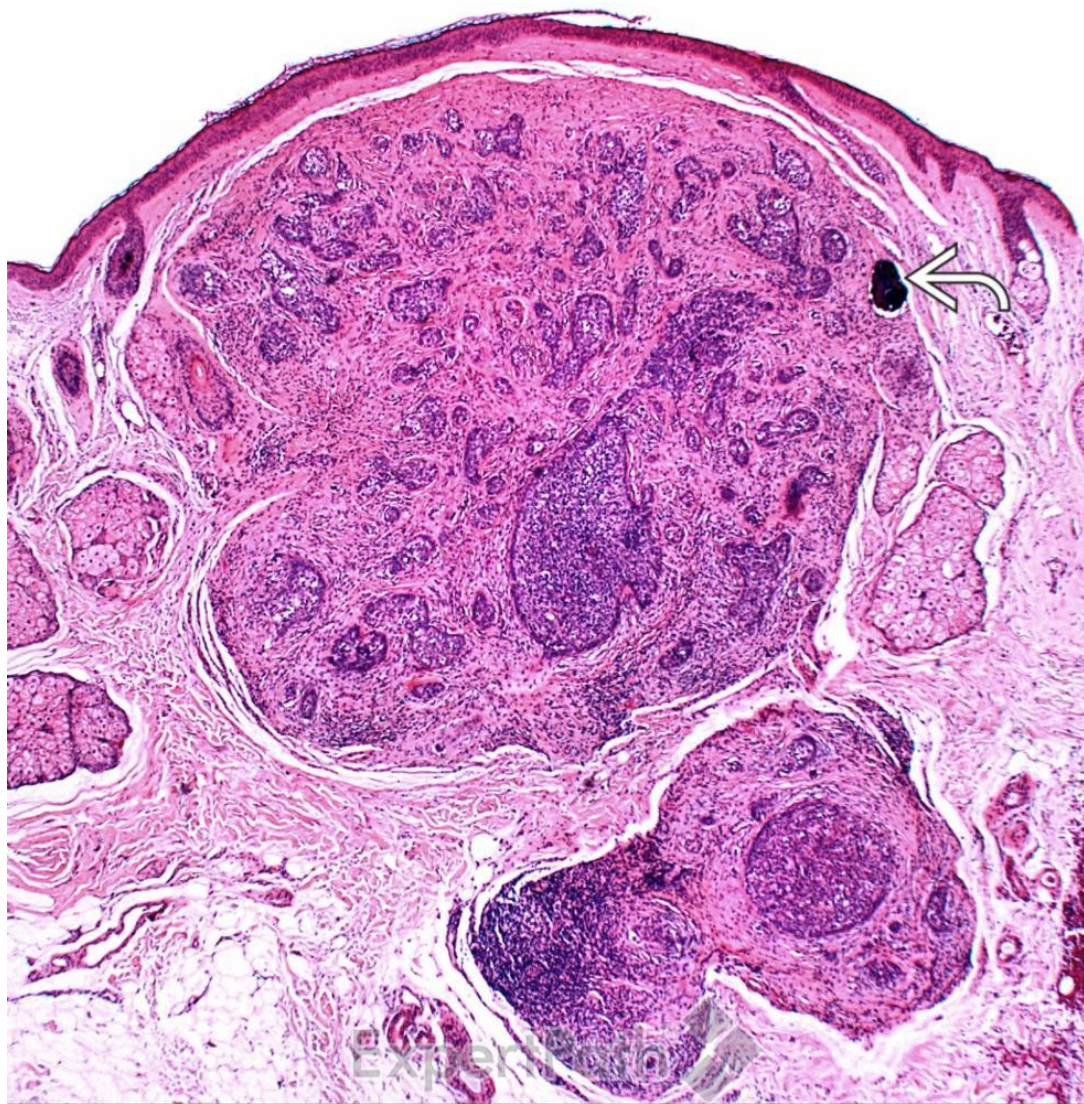
# CUTANEOUS LYMPHADENOMA

- Differentiation: pilosebaceous unit or variant of trichoblastoma
- Papule, nodule on the head, face
- Benign, indolent course
- Epithelial component, rimmed by basaloid cells
  - Small lymphocytes
  - Rare isolated sebaceous cells
  - Small ducts
- Lymphoid follicles in the stroma
- DDX: lymphoepithelial-like carcinoma

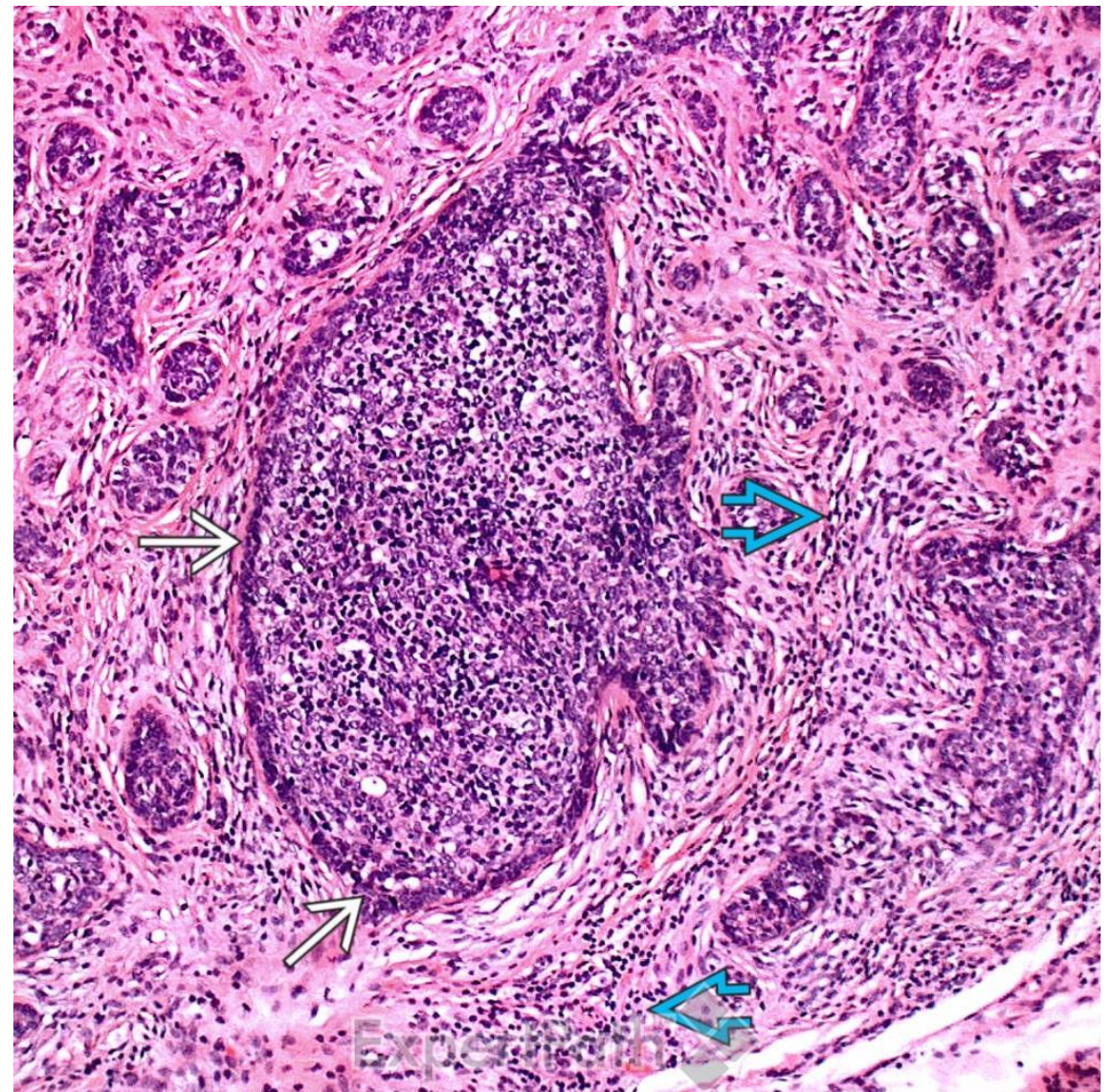


Center: large epithelioid cells and lymphocytes





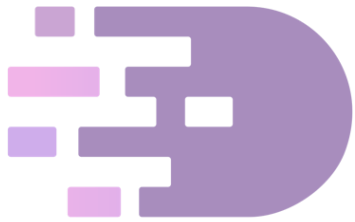
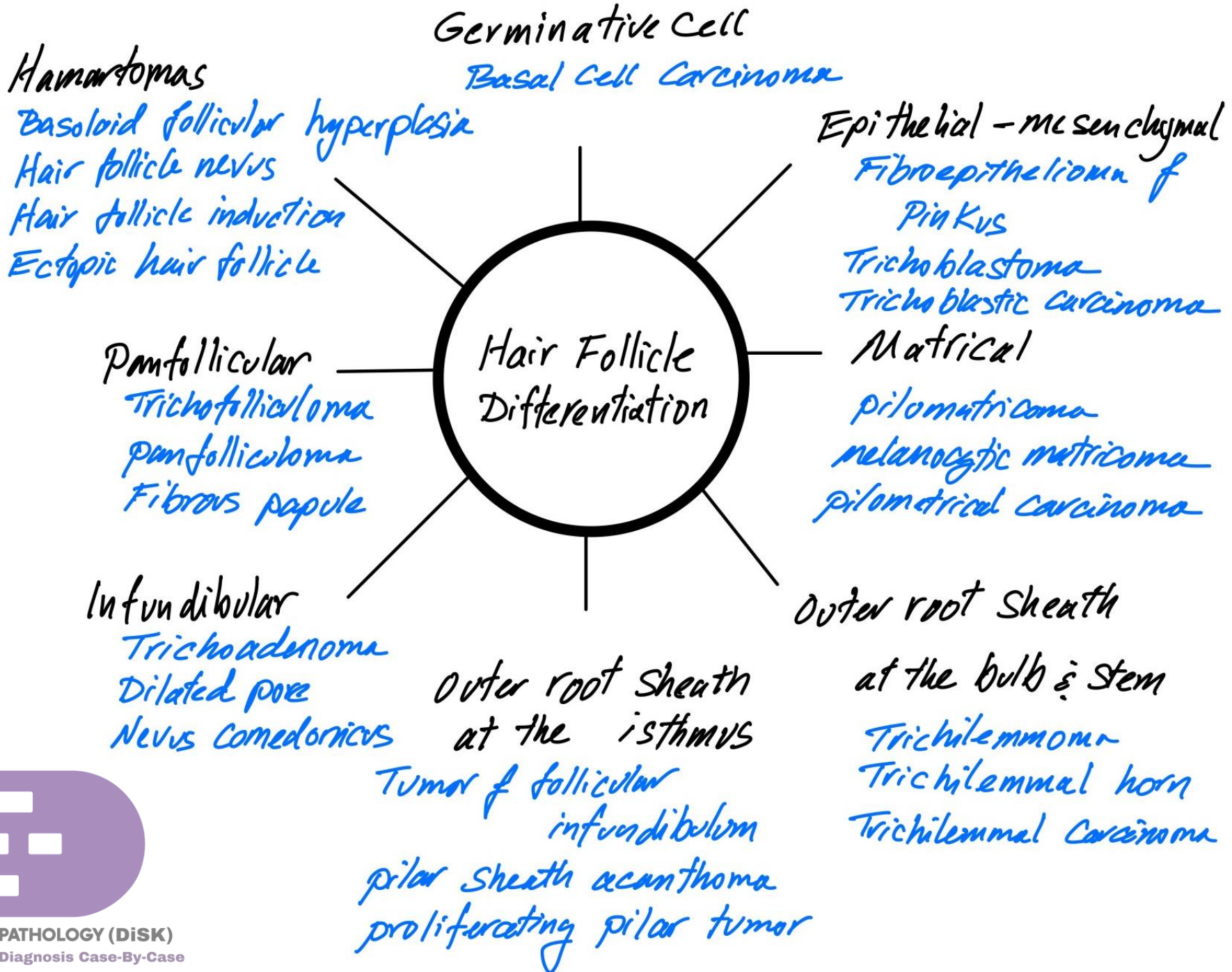
Multinodular tumor in the dermis associated with a prominent fibrotic stroma and focal microcalcifications (white curved arrow).



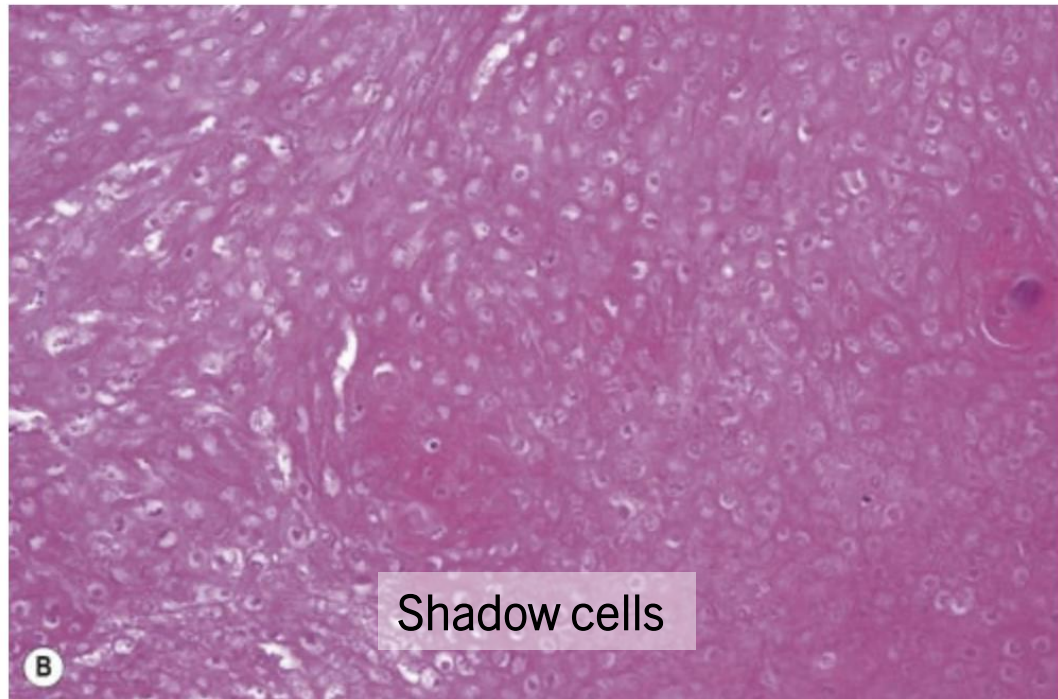
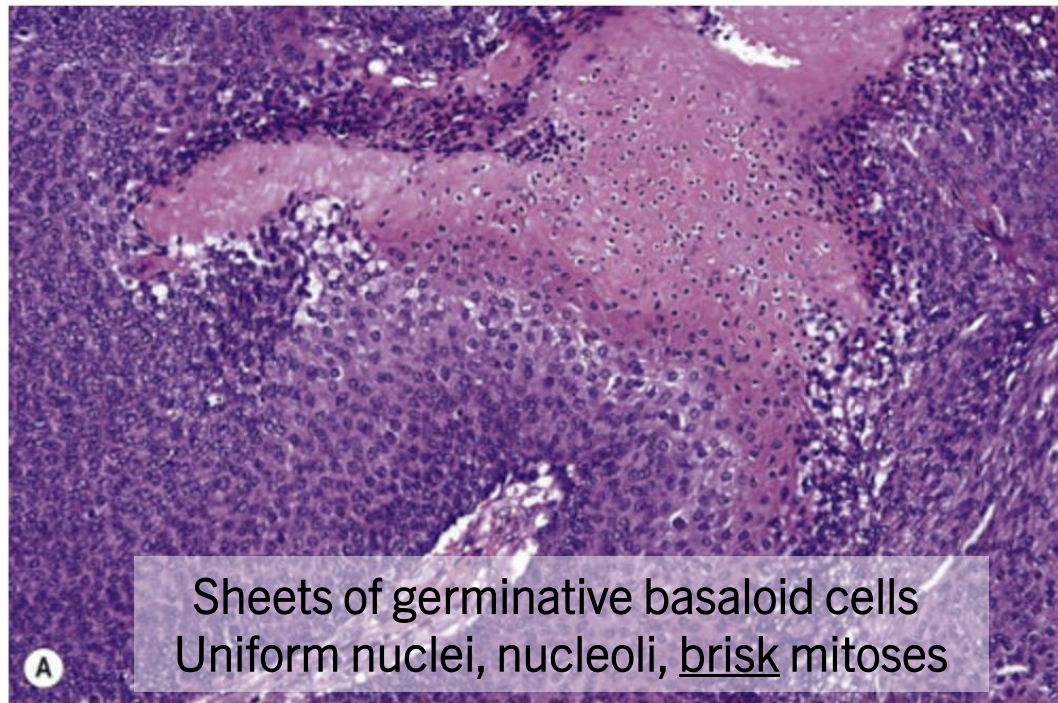
Small lobules and nests of basaloid cells with peripheral palisading (white solid arrow). Note the associated cellular fibrotic stroma with chronic inflammation (cyan open arrow). Although the palisading can mimic BCC, the lymphoid infiltrate and stroma are typical of TB.



# Outline: Neoplasms with follicular differentiation





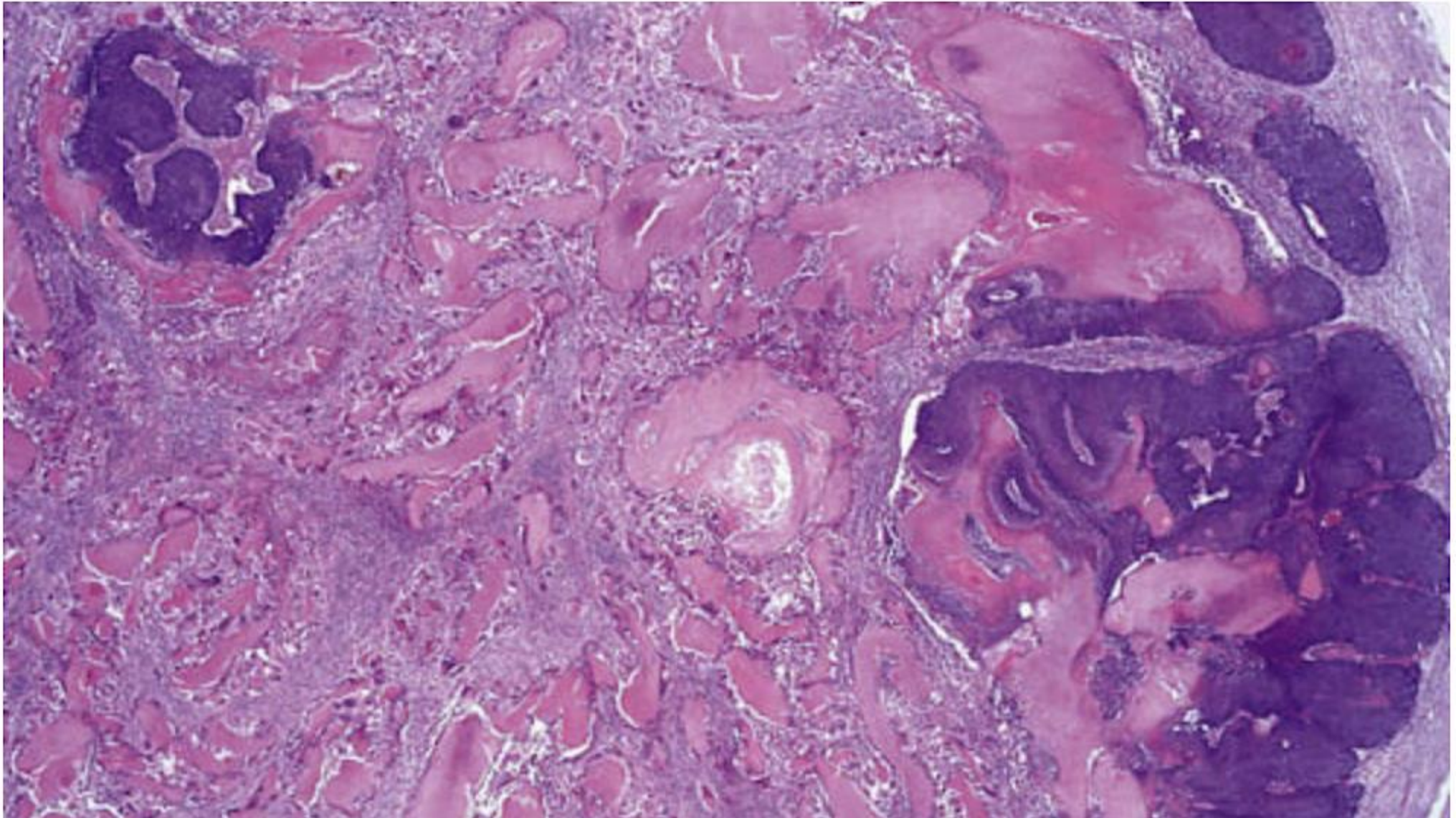


## PILOMATRICOMA

- Differentiation toward the hair matrix
- Solitary or multiple (AD disorder)
- Rare: dermatological marker of myotonic dystrophy, Gardner syndrome, MYH-associated polyposis
- Head, upper limbs, neck, trunk, and lower limbs
- Large chalky deposits especially in young children
- Beta-catenin mutations
- IHC: shadow cells BMP-2+



May resemble necrosis or ruptured cyst



Biphasic, mixed eosinophilic and basophilic tumor lobules



# MALIGNANT PILAR TUMOR (CARCINOMA)

- DDX: SCC



Pilar tumor

This histological section shows a malignant pilar tumor. The upper portion of the image displays a pilar tumor component, characterized by large, keratin-filled cysts with a thick, eosinophilic wall. Below this, there is an infiltrating carcinomatous component, which consists of nests and cords of atypical epithelial cells with hyperchromatic nuclei and increased mitotic activity, invading the surrounding stroma.

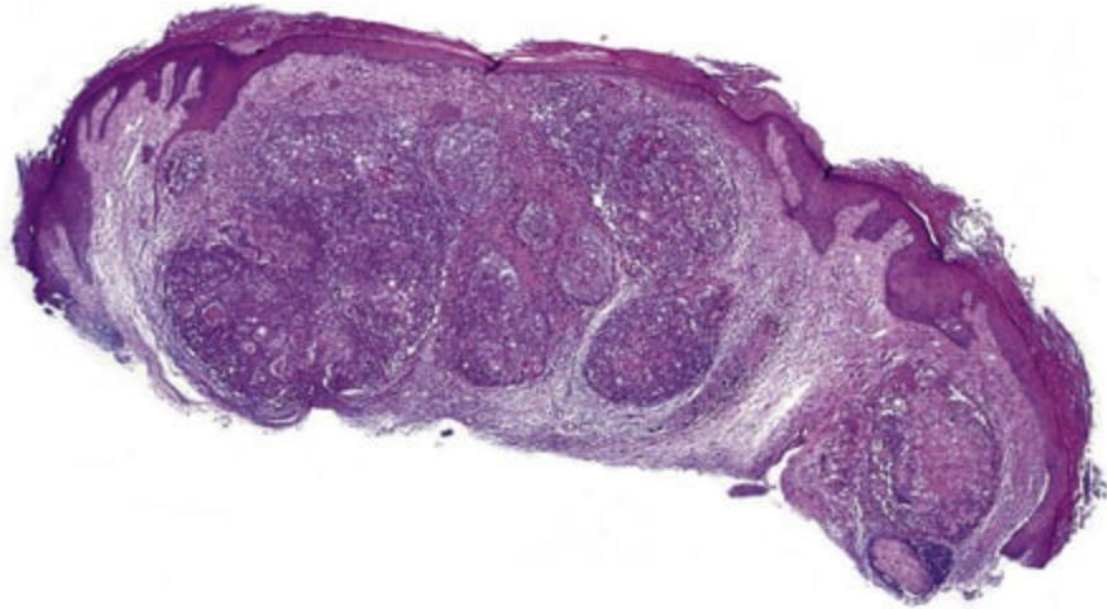
Infiltrating carcinomatous component



Jagged infiltrating edges

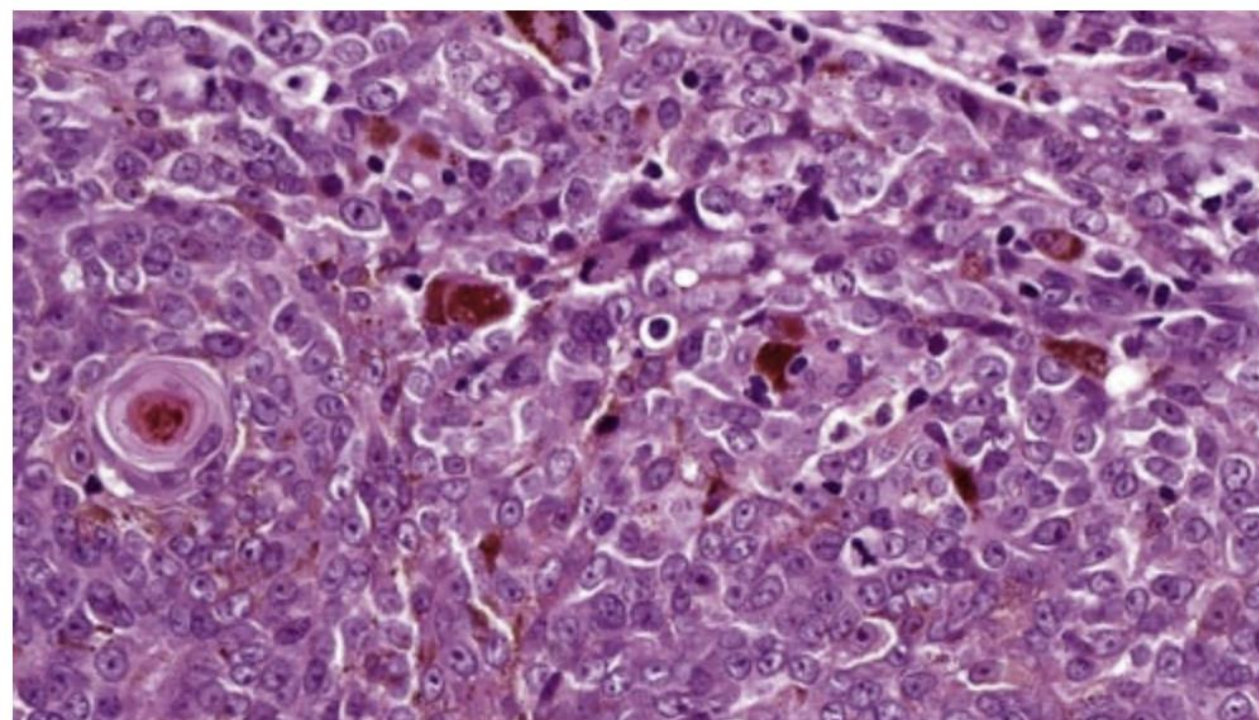
This higher magnification histological section focuses on the interface between the tumor and the surrounding tissue. It clearly shows the jagged, infiltrating edges of the malignant tumor, where the tumor cells are invading the adjacent stroma in an irregular, finger-like pattern. The tumor cells exhibit significant nuclear atypia and are arranged in disorganized nests and cords.





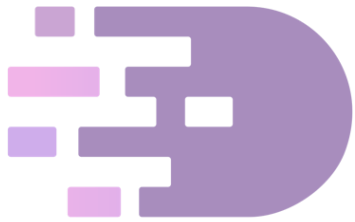
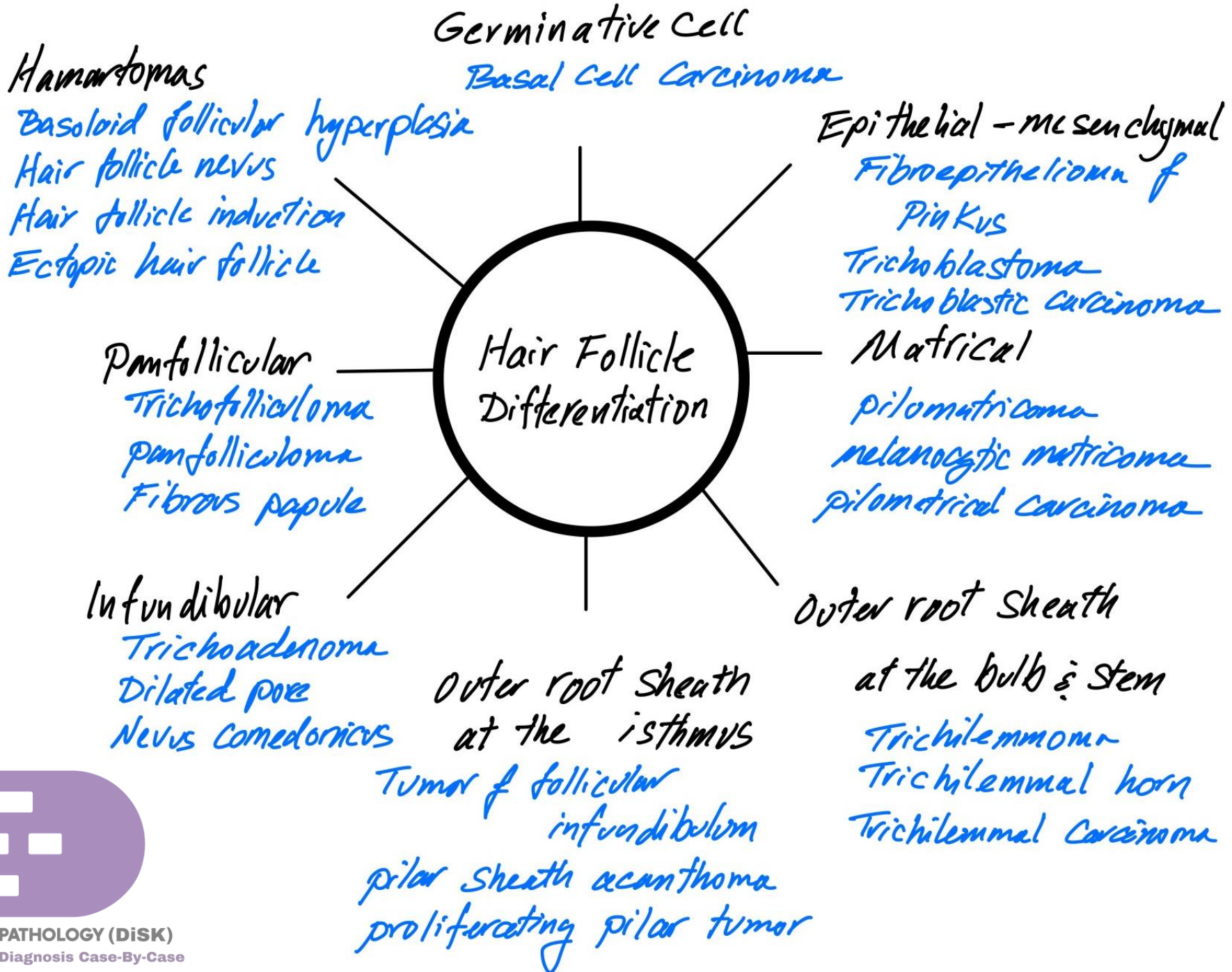
## MELANOCYTTIC MATRICOMA

- Sun-damaged skin, elderly
- Nose, preauricular, chest, back, hand, and forearm
- Clinical DDX: pigmented BCC, hemangioma, melanoma
- Dermal solid nests and lobules
- Basaloid cells with scant cytoplasm and prominent nucleoli
- Mitoses
- IHC: matrical cells Keratin+  
Dendritic cells HMB-45+





# Outline: Neoplasms with follicular differentiation





Warty silhouette

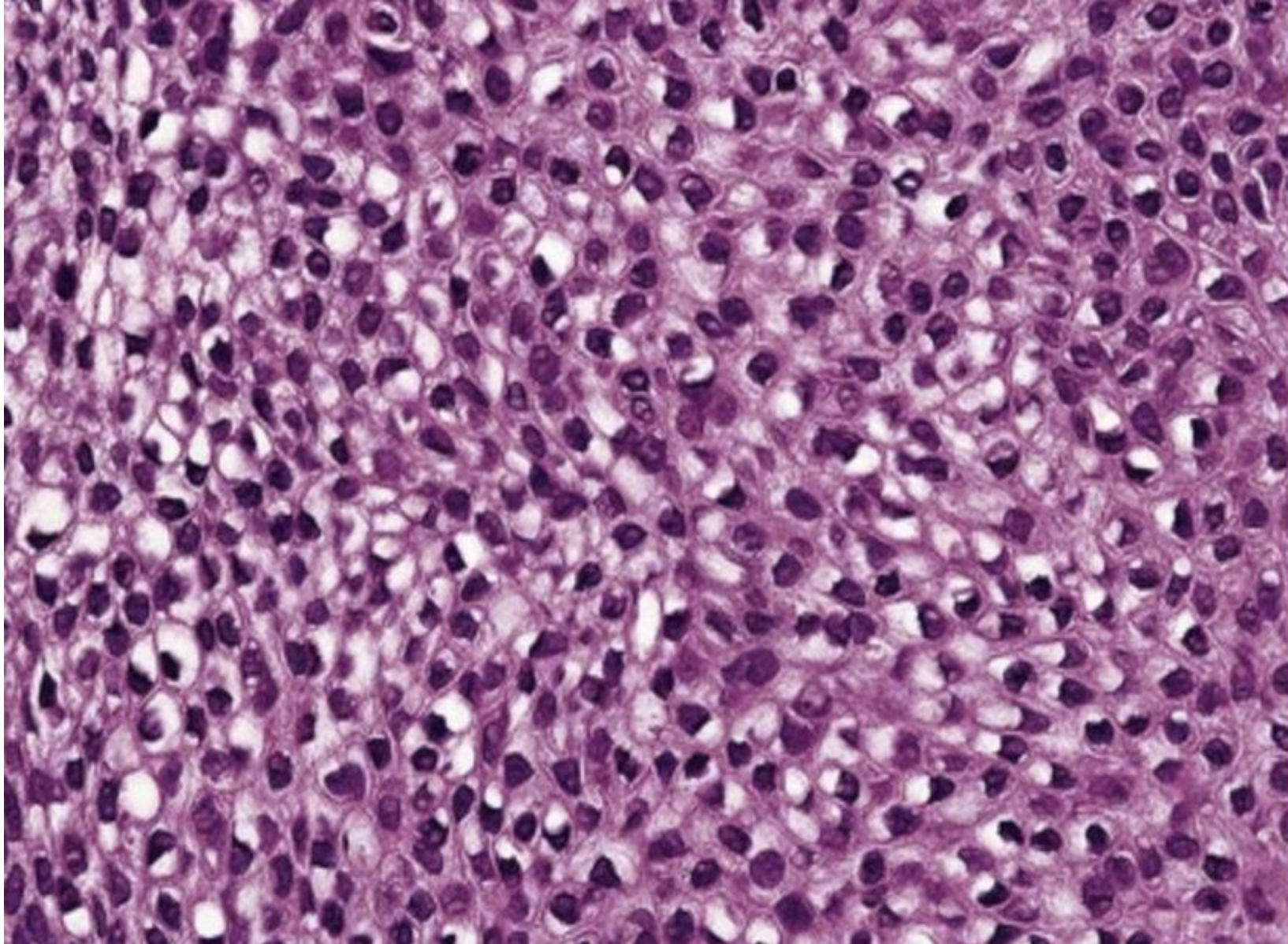


Cutaneous horn

## TRICHILEMMOMA

- Solitary (sporadic) or multiple (familial)
- Cowden disease
- Resembles follicular outer root sheath
- Trichilemmal keratinization: no keratohyalin granules (epidermal keratinization)
- Solid lobular growth
- Well-defined round smooth borders
- DDX: inverted follicular keratosis, verruca





## TRICHILEMMOMA: CYTOPATHOLOGY

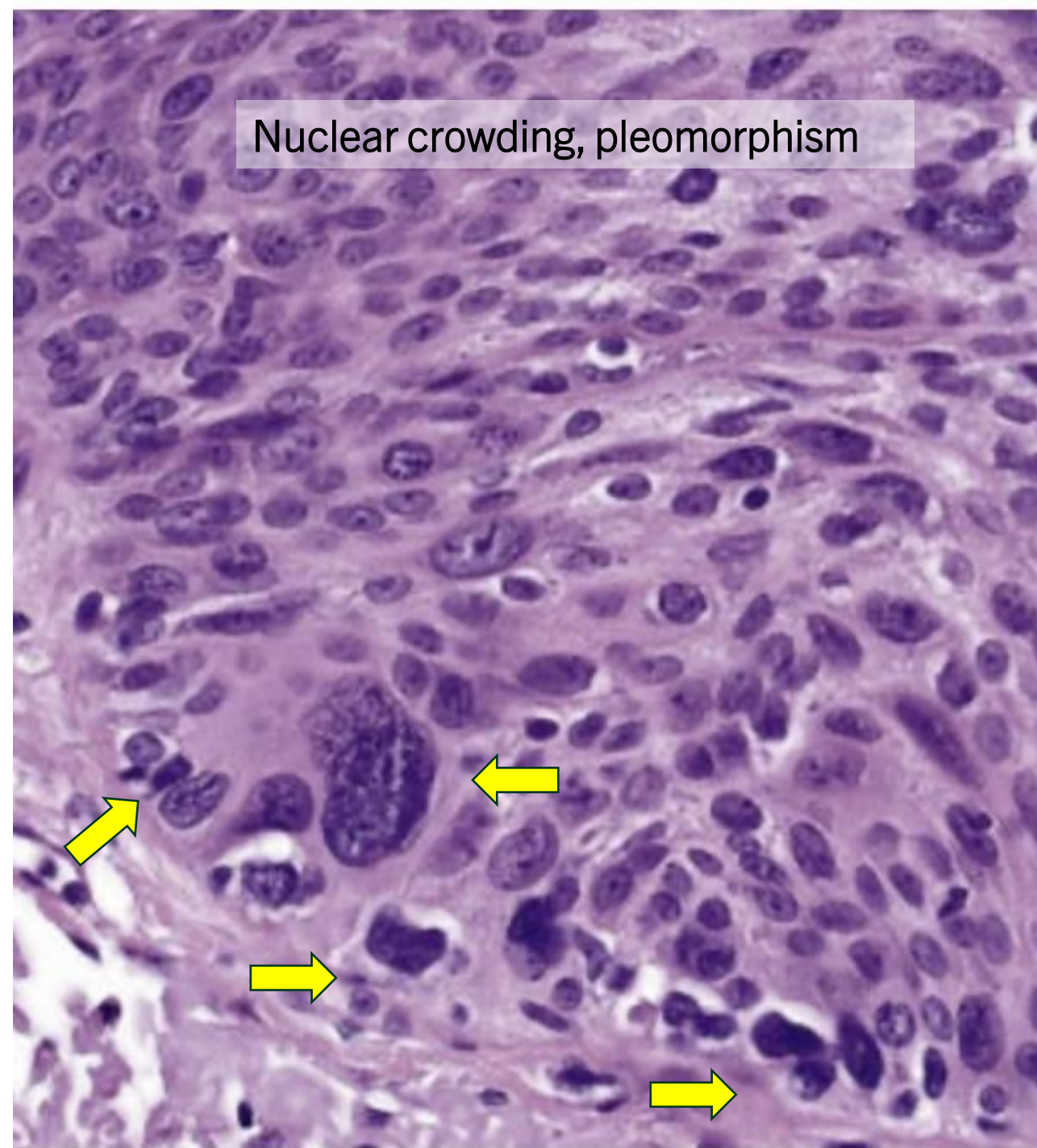
Small, uniform  
keratinocytes

Round vesicular nuclei  
Cytoplasmic vacuolation  
Cytoplasmic glycogen



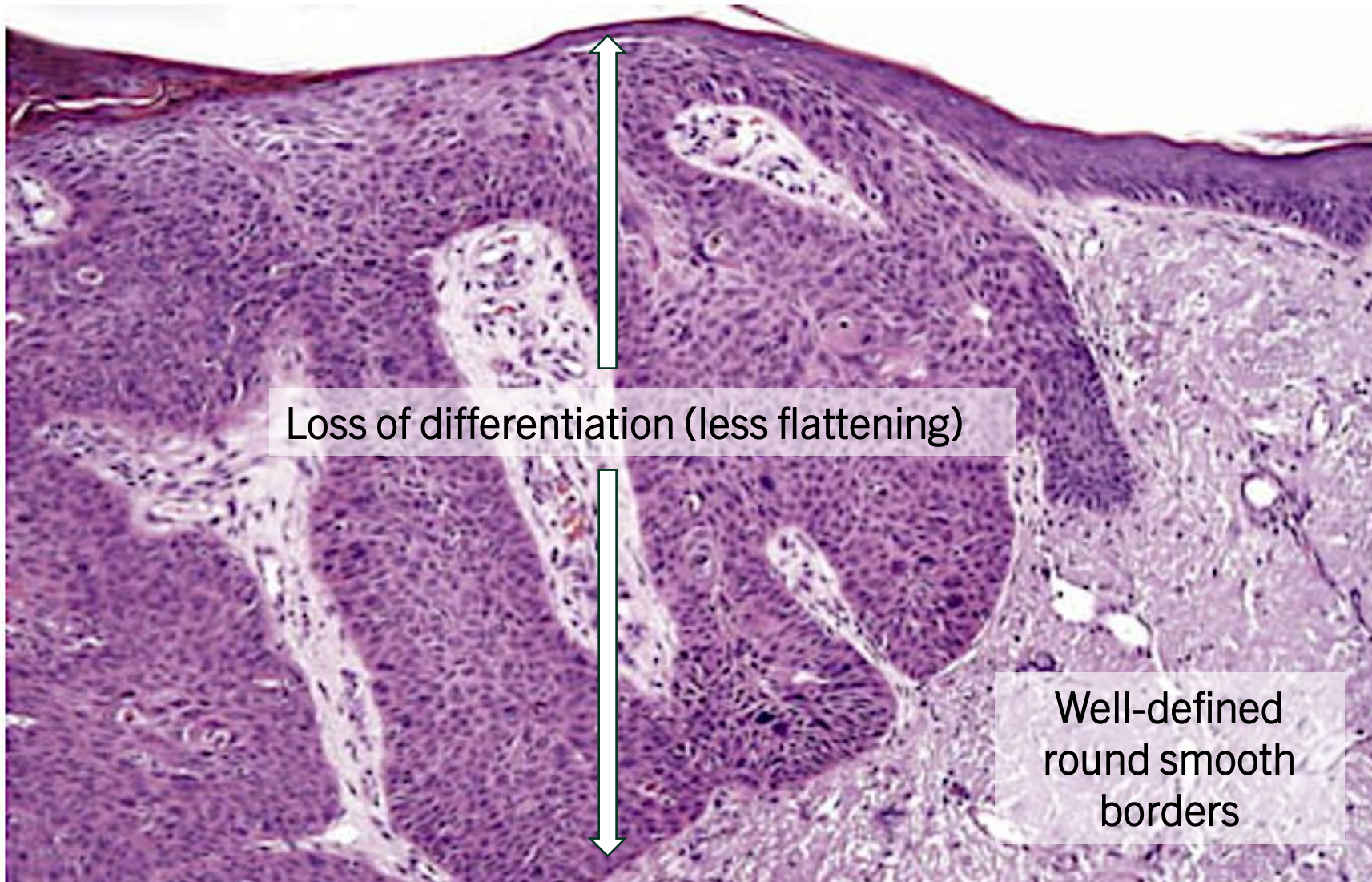
# TRICHILEMMAL CARCINOMA

- Sun-exposed skin, elderly
- Face, scalp, neck, dorsal hand
- Despite malignant histopathology have indolent clinical course
- May invade deep into the subcutis
- Invasion: bushing border vs. infiltrating
- Absent granular cell layer
- IHC: CEA-, EMA-
- DDX: moderately differentiated clear cell SCC, porocarcinoma, or hidradenocarcinoma (ductal differentiation)





# TRICHILEMMAL CARCINOMA: HISTOPATHOLOGY



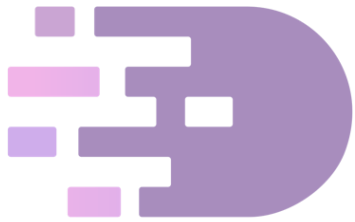
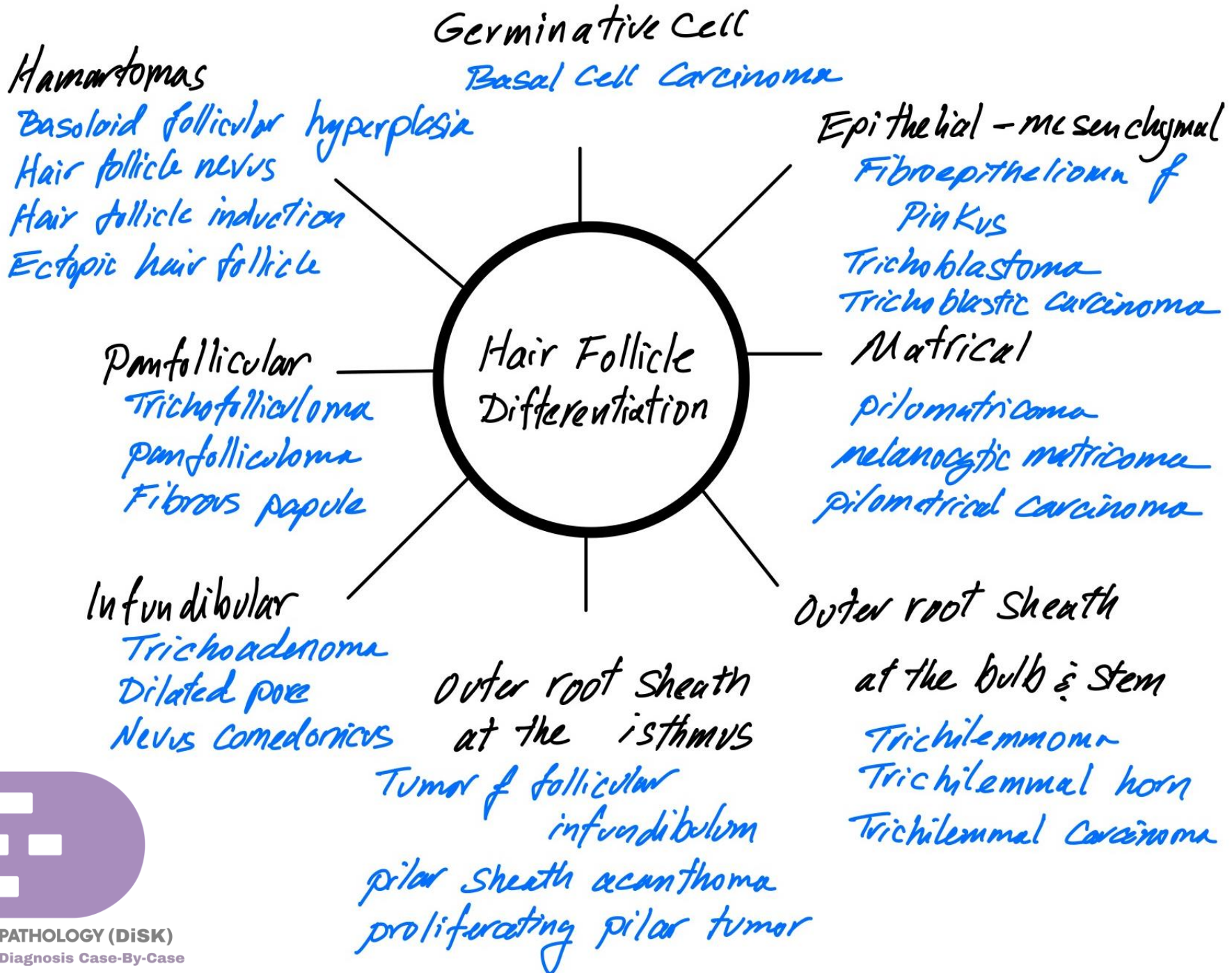
Loss of differentiation (less flattening)

Well-defined  
round smooth  
borders

Nuclear features:  
Hyperchromatic nuclei  
Mitoses

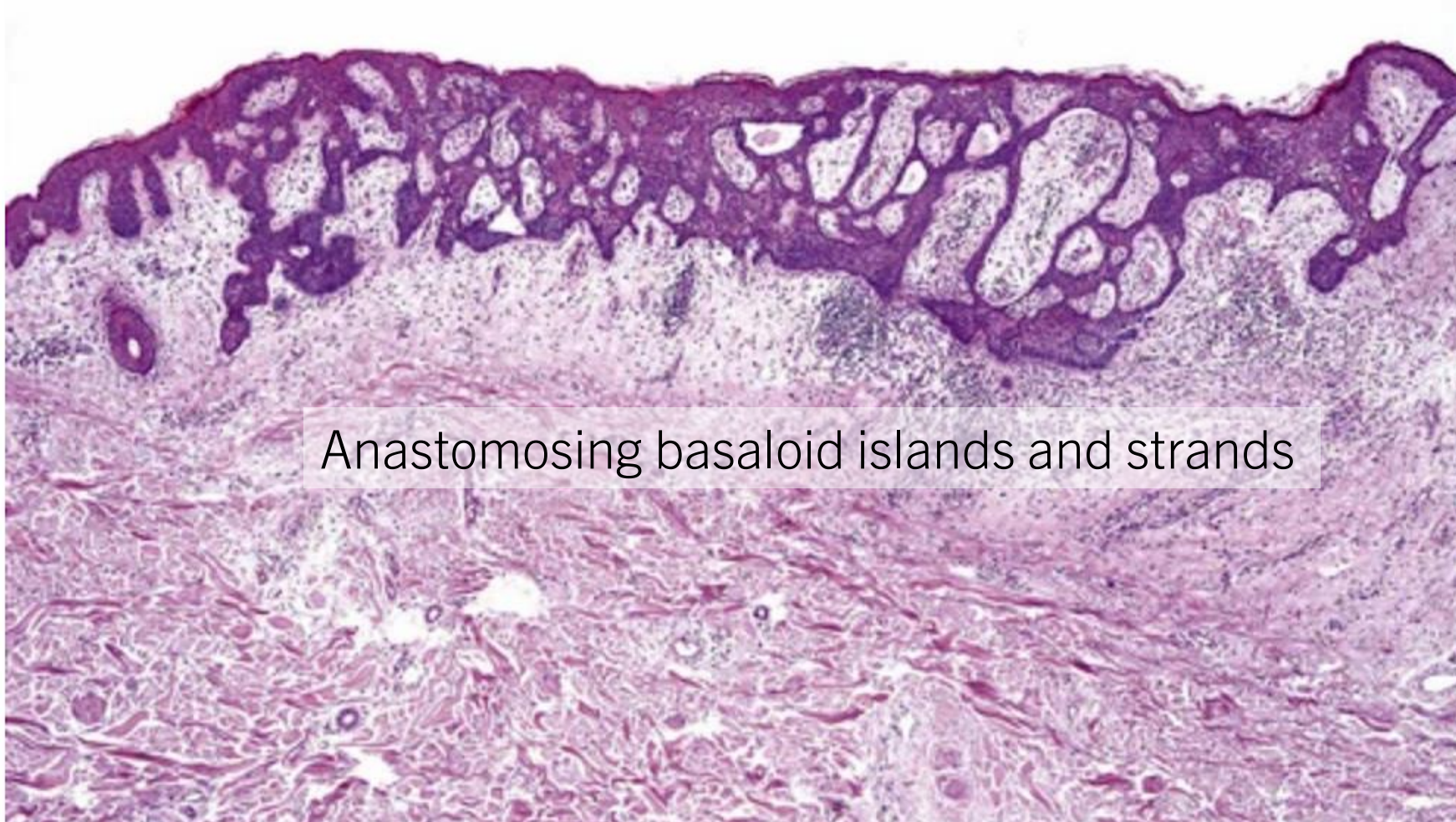


# Outline: Neoplasms with follicular differentiation





# TUMOR OF FOLLICULAR INFUNDIBULUM



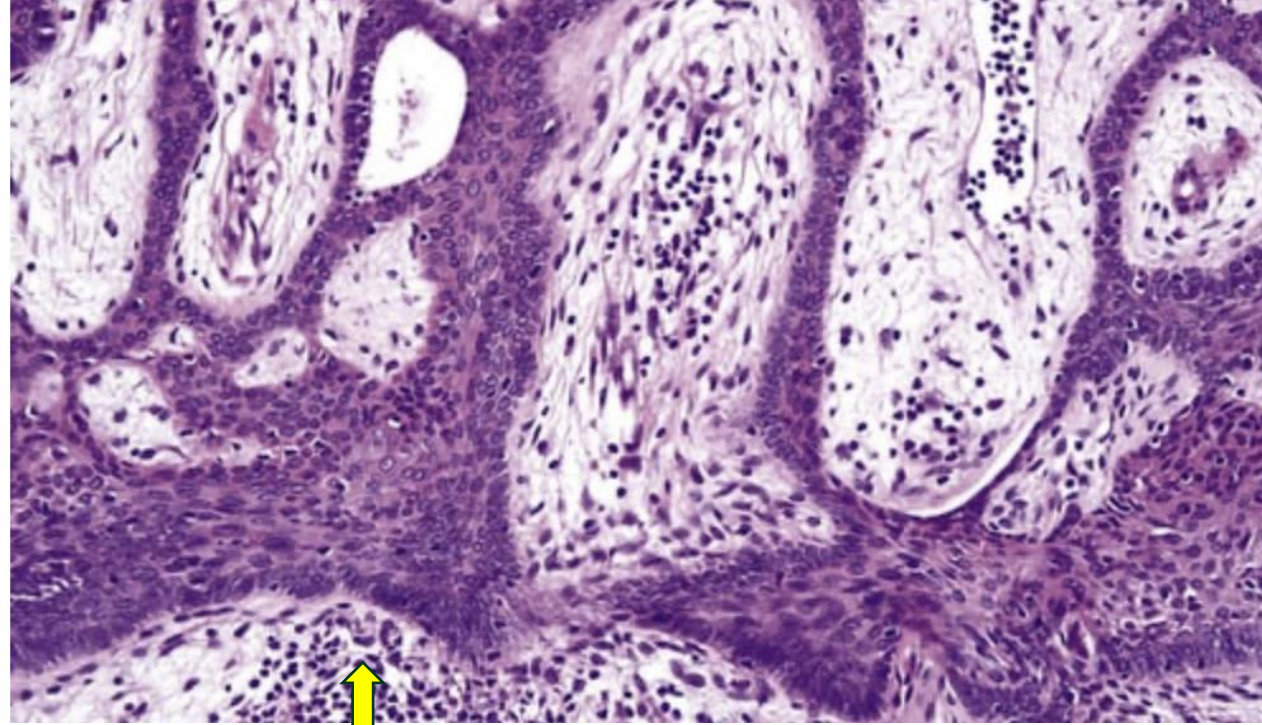
Anastomosing basaloid islands and strands

Forms an epidermal plaque, parallel to the surface



# TUMOR OF FOLLICULAR INFUNDIBULUM

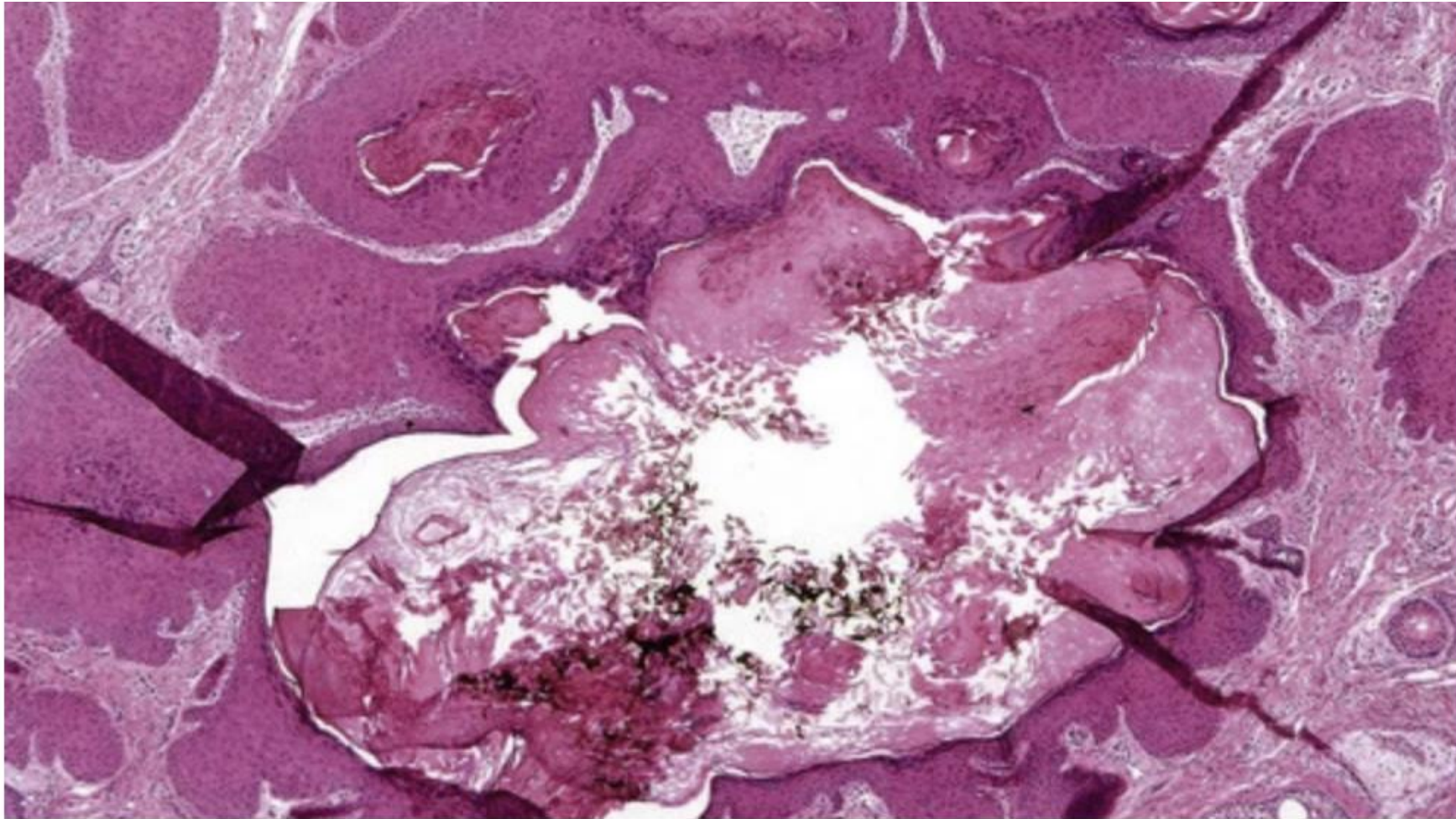
- Solitary lesion on the head and neck
- Maybe associated with Cowden disease
- Point of attachment of vellus hairs via follicular external root sheath
- IHC: intratumoral Merkel cells CK20+; tumor cells Ber-EP4-



Peripheral nuclear palisading



# PILAR SHEATH ACANTHOMA



Lobular benign epithelial proliferation  
Cystic invagination, arising from the epidermis



# PILAR SHEATH ACANTHOMA

- On the lip with central pore, containing keratinous debris
- Can extend deep, involving the subcutaneous fat and skeletal muscle (not malignant)
- PAS+ hyaline sheath encircles the lobules

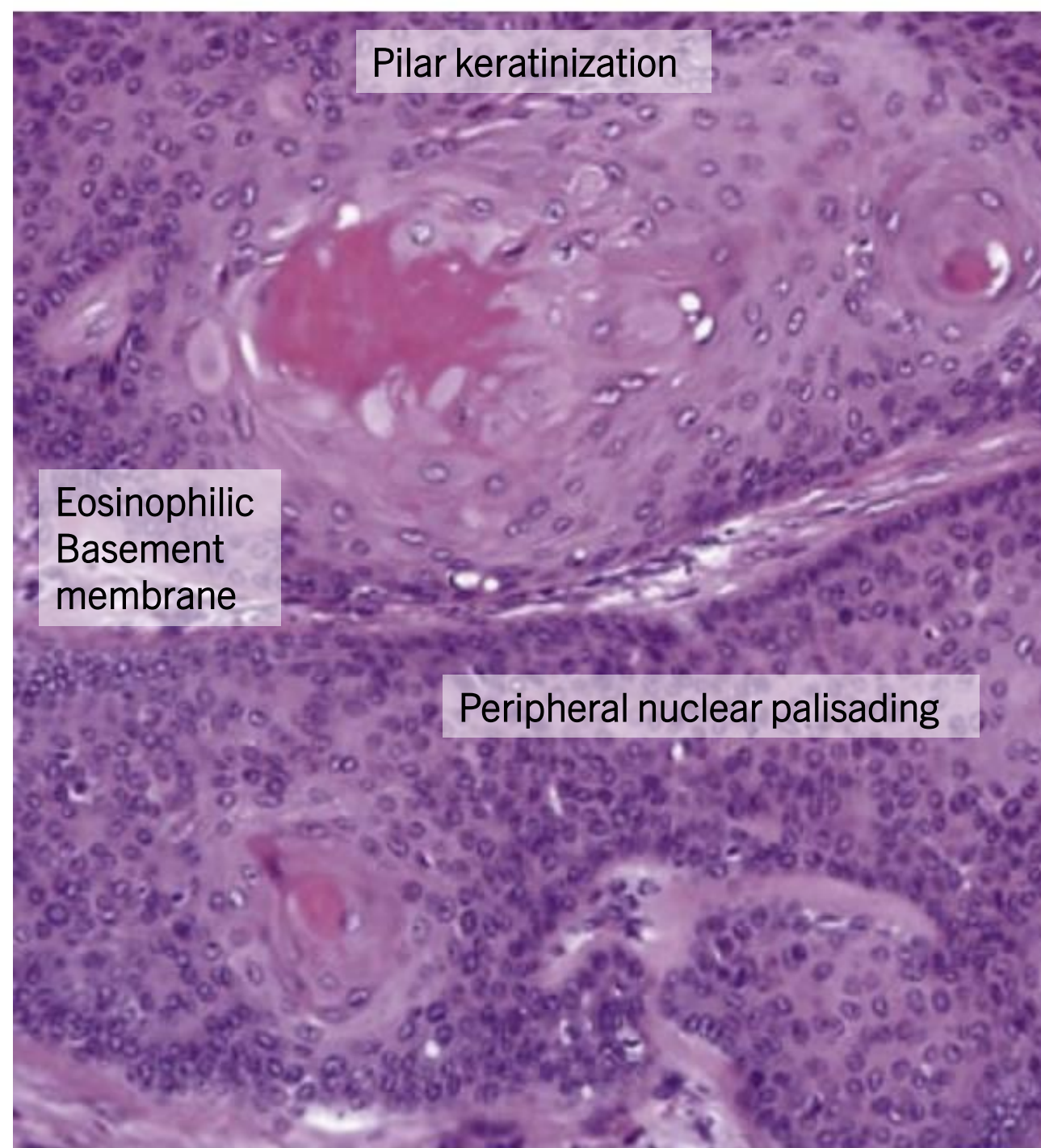


Lobules resemble outer root sheath squamous epithelium



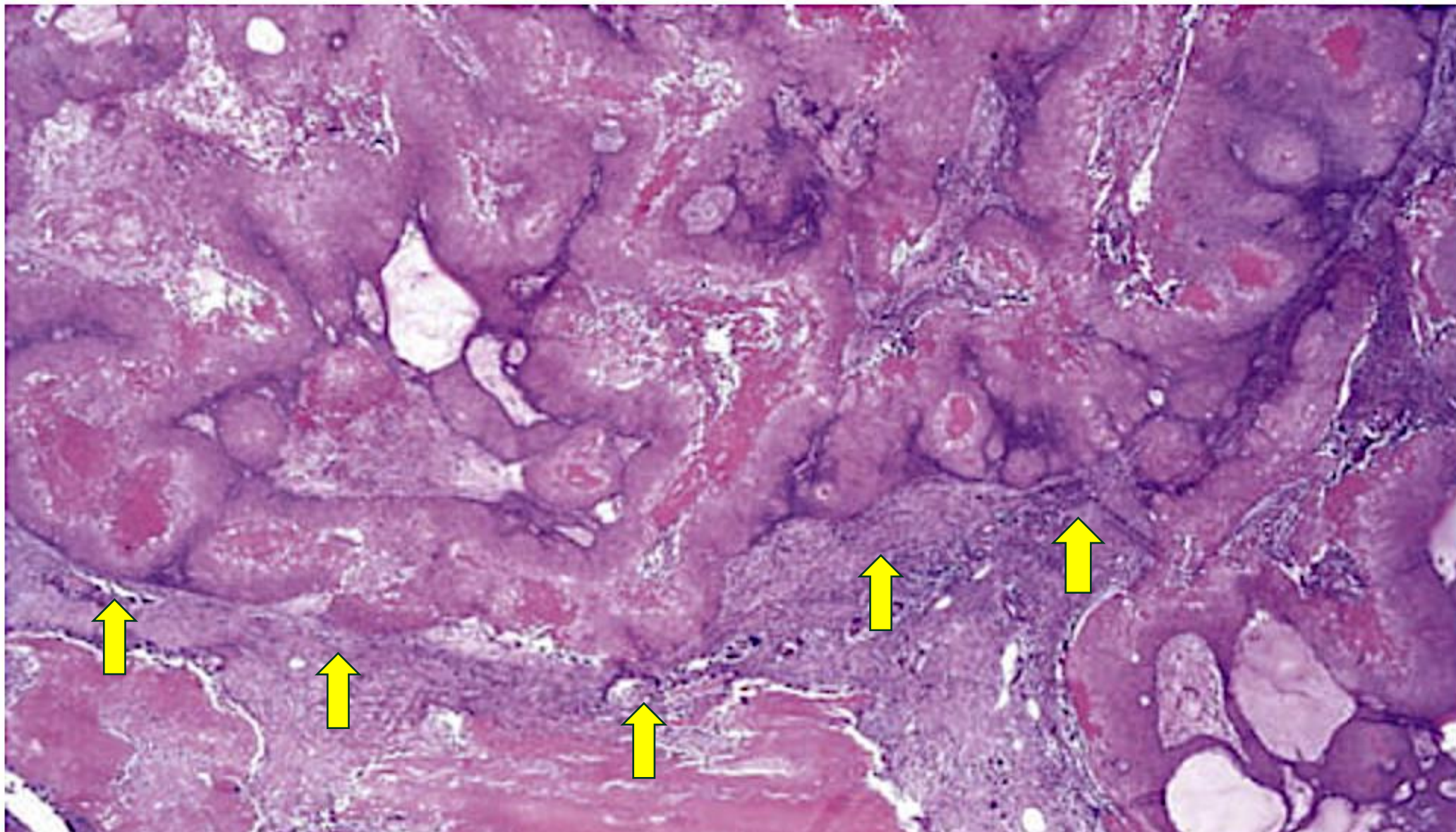
# PROLIFERATING TRICHILEMMAL (PILAR) CYST/TUMOR

- External root sheath derivation
- Develops within the wall of pre-existent pilar cyst
- Scalp, trunk, nose, eyelid, vulva, and rarely the extremities
- Mostly females, large solitary, slowly, growing tumor
- May extend into the subcutis or bone
- Recurrences uncommon
- Local destruction, metastasis to regional lymph nodes, rare
- DDX: cystic SCC





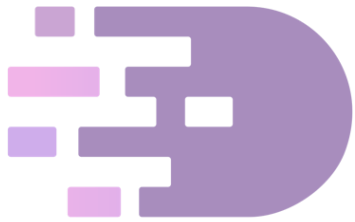
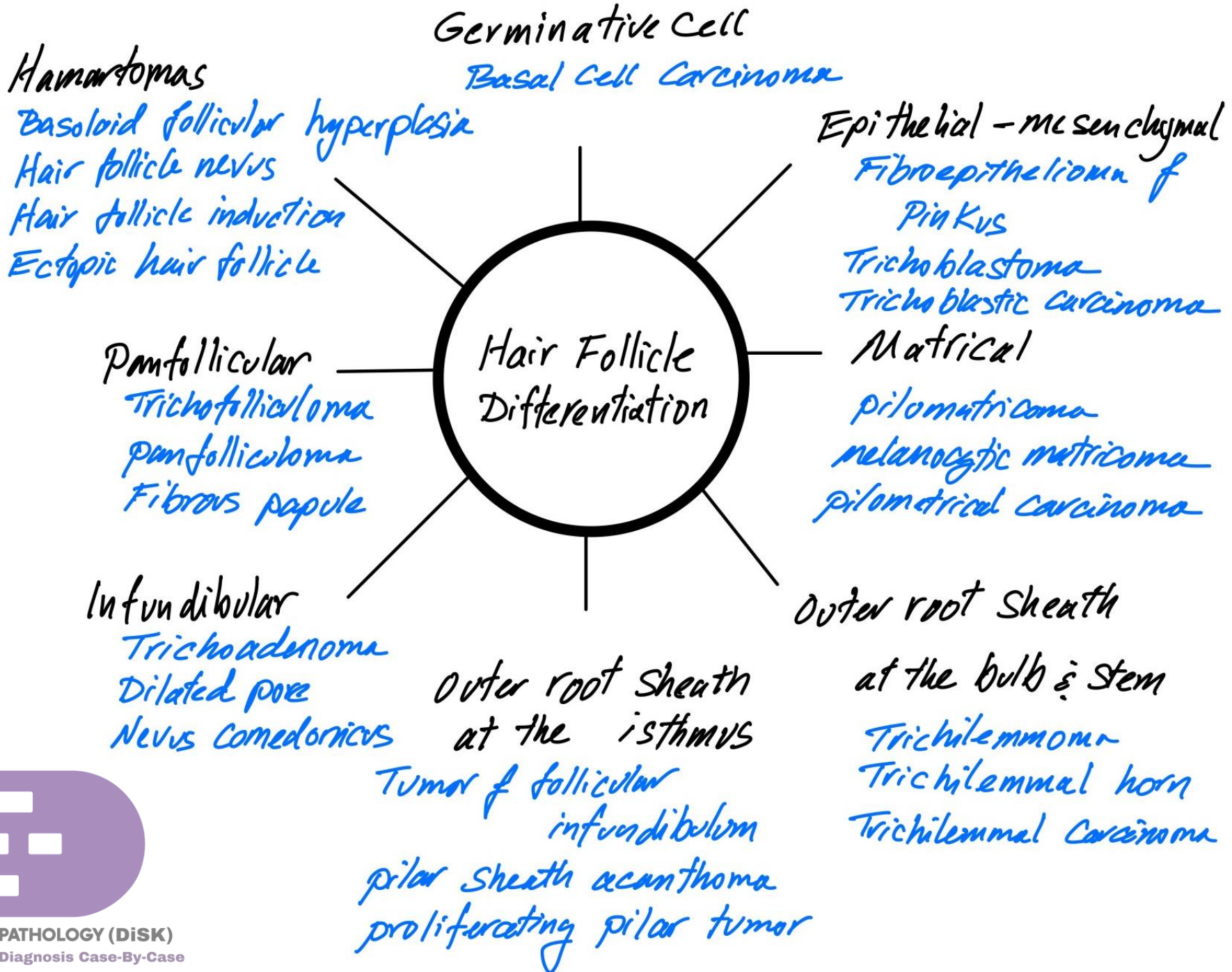
# Multiple lobules of squamous epithelium growing in complex pattern



Pushing, non-infiltrating margin/edge



# Outline: Neoplasms with follicular differentiation







Cystically dilated  
Hair follicle

Keratin plug



Epithelial cyst lining: irregular budding

## DILATED PORE (WINER)

- Large comedone on face or neck
- May extend into subcutaneous adipose tissue
- The cyst wall may contain villus hairs and sebaceous glands

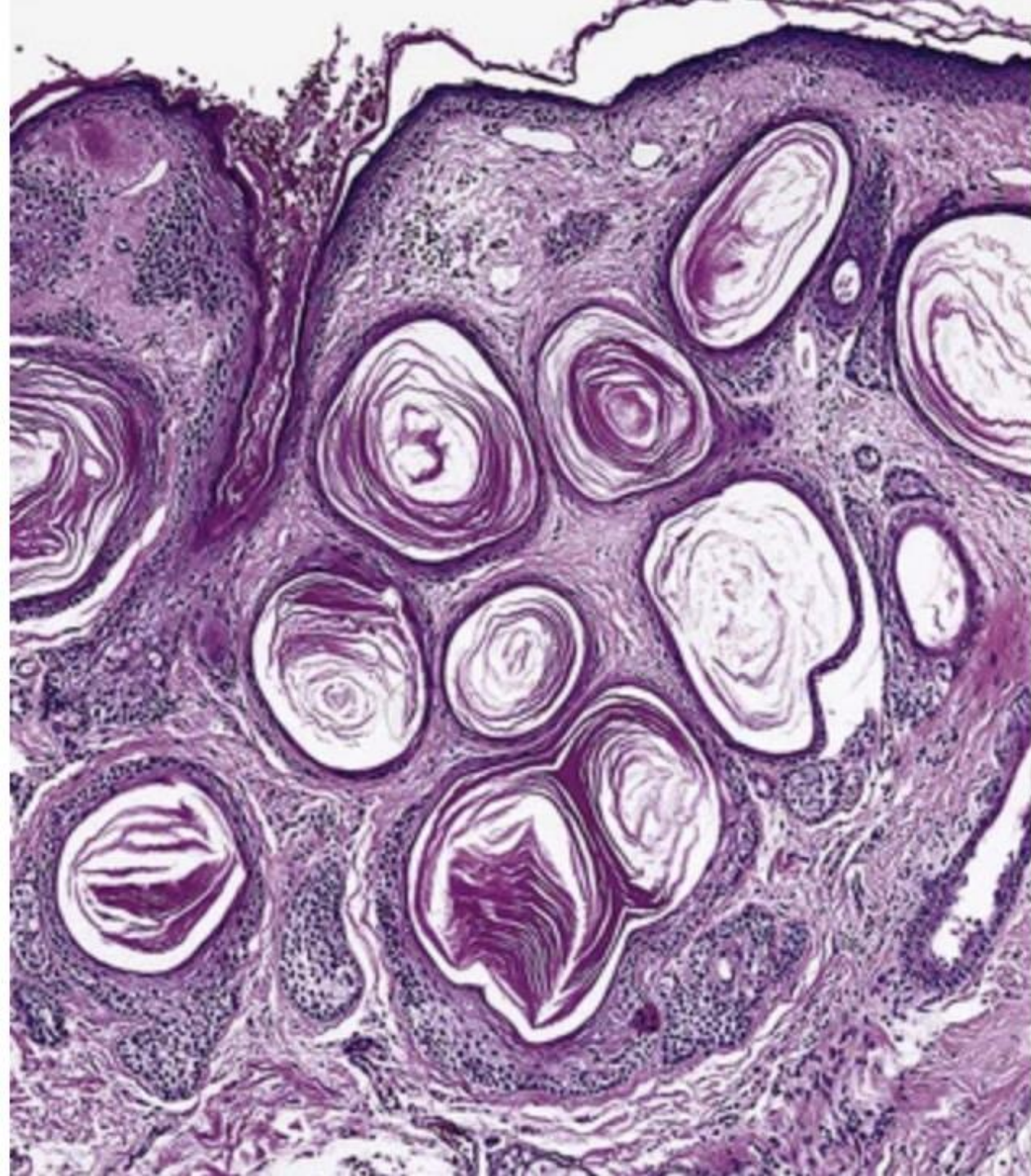


# TRICHOADENOMA

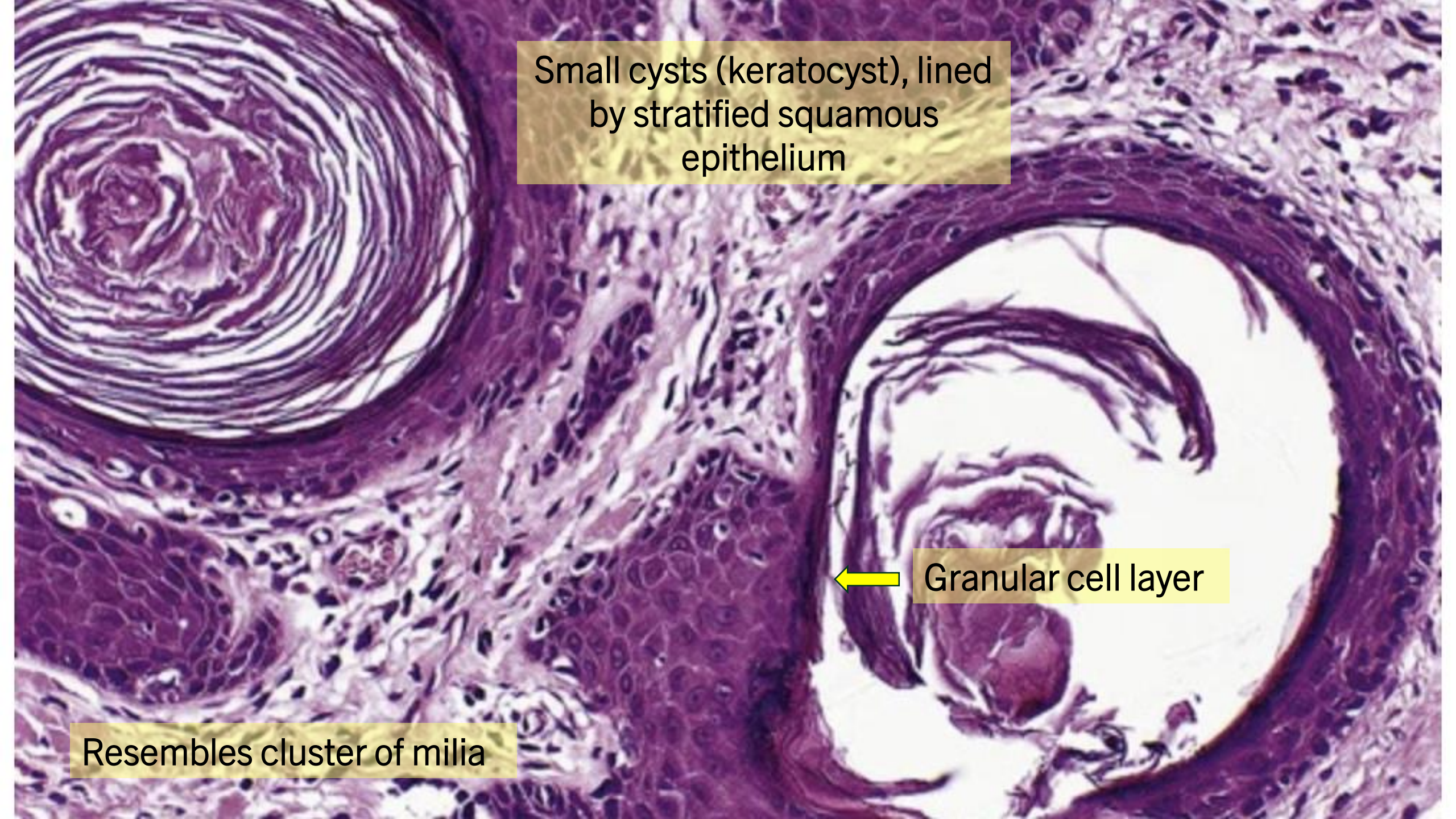
- Located on the face >> buttocks
- Yellow or erythematous nodules
- Differentiation toward the infundibular portion of hair follicle

Trichoepithelioma -> Trichoadenoma -> Trichofolliculoma

- Epidermal keratinization
- No hair follicle formation
- IHC: intratumoral Merkel cells CK20+  
tumor cells Ber-EP4-







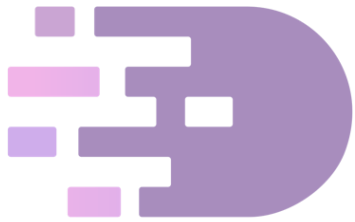
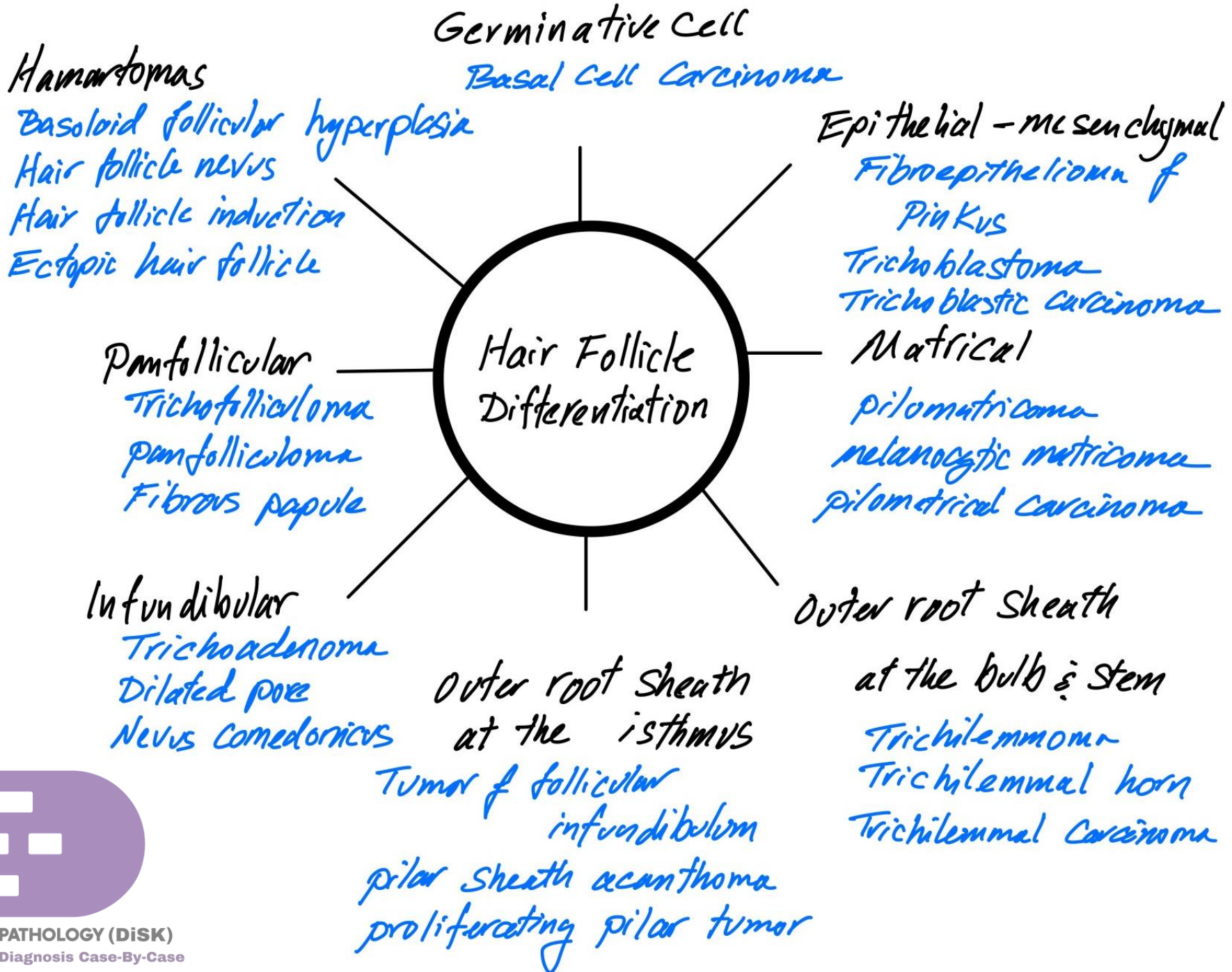
Small cysts (keratocyst), lined by stratified squamous epithelium

← Granular cell layer

Resembles cluster of milia



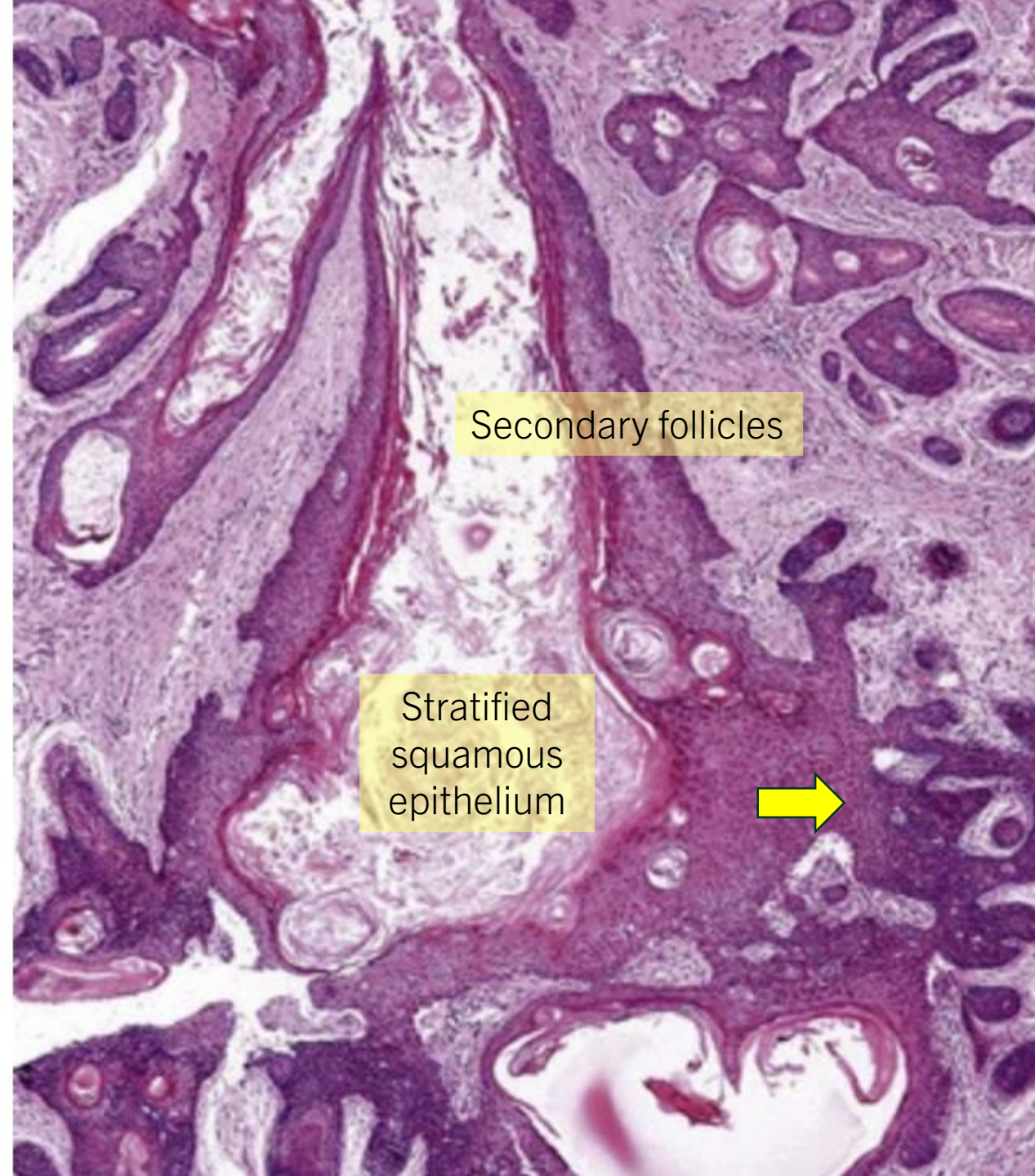
# Outline: Neoplasms with follicular differentiation





# TRICHOFOLLICULOMA

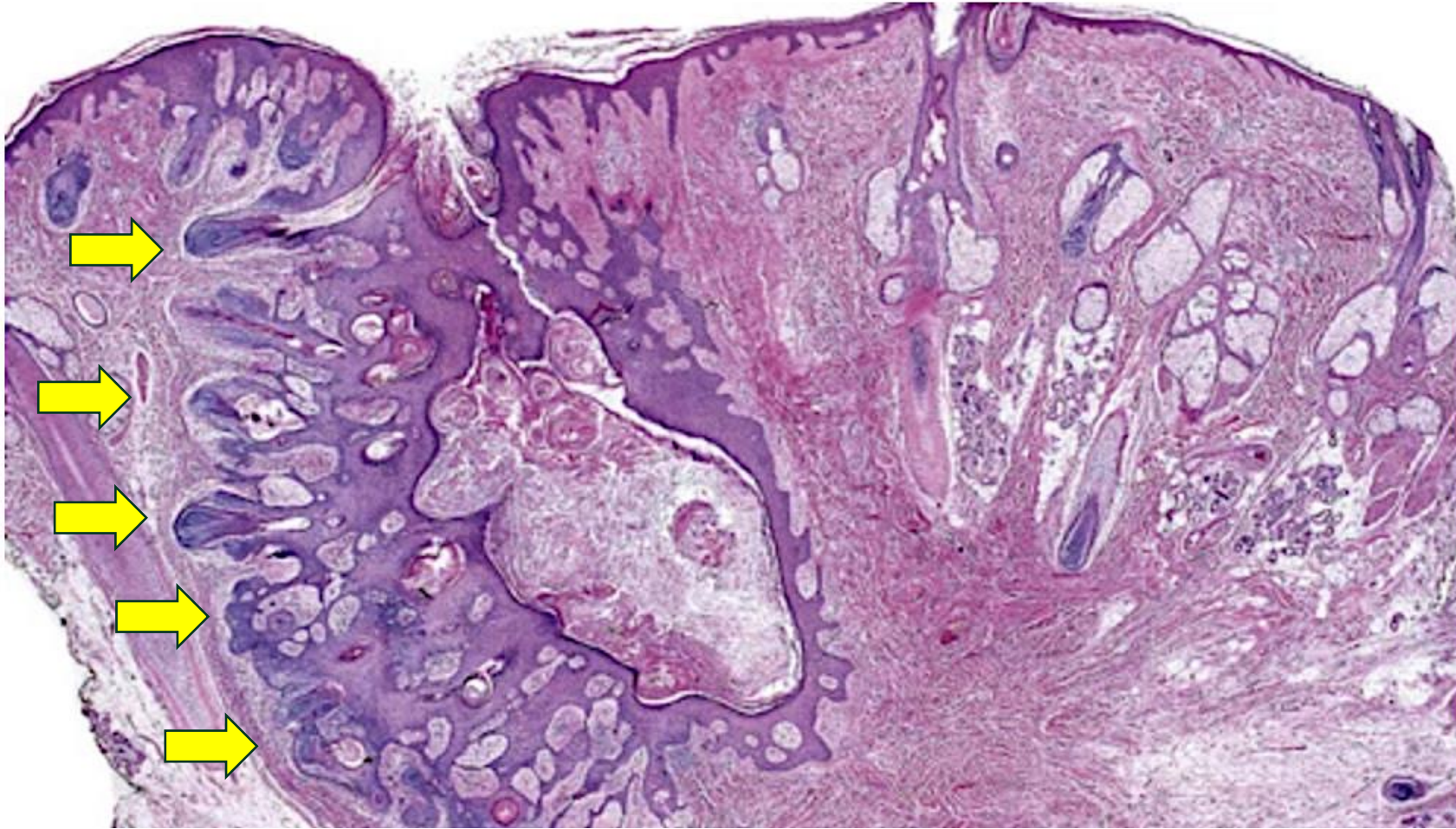
- Single dome-shaped papule on the face, scalp, or neck
- Silky thread-like hairs emanating from the central follicle
- Secondary hair follicles show abortive pilar differentiation
- Fibrous stroma: perifollicular sheath
- Similar to folliculosebaceous cystic hamartoma





# TRICHOFOLLICULOMA

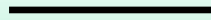
Secondary  
follicles  
geminate  
from the  
lateral wall



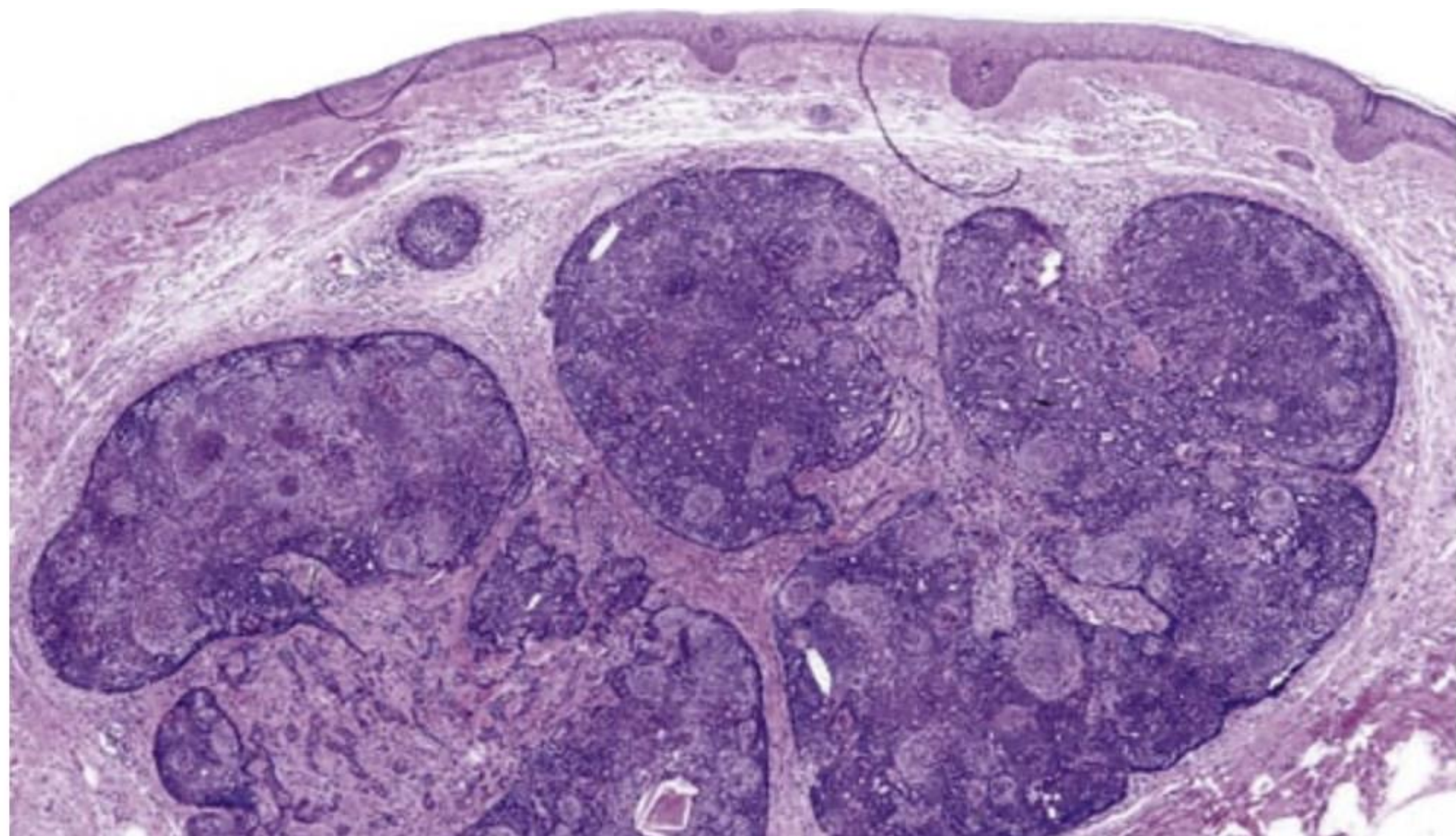
Center: Cystically dilated follicle



**QUIZLET**



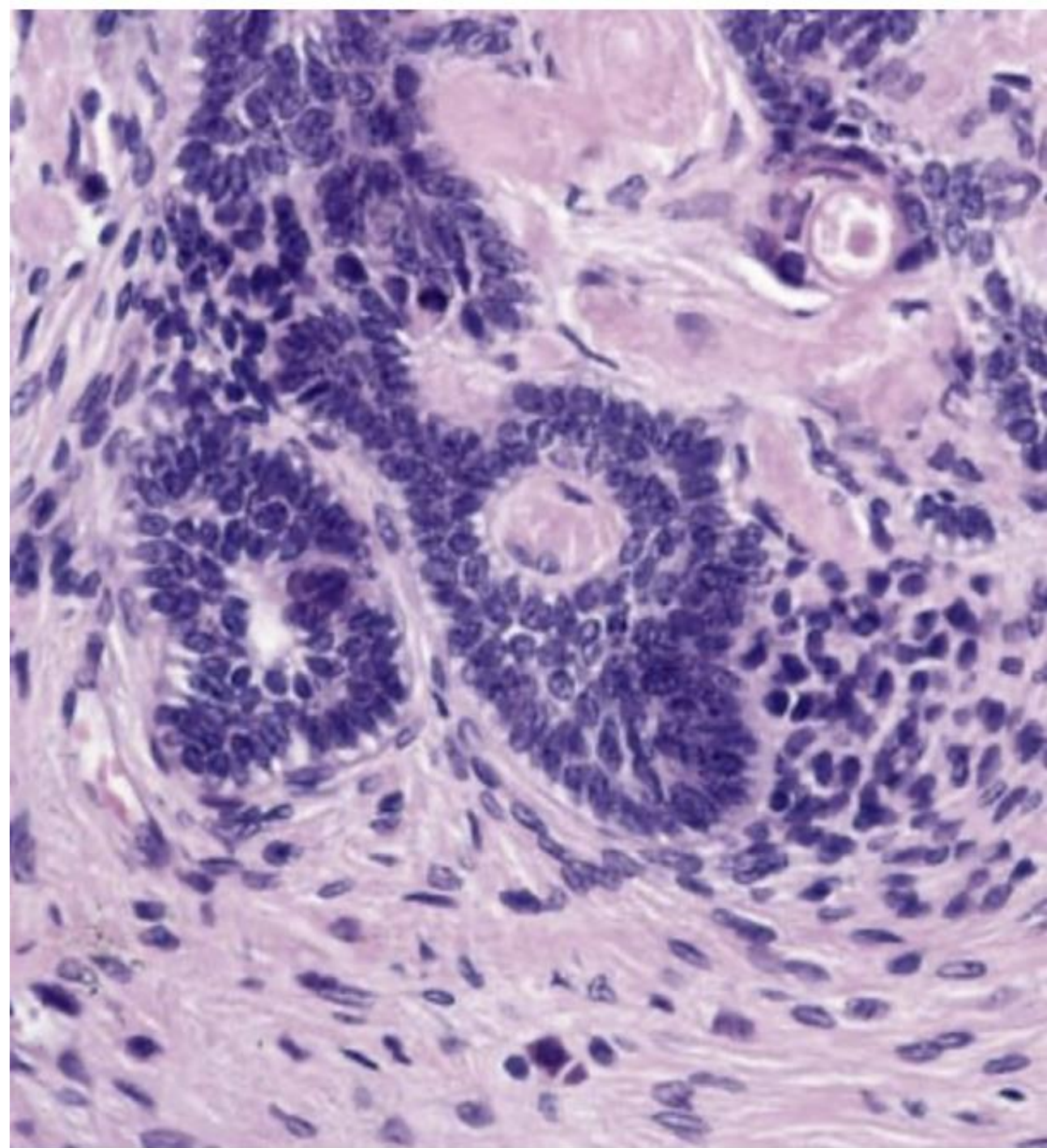






# WHAT IS YOUR DIAGNOSIS?

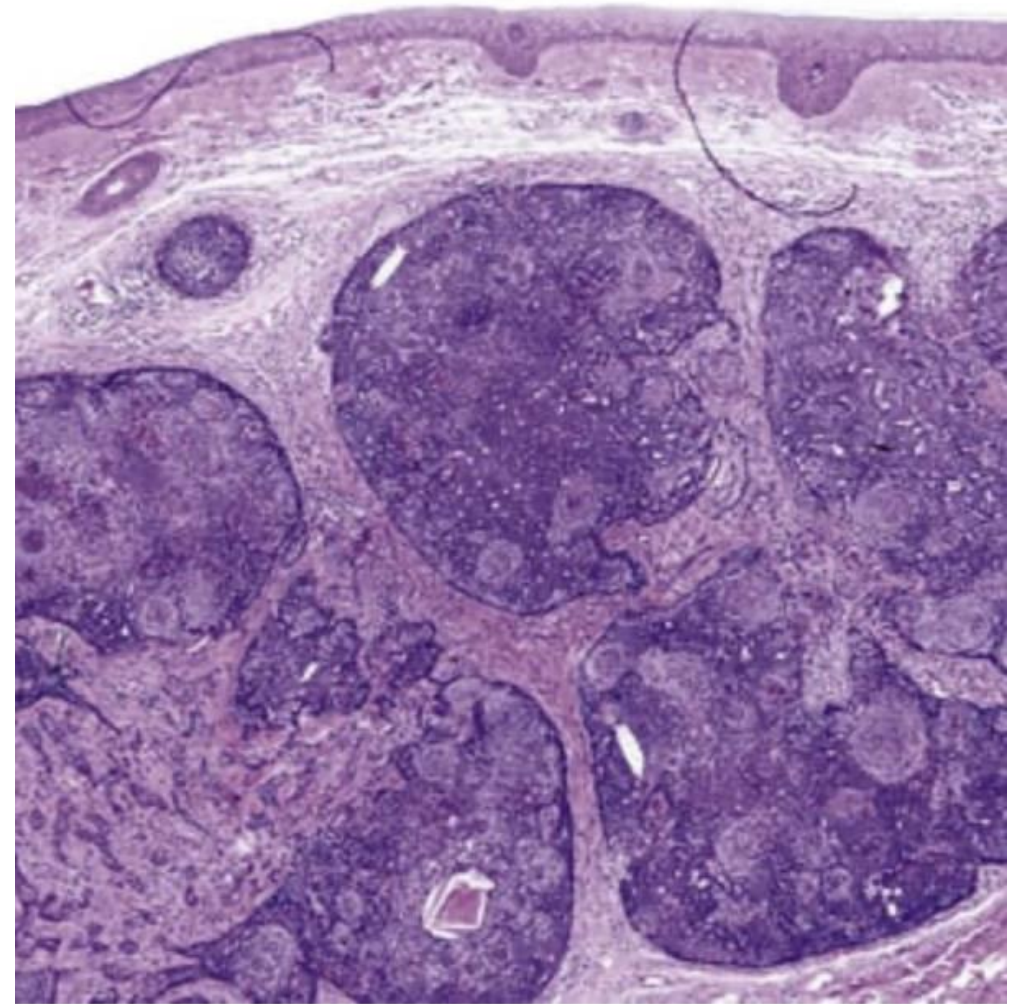
- A. Nodular basal cell carcinoma with follicular differentiation
- B. Trichoblastoma
- C. Trichoepithelioma
- D. Trichoadenoma
- E. Trichilemmoma





# ANSWER: TRICHOBLASTOMA

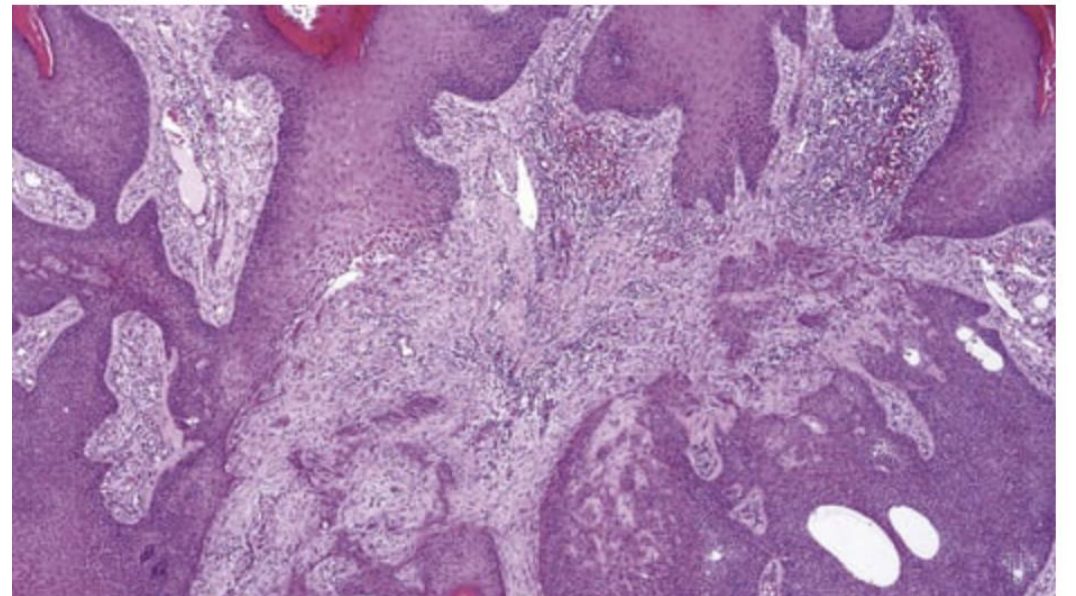
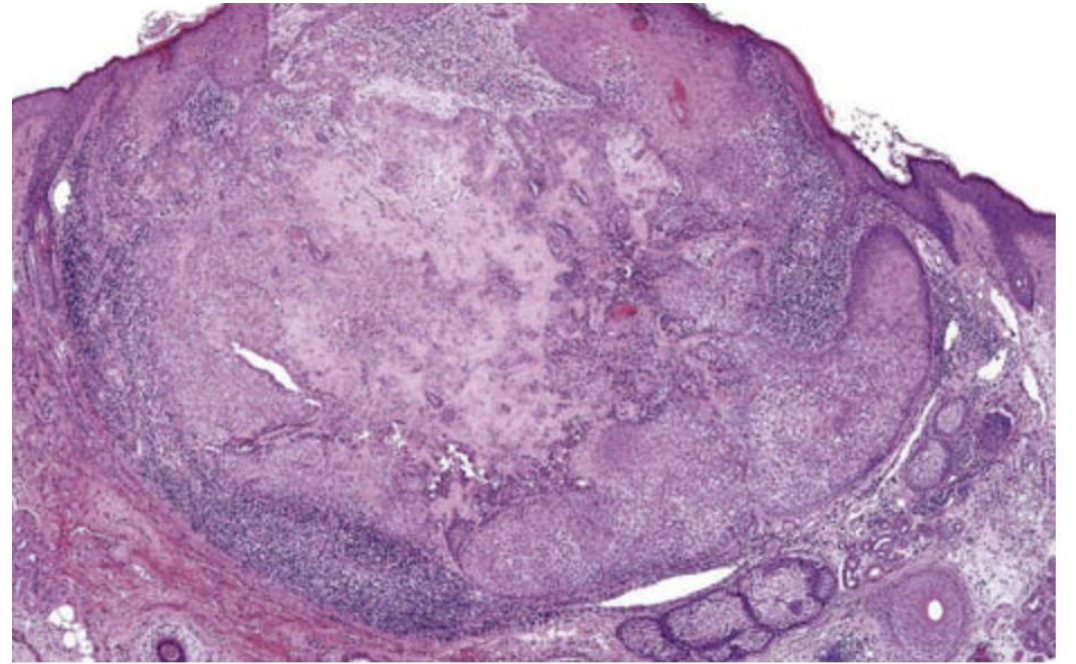
- Multinodular basaloid proliferation
- No retraction artifact
- No mucin
- Primitive hair papilla
- Cellular fibrous stroma surrounding the papilla





# WHAT IS YOUR DIAGNOSIS?

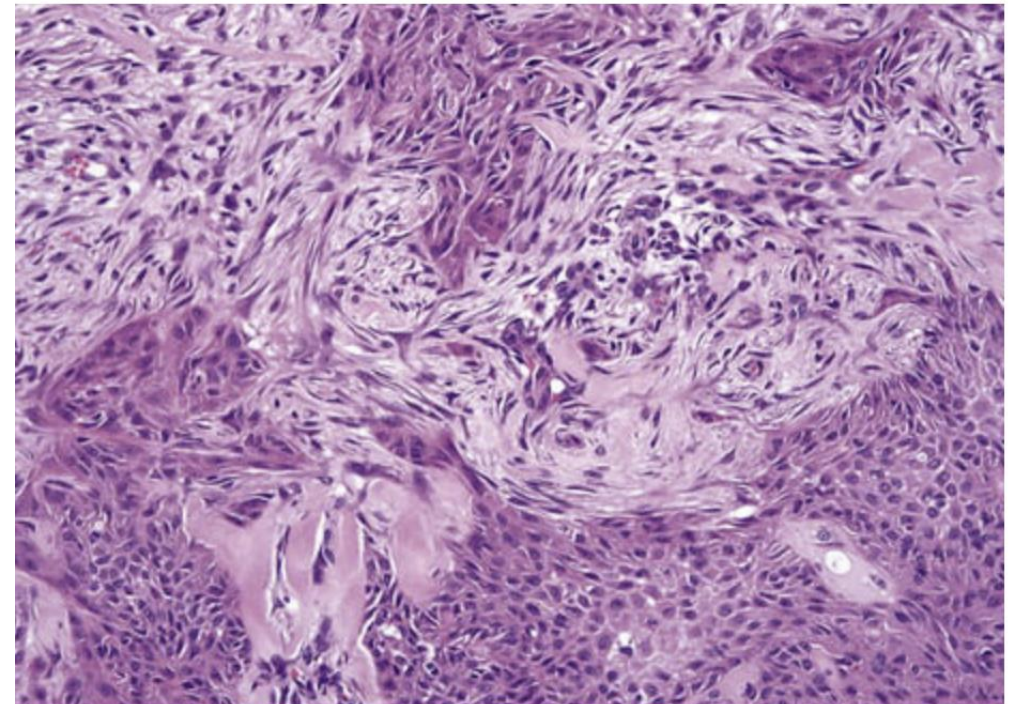
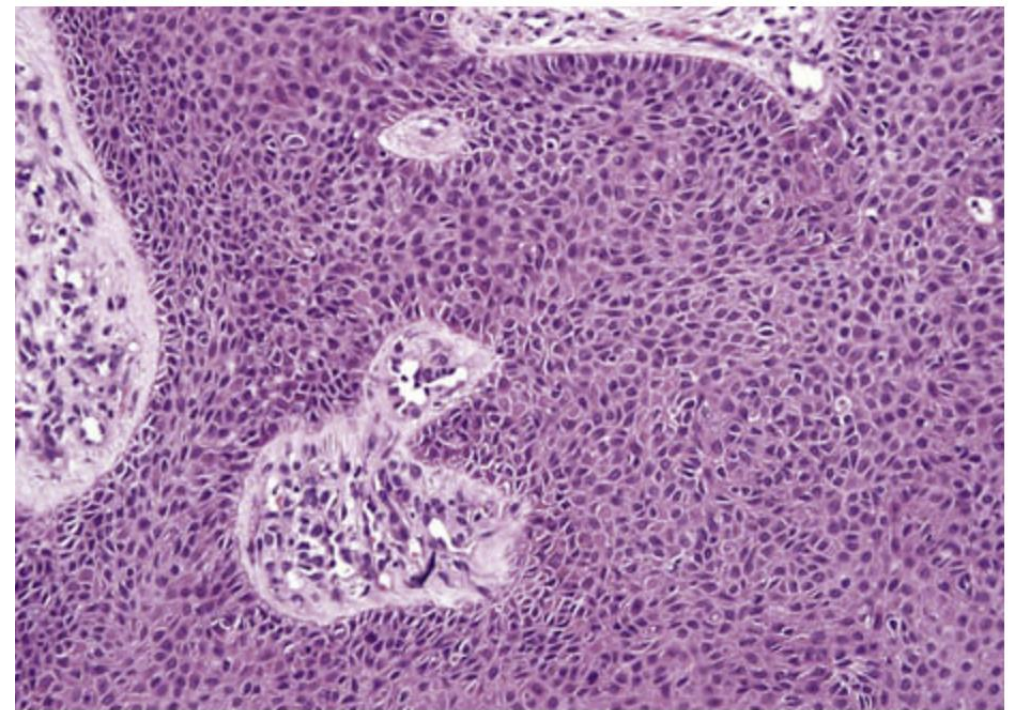
- A. Hidradenocarcinoma
- B. Poorly to moderately differentiated squamous cell carcinoma
- C. Desmoplastic trichoepithelioma
- D. Desmoplastic trichilemmoma
- E. Fibrofolliculoma



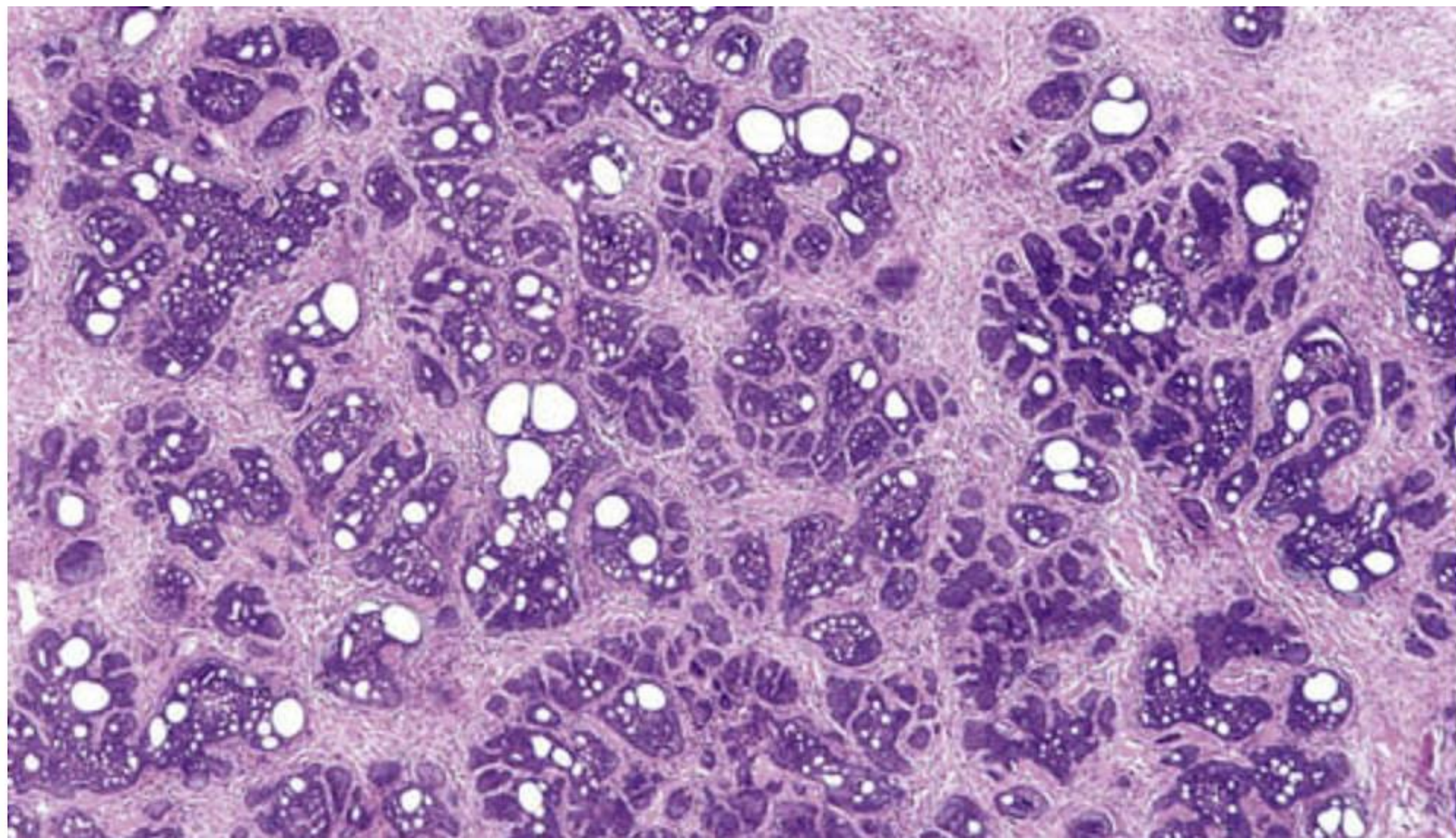


# ANSWER: DESMOPLASTIC TRICHILEMMOMA

- At periphery: typical small cells keeping with trichilemmal differentiation
- Small uniform cells
- No atypia, no mitoses
- Center: irregular cords of epithelial cells (jagged edges, 'infiltrative pattern') and dense hyalinized collagen (lichen sclerosis)



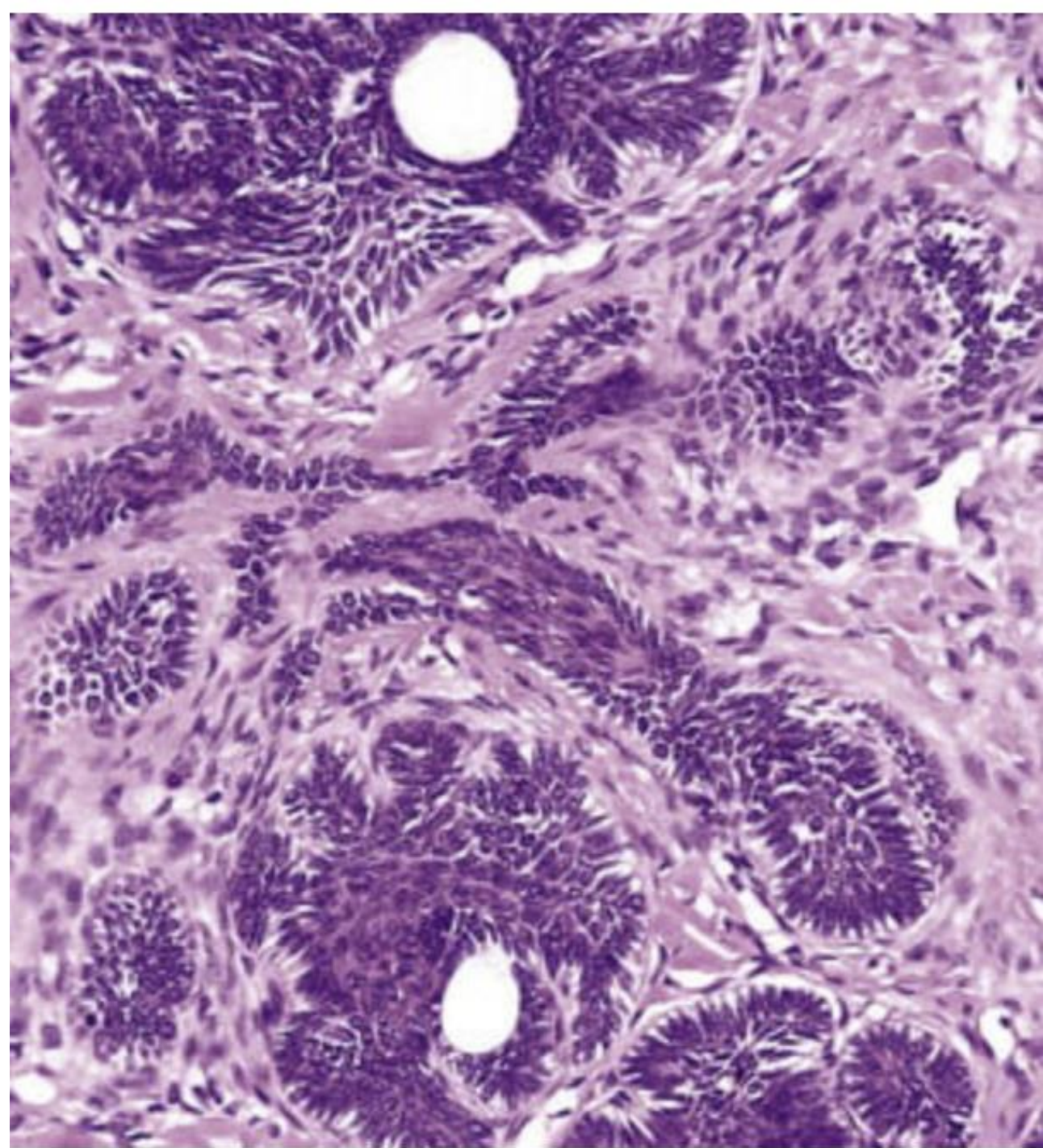






# WHAT IS YOUR DIAGNOSIS?

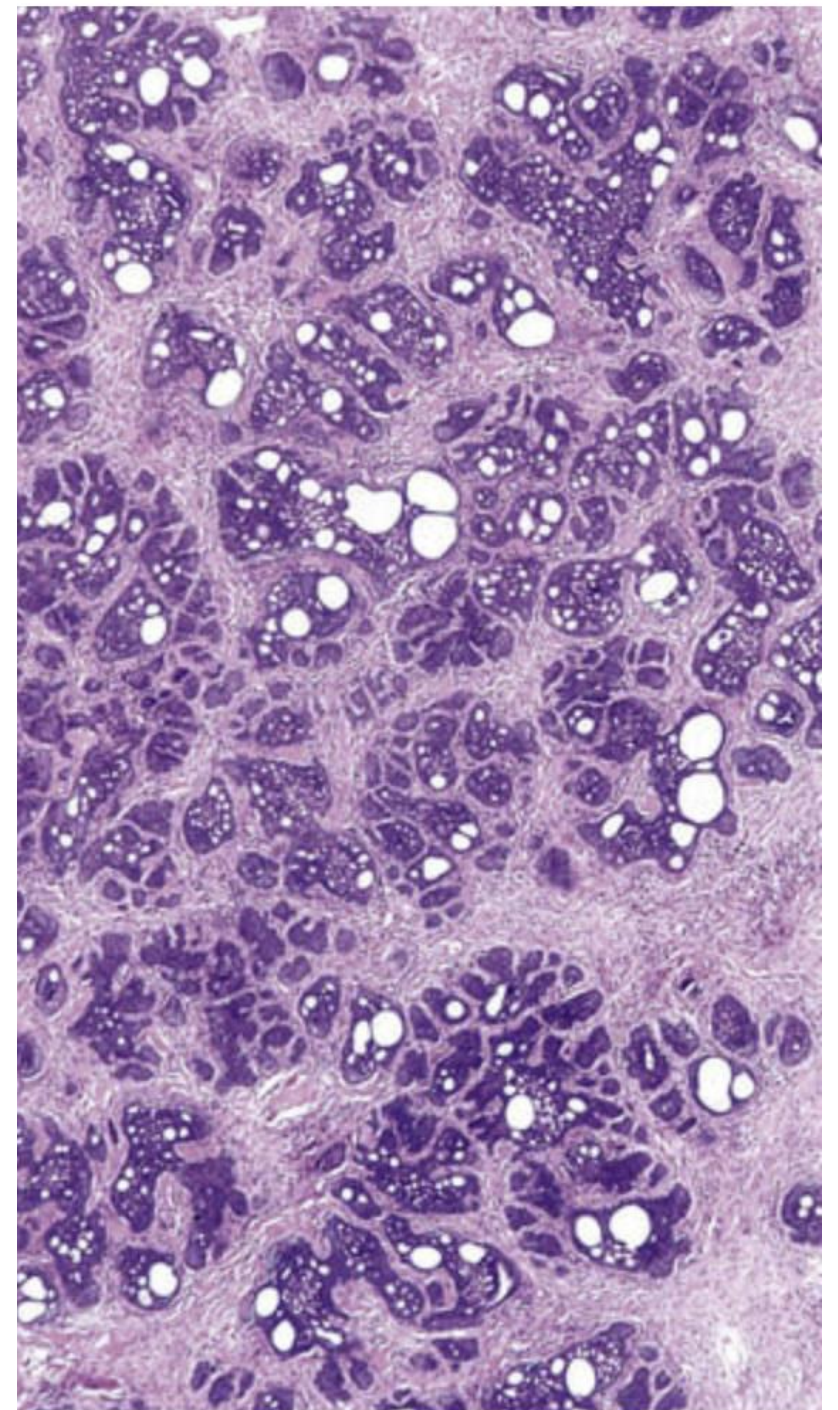
- A. Nodular basal cell carcinoma with follicular differentiation
- B. Adenoid cystic carcinoma
- C. Metastatic carcinoma (of head and neck)
- D. Trichoblastoma
- E. Trichoepithelioma



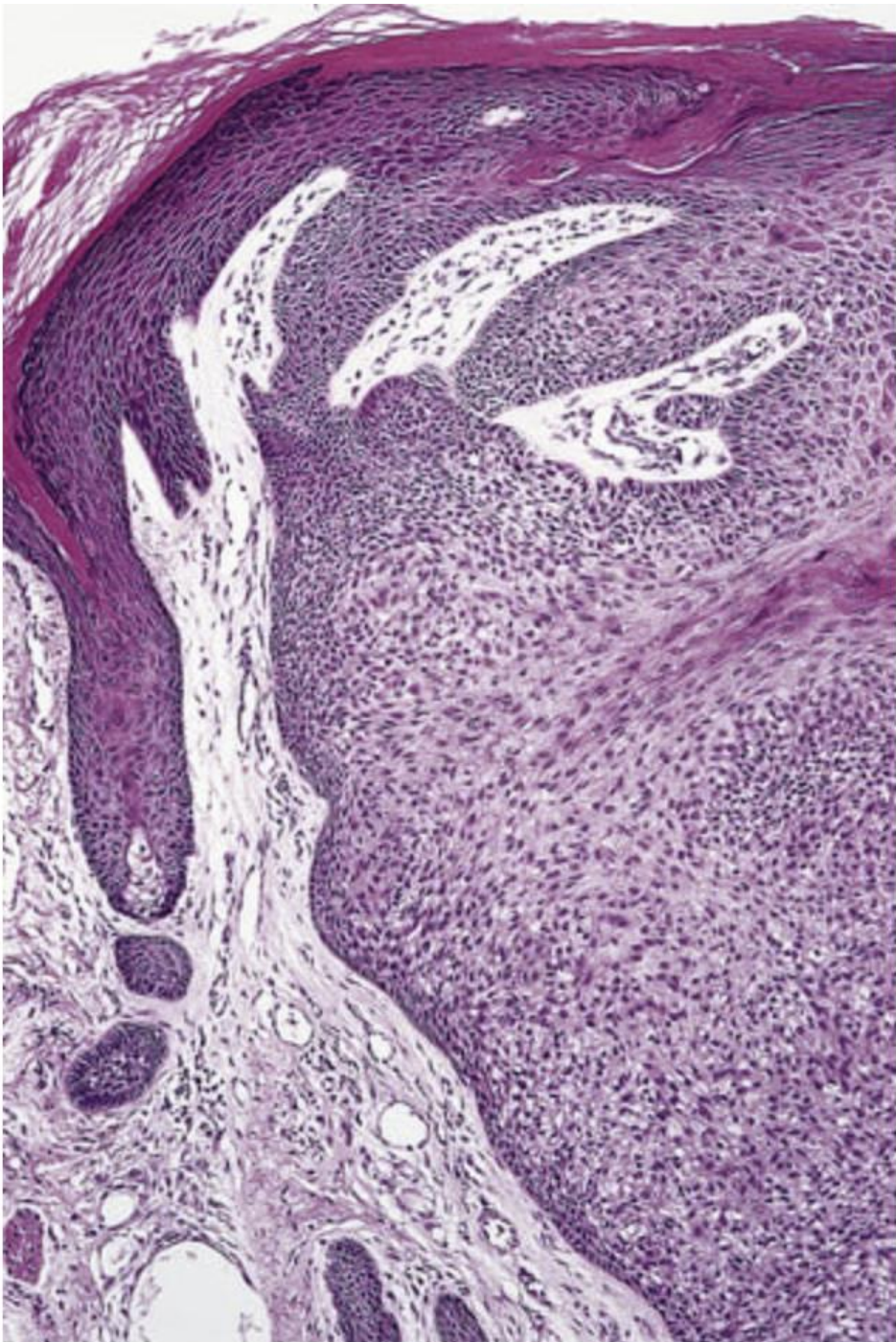


# ANSWER: TRICHOBLASTOMA

- Back-to-black empty spaces (not glands)
- Keratocyst
- Biphasic tumor: basaloid epithelial element and cellular fibrotic stroma
- Basaloid islands cluster, some smaller and detached
- Primitive hair papilla, not invasion







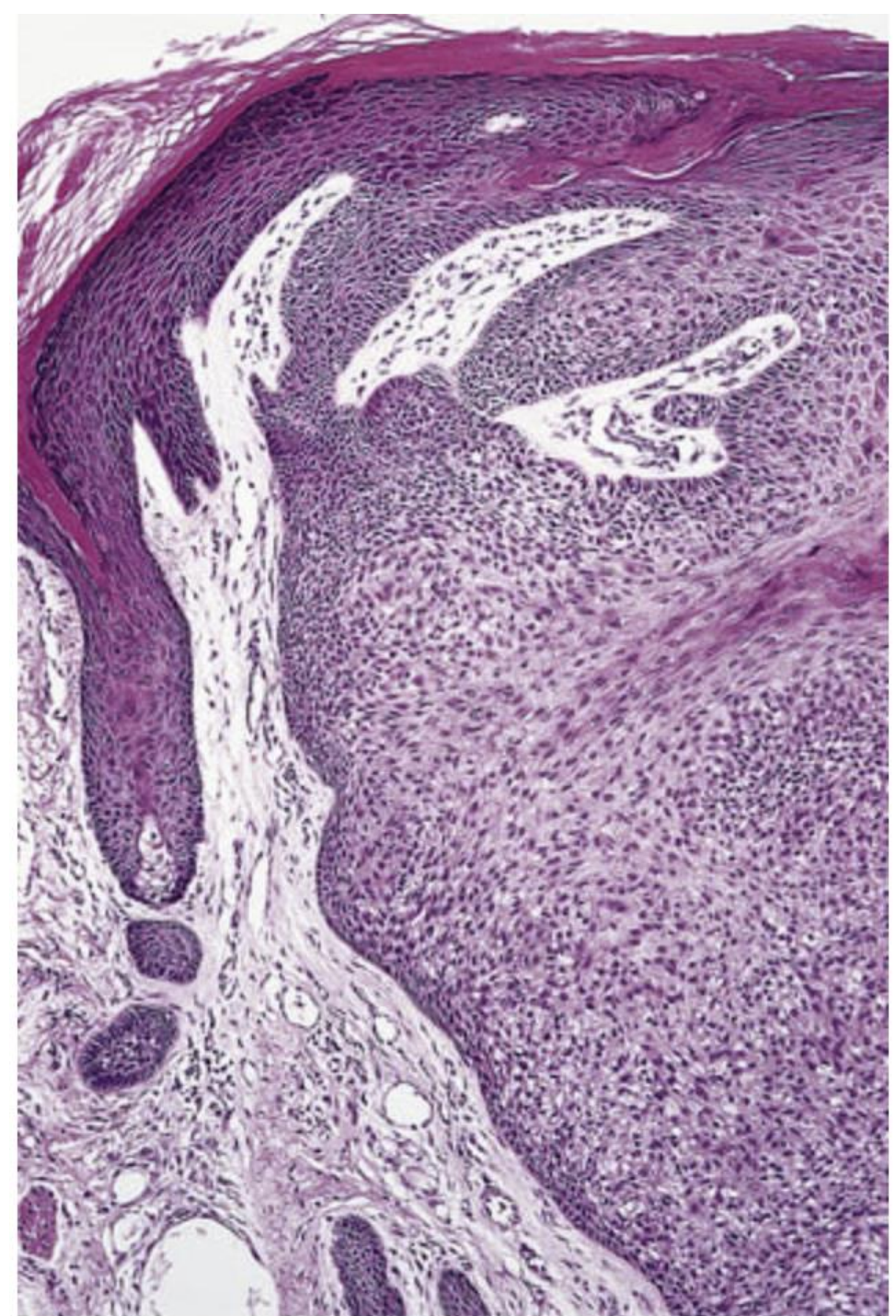
## WHAT IS YOUR DIAGNOSIS?

- A. Hidradenocarcinoma
- B. Poorly to moderately differentiated SCC
- C. Trichilemmoma
- D. Desmoplastic trichoepithelioma
- E. Nodular basal cell carcinoma



## ANSWER: TRICHILEMMOMA

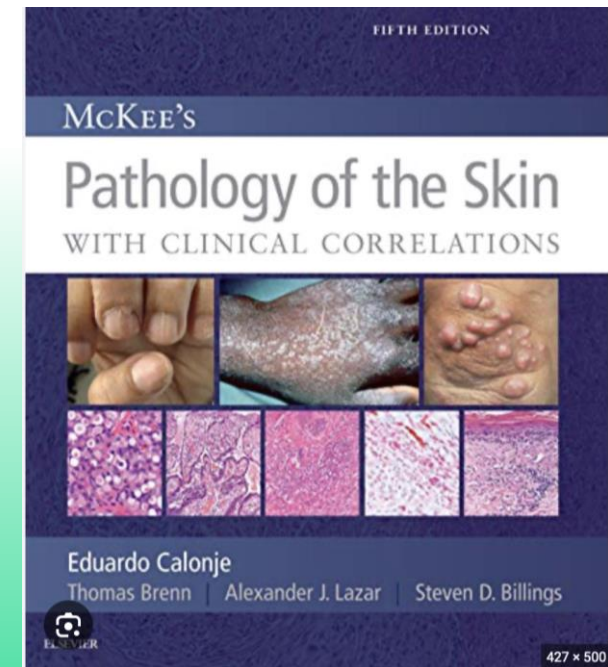
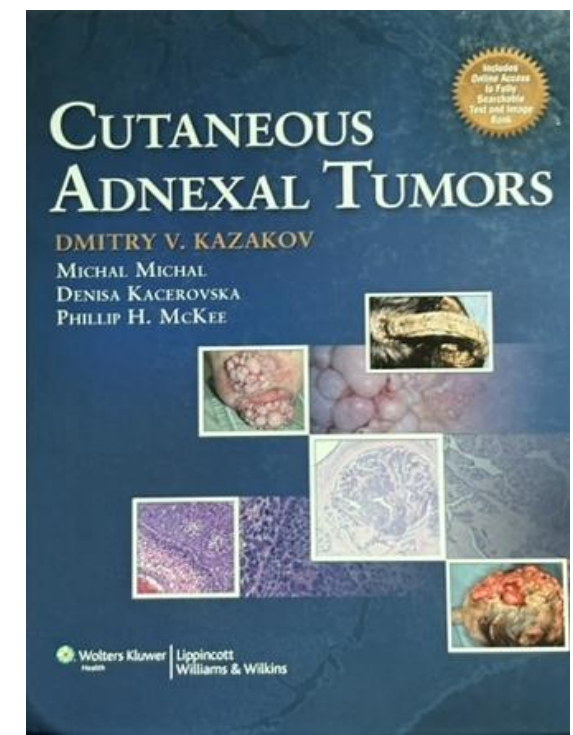
- Smooth-edged lobule, endophytic
- Composed of small cell with cytoplasmic vacuolation
- Nuclear palisading
- No cytologic atypia, no mitoses



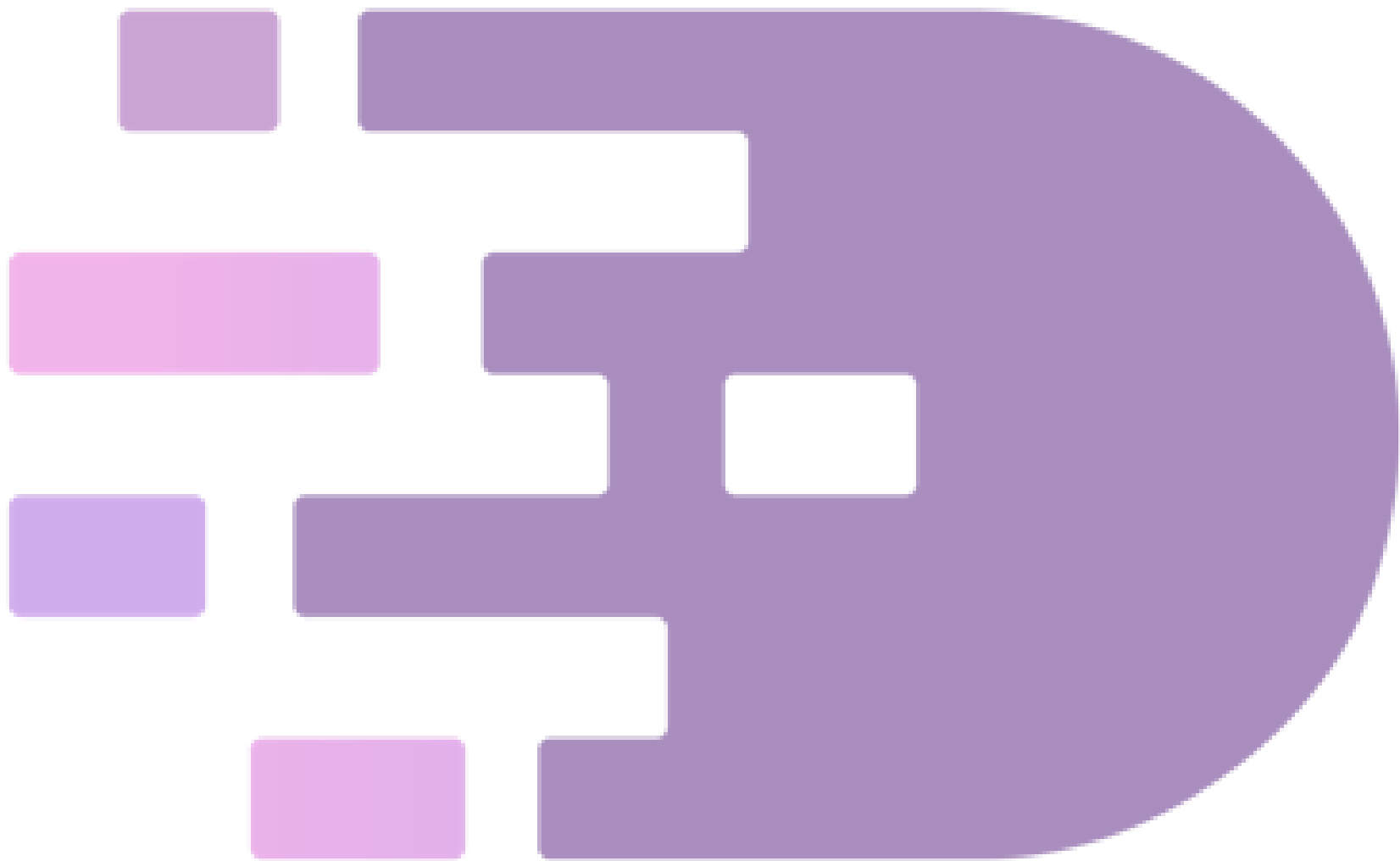


# REFERENCES

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- *Neoplastic Dermatopathology* by David Cassarino and Soheil Dadras, third edition
- *McKee's Pathology of the Skin* by Eduardo Calonje
- *Dermatopathology* by Raymond L. Barnhill, third edition
- *Digital Skin Pathology*  
<https://digitalskinpathology.com/>







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**Learn Histologic Diagnosis Case-By-Case**