



# TUMORS WITH HAIR FOLLICLE DIFFERENTIATION

---

Soheil S Dadras MD-PhD

# LECTURE OUTLINE

- Will briefly introduce tumors with sebaceous differentiation for completeness
- Complete list of adnexal neoplasms, many are hamartomas
- Present as an unknown, then reveal diagnosis and specific features
- Syndromic conditions
- Quizlet (to emphasize the features and make you think)
- Go over scanned cases (time allowing)



Birt-Hogg-Dube syndrome

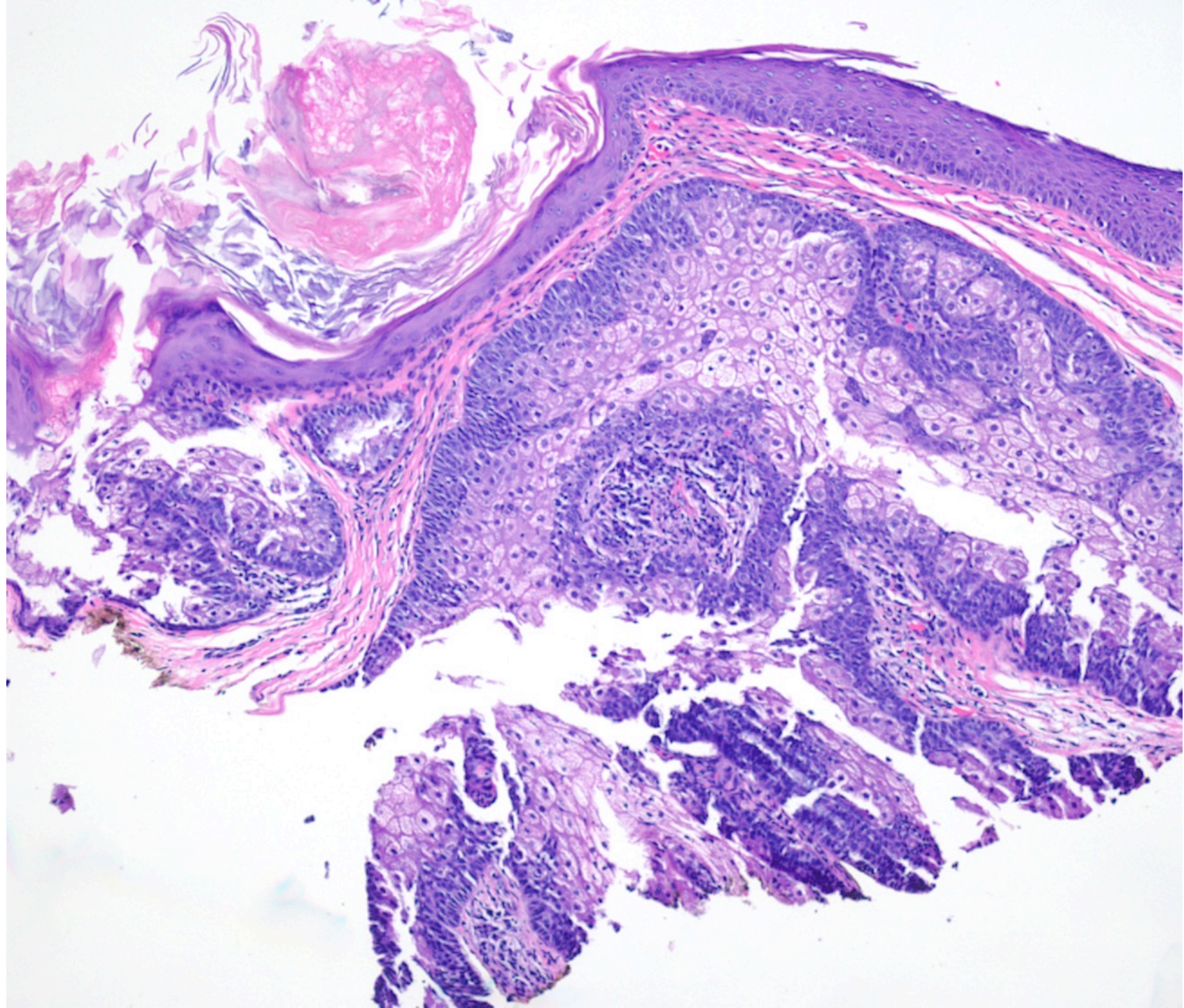
# GENERAL CONSIDERATIONS

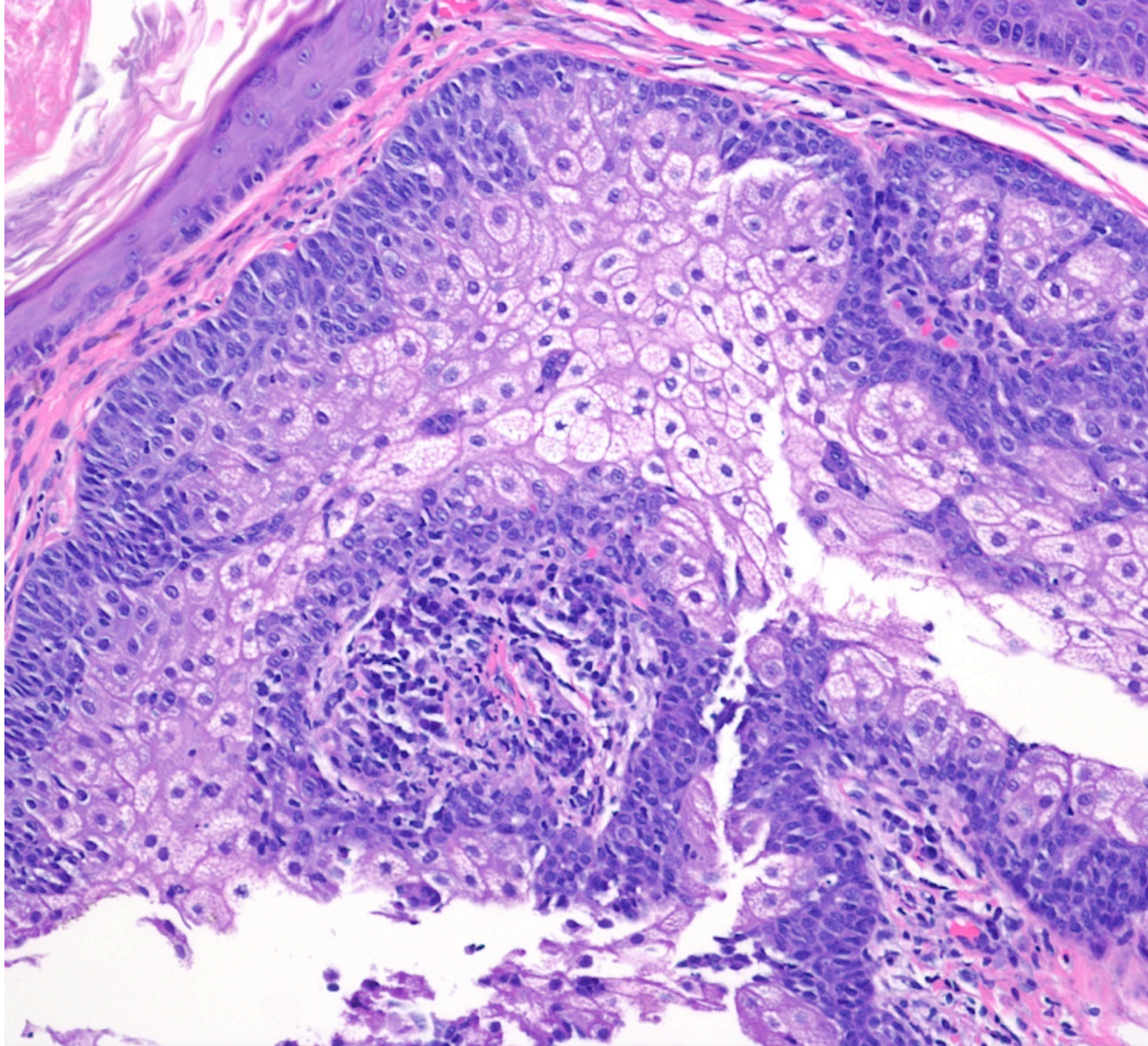
- Lack of specific IHC and molecular diagnostic markers(not used in practice)
- Disputed classification
- Classification of adnexal tumors is currently based on embryologic origin (Dev. Biology):
  1. Folliculo-sebaceous-apocrine
  2. Eccrine

## Tips:

1. Associate the name with hair follicle microanatomy, e.g., trichoblastoma
2. See as many examples (Quiz yourself)
3. Most benign, malignant version exist
4. Interplay between epithelium and stroma

- Function of hair, follicle:
  1. Grow hair shaft
  2. Stem compartment
- A reserve for future need of epidermis and matrical cells
- Neoplasms consistently show two or more lines of differentiation:
  1. Carcinoma with biphasic/divergent differentiation
  2. Hamartoma with biphasic/divergent differentiation

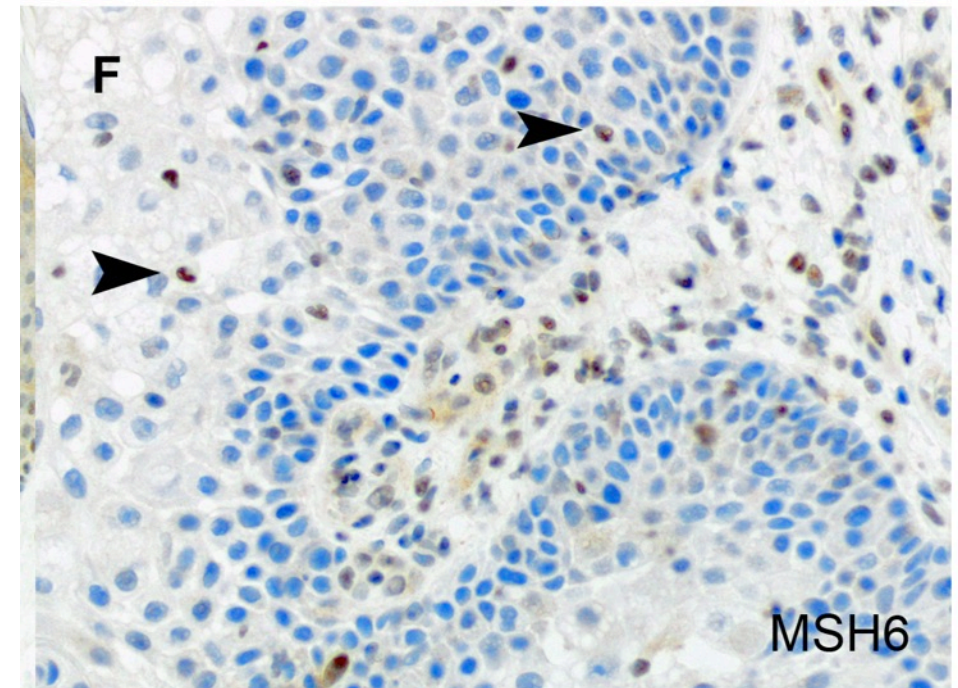
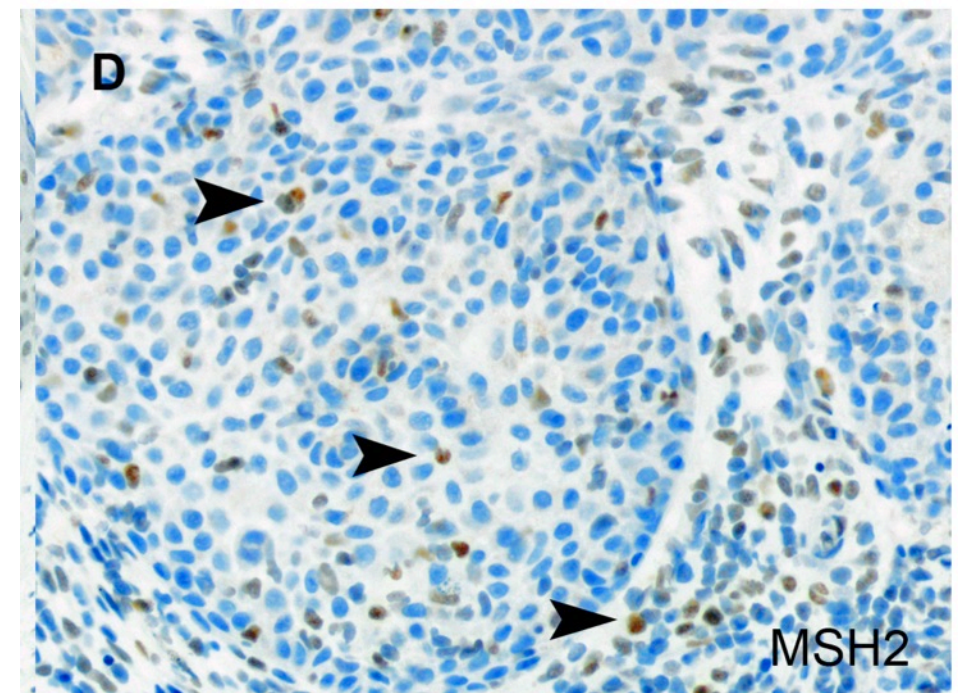






# LYNCH SYNDROME: TRUNCATED *MSH2*, PATHOGENIC VARIANT

- IHC is a reasonable approach to screen for MSI
- Sequencing can be more costly as a first step
- If the IHC shows MSI-H (microsatellite instability-high), then spending more on genetic testing is better justified.
- Skipping IHC by jumping to sequencing could potentially miss a true case of MTS in rare situations where novel regions of the genome including the promoter or non-coding areas are affected
- Sequencing protocol focuses only on the exon sequences.
- Family members of affected individuals should also be closely monitored since the inheritance pattern is autosomal dominant
- The patient's son was found to have colon cancer in association with MTS as well.



# Muir–Torre Syndrome

## A Case Report in a Woman Without Personal Cancer History

Torre, Kristin, BS<sup>\*</sup>; Ricketts, Janelle, MD, MBA<sup>†</sup>; Dadras, Soheil S., MD, PhD<sup>†,‡</sup>

The American Journal of Dermatopathology: June 14, 2018 - Volume Publish Ahead of Print - Issue - p

doi: 10.1097/DAD.0000000000001210

Extraordinary Case Report: PDF Only

BUY

PAP

Abstract

Author Information

Article Metrics

**Abstract:** We report a case of a 68-year-old white woman presenting with 5 sebaceous neoplasms, ranging from sebaceous adenoma to sebaceoma on histopathology. Despite the lack of a personal cancer history, her multiple sebaceous neoplasms and a paternal history of colon cancer prompted testing her sebaceous adenomas for microsatellite instability (MSI) by immunohistochemistry. The results showed retained nuclear expressions of MLH1 and PMS2 while MSH2 and MSH6 proteins were absent. The tumor infiltrating lymphocytes expressed both MSH2 and MSH6, providing reliable internal positive controls. Having a high probability for MSI, she was found to be heterozygous for a germline point mutation in *MSH2* gene, where a pathologic variant, c.1165C > T (p.Arg389\*), determined by sequencing confirmed Muir–Torre syndrome (MTS). On further genetic counseling recommendations, one of her 2 sons was found to have colon cancer in the context of his MTS. In this article, we highlight and review the implications of MSI testing by both immunohistochemistry and sequencing as they relate to confirming the diagnosis of a suspected case of MTS.

# 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
- Hair nevi
- Hair follicle nevus
- Woolly hair nevus
- Comedo nevus
- Basaloid follicular hamartoma

## HAIR NEVI

Clinical: increased hair growth of follicle

Histological: normal

Example: Becker nevus, hairy congenital melanocytic nevus

## HAIR FOLLICLE NEVUS (CONGENITAL VELLUS HAMARTOMA)

Clinical: solitary papule on face (linear, Blaschko lines)

Histological: proliferation of mature vellus hair follicles, perifollicular fibrous sheath, and skeletal muscle

Example: looks like accessory tragus, without cartilage and fat

## WOOLY HAIR NEVUS

Clinical: extremely curled patch of lighter hair on scalp

Histological: normal, some curving of the lower third of the follicle



Open comedone



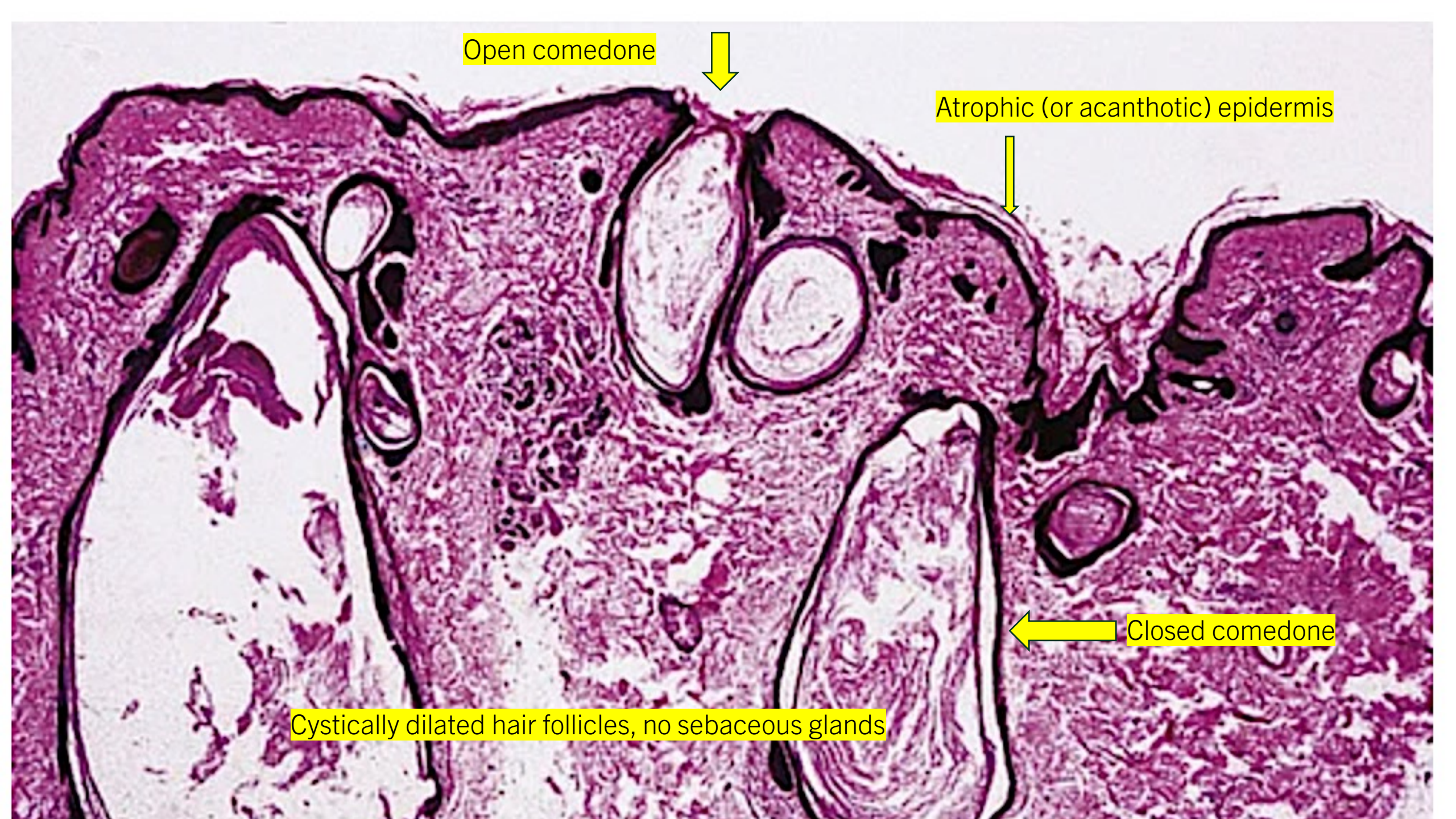
Atrophic (or acanthotic) epidermis



Closed comedone



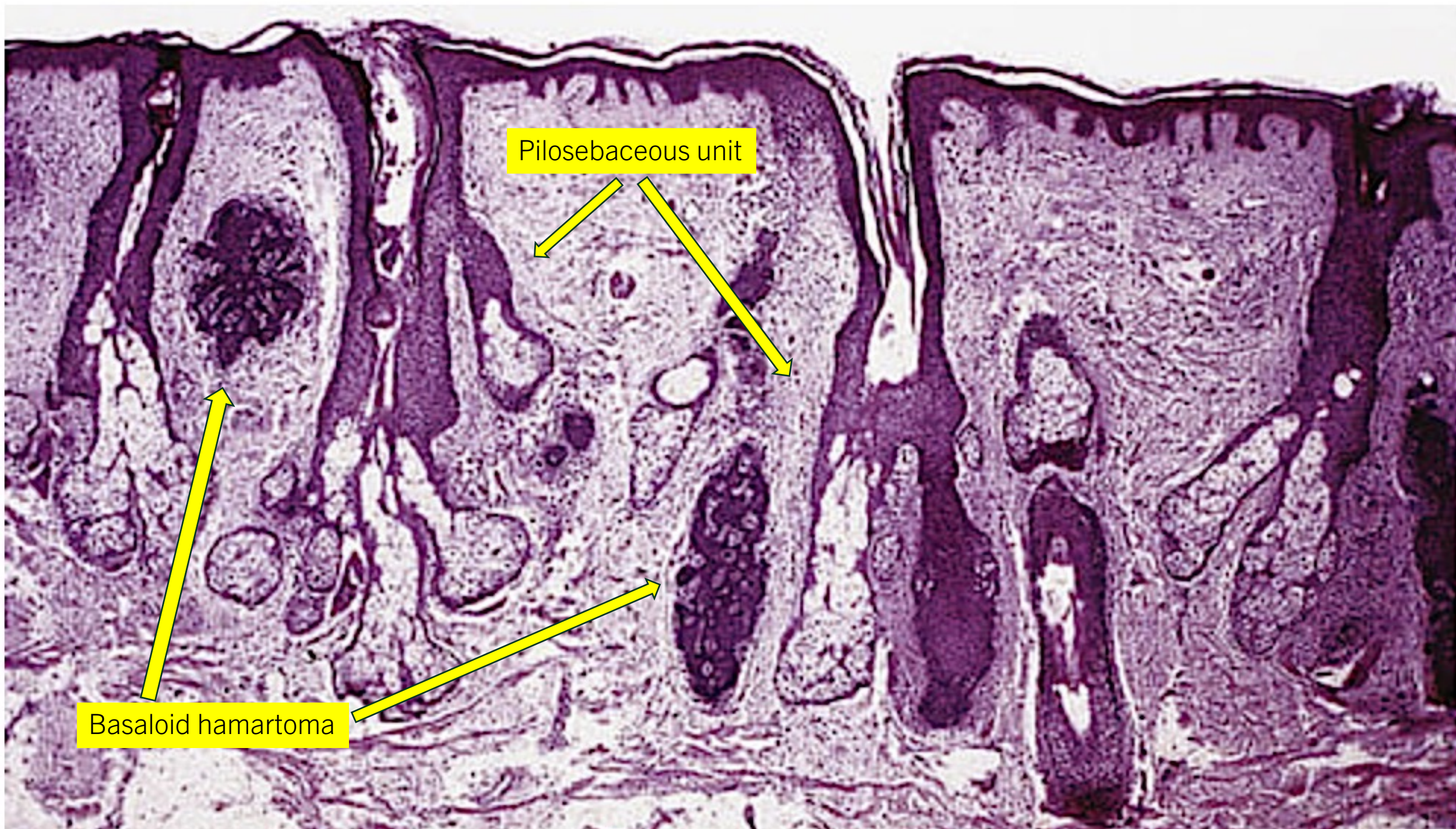
Cystically dilated hair follicles, no sebaceous glands



# COMEDONE NEVUS

- Grouped comedones, linear, zosteriform or lines of Blaschko
- Face, neck, and upper trunk
- Fibroblast growth factor receptor 3 (FGFR3) gene mutation (~Apert syndrome)
- *NEK9* mutation





Pilosebaceous unit

Basaloid hamartoma



Anastomosing strands of basaloid cells, CK20+ Merkel cells

## BASALOID FOLLICULAR HAMARTOMA

- Varied presentation: solitary, localized, linear nevoid, generalized, and inherited
- Sonic hedgehog (Shh) pathway in BCC and BFH
- DDX: trichoepithelioma
- IHC: CK20 highlights Merkel cells  
CD34 highlights spindle cells

Peripheral nuclear palisading

Spindle cells, CD34+



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



Lobular benign epithelial proliferation

This histological image shows a cross-section of skin. A large, irregularly shaped cystic space is visible, lined by a thick layer of pink-stained epithelial cells. The cells show some degree of proliferation, with increased cellularity and some architectural complexity. The cyst is situated within the dermis, having invaginated from the overlying epidermis. The surrounding dermal tissue contains various structures, including smaller cysts and connective tissue stroma.

Cystic invagination, arising from the epidermis

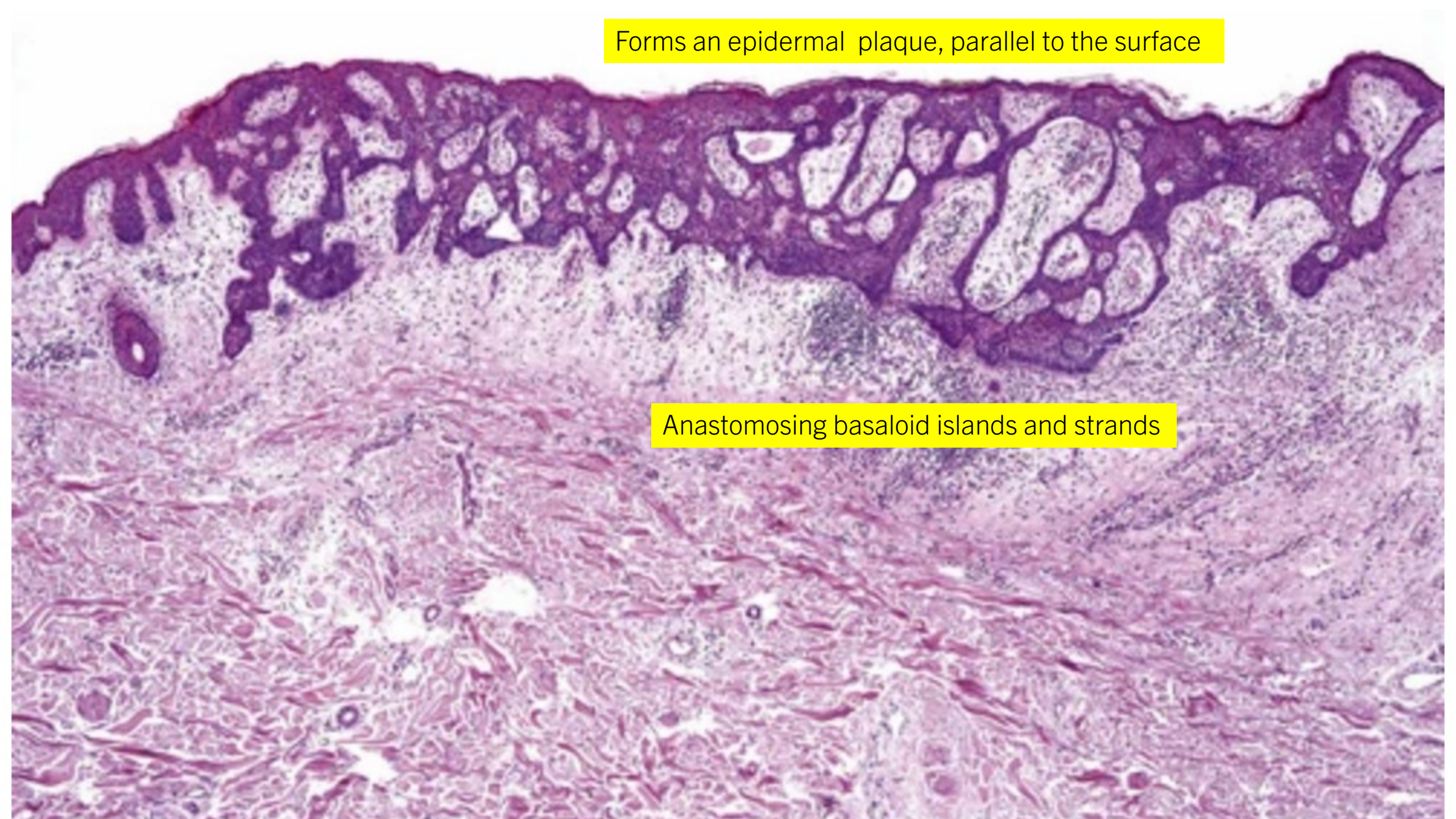
# PILAR SHEATH ACANTHOMA

- 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



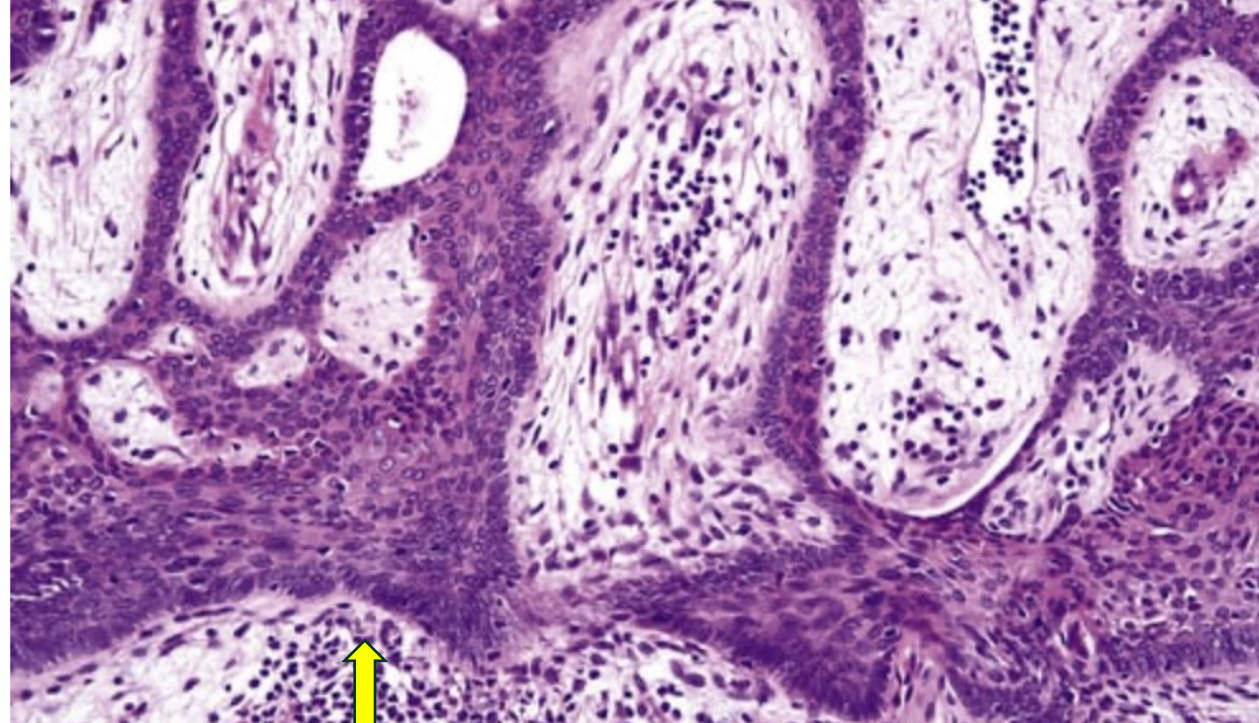
Forms an epidermal plaque, parallel to the surface

Anastomosing basaloid islands and strands

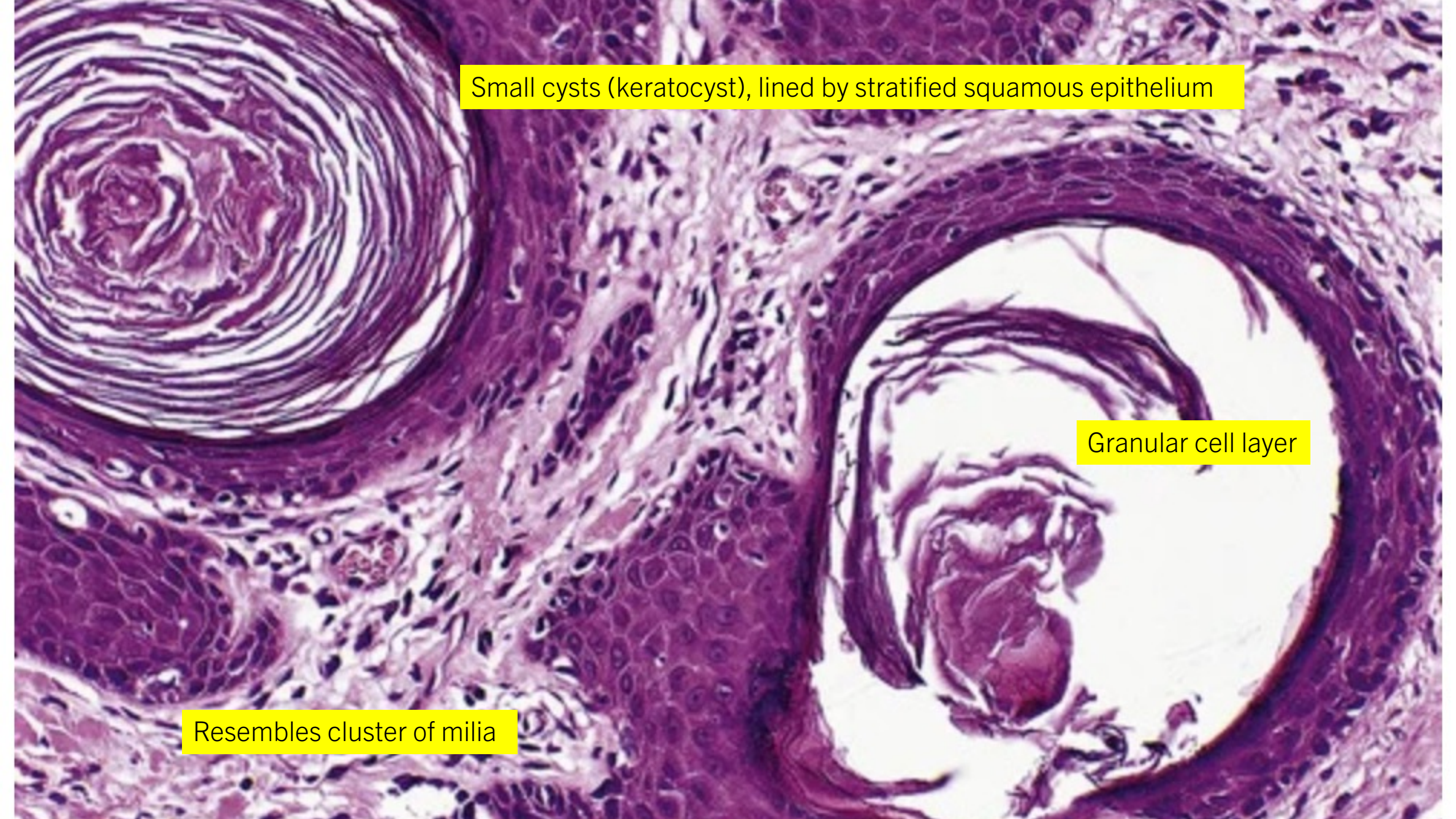


# FOLLICULAR INFUNDIBULUM TUMOR

- 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



Small cysts (keratocyst), lined by stratified squamous epithelium

This histological image shows a section of skin with several keratocysts. The cysts are characterized by their circular or oval shape and are lined by a thick, multi-layered (stratified) squamous epithelium. The surrounding tissue is composed of dense, fibrous connective tissue. The overall appearance is reminiscent of a cluster of milium cysts.

Granular cell layer

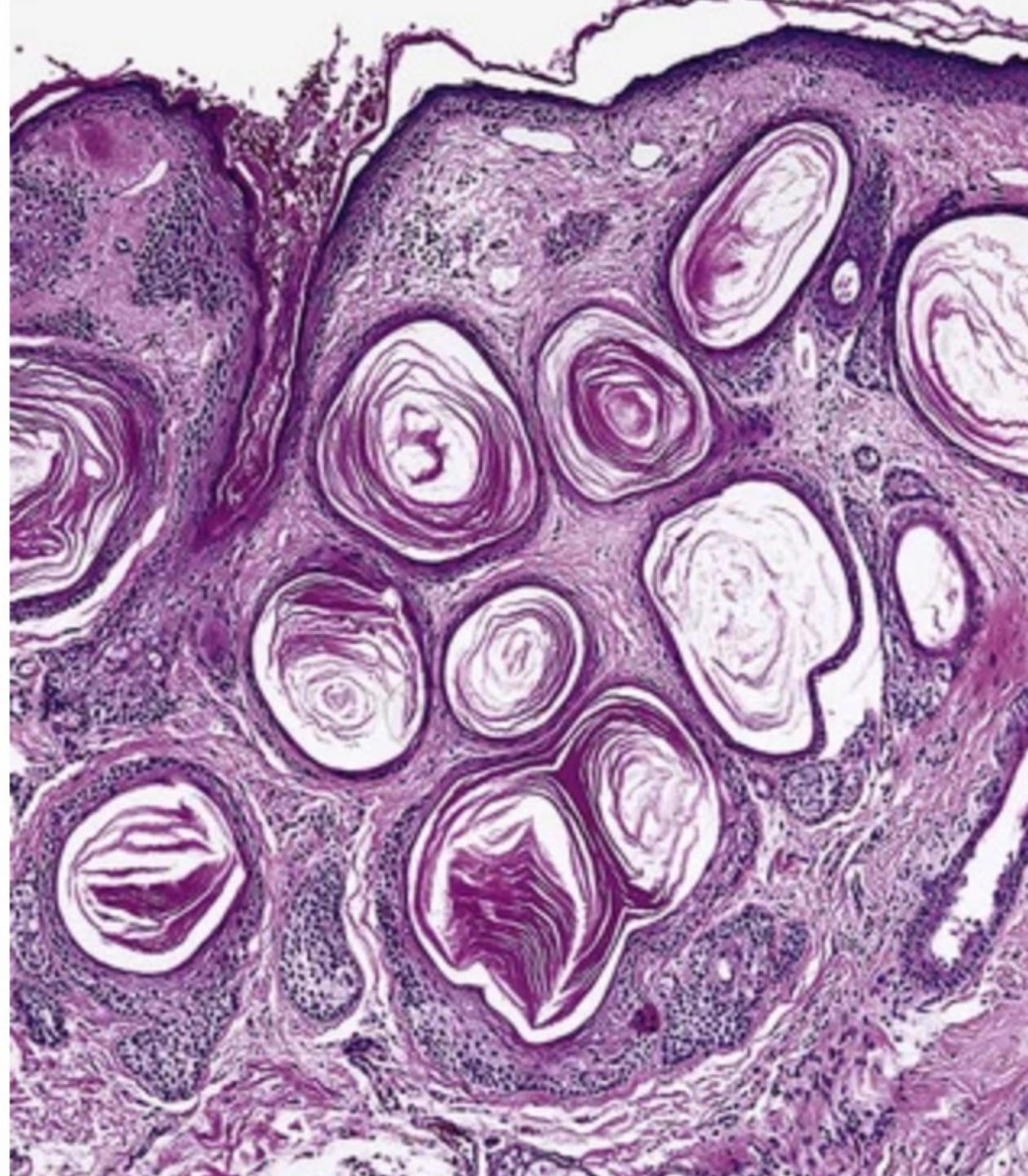
Resembles cluster of milia

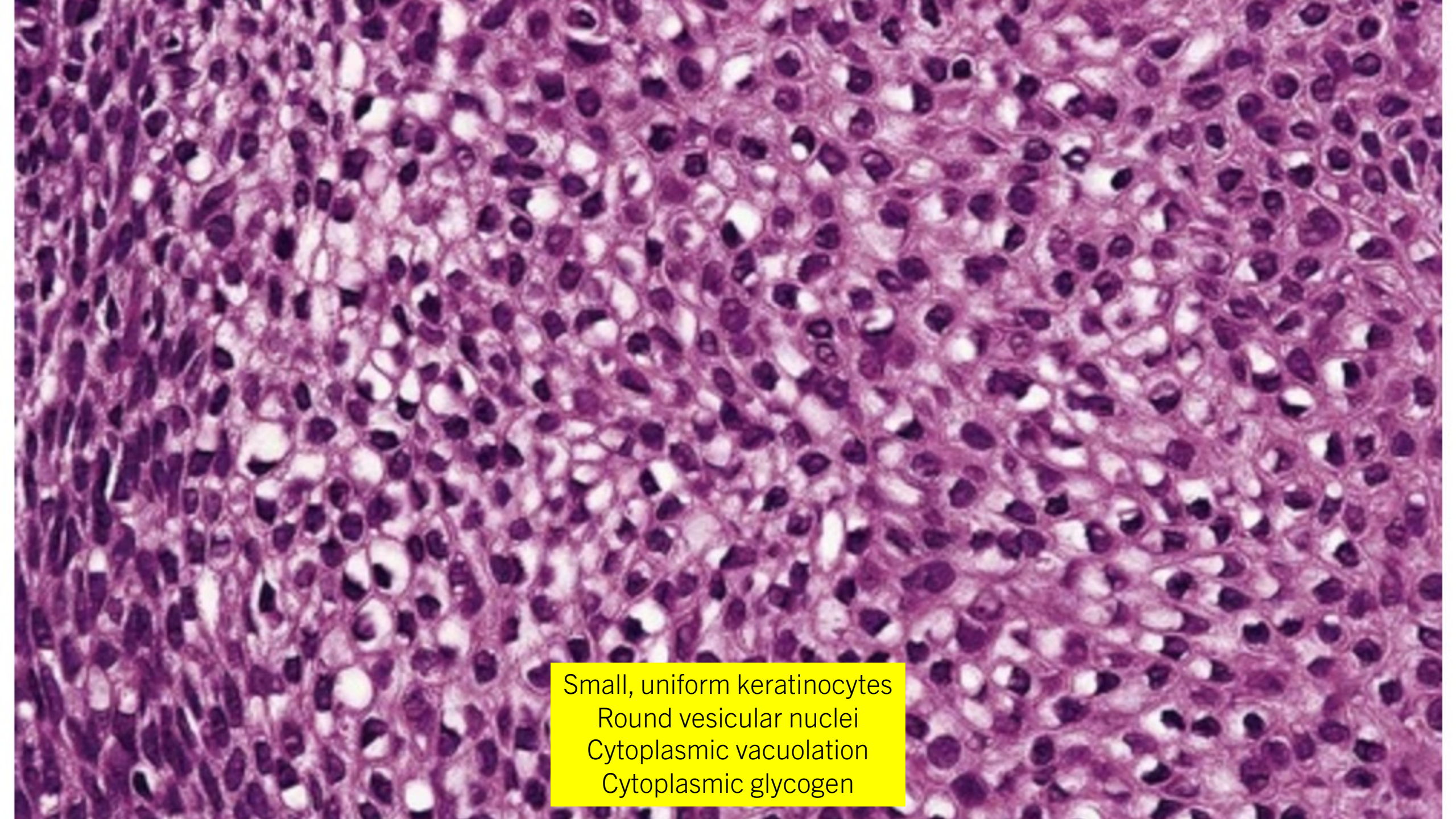
# TRICHOADENOMA

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

Trichoepithelioma -> Trichoadenoma ->  
Trichofolliculoma

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



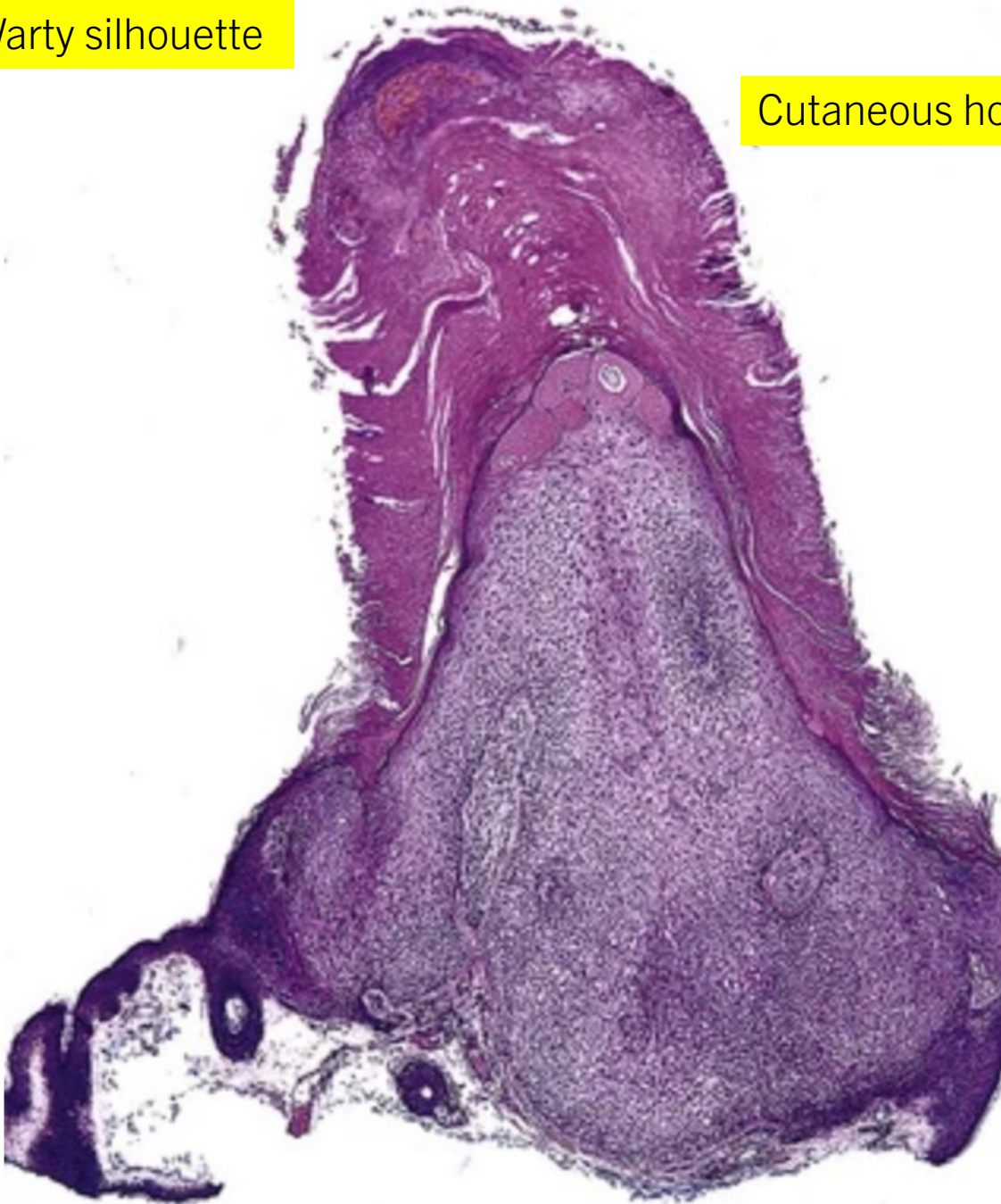


A high-magnification histological micrograph of a tissue section stained with hematoxylin and eosin (H&E). The image displays a dense population of small, uniform keratinocytes. These cells are characterized by their round, vesicular nuclei, which are darkly stained with hematoxylin. The cytoplasm of these cells is filled with numerous small, clear vacuoles, giving it a foamy or vacuolated appearance. The overall architecture is a solid sheet of these uniform cells, with minimal stromal component visible between them.

Small, uniform keratinocytes  
Round vesicular nuclei  
Cytoplasmic vacuolation  
Cytoplasmic glycogen

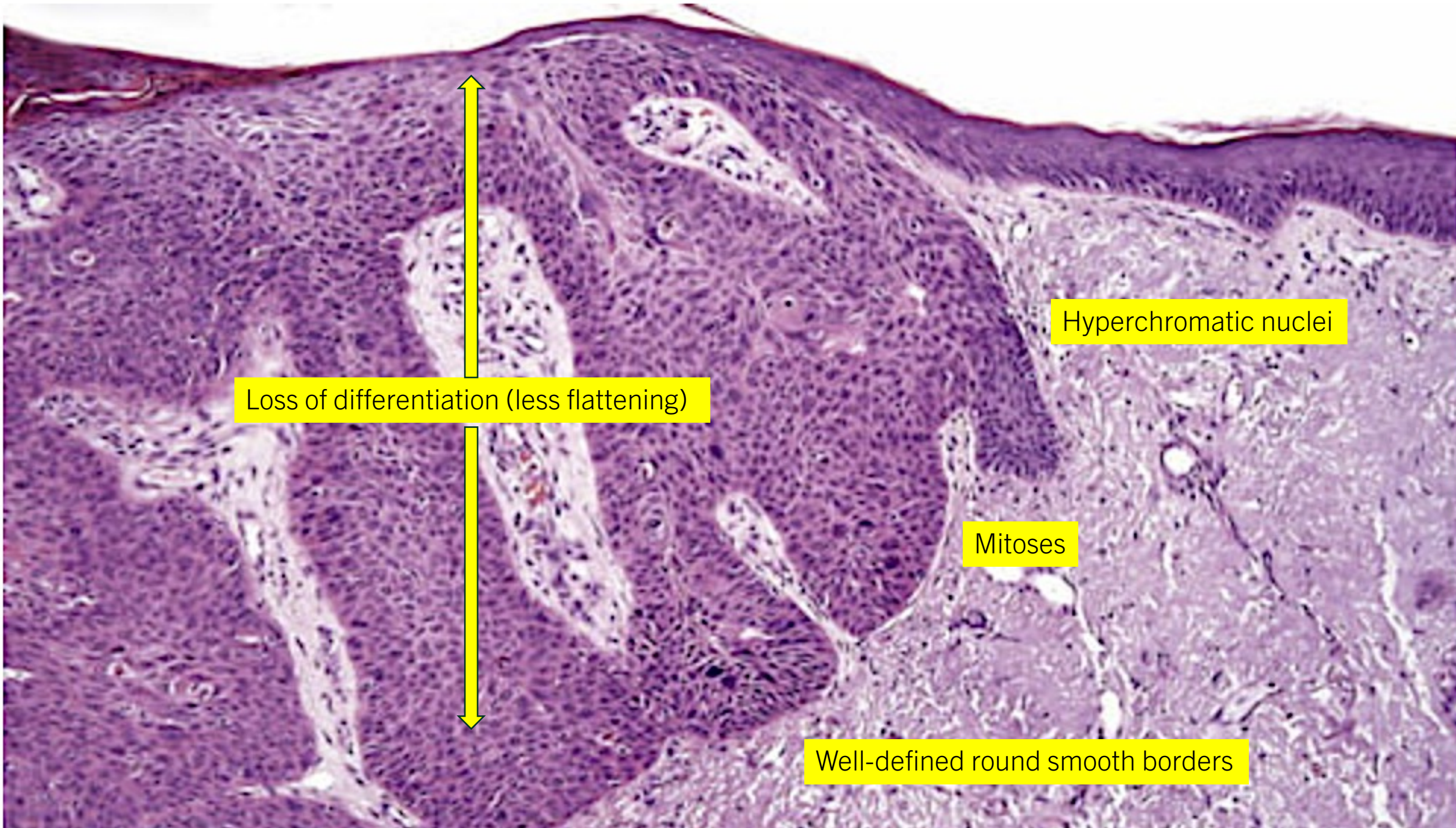
Warty silhouette

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



Loss of differentiation (less flattening)

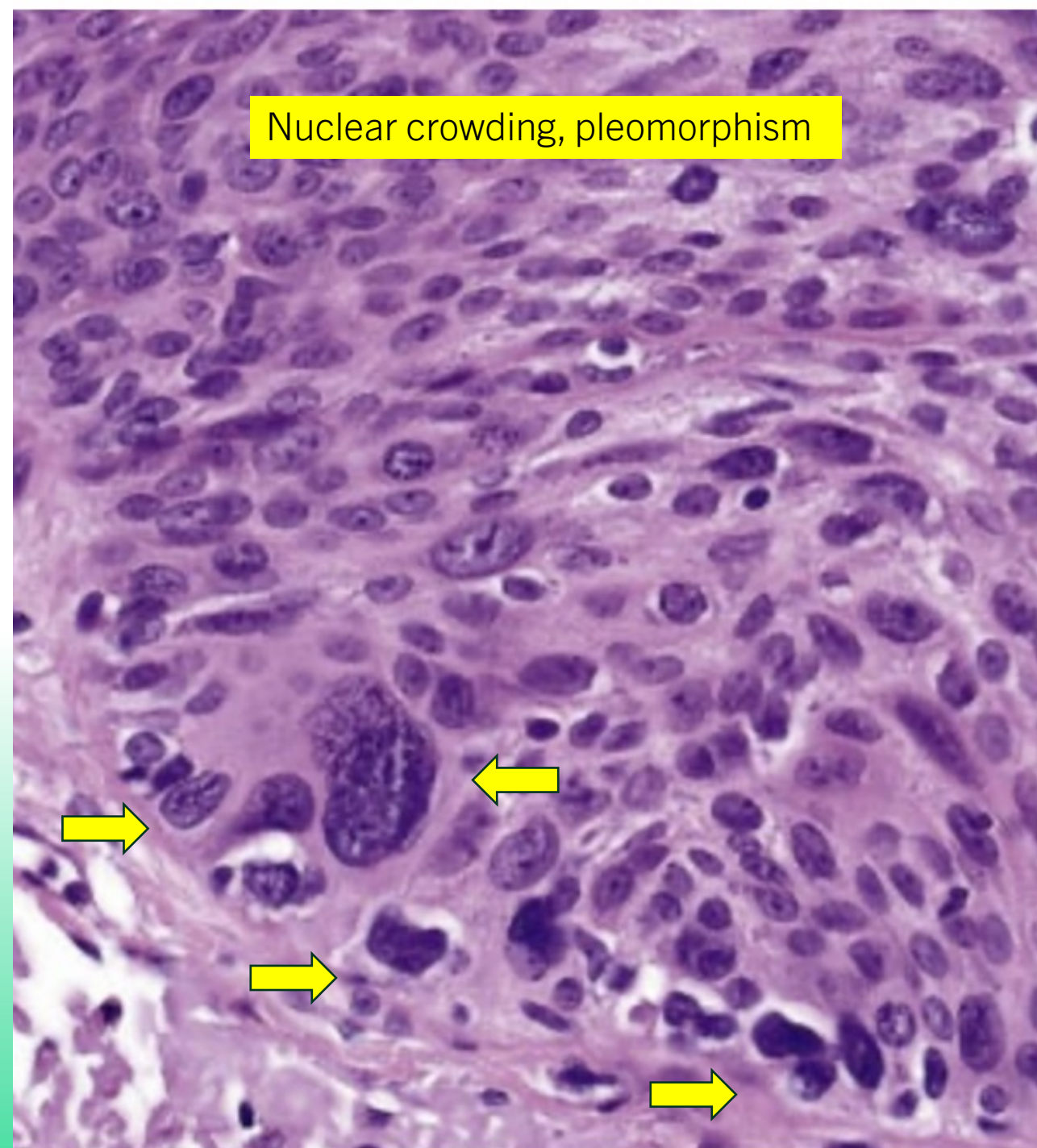
Hyperchromatic nuclei

Mitoses

Well-defined round smooth borders

# 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)





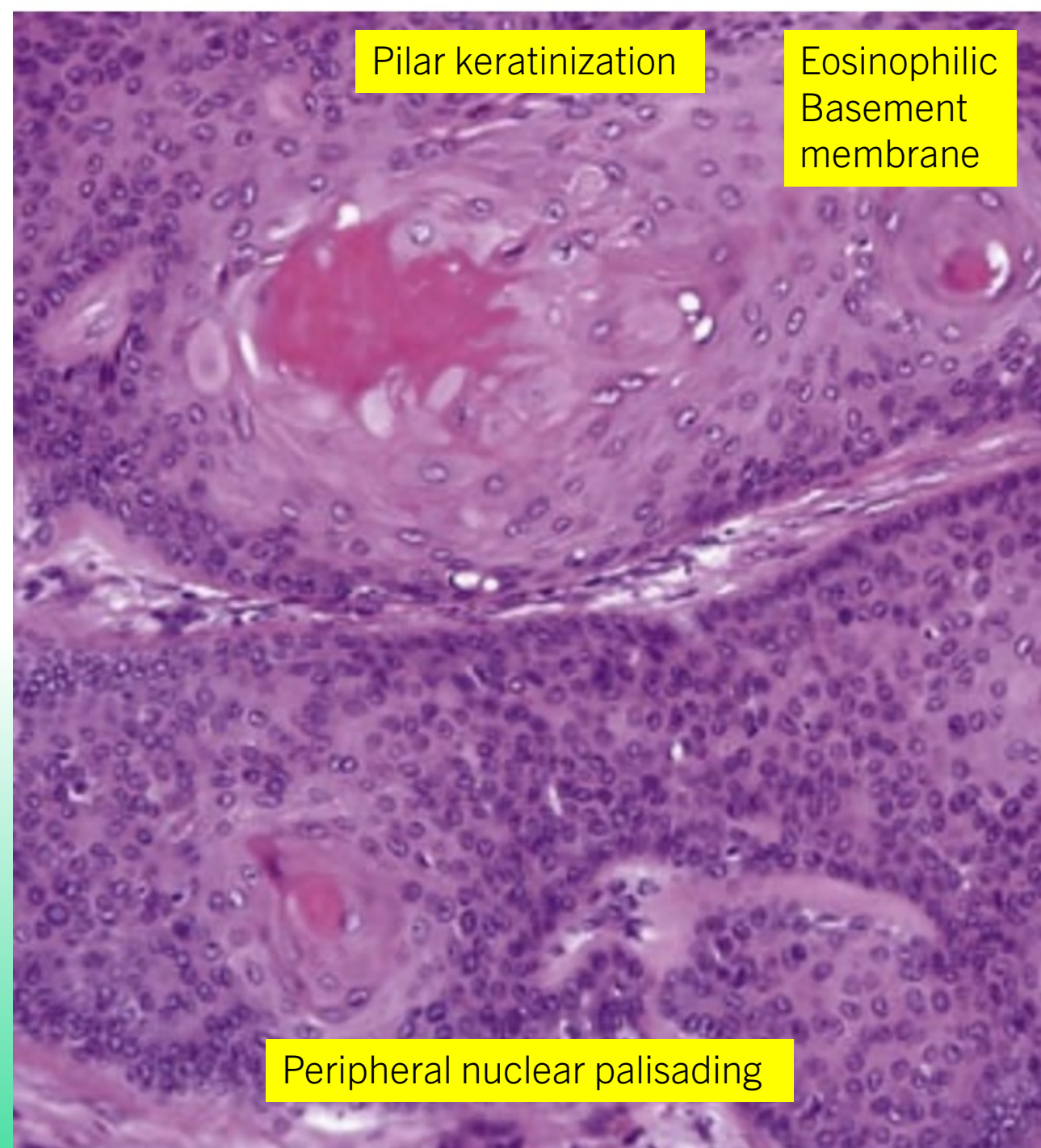
Multiple lobules of squamous epithelium

This histological image shows a tissue section stained with hematoxylin and eosin (H&E). The tissue is composed of numerous lobules of squamous epithelium, which are clusters of cells with large, flat, squamous nuclei. The lobules are separated by thin layers of connective tissue. The overall architecture is organized, with the lobules pushing against the surrounding stroma rather than infiltrating it. Yellow arrows point to the margins of these lobules, highlighting their non-infiltrating nature.

Pushing, non-infiltrating margin/edge

# 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





Pilar tumor

# MALIGNANT PILAR TUMOR (CARCINOMA)

- DDX: SCC

Infiltrating carcinomatous component



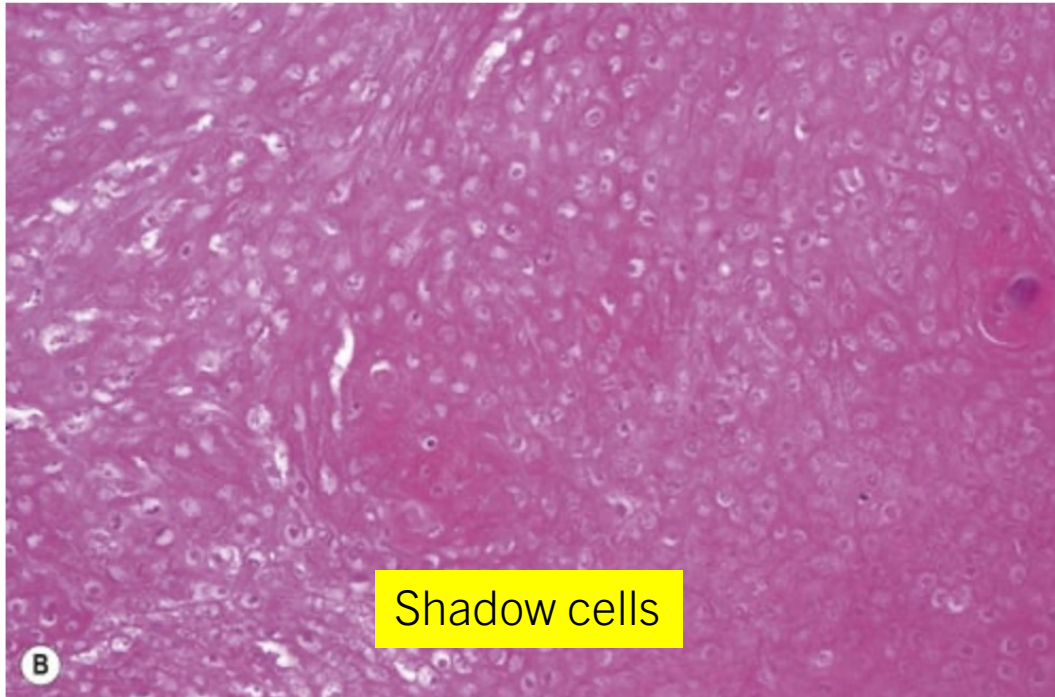
Jagged infiltrating edges



May resemble necrosis or ruptured cyst

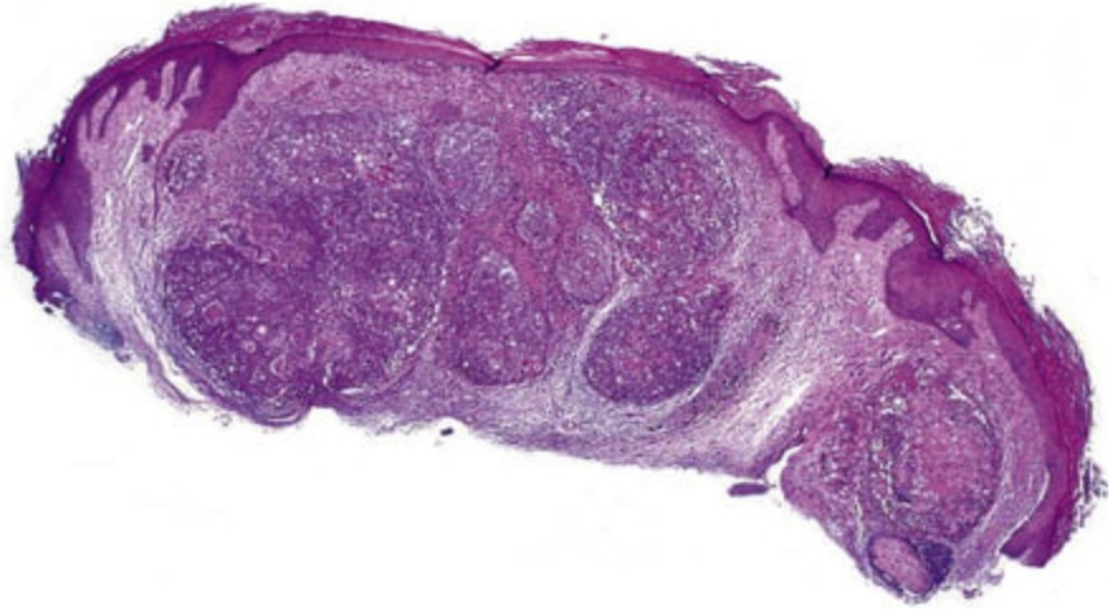
This histological image shows a biphasic tumor with two distinct components. The upper portion of the image features dark, basophilic lobules, which are clusters of cells with high nuclear density. The lower portion consists of larger, more irregular lobules that are predominantly eosinophilic (pink), indicating a higher cytoplasmic or extracellular matrix content. The interface between these two components is irregular, and the overall architecture suggests a complex growth pattern that could be mistaken for necrosis or a ruptured cyst.

Biphasic, mixed eosinophilic and basophilic tumor lobules



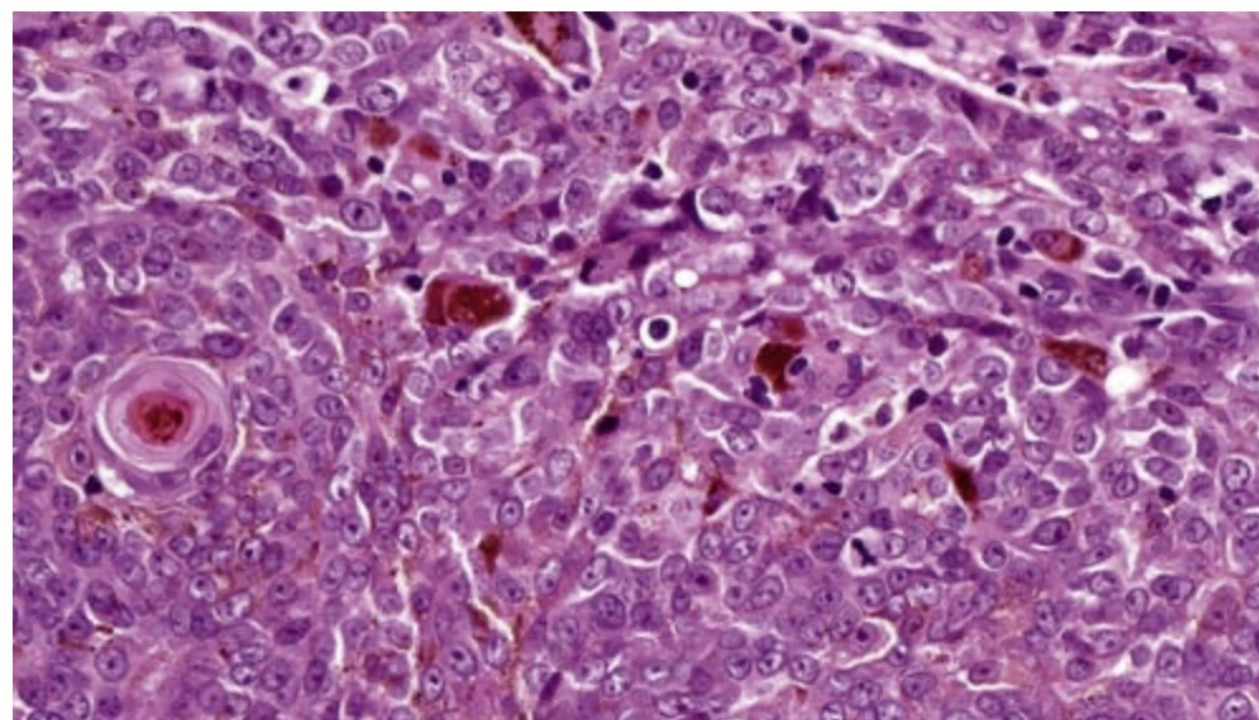
# PILOMATRIXOMA

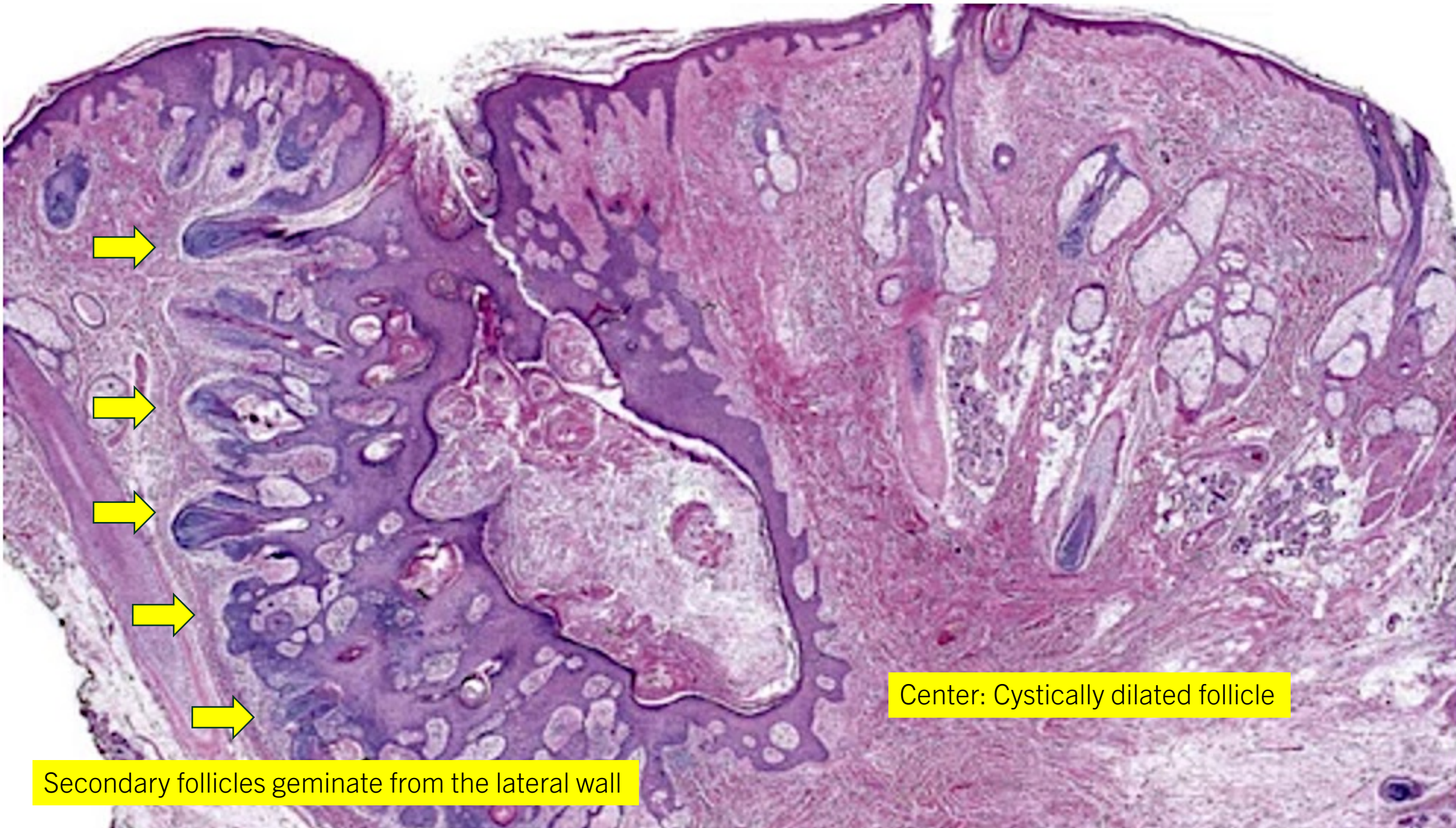
- Differentiation toward the hair matrix
- Solitary or multiple (AD disorder)
- Rare: dermatological marker of myotonic dystrophy, Gardner syndrome, MYH-associated polyposis
- Head, upper limbs, neck, trunk, and lower limbs
- Large chalky deposits especially in young children
- Beta-catenin mutations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



## MELANOCYTIC 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+





Center: Cystically dilated follicle

Secondary follicles geminate from the lateral wall

# 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





Small sebaceous lobules

Mature adipocytes

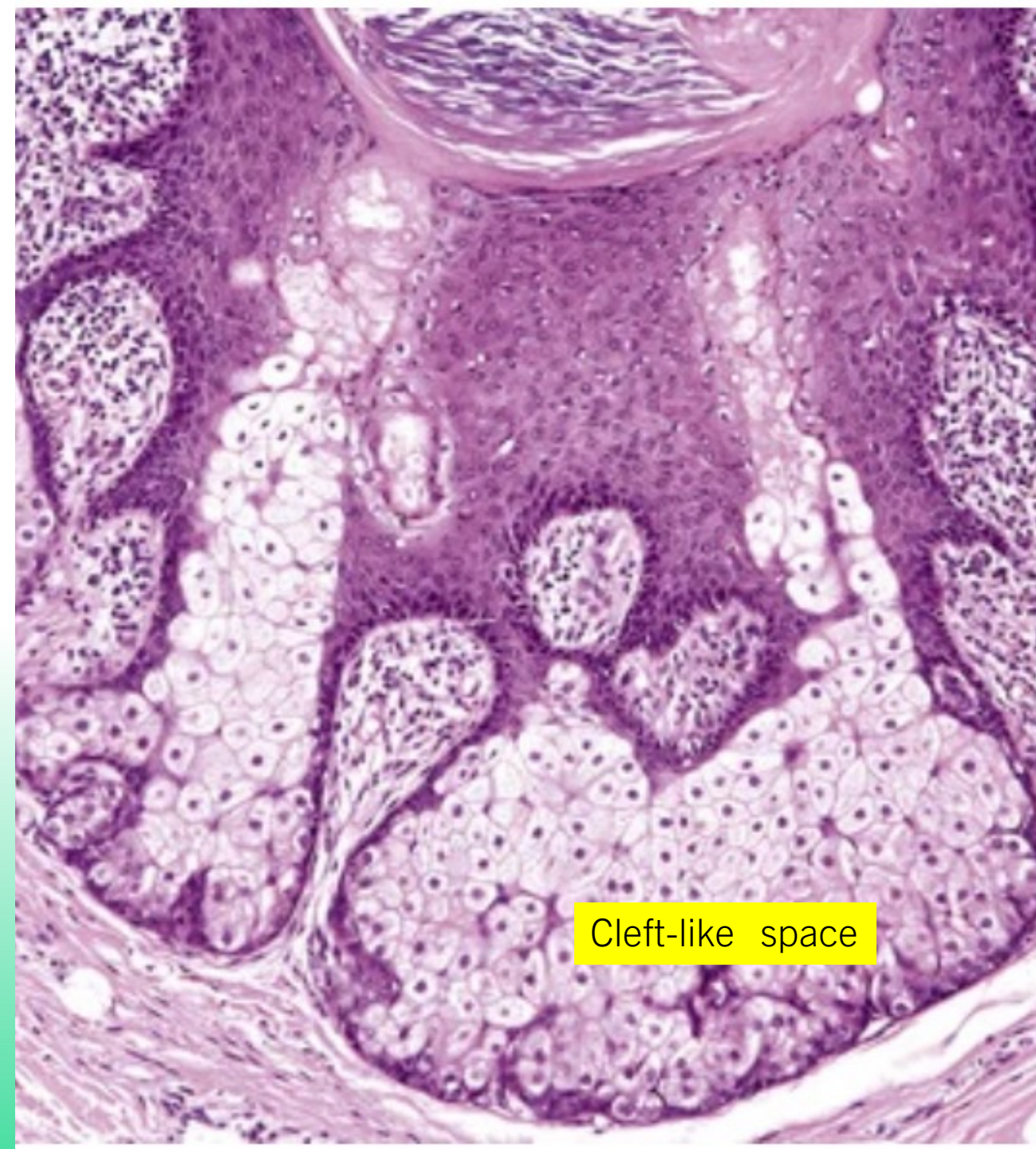
Stromal fibroplasia

Infundibular cystic cavity

Stratified  
squamous  
epithelium

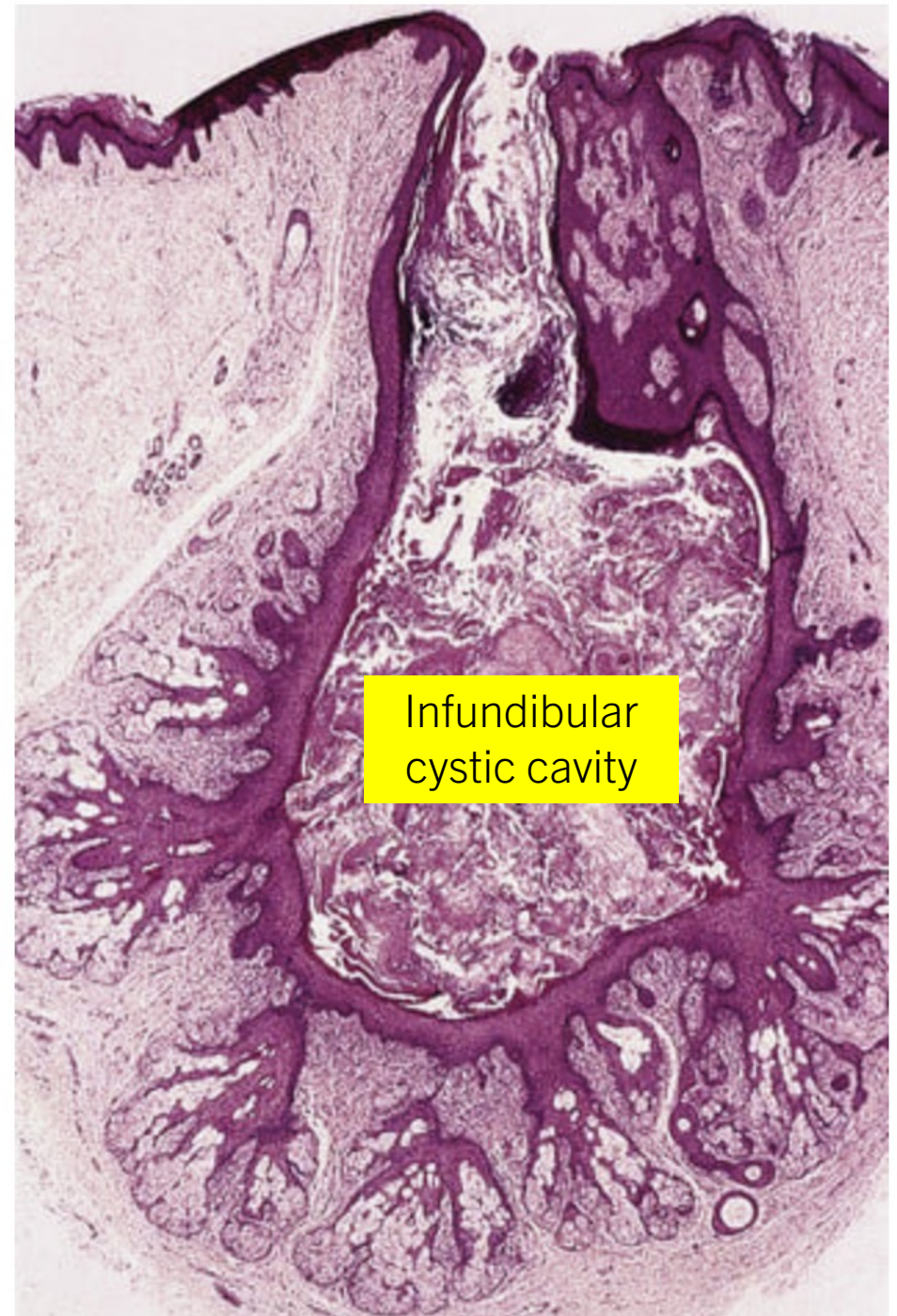
# FOLLICULOSEBACEOUS CYSTIC HAMARTOMA

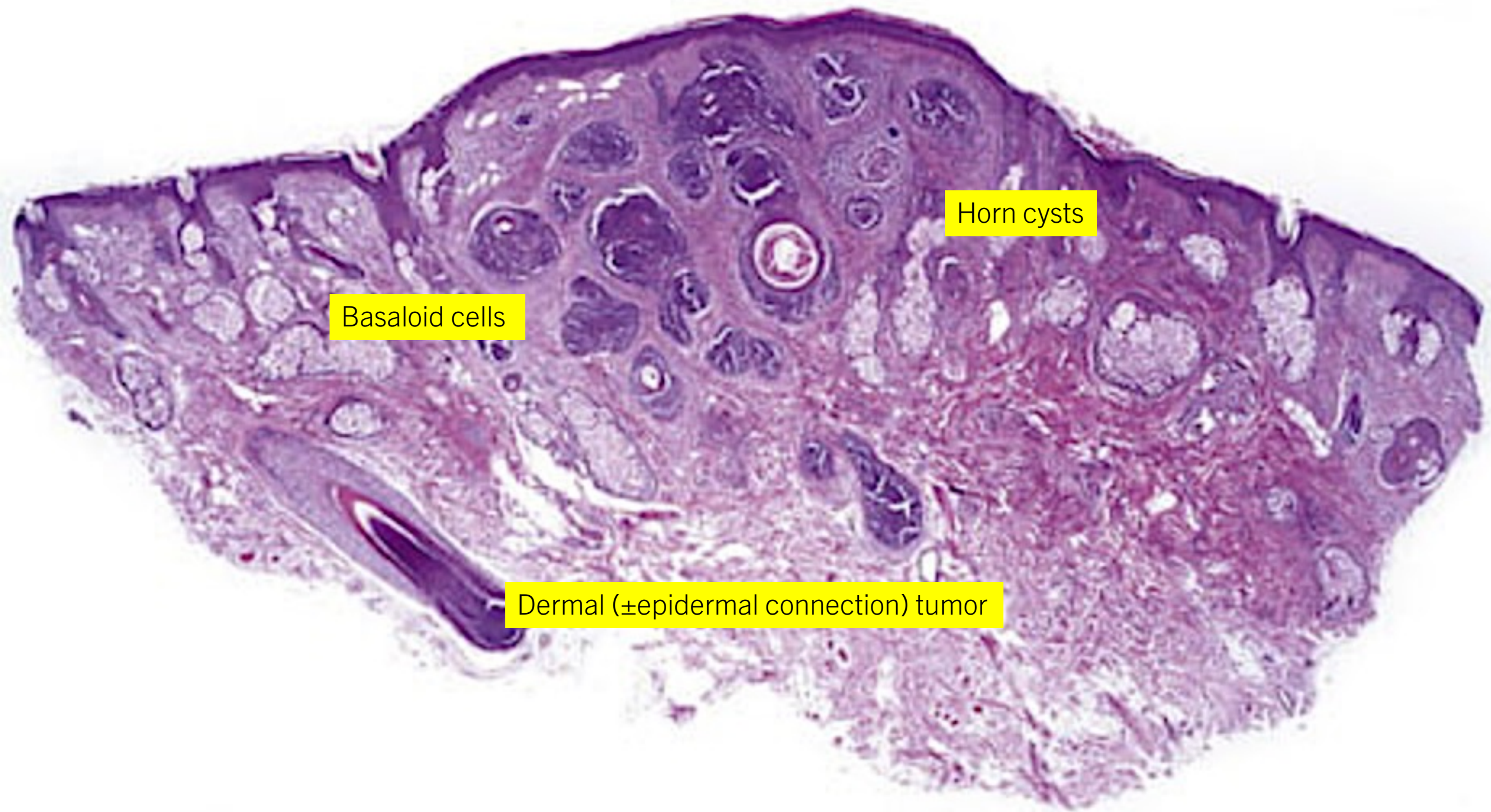
- Hamartoma: follicular, sebaceous and mesenchymal element
- Papule on the central face, nose
- Dermal based infundibular cystic cavity similar to trichofolliculoma
- Malformed hair follicles
- Mesenchymal elements: collagen, elastic fibers, adipose and vascular tissue
- DDX: trichofolliculoma



# SEBACEOUS TRICHOFOLLICULOMA

- Hamartoma similar to trichofolliculoma
- Solitary, depressed lesion on the nose, scrotum and penis
- Squamous-lined epithelium with infundibular keratinization
- Numerous sebaceous lobules
- DDX: dermoid cyst, median nasal dermoid fistula, sebaceous hyperplasia, folliculosebaceous cystic hamartoma

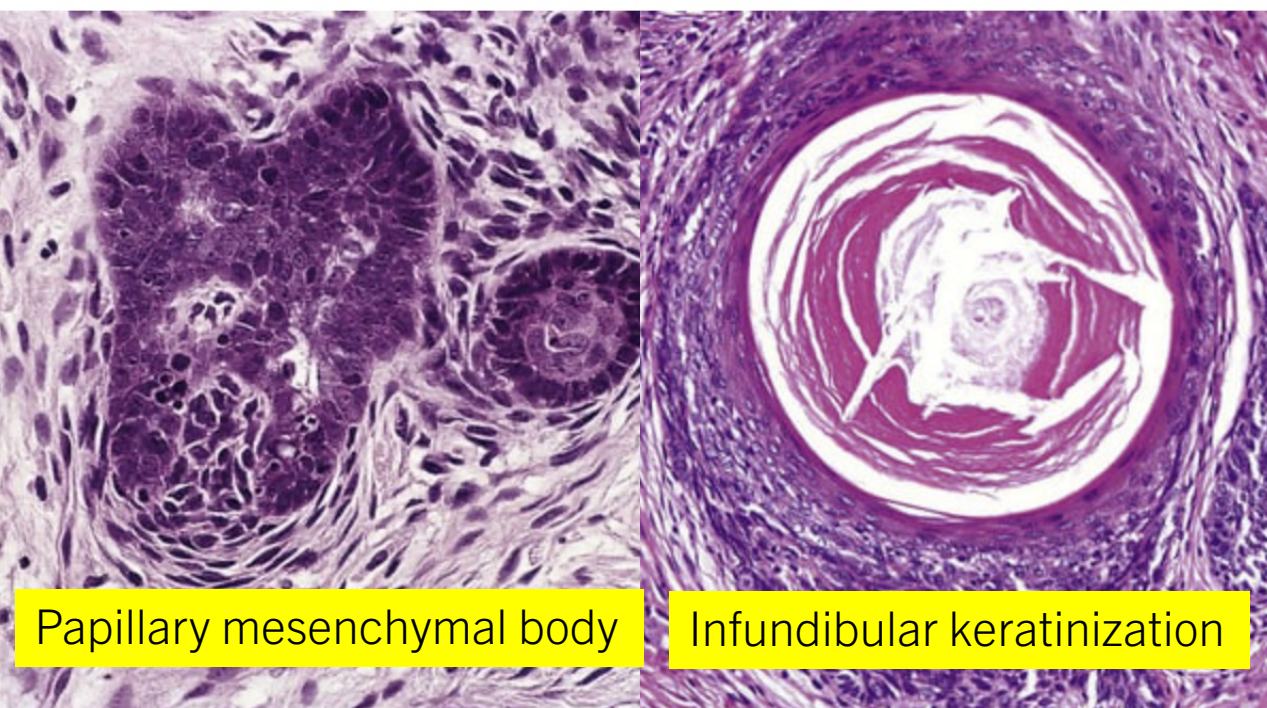




Basaloid cells

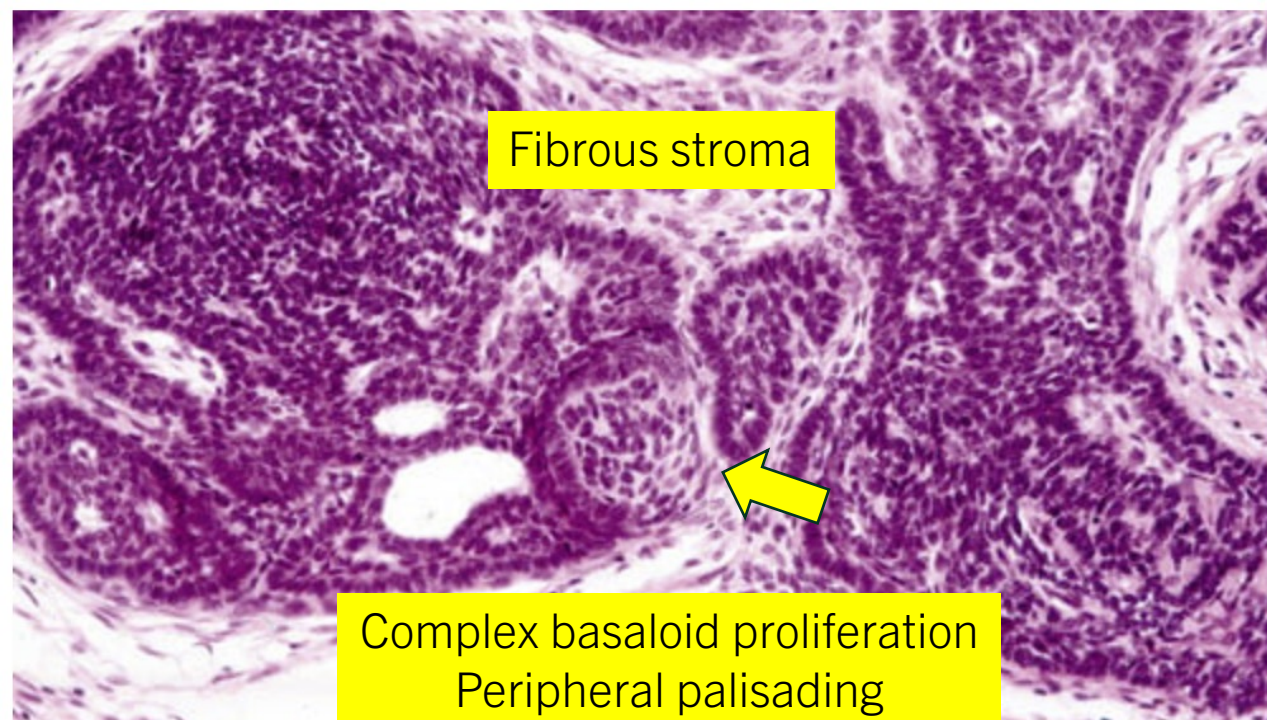
Horn cysts

Dermal ( $\pm$ epidermal connection) tumor



Papillary mesenchymal body

Infundibular keratinization



Fibrous stroma

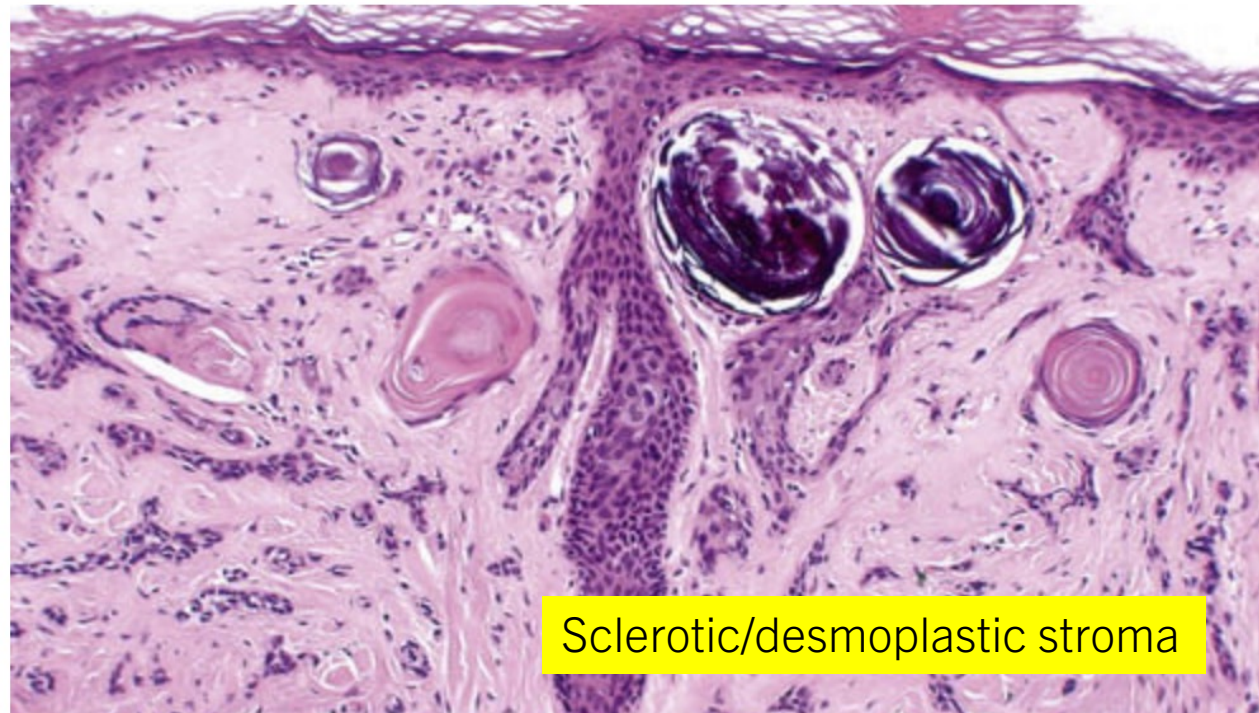
Complex basaloid proliferation  
Peripheral palisading

# TRICHOEPITHELIOMA

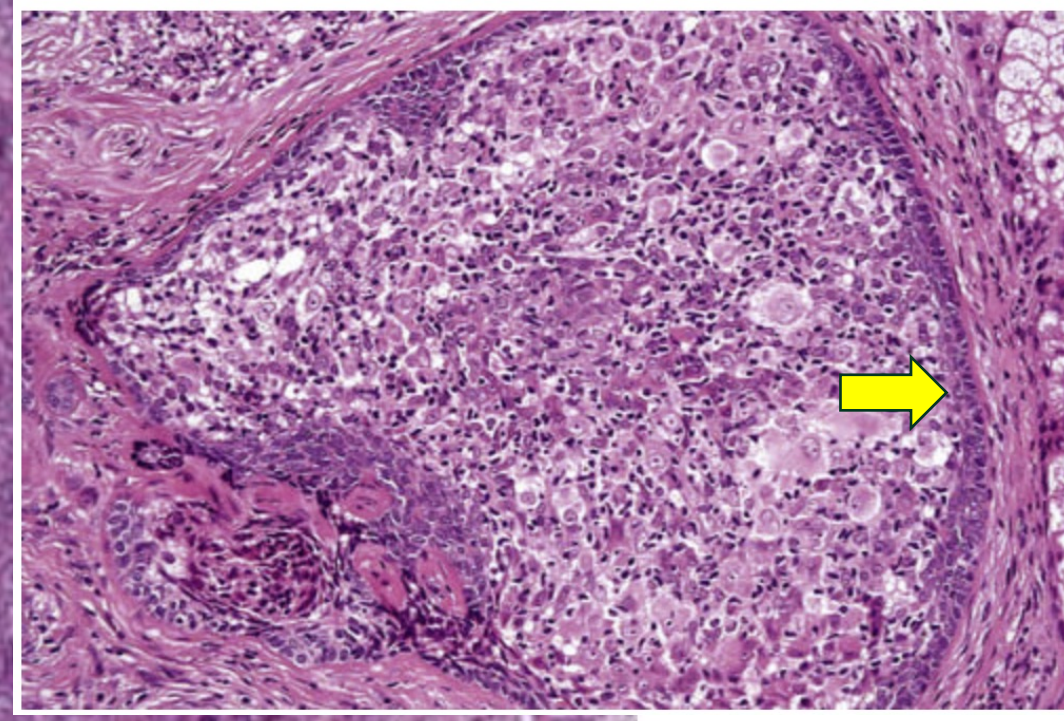
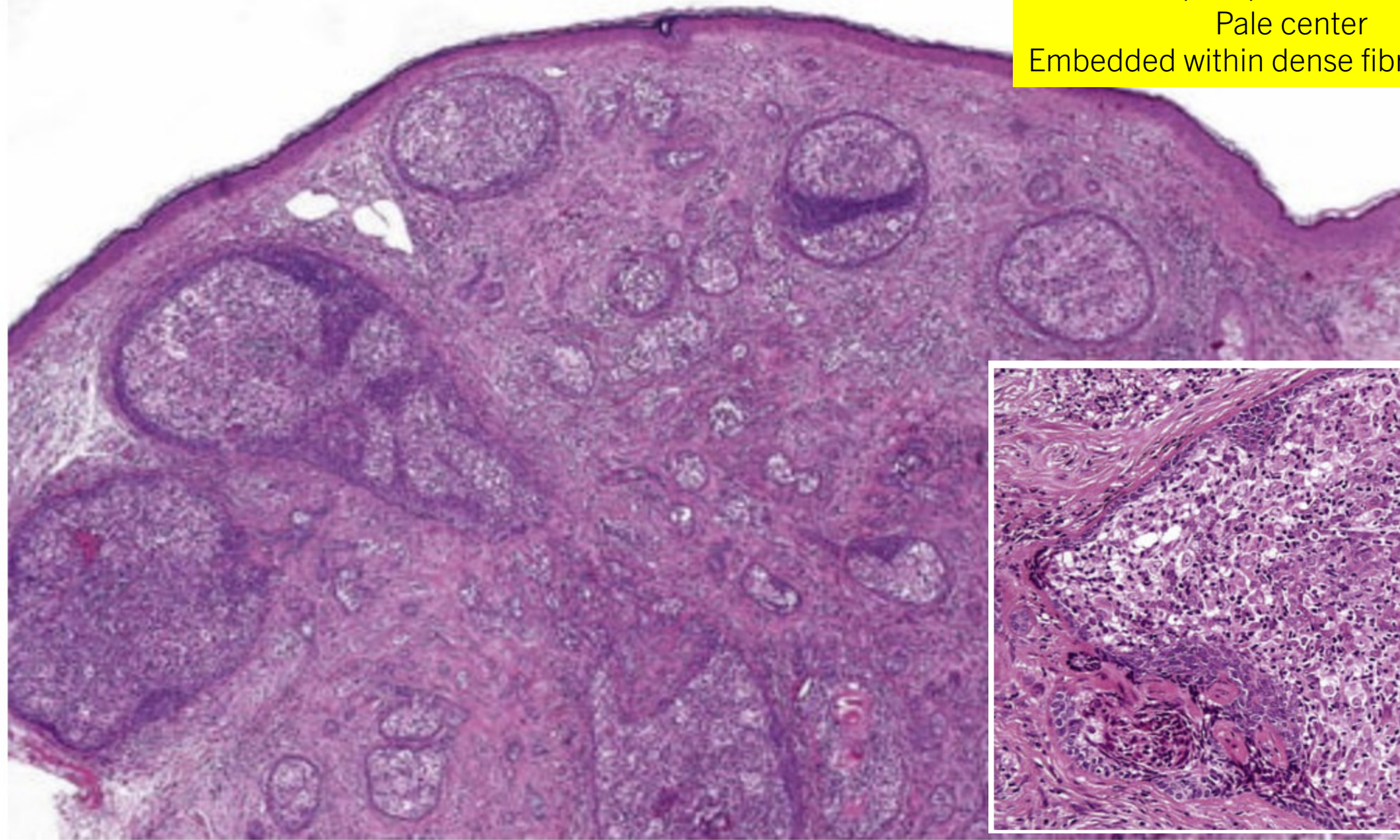
- Hamartoma with follicular differentiation
- Skin-colored papules, symmetrical
- Face
- *CYLD* gene mutations
- DDX: keratotic basal cell carcinoma (mucin, retraction), trichoblastoma
- IHC: trichoepithelioma CK15+  
Trichoblastoma (CK20+ Merkel cells)  
BCC (BCL-2+)  
Trichoepithelioma (CD34+ stromal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

# 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+)

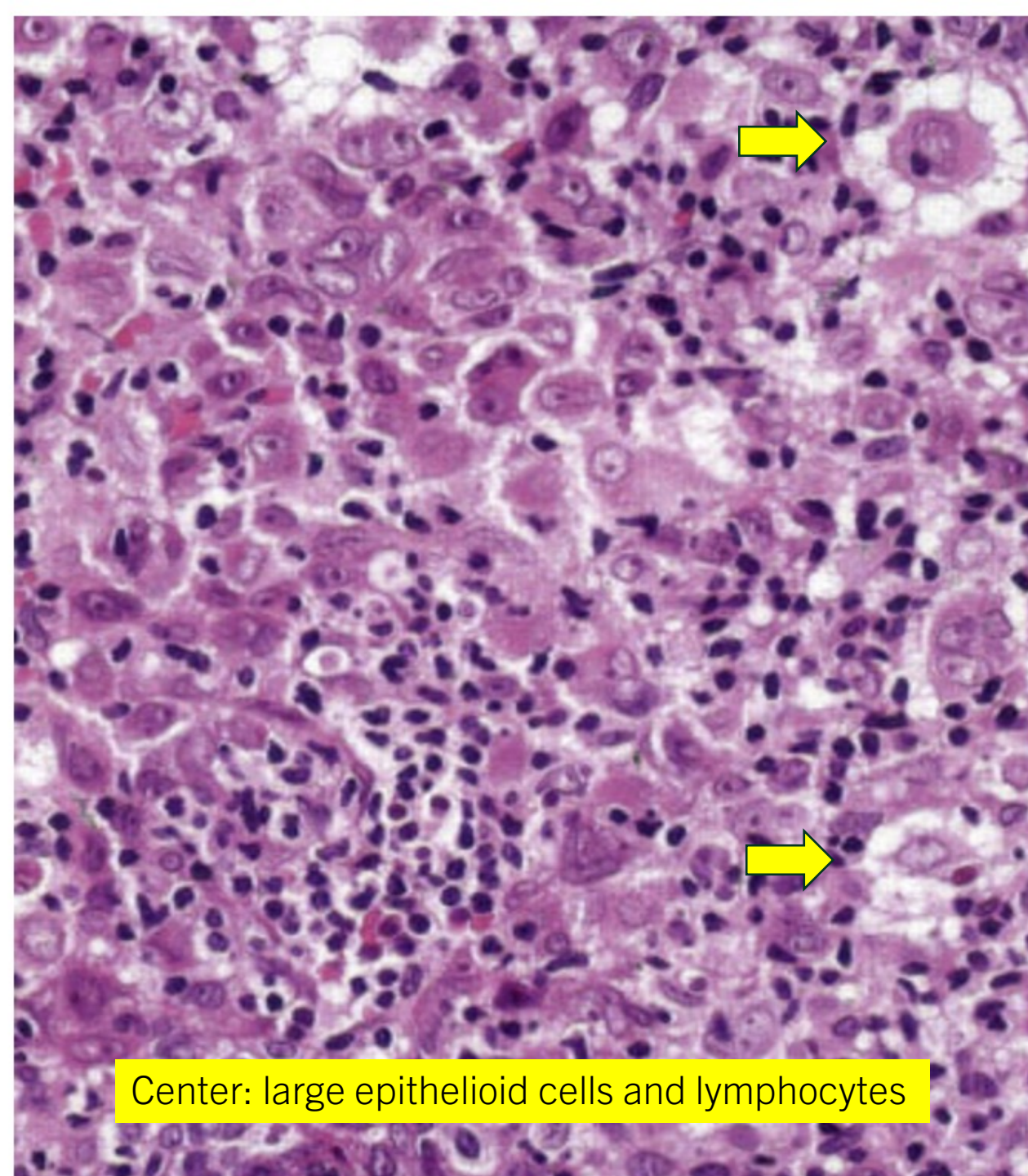


Multiple epithelial nodules  
Pale center  
Embedded within dense fibrous stroma



# CUTANEOUS LYMPHADENOMA

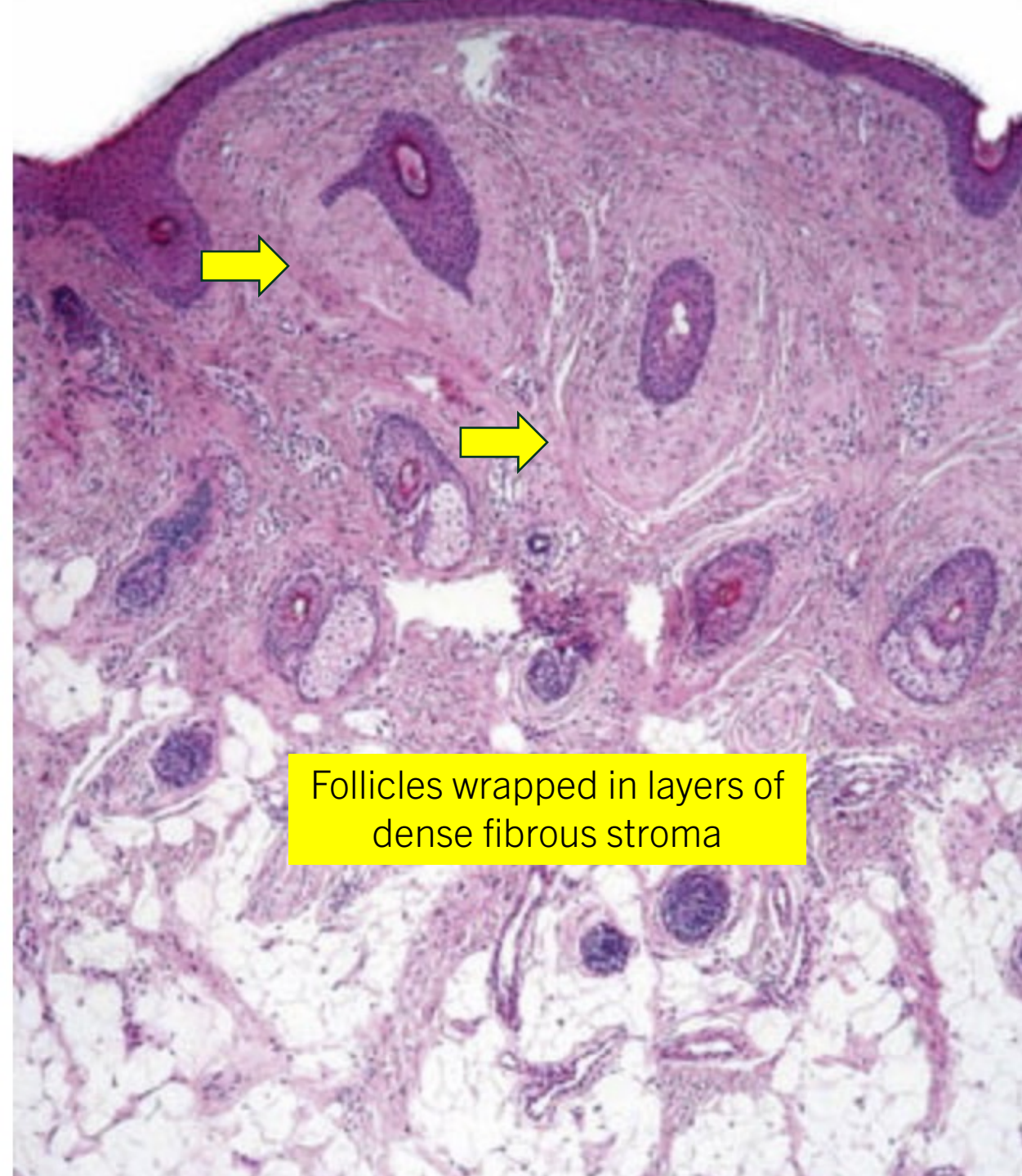
- Differentiation: pilosebaceous unit or variant of trichoblastoma
- Papule, nodule on the head, face
- Benign, indolent course
- Epithelial component, rimmed by basaloid cells
  - Small lymphocytes
  - Rare isolated sebaceous cells
  - Small ducts
- Lymphoid follicles in the stroma
- DDX: lymphoepithelial-like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

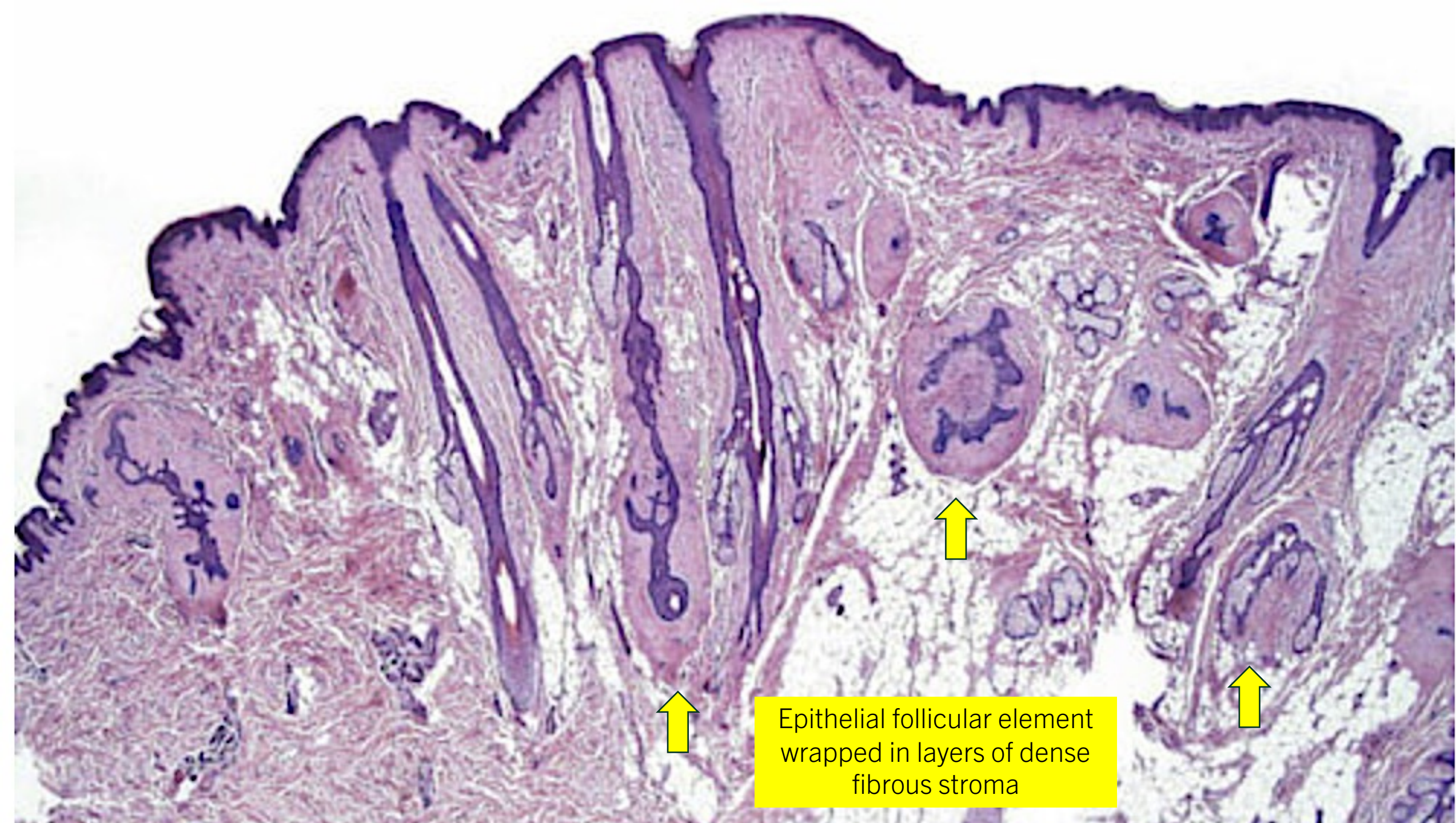


Center: large epithelioid cells and lymphocytes

# PERIFOLLICULAR FIBROMA

- Nevoid/hamartoma of perifollicular sheath
- Skin-colored papule on the face
- Inherited PFs + colonic polyps = Birt-Hogg-Dube and Hornstein-Knickenberg syndromes
- Layers of fibrous stroma 'onion skin'
- Cleft: stroma pulls away from dermal collagen





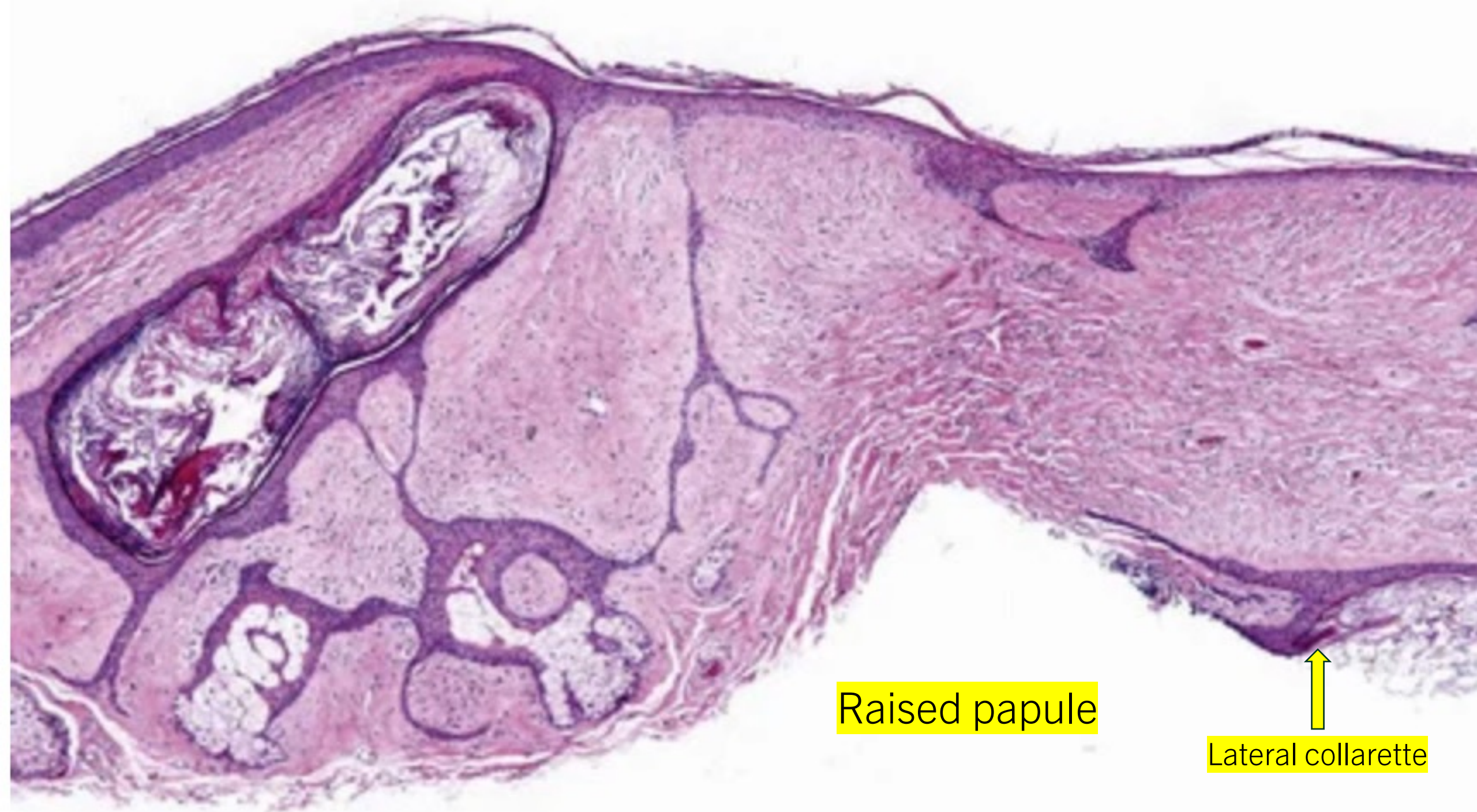
Epithelial follicular element  
wrapped in layers of dense  
fibrous stroma

# FIBROFOLLICULOMA

- Solitary facial, pale yellow papule
- If multiple: isolated or syndrome
  - Connective tissue nevus
  - Tuberous sclerosis
  - Birt-Hogg-Dube syndrome
- Hamartoma: external root sheath epithelial component + excess fibrous stroma
- DDX: perifollicular fibroma



Infundibulum surrounded by thick fibrous stroma

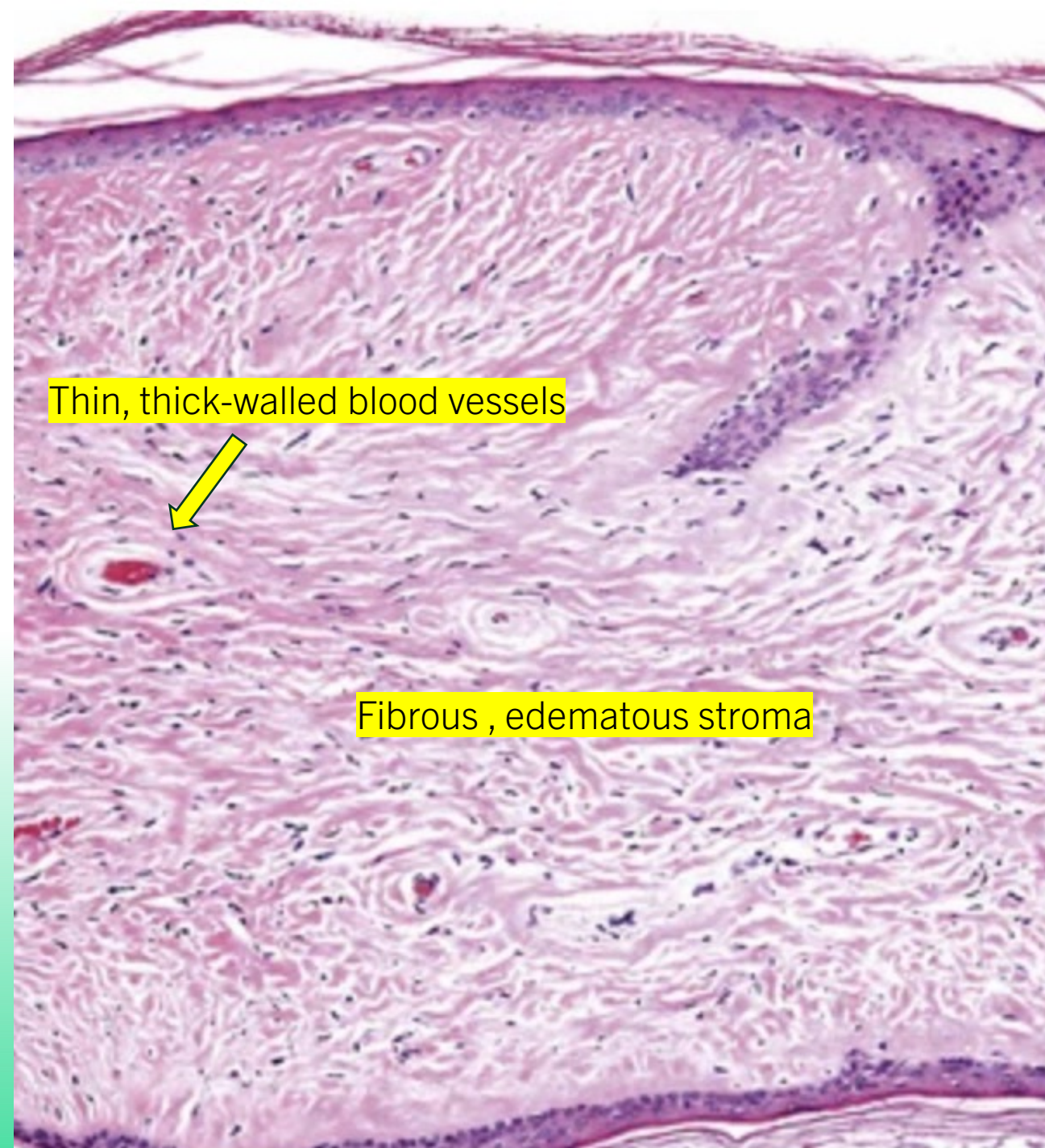


Raised papule

Lateral collarette

# TRICHODISCOMA

- Hundreds of 1-5 mm skin-colored  
**Birt-Hogg-Dube syndrome**
- Hamartoma of hair disc
- Related to a hair follicle (needs levels)
- Edema: acid mucopolysaccharides
- Merkel cells absent
- IHC: spindle cells CD34+  
S100, SMA, EMA and desmin-

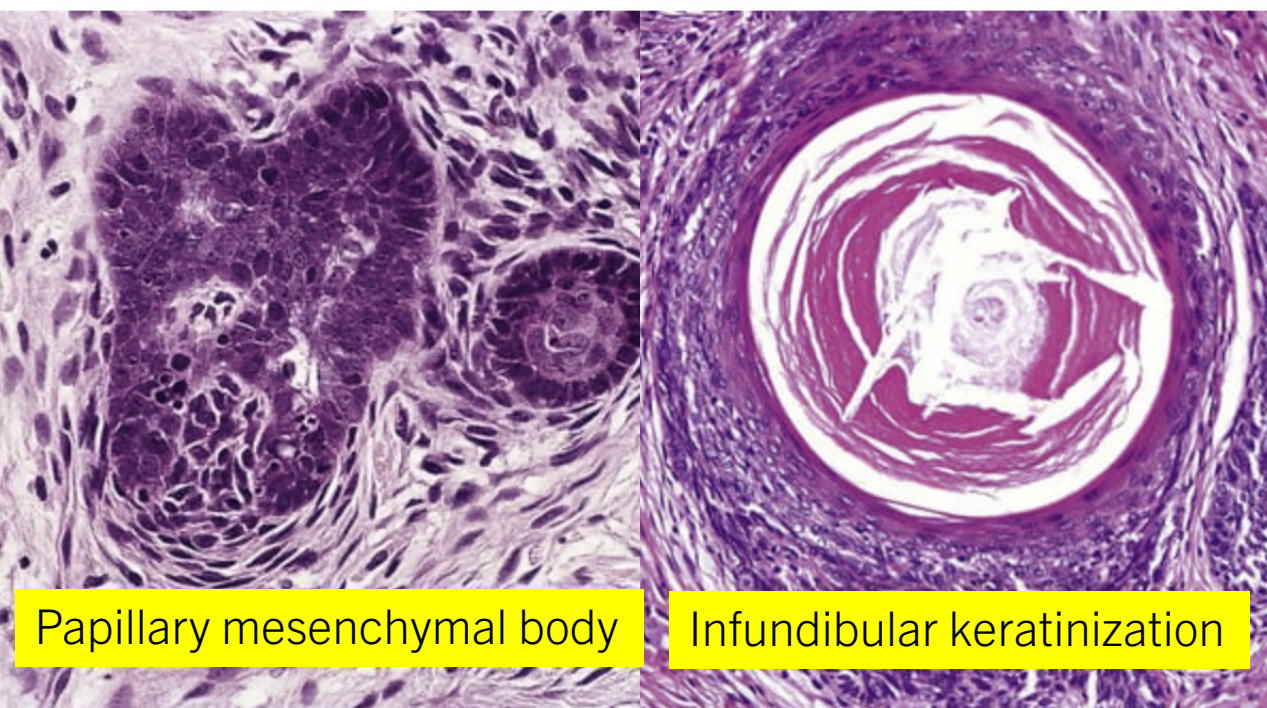


# BIRT-HOGG-DUBE SYNDROME

- Susceptibility locus *BHD* gene, encodes for folliculin
  - Putative tumor suppressor gene in mTOR
- Skin: multiple trichodiscoma, fibrofolliculoma, and acrochorda
- Hundreds of 1-5 mm skin-colored firm papules
- Face, neck and trunk
- Renal: bilateral oncocytoma, chromophobe, RCC, clear cell RCC
- Lung disease: Pulmonary cysts, spontaneous pneumothorax, and bullous emphysema
- Thyroid disease: medullary thyroid carcinoma, follicular adenoma, and goiter

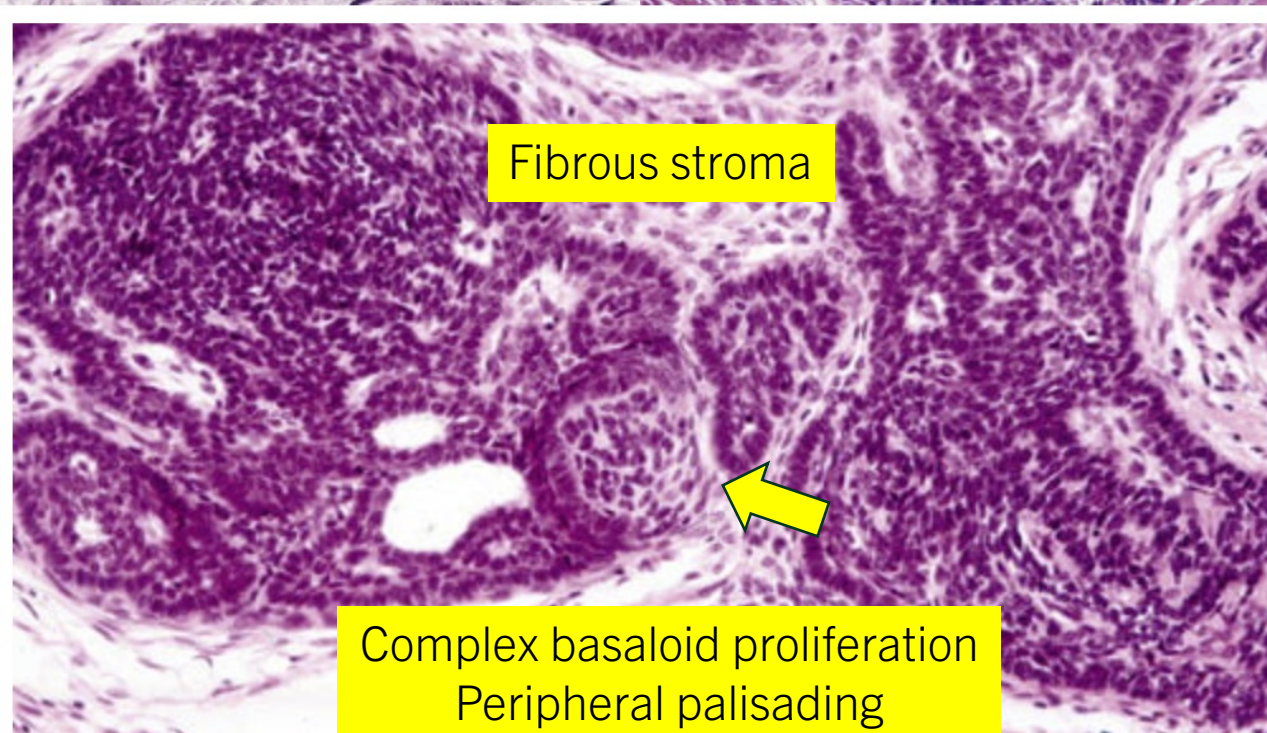
## Hornstein-Knickenberg syndrome

- Skin: numerous papules on face, neck, and trunk, perifollicular fibromas
- Colon: adenocarcinoma and adenomatous polyps
- Maybe manifestations of the same disease



# 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)



# SYNDROME ASSOCIATED WITH FOLLICULAR TUMORS

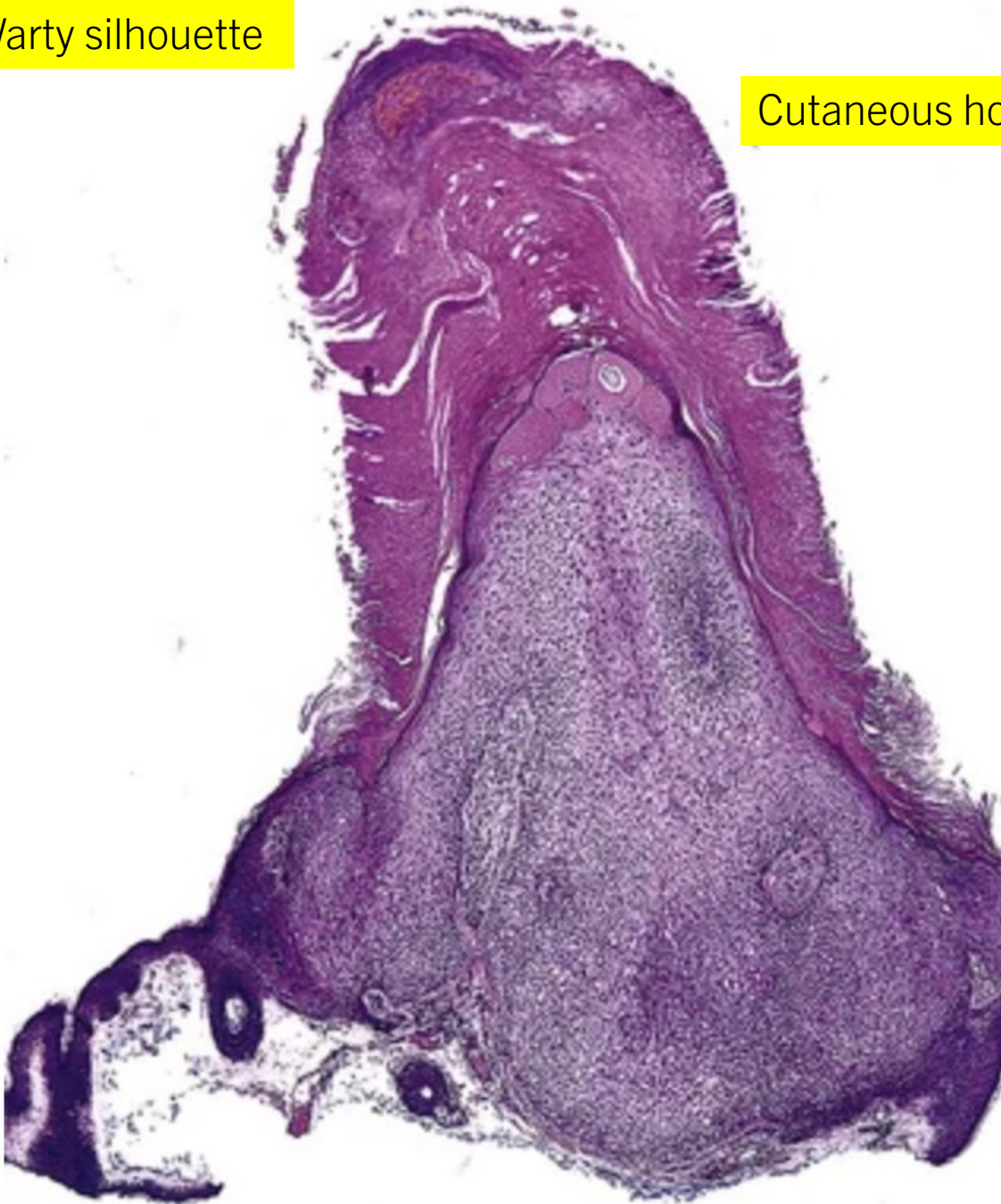
Broke-Spiegler syndrome:

- Spiroadenomas, cylindromas, trichoepitheliomas (NLF), and milia
- Salivary gland tumor – basal cell adenoma
- Renal and pulmonary cysts
- Mutations in *CYLD*, tumor suppressor gene
- Rombo syndrome: Multiple trichoepitheliomas, milia, BCC, and vellus hair cysts



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

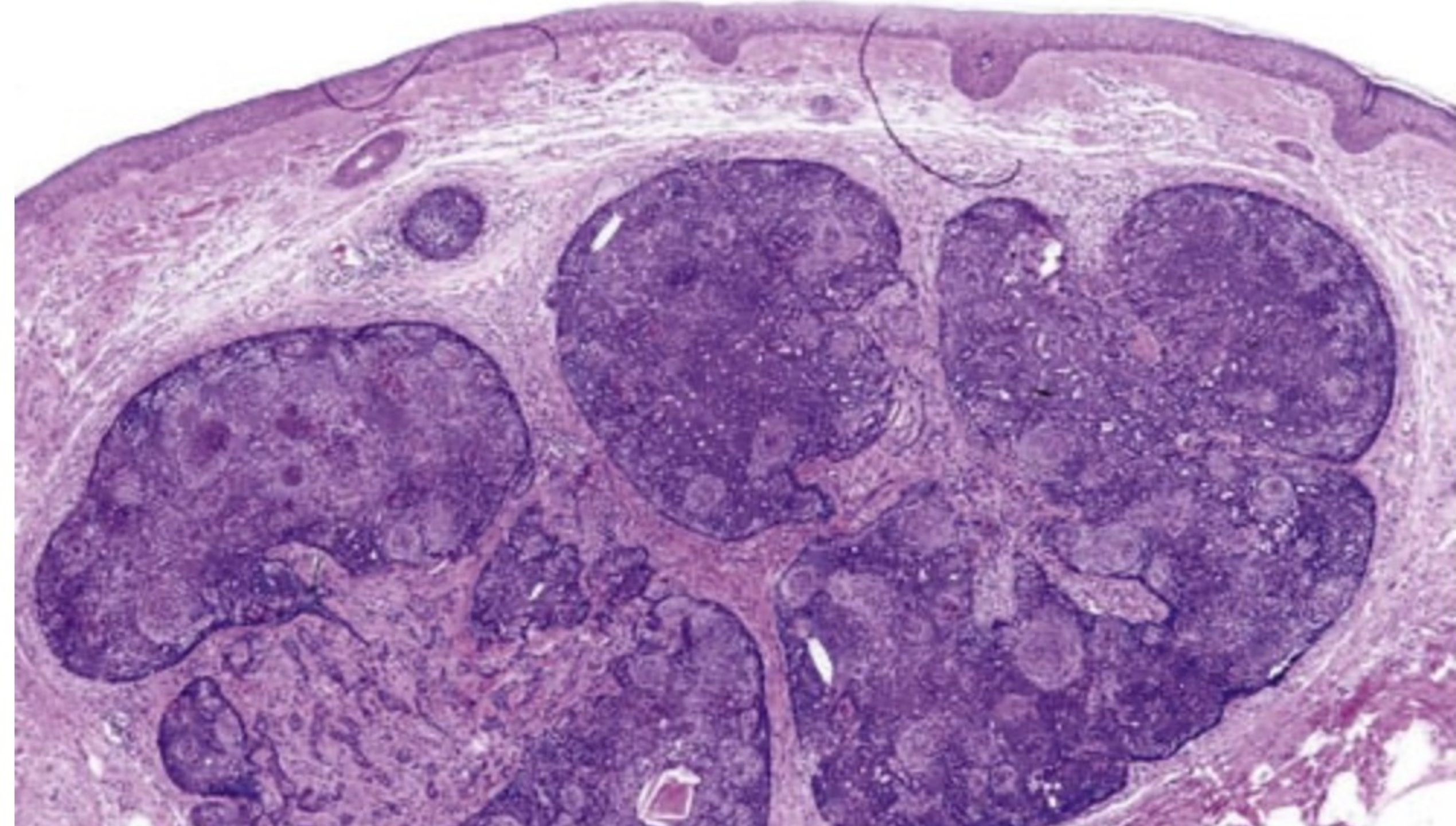
# COWDEN (MULTIPLE HAMARTOMA) DISEASE

- Multiple trichilemmomas, dermal fibromas, and acrochorda
- Located on face, around the mouth, nose, and ears
- Skin colored or brownish scaly acral keratoses on dorsal and ventral hands and feet
- Oral mucosa: papules and polyps
- Breast carcinoma
- Thyroid, carcinoma, especially follicular thyroid
- *PTEN* tumor suppressor gene (cell cycle arrest and apoptosis)
- IHC: complete loss of PTEN (phosphatase tensin gene) expression in trichilemmomas (Cowden)

Mucocutaneous lesions: trichilemmomas, fibromas, oral papillomatosis

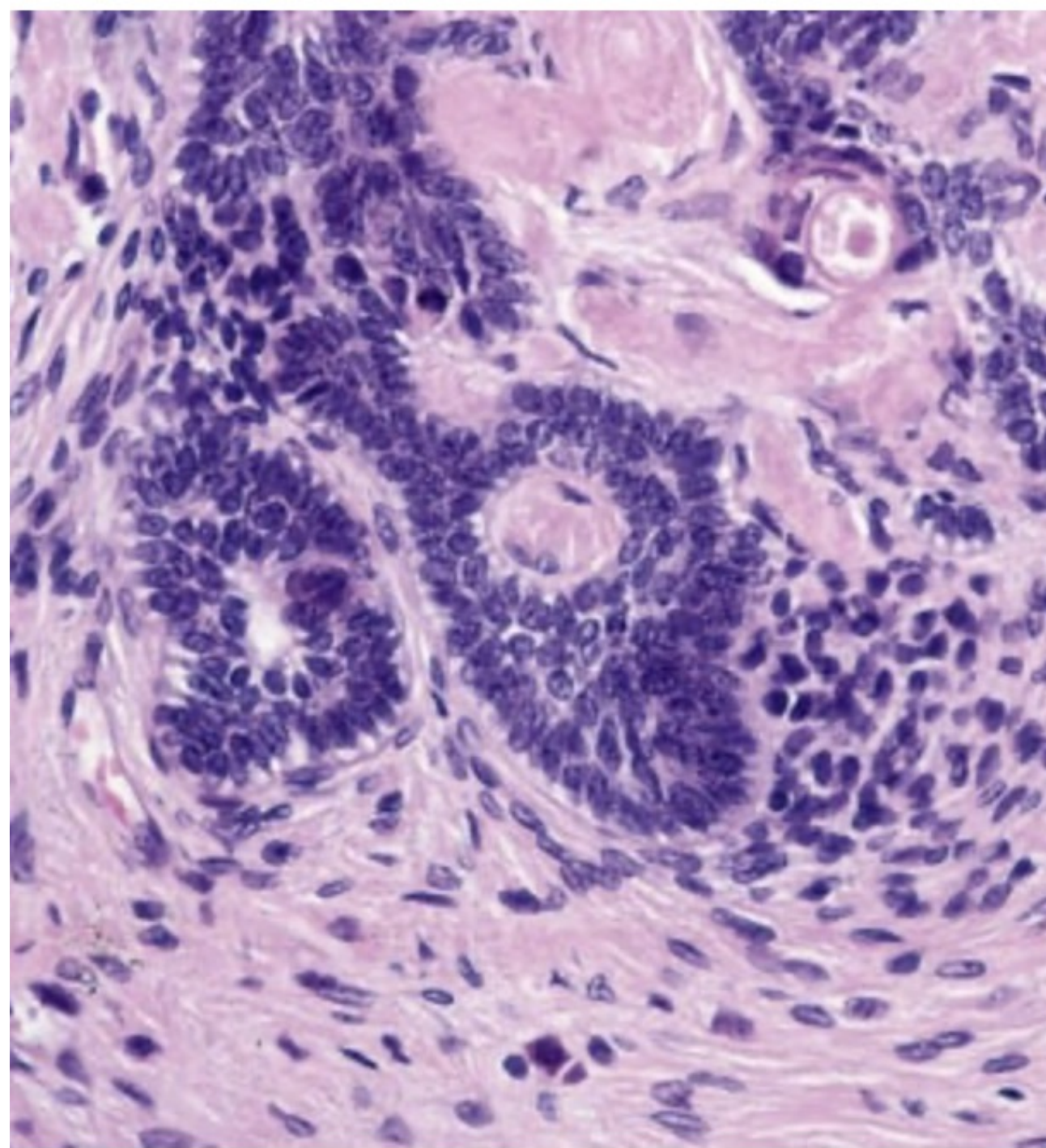


**QUIZLET**



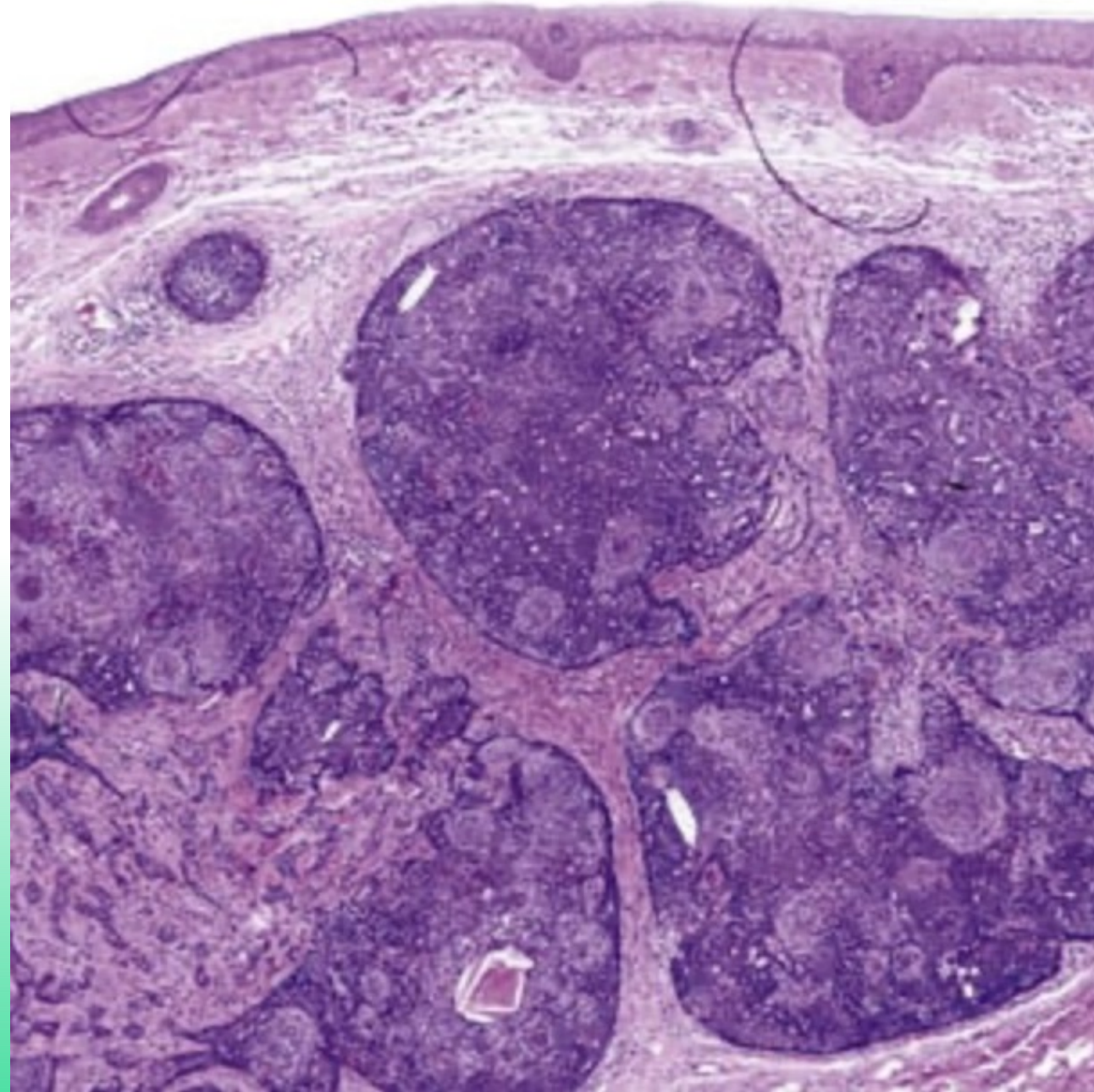
# WHAT IS YOUR DIAGNOSIS?

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



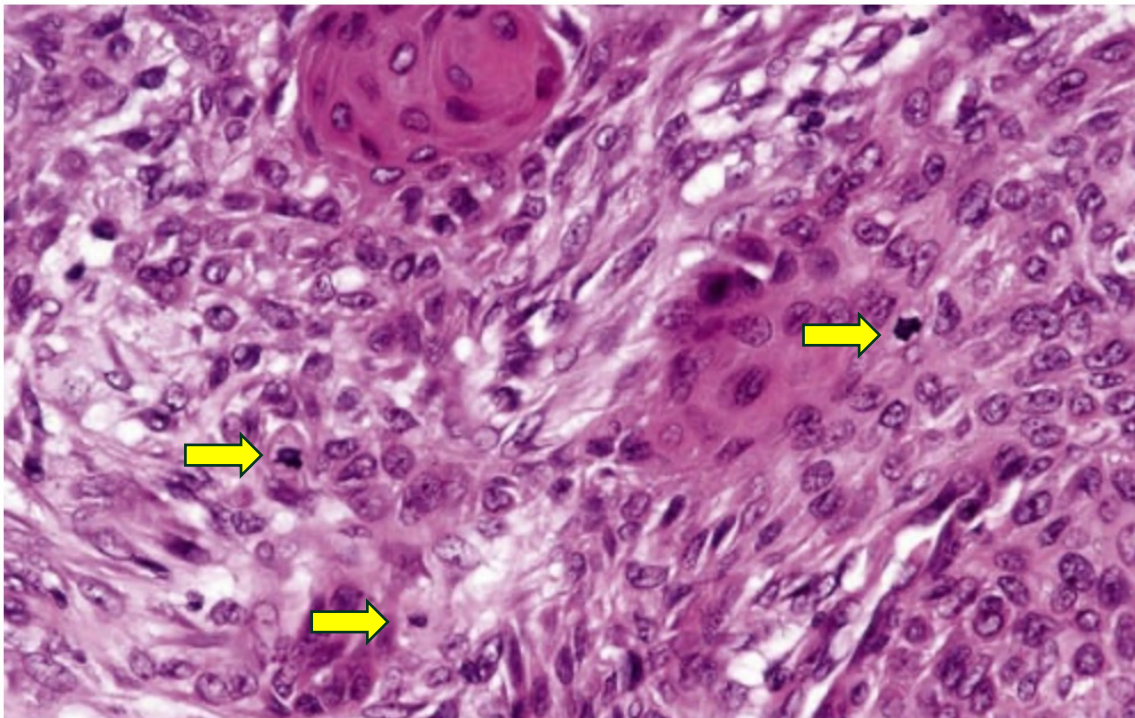
# ANSWER: TRICHOBLASTOMA

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



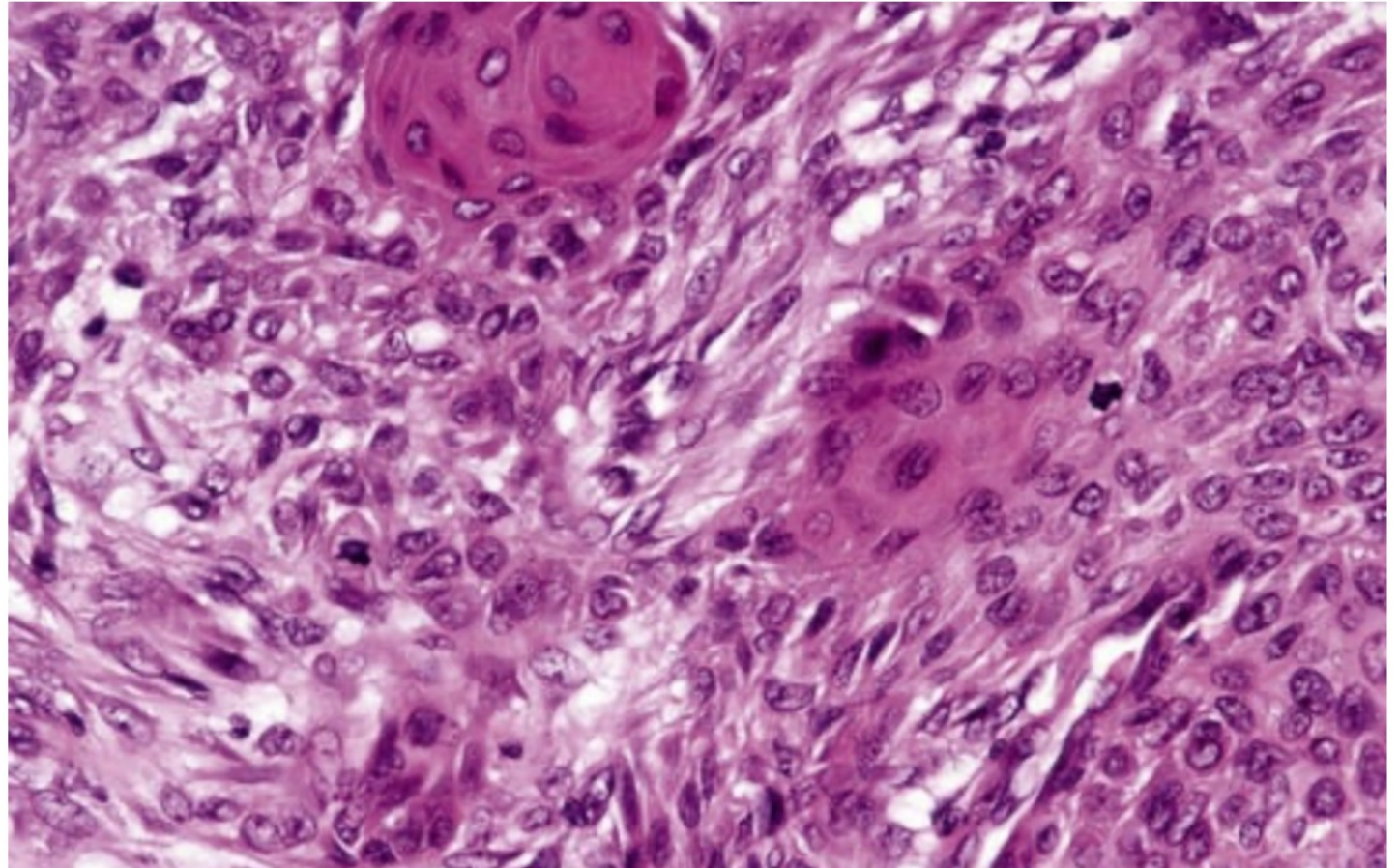
78M with keratotic tumor left lower eyelid  
What is your diagnosis?

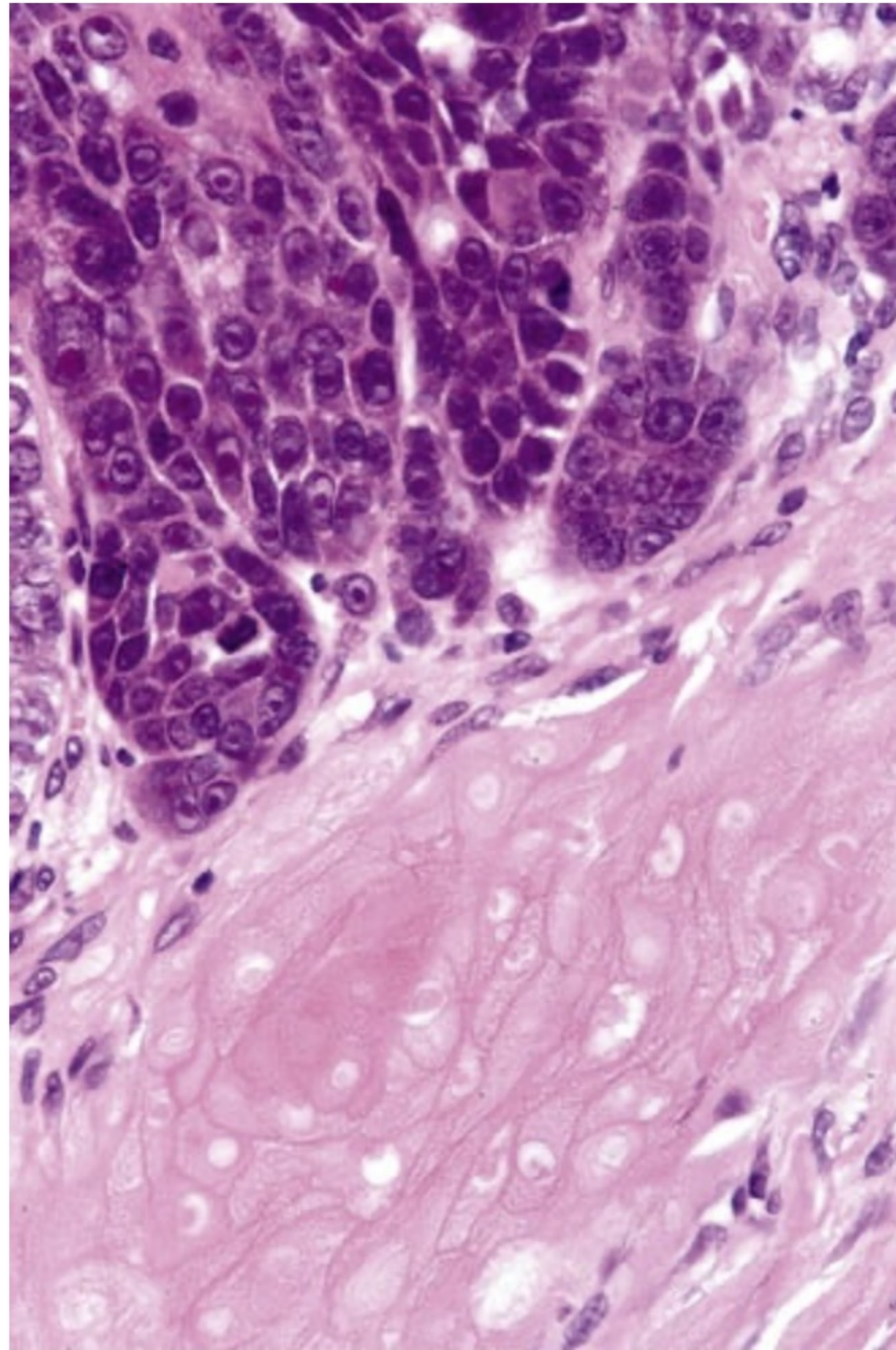
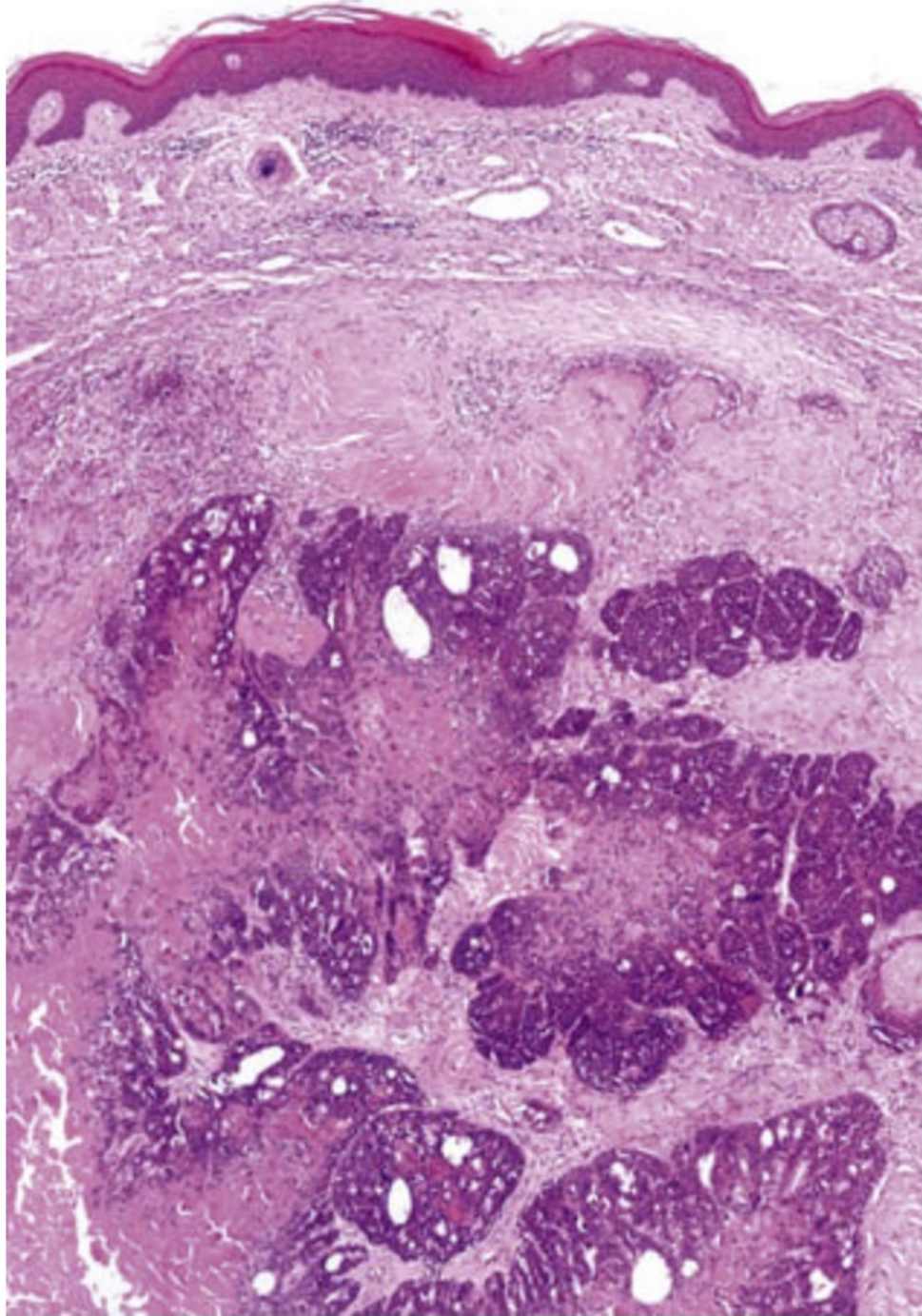
- A. Desmoplastic trichilemmoma
- B. Porocarcinoma
- C. Squamous cell carcinoma
- D. Trichilemmal carcinoma
- E. Inverted follicular keratosis



# ANSWER: TRICHILEMMAL CARCINOMA

- Infiltrating edge, atypia -> carcinoma
- Lack of granular cells -> trichilemmal differentiation
- IHC: negative CEA, EMA



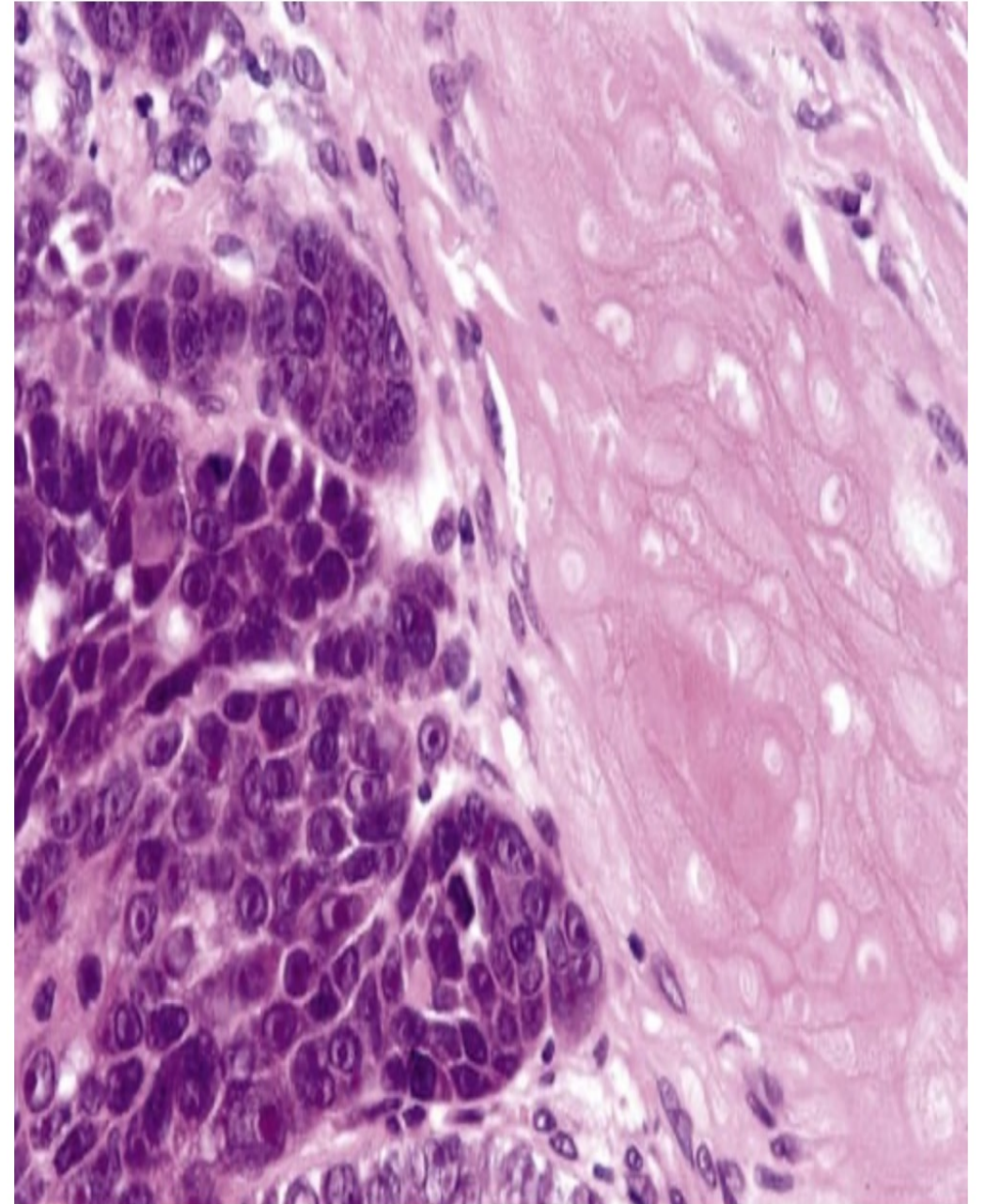


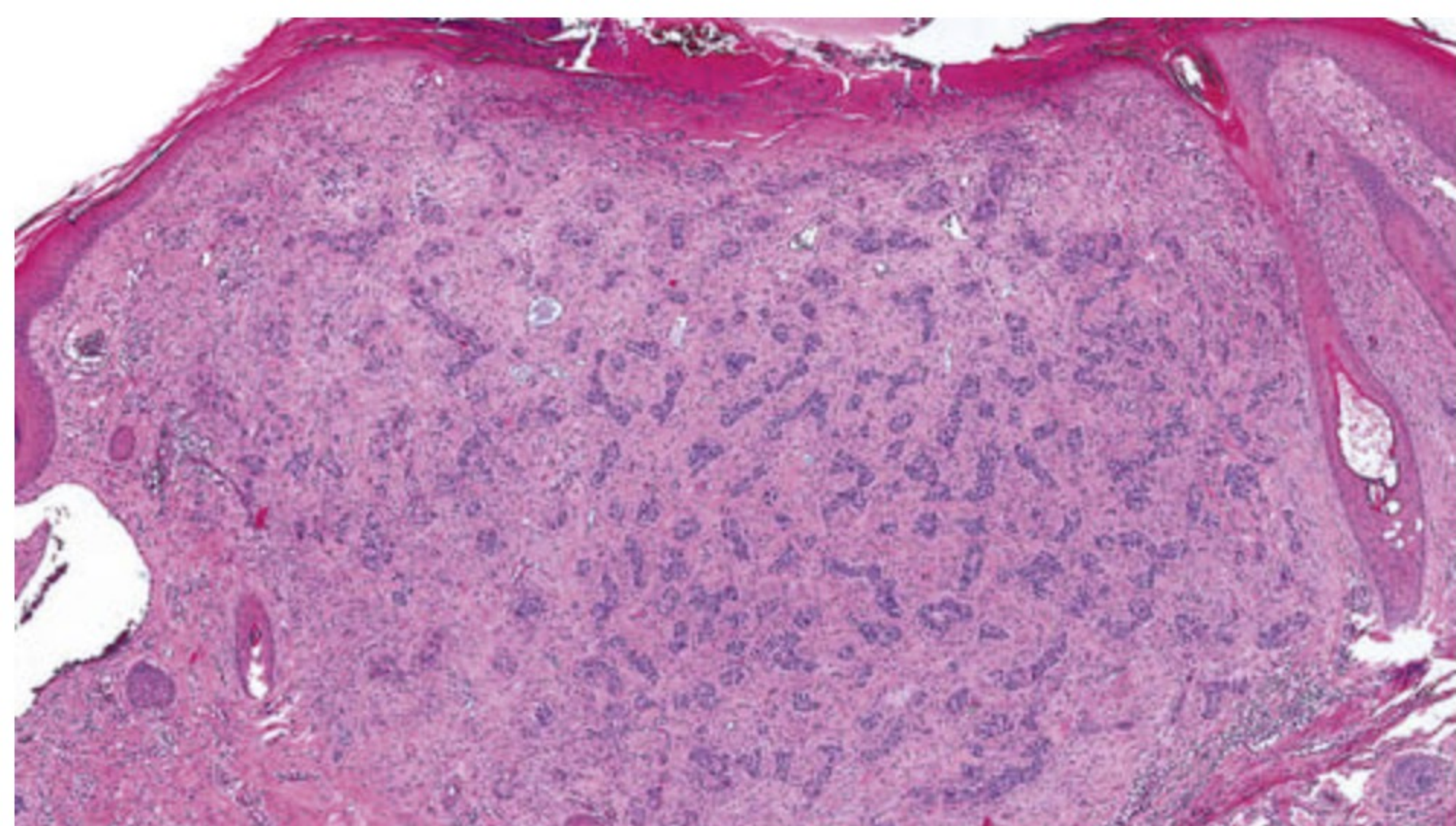
## WHAT IS YOUR DIAGNOSIS?

- A. Basal cell carcinoma
- B. Hidradenoma
- C. Squamous cell carcinoma
- D. Pilomatrixoma
- E. Pilomatrix carcinoma

# ANSWER: PILOMATRIX CARCINOMA

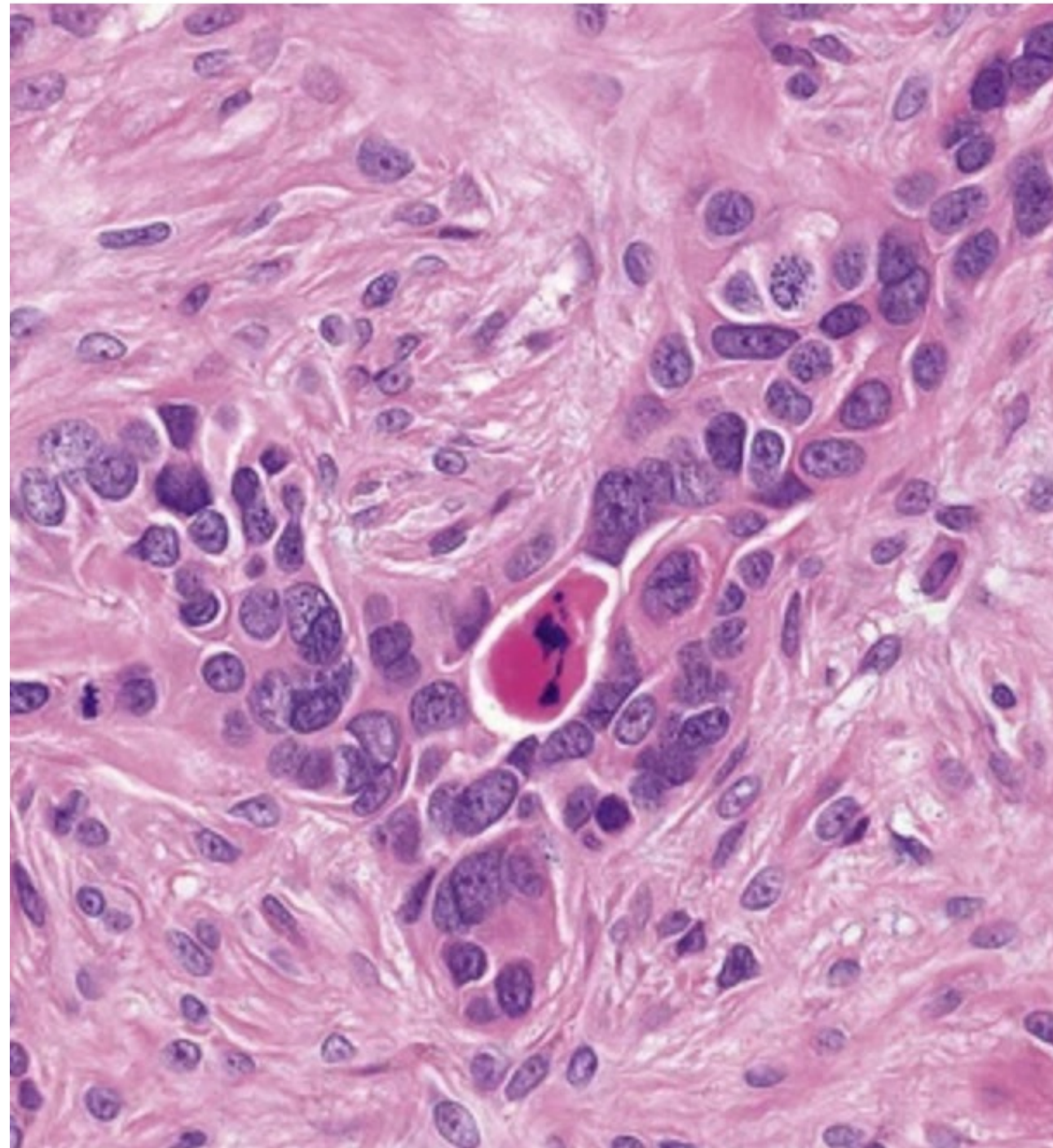
- Biphasic morphology: atypical basaloid cells and shadow cells
- Infiltrating edge, atypia -> carcinoma
- Recurrences common
- Limited metastatic potential





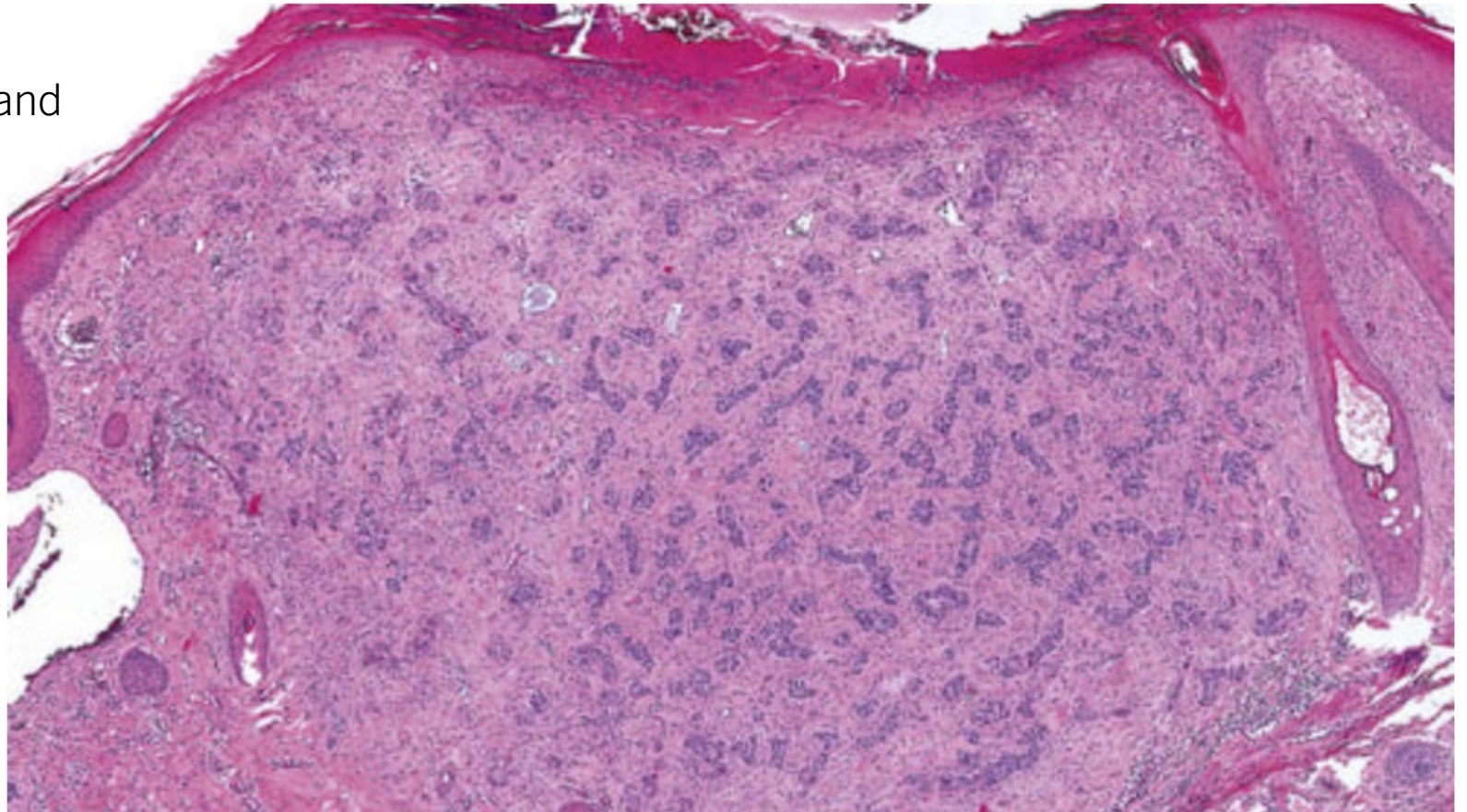
# WHAT IS YOUR DIAGNOSIS?

- A. Trichoepithelioma
- B. Trichoblastoma
- C. Syringoma
- D. Microcystic adnexal carcinoma
- E. Malignant trichoblastoma



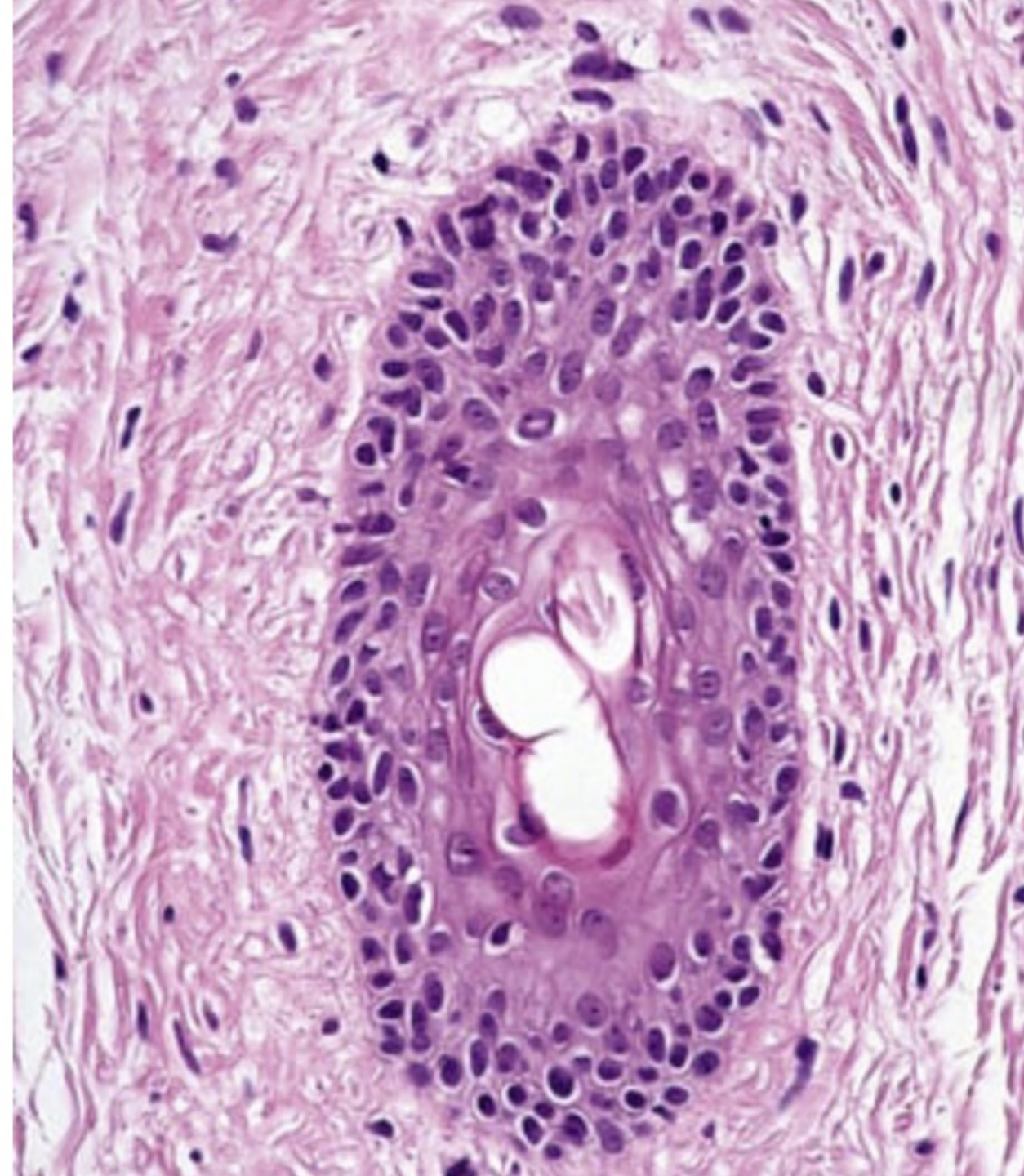
# ANSWER: MALIGNANT TRICHOBLASTOMA

- Biphasic basaloid proliferation and fibrotic stroma
- Ulcerated
- Infiltrating pattern
- Nuclear pleomorphism
- Mitoses



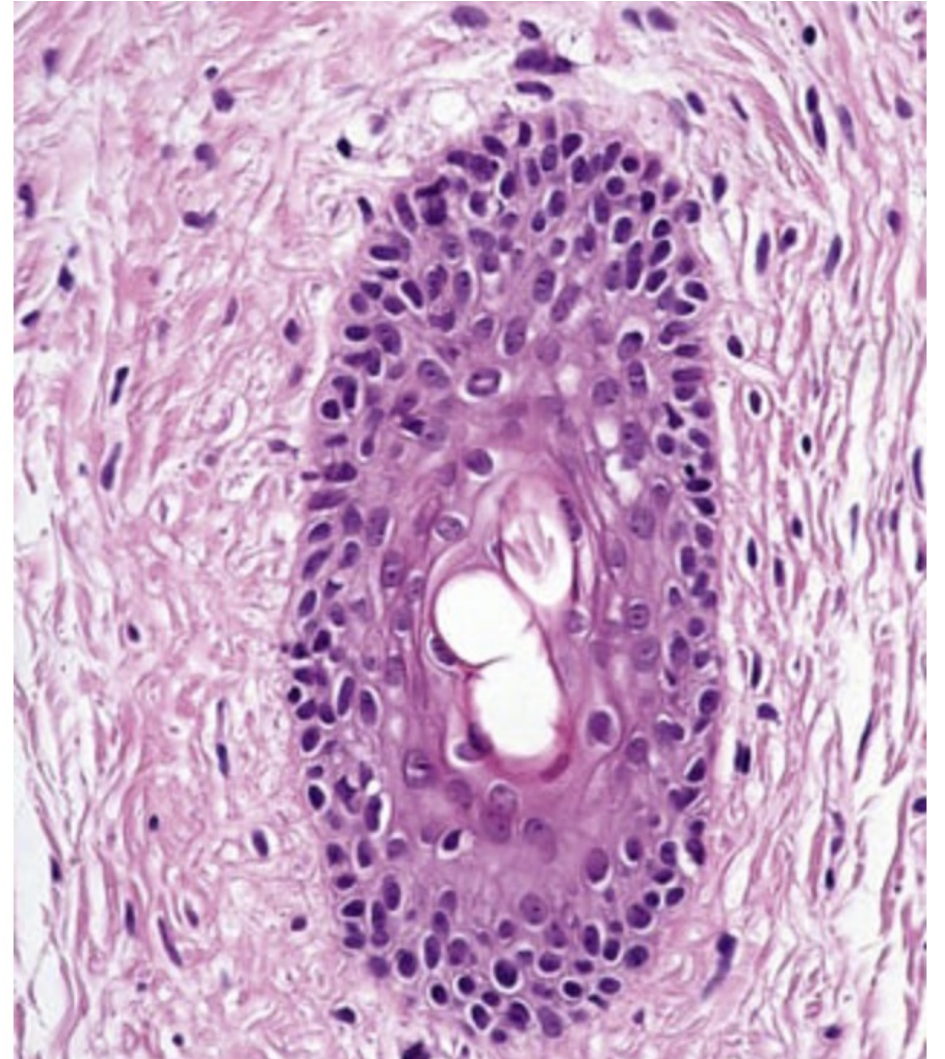
# WHAT IS YOUR DIAGNOSIS?

- A. Fibrofolliculoma
- B. Perifollicular fibroma
- C. Trichofolliculoma
- D. Trichodiscoma
- E. Normal hair follicle



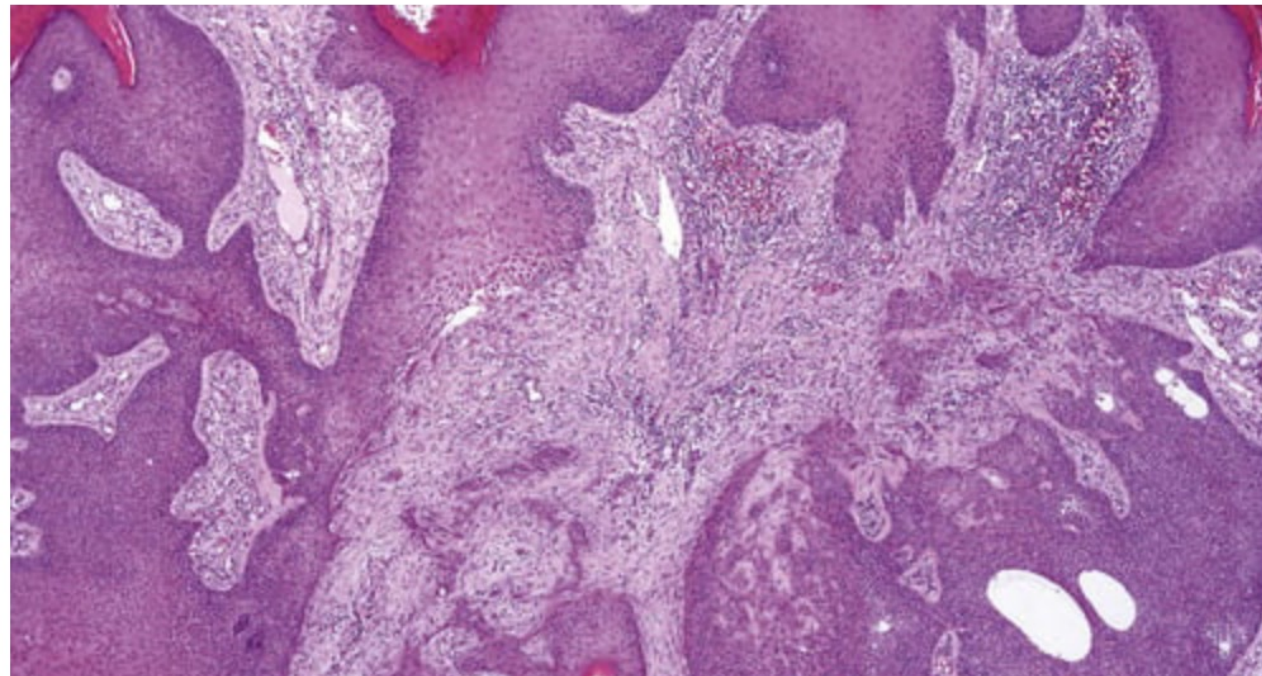
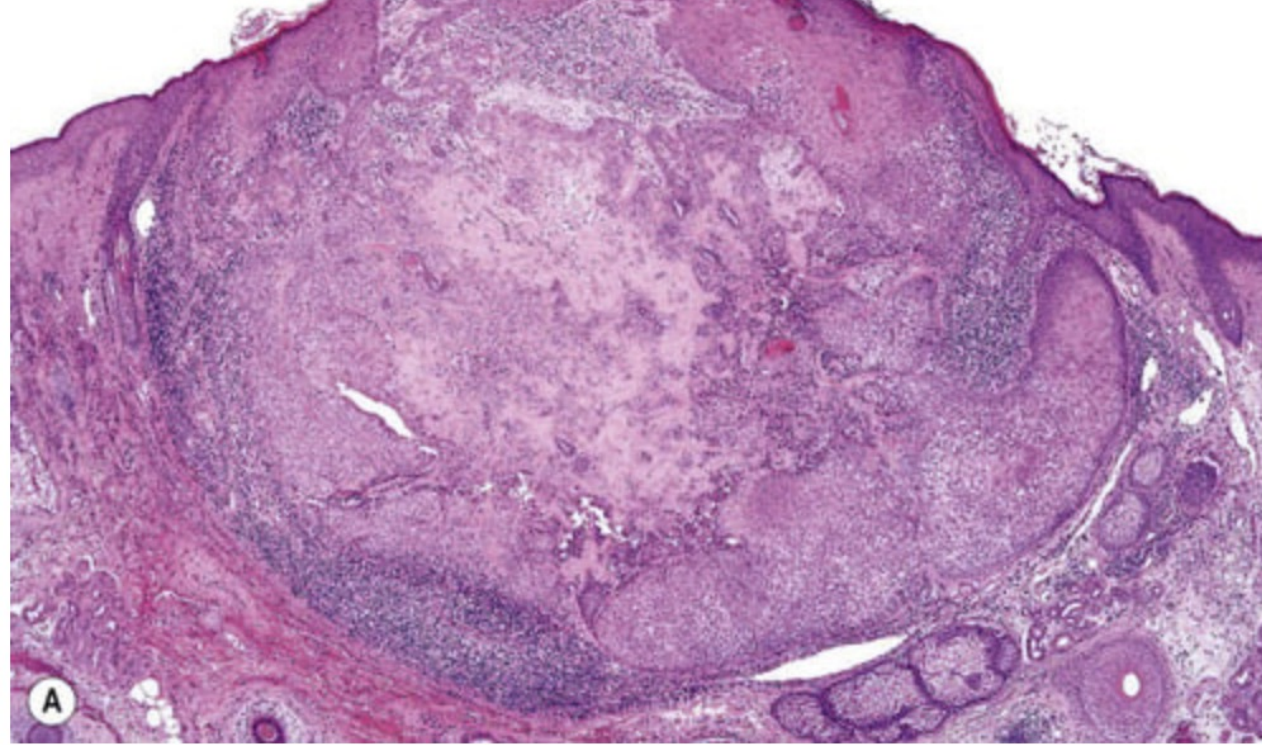
# ANSWER: PERIFOLLICULAR FIBROMA

- Normal hair follicle
- Layers of thickened fibrous stroma
- Retraction artifact (space between dense stroma and dermal collagen)



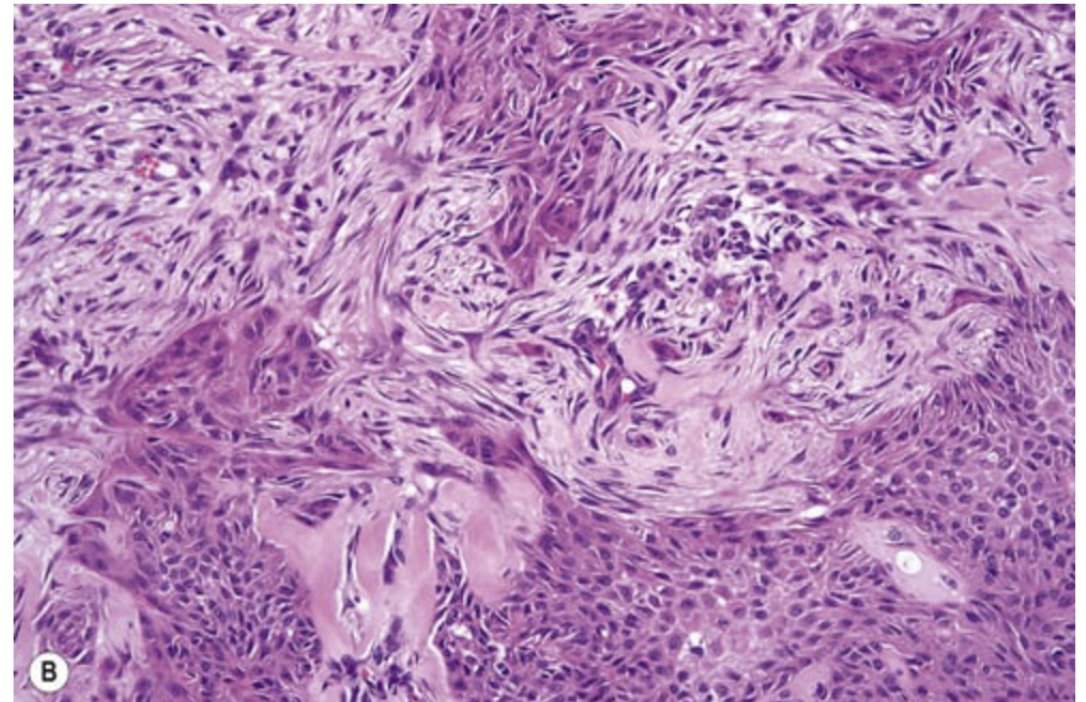
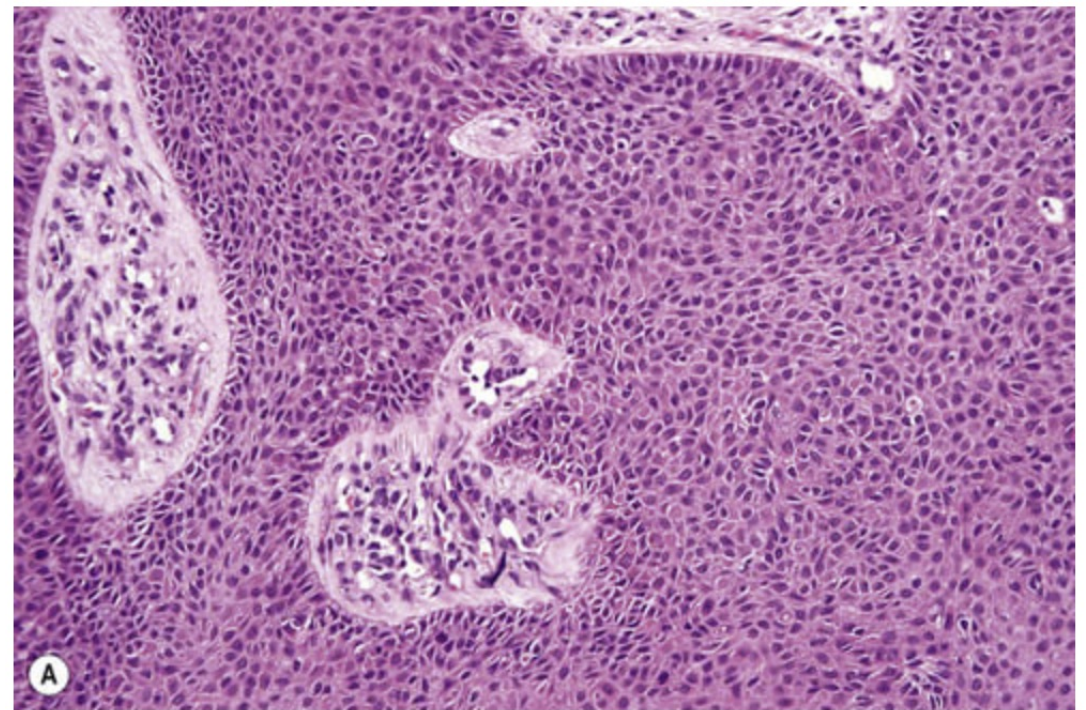
# WHAT IS YOUR DIAGNOSIS?

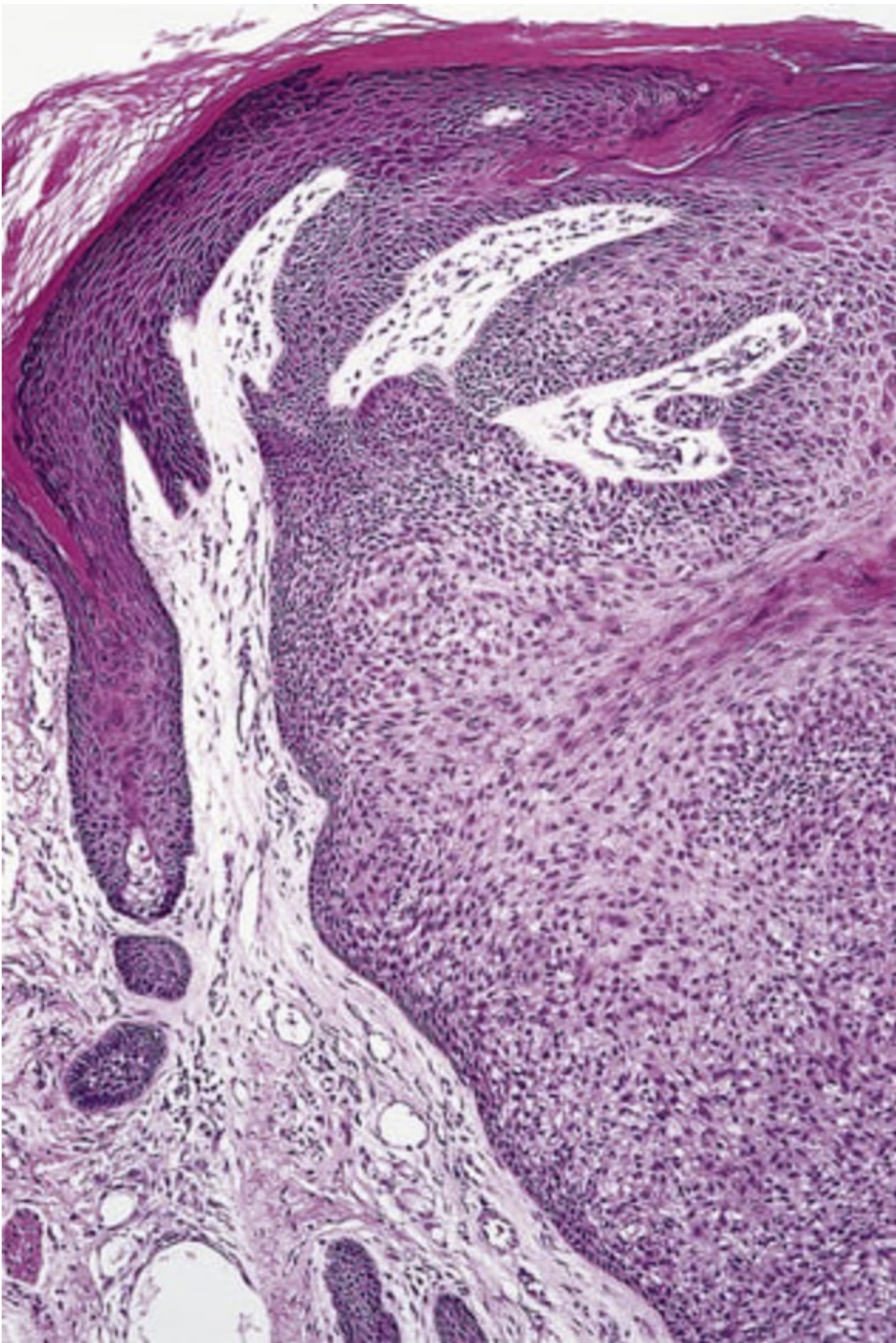
- A. Hidradenocarcinoma
- B. Poorly to moderately differentiated SCC
- C. Desmoplastic trichoepithelioma
- D. Desmoplastic trichilemmoma
- E. Fibrofolliculoma



# 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)



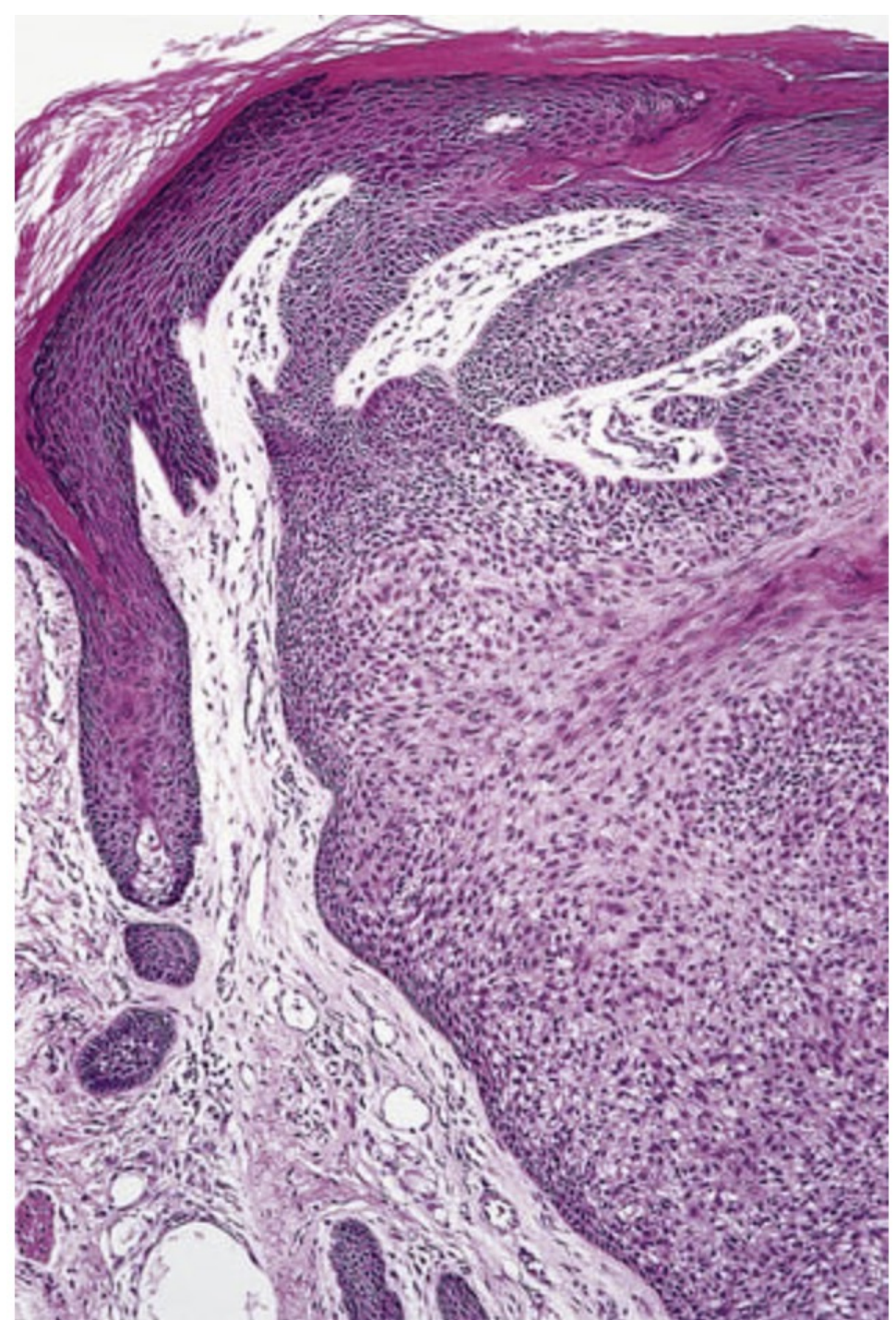


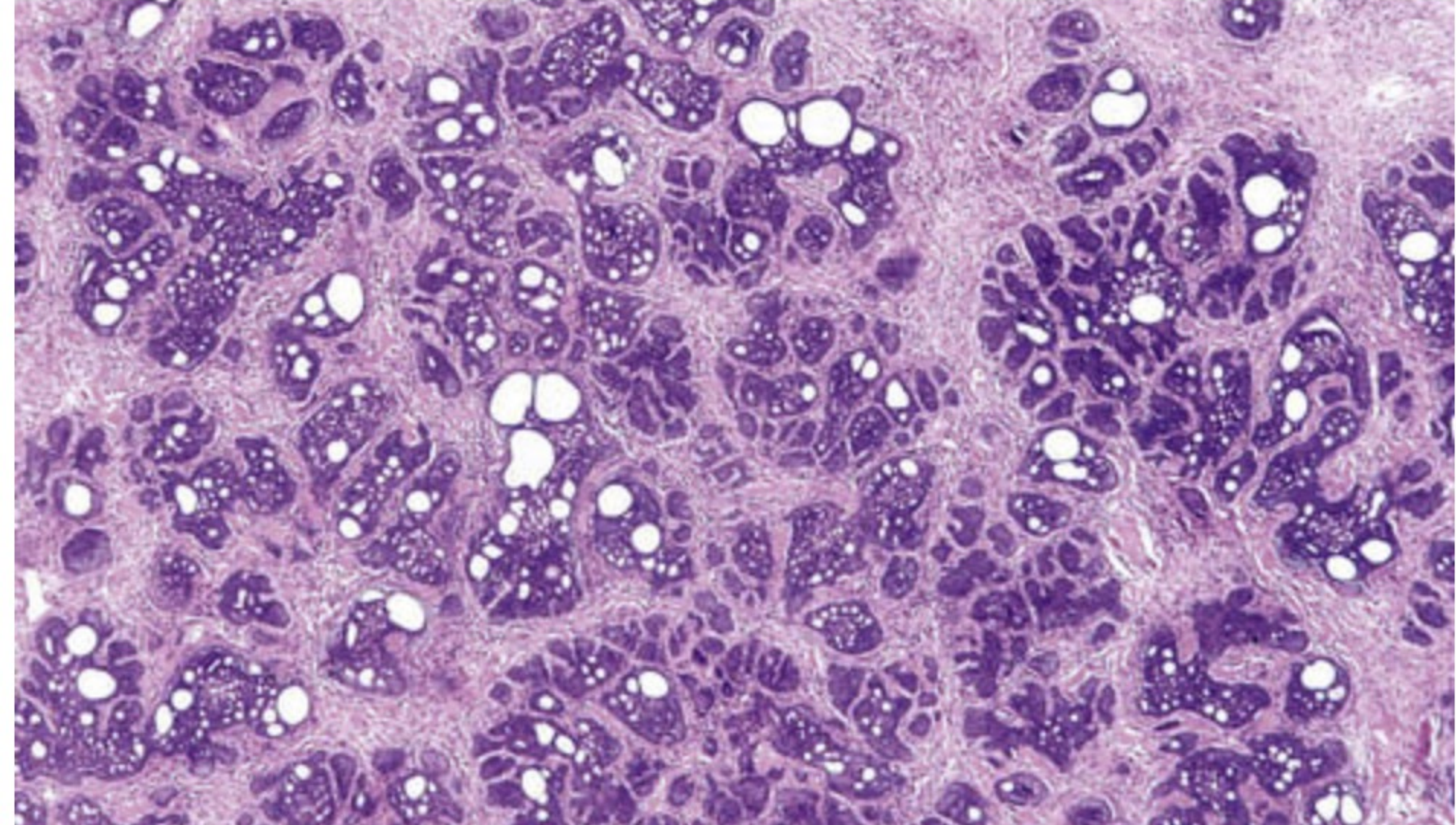
## WHAT IS YOUR DIAGNOSIS?

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

## ANSWER: TRICHILEMMOMA

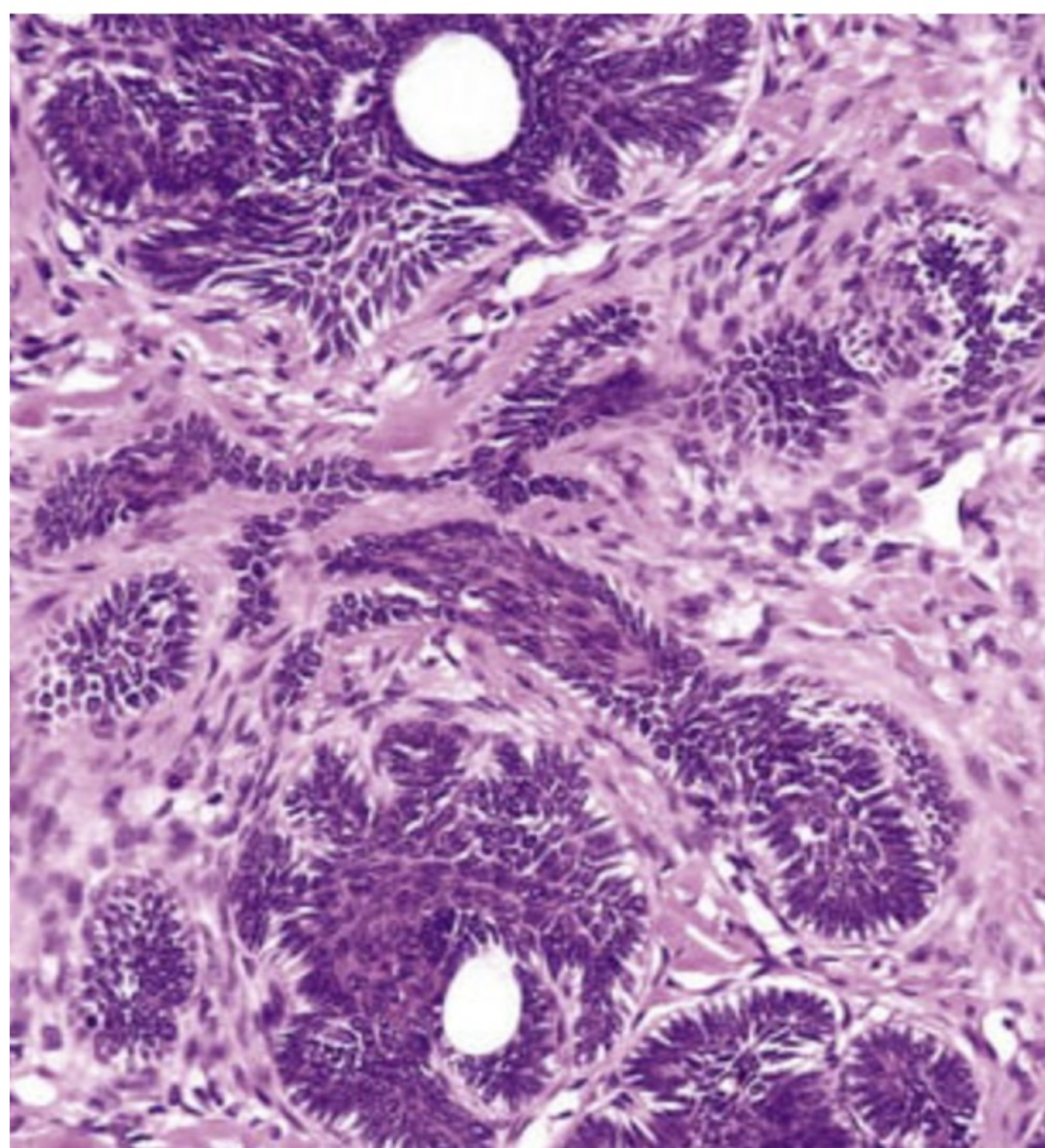
- Smooth-edged lobule, endophytic
- Composed of small cell with cytoplasmic vacuolation
- Nuclear palisading
- No cytologic atypia, no mitoses





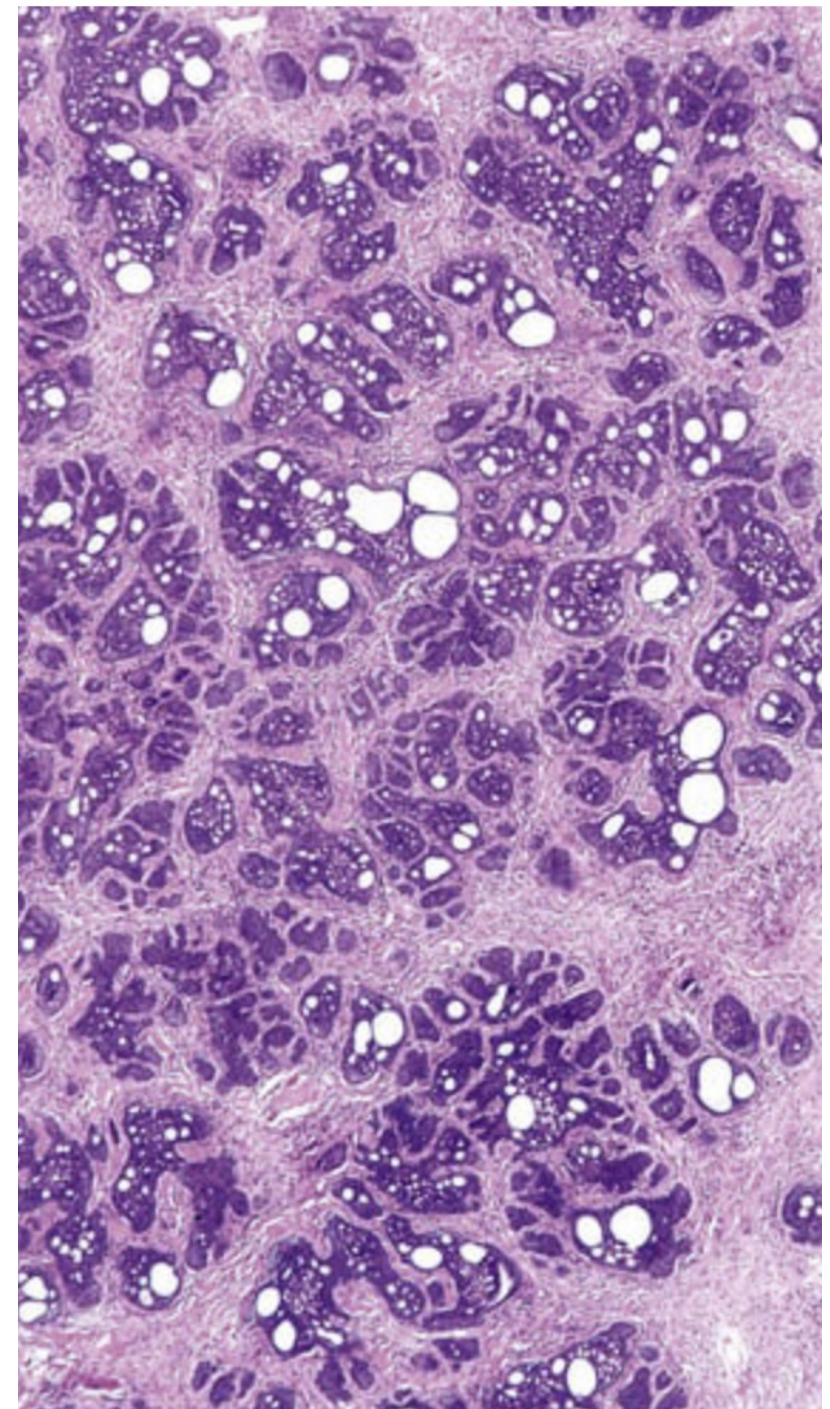
# WHAT IS YOUR DIAGNOSIS?

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



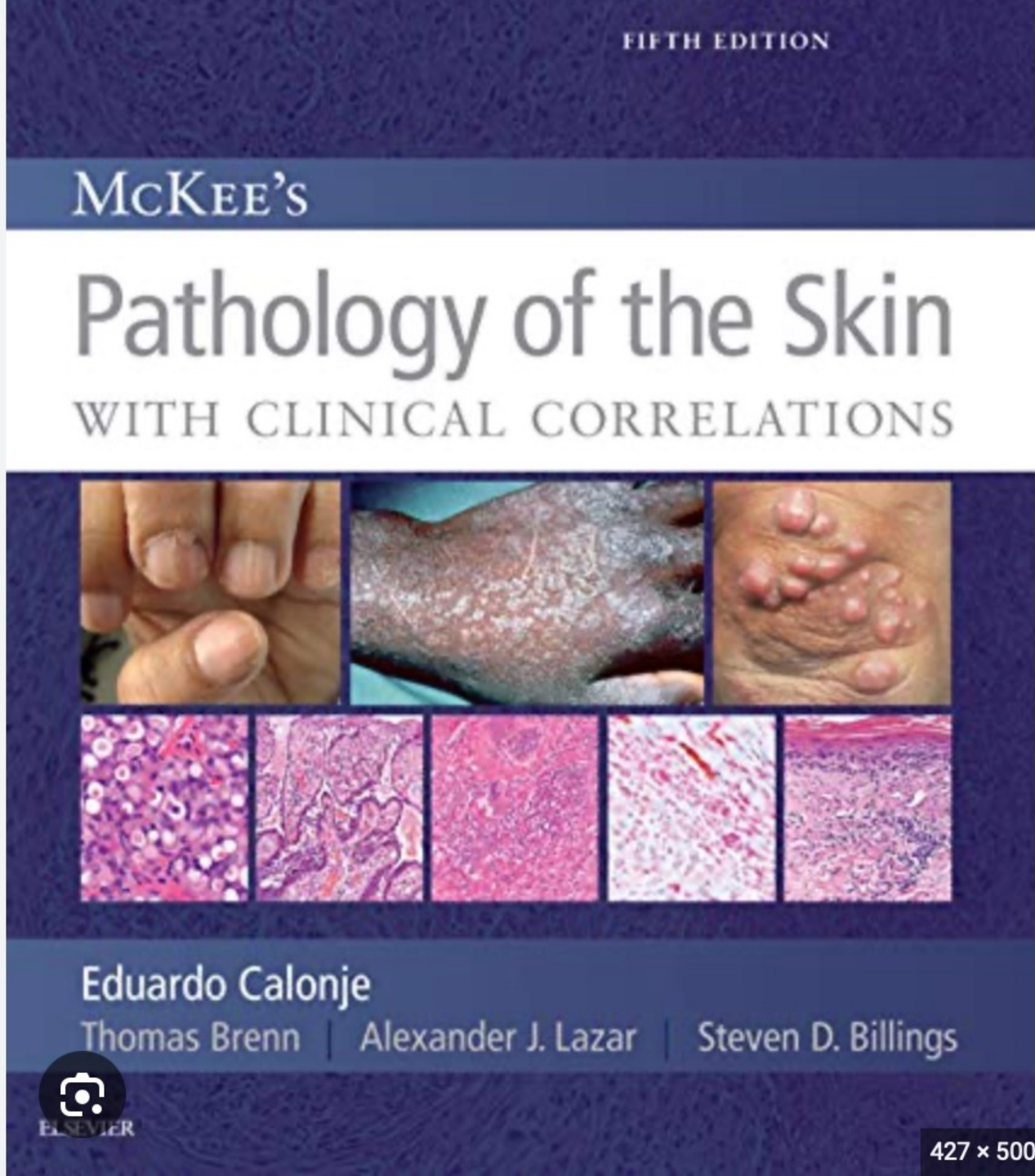
# ANSWER: TRICHOBLASTOMA

- 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



# REFERENCES

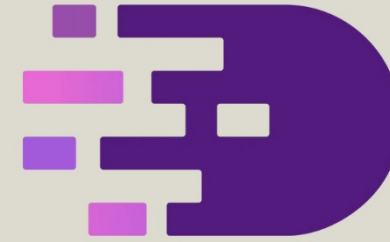
- *McKee's Pathology of the Skin* Eduardo Calonje
- *Dermatopathology*  
Raymond L Barnhill,  
third edition



# DIGITAL SKIN PATHOLOGY

[HTTPS://DIGITALSKINPATHOLOGY.COM/](https://digitalskinpathology.com/)

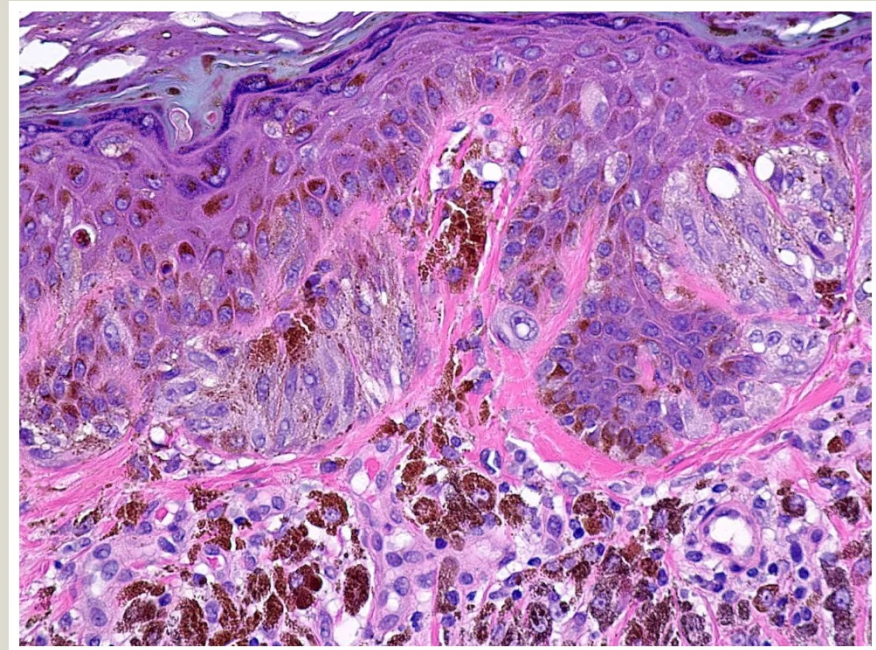
- Example of trichoadenoma
- Lecture



**DIGITAL SKIN PATHOLOGY (DiSK)**

Learn Histologic Diagnosis Case-By-Case

**DERMATOPATHOLOGY: LEARN HOW TO  
DIAGNOSE SKIN DISEASES DERM PATH  
DIAGNOSTICS**



**Understand your patient's dermatopathology diagnostic report to  
provide better clinical care** (how to diagnose skin diseases). derm  
path diagnostics