SKIN
BASAL CELL AND SQUAMOUS CARCINOMAS

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Disorders of epidermal maturation

- Ichthyosis
- Chronic, mild, generalized hyperkeratosis manifest as fine powdery scaling associated with dry skin (xerosis).
- Perifollicular keratosis as well.
- Compacted stratum corneum that is associated with loss of the normal basket weave pattern
- Failure of normal cell separation
- Lower legs

Disorders of epidermal maturation

- Ichthyiosis vulgaris
- Onset 3-12 months
- No sex predominance
- Autosomal dominant form
- Associated with atopy
- Acquired form
- Associated with lymphoid or visceral malignancy
- Legs, primarily
- Loss of FLG gene at 1q22.1 (filaggrin)
- Maintain structural proteins of stratum corneum)

Disorders of epidermal maturation

- Congenital ichthyosiform erythroderma
- Autosomal recessive
- GJB2 gene mutation at 13q12.11
- Maintain gap junction
- May be associated with hearing loss
- Lamellar ichthyosis
- Autosomal recessive
- TGM1 gene mutation at 14q12
- Maintains cornified envelope

Disorders of epidermal maturation

- X-linked ichthyosis
- Mutation in STS gene at Xp22.31
- Deficiency of steroid sulfatase
- Retention of cholesterol sulfatase increases adhesion of epithelium

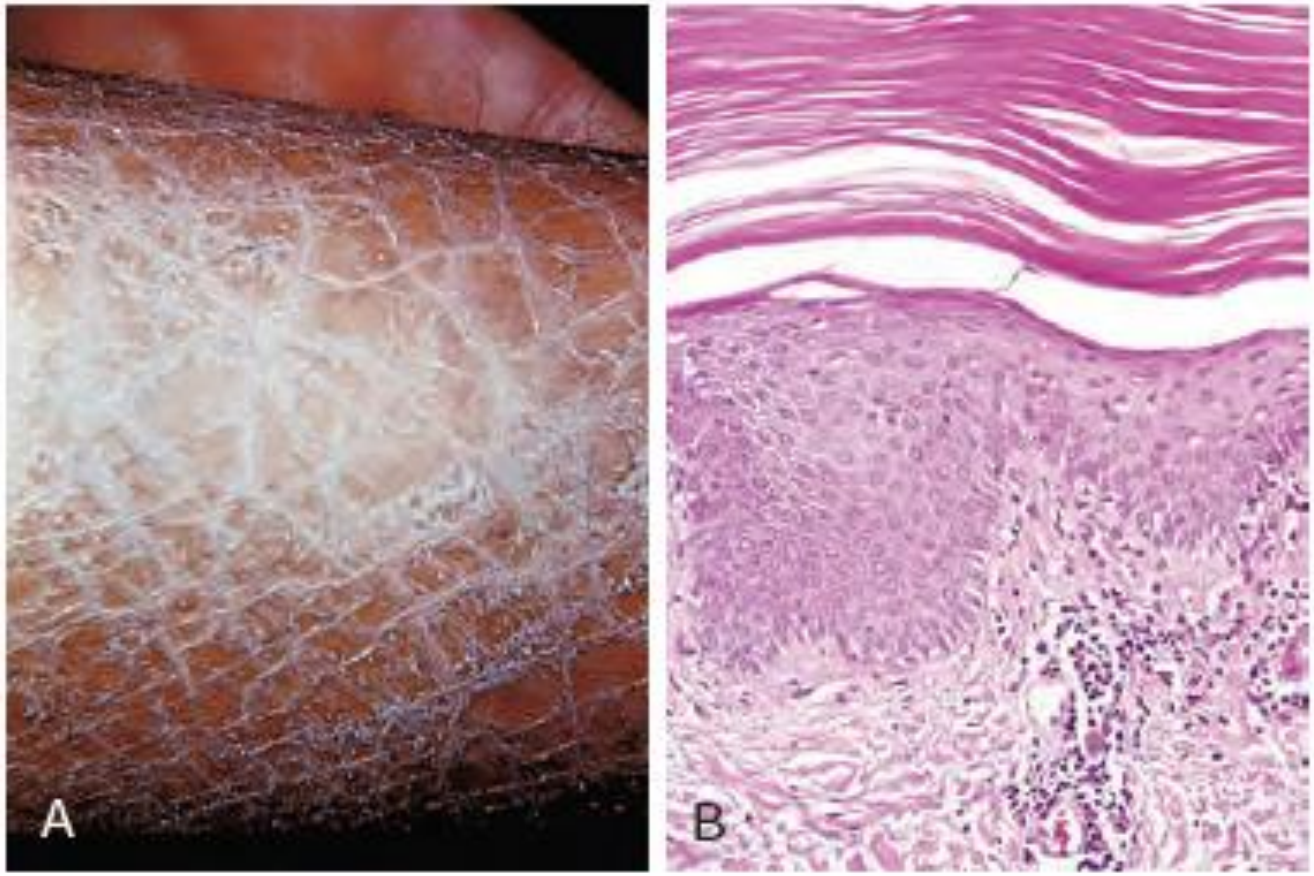


Figure 25-20 Ichthyosis. Note prominent fishlike scales (**A**) and compacted, thickened stratum corneum (**B**).

EPITHELIAL NEOPLASMS

Seborrheic keratosis

- Frequently in older adults
- Slight male preponderance
- Autosomal dominant
- FGFR3 activating mutation.
- Uniformly tan to dark brown and usually have a velvety to granular surface with “stuck on” appearance. Waxy.
- Small, round, porelike ostia impacted with keratin

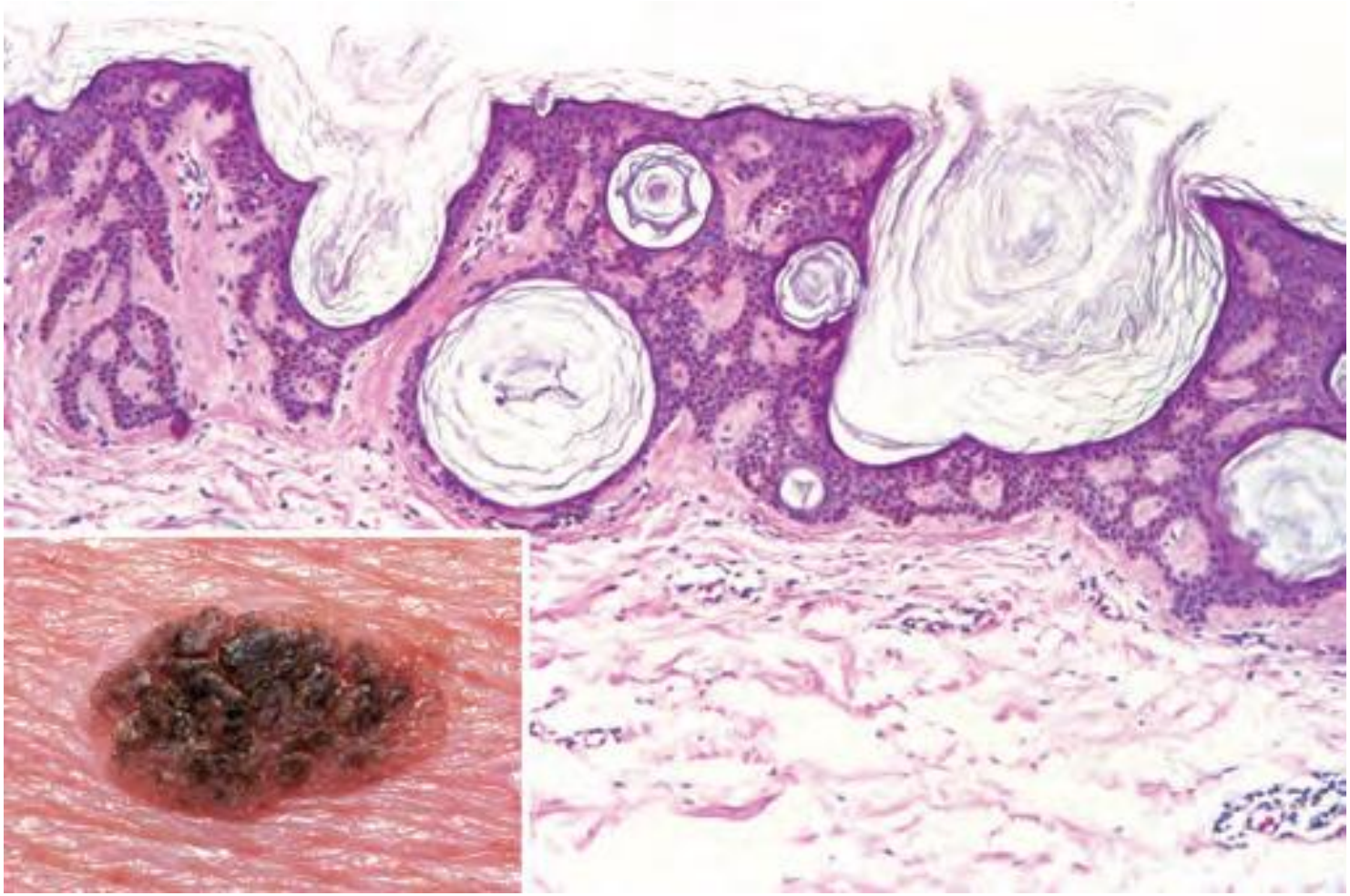
Seborrheic keratosis

- Exophytic and sharply demarcated from the adjacent epidermis.
- Composed of sheets of small cells that most resemble basal cells of the normal epidermis.
- Variable melanin pigmentation is present within these basaloid cells, accounting for the brown coloration.
- Exuberant keratin production (hyperkeratosis) occurs at the surface, and small keratin-filled cysts (horn cysts) and invaginations of keratin into the main mass (invagination cysts) are characteristic features.

Seborrheic keratosis

- If irritated and inflamed, seborrheic keratoses develop whirling foci of squamous differentiation resembling eddy currents in a stream.
- May suddenly appear in large numbers as part of a paraneoplastic syndrome (Leser-Trélat sign)
- TGF-α produced by tumor cells stimulate keratinocytes
- Commonly carcinomas of the gastrointestinal tract.

Seborrheic keratosis



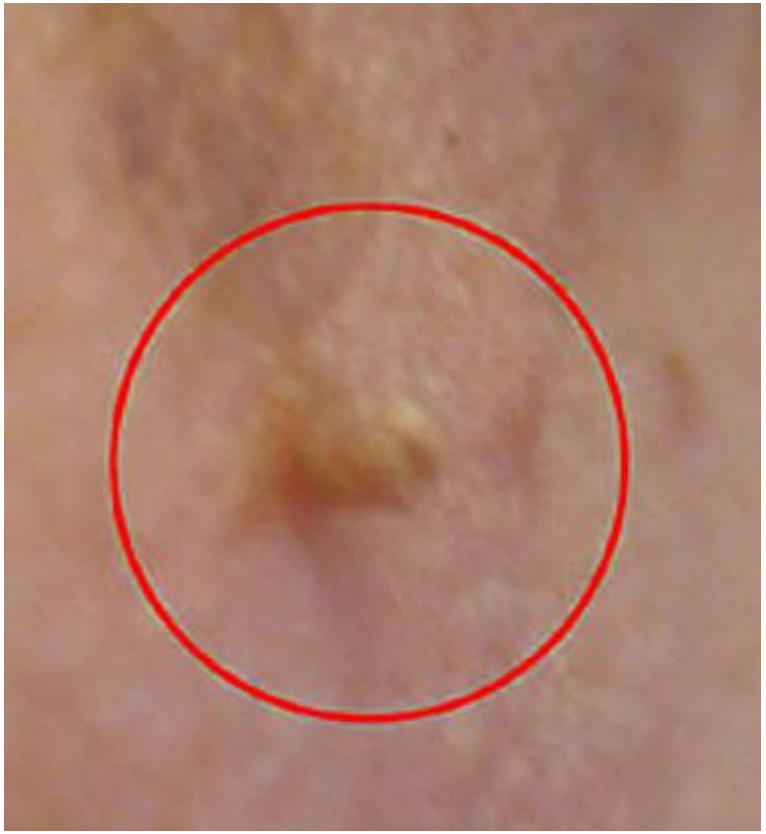
A well-demarcated coinlike pigmented lesion containing dark keratin-filled surface plugs (inset)

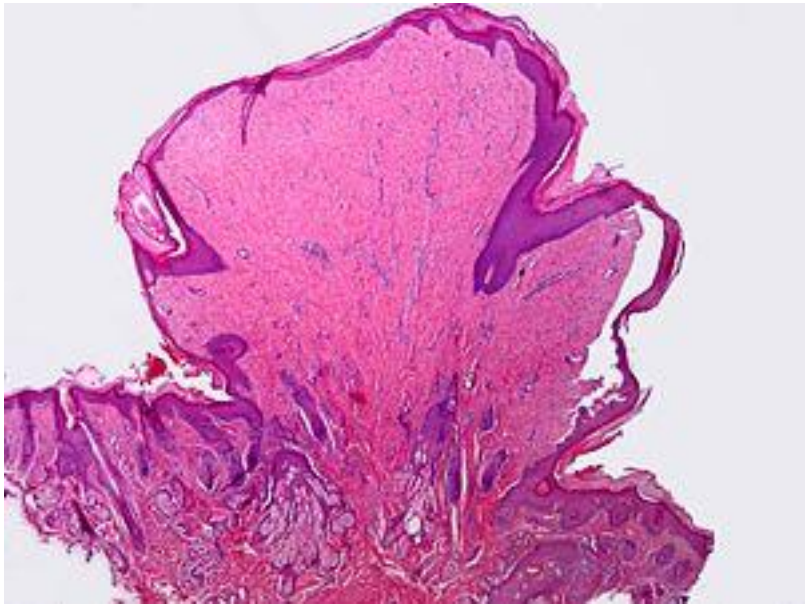
Lazar, AJF, Murphy, GF, in Kumar, V, Abbas, AK, Aster, JC (eds.), Robinns and Cotran Pathologic Basis of Disease (9th edition) 2015. Fig. 25-9

Fibroepithelial polyp

- Soft, flesh-colored, bag-like tumors of mesodermal origin that are often attached to the surrounding skin by a slender stalk.
- May be seen in Birt-Hogg-Dubé syndrome of adnexal tumors of face and neck, lung cysts inferior to the carina, and renal cell carcinoma (gene at 17p11.2)
- Histopathology
- Consist of fibrovascular cores covered by benign squamous epithelium.
- May undergo ischemic necrosis due to torsion

Fibroepithelial polyp



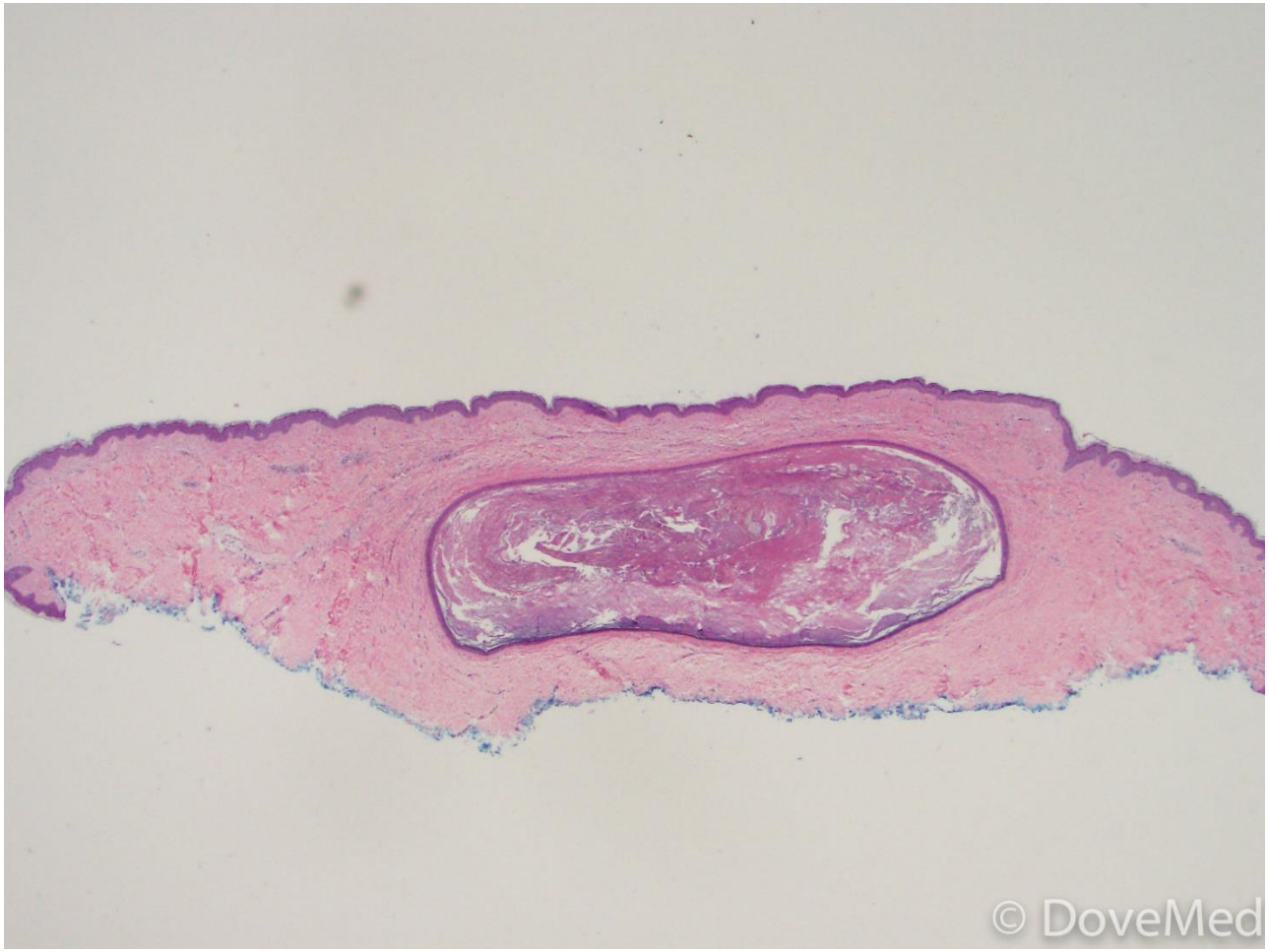


Left:
https://librepathology.org/wiki/File:
Above:
Skintagblemish.jpg
https://librepathology.org/wiki/Fibroepithelial_polyp

Epithelial cysts

- Formed by the invagination and cystic expansion of the epidermis or, perhaps more commonly, a hair follicle.
- With rupture, spill keratin into dermis and induce granulomatous response

Epithelial cysts



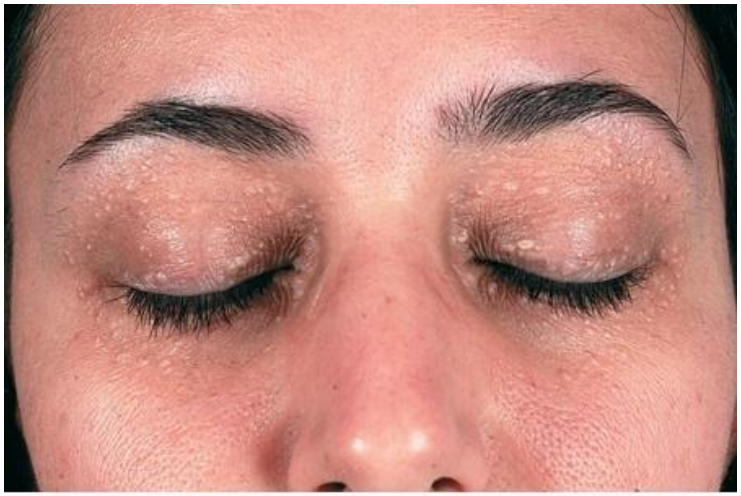
https://prod-dovemed.s3.amazonaws.com/media/original_images/P7310130.jpg

Appendage tumors

- Eccrine poroma occurs predominantly on the palms and soles where sweat glands are numerous.
- Cylindroma, an appendage tumor with ductal (apocrine or eccrine) differentiation, usually occurs on the forehead and scalp.
- May coalesce into hat-like configuration(turban tumor)
- Inactivating mutations in CYLD gene at 16q12.1
- Encodes a deubiquitinating enzyme that negatively regulates NF-κB
- Syringoma, eccrine differentiation, usually occur as multiple, small, tan papules in the vicinity of the lower eyelids.

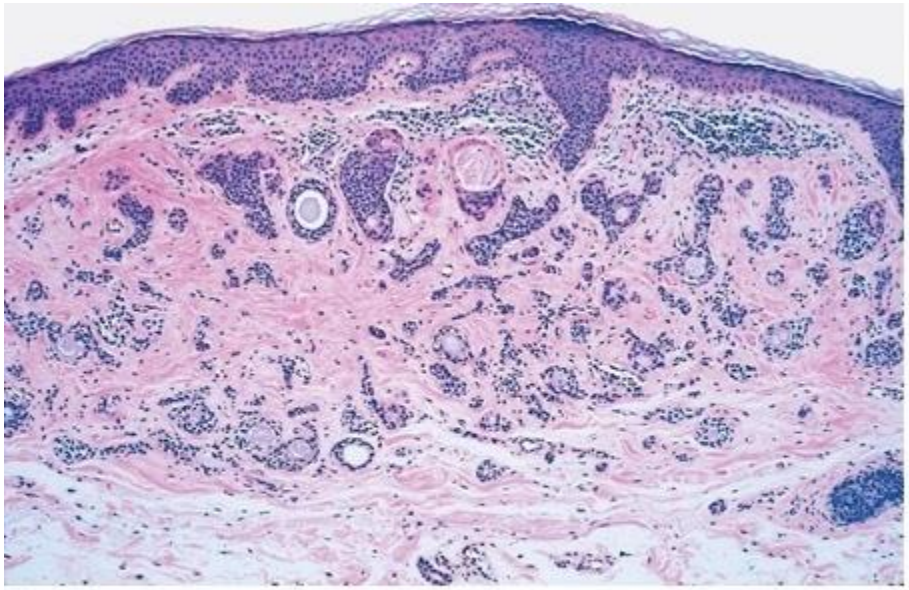
Syringoma

- Eccrine duct lined by membranous eosinophilic cuticles. Tadpole like epithelial structures.
- Resemble adnexal cells.



Source: Wolff K, Johnson RA: *Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology, 6th Edition:* http://www.accessmedicine.com

Fig. 9-44 Accessed 07/16/2010



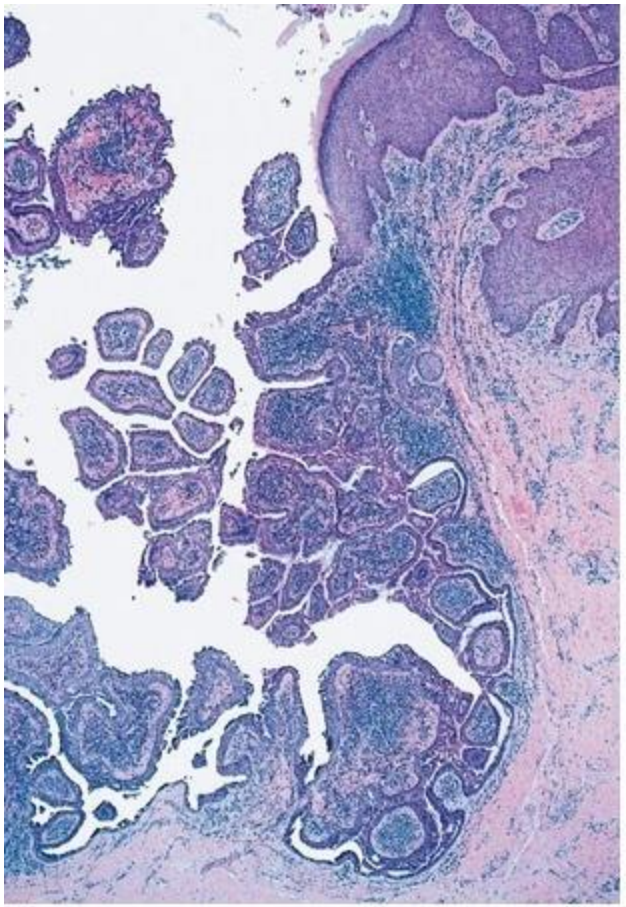
B

Source: Wolff K, Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ: *Fitzpatrick's Dermatology in General Medicine,* 7th Edition: http://www.accessmedicine.com

Fig. 119=9B Accessed 07/16/2010

Syringocystadenoma

- As with eccrine or sebaceous lesions, may be confused with basal cell carcinoma.
- Apocrine cells line papillary folds of submucosa.



B

Fig. 119-4B Accessed 07/20/2010

Appendage tumors

- Sebaceous adenomas
- As part of the Muir-Torre syndrome, associated with hereditary nonpolyposis colorectal carcinoma syndrome (mismatch repair mutations)
- Pilomatricomas, showing follicular differentiation, are associated with activating mutations in CTNNB1 gene at 3p22.1 (β-catenin).
- Trichoepithelioma is a proliferation of basal cells that resemble a hair follicle.

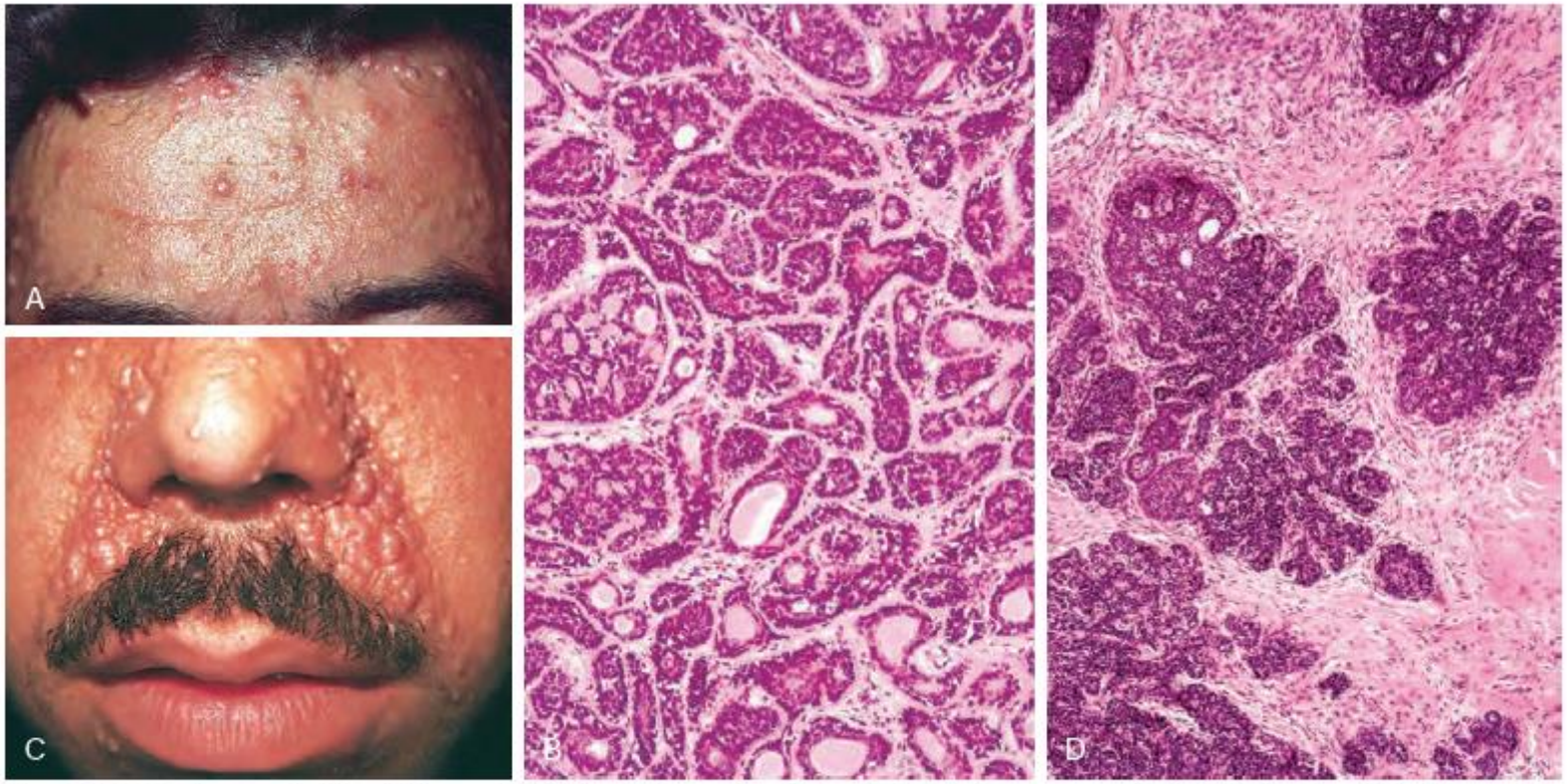


Figure 25-10 Cylindroma and trichoepithelioma. **A,** Multiple cylindromas (papules) on the forehead are composed (**B**) of islands of basaloid cells containing occasional ducts that fit together like pieces of a jigsaw puzzle. **C,** Perinasal papules and small nodules of trichoepithelioma are composed (**D**) of buds of basaloid cells that resemble primitive hair follicles.

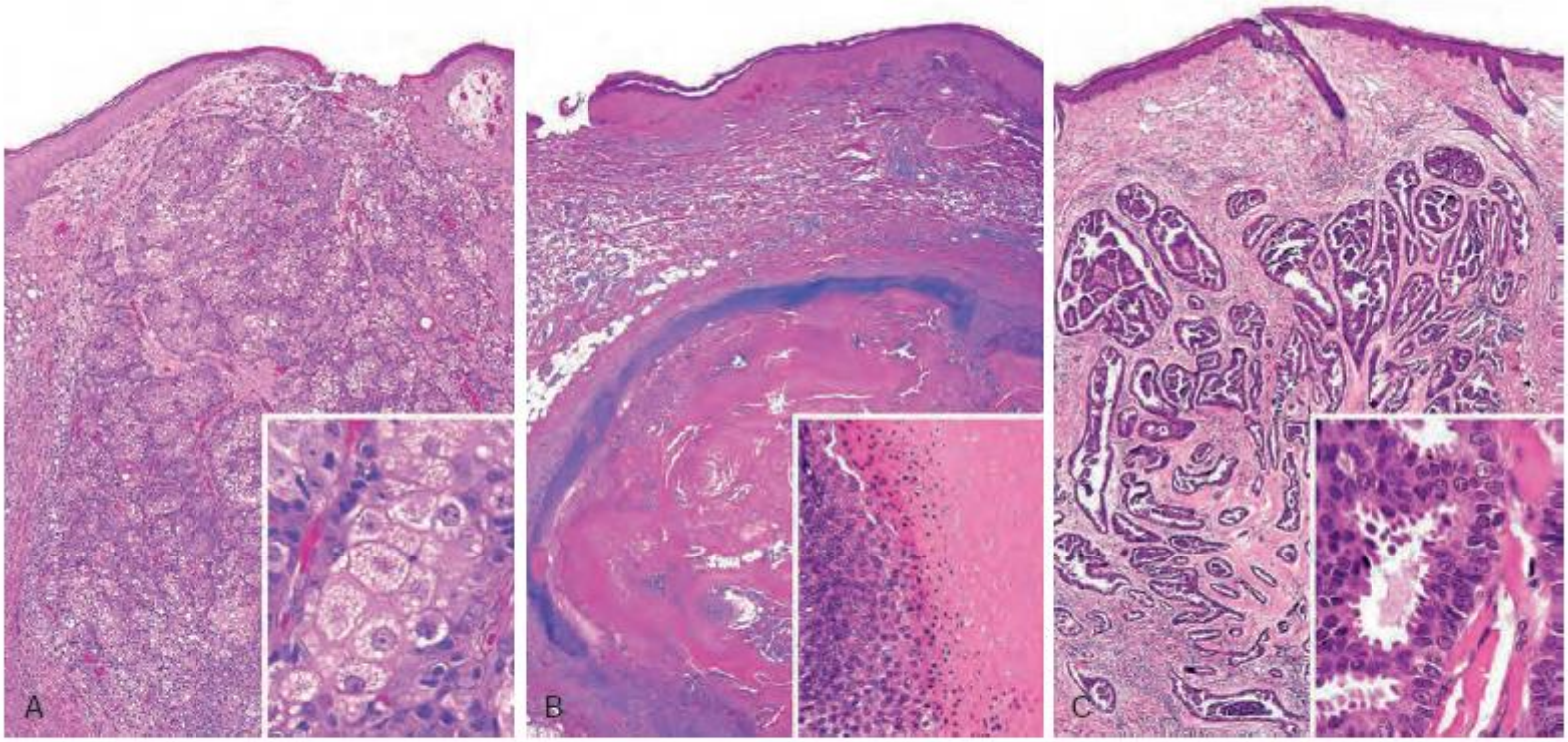
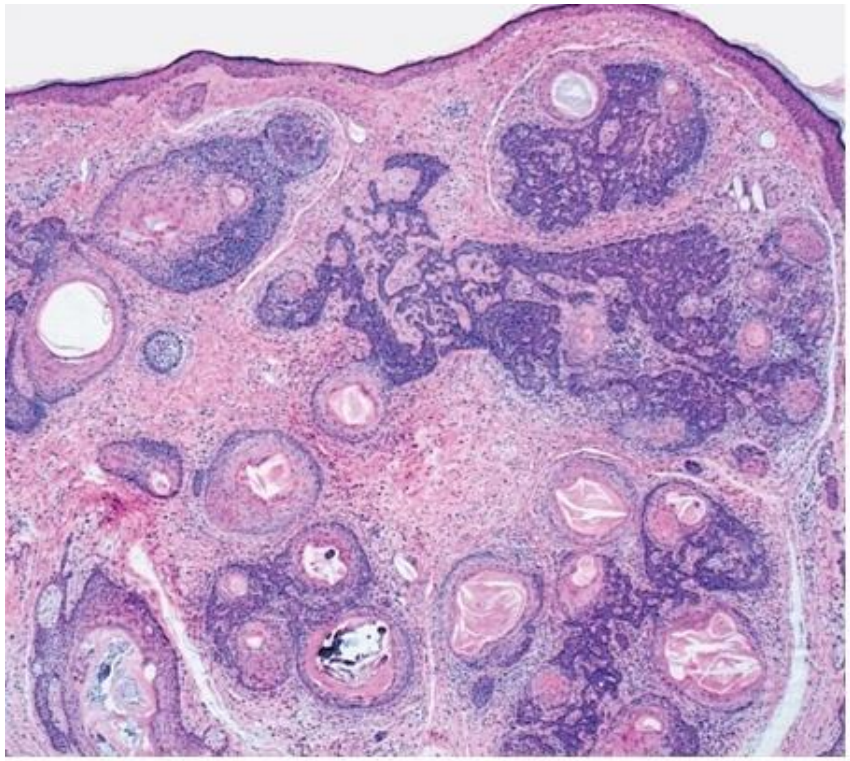


Figure 25-11 Diverse adnexal tumors. **A,** Sebaceous adenoma; *inset* demonstrates sebaceous differentiation. **B,** Pilomatrixoma; *inset* shows hair matrix differentiation to anucleate "ghost cells." **C,** Apocrine carcinoma (well-differentiated); *inset* shows apocrine differentiation and luminal secretions produced by "decapitation" of the lining cells.

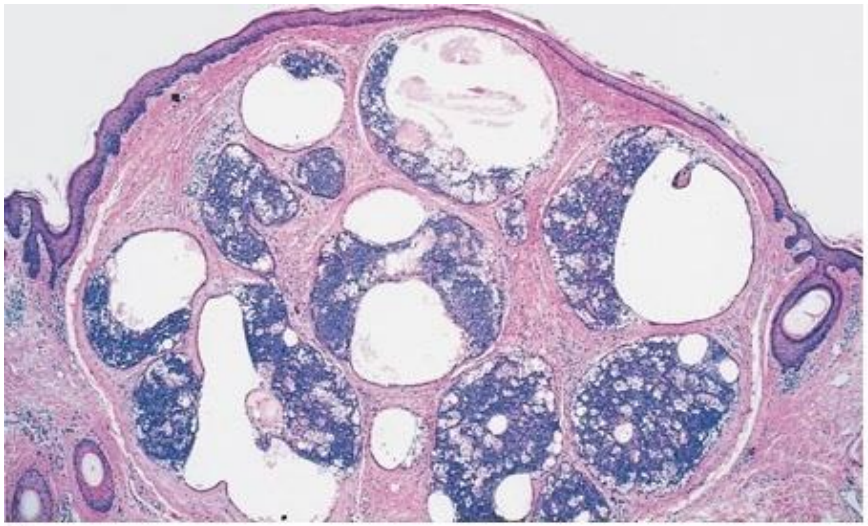
Other appendage tumors



B

Trichoepithelioma

Fig. 119-16B Accessed 07/20/2010



B

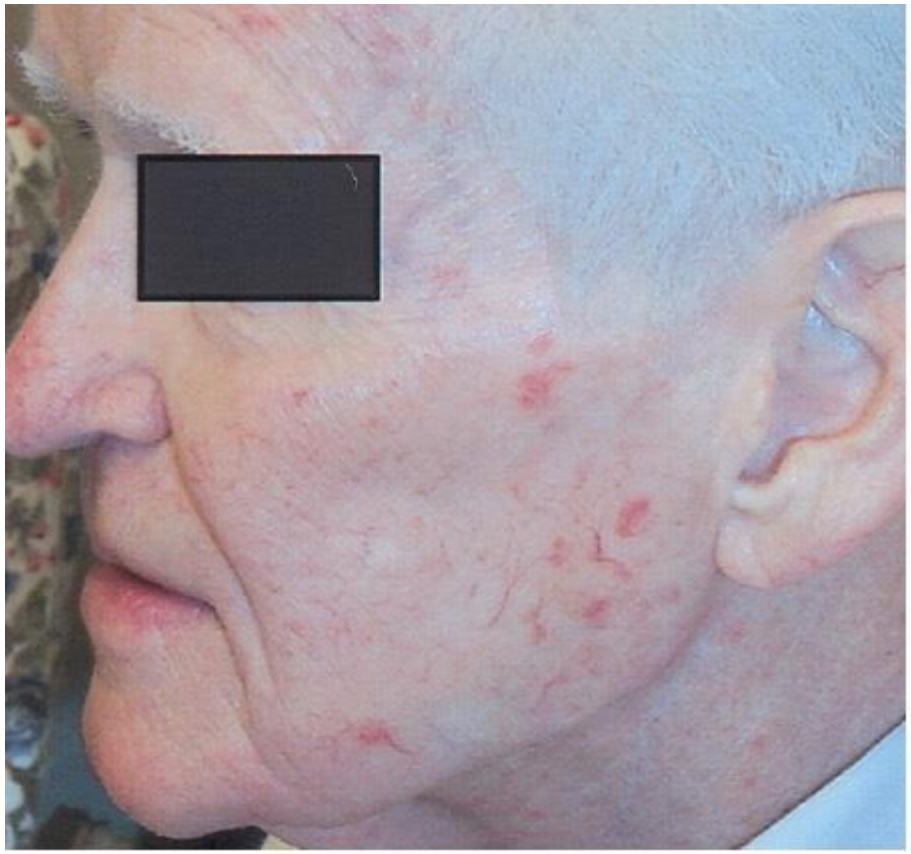
Sebaceoma

Fig. 119-20B Accessed 07/20/2010

Actinic keratosis

- Precursor lesion of squamous carcinoma.
- Sun damaged skin (TP53 affected).
- Sandpaper texture.
- Dysplastic changes are confined to the basal cells of the lower epidermis. Intercellular bridges are intact.
- Stratum corneum prominent (may develop “cutaneous horn”).
- Elastosis in dermis. (Blue-gray fibers on stain).
- (Arsenic induced changes are similar.)
- Excision with 4-6mm margins is curative.
- Imiquimod activates Toll-Like receptors, eradicates 50% of lesions

Actinic keratosis



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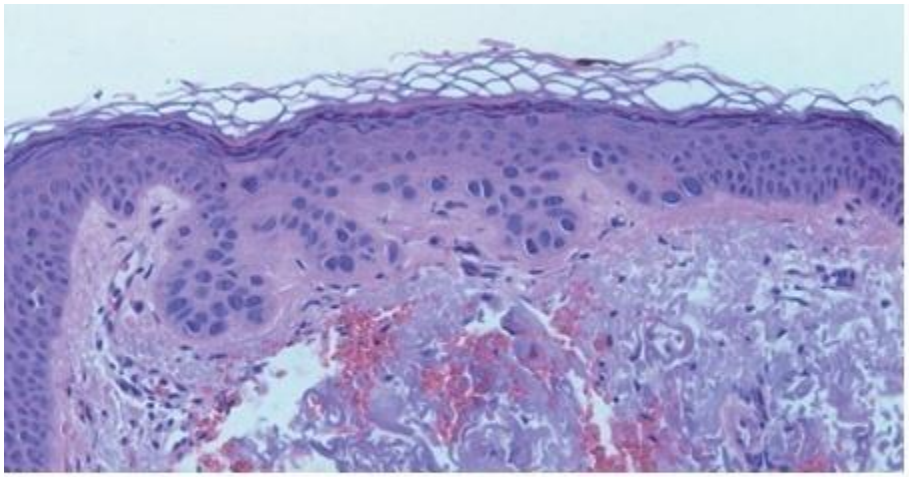
Actinic keratosis



B

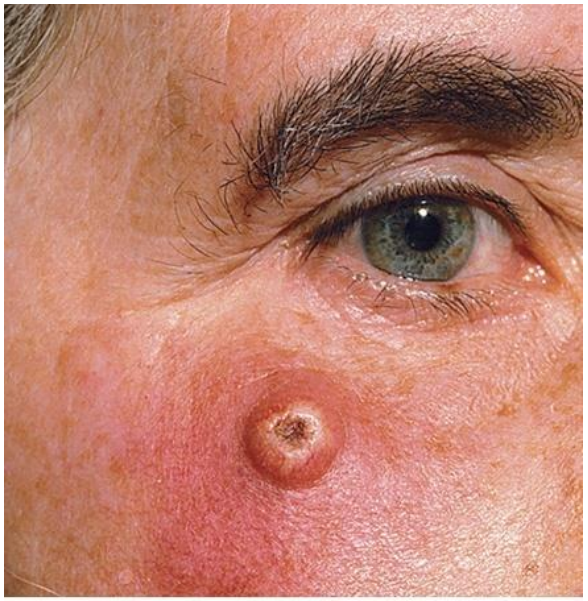
Source: Wolff K, Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ: *Fitzpatrick's Dermatology in General Medicine*, 7th Edition: http://www.accessmedicine.com

Histopathologic preparation of actinic keratosis demonstrates atypical cells along the basal layer with sparing of adnexal epithelium.

Fig. 113-3
Accessed 07/16/2010

Keratoacanthoma

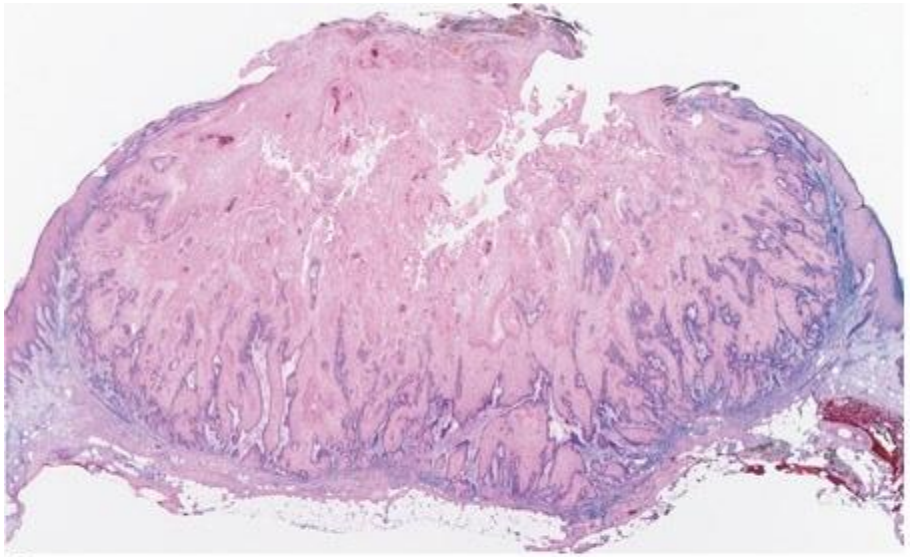
- Symmetric crater-like nodule with a central keratin plug.
- Large glassy squamous cells with central islands of eosinophilic keratin.
- Possible viral onset.
- Usually >50 years-old
- Twice as common in men
- Rare in blacks, Asians
- Do not metastasize.
- Excision is curative.



A

Source: Wolff K, Johnson RA: *Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology, 6th Edition:* http://www.accessmedicine.com

Keratoacanthoma



A

Symmetric epithelial tumor with a central keratotic crater surrounded by epithelial lipping. Perineural growth may be seen.

Fig. 117-6
Accessed 07/20/2010

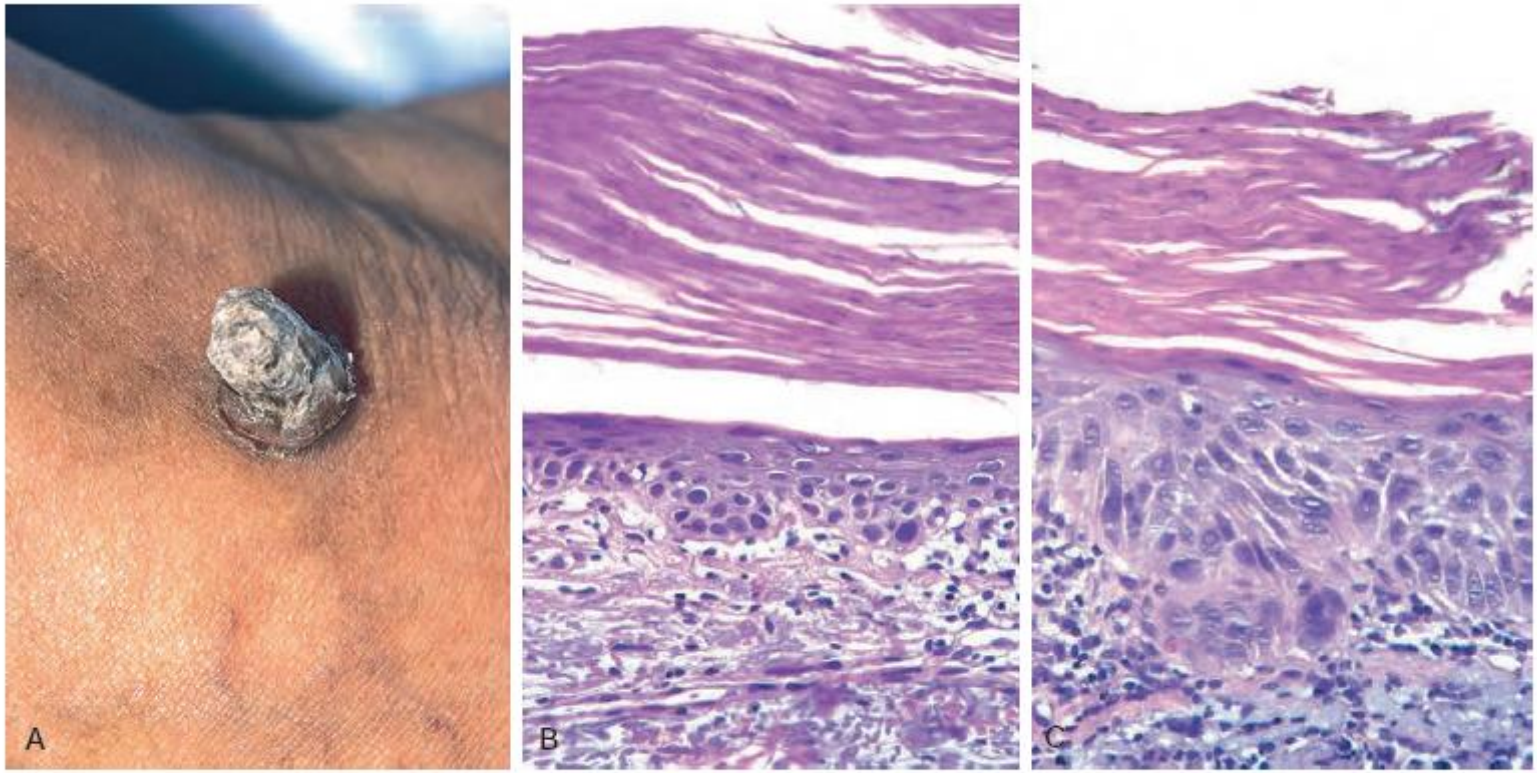


Figure 25-12 Actinic keratosis. **A,** Excessive keratotic scale in this lesion has produced a "cutaneous horn." **B,** Basal cell layer atypia (dysplasia) is associated with marked hyperkeratosis and parakeratosis. **C,** Progression to full-thickness nuclear atypia, with or without the presence of superficial epidermal maturation, heralds the development of squamous cell carcinoma in situ.

Origin of basal cell and cutaneous squamous cell carcinomas

- Derived from epidermal keratinocytes that are chronically exposed to ultraviolet light.
- These cancers show the highest tumor mutational burden (TMB) among all cancer types.
- Despite high TMB overall, most basal cell carcinomas (BCCs) are driven by genetic alterations affecting Sonic Hedgehog (SHHH) pathway signaling.

Origin of basal cell and cutaneous squamous cell carcinomas

- BCCs are characterized by the presence of cilia, for which persistence is associated with the upstream activation of SHH pathway signaling.
- Cilia have a dual role in tumorigenesis, favoring Smoothened (SMO)-dependent tumorigenesis and suppressing the SMO-independent growth.
- Mutations in the genes related to the WNT-pathway are also frequently observed in BCC, resulting in activation of the pathway and β-catenin overexpression.
- C-MYC is downregulated

Origin of basal cell and cutaneous squamous cell carcinomas

- A different genetic mutational profile is typically observed in the case of cutaneous squamous cell carcinoma (CSCC).
- The most common alterations involve TP53, NOTCH1 (43%), and PTCH1 (11%).
- The majority of the mutations in CSCC occur in tumor suppressor genes rather than oncogenes.

Origin of basal cell and cutaneous squamous cell carcinomas

- Both BCC and CSCC are known to express cancer-testis antigens (CTAs), which are typically only expressed in trophoblastic and male germline cells.
- Expression in cancer cells is believed to arise from demethylation of their promoter

Squamous cell carcinoma

- Sun exposed areas.
- Rarely metastasize.
- (Lesions of the lip, however, are at the greatest risk of metastasis.)
- More advanced lesions are nodular
- May ulcerate.
- TP53 damaged at pyrimidine dimers
- Failure of nucleotide excision repair
- RAS signaling increased
- Notch signaling decreased

Squamous cell carcinoma in situ

- Bowen's disease
- Sun exposed areas
- Slowly enlarging red plaque with sharp border
- May scale
- Erythroplasia of Queyrat (EQ)
- Glans penis usually
- May occur on prepuce
- May occur on vulva
- Both show full thickness dysplasia of epidermis without dermal invasion
- EQ may metastasize

Squamous cell carcinoma

- Histopathology
- Full thickness dysplasia of the epidermis (carcinoma in situ)
- If dermal invasion, carcinoma.
- May have associated lymphocytic inflammatory response and reactive dermal fibrosis.
- Anaplastic types may only demonstrate single-cell keratinization (dyskeratosis)

Squamous cell carcinoma syndromes

- Xeroderma pigmentosum
- XPC gene at 3p25.1 detects DNA damage
- XPA gene at 9q22.33 stabilizes DNA as it undergoes nucleotide excision repair
- ERRC5 gene at 19q13.32 encodes XPD, a helicase that functions in DNA repair as well as with gene transcription
- POLH gene at 6p21.1 encodes DNA polymerase-ε

Squamous cell carcinoma syndromes

- Epidermodysplasia verruciformis
- May present in childhood
- Autosomal recessive
- Prone to chronic infection with HPV 5 and 8 (80%)
- Loss of function of EVER1 or 2 genes at 17q25.3 (codes proteins that complex with Zinc finger transport protein 1 in keratinocyte endoplasmic reticulum)

Squamous cell carcinoma syndromes

- Histology
- Verruca like lesions with mild hyperkeratosis, hypergranulosis and acanthosis of the epidermis. Keratinocytes of the upper epidermal layers are enlarged with perinuclear vacuolization and a typical blue-gray pallor

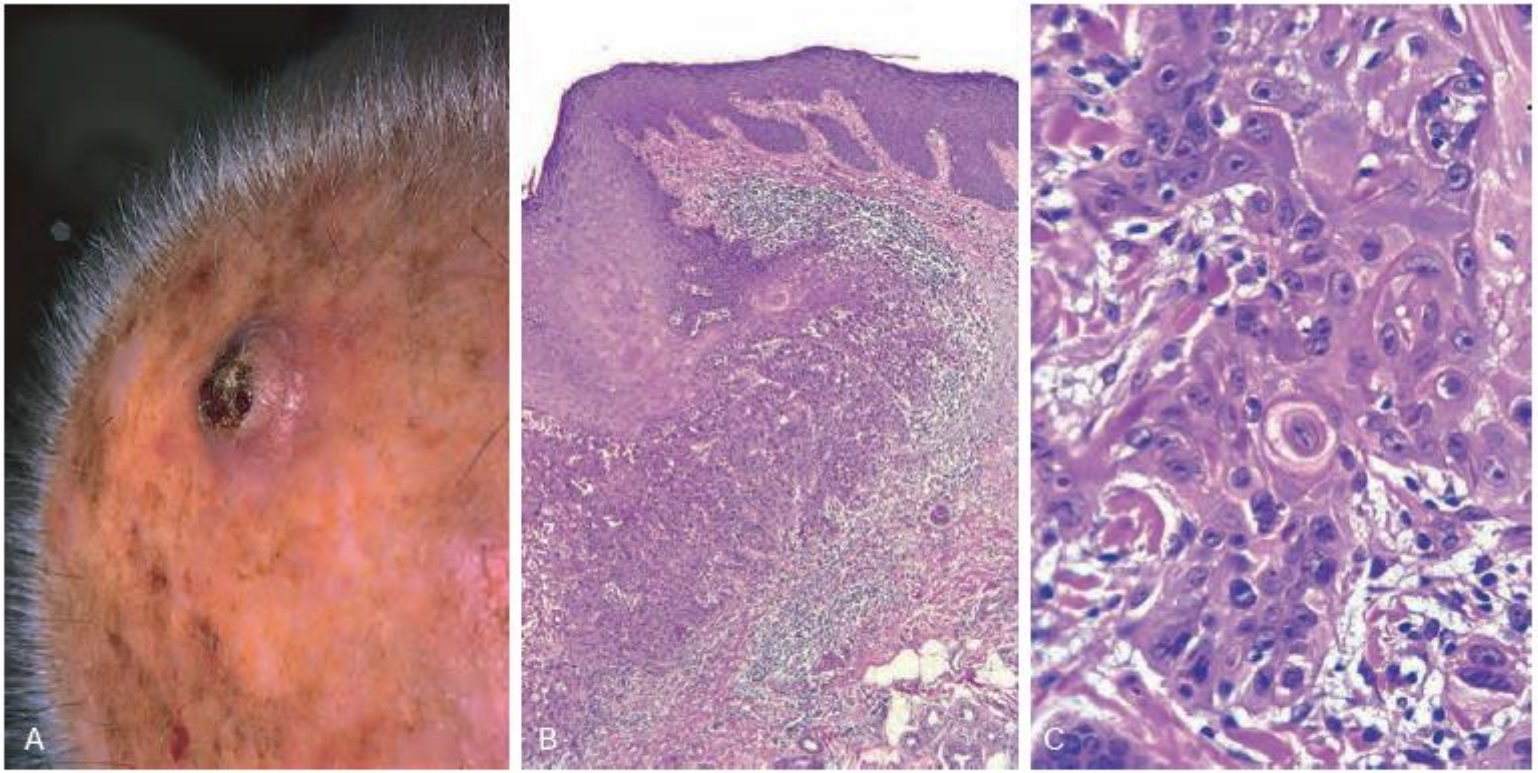
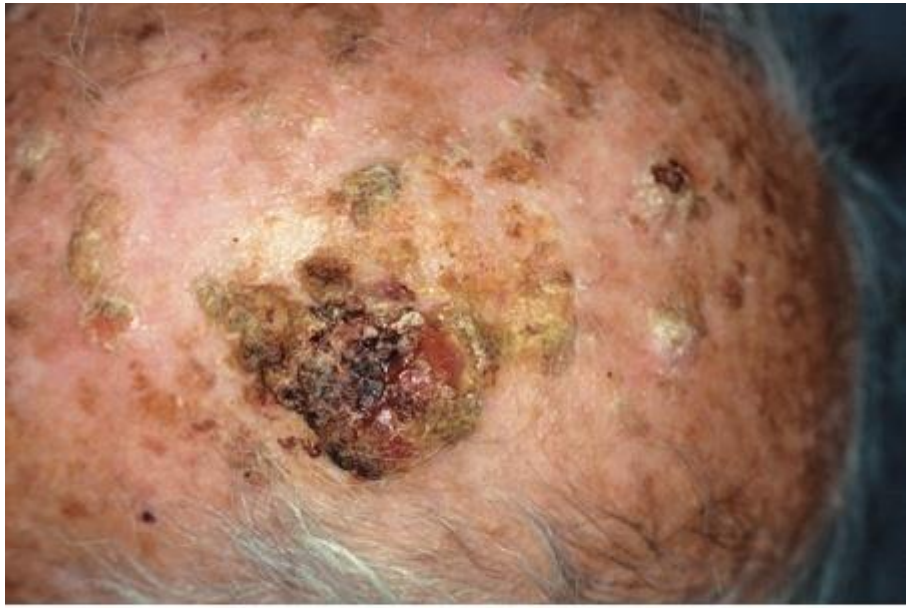


Figure 25-13 Invasive squamous cell carcinoma. **A,** Lesions are often nodular and ulcerated, as seen in this scalp tumor. **B,** Tongues of atypical squamous epithelium have transgressed the basement membrane and invaded deeply into the dermis. **C,** Invasive tumor cells show enlarged nuclei with angulated contours and prominent nucleoli.

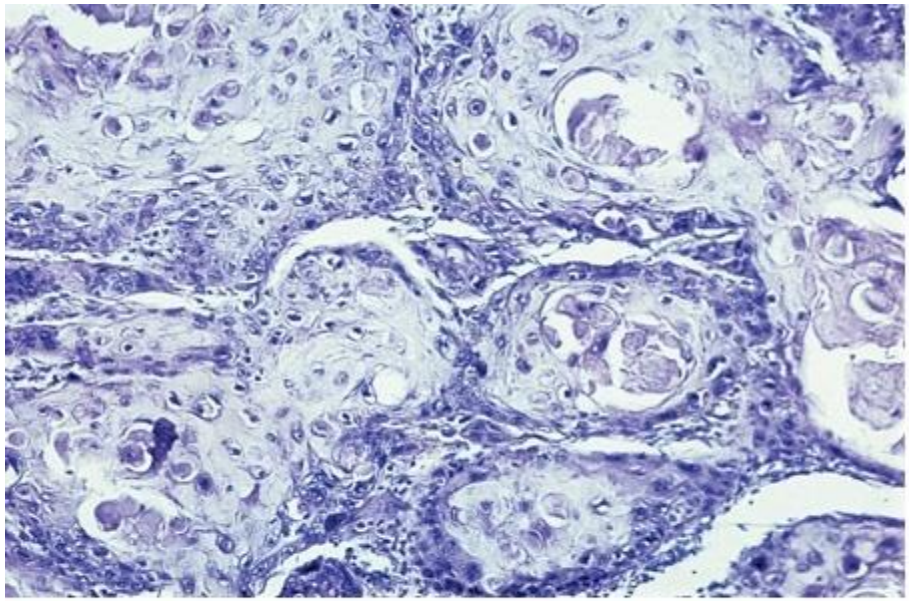
Squamous carcinoma



Multiple, tightly adherent dirty looking solar keratoses . The large nodule shown here is covered by hyperkeratoses and hemorrhagic crusts; it is partially eroded and firm. This nodule is invasive squamous cell carcinoma.
The image is shown to demonstrate the transition from precancerous lesions to frank carcinoma.

Fig. 11-1 Accessed 07/16/2010

Squamous cell carcinoma



Squamous cell carcinoma demonstrating invasive cancer with atypical keratinocytes and foci of keratinization.

Fig. 114-10
Accessed 07/20/2010

Basal cell lesions

- Rare in non-Europeans
- Nose is most common site.
- Only 15% of basal cell carcinomas develop on sun-protected skin.
- Rarely metastasize.
- May be pearly white and telangiectatic.
- Ulcerate. Locally aggressive ("rodent ulcer")
- Tumor cells arise from basal cell layer of epidermis or follicular epithelium (hair).
- Multifocal or nodular growths noted.
- May see superficial vasodilatation.
- May be pigmented.

Basal cell lesions

- Histopathology
- Arise from epidermis or follicular epithelium
- Multifollicular or nodular patterns
- Nests of basaloid cells in dermis are surrounded by similar cells arranged in palisade about the tumor.
- A similar picture about hair shafts is associated with trichoepithelioma.
- A similar picture about adnexal glands is associated with cylindroma.

Basal cell lesions

- Mutation in PTCH gene at 9q22.32 common in basal cell carcinoma
- C-T transitions
- SHH-PTCH binding releases SMO, leading to activation of transcription factor GLI1
- Loss of cell polarity
- Associated with nevoid basal cell carcinoma syndrome (Gorlin syndrome)
- Keratocystic odontogenic tumors develop in most cases
- A subset may develop medulloblastoma or ovarian fibroma

Basal cell lesions

- Basal cell carcinoma has lower immunogenicity than does cutaneous squamous cell carcinoma.
- A strong presence of immature dendritic cells has been reported in the stroma of BCC
- Is both a cause and a consequence of the overexpression of IL-10 reported in the tumor microenvironment of BCC.
- Treat advanced or metastatic BCC with SHH pathway inhibitors (vismodegib and sonidegib)

Basal cell lesions

- Pilar matrix (hair shaft) lesions associated with activating lesions of CTNNB1 at 3p22.1 (β-catenin).
- WNT signaling increased.
- Adnexal gland lesions associated with CYLD gene mutation (16q12.1)
- Codes de-ubiquinating enzyme that regulates NF-κB
- Excision is curative appendage gland tumors.

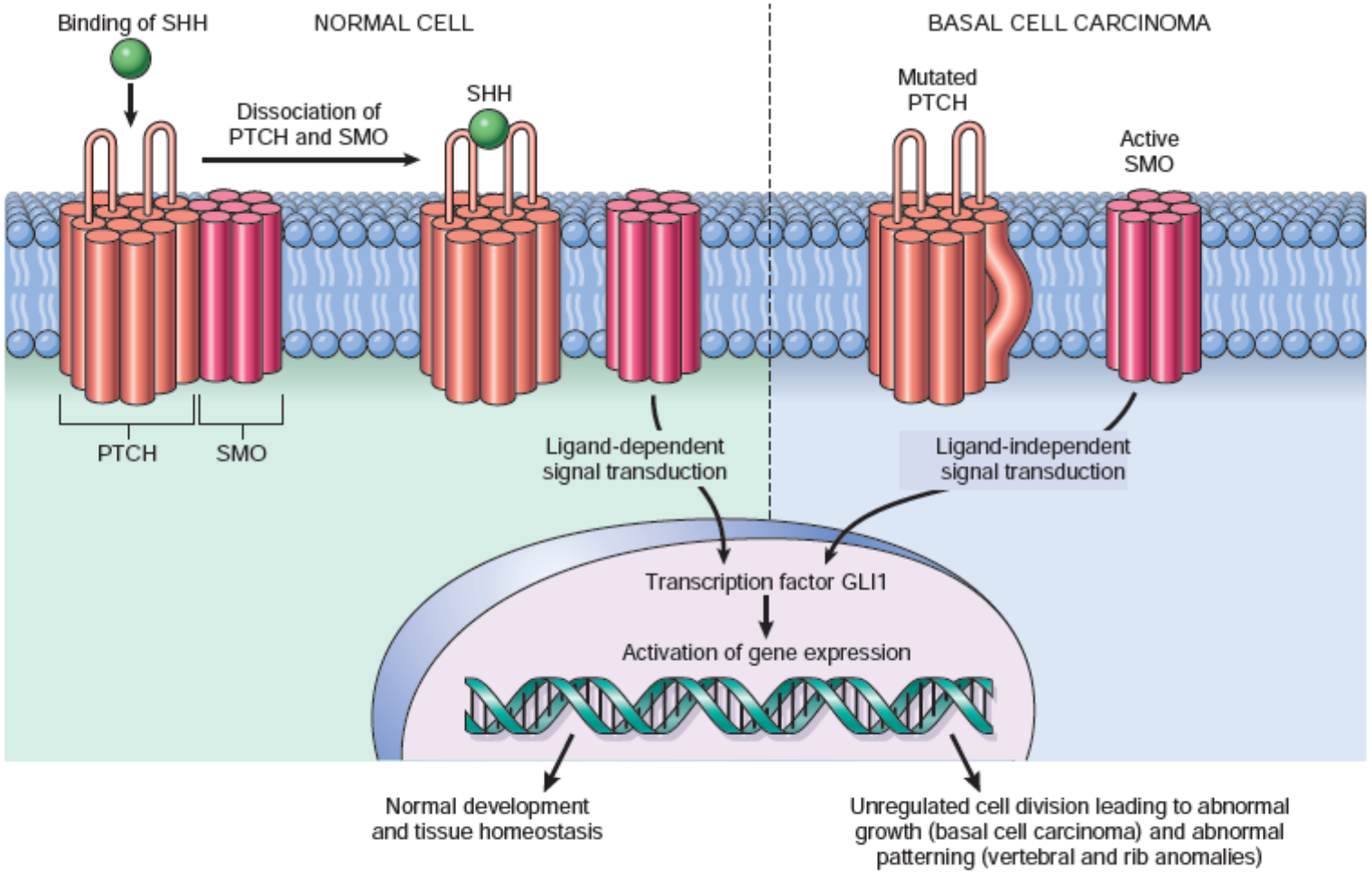
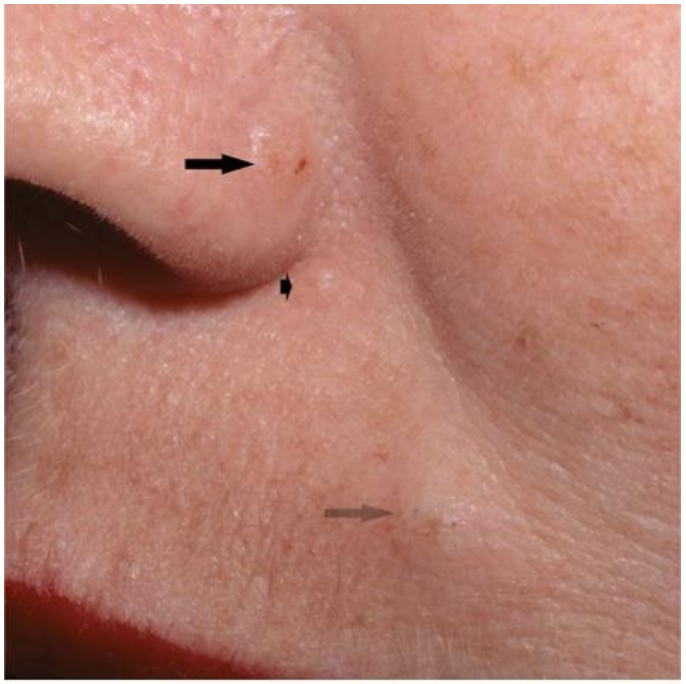


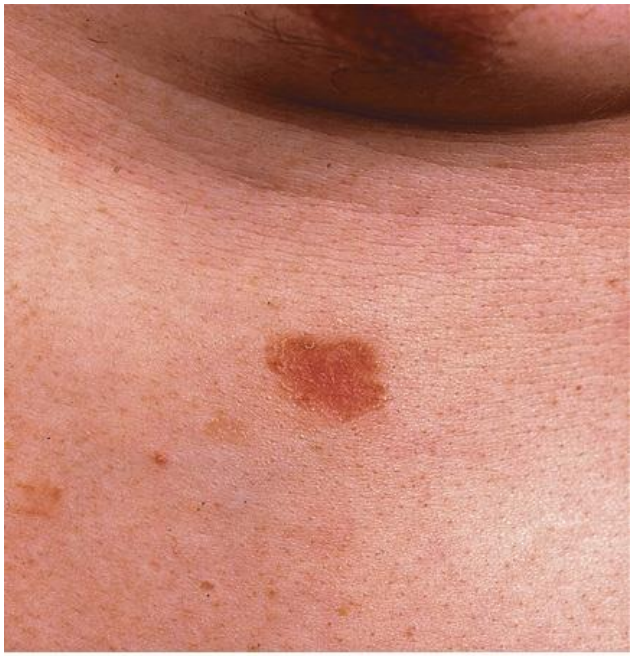
Figure 25-14 Normal and oncogenic hedgehog signaling. *Left,* Normally, PTCH and SMO form a receptor complex that can bind sonic hedgehog (SHH). In the absence of SHH, PTCH blocks SMO activity. When SHH binds PTCH, SMO is released to trigger a signal transduction cascade that leads to activation of GLI1 and other transcription factors. *Right,* Mutations in *PTCH*, and less often in *SMO*, allow SMO to signal without SHH binding and produce constitutive activation of GLI1. GLI signaling is a characteristic feature of sporadic basal cell carcinomas and tumors associated with the nevoid basal cell carcinoma (Gorlin) syndrome.

Basal cell carcinoma



A

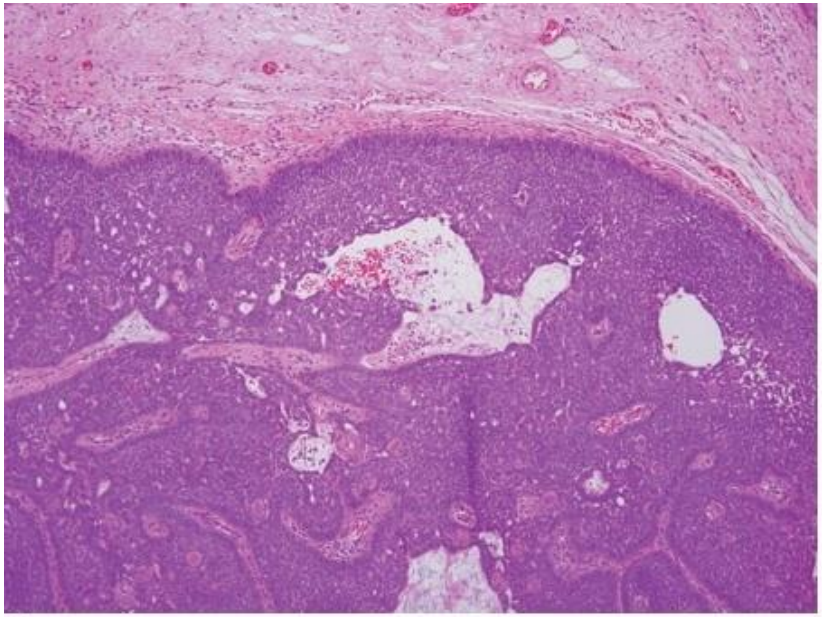
- Nodular Fig. 11-16A
- Accessed 07/16/2010



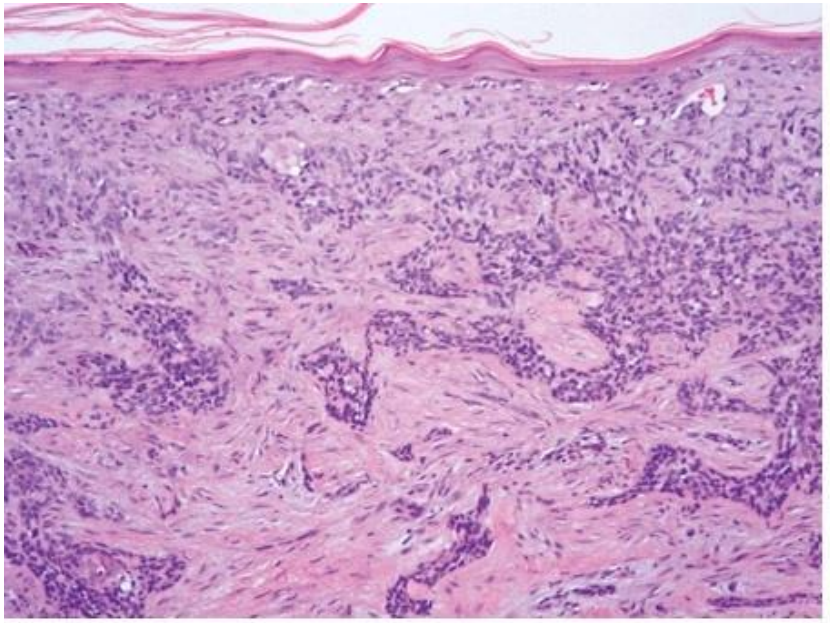
A

Superficial spreading Fig. 11-22A

Basal cell carcinoma



A



C

A. Nodular

C. Infiltrative

(Used with permission from Dr. Cynthia Magro.)
Fig. 115-8 Accessed 07/20/2010

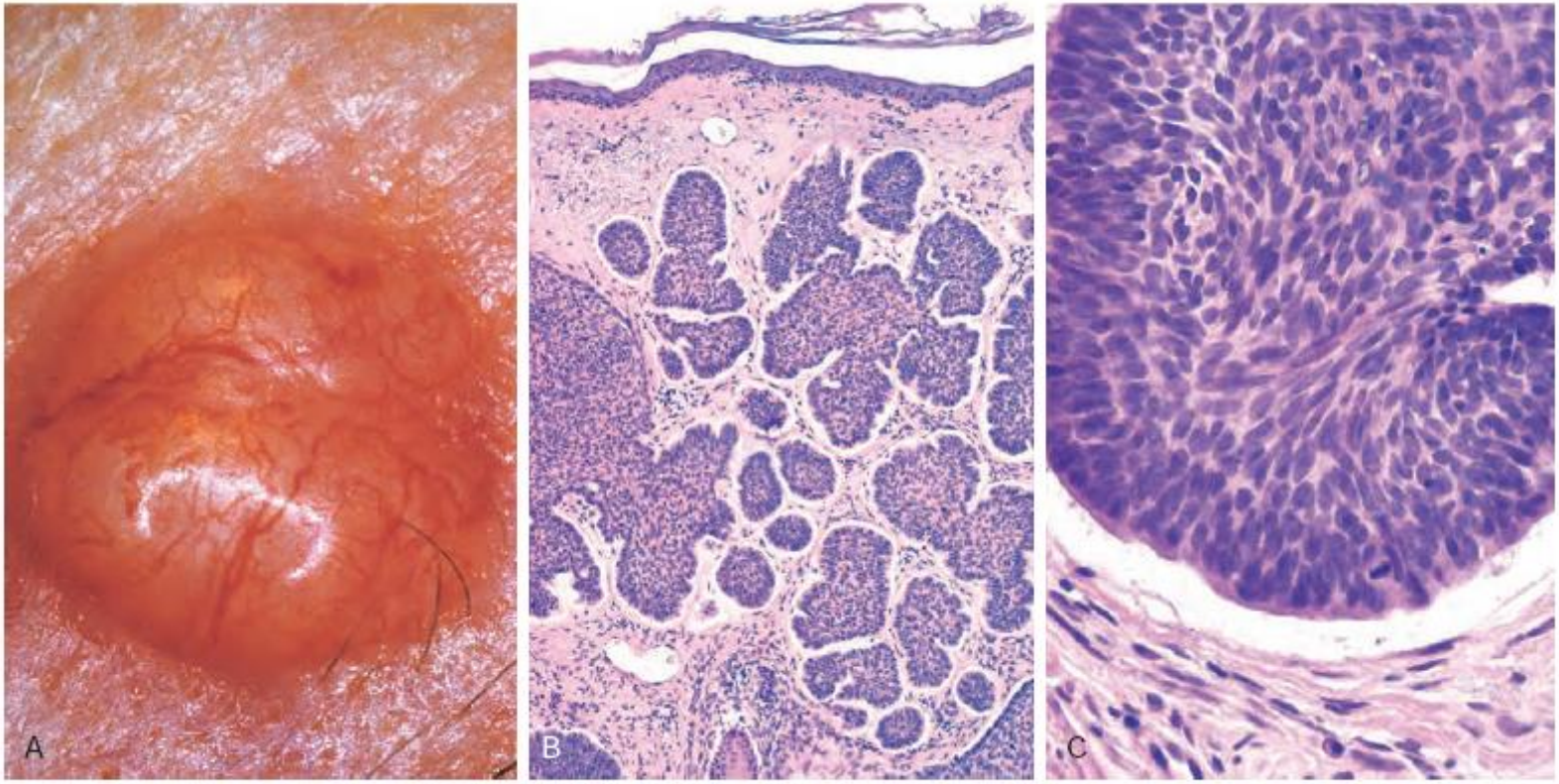


Figure 25-15 Basal cell carcinoma. Pearly, telangiectatic nodules **(A)** are composed of nests of uniform basaloid cells within the dermis **(B)** that are often separated from the adjacent stroma by thin clefts **(C)**, an artifact of sectioning.

Table 25-3 Survey of Familial Cancer Syndromes with Cutaneous Manifestations

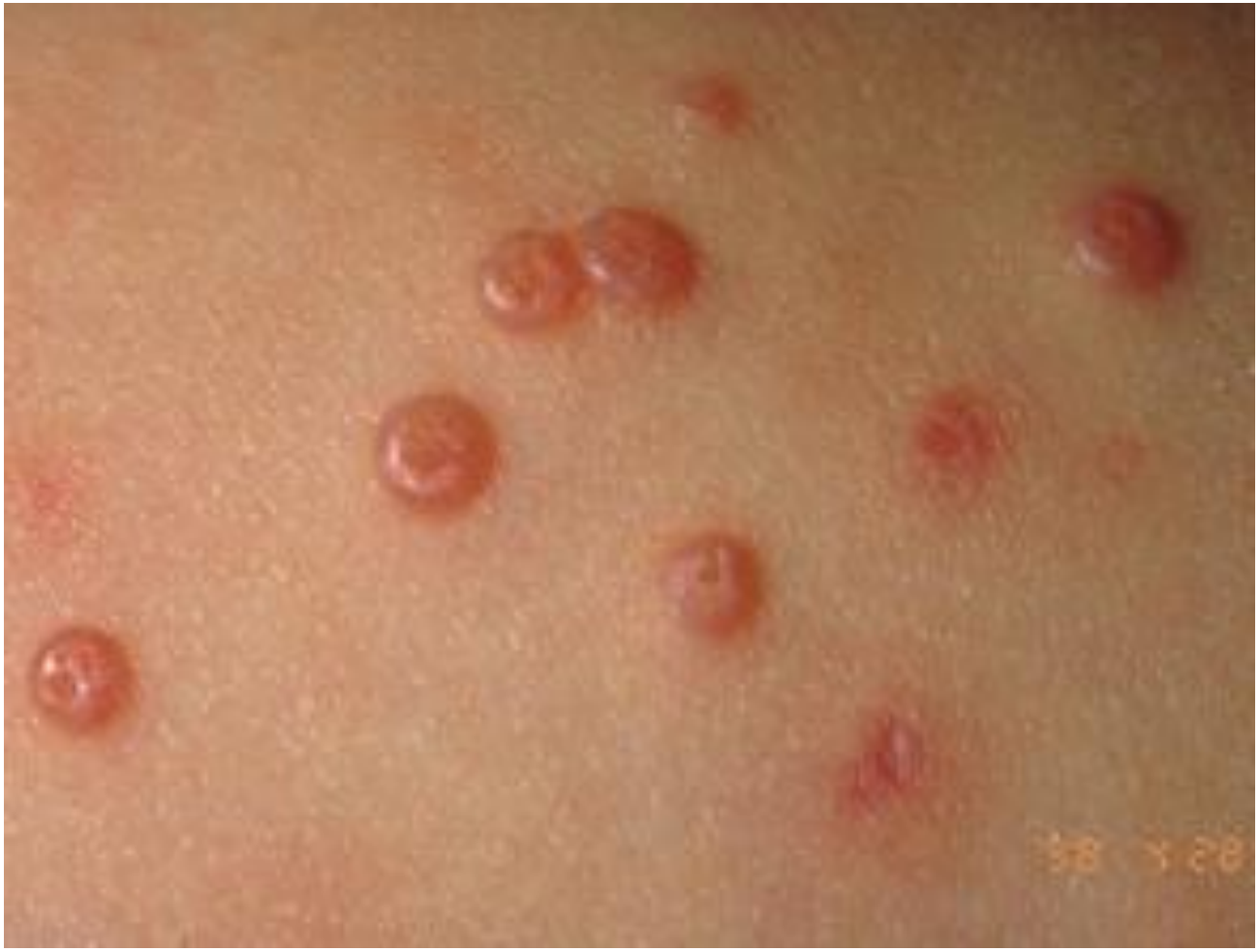
Disease	Inheritance	Chromosomal Location	Gene/Protein	Normal Function/Manifestation of Loss
Ataxia-telangiectasia	AR	11q22.3	*ATM*/ATM	DNA repair after radiation injury/neurologic and vascular lesions
Nevoid basal cell carcinoma syndrome	AD	9q22	*PTCH*/PTCH	Developmental patterning gene/multiple basal cell carcinomas; medulloblastoma, jaw cysts
Cowden syndrome	AD	10q23	*PTEN*/PTEN	Lipid phosphatase/benign follicular appendage tumors (trichilemmomas); internal adenocarcinoma (often breast or endometrial)
Familial melanoma syndrome	AD	9p21	*CDKN2*/p16/INK4 *CDKN2*/p14/ARF	Inhibits CDK4/6 phosphorylation of RB, promoting cell cycle arrest/melanoma; pancreatic carcinoma Binds MDM2, promoting p53 function/melanoma; pancreatic carcinoma
Muir-Torre syndrome	AD	2p22 3p21	*MSH2*/MSH2 *MLH1*/MLH1	Involved in DNA mismatch repair/sebaceous neoplasia; internal malignancy (colon and others)
Neurofibromatosis I	AD	17q11	*NF1*/neurofibromin	Negatively regulates RAS signaling/neurofibromas
Neurofibromatosis II	AD	22q12	*NF2*/merlin	Integrates cytoskeletal signaling/neurofibromas and acoustic neuromas
Tuberous sclerosis	AD	9q34 16p13	*TSC1*/hamartin *TSC2*/tuberin	Work together in a complex that negatively regulates mTOR/angiofibromas/mental retardation
Xeroderma pigmentosum	AR	9q22 and others	*XPA*/XPA and others	Nucleotide excision repair/melanoma and nonmelanoma skin cancers

AD, Autosomal dominant; AR, autosomal recessive.
From Tsai KY, Tsao H: The genetics of skin cancer. Am J Med Genet C Semin Med Genet 131C:82, 2004.

VERRUCAE

Molluscum contagiosum

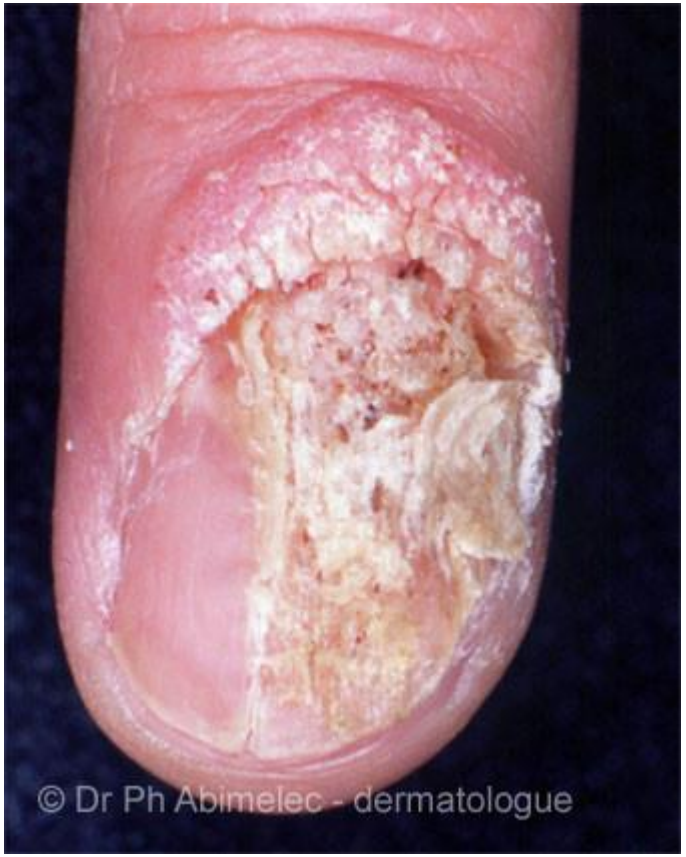
- Infants and children <10 years of age
- Clusters of small papules, many umbilicated
- Frequently in warm, moist areas of skin
- Never on palms or soles
- As papules resolve may develop inflammation about them and are pruritic
- Lesions more extensive in those with atopy or HIV
- More common in warm climates
- Direct skin to skin contact transmits named virus
- Papules clear within 2 years in immunocompetent persons

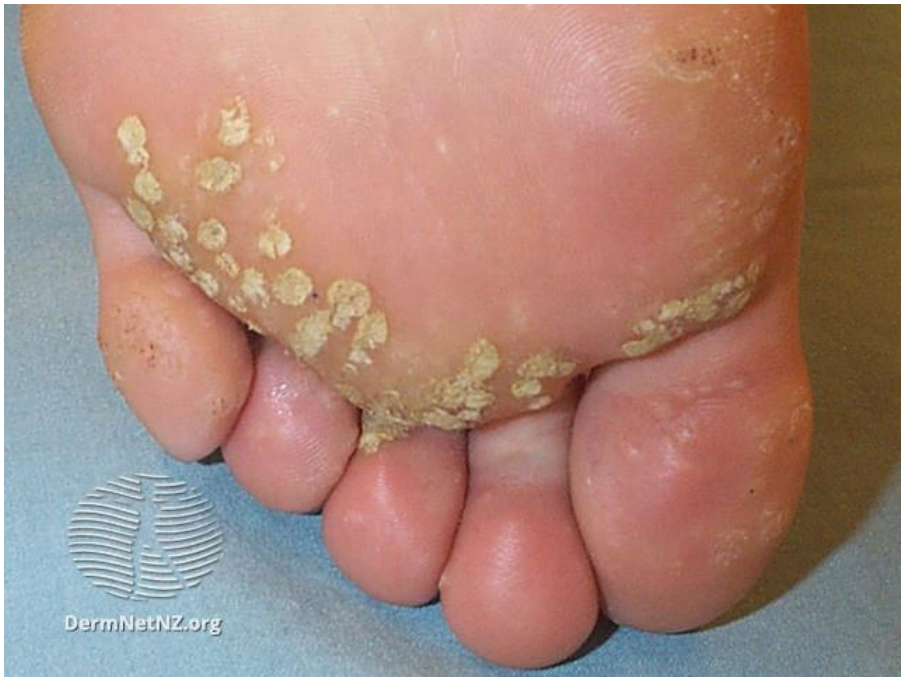


https://dermnetnz.org/topics/molluscum-contagiosum/
Accessed 03/30/2020

Common warts

- Present as papules
- Are rough, papillomatous and hyperkeratotic
- Commonly arise on backs of fingers or toes, around the and on the knees
- May resemble a cauliflower (butcher's warts)
- Familial forms described





https://dermnetnz.org/topics/viral-wart/
Accessed 03/20/2020

Verruca vulgaris

- Human papilloma virus infection
- Common types are 2, 3, 4, 27, 29, and 57.
- Arise at any age
- Direct skin to skin contact
- Eczema with loss of skin barrier may predispose
- In the immunocompromised, may never resolve
- High recurrence rate, particularly in smokers
- Cutaneous viral warts have a hard, keratinous surface. A tiny black dot may be observed in the middle of each scaly spot (intracorneal hemorrhage).

Plantar wart

- Also known as myrmecia wart
- May be tender inwardly growing and painful on the sole
- With clusters of less painful mosaic warts.
- Plantar epidermoid cysts are associated with warts.
- Persistent plantar warts may rarely be complicated by the development of verrucoid squamous carcinoma

Plane wart

- Have a flat surface
- The most common sites are the face, hands and shins.
- They are often numerous
- They may be inoculated by shaving or scratching
- Appear in a linear distribution (pseudo-Koebner response).
- Usually caused by HPV types 3 and 10.

Other warts

- Filiform wart
- On a long stalk like a thread.
- They commonly appear on the face.
- They are also described as finger-like
- Mucosal wart
- Oral warts can affect the lips and even inside the cheeks
- May be called squamous cell papillomas.
- Found in ano-genital region as well (condylomata)

Condylomata

- Histopathology
- Hyperkeratotic, parakeratotic, acanthotic with both upward and downward proliferation .
- Koilocytic change. (HPV).
- Pictured are condylomata.
- Pre-malignant

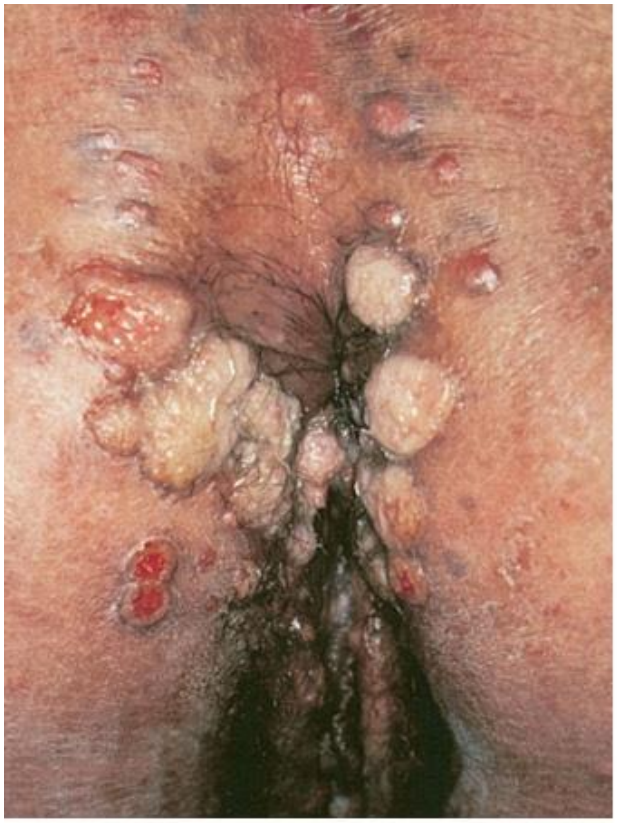


Fig. e10-48
Accessed 07/16/2010

Treatment

- 50% disappear within 6 months if untreated
- 90% disappear within 12 months
- Topical therapy:
- Soften the wart with hot water (soaks)
- Rub surface with pumice
- Paint on gel (usually salicylic acid)
- Cover
- Generally resolves within 12 weeks of daily therapy
- Cryotherapy
- Electrocautery
- Surgical removal

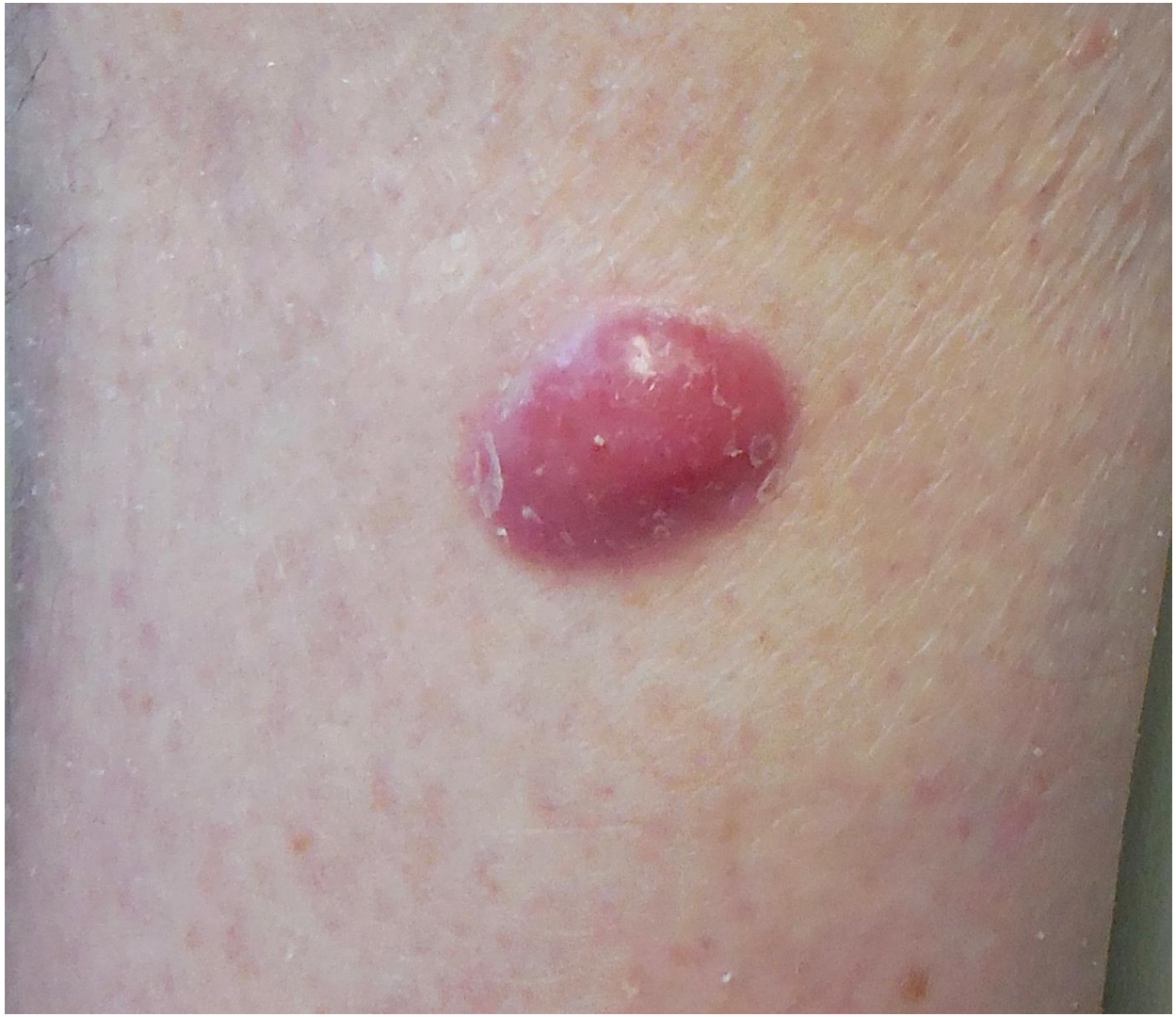
NEUROENDOCRINE TUMOR

Merkel cell carcinoma

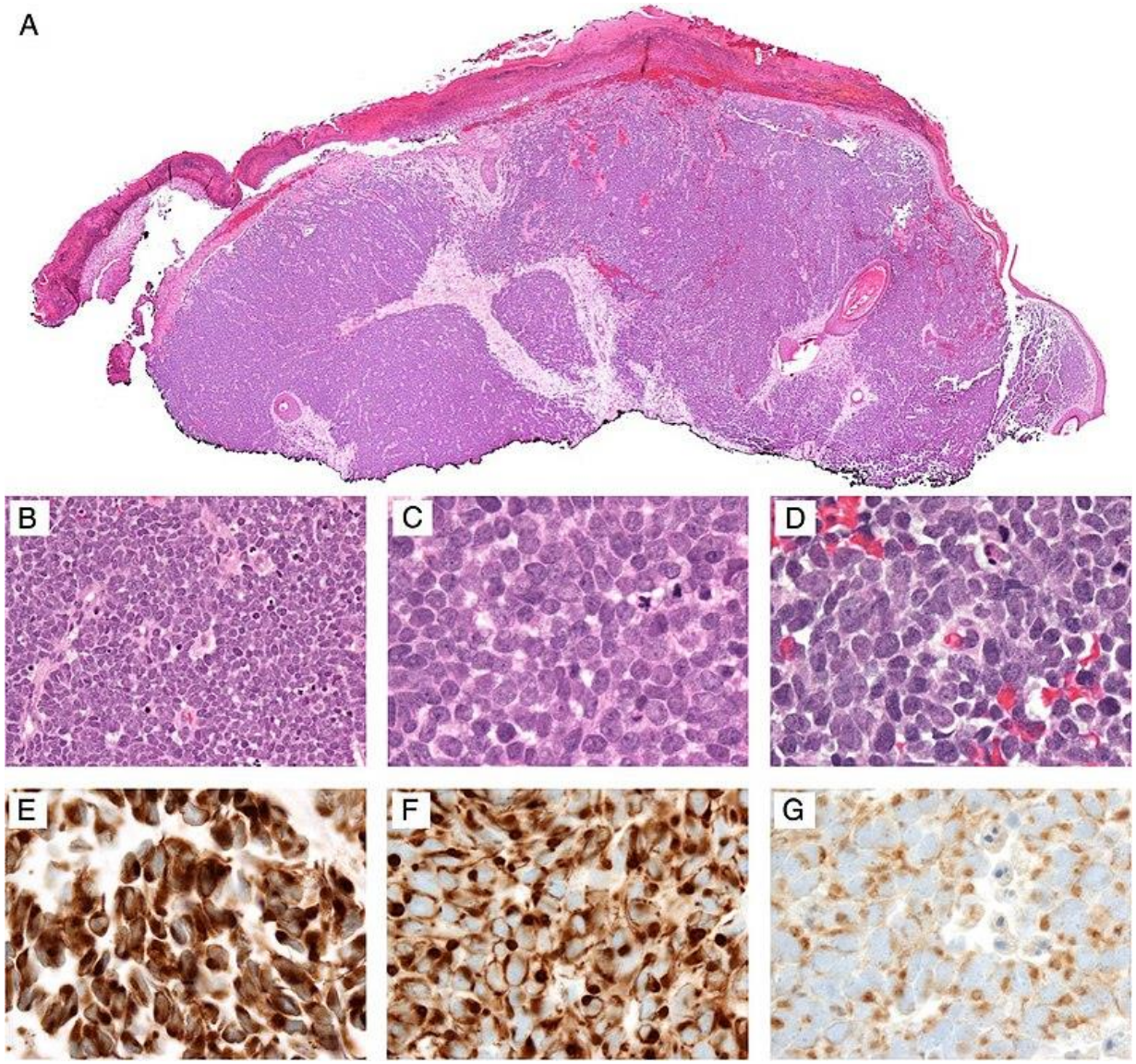
- Rare
- Usually develops as a single, painless, bump on sun-exposed skin.
- The bump may be skin-colored or red-violet
- Tends to grow rapidly over weeks to months.
- It may spread quickly
- Factors associated with developing MCC include increasing age, fair skin, a history of extensive sun exposure, chronic immune suppression

Merkel cell carcinoma

- Merkel cells are located deep in the top layer of skin.
- Merkel cells are connected to nerves, signaling touch sensation as “touch receptors.”
- It is unlikely that MCC originates directly from normal Merkel cells.



https://www.skincancer.org/skin-cancer-information/merkel-cell-carcinoma/



A, B, C. H&E staining demonstrates small, undifferentiated cells with high N/C ratio and scanty cytoplasm.
E. Positive cytokeratin AE1/AE3
F. Positive CK 20
G. Positive chromogranin

DOI:10.1186/s40661-017-0037-x

Merkel cell carcinoma

- 80% of cases in US and Europe associated with Merkel cell polyomavirus
- The remaining 20% of MCC cases in the United States and Europe (and approximately 70% in Australia) lack detectable tumor-associated viral DNA
- The mutational burden of virus negative MCC exceeds that of melanoma
- The pattern of mutations strongly implicates ultraviolet-induced DNA damage as the causative mechanism.

Merkel cell carcinoma

- MCC tumors can downregulate antigen presentation, including by major histocompatibility complex I (MHC-I) loss
- MCC cells also induce an immunosuppressive microenvironment by producing immunosuppressive cytokines or via recruitment of immunosuppressive cells, such as $CD4^{+}CD25^{+}$ regulatory T cells (T regs) or myeloid-derived suppressor cells.

Merkel cell carcinoma

- In response to chronic antigen exposure, antigen-specific $CD8^+$ T cells in the MCC tumor microenvironment commonly develop an exhausted phenotype with poor effector function, sustained expression of inhibitory receptors (e.g., PD-1, Tim3), and a transcriptional state distinct from that of functional effector or memory T cells.

Merkel cell carcinoma

- MCCs that have overexpression of immune response genes and higher intra-tumoral infiltration of $CD8^+$ lymphocytes are generally found to have more favorable prognoses
- Pembrolizumab for locally advanced or metastatic MCC