

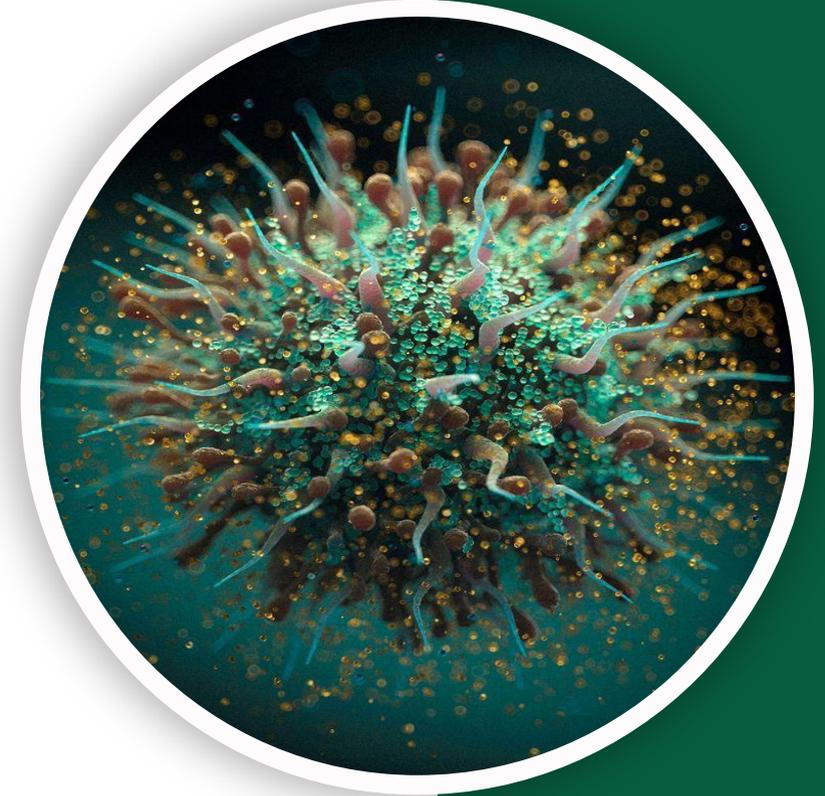
بِسْمِ اللّٰهِ الرَّحْمٰنِ الرَّحِیْمِ
(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)



جراح

MSS Pathology | FINAL 5

MSS & Skin Tumors pt.11

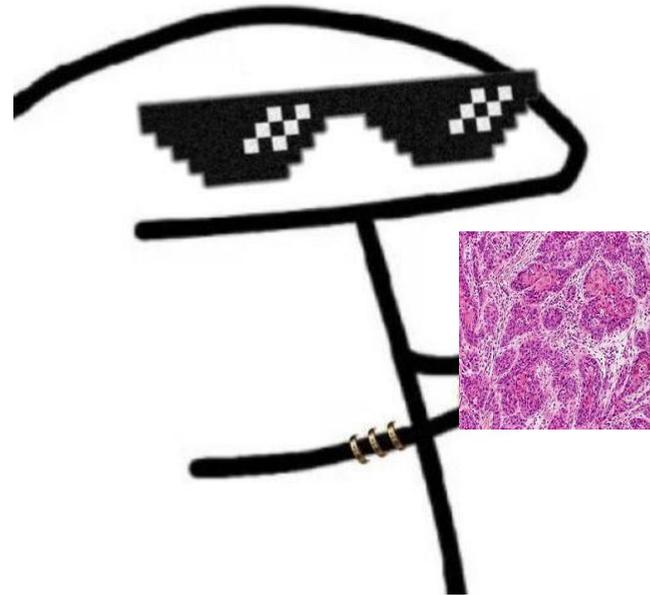


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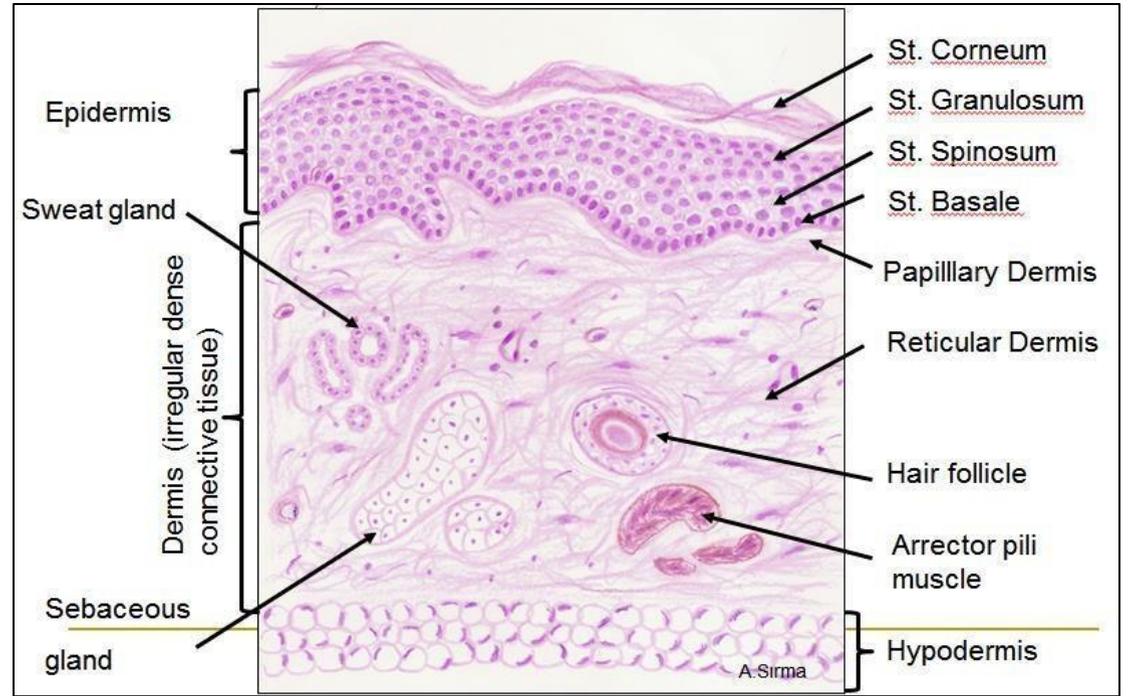
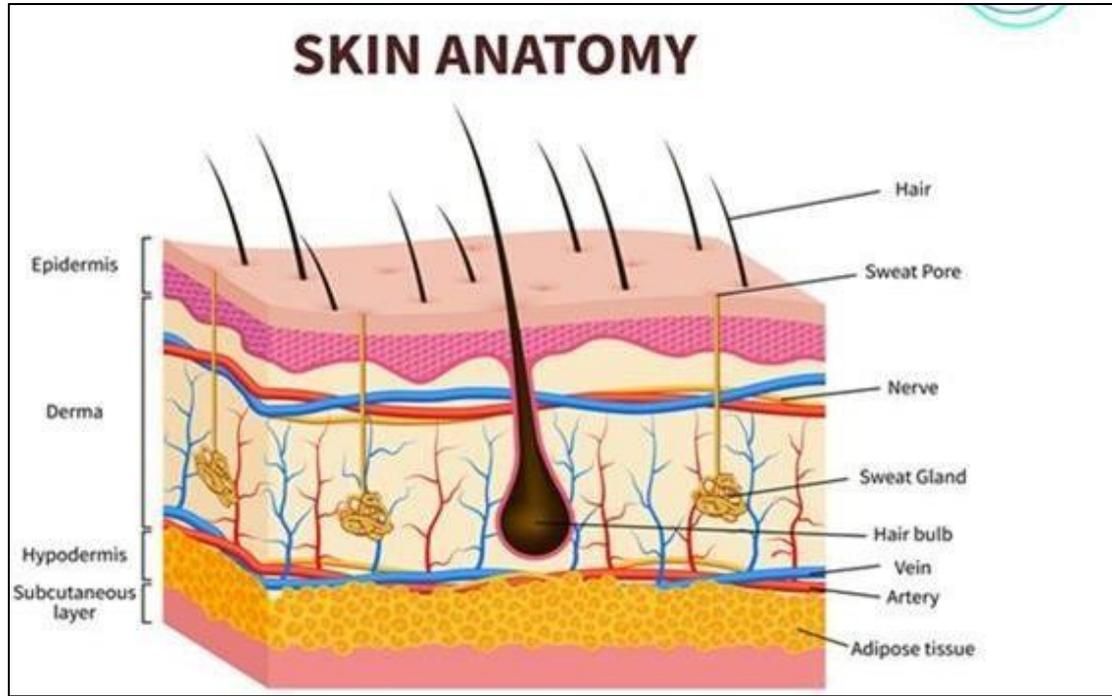
Capture the specimen....



(اللهم أعني و لا تعن عليّ و انصرني و لا تنصر عليّ و امكر لي و لا تمكر عليّ و اهدني و يسر الهدى لي)

✓ *Skin Pathology: cysts and (neoplasms)*

- Inflammatory and infectious dermatosis (dermatology rotation)
- Very common lesions
- Increase with increasing age
- Rarely fatal (except melanomas) , **most of them are benign**
- More common in sun exposed areas
- Associated with sun damage (solar elastosis)
- **Ultraviolet (UV) radiation from sun exposure is one of the most significant predisposing and high-risk etiological factors for the development of skin tumors, including squamous cell carcinoma, basal cell carcinoma, and the more aggressive melanoma.**



☐ *Solar (actinic) elastosis*

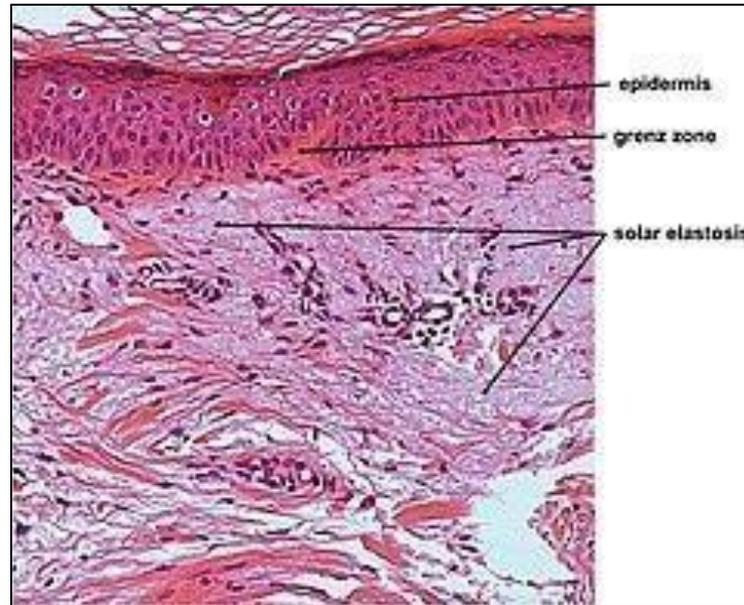
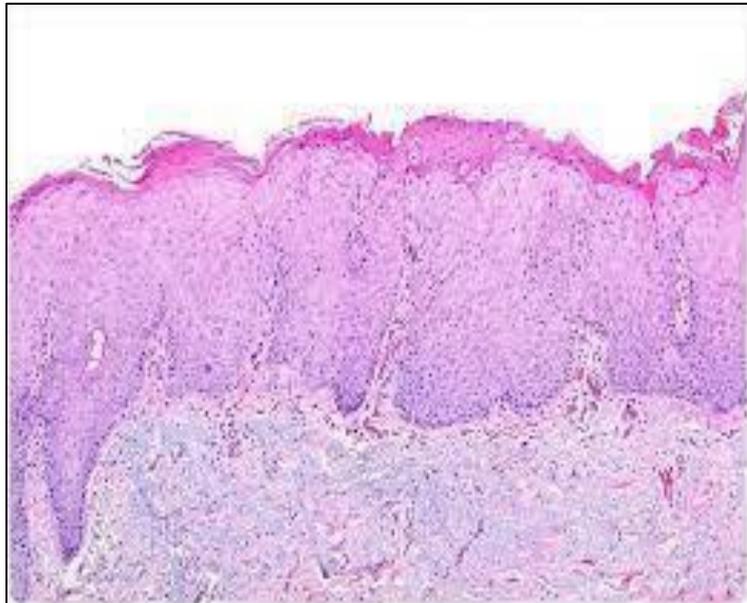
- Elastosis = elastic fibers of the superficial dermis are damaged
- Chronic sun damage leading to: thickened and yellow skin
- “Damage to skin elasticity (**tissue components**) from sun exposure”
- Preventable disease
- **One of the early histological changes observed in sun-damaged skin**
- UV rays damage collagen and elastic fibers of the skin
- **While solar elastosis itself is not cancerous**, it will increase the risk of many skin pre-malignancies (Actinic keratosis) and malignancies (melanomas, squamous cell carcinomas, basal cell carcinomas)
- It is common to observe basal cell carcinoma arising in tissue that shows background solar elastosis, indicating the chronic UV damage that predisposed to tumor development.

Morphology

Clinically, solar elastosis presents as skin changes due to chronic sun exposure and may precede the onset of malignancies.



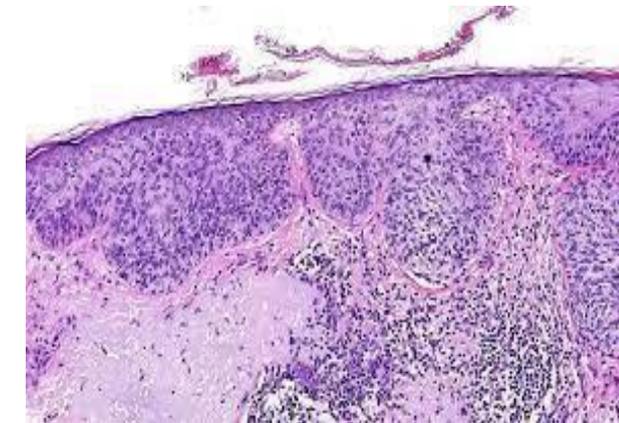
This is how it looks clinically: the skin is slightly scaly and yellow.



When a skin biopsy is taken from sun-exposed areas, the squamous epithelium may appear histologically normal, but the superficial dermis often shows prominent changes. One of these is **garish discoloration** and degeneration of elastic fibers (solar elastosis).

□ *Actinic keratosis*

- After prolonged UV exposure, molecular damage to the nuclear DNA of keratinocytes occurs. These changes, often accompanied by solar elastosis, can lead to the development of actinic keratosis.
- Premalignant skin disease due to sun damage
- It considered a precursor to squamous cell carcinoma
- Some consider actinic keratosis a form of carcinoma in situ , as the atypical keratinocytes remain confined to the epidermis. To evaluate potential progression to invasive squamous cell carcinoma
- UV light damage DNA via mutations in TP53
- They progress to squamous cell carcinoma (rate: 1-3%)



Actinic keratosis

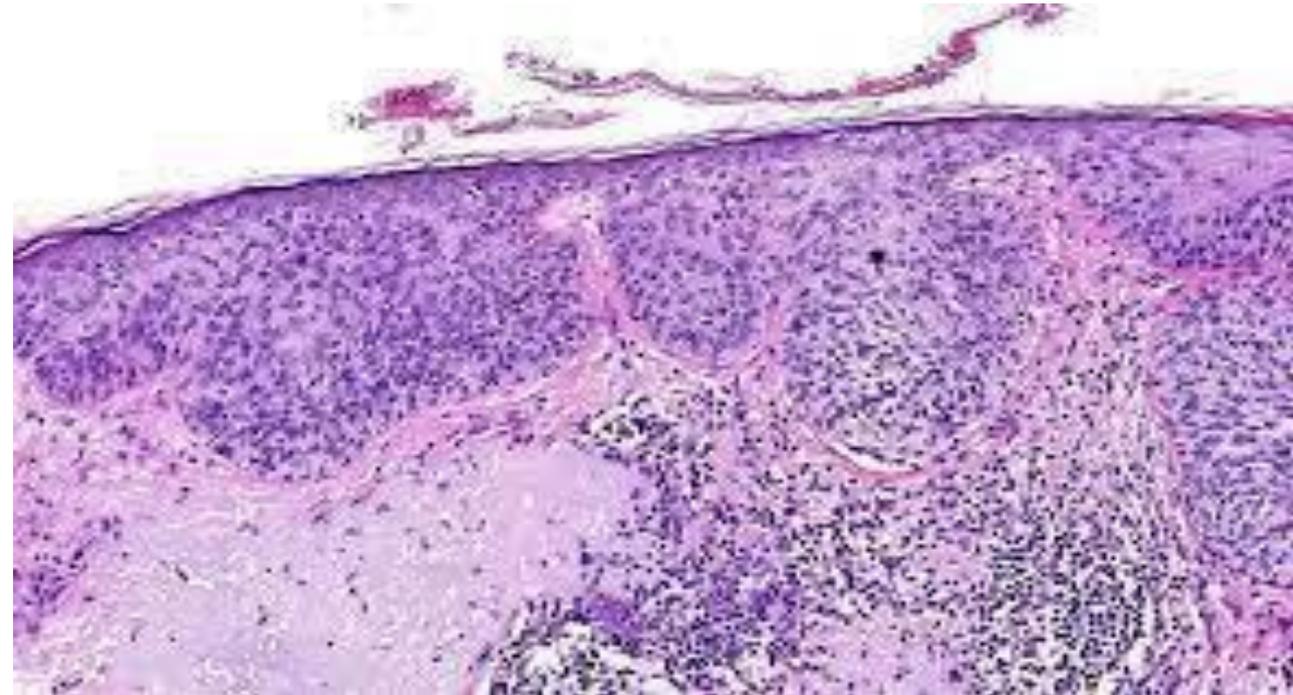
Diffuse Actinic keratosis

Localized Actinic keratosis

This is how it appears clinically



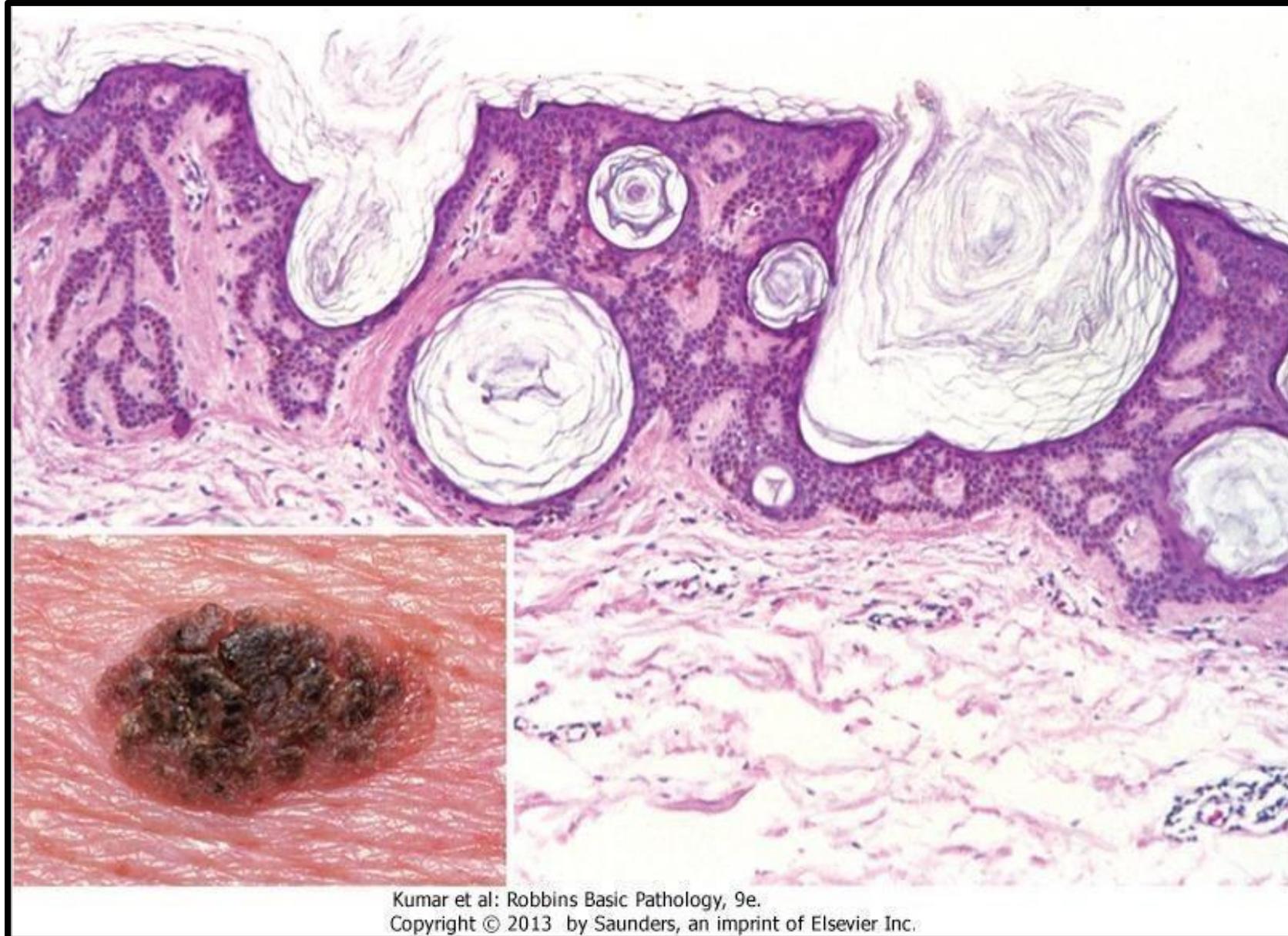
Microscopically, squamous cells are completely abnormal, but the basement membrane is intact with no invasion. This indicates actinic keratosis (squamous cell carcinoma in situ).



□ *Seborrheic keratosis*

- It is a benign neoplasm and not a premalignant lesion.
- Very common pigmented neoplasms (although it may lack pigmentation)
- Middle age- older patients; anywhere but mainly trunk
- FGFR3 mutations (different pathogenesis)
- Clinically insignificant (removed to R/O malignancy)
- These lesions are often removed to exclude malignancy or for cosmetic reasons
- Coin-like lesions, usually pigmented, elevated “Stuck-on”
- Clinically, SK often appears as a well-demarcated, “stuck-on” lesion, usually brown to black in color.
- Histologically, it consists of proliferating squamous epithelium with features such as keratin-filled cysts (horn cysts) and surface hyperkeratosis (PLEASE SEE NEXT SLIDE)

Seborrheic keratosis



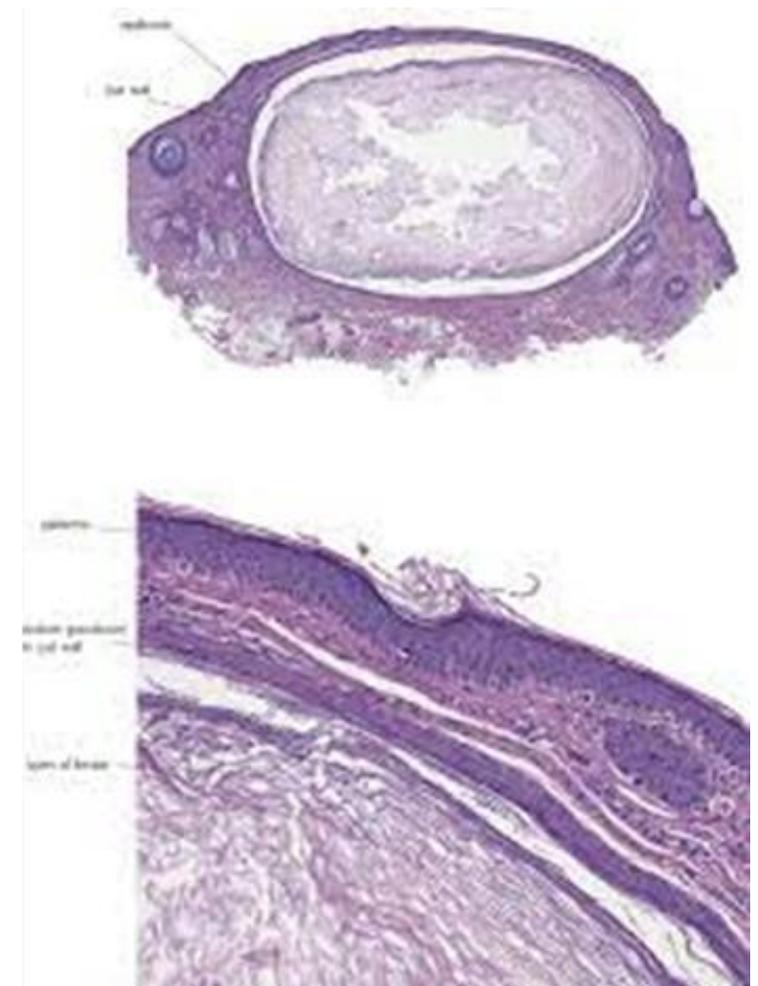
□ *Cysts*

- Very common (one of the most common pathologies of the skin)
- Almost all are benign (Skin bumps)
- Clinically: the surgeon call them “Sebaceous cyst” , but histologically they are not sebaceous .
- Malignant transformation is extremely rare
- They are generally benign, but can become inflamed or infected, prompting removal.
- The cyst can be completely excised. However, it may rupture, leading to an open and inflamed lesion, in this case it is referred to as a ruptured epithelial inclusion cyst.
- Many types:
 - Epidermal inclusion cyst (the most common)
 - Dermoid cyst
 - Trichilemmal cyst is typically found around the hair shafts on the scalp

Epidermal (epithelial) inclusion cyst

Be careful not to confuse it with a dermatoid cyst.

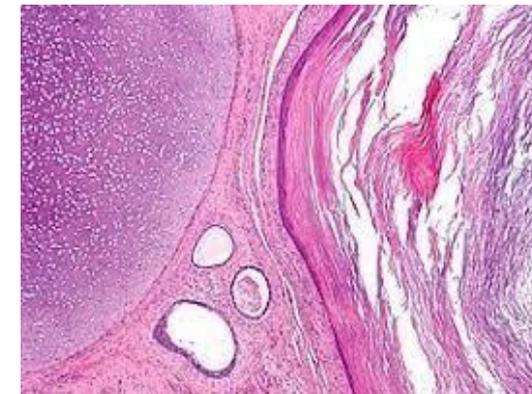
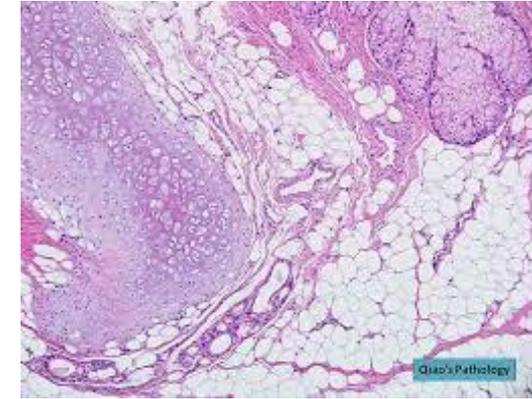
These are true cysts, meaning they are lined by stratified squamous epithelium and contain keratinous debris, and they can occur anywhere in the body.



❑ *Dermoid cyst*

- A dermoid cyst is a growth of normal tissue enclosed in a pocket of cells called a sac. This tissue grows in or under your skin in an unexpected location (**deeper than the epidermal inclusion cyst**)
- A cyst is a lump or bump that may contain fluid or other material. Most often , dermoid cysts contain a greasy yellow material, but they may contain :mature tissues (bone ,hair ,muscle , teeth...etc)
- Dermoid cysts can be any where on your body , **but they are most commonly found in ovary and testis .**
- **If the cysts are completely mature, they are considered non-threatening, and complete surgical excision is typically curative.**
- Rarely they can have immature or malignant elements (malignant dermoid cysts or teratoma).
- Peri-orbital, ovarian, spinal...etc

Dermoidcyst



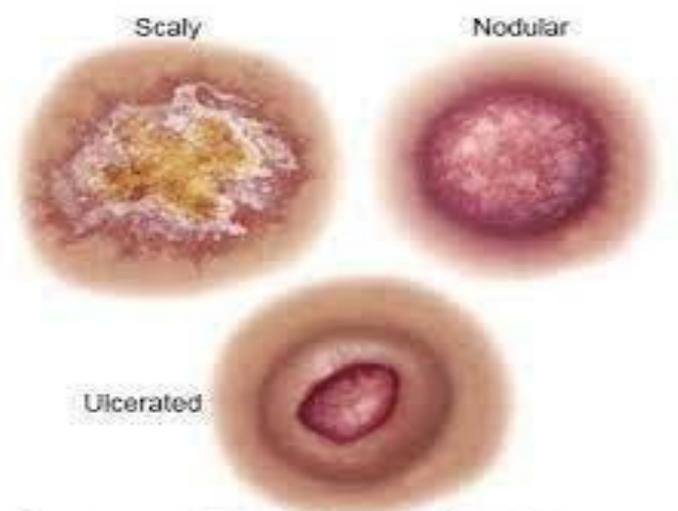
The images show an ovarian dermoid cyst containing mature elements such as teeth and hair, consistent with a mature cystic teratoma. Radiological findings and histological confirmation support the diagnosis.

Careful and adequate sampling of a dermoid cyst is essential to exclude the presence of any immature elements, most commonly immature neural tissue.

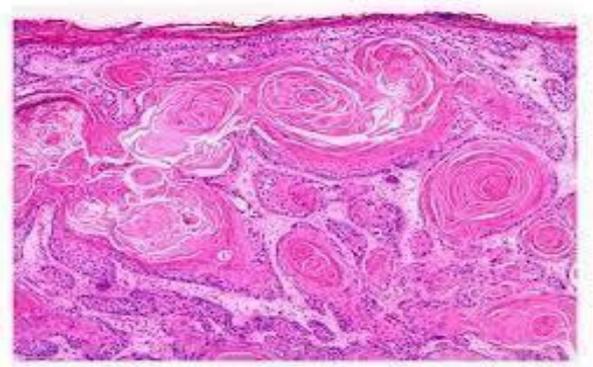
□ *Squamous cell carcinoma*

- The most common malignancies of the skin are basal cell carcinoma, squamous cell carcinoma, and melanoma (the most fatal)
- Common neoplasms
- Sun damage (sun exposed areas)
- Most commonly localized with rare deep infiltration or metastasis.
- Invasive, usually keratinizing squamous cell carcinoma
- Risk increases: immunosuppression (HPV), prolonged sun exposure (**the most common**), tars & oils (chewing tobacco may leads to chronic irritation of the mucosa = SCC) , old burns, ionizing radiation.
- **Before invasion , lesions are called Bowen's disease, actinic keratosis, or carcinoma in situ.**

-Squamous cell carcinoma appears variable (clinically) . It can look scaly, nodular, or even have an ulcer.
 - Histologically , the diagnosis is very straightforward.
 -Metastases don't mean invasion. Invasion means it reaches the tissue below it while metastases is a tumor spreading to another part of the body.



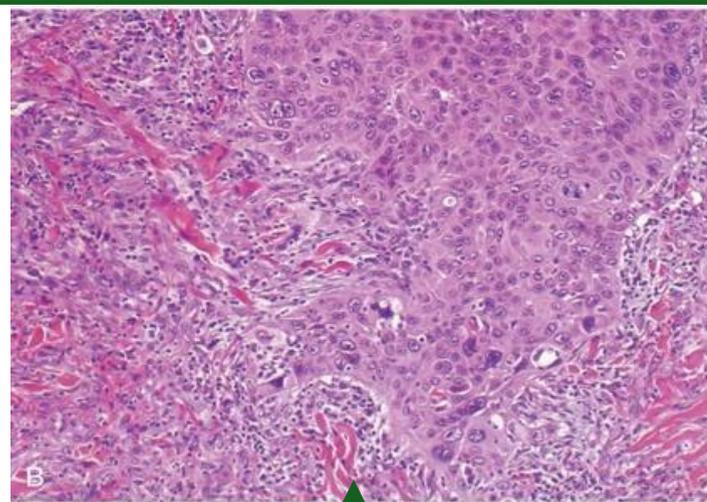
Squamous Cell Carcinoma of the Skin



This is well-differentiated squamous cell carcinoma with prominent keratin pearl formation and cells resembling normal squamous epithelium.

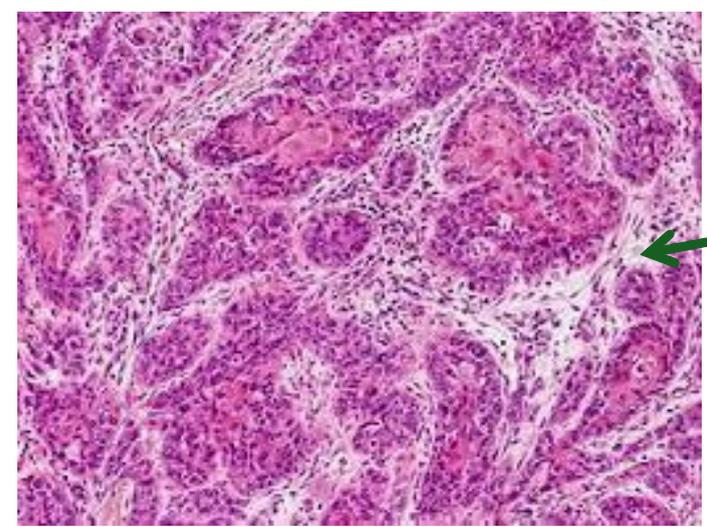


This looks scaly and ulcerative



This is poorly differentiated squamous cell carcinoma composed of markedly atypical cells with minimal keratinization.

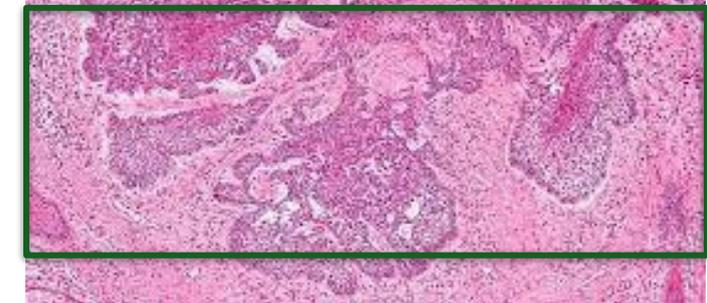
Kumar et al: Robbins Basic Pathology, 9e. Copyright © 2013 by Saunders, an imprint of Elsevier Inc.



This is invasive carcinoma



This is the normal squamous epithelium



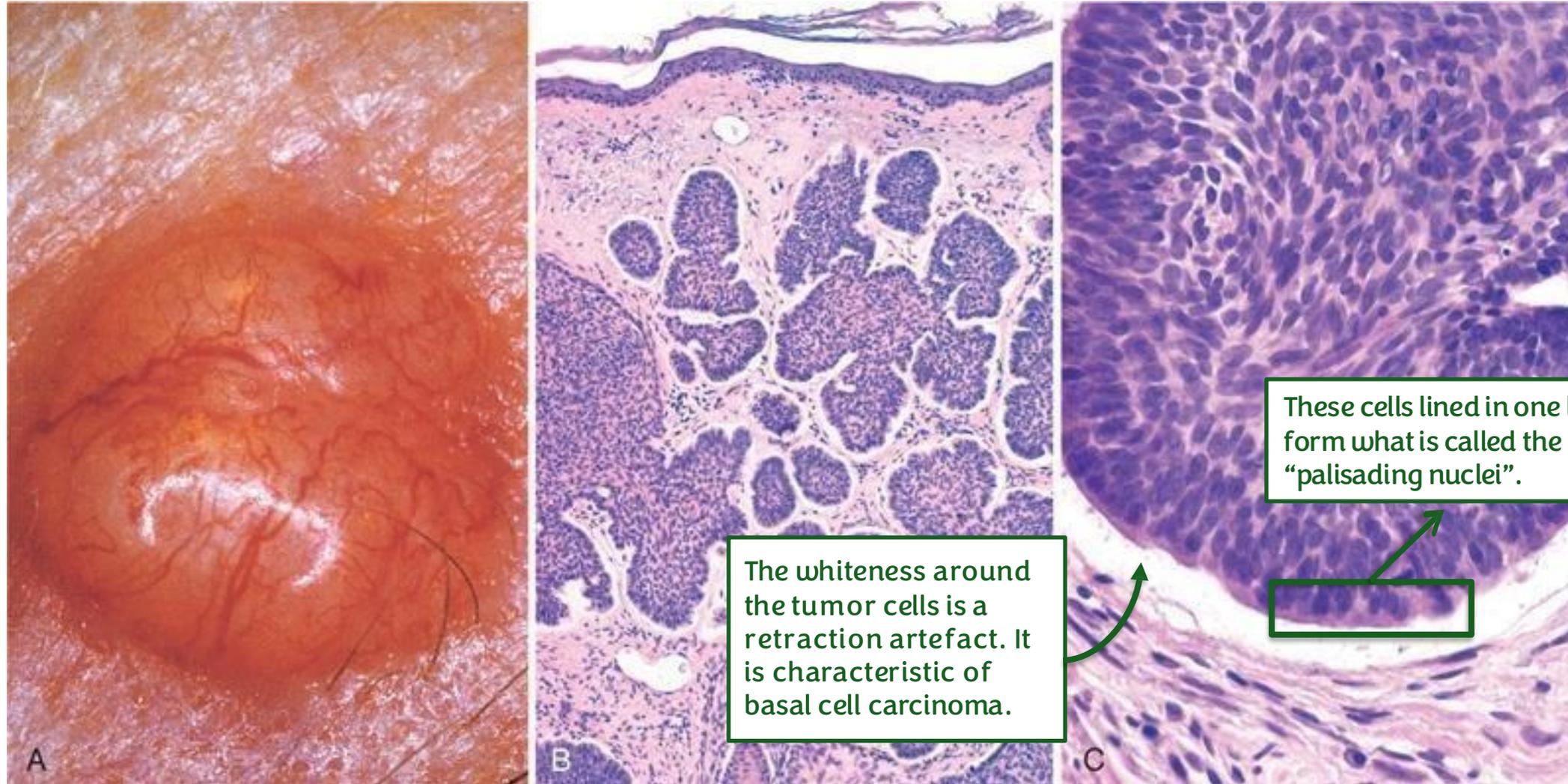
This is invasive tumor -unlike actinic keratosis that is not invasive.

□ *Basal cell carcinoma:*

- Arise from basal cells of epidermis (Actually, both basal cell carcinoma and squamous cell carcinoma arise from epidermal squamous cells derived from the basal layer. However, basal cell carcinoma is named this way because the tumor cells resemble basal cells – small, with large nuclei and an immature appearance – indicating differentiation toward basal cells.)
- Sun exposure
- Can be multiple (several independent lesions occurring in the same patient)
Multifocality is common in skin carcinomas, & most common in Basal cell carcinomas.
- You typically see Papules, slightly pigmented
- It is Localized (locally invasive)
- Deep infiltration and metastasis are extremely rare
- We commonly see *PTCH1* mutations and *TP53* mutations
- Gorlin syndrome: multiple basal cell carcinoma (AKA “Basal cell nevus syndrome”)

□ *Basal cell carcinoma:*

Quick rev:
It is a very common tumor, removed completely to cure the patient, doesn't usually metastasize, and rarely invades - unlike melanoma.



The whiteness around the tumor cells is a retraction artefact. It is characteristic of basal cell carcinoma.

These cells lined in one line form what is called the "palisading nuclei".

○ Histologically, some redness, elevated, sometimes pigmented. Differ in morphology from squamous cell carcinoma -keratinizing squamous cell. Basal cell carcinomas are smaller with higher N:C ratio

☐ *Melanocytic neoplasms:* (most dangerous)

- Nevus (الشامة): It is a benign congenital melanocytic neoplasm
- Melanocytic nevus: any melanocytic neoplasm (congenital or acquired)

- Sometimes, young patients remove a nevus out of concern that it may become malignant. This type of nevus is called a compound nevus with congenital features.
- Some nevi are congenital, while most are acquired.



- A Nevus is a benign tumor, but with factors like irritation or increased UV exposure, it can develop into a dysplastic/atypical nevus, which is considered premalignant. If left untreated, it may progress to melanoma. This distinction is important. Although pathologists may occasionally find it challenging, specific features help differentiate a regular nevus from a dysplastic one. It's essential to accurately label them as either intradermal nevus or dysplastic nevus. In contrast, melanoma is generally easier to recognize histologically.

☐ *NEVUS*

- Benign pigmented melanocytic proliferation
- Caused by somatic gain of function mutation *RAS* or *BRAF*
- This is followed by inactivity “Senescence”
- Clinically: sharply demarcated, elevated and pigmented. → Clinician would know it’s benign mostly.
- Removed surgically for cosmetic reasons, to prevent irritation and to rule out dysplasia or melanoma

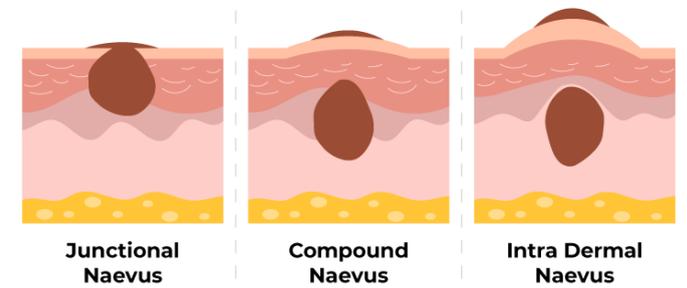
• Junctional N. → Compound N. → Intradermal N

Junction btwn epidermis & dermis (basal cell of squamous)

On junction and deep in dermis.

Intradermal (only deep without junction)

((All are benign))

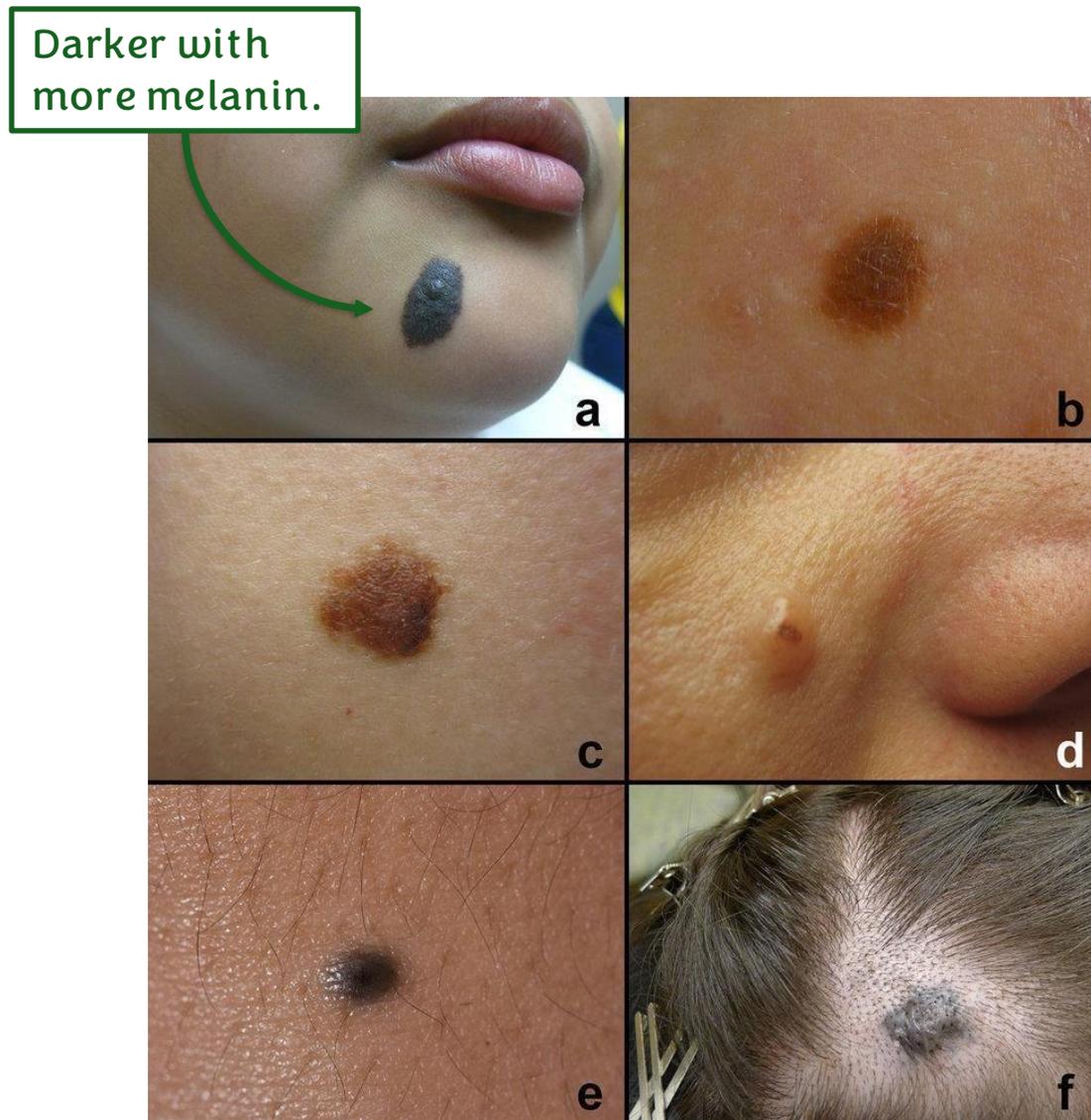


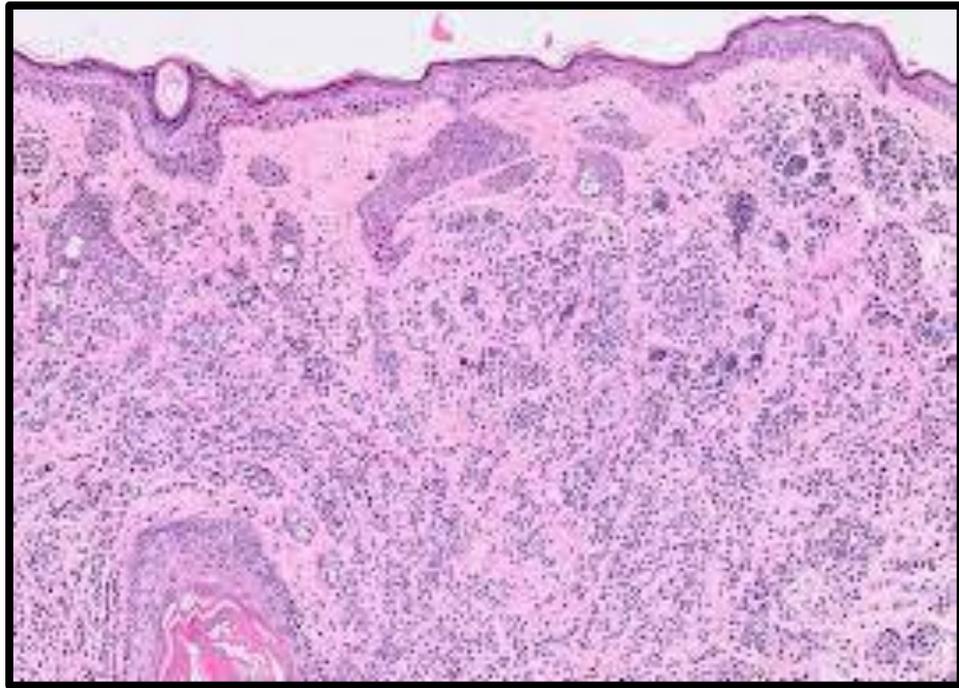
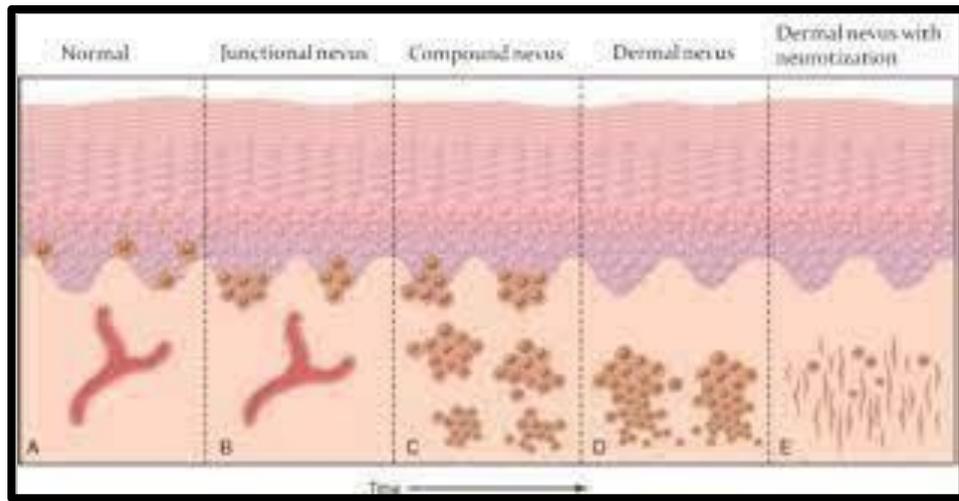
~just for clarification~



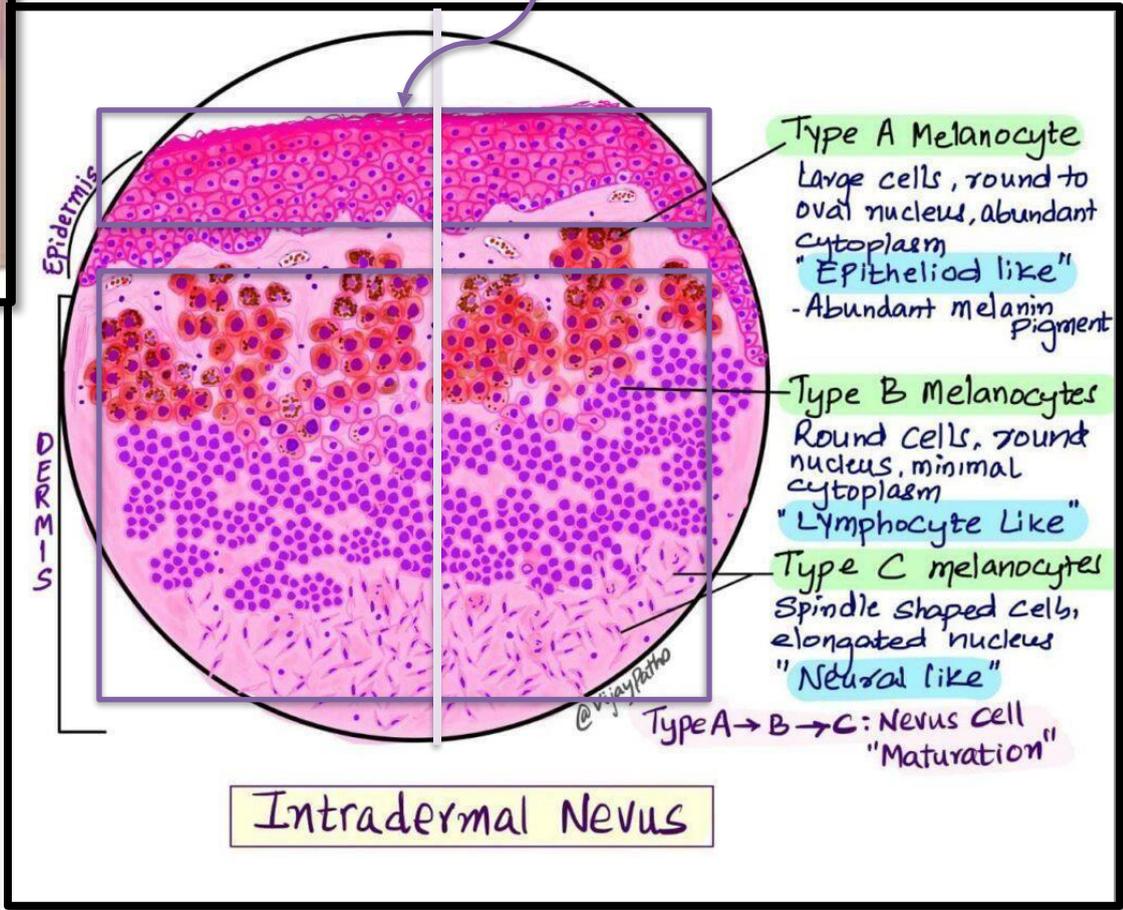
Benign features:

- Well-demarcated
- Sharp borders
- No significant change over time
- Histology: symmetry, absence of atypia (cellular enlargement, nuclear enlargement, nuclear chromatin abnormalities, prominent nucleoli, mitosis, maturation as you move deep into dermis).





Squamous epithelium



Features of benignity:-

- When you examine a nevus, you split it in half like a mirror – the right side is similar to the left ;we call this symmetry. Nevi are symmetric.
- The other feature: As you go deeper, cells + nucleus get smaller, while cytoplasm gets bigger -> we call this neurotization/maturation
- No mitosis, no necrosis, no atypia – all benign features.

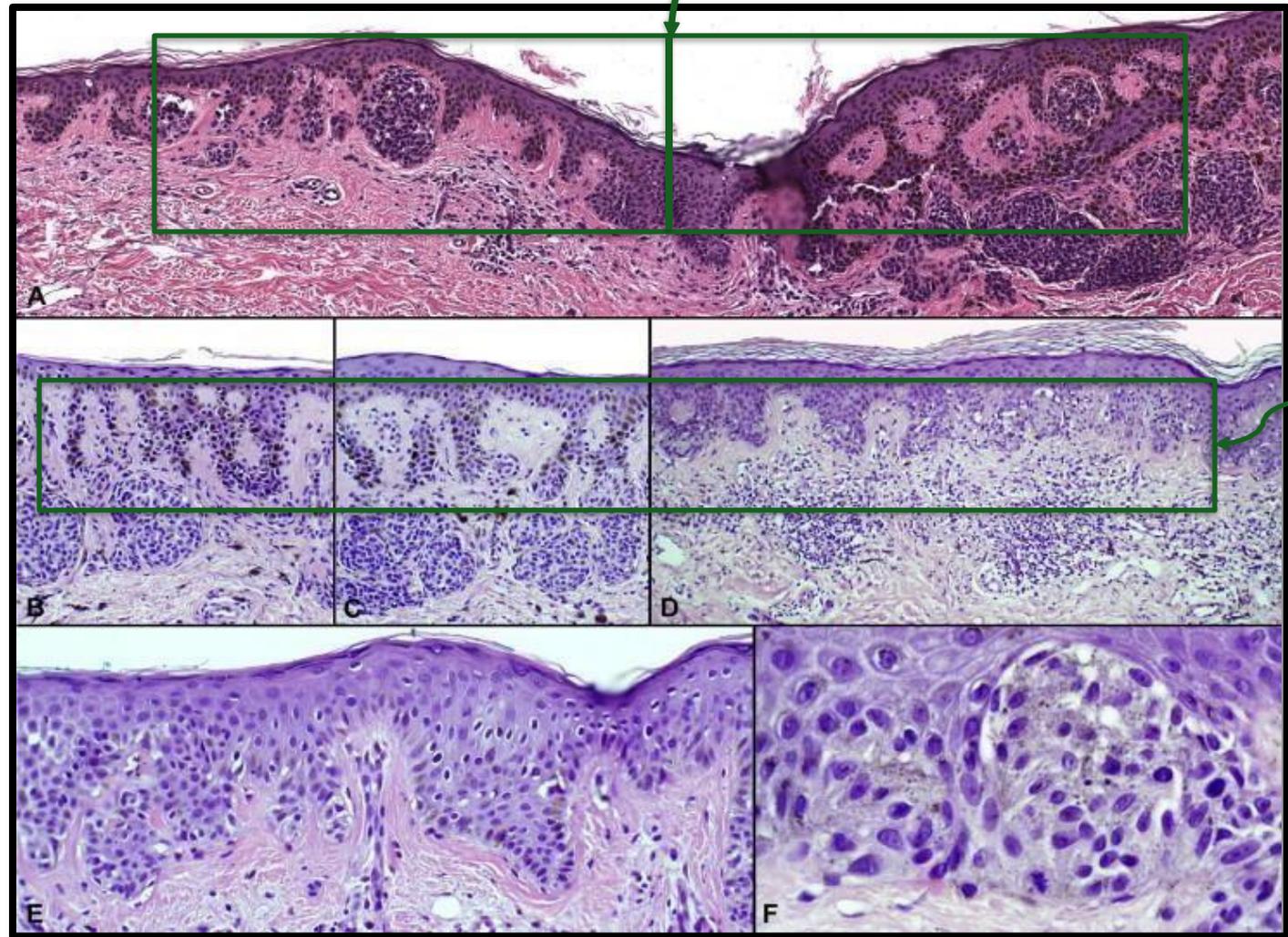
❑ *DYSPLASTIC NEVUS:*

- Nevi with atypical features, usually larger (>5 mm)
- Sporadic or familial
- Occur on both sun exposed as well non sun exposed
- Can be multiple (especially familial type)
- Risk of melanoma is higher than non dysplastic
- However: risk is low and most melanomas occur “de novo”
- *Familial dysplastic nevus syndrome:* high life-time risk

- Dysplastic nevi show asymmetry, mitoses, and sometimes necrosis. Even one mitosis in a nevus warrants concern for dysplasia or melanoma.
- Familial dysplastic nevus syndrome increases melanoma risk—regular monitoring is essential.
- Chronic irritation and UV exposure can turn a benign nevus into dysplastic, then into melanoma. Suspicious lesions should be removed early.

Histopathological features:

- Loss of symmetry
- Fusion of junctional nests
- Cellular and nuclear atypia
- Superficial dermal fibrosis
- Lymphocytic infiltration
- Melanin incontinence



Loss of symmetry,
dysplastic nevus.

Junctional
nevus has
atypia.

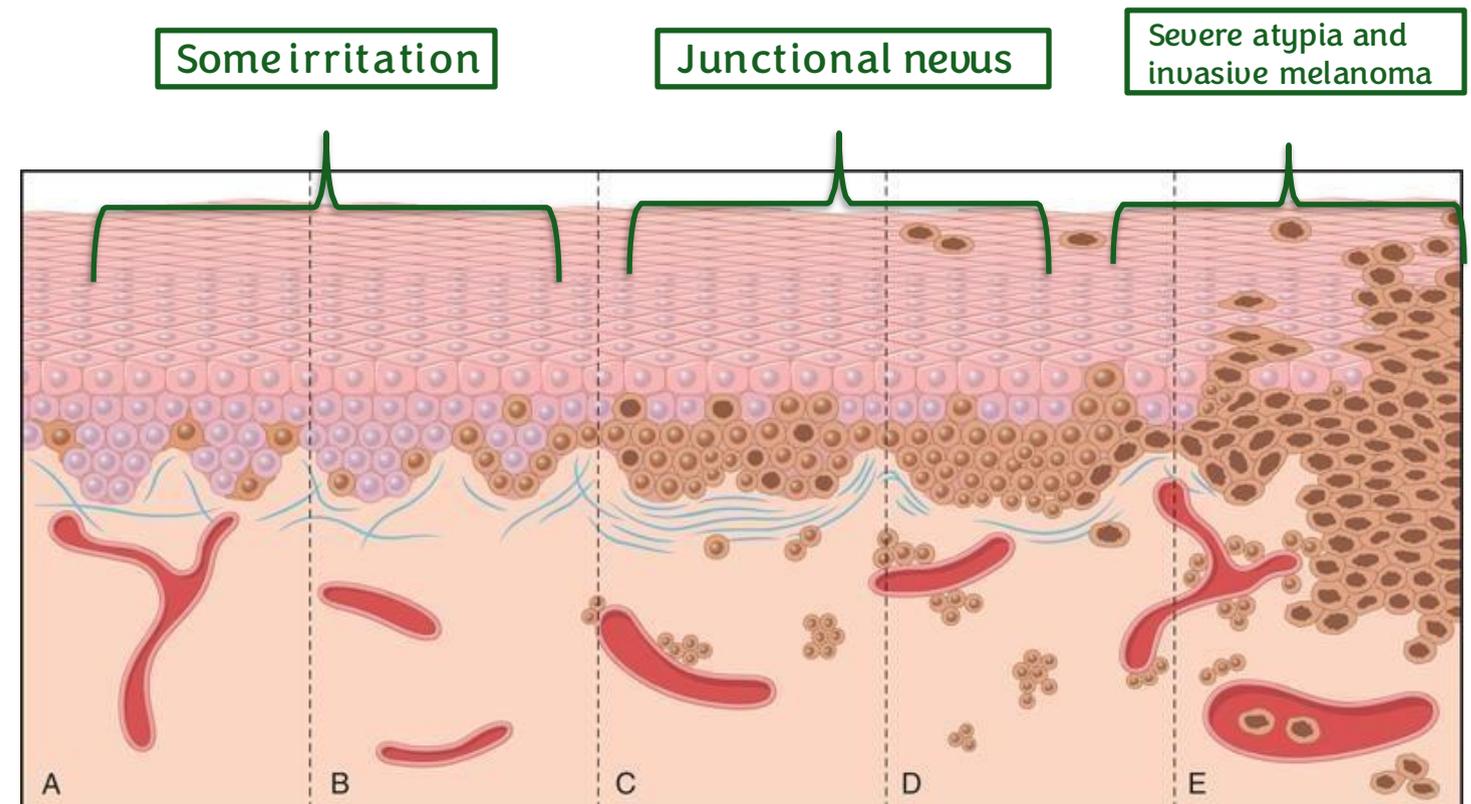
□ **MELANOMA** (so dangerous)

- Malignant neoplasm of melanocytes, **can metastasize** and can be fatal
- Less common than Sq. CCa, Basal CCa and nevi
- Currently: most melanomas are cured surgically
- The incidence is on the rise **due to:**
 - More sun exposure
 - More surveillance
 - More public awareness
 - **The incidence of melanomas could be rising due to more sunbathing or that people are visiting doctors more frequently to check for dysplastic changes**
 - Due to more awareness among people, most melanomas are caught surgically early as dysplastic before invasion. But there are still late cases.

MELANOMA EVOLUTION

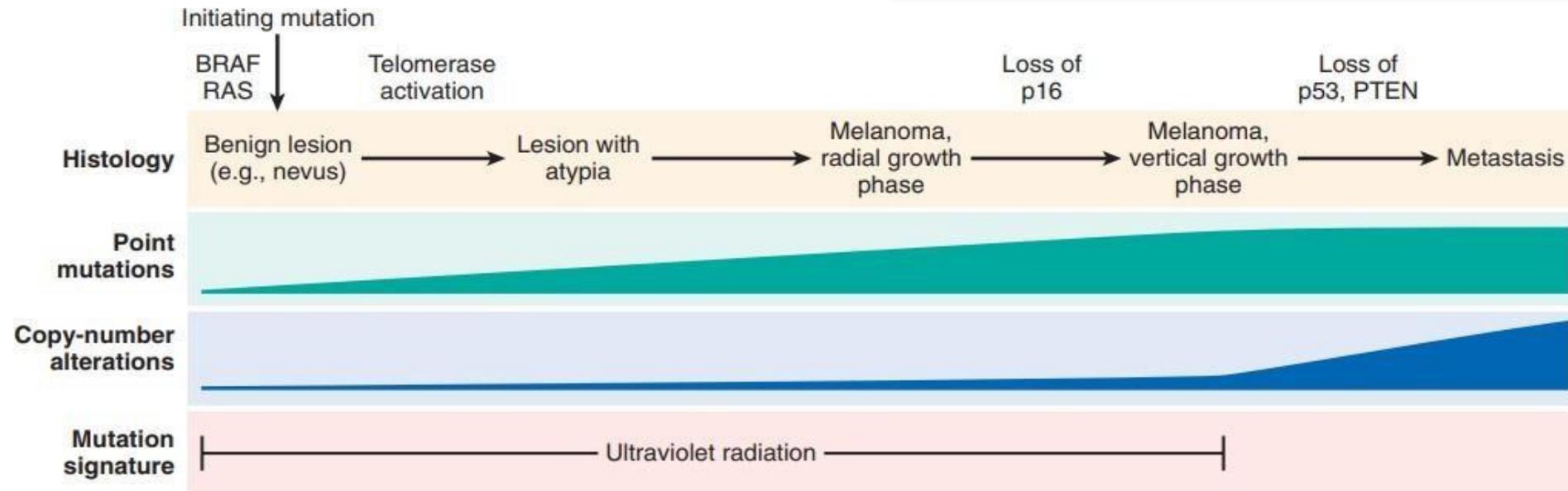
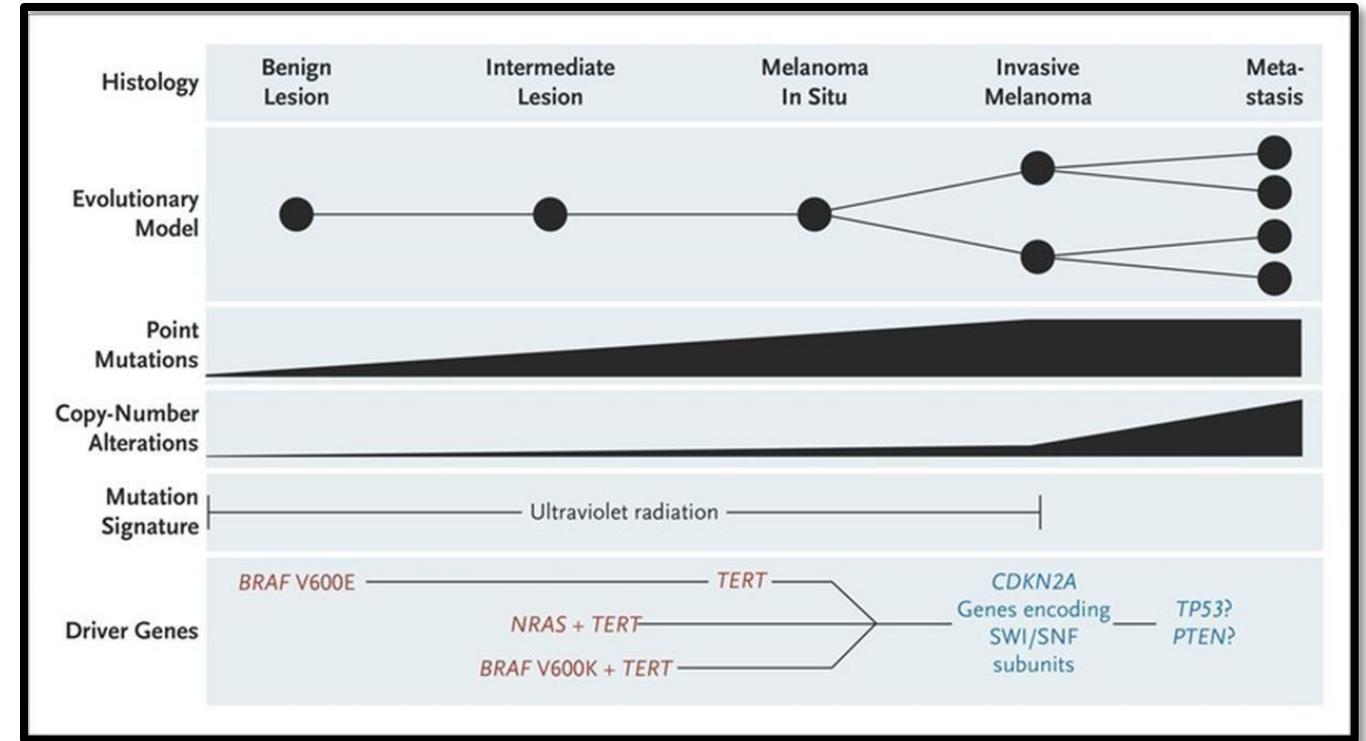
- Melanoma begins as a proliferation of atypical melanocytes in the epidermis (radial growth phase), where the cells spread horizontally, then the tumor becomes more atypical and invades deeper into the dermis (vertical growth phase).
- Most important prognostic factor is depth of invasion (Breslow thickness)

Stage	Benign nevus	Dysplastic nevus	Radial-growth phase	Vertical-growth phase	Metastatic melanoma
Biologic events	Benign Limited growth	Premalignant Lesions may regress Random atypia	Decreased differentiation Unlimited hyperplasia Cannot grow in soft agar Clonal proliferation	Crosses basement membrane Grows in soft agar Forms tumor	Dissociates from primary tumor Grows at distant sites
Molecular lesions	<i>BRAF</i> mutation	CDKN2A loss PTEN loss	Increased CD1	E-cadherin loss N-cadherin expression αVβ3 integrin expression MMP-2 expression Survivin Reduced TRPM1	Absent TRPM1



➤ This process has **both early and late changes.**
(important to know them)

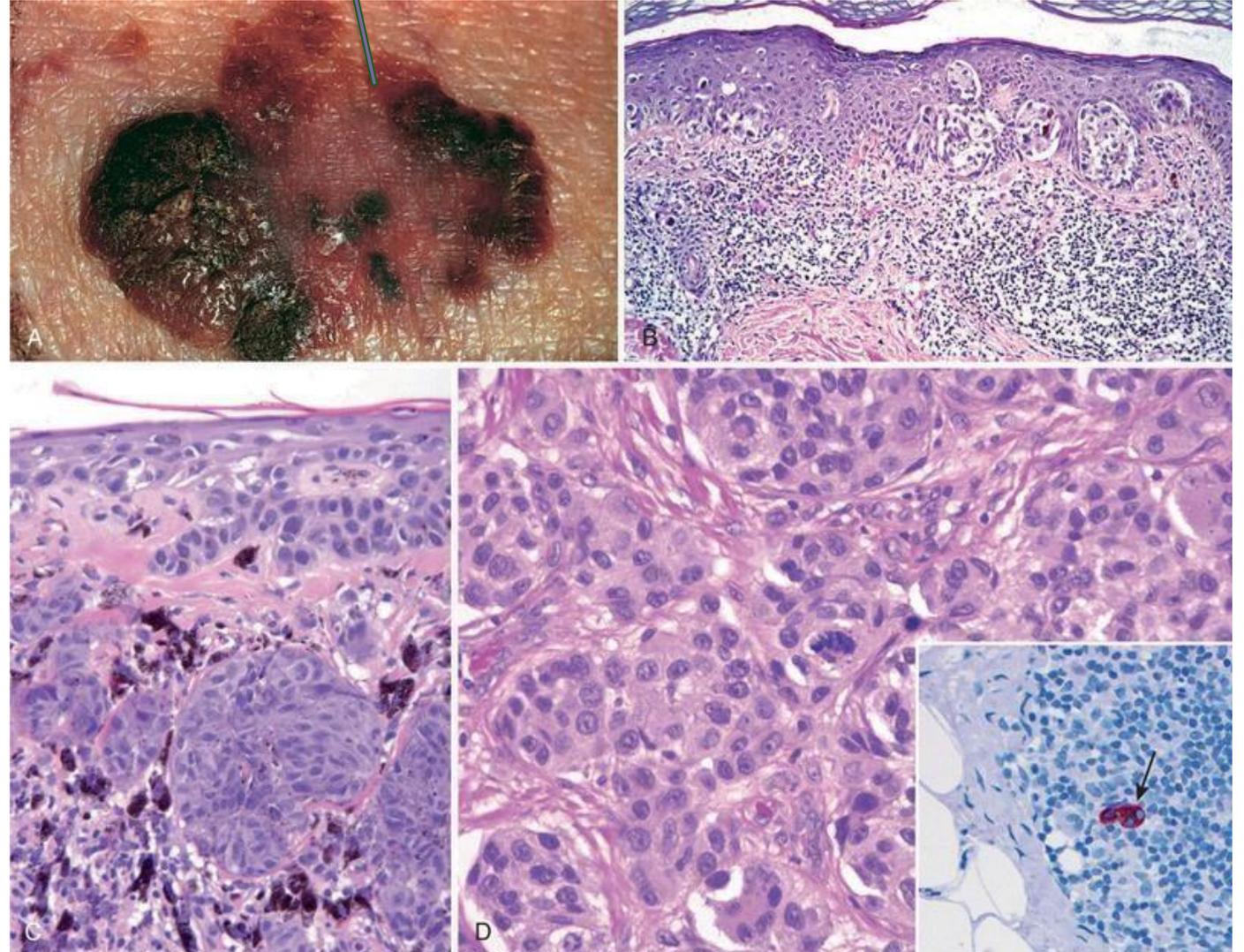
BRAF mutation is early,
TP53, PTEN & TERT mutations are late
(and more dangerous as they lead to
invasion & metastasis)



Pathological features:

- Irregular borders and pigmentation
- Irregular nesting with
- Increased numbers of single cells
- Radial and vertical growth
- Increased thickness (Breslow thickness)
- Deeper invasion
- Larger atypical cells
- Atypical larger nuclei with prominent cherry-red nucleoli

clinically, worrisome signs: asymmetric borders, variable pigmentation.



WARNING SIGNS OF MELANOMA:



- Rapid enlargement of a preexisting nevus
- Itching or pain
- New pigmented lesions development
- Irregular borders of a pigmented lesion
- Variiegation (**Intensity**) of color within a pigmented lesion
(Some areas are darker than others)

CLINICAL FEATURES AND PROGNOSIS:

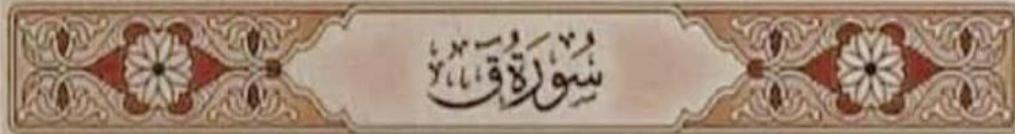
- Most can be cured surgically
- Stage is critical (depth of invasion)
- Metastatic disease exhibits poor prognosis
- “Sentinel node” evaluation may help in stage determination
- Recent evolution in treatment options (targeted therapy):
 - Anti *BRAF* and *KIT* agents
 - Immune check point inhibitors (T-cell mediated immunotherapy)

رسالة من الفريق العلمي:

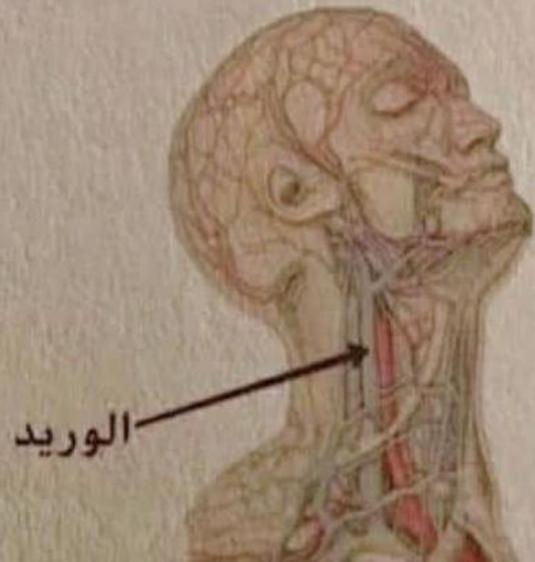
(وَنَحْنُ أَقْرَبُ إِلَيْهِ مِنْ حَبْلِ الْوَرِيدِ)

في كلّ مرّة تشعر فيها أنك لوحدك ، و أنّه لا أحد يفهم ما في قلبك ، تذكر أنّ الله أقرب إليك من نفسك ، يسمع أنين قلبك قبل أن يُترجم لسانك و يرى ما تعجز عنه العيون ، يعلم خفاياك و ما استتر بينك و بين نفسك ، و يعلم كلّ دعوة ترددت على أعتاب روحك و لم تخرج و كلّ أمنية خبأتها في زوايا الرّجاء .

هو العليم بما تُريد حتّى قبل أن تسأل ، و بما تحتاج حتى قبل أن تُدرك . فلا تُثقل قلبك بالشرح ، و لا تُرهق روحك بالتفصيل ، يكفي أن ترفع يقينك إليه ، فهو السميع القريب الذي لا يخفى عليه همسٌ و لا يضيع عنده رجاء .



وَنَحْنُ أَقْرَبُ إِلَيْهِ مِنْ حَبْلِ الْوَرِيدِ



For any feedback, scan the code or click on it.



Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
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