Hashemite University
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Medical School Committee

Scientific Team
الفريق العلمي

PATHOLOGY

Final Lecture 5 + 6/ Skin Tumors

DONE BY : Suha Al Sarhan

Benign & Premalignant Epithelial Lesions

- Benign epithelial T are common & are probably derived from stem cells that reside in the epidermis & hair follicles, that tend to differentiate toward cells & structures in the epidermis & adenexa.
- The majority of these tumors show limited growth & do not undergo malignant transformation.

1. Seborrheic Keratosis = Basal cell papilloma

- Common epidermal T, occur most frequently in middle-aged or older individuals, arise spontaneously & may become particularly numerous on the trunk, although the extremities, head, neck may also be involved.

- **Pathogenesis**

❖ Significant fraction of these T harbor activating mutations in fibroblast (FGF) receptor 3.
❖ In rare cases, the explosive onset of hundreds of lesions may occur as a paraneoplastic syndrome (sign of Lesser-Trelat) & patients with this presentation may harbor internal malignancies that produce GFs that stimulate epidermal proliferation.

- **Clinically:**
  - ❖ Basal cell papillomas are exophytic نمو الى خارج السطح, round, flat, coin-like plaques that vary in diameter from mms to cms, tan to dark brown & usually show a velvety to granular surface.
  - ❖ Occasionally, they become inflamed,

- **H:**

❖ 1. they composed of sheets of small cells that resemble monotonous basal cells of the normal epidermis
❖ 2. Hyperkeratosis occurs at the surface & the presence of small keratin-filled cysts (horn cysts) is characteristic feature.
❖ 3. Variable melanin pigmentation is present within these basaloid cells, accounting for the brown coloration seen; sometimes mimicking melanoma, warranting their removal.

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2. Sebaceous Adenoma

- are rare T that primarily occur in the head & neck region of older individuals.
- They usually present as flesh-colored papules & can be a marker for an internal malignancy. Knowledge of this association can save a life!

- **Pathogenesis:**

❖ Much has been learned about the pathogenesis of these T by their association with the Muir-Torre syndrome.
❖ In this condition, the T may be multiple or be distributed outside of the head & neck region.
❖ In addition there may be internal malignancy, most often colon carcinoma.
❖ These cases are a subset of the hereditary nonpolyposis colorectal carcinoma syndrome (HNPCC) which is associated with microsatellite instability due to loss of a DNA mismatch repair protein, either MLH1 or MSH2.

- **H:**

❖ 1. Sebaceous adenomas show a lobular proliferation of sebocytes that maintain an organoid appearance
❖ 2. The basal cell layer is normally two cells thick, but this is variably expanded in adenomas with maturation to mature sebocytes in the center of the lesion.
❖ 3. These cells have clear cytoplasm vacuolated by vesicles filled with sebum.

- **Clinical Features**

❖ Sebaceous adenomas are benign & self-limited, tend to occur in the face.

❖ Clinically these can be separated from the much more common sebaceous hyperplasia, which has:مهم
(1) an umbilicated (dimpled) center نقطة على شكل سرة
(2) consists of hypertrophic sebaceous glands surrounding a centralhair follicle.

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3. Actinic Keratosis

- Before the development of overt malignancy of the epidermis, a series of progressively dysplastic changes occurs.
- Because such skin dysplasia is usually the result of chronic exposure to sunlight & is associated with hyperkeratosis, these lesions are called actinic (i.e., sun-related) keratoses.

- **Pathogenesis**

- Although some actinic keratosis regress or remain stable, however, many do become malignant to warrant their local eradication.
- Mutation of p53 is often an early event with molecular changes suggestive of ultraviolet light injury.

- **H:**

❖ Lower portions of the epidermis show cytologic atypia, often with hyperplasia of basal cells or with early atrophy that results in diffuse thinning of the epidermal surface of the lesion.

❖ The dermis contains thickened, blue-gray elastic fibers (solar elastosis), the result of chronic sun damage.

❖ There are hyperkeratosis & parakeratosis.

❖ Some, but not all lesions, progress to full-thickness atypia amounting to squamous cell ca in situ

❖ Sandpaper like keratinization

☼ Useful for remembering the histologic features is SPAIN:
a sun-soaked country perfect for acquiring such lesions:-
(S) Solar elastosis (dermal sun damage)
(P) Parakeratosis
(A) Atypia (keratinocytic)
(I) Inflammation (lymphocytes in the superficial dermis)
(N) Not full thickness atypia.

- **Clinically:**

❖ actinic keratosis is very common in fair- skinned individuals, usually less than 1 cm in diameter;

❖ tan- brown or red & has a rough, sandpaper-like consistency with predilection for sun-exposed areas (face, arms, dorsum of the hands).

❖ Lesions accumulate with age & degree of sun exposure.

❖ The lesions can be treated with local cryotherapy (superficial freezing) or topical chemotherapeutic.

Malignant Epidermal Tumors

1. Squamous Cell Carcinoma

- SCCa is a common T, arising on sun-exposed sites in older people. with a higher incidence in men than in women.
- **Predisposing factors** include → مهم
  a. sunlight b. ionizing radiation c. industrial carcinogens (tars & oils)
  d. chronic ulcers e. old burn scars f. ingestion of arsenicals.

- **Pathogenesis**
- The most common exogenous cause of skin SCCa is UV light exposure, with subsequent unrepaired DNA damage.
- Both Xeroderma pigmentosum patients & Immunosuppressed patients from chemotherapy or organ transplantation, whom are likely to be associated with high-risk HPV types infections are at ↑ risk.

UV light →
(1) inducing mutations
(2) may have a transient immunosuppressive effect on skin by impairing antigen presentation by Langerhans cells.
(3) This may contribute to tumorigenesis by weakening immunosurveillance.
(4) p53 mutations with associated UV mutation signatures are common, as are activating mutations in RAS.

- As with SCCa at other sites, those in the skin may be preceded by in situ lesions.

- **SCCa in situ**
  characterized microscopically by full thickness epidermal squamous dyplasia, with atypical cells at all levels of the epidermis, with nuclear crowding & disorganization, BUT, with intact basement membrane.مهم
  When these cells break through the basement membrane, the in situ SCCa become invasive SCCa

- **Invasive SCCa**
  differentiation ranges from :
  a. well-differentiated tumors → formed by atypical squamous cells arranged in orderly lobules showing central keratinization (epithelial pearls or cell nests)
  b. poorly-differentiated (anaplastic) → with rounded cells, foci of necrosis & single-cell keratinization (dyskeratosis).

While morphologic variation is wide, all SCCa share the feature of **keratinization**.

14-50: Squamous cell carcinoma.
Malignant squamous epithelial cells forming long strands, containing
(1) foci of laminated sheets of deeply eosinophilic keratinized epithelial cells (cell nests or epithelial pearls)
(2) At the periphery of the strands, there are larger squamouscells with large hyperchromatic & pleomorphic nuclei & numerous mitotic figures.
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- **Clinically:**
- **SCCa in situ** → appears as sharply defined, red, scaling plaques; many arise from prior actinic keratoses.
- **Invasive SCCa** → lesions are nodular, show variable scale, & may ulcerate
  They usually discovered while small & resectable; less than 5% have metastases to regional LN at diagnosis.
  The likelihood of metastasis is related to the tumor thickness & the degree of invasion into the subcutis.
- SCCa arising in the context of actinic keratoses may behave in a less aggressive fashion, while SCCa arising in burn scars, ulcers, & skin not exposed to the sun tend to behave less predictably.

- **Mucosal SCCa** مهم جدا
  (oral, pulmonary, esophageal, etc.) are generally a much more aggressive cancers.

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2. Basal Cell Carcinoma

- is the most common human cancer world-wide. مهم
- BCCa is a slow-growing invasive T that rarely metastasizes.
- tends to occur at sites subject to chronic sun exposure (especially the face) & in lightly pigmented people.
- occurs predominantly in fair- skinned people (as in this patient), in the part of the face bounded by the hairline, ears & upper lip.النقطة مهمة جداااا

- As with SCCa, the incidence of BCCa ↑ with:
  (1) immunosuppression (though not as dramatically as that of SCCa)
  (2) in individuals with inherited defects in DNA repair.

- **Pathogenesis**

❖ BCCa has been associated with dysregulation of the sonic hedgehog, or PTCH,مهم pathway.
❖ Inherited defects in the PTCH gene with subsequent loss of heterozygosity in the numerous individual T foci cause the familial basal cell carcinoma syndrome "Gorlin syndrome".

Thus, PTCH functions as a classic tumor suppressor. Some component of the PTCH pathway is also mutated in the great majority of sporadic BCCa; mutations in p53 are also common.

- **Morphology**

❖ Small BCCa cells resemble the normal epidermal basal cell layer from which they are derived
Because they arise from the epidermis or, sometimes, follicular epithelium, they are not encountered on mucosal surfaces.

❖ **The two common patterns seen are either**
1. multifocal growths originating from the epidermis (superficial type)
2. nodular lesions growing downward into the dermis as cords & islands of basophilic baseloid cells with hyperchromatic nuclei, embedded in a fibrotic to mucinous matrix

Peripheral T cell nuclei align in the outermost layer (palisading) + with separation from the stroma, creating a **cleft or separation artifact**

Basal cell carcinoma (Rodent ulcer)
☼This is the cicatricial type of BCCa which is characterized by:
(1) superficial peripheral spread with ulceration
(2) subsequent central scarring (so-called fire in the field).

- **Clinically:**

❖ BCCa present as pearly papules, often containing prominent, dilated subepidermal blood vessels (telangiectasia).
❖ Some BCCa contain melanin pigment & thus appear similar to melanocytic nevi or melanomas.
❖ Although BCCa may ulcerate (Rodent ulcer) & may show extensive local invasion of bone or of facial sinuses after many years of neglect
❖ BCCa metastasis is extremely rare.
❖ BCCa is usually treated by complete local excision.

Tumors & Tumor-Like Lesions of Melanocytes

1. Melanocytic Nevi

- Nevus : Strictly speaking, the term nevus denotes any congenital lesion of the skin.
- Melanocytic nevus : however, refers to any benign congenital or acquired neoplasm of melanocytes.

Common Nevus (Melanocytic nevus)

- **Pathogenesis**

❖ Melanocytic nevi are derived from the transformation of highly dendritic melanocytes {that are normally interspersed among basal keratinocytes}.
❖ Progressive growth of nevus cells from the dermoepidermal junction into the underlying dermis is accompanied by maturation.

❖ **Superficial nevus cells** → are larger & less mature, tend to produce melanin pigment, & grow in nests
❖ **Deeper nevus cells** → are smaller & more mature, produce little or no pigment, & grow in cords.

❖ This maturation is of diagnostic importance,→ since melanomas usually show little or no maturation.

❖ The majority of benign nevi have been shown to harbor an activating mutation in BRAF (a protein downstream from RAS in the extracellular receptor kinase pathway) or, less commonly, in RAS itself.
❖ These two mutations are mutually exclusive; the growth of melanocytic nevi is self-limited.

- **Development:**

1. Initially, early melanocytic nevi are composed of round-to- oval cells that grow in "nests" along the dermoepidermal junction, with uniform & round nuclei, inconspicuous nucleoli & little or no mitotic activity. These are called junctional nevi.
2. Later, junctional nevi grow into the underlying dermis as nests or cords of cells, forming compound nevi.
3. In older lesions, the epidermal nests may be lost entirely to leave pure intra-dermal nevi.
   Compound &dermal nevi are more elevated than junctional nevi

- **Clinically:**

❖ numerous types of melanocytic nevi are present, the commonest are tan-to-brown, uniformly pigmented, small (usually ≤5 mm Ø), papules, with well-defined, rounded borders

❖ Although these lesions are of cosmetic interest only & even referred to as"beauty spots“, prominently displayed on some celebrated faces, they can become irritating or mimic melanoma & thus may be surgically removed.

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2. Dysplastic Nevus

- may occur sporadically (in which the risk of malignant transformation seems very low).
- or in a familial form (inherited as an autosomal dominant & is considered precursors of melanoma).

- **Pathogenesis**

❖ A subset of dysplastic nevi are precursors of melanoma.

❖ In individuals with a family history of melanoma, the melanomas occur only in individuals who first develop dysplastic nevi. In these cases, the lifetime risk of developing melanoma is 100%.

❖ The number of dysplastic nevi correlates with the risk of developing melanoma & transition from dysplastic nevus to early melanoma has been documented both clinically & histologically.

❖ Despite such documented evolution from dysplastic nevi to melanoma, Most melanomas arise de novo & not from a preexisting nevus. مهم

❖ Thus, the likelihood that any particular individual nevus, dysplastic or otherwise, would develop into melanoma is exceedingly low. Consequently, these lesions should be viewed as markers of melanoma risk.

❖ Activating RAS or BRAF mutations are encountered in dysplastic as well as in melanocytic nevi; additional complementing mutations occur in melanoma.مهم

- **Morphology**

❖ Dysplastic nevi consist mainly of compound nevi, with both architectural & cytologic evidence of abnormal growth.

❖ In this sense they have some histologic & clinical properties that are reminiscent of both benign nevi & melanoma.

❖ Nevus cell nests within the epidermis may be enlarged & exhibit abnormal fusion or coalescence with adjacent nests; with single nevus cells beginning to replace the normal basal cell layer along the dermoepidermal junction, producing so- called **lentiginous hyperplasia**.

❖ cytologic atypia {irregular, angulated nuclear contours & hyperchromasia is frequently observed}

❖ **Host response to these lesions occur in the superficial dermis including: تحدث نتيجة ال**

(1) sparse lymphocytic infiltrate
(2) loss of melanin pigment with phagocytosis by dermal macrophages (melanin pigment incontinence)
(3) linear fibrosis surrounding epidermal nests of melanocytes.

- **Clinical Features:**

Dysplastic nevi are:

1. usually larger than most acquired nevi (>5 mm in Ø)
2. may occur as hundreds of lesions on the body surface
3. unlike ordinary nevi, they have a tendency to occur on body surfaces not exposed to the sun as well as on sun-exposed body surfaces
4. are flat to slightly raised plaques, with a "pebbly" surface, & usually show variable pigmentation & irregular borders
5. Dysplastic nevi have been documented in multiple members of families to be prone to the development of malignant melanoma (the "familial melanoma syndrome").

3. Melanoma

- is less common, but much more deadly than BCCa or SCCa.
- Today, as a result of ↑ public awareness of the earliest signs of skin melanomas, most melanomas are cured surgically.
- Nonetheless, the incidence of melanoma has ↑ dramatically over the last several decades, at least in part a result of ↑ sun exposure, necessitating vigorous surveillance.

- **Pathogenesis**

❖ As with other skin cancers, sunlight plays an important role in the development of melanoma. Intense intermittent exposure at an early age is particularly harmful.

❖ The incidence is highest in sun-exposed skin & in geographic locales such as New Zealand & Australia where sun exposure is high & the protective mantle of melanin is sparse (fair skin).مهم

❖ Sunlight, however, does not seem to be the only predisposing factor; the presence of preexisting nevi & hereditary predisposition also play a role.

❖ Central to an understanding of the complicated histology of melanoma is the concept of progression from an intraepithelial (in situ) to invasive (dermal) growth, or from the radial to the vertical growth.

❖ **Radial growth** indicates the initial tendency of a melanoma to grow horizontally within the epidermis as an مهمممممم
(1) in situ, & in the superficial dermal layers, often for a prolonged period. In this stage, melanoma cells
(2) do not have the capacity to metastasize
(3) no evidence of angiogenesis
(4) vast majority of these lesions are surgically curable

❖ **With time, the pattern of growth assumes a**
(1) vertical component, & the melanoma now grows downward into the deeper dermal layers as an expansile mass lacking cellular maturation. (very bad prognosis)
Vertical growth is heralded clinically by the development of a nodule in the relatively flat radial growth phase
(2) correlates with the emergence of a clone of cells with metastatic potential.

- Melanoma is a highly aggressive malignancy; tumor only a few millimeters in thickness can give rise to metastasis & ultimately the death of the patient.

- The probability of metastasis is predicted by measuring the depth of invasion in mms of this vertical growth phase nodule below the top of the granular cell layer of the overlying epidermis (**Breslow thickness**). Other indicators of metastatic potential are lymphatic density, mitotic rate, & overlying ulceration.

- Metastases involve not only regional LNs, but also liver, lungs, brain, & virtually any other site that can be seeded by the hematogenous route! مهم
- Sentinel LN biopsy (first draining node (s) of a primary melanoma) at the time of surgery provides additional information on biological aggressiveness.

- In some cases, metastases may appear for the first time many years after complete surgical excision of the primary tumor (in one personal case, in Newcastle upon Tyne RVI (UK) 1978, after 20 years!), suggesting a long phase of dormancy.

- Most melanomas occur sporadically, but a few are hereditary (<5% to 10 %). Molecular genetic analysis of such familial as well as sporadic cases has provided important insights into the pathogenesis of melanoma.

> Germ-line mutations in the CDKN2A gene (located on 9p21) are found in 40% of the rare individuals with familial melanoma.
>
> This gene encodes p16INK4A, a cyclin- dependent kinase inhibitor → that regulates the G1-S transition of the cell cycle in a retinoblastoma protein (pRB)-dependent fashion. The CDNK2A gene can also be silenced by methylation.

- **Morphology**

❖ Individual melanoma cells are
(1) usually much larger than nevus cells
(2) contain large nuclei with irregular contours having chromatin characteristically clumped at the periphery of the nuclear membrane
(3) prominent eosinophilic nucleoli often described as "cherry red" مهم جدا!!

❖ Malignant cells grow as poorly formed nests or individual cells at all levels of the epidermis & as dermal expansile, balloon-like nodules; these constitute the radial & vertical growth phases, respectively مهم

❖ It is important to observe & record the nature & extent of the vertical growth & mitotic rate of melanoma cells. By using these & other variables in aggregate, accurate predictive statements regarding prognosis are possible.

- **Clinically:**

1. Although most melanomas arise in the skin, other less common sites of origin include the oral & anogenital mucosa, the esophagus, the meninges, & notably the eye.

2. The following comments apply to skin melanomas:
*Are usually asymptomatic, although itching may be an early manifestation.
*The most important clinical sign of melanoma is a change in the color or size of a pigmented lesion.
*Unlike benign nevi, melanomas exhibit striking variations in pigmentation, appearing in shades of black, brown, red, dark blue, & gray.
*The borders of melanomas are irregular & often "notched."

- **Clinical warning signs of melanoma in a preexisting mole are:**

(1) Enlargement
(2) Itching or pain
(3) Irregularity of the borders
(4) Variegation of color within a pigmented lesion &
(5) Development of a new pigmented lesion during adult life,

- These principles are expressed in the ABCDE of melanoma: Asymmetry, Border, Color, Diameter, & Evolution (change of an existing nevus).

- <u>It is vitally important to recognize & intervene in melanoma as rapidly as possible.</u>

- Vast majority of superficial melanoma are cured surgically, BUT, currently, melanomas that become metastatic have uniformly poor prognosis, with no effective therapy.