PATHOLOGY OF EYELIDS

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Objectives

1- To become familiar with the Glossary of terms used in Dermatopathology which are applicable on eyelid pathology.
2- To apply the basic knowledge of the eyelid development for better understanding of the congenital disorders.
3- To be able to recognize the pathologic changes of aging process based on the normal anatomy and histology of the eyelid.
4- To be able to reach the diagnosis of inflammatory and structural skin lesions by proper clinicopathologic correlation.

Basic Terminology

- **Acanthosis**: Increased thickness of squamous epithelium: regular or irregular

- **Acantholysis**: Rupture of intercellular bridges

- **Hyperkeratosis**: Excess production of the superficial keratin layer
- **Parakeratosis**: Presence of retained pyknotic nuclei in the keratin layer.

- **Dyskeratosis**: Intraepithelial individual aberrant keratinization of single cells.

- **Squamous eddies**: Circular whorls of squamous cells.

- **Dysplasia**: Disturbance of normal maturation sequence of epithelial cells.
- **Anaplasia**: Cytologic features of malignancy:
  - Pleomorphism, abnormal nuclei and mitotic figures.
I-Anatomy & Histology
Each human eyelid is composed of six layers:

1) **Epidermis**
   - 2 cell types: Keratinocytes and dendritic cells.
   - **A-Keratinocytes:**
     - Basal single row
     - Squamous cell layer
     - Granular layer
     - Horn layer Histology

   **B-Dendritic Cells:**
     - Clear cell melanocytes
     - Langerhans

2) **Dermis**

3) **Subcutaneous Layer**
II-Congenital and Developmental abnormalities

1) Abnormal development of lid folds
   - 6 - 8 weeks gestation
   - results in gross abnormality eg. Cryptophthalmia
2) **Abnormal differentiation during lid fusion:**
- 8th week - fifth month of gestation
- premature separation: small coloboma
- also: ankyloblepharon / rare ankyloblepharon filiforme adnatum

3) **Others:** Blepharophimosis, epicanthus, epiblepharon, distichiasis and ptosis

**III - Aging Changes**

**Causes:**
- Atrophy and laxity of the skin
- Loss of subcutaneous tissue.
- Relaxation of ligaments and attenuation of the orbital septum.
- Histologic degeneration of the collagen bundles of upper dermis, replaced by amorphous basophilic material + increase in the number of elastic fibers (curled and interwoven).
**Changes:**

- Dermatochalasis
- **Senile ectropion**

**Entropion**

**Tarsal Scarring**

**Tarsal Plate**
Inflammatory lesions
- **Chalazion**: Most frequent granulomatous lesion of the eyelids.
  Histopathology: - epithelioid and giant cell response to liberated fat from sebaceous gland forming a ring around nonstainable lipid droplets.
  Old lesions: + fibrosis and scarring.
DDx: Sarcoidosis, TB, fungal disease.

Lipid with surrounding granulomatous reaction

Molluscum contagiosum:
  Clinically: - raised skin nodule with umbilicated center.
  Cause: - Pox virus
  Histopathology: - Acanthotic epithelium
    - Molluscum (inclusion) bodies: infected epithelial cells with clusters of virus
become basophilic, replace the cytoplasm and increase in size. = Henderson - Patterson corpuscles.

Secondary Follicular conjunctivitis
**Xanthelasma:**
- Usually in normal patients (2/3)
- Lipid analysis is necessary to R/O hypercholesterolemia
- Recurrence is more likely if:
  Multiple lesions or hyperlipidemia syndrome.

Eyelid xanthelasma = xanthelasma palpebrarum
soft flat or slightly elevated yellowish plaques.

- Histopathology:
- Nests of xanthoma or foam cells in superficial dermis
- cells: lipid - laden histiocytes
• **Fungal:**
  Blastomycosis: In North America
  Pseudoepitheliomatous hyperplasia
  Granulomatous reaction
  Microabcesses containing budding yeast of Blastomyces Dermatitidis.

• **Parasitic:**
  1-Phthiriasis Palpebrarum: Pubic louse. can cause follicular conjunctivitis.
  2-Demodicosis: Demodex folliculorum/ brevis
    chronic blepharitis

**Cysts**

Skin cysts are named according to the derivation and type of epithelium that lines the lumen.

1) **Epidermoid cyst:**
   - lined by keratinized stratified squamous epithelium
   - contents: cheesy keratin material
   - Epidermal inclusion cyst: (deposited epithelial cells within the dermis) Post Trauma or Surgery

In case of rupture: foreign body granulomatous inflammatory reaction.

- Others: Pilar/ Trichilemmal cysts
2) Dermoid cyst:

- lined by keratinized squamous epithelium
- Skin appendages: hair, sweat & sebaceous glands.
- Contents: Keratin
3) Sweat gland cyst:
   = hidrocystoma or sudoriferous cyst.
   - Eccrine lined by 1-2 layers of cuboidal epithelium resembling sweat duct, contains serous fluid.
   - Apocrine: Similar but cells may show decapitation, clinically: often pigmented.

4) Ductal cyst: Dacryops
Vascular

- Capillary hemangioma is the most common, congenital
- Histology: endothelial - lined vascular channels similar to normal capillaries in contrast to large spaces in the cavernous type.

Glandular / Adnexal Tumors:

I – Eccrine/Apocrine Gland Origin:

A) Benign Tumors:
   1. Syringoma:
      Clinically:
      - Young women, common, benign
      - Multiple yellowish, waxy nodules (1-2 mm)

Syringoma

Paisley-tie pattern of tadpole-shaped ducts with horn cysts
Dense sclerotic strom
I - Eccrine/Apocrine Gland Origin:

2. Eccrine Acrospiroma = clear cell Hidradenoma

Histopathology:

- Cuboidal cells with pink cytoplasm
- Clear cell
- Cuticle-lined ducts & cystic degeneration

I - Eccrine/Apocrine Gland Origin:

3. Syringocystadenoma Papilliferum

Raised warty plaque.
One third occur within nevus sebaceus

Opens to surface.
Papillary fronds
Decapitation secretion
I - Eccrine/Apocrine Gland Origin:

B) Malignant tumors:

Adenoid cystic carcinoma:
- May resemble adenoid basal cell ca.
- Rare.
- Metastasis: uncommon.

- Histopathology: cribriform and tubular patterns

II - Hair Follicle Origin:

1. Trichoepithelioma = Brooke’s tumor

   a. Solitary

   b. Multiple - autosomal dominant

Microscopy: Multiple horny cysts showing fully Keratinized center surrounded by islands of basaloïd cells.
III - Hair Follicle Origin cont’d.:

2. Trichofolliculoma:
   a. **Hamartomatous:** most differentiated form of a pilar tumor.
   b. **Clinically:** elevated nodule with central umbilicated area.
      Central pore with small white hairs growing is strongly suggestive.

   Small hair follicles emptying into a central infundibulum

3. Trichilemmoma:
   a. Benign tumor of outer hair sheath.
   b. **Clinically:** Predilection for the face
      - Eyelid: most common after the nose.
      - Cowden disease: AD, associated with breast and thyroid lesions, multiple skin lesions.
   c. **Histologically:** Lobular acanthosis, composed of clear glycogen rich cells outlined by thick basement membrane
4. **Pilomatrixoma:**

= Calcifying epithelioma of Malherbe.

- **Clinically:** Subcutaneous nodule covered by normal skin.

  Solitary, peculiar pink to purple color, tend to occur in children

  Most common sites: face & upper extremities

- **Histopathology:** Basophilic cells & shadow cells which often calcify
1. **Adenomatoid sebaceous hyperplasia**

   Cluster of sebaceous glands, around follicular opening.

   Normal germative basaloid layer at lobule periphery.

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**Muir-Torre Syndrome**

= Association of sebaceous gland tumors of skin (mostly adenomas) and visceral malignancy (most common colorectal ca., genitourinary & breast.)

**Sebaceous gland carcinoma:**

- Arise from sebaceous glands (meibomian, glands of Zeis, hair associated or of the caruncle)
- Site: eyelid is the most common site in the body mostly on the upper lids (2/3) because meibomian glands are more numerous (x2)
- 1 - 3% of all malignant lid tumors.
Histologically:

- Differentiation: well, moderate and poor = anaplastic carcinoma, with atypical and bizarre mistoses => frozen section with oil red 0 stain.

b) Patterns:

<table>
<thead>
<tr>
<th>Lobular</th>
<th>Basaloid features</th>
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<tbody>
<tr>
<td>Comedocca</td>
<td>Central foci of necrosis</td>
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<tr>
<td>Papillary</td>
<td>Fronds of neoplastic cells =&gt; resemble squamous cell + foci of cells with sebaceous differentiation (foamy, vaculated) mixed</td>
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c) Spread:

**Pagetoid:**
- Invade overlying epithelium
- Direct extension: ± perineural, into lymphatics
- Vascular invasion -> distant metastasis after regional L.N.

Pagetoid spread to conjunctiva/skin

**Intralymphatic spread**
Sebaceous gland carcinoma:

- Prognosis: Bad prognostic factors
  a) location: in upper lid
  b) size: 10 mm or more in max diameter
  c) origin: meibomian gland
  d) duration: symptoms > 6/12
  e) growth pattern: infiltrative
  f) differentiation: moderate to poor
  g) others: multicentric, intraepithelial carcinomatous changes (pagetoid), lymphatic or vascular invasion.
- Tm: Wide surgical excision + frozen section control
- Palliative radiotherapy: in none surgical cases
- Mortality: 15% old AFIP series.

Epithelial Tumors cont’d.:

1. Benign:

1) Squamous papilloma:

   - most common benign lesions of the eyelid.
   - Sessile or pedunculated.
   - Often multiple ± small Keratin crust.
   - Histology: benign hyperplasia of squamous epithelium overlying fibrovascular core: derived from dermis, epidermis = acanthotic ± hyper & parakeratosis.

   NOTE: Verruca vulgaris is similar but with viral inclusions (HPV₂)
2) Pseudocarcinomatous Hyperplasia:
   
a. associated with chronic inflammation.
   
b. Histologically:
      - interconnected islands of well-dif. Squamous epithelium + invasive acanthosis.
      - moderate inflammatory rx.

3) Keratoacanthoma:
   
a. Special variant of pseudocarcinomatous hyperplasia that occurs in exposed areas of skin vs. variant of squamous cell ca.
   
b. Clinically: rapid onset dome-shaped nodule with central keratin filled crater and elevated margins.
   
   Spontaneous regression.
   
   Can occur in immunosuppressed individuals.
   
c. Histology:

   Islands of well-dif. squamous epithelium surrounding central mass of keratin.
   
   Base is well demarcated by moderate inflammatory rx.
   
   + epithelial infiltration of striated ms (orbicularis fibers) and around nerves.
4. Seborrheic keratosis:

a. Common benign lesions of the eyelid in elderly.
b. Clinically: Raised mass usually hyperpigmented +
c. Histology:

Three types:

- hyperkeratotic: tendency for papillomatosis
- acanthotic: horn cysts
- adenoid: less keratinization, branching strands: double row of basaloid cells.

+ increased melanin in keratinocytes.
+ chronic inflamm. In dermis = irritated Seborrheic Keratosis
5. Inverted follicular keratosis:

- nodular keratotic mass + pigmented
- tendency to recur if incompletely excised
- histology: proliferation of both basaloid and squamoid elements with area of acantholysis + squamoid eddies.
  - Form of irritated seborrheic keratosis.

II. Precancerous:

1) Actinic Keratosis:

= solar or senile keratosis.
- most common precancerous cutaneous lesion.

a. Clinically:

Most common sites: face (including eyelids), dorsum of hand, scalp.
Sun exposed areas
Fair - skinned middle-aged to elderly
Single or multiple scaly keratotic flat-topped lesions
Size: few millimeters
Early lesions: erythematous scales.
more other cutaneous lesions.

b. Histology:

- Epithelium:
  - acanthosis, hyper & parakeratosis and individual cell dyskeratosis as an indicator of propensity toward malignancy.
  - Atypical Keratinocytes (epithelial dysplasia), loss of intercellular bridges => clefts with sparing of the ostia of pilosebaceous structures.

- Dermis:
  - basophilic degeneration of collagen = solar elastosis
  - chronic inflammation
  - Types: hypertrophic atrophic
  - Types: bowenoid
  - Solitary lichen planus - like keratosis
c. Prognosis:

- Progression to squamous cell carcinoma: variable, old series 12-13%.
  As high as 25% and recently much lower incidence 0.1%
- Excellent prognosis of squamous cell ca. arising in actinic keratosis, rarely metastasize (0.5%)

2) Bowen’s Disease
  = carcinoma in situ.
  Occurs only in both non-exposed and sun-exposed areas of skin association with internal or visceral malignancies (≥ 25%)
  a. Clinically:
     erythematous, pigmented, nodular or ulcerated
     average age 55 yrs.
     ? Arsenic exposure.
  b. histologically:

    - Epidermis:
      striking loss of polarity
      atypical epithelial proliferation at all levels
      Involvements of the ducts of hair follicles and sebaceous glands.
      Intact basement membrane. (PAS)
    - Dermis:
      lack of penetration of cancerous cells into the underlying dermis is the histologic hallmark.
3) Radiation Dermatosis:
   a. associated with high radiation doses 8000 - 12,000 rads
   b. basal keratinocytes are more susceptible
   c. Principal lid changes:
      - loss of lashes
      - chronic dermatitis
      - pigment. Changes
      - atrophy
      - telangiectasis
      - postradiation tumors.

4) Xeroderma pigmentosum:
   - Progressive, sun-exposed skin starting in early childhood.
   - Autosomal recessive
   - Defect in DNA repair secondary to deficiency of ultraviolet light - specific endonuclease.

   - Stages of skin manifestation:
     a) Erythema, scaling and freckles
     b) pigmentation and telangiectasis
     c) various malignant neoplasms: sq. cell ca., BCC, sarcoma and 3% incidence of malignant melanoma.
   - Also: conjunctival malignancy, reported malignant melanoma of the iris.
   - Prognosis: metastasis, death can occur.

EPITHELIAL TUMORS, cont’d.:

III. Malignant:

1) Basal cell Carcinoma:

   c. Histology

   - Histogenesis is disputed

   - Theory: ? From primary basal epithelial germ cells (primordial cell derived from surface ectoderm).

     Pluripotential embryonal cells remain within epidermis throughout life -> propensity of BCC to differentiate toward a wide variety of skin and skin appendage - like structures.

   - Differentiation:
- Differentiated:

features of several cutaneous appendages & named accordingly (keratotic - hair structures, cystic - sebaceous gland, adenoid - apocrine & eccrine glands)
more in nodulo-ulcerative type of BCC.

- Undifferentiated:

  solid epithelial lobules with prominent peripheral palisading.

- Metatypical = basosquamous
  intermediate morphology between BCC & SCC.
III. Malignant:

1) Basal cell Carcinoma:
   - Growth pattern:
     - Nodular - localized lobules of tumor with pseudocapsule can be solid or cystic - retraction artifact.
     - Ulcerative - chronic dermal inflammatory infiltrate.
   - Sclerosing - strands of basaloid cells embedded in dense fibrous stroma (stromal desmoplasia). These strands are often called Indian file => aggressive and deeply infiltrating into dermis and subcutis.
   - Multicentric - diffuse involvement of epidermis & superficial dermis.

The last three types often extend beyond the margins of apparent clinical involvement
-> Frozen section control is essential at time of surgical excision.
d. Prognosis:

- Recurrence rate: Variable - depends on surgical technique (some report no evidence of recurrence with frozen sections)
- Invasion: Rare intraocular invasion.
  May invade cranial cavity -> 2° meningitis
- Metastasis: Rare incidence range 0.028% to 0.55%

2) Squamous cell carcinoma:

a. Incidence: - elderly, fair - skinned
- most commonly lower lid margin
- accounts for less than 5% of epithelial neoplasm of eyelids.
- arise de novo or from preexisting lesions.
b. Clinical:  
- elevated indurated plaque or nodule, may ulcerate.  
- ± grayish - white in well differentiated tumors (keratin)  
- early lesions: excellent prognosis (especially within actinic keratosis), wide local excision is curative.

c. Histology:  
Variable differentiation.

- Well diff.: polygonal cells with prominent nuclei, keratin pearls, intercellular bridges, dyskeratotic cells.
- Spindle cell variant: confused with fibrous histiocytoma or fibrosarcoma

c. Histology:  
- Adenoid variant: uncommon eyelid involvement  
atypical cuboidal epithelial cells forming pseudo-glandular structures. Good prognosis, wide local excision is curative
Melanocytic Tumors:

I - Benign:

1) Nevocellular Nevi:
   - Has variable clinical appearance.
   - Kissing nevus:
     simultaneous involvement of upper and lower lids (with lid margin involvement) - embryologic nests of nevus cells meet during lid fusion (18th week until 5th month)
   - Classification: Depends on the position of nevus cells in the skin layers.
     a. Junctional:
        - Proliferation at nevus cells in the deeper layers of epithelium and at the epidermal - dermal junction.
        - Have the capacity of “dropping off” into the dermis.
        - Clinically flat pigmented lesions.
     b. Compound:
        - Junctional activity + intradermal nests of nevus cells.
        - More common than pure junctional nevus.
        - Both can undergo malignant change.
c. Intradermal:
- Most common & most benign.
- Clinically: papillomatous or pedunculated + hair, can be amelanotic
- Histology: nests of nevus cells totally confined to the dermis, separated from the epidermis by a band of collagen = Grenz Zone. In the eyelid nevus cells may extend into deeper dermis reaching orbicularis ms.
- Giant multinucleated nevus cells occur only in mature intradermal nevi -> indicate the benign nature of the lesion.

- Types of nevus cells: depending on their location in the dermis
  Type A: upper dermis
    resemble epithelioid cells.
  Type B: middle dermis
    smaller, resemble lymphoid cells
  Type C: lower dermis
    elongated, resemble fibroblasts, little or no melanin.
2) Other variants of nevi

- Balloon cell nevi
- Spindle or epithelioid nevi = compound nevus mainly affecting children & young adults.
- Giant congenital melanocytic nevi
- Blue nevi - from dermal melanocytes
- Freckle - from epidermal melanocytes
II – Malignant Melanoma:

a) Incidence:
- 1% of all malignant neoplasms of the eyelid in USA.
- Recent 3 - 5 fold increase in the incidence of cutaneous m.m.? Due to increased voluntary exposure to sun.
- almost 2/3 of all deaths from cutaneous cancer are by m.m.
- involves lower lid more often than upper.
- may arise from pre-existing nevus, may arise de novo.
b) Types:

1. Lentigo maligna melanoma:
   develops in a preinvasive lesion called:
   - Hutchinson’s Melanotic Freckle or lentigo maligna =
     - Flat macule with variable degree of pigmentation in elderly individuals (sixth decade), sun-exposed skin.
     - Histopathologically:
       - diffuse hyperplasia of atypical pleomorphic melanocytes along the basal cell layer of epidermis = (radial growth phase)
       - extends into outer sheaths of pilosebaceous structures.

2. Superficial spreading melanoma:
   = pagetoid Melanoma
   - Younger individuals (fifth decade), nonexposed skin.
   - Most commonly: upper back, legs
   - Clinically:
     - spreading pigmented macule (variable color) with irregular outline & palpable borders.
     - white areas of spontaneous regression
   - Microscopically:
     - Atypical melanocytes with pagetoid features invasive vertical growth:
       variable types of melanoma cells.
   - 5 - year survival 69%

3. Nodular melanoma:
   - Small blue-black or amelanotic pedunculated nodule rapidly growing.
   - usually in 40-50 y., twice as common in men as in women.
   - microscopically: adenoid structures - large anaplastic epithelioid cells, only vertical growth phase.
   - 5 - year survival 44%

4. Acral Lentiginous Melanoma:
   - Mainly on palms & soles.
Note:
  a. 20% of nodular melanoma & 50% of superficial spreading m. arise from nevi.
Clinical signs of malignant transformation:
  - Change in color, size or shape
  - Crusting, bleeding or ulceration
  - Pain, itching or tenderness
  - Change in surrounding skin
b. In eyelid malignant melanoma, lid margin or conjunctival involvement has ? worse prognosis.

- Clark Classification:
  c) Prognostic Factors:
      Level of Invasion (5 - year survival)
      Level 1 - confined to epidermis with intact B.M.  100%
      Level 2 - early invasion of papillary dermis  100%
      Level 3 - fills papillary dermis & reaches interface (papillary/reticular)  80%
      Level 4 - penetrates reticular dermis  65%
      Level 5 - invades subcutaneous tissue  15%

III – Dysplastic Nevus Syndrome:
  - Atypical cutaneous nevi in children and adolescence.
  - Autosomal dominant.
  - Family members are at high risk for cutaneous melanoma.
  - Histologically:
    identical to areas of regression frequently observed in superficial spreading m.

Miscellaneous lesions:

I - Lipoid Proteinosis:
  a) Autosomal recessive
  b) Clinically:
      1. Small nodules along lid margins
      2. Waxy appearance
      3. Distortion of cilia
  c) Microscopic:
      1. Early lesions: thickening of capillary wall + deposition of hyaline material around basement m.
      2. Fully developed lesions: homogenous eosinophilic hyaline material in dermis => strongly PAS positive.

II - Merkel Cell Tumor:
  a) Uncommon generally in the skin.
  b) Origin:  - Merkel tough spots in the deeper layers of epidermis adjacent to hair follicles (cilia in eyelid)
  c) Merkel cell CA of the eyelid: 1st case reported in 1980.
d) Clinically: painless nodule with reddish-blue hue resembling an angiomatous lesion.
e) Microscopic: poorly differentiated with immunohistochemical studies similar to apudomas.
f) Tm: wide surgical excision with frozen section control, to overcome the high incidence of local recurrence.

III - Carney’s Complex:

a) Clinical:
   1. Cutaneous and cardiac myxomas
   2. Multiple pigmented skin lesions (also conjunctival)
   3. Endocrine overactivity.

b) Eyelid myxomas:
   1. Found in up to 70% of patients.
   2. Histologically:
      Nonencapsulated dermal hyaluronic acid substance with stellate mesenchymal cells -> myxoid stroma.

IV - Calcinosis Cutis:

a) Types of calcnosis cutis:
   1. Metastatic
   2. Dystrophic
   3. Idiopathic

4. Subepidermal calcified nodule:
   - small raised yellowish-white nodule
   - firm or hard on palpation.
   - histopathology: epidermis: acanthosis
dermis: homogenous masses of calcified material.
+ macrophages & FB-type giant cells.
- pathogenesis: unknown
  ? From pre-existing structure (e.g. sweat ducts or nevus cells)
Neurofibroma
PATHOLOGY OF EYELIDS

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