Benign Epidermal and Dermal Tumors

St. Barnabas Hospital Dermatology Residency Program, Bronx, NY

Program Director: Cindy Hoffman, DO

Chief Resident: Lacey Elwyn, DO, OGME-IV

Christopher Mancuso, DO, OGME-III

Monica Huynh, DO, OGME-II
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Outline

• What makes a tumor benign?
• Benign Epidermal Tumors
• Benign Dermal Tumors
  • Clinical Overview
  • Diagnostic Pearl
  • What’s new?
    -- Literature Highlights
    -- Syndrome Associations?
Tumor

- Signals
  - Proliferation
  - Differentiation
  - Cell death

- Triggers
  - Blood supply
  - Matrix-cell
  - Cell-cell
Benign Tumor

- Mass of cells that lack ability to invade neighboring tissue
- Slower growth rate
- More differentiated
- Surrounded by fibrous sheath of connective tissue or remain within epithelium
- Do not recur when completely excised
- May compress surrounding tissue
Epidermis
Benign Epidermal Tumors

1. Seborrheic Keratosis
2. Clear Cell Acanthoma
3. Epidermolytic Acanthoma
4. Porokeratosis
5. Inverted Follicular Keratosis
6. Warty Dyskeratoma
7. Lichen Planus Like Keratosis
8. Epidermal Nevus
1. Seborrheic Keratosis – Clinical Overview

• Pathogenesis: AD with Incomplete Penetrance
  • Clonal expansion of a mutated epidermal keratinocyte
  • More than 80% of seborrheic keratoses have at least one mutation
  • 45% have more than one mutation in an oncogene such as $FGFR2$, $FGFR3$, $PIK3CA$, $KRAS$, $EGFR$
Seborrheic Keratosis – Clinical Overview

Sign of Leser-Trélat

- Abrupt increase in size or number is a cutaneous sign of internal malignancy

- 60% of neoplasms are adenocarcinomas (primarily of GI tract)
  - Others: lymphoma, breast cancer, SCC of lungs

- May be accompanied with:
  - Acanthosis nigricans
  - Tripe palms
Seborrheic Keratosis - Diagnostic Pearl
Dermoscopy

- Milia-like cysts
- Irregular crypts
- Fissures/ridges
- Blue-gray lobules
- Light brown fingerprint-like parallel structures
- Fat fingers (the gyri of a cerebriform surface)
Suggestive for melanoma
- Clusters irregular dots/globules
- Areas pigment network atypia
- Diffuse, irregular hyper- or hypopigmentation

Multicomponent (n = 32; 19.9%) (Combination of 3 or more distinctive dermoscopic structures)
Seborrheic Keratosis – Clinical Overview

Malignancy

• Instances of malignant neoplasms arising within and adjacent to SKs were reported as early as 1932

• Likely coincidental, although it is possible that the various cell types present in an SK could develop into their respective neoplasms

  • Spinous cells
    • Invasive SCC
    • KA
    • SCCIS

  • Melanocytes
    • Melanoma

• Basaloid cells
  • BCC: Most frequent neoplasm seen in association with SKs
  • SKs and BCC derived from the infundibular portion of the hair follicle

Seborrheic Keratosis – Diagnostic Pearls
Borst-Jadassohn Phenomenon

- Morphologic pattern:
  - Nested atypical keratinocytes situated within normal epidermis

- Clonal Bowens Disease
- Hidroacanthoma Simplex
- Clonal Seborrheic Keratosis
Seborrheic Keratosis – What’s new?
6 Histologic Types

- Acanthotic SK
- Hyperkeratotic SK
- Reticulated SK
- Clonal SK
- Melanoacanthoma SK
- Irritated SK
Seborrheic Keratosis with Pseudorosettes and Adamantinoid Seborrheic Keratosis: Two New Histopathologic Variants

J Cutan Pathol. 2006 Sep;33 Suppl 2:42-5

- One lesion showed abundant intercellular mucin, closely resembling to adamantinoma, and therefore was named **adamantinoid seborrheic keratosis**

- The other one exhibited a peculiar distribution of the basaloid keratinocytes, which were arranged radially around small central spaces, resulting in **pseudorosette formation**
2. Clear Cell Acanthoma (Pale Cell Acanthoma, Degos Acanthoma) – Clinical Overview

• Morphology/Distribution
  • Moist erythematous nodule with a collarette
  • Measures 1-2 cm
  • Most commonly on legs
  • Eruptive form - produce up to 400 lesions

• Histology
  • Discrete acanthoma with overlying parakeratosis
  • *Distinct transition between normal epidermis and pale cells in stratum spinosum*
  • *Excess glycogen in the cells accounts for their clear appearance and is due to a defect in phosphorylase*
  • Peppered with neutrophils
Clear Cell Acanthoma – Diagnostic Pearl

Dermoscopy

Blood vessels lined up - “string of pearls”
3. Epidermolytic Acanthoma – Clinical Overview

- Pathogenesis: theories include...
  - Exogenous factors: UV, Viral, Trauma
  - Increased keratinocyte metabolic activity
  - Aberrant keratin gene expression

- Morphology/Distribution
  - Pigmented keratotic papules
  - Solitary or disseminated
  - Mainly trunk
Epidermolytic Acanthoma – Diagnostic Pearl

• Histology
  • Often crateriform
  • Epidermolytic hyperkeratosis
  • Granular layer is thick and contains irregularly shaped keratohyalin granules and cytoplasmic borders are indistinct
Epidermolytic Acanthoma – What’s new?

Case of isolated epidermolytic acanthoma: Genetic and immunohistochemical analysis

*The Journal of Dermatology 43.8 (2016): 974-75*

- Histologic findings of isolated epidermolytic acanthoma (iEA) is also noted in Bullous Congenital Ichthyosiform Erythroderma (BCIE) which is caused by genetic mutations in K1 and K10.

- Authors examined lesional cytokeratin via immunohistochemical microscopy which showed reduced staining of CK1 and CK10.

- Based on histological similarity with BCIE and reduced staining of CK1 and CK10, somatic mutation of K1 and K10 has been hypothesized to be pathogenesis of iEA.
4. Porokeratosis – Clinical Overview

- **Pathogenesis:**
  - Reed theorized lesions represent expanding mutant clone of keratinocytes in genetically-susceptible individuals
  - Induced by triggering factors (UV exposure, immunosuppression)
  - SCC in lesions of all porokeratosis (except punctate) reported
  - **Lesions in older patients, those of long standing duration, and linear variants all have higher rates of malignant degeneration**
Porokeratosis – Clinical Overview

1. Classic Porokeratosis of Mibelli
2. Disseminated superficial actinic porokeratosis (DSAP)
3. Linear Porokeratosis
4. Porokeratosis Palmaris et Plantaris Disseminata (PPPD)
5. Punctate Porokeratosis

• **DSAP:** Most common type of all porokeratosis
  - Multiple thin papules
  - Most commonly on the legs of adult women
  - **SART3, SSH1, and ARPC3** are possible gene mutations
  - **Lowest risk of malignant conversion**
Porokeratosis – Diagnostic Pearl

Histology

- **Cornoid Lamella** - thin column of tightly packed parakeratotic cells extending from an invagination of epidermis through the adjacent stratum corneum

- **Granular layer is absent** or markedly attenuated

- **Dyskeratosis and pyknotic keratinocytes** with perinuclear edema in the spinous layer
Porokeratosis – What’s new?
Craniosynostosis, anal anomalies, and porokeratosis (CDAGS syndrome): case report and literature review

- Craniosynostosis
- Large open fontanelles
- Hearing loss
- Anal anomalies
- Genitourinary malformations
- Porokeratosis (erythematous plaques on face and extremities)
- AR - No molecular defect has been identified
5. Inverted Follicular Keratosis – Clinical Overview

• Pathogenesis
  • Derived from infundibulum of hair follicle

• Morphology/Distribution
  • Firm, white-tan to pink papule
  • 85% occur on the face
Inverted Follicular Keratosis – Diagnostic Pearl

- Histology
  - Endophytic
  - Squamous eddies
  - Lack of epithelial dysplasia
Inverted Follicular Keratosis – Associations

- Associated with:
  - Cowden’s Syndrome
6. Warty Dyskeratoma – Clinical Overview

- In 1954, Helwig coined “Isolated Darier’s”
- Aka follicular dyskeratoma
- Pathogenesis:
  - Acquired ATP2A2 gene mutation → lack SERCA2 → malunion and keratinization of epithelial cells
- Morphology/Distribution:
  - Verrucous papule with central keratotic plug
  - Solitary, rarely multiple
  - Often involving the face, scalp, or back
  - Measure <1-2 cm
Warty Dyskeratoma – Diagnostic Pearl

- Histology:
  - Endophytic growth
  - Corps ronds and grains
  - Parakeratotic crust

Acantholytic Dyskeratosis
Differential Diagnosis
- Warty Dyskeratoma
- Darier’s Disease
- Grover’s Disease
Warty Dyskeratoma – What’s New Dermoscopy

- White homogeneous area with 3 yellow clods with intervening hair follicles
7. Lichen Planus-Like Keratosis – Clinical Overview

- **Pathogenesis:**
  - Inflammation of a benign lentigo, actinic keratosis, or seborrheic keratosis
  - Theory: increased number of Langerhan cells process an unidentified epidermal antigen → infiltration of lymphocytes
  - At least half are related to “precancerous” actinic keratosis

- **Morphology/Distribution:**
  - Initially pink-to-red
  - Upper chest, forearms
  - Over time, melanin deposited to form a gray hue

- **Histology:**
  - Lichenoid infiltrate of mainly lymphocytes with scattered histiocytes
Lichen Planus-Like Keratosis – Diagnostic Pearl

- Term LPLK refers to histologic features seen on biopsy
- Immune reaction with the underlying lesion being anything from a solar lentigo or seborrheic keratosis to a melanoma
- Benign lesions most common, but significant regression of a melanoma can look like an LPLK
- Vessels seen in an early inflamed LPLK can be polymorphic and dot like similar to an amelanotic melanoma

Dermoscopy teaching blog of the Australian Institute of Dermatology and the Skin Cancer College of Australia and New Zealand
Lichen Planus-Like Keratosis - What’s new?
Differentiating Regressed Melanoma from Regressed Lichenoid Keratosis

Results

• 40% regressed melanomas demonstrated complete / near complete loss of melanocytes within the epidermis with Melan-A and MiTF immunostaining, while 8% of regressed LPLK exhibited this finding

• Necrotic keratinocytes were seen in the epidermis in 33% regressed melanomas as opposed to all of the regressed LPLK

• A dense infiltrate of melanophages in the papillary dermis was seen in 40% of regressed melanomas, a feature not seen in regressed LPLK
8. Epidermal Nevus – Clinical Overview

• Pathogenesis:
  • Originate from pluripotent cells in basal layer of embryonic epidermis
  • Genetic mosaicism implicated involving KRT1, KRT10, PIK3CA
Epidermal Nevus – Diagnostic Pearls

- Develop within first year of life
- Single linear lesion of well-circumscribed hyperpigmented, papillomatous papules or plaques in linear array along Blaschko’s lines
  - Acanthosis, papillomatosis, hyperkeratosis
- Nevus verrucous has a warty appearance
- Nevus unius lateris - extensive unilateral plaques
- Ichthyosis hystrix - variant with extensive bilateral involvement
- Epidermal Nevus Syndrome - occur in combination with developmental anomalies
  - Neurologic
  - Musculoskeletal
Associations- Epidermal Nevus Syndromes
Happle (J Am Acad Dermatol 2010)

- Schimmelpenning syndrome (PTCH)
  - Multiple sebaceous nevi and neurologic (seizures), ocular (coloboma), and musculoskeletal defects
- Phacomatosis pigmentokeratotica (PTCH)
  - Multiple sebaceous nevi and papular speckled lentiginous nevus, neurologic, hypophosphatemic vitamin D-resistant rickets
- Proteus Syndrome (AKT1)
- Type 2 Segmental Cowden disease (Proteus-Like Syndrome, SOLAMEN Syndrome) (PTEN)
- Becker nevus syndrome
- CHILD syndrome (NSDHL)
- Nevus comedonicus syndrome (FGFR2)
- Angora hair nevus syndrome
- Garcia-Hafner-Happle syndrome
PTEN Hamartoma Syndromes
Phosphatase and tensin homolog

**Cowden Disease - AD**
- Trichilemmomas
- Mucosal neuromas
- Sclerotic fibromas
- <10% patients have CALMs
- Hamartomas AND carcinomas of the Breast, Thyroid, and Colon

**PTEN (Cowden) Epidermal Nevus (Proteus-Like Syndrome (SOLAMEN))**
- Segmental overgrowth
- Lipomatosi
- Arteriovenous malformations
- Epidermal Nevi
- Features of Cowden Disease/Banayan-Riley Ruvalcaba Syndrome

**Banayan-Riley Ruvalcaba Syndrome - AD**
- Penile lentigenes
- Vascular malformations
- Lipomas
- Mucosal neuromas
- <10% have CALMs
- Intestinal hamartomas
Benign Dermal Tumors

- Tumor origins:
- Neural
- Fibrohistiocytic
- Vascular
- Smooth muscle
- Adipose
- Follicular
- Eccrine
- Apocrine
- Sebaceous
Benign Dermal Tumors of Neural Differentiation

1. Neuroma
2. Schwannoma
3. Neurofibroma
4. Granular Cell Tumor
Neural Tumors - Peripheral Nerve Sheath Tumors

- Hamartomas
  - Neuromas
    - PEN
  - Traumatic

- True Nerve Sheath Neoplasms
  - Schwannomas
  - Neurofibromas
  - Neurothekeoma

- Miscellaneous
  - Granular cell tumor

Schwann cells
- S100+
- EMA-
Perineural cells
- S100-
- EMA+
1. Neuroma – Clinical Overview

• Pathogenesis:
  • Hamartoma
  • Proliferations of neural tissue: *axons and Schwann cells are in equal numbers*
  • Traumatic: Regenerative proliferation of axons and Schwann cells with fibrous tissue

• Clinically:
  • Solitary skin colored to erythematous, firm, papules or nodule, sometimes painful
  • **Traumatic**: seen at sites of nerve injury
  • **PEN**: seen on face or mucocutaneous junction
Neuroma – Associated Syndromes

- Mucosal neuromas
  - MEN2b
  - Cowden disease
  - Bannayan–Riley–Ruvalcaba syndrome
Schwannoma (Neurilemmoma) - Clinical Overview

- **Pathogenesis:**
  - True nerve sheath neoplasm of schwann cells

- **Clinically:**
  - Subcutaneous skin colored papulonodule on the flexural aspect of an extremity, along a peripheral nerve
  - May be painful (**BENGAL**)

- **Description:** Well circumscribed, encapsulated deep dermal or subcutaneous tumor consisting of two areas:
  - **Antoni A** - cellular areas consisting of spindle cells with palisaded nuclei arranged in parallel rows with intervening acellular areas (**Verokey bodies**)
  - **Antoni B** - hypocellular myxoid areas

  - **S100+, EMA+, NF-** (Axons are usually absent)
Schwannoma - Associated Syndromes

- Associations
  - NF2 (bilateral acoustic neuromas, meningiomas)
  - Familial Schwannomatosis (INII/SMARCB1)
Not to be confused with…
Psammomatous Melanotic Schwannoma

- Carney Complex, AD: PRKAR1A gene

- **NAMB/LAMB**
  - Nevi, atrial myxomas, myxoid neurofibroma, ephelides
  - Lentigenes, atrial myxoma, mucocutaneous myxoma, blue nevi

- **Endocrine neoplasia**
  - Adrenal glands
  - Pituitary gland (GH secreting tumors)
  - Testes (Sertoli cell tumors)
3. Neurofibroma – Clinical Overview

• Pathogenesis:
  • Proliferation of the entire neuromesenchyme: Schwann cells, endoneurial fibroblasts, perineurial cells, mast cells

• Clinical/Histology: “Buttonhole Sign”
  • Usually solitary, skin colored, soft, rubbery papulonodule
  • Plexiform Neurofibroma: subcutaneous mass “bag of worms” on palpation

• Unencapsulted nodular proliferation in dermis consisting of spindle cells with wavy nuclei, pale stroma and few mast cells
  • NF+, S100+, EMA-
Associations: Neurofibromatosis-1 (von Recklinghausen Disease)

AD

2 or more of the following:

- 6+ Cafe-au-lait macules
  - >5mm pre-pubertal
  - >15mm postpubertal
- 2+ Neurofibromas
- 1 Plexiform Neurofibroma
- Freckling in the axillae (Crowe sign) and groin
- 2+ iris hamartomas (Lisch nodules)
- Optic glioma
- Bony defects (Sphenoid wing dysplasia)
- First degree relative with NF-1
Sphenoid Wing Dysplasia

Diagnostic Pearl: Strain Patterns
Neurofibromatosis-1 Highlights

- Patients with NF-1 have increased risk of tumors:
  - Protein product of NF1 gene, neurofibromin, is involved in negative regulation of RAS signaling
    - Juvenile myelomonocytic leukemia
    - Optic gliomas
    - Malignant peripheral nerve sheath tumors
    - Pheochromocytoma
    - CNS tumors

- NF-1 + JXG + JML = “Triple Association”:
  - 18% of children with NF-1 are diagnosed with one or more JXGs within the first 3 years of life
  - Children with NF-1 have 500-fold greater risk of developing JML compared to general pediatric population
    - Risk of JML is 30 times higher if JXGs are present
4. Granular Cell Tumor – Clinical Overview

- **Pathogenesis:**
  - Neural crest derived with peripheral nerve-related cellular differentiation

- **Clinically:**
  - Adult, women, African American
  - Solitary asymptomatic skin colored/ brown sessile dermal or subcutaneous papulonodule often on the
    - Head and neck (70%)
      - Esp. tongue (30% of cases)
    - Breast (5-15%)
    - Proximal extremities
Granular Cell Tumor Histology – Diagnostic Pearl

- Description: Poorly demarcated nodule in dermis made of large pale cells with granular cytoplasm (accumulation of lysosomal granules) and centrally located nuclei
- PAS +, Diastase-resistant, S100+, CD57+ (neuronally expressed adhesion molecule)
- Intracytoplasmic granules named **Pustulo-Ovoid Bodies of Milan**
Granular Cell Tumor – What’s New?

Histologically may be confused with SCC due to marked pseudoepithelial hyperplasia

May need immunohistochemical studies to differentiate

S-100, vimentin, CD68, p53, Ki-67, E-cadherin, collagen IV and cytokeratin AE1/AE3 antibodies

- Strong staining of S-100 protein, CD68, vimentin, E-cadherin and low proliferative activity observed with Ki-67 expression confirmed the diagnosis of a granular cell tumor
Benign Dermal Tumors of Fibrohistiocytic Differentiation

1. Angiofibroma
2. Dermatofibroma
3. Sclerotic Fibroma
4. Keloid
1. Angiofibroma – Clinical Overview

- Clinically: Skin colored/red firm papules
  - Face, esp nose (fibrous papule)
  - Periungual (koenen’s tumor)
  - Penis (pearly penile papules)
Angiofibroma – Associated Syndromes

- Tuberous sclerosis (adenoma sebaceum)
- MEN-1 Syndrome
- Birt-Hogg-Dube Syndrome
Angiofibroma – What’s new?

Topical sirolimus for the treatment of angiofibromas in tuberous sclerosis

Indian J Dermatol Venereol Leprol. 2017 Jan-Feb;83(1):27-32

- Sirolimus is an immunosuppressive and anti-cancer agent, known as mammalian target of rapamycin (mTOR) inhibitors

- It inhibits cancer cell induced angiogenesis and proliferation. For this reason, it has been used for the treatment of angiomyolipomas, lymphangioleiomyomatosis and angiofibromas

Initial Presentation

After 15 months
2. Dermatofibroma – Clinical Overview

- Common pigmented or pink firm, dome shaped papule with central induration
- +Dimple sign, F>M
- Possibly caused by injury
Dermatofibroma (Benign Fibrous Histiocytoma) – Associated Syndromes “S.A.P.I.”

Multiple DFs found in

- SLE
- Atopic dermatitis
- Pregnancy
- Immunosuppression
3. Sclerotic Fibroma – Clinical Overview

- Clinically:
  - Solitary or multiple on skin or mucous membranes
  - Pearly papules or nodules
  - Develop during adulthood

- Histology:
  - Well circumscribed, dome shaped, dermal hypocellular nodules composed of sclerotic thick collagen bundles arranged as short intersecting stacks in a parallel arrangement and separated by spaces containing connective tissue mucin
  - Between collagen bundles, thin spindled cells with scanty cytoplasm and small nuceli
  - Vimentin+, Muscle-Specific Actin+, CD34+
Sclerotic Fibroma – Associated Syndromes

- Cowden Disease
4. Keloid – Clinical Overview

- Clinical / Histology:
  - Commonly on chest, back and earlobes, darker skin and skin wounds
  - **Collagen III**
    - Firm, smooth, papule or plaque
    - May be painful or pruritic
    - Broad, haphazardly arranged brightly eosinophilic collagen bundles, increased fibroblasts and atrophic epidermis
Keloid – Associated Syndromes

- Rubinstein – Taybi Syndrome (CREB binding protein)
  - *Keloids* are apt to develop spontaneously in adolescence or early adulthood
- Microcephaly
- Mental retardation
- Beaking of the nose
- Characteristic broadening of the terminal phalanges of the thumbs and first toes
- Multiple pilomatrixicomas
Keloid – Updates From The Literature

- Current standards recommend avoiding surgical procedures for 6-12 months after taking oral isotretinoin
- Avoidance Includes: Chemical peels, dermabrasions, lasers
- Study shows only one case of keloid development out of 504 surgical patients who used isotretinoin

- Isotretinoin causes atrophy of the pilosebaceous unit, which is where reepithelialization originates
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References


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Thank You

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