Atypical Nevi
When to Re-excise

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Why talk about skin cancer?

Because it’s the most common type of cancer!
Non-melanoma Skin Cancers

- Basal Cell Carcinoma
- Squamous Cell Carcinoma
- Leiomyosarcoma
- Dermatofibrosarcoma Protuberans
- Sebaceous Carcinoma
- Merkel Cell Carcinoma
- Microcystic Adnexal Carcinoma

There are even more than these!
Non Melanoma Skin Cancer

- > 1,300,000 per year
- 20% lifetime risk in fair-skinned individuals
- Incidence rising
  - Increased leisure time?
  - Increased UV radiation?
  - Increased awareness?
Most Common Skin Cancers

• Basal Cell Carcinoma
  1 million/year

• Squamous Cell Carcinoma
  250,000/year

• Malignant Melanoma
  50,000/year
Cells of Origin

- Basal keratinocyte
- Keratinocyte
- Melanocyte
Skin Cancer Deaths

- 10,000 deaths/year in U.S.
- 7,000 from Melanoma
Etiology

- Ultraviolet Light induced mutations
  - BCC
    - PTCH gene mutations
    - p53 mutations
  - SCC
    - P53 mutations
  - Melanoma
    - Less clear
Introduction

- Melanocytes
- Overview of benign nevi
- Selected benign pigmented lesions
- Aypical Melanocytic Lesions /Melanoma precursors
- Malignant melanoma
Overview

• Selected benign pigmented lesions
  – Freckle (ephelides)
  – Labial melanotic macule
  – Solar lentigo
  – Lentigo simplex
  – Lentiginous junctional melanocytic nevus
  – Lentiginous compound melanocytic nevus

• Atypical Melanocytic Lesions /Melanoma precursors
  – Dysplastic nevi / Clark’s nevus / B-K mole
    • Mild
    • Moderate
    • Severe
  – Margins
  – Treatment and re-exision

• Malignant melanoma
  – Margins
  – Re-excision
The Melanocyte
Normal Melanocytes

- Dispersed within the basal layer approximately one melanocyte per 10 keratinocytes
- Varies with location
  - Highest – face and male genitailia
  - Lowest – trunk
Melanocytes Overview

- highly branched
- connected to approximately 36 keratinocytes through dendritic processes
- The number of melanocytes is the same between all races
- In African Americans the melanocytes are larger and contain more highly dendritic melanocytes
- The color of your skin is determined by the number of melanosomes contained within the melanocytes
- The number of melanosomes is greater in the basal layer and they get degraded within the keratinocytes as they move upwards and are shed
• With exposure to UV light melanocytes increase in size and functional activity but not in number
• Specialized organelles of the melanocytes called melanosomes.
• Melanosomes develop in four stages and move from the cytoplasm to the dendritic processes
• Receptors on keratinocytes is a key receptor involved in the melanosome transfer
• These are transferred to the keratinocytes by a receptor on the keratinocyte (protease-activated receptor 2, PAR-2)
• Pinocytotic process where they fuse with acid lysosomes.
• With time the keratinocytes and melanocytes migrate to the surface of the skin and are shed
Melanin granules (Warthin-Starry Stain)

- Melanin gets impregnanted by silver nitrate solutions.
- When reduced to silver it turns black.
Increased Melanin in Keratinocytes

- Freckle (ephelides)
- Labial melanotic macule
- Lentigo simplex
- Solar lentigo
Freckle (ephelides)
Labial and Genital Melanotic Macules
Lentigo Simplex (Simple Lentigo)

- Variable basal hyperpigmentation
- Increased number of single melanocytes in the basal layer
- Elongation of rete ridges
Multiple Lentigines

- Xeroderma pigmentosum
- Peutz-Jeghers
- Laugier-Hunziker
- Myxoma Syndromes
  - LAMB
  - NAME
  - Carney
- LEOPARD Syndrome
Solar (Senile) Lentigo
PUVA Lentigo

- Clinical
  - Occurs after exposure to psoralens (methoxsalen) and ultraviolet-A radiation (PUVA)
  - Especially in sun protected areas
Increased Melanin in Keratinocytes and nests of melanocytes

- Lentiginous nevus
  - Lentiginous junctional melanocytic nevus
  - Lentiginous compound melanocytic nevus

- Nevus spilius
Lentiginous Nevus
Speckled Lentiginous Nevus (Nevus Spilus)

- Present at birth or appear in childhood
- Considered a variant of congenital nevus
Immunohistochemistry

- S100 – stains dermal melanocytes that other stains may not, also stains Langerhan’s cells
- Mel-A (Mart-1)
- HMB45
- Tyrosinase
- MITF - Microphthalmia Transcription Factor
- NKI/C-3
Melanocytic Nevi

- Junctional Nevus
- Compound Nevus
- Intradermal Nevus
- Meyerson’s Nevus
- Ancient Nevus
- Deep Penetrating Nevus
- Balloon Cell Nevus
- Halo Nevus
- Cockarde Nevus
- Eccrine Centered Nevus
- Recurrent Nevus
- Spitz Nevus (Spindled and Epitheliod Cell Nevus)
- Pigmented Spindled Cell Nevus
- Congenital Nevus

Most common
Benign Proliferation of Melanocytes = Nevus

- Junctional nevus
- Compound nevus
- Intradermal nevus
Junctional Nevus

• Clinical
  – Well circumscribed, brown black macule, develops anywhere on the body surface
  – Usually appears during childhood or adolescence
  – Skin lines are preserved
Compound Nevus

• Clinical
  – Most common in children and adolescents
  – Dome shaped to polypoid and may be tan or dark brown
Intradermal Nevus

• Clinical
  – most common type of nevi, the majority are found in adults
  – Dome shaped, nodular or polypoid, pink or slightly pigmented
  – Coarse hairs may protrude from the surface
Other Dermal Melanocytic Lesions

- Mongolian Spot
- Nevus of Ota and Nevus of Ito
- Blue Nevus
- Cellular Blue Nevus
- Blue Nevus-like Metastatic Melanoma
- Malignant Blue Nevus
- Dermal Melanocytic Hamartoma
- Phakomatosis Pigmentovascularis
- Cutaneous Neurocristic Hamartoma
Atypical Melanocytic Lesions
Melanoma precursors

- Dysplastic nevi / Clark’s nevus / B-K mole
- Margins
- Treatment and re-exision
Correct terminology

• Dated terminology
  – Dysplastic nevi – originally described in 1978 by Wallace H. Clark
  – Clark’s nevus
  – B-K mole
• Correct
  – (Compound/Junctional) melanocytic nevus with architectural disorder and (mild/moderate/severe) atypia
Atypical Nevus

- 10% of melanocytic lesions received by pathology
- Dysplastic nevus syndrome
  - In 1820 Norris reported the first case of what was originally called BK mole syndrome is now recognized as familial atypical mole/malignant melanoma syndrome (FAMM) syndrome
  - Lifetime risk for melanoma 10%
  - Familial or sporadic occurrence of multiple dysplastic (atypical) nevi in an individual
  - May have up to 80 or more nevi that appear normal in childhood
Not all of these criteria need to be met
Some melanomas only have one “strike” against them!
A= Asymmetry
B= Border
C= Color
D= Diameter > 6mm
E= Evolution
– our newest and perhaps most important criteria!
E= Evolution

• “My mole is changing”
• “My mole is growing”
• “My mole is itching”
• “This is a new mole”
Atypical Nevus

- Clinical
  - Larger than ordinary nevi
  - Mixture of colors
  - Pebbly surface
Atypical Nevus

• Junctional and compound melanocytic nevi can be atypical
• Histologically there are two components
  – Architectural disorder
  – Cytological atypia
    • Mild
    • Moderate – re-excise if margin involved
    • Severe – re-excise if margin involved
Atypical Nevus
Architectural Disorder

- Poorly circumscribed
- Broad extension
Atypical Nevus
Architectural Disorder

Shouldering – junctional nests of melanocytes extending beyond the dermal component

Bridging of the rete ridges
Single and nested melanocytes along the sides and tips of the rete ridges
Chronic inflammation
Pigment incontinence
Fibroplasia
Atypical Nevus
Cytological Atypia

• Mild
  – Nucleus approximates size of keratinocyte nucleus
  – Fine dusty cytoplasm
  – Hyperchromatic nucleus, with mild pleomorphism
  – Absent nucleolus

• Moderate – re-excise
  – 1-2x keratinocyte nucleus
  – Fine dusty cytoplasm
  – Hyperchromatic nucleus, with moderate pleomorphism
  – Absent nucleus

• Severe – re-excise
  – 2x or greater keratinocyte nucleus
  – Fine dusty cytoplasm
  – Vesicular nucleus, with severe pleomorphism
  – Prominent nucleolus
  – Abundant cytoplasm
Atypical Nevus

1. Architectural disorder
   - Shouldering – proliferation of junctional nests of melanocytes extending beyond the dermal component
   - Intraepidermal lentiginous hyperplasia of melanocytes
   - Proliferation of melanocytes singly and in nests along the basal layer (sides and tips of rete ridges)

2. Cytological atypia
   - Large hyperchromatic cells with prominent nucleoli (nuclei equal or larger than the nucleus of the overlying keratinocytes)
     - Spindled
     - Large epithelioid

Stromal response
   - Concentric lamellar fibroplasia
   - Proliferation of dermal dendrocytes
   - Patchy lymphocytic infiltrate
   - Small vessel proliferation
SAMPLE PATHOLOGY REPORT

• SKIN, RIGHT ARM, SHAVE BIOPSY:
  – Compound melanocytic nevus with architectural disorder and mild cytological atypia
  – Margins involved
  – No re-excision necessary
  – Close clinical follow up. If the lesion returns in 6 months re-excision may be necessary
SKIN, RIGHT ARM, SHAVE BIOPSY:
- Compound melanocytic nevus with architectural disorder and moderate/severe cytological atypia
- Margins involved
- RE-EXCISE – 2-5mm clinical margins
Malignant proliferation of melanocytes = Melanoma
Melanoma

- 1 in 80 Americans
- Incidence increased 1000% in past 50 years
- Risks
  - Light complexions
  - Light eyes
  - Blond or red hair
  - Blistering sunburns
  - Heavy freckling
  - Tanning poorly
Melanoma

- Most often begin from melanocytes at dermal-epidermal junction
- About half evolve from pre-existing nevi
- Horizontal and vertical growth phase
- Survival nearly ensured if lesion caught early!
Melanoma in situ

- Confined to the epidermis
- Often found on face of elderly patients with sun damage
- Melanoma caught early has the best prognosis

©1994, Arthur C. Huntley, MD
Melanoma in situ = confined to the epidermis
Melanoma in situ

• Bottm line
  – Re-excision with 5mm clinical margins
Invasive Melanoma

- Melanoma which has grown into the dermis
- This happens quickly in some patients but slowly in others
- Prognosis based on depth of invasion and presence of ulceration
- Sentinel node biopsy is a newer prognostic test
Invasive Melanoma

- Biopsy
  - Critical
  - Need to sample the entire lesion if possible
  - Often requires excision either with sutures or deep shave
  - If excision is not possible, do an incisional biopsy

But tell your pathologist you are sending a piece of a very large lesion!
How to biopsy this lesion?

Remove entire lesion with a margin, deep to fat
Amelanotic melanoma - difficult to diagnose
Acral lentiginous melanoma

• Most common type of melanoma in darker skinned patients
• Which famous singer died of this?
Invasive melanoma

- Breslow Depth <1mm
  - Re-excision with 1cm clinical margins results in 90% survival
ABCDE’s of Melanoma

• Not all of these criteria need to be met
• Some melanomas only have one “strike” against them!
• A= Asymmetry
• B= Border
• C= Color
• D= Diameter > 6mm
• E= Evolution
  – our newest and perhaps most important criteria!
E= Evolution

- “My mole is changing”
- “My mole is growing”
- “My mole is itching”
- “This is a new mole”
Primary Melanoma: What factors influence prognosis?

Depth of invasion is the single most important factor in survival.

--ulceration is next
Excision and FNA of Left Groin Mass
BRAF V600E mutation

- BRAF is a proto-oncogene.
- Mutations result in activation of signaling pathways that lead to uncontrolled cell growth and oncogenesis.
- Roughly 50% of melanomas carry one of these mutations, most commonly a single amino acid change at position 600, V600E.
Treatment

- Surgical metastasectomy
- Immunotherapy
  - High dose IL-2
  - Ipilimumab
  - Monoclonal antibodies against programmed death 1 protein (PD-1) and its ligand (PD1-L1)
- MAPK pathway inhibition for BRAF positive patients
  - Vemurafenib
  - Dahrafenib
- Radiation
- Chemotherapy
Treatment

Diagnostic workup
- Patient and tumor data reviewed by multidisciplinary team
- Staging confirmed including pathology, imaging, serum LDH and mutation analysis of tumor
- Evaluation for metastasectomy
- Special attention to the presence of CNS disease

Patient selection
- Surgical candidate
  - Yes: Proceed with surgery
  - No:
    - BRAF+
      - Poor PS
        - CNS disease: 1st - Vemurafenib, dabrafenib, and/or trametinib
        - 2nd - Immunotherapy*
        - 3rd - Chemotherapy
    - Good PS
      - 1st - Immunotherapy*
      - 2nd - Vemurafenib, dabrafenib, and/or trametinib
      - 3rd - Chemotherapy

- BRAF-
  - Good PS
    - Treated CNS disease: 1st - Immunotherapy*
    - 2nd - Chemotherapy
  - Untreated CNS disease: 1st - Immunotherapy with ipilimumab
    - 2nd - Chemotherapy
    - 3rd - Chemotherapy

- KIT+
  - Poor PS
    - Untreated CNS disease: 1st - KIT inhibitor
    - 2nd - Immunotherapy*
    - 3rd - Chemotherapy

Treatment cessation
- Treatment until response, progression or unacceptable adverse affects
Melanoma Survival

Comparison of survival curves in four stages of melanoma:

- Stage I (n=9175)
- Stage II (n=5739)
- Stage III (n=1528)
- Stage IV (n=1158)
Melanoma Prevention

Wear broad-spectrum sunblock! UVA and UVB blockers like titanium dioxide, zinc oxide, and mexoryl- and REAPPLY!

Avoid mid-day sun exposure