Dysplastic Nevi
Little Brown Dots: Harmless or Not?

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Introduction

• Dysplastic Nevi:
  – What are they?
  – Why do we care?
• What:
  – Nevus: A spot on the skin, like a mole or birthmark
  – Dysplastic: A microscopic cellular appearance suggestive of pre-cancerous changes
• Why we care:
  – Can be associated with a risk of developing melanoma, a potentially deadly cancer
    • Predicting cancer is hard
    • Any significant risk factor for developing it should be taken seriously
  – Can be an “out of the blue” source of debits
    • The producer/client may not know about the risks
    • Can be a source of conflict
Agenda

- Tour of normal skin
  - Microscopic anatomy
- Anatomy of a nevus
- Distinguishing features of dysplastic nevi
- Relationship with melanoma
  - Explore those factors which increase the risk of melanoma
- Cases
- Practicum
  - Identify, biopsy, process, stain and examine at least one nevus from the person to your right
Normal Skin

- Epidermis
- Dermis
- Subcutaneous tissue
- Hair follicle
- Hair shaft
- Oil gland
- Lymph vessel
- Nerve
- Fatty tissue
- Vein
- Artery
- Sweat gland
Normal Skin

• 7 Layers (?)
  – Really 2 with some subdivisions
    • Epidermis – what you see
      – Flat, stacked cells - “Keratinocytes”
      – Divided into 5 strata
        » Stratum germinativum – bottom layer
        » Stratum corneum – top layer
        » One other important denizen
          » Melanocytes – the pigment producing cells
    • Dermis - the elastic portion of the skin
      – Contains structural proteins, hair follicles, blood vessels, nerve endings
      – Divided into 2 layers
        » Papillary dermis – finger-like projections into the epidermis
        » Reticular dermis
Epidermis
Melanocytes

- Melanocytes are “strangers” in the skin
  - Skin derives from the ectoderm of the developing fetus
  - Melanocytes come from the neural crest
    - Same place where nerve/brain cells come from
Describing a Mole (Nevus)

• When you got it
  – Congenital – present at birth
  – Acquired – came on later
• Where the excess melanocytes are
  – Lentiginous – melanocytes at dermal/epidermal junction
    • Very small and flat
  – Junctional – they are near the dermal/epidermal junction
    • Flat in contour and dark in color
  – Compound – they are in the “junction” and in the higher levels of the epidermis
    • Slightly raised and dark in color
  – Intradermal – melanocytes now nerve-like (“nevroid”)
    • Raised and flesh-colored
• What they look like
  – Giant, blue, star-nosed
Moles and melanoma – The Mole Cycle

- New moles are rare in childhood, common in the 20's to 40's and rare after that
  - Junctional and compound nevi can become dysplastic
  - Intradermal nevi almost never do
    - Cells have fully matured

Lentiginous nevus

\[\downarrow\]

Junctional nevus

\[\downarrow\]

Compound nevus

\[\downarrow\]

Intradermal nevus

\[\downarrow\]

Dysplastic Nevus

\[\downarrow\]

Melanoma
Dysplastic Nevi

• Also called “atypical moles”
  – Some doctors resist the term “dysplastic” unless the lesion has been examined under the microscope
  – This is far from universal

• Clinical “eyeball” features
  – Typically larger than 5mm
  – Multiple colors
  – Irregular borders
  – Indistinct borders
  – Redness that blanches with pressure
Dysplastic Nevi

• Pathologic “microscope” features
  – “Cytologic atypia”
    • The melanocytes look weird
  – “Architectural disorder”
    • The normal structure of the skin layer is changed or disrupted
    • “Bridging” of the rete ridges
    • Lamellar fibrosis
  – The degree of atypia can be graded as mild/moderate/severe
Dysplastic Nevi

- **History**
  - First described in 1978 by Clark
    - “Clark nevi”
  - Studied families with several cases of melanoma
  - Identified that many of the family members had multiple odd-looking moles
    - Sometimes called “B-K moles” after the names of the families involved

- **Importance**
  - Simulant of melanoma
  - Dysplastic nevi may actually become melanomas (rare)
  - Marker of increased risk for melanoma
Dysplastic Nevi vs. Melanoma
Dysplastic Nevi vs. Melanoma

- Histology is the best way to make the call of dysplastic vs. melanoma
  - Even that is not sure-fire
  - One study
    - Community-based diagnosis of melanoma vs. expert panel
    - 17% of dysplastic nevi were misdiagnosed as melanoma in-situ
    - 3% misdiagnosed as invasive melanoma
    - 12% of initially diagnosed melanomas were felt to be dysplastic nevi by the experts
  - This is a common area for pathological second opinions and referrals
Dysplastic Nevi – Becoming Melanoma

- Dysplastic nevi are fairly common
  - Around 10% of the population has at least one
  - About 50% of the population of people with a history of melanoma have at least one
- Melanoma is comparatively rare
  - Only about 1/300 people has a history of melanoma
- About half of melanomas seem to be associated with dysplastic nevi
  - Nevus cells in the pathological specimen
- Despite that, only a very small minority of dysplastic nevi ever become melanoma
  - Risk of developing melanoma in any given nevus is about 1:3000 over a lifetime
From Normal Skin to Melanoma

UVB
UVA

NRAS
BRAF

CDKN2A
PTEN

AKT
TP53

Normal skin
Nevus
RGP
VGP
Metastasis

Heritable mutations in human and mouse
CDKN2A, CDK4, PTEN, TP53

APC

PTEN
CDK2A
SYK
MGMT
RASSF1

MTAP
APAF1
CDH1
CDH2

MTA2
MAGE

Epigenetic modulations
Dysplastic Nevi & Risk of Melanoma

• The presence of dysplastic nevi, along with family history, are the strongest risk factors for melanoma.
• Does that matter?
  – How important is melanoma anyway?
    • Frequency:
      – 5th most common malignancy in men
      – 7th most common in women
    • Deaths: Not in the top 10
    • The most common form of cancer in ages 25-29
    • Second most common form of cancer in ages 15-29
    • Increasing in incidence for the last 30 years
      – Tanning behavior (tanning beds)
      – Increased awareness
    • Decreasing mortality

Leading New Cancer Cases and Deaths – 2013 Estimates

<table>
<thead>
<tr>
<th>Male</th>
<th>Female</th>
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</thead>
<tbody>
<tr>
<td>Prostate 238,590 (28%)</td>
<td>Breast 232,340 (29%)</td>
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<tr>
<td>Lung &amp; bronchus 118,080 (14%)</td>
<td>Lung &amp; bronchus 110,110 (14%)</td>
</tr>
<tr>
<td>Colon &amp; rectum 73,680 (9%)</td>
<td>Colon &amp; rectum 69,140 (9%)</td>
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<tr>
<td>Urinary bladder 54,610 (6%)</td>
<td>Uterine corpus 49,560 (6%)</td>
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<tr>
<td>Melanoma of the skin 45,060 (5%)</td>
<td>Thyroid 45,310 (6%)</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis 40,430 (5%)</td>
<td>Non-Hodgkin lymphoma 32,140 (4%)</td>
</tr>
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<td>Non-Hodgkin lymphoma 37,600 (4%)</td>
<td>Melanoma of the skin 31,630 (4%)</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx 29,620 (3%)</td>
<td>Kidney &amp; renal pelvis 24,720 (3%)</td>
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<tr>
<td>Leukemia 27,880 (3%)</td>
<td>Pancreas 22,480 (3%)</td>
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<tr>
<td>Pancreas 22,740 (3%)</td>
<td>Ovary 22,240 (3%)</td>
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<tr>
<td>All sites 854,790 (100%)</td>
<td>All sites 805,500 (100%)</td>
</tr>
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# Sex-based Incidence of Melanoma

<table>
<thead>
<tr>
<th>Probability (%) of Developing Invasive Cancers during Selected Age Intervals by Sex, US, 2007-2009*</th>
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<tbody>
<tr>
<td><strong>Birth to 39</strong></td>
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<tr>
<td><strong>All sites</strong></td>
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<tr>
<td><strong>Prostate</strong></td>
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<tr>
<td><strong>Uterine cervix</strong></td>
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<tr>
<td><strong>Uterine corpus</strong></td>
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*For those who are cancer-free at the beginning of each age interval. †All sites excludes basal cell and squamous cell skin cancers and in situ cancers except urinary bladder. ‡Includes invasive and in situ cancers. §Statistic is for whites only.


American Cancer Society, Surveillance Research, 2013
<table>
<thead>
<tr>
<th>Sex/Tumor Thickness</th>
<th>Cases</th>
<th>Percent</th>
<th>1-Year</th>
<th>2-Year</th>
<th>3-Year</th>
<th>5-Year</th>
<th>8-Year</th>
<th>10-Year</th>
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<td>&lt; 0.75 mm</td>
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<td>100.0</td>
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<td>97.2</td>
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<tr>
<td>&lt; 0.75 mm</td>
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<td>97.8</td>
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<td>1,002</td>
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<td>4.00+ mm</td>
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<td>82.7</td>
<td>79.7</td>
<td>77.8</td>
<td>77.2</td>
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World Literature on Mortality Risk of DN
A Little Math

- Risk of death given a melanoma
  - About 12% over 10 years (excess deaths)
  - Which is 120 deaths per thousand over 10 years or 12 deaths per thousand per year
- Baseline risk of melanoma
  - About 1 in 160 between ages of 40 and 59
- Hypothetically double the risk
  - Now we have an excess risk of 1 in 160 of developing a condition which kills 12% of folks in a 10 year period
  - Averages 0.75 excess deaths over 10 years or 0.075 excess deaths per thousand per year
- Hypothetical 11x the risk
  - Excess 10 in 160 risk of 12% mortality
  - Averages 0.75 excess deaths per thousand per year
- Hypothetical 101x the risk
  - Excess 100 in 160 risk of 12% mortality
  - Averages 7.5 excess deaths per thousand per year
Dysplastic Nevi

- Risk of melanoma
  - Baseline risk – about 20 cases per 100,000 person-years
    - Risk increased by:
      - Tanning bed use: 1.15x
      - Freckling skin: 1.5x
      - Tanning bed use prior to age 35: 1.75x
      - Sunburn at any age: 1.9x
      - Family history of sporadic melanoma: 2.2x
      - Pale, non-tanning skin: 3x
      - Personal history of non-melanoma skin cancer: 4x
      - 25-50 non-dysplastic nevi: 4.4x
      - Large congenital nevi (8 inches or bigger): 10x
      - 100 or more non-dysplastic nevi: 10x
      - 5 or more dysplastic nevi: 10x
      - Personal history of melanoma: 40x
      - Dysplastic nevus syndrome: 50x
      - Personal history of melanoma with positive family history of melanoma: up to 1200x
Protective Factors

• Race

• Ambient solar exposure
  – AZ vs. CT: Offers about 70% protection

• Sun protection – sunscreen, sun avoidance
  – Seek, slip, slop, slap, slide
Dysplastic Nevus Syndrome

- Definition is inconsistent
  - Use of this term may be arbitrary
  - "Classic" dysplastic nevus syndrome
  - Can be sporadic or familial
    - Three features
      - 100 or more benign nevi
      - At least one nevus larger than 8mm
      - At least one clinically dysplastic nevus
    - Risk is about 18x that of the background population
      - Can be higher if family or personal history is positive for melanoma
Familial Atypical Mole and Melanoma

- First described by Lynch in 1978
  - Current “official definition” based on a 1992 conference of dermatologists
    - At least one first or second degree relative with melanoma
    - Many nevi (50 or more), some of which are clinically atypical
    - Some lesions with have histological atypia
- Dysplastic nevi plus family history
  - Autosomal dominant pattern
  - Risk: up to 1200x and not limited to melanoma
  - About 50% of individuals develop melanoma by age 50, and 82% by age 72
Familial atypical multiple mole-melanoma syndrome

Genetics

CDKN2A

DNA

p16
CDK4
RB
Proteins

inhibits

Inhibits Cancer
Genetics

- CDKN2A Mutation
  - Who actually has this?
  - Melanoma prone families
    - Primarily in Northern Europe
    - P16 Leiden – identified in the Netherlands
  - Not everyone with the mutation has atypical moles or melanoma
    - Some other interacting genes may play a role
  - Risk is generally high and unaffected by environmental factors
  - Test is available in a research setting but not recommended in clinical practice
    - We are unlikely to see it
A 53 year old man is applying for $3.5 million in term life insurance. As part of application requirements, a record from his dermatologist is submitted. He was first seen about 6 months ago for a complete skin exam. At this exam the dermatologist discovered several actinic keratoses, some solar lentigines, a few seborrheic keratoses, and 7 “suspicious nevi”. All 7 of the nevi were removed and pathology confirmed dysplastic nevi with moderate atypia in 5 of them. These 5 also all had positive margins. Re-excision was done on all 5 and there were no residual nevus cells noted. Three months later, 3 more nevi were biopsied: 2 were bland nevi, and one was dysplastic. The dysplastic one was again positive at the margins. No re-excision has been done.
Case 1

• What more would we like to know?
  – Is there a family history of melanoma?
  – Is there a family history of cancer?
  – Is re-excision planned or not?
  – What is the plan for ongoing monitoring?

• Is it necessary to re-excise?
  – Perhaps not, if the plan is to monitor closely

• Is it necessary to remove all clinically dysplastic nevi?
  – No, in fact this is not advisable
  – Better to monitor with photographs and biopsy only “ugly ducklings”
Making the Call without a Scalpel

• Dermoscopy
  – Using bright light to get a better view of a pigmented lesion without having to excise it
    • Can improve diagnostic accuracy
    • Very much experience-dependent

• MelaFind
  – Computer-aided dermoscopy
  – Found to be more accurate than an unaided dermatologist (by a little)

• Sniffer Dogs
Case 2

- A 61 year old man is applying for $10 million in permanent life insurance. He has a history of a stage I superficial spreading melanoma discovered 8 years ago. It was removed successfully and a sentinel lymph node biopsy was negative. About 2 years ago, at his regular dermatology follow-up a new atypical mole on the back was noted. It was 8mm in size. It was not biopsied, and it was noted again 3 months later, this time 1.1cm in size. There has been no dermatology follow up since then. At a physical with his primary care doctor, the skin portion of the exam stated “intact, no lesions”.
Case 2

• Is this risk acceptable now – without further visits or procedures?
  – Probably not
  – New clinically dysplastic nevi in people over the age of 50 turn out to be melanoma 30% of the time
  – In this man, the risk is higher because he has a personal history of melanoma

• Suppose he gets the lesion removed and it turned out to be a dysplastic nevus with mild atypia – is the risk acceptable now?
  – Probably
  – Remains at elevated risk for melanoma (about 40x the background risk)
  – Would be nice to know family history
  – Decision to not biopsy seems a little odd
Care for Pigmented Lesions

• What to expect from dermatologic care
  – According to guidelines written by dermatologists for dermatologists
    • Thorough family history
      – First and second degree relatives
      – Melanoma and dysplastic nevi
    • Frequent follow up
      – For highest risk melanoma prone families: every 3-6 months
        » Consider referral to pigmented lesion clinic
      – For multiple nevi with some dysplastic nevi: every 6-12 months
    • Biopsy of “suspicious” lesions
      – May be useful to photograph lesions
      – Look for “ugly ducklings”
      – Look for significant changes (though most moles do change)
  • Sun avoidance and sunscreen advice
  • What not to expect
    – Biopsy of every lesion
    – Genetic testing
Care for Pigmented Lesions

- What dermatologists actually do:
  - Follow up exams:
    - 78% do them on all patients with dysplastic nevi
    - 22% do so for some
  - Photography
    - 49% order them for some or all of their patients with multiple dysplastic nevi
  - Re-excision of lesions with positive margins
    - 67% do this routinely
    - Others base it on severity of histologic atypia
  - Examination of relatives
    - 12% do so routinely
    - 81% recommend it for some patients
  - Sun avoidance and sunscreen
    - 99% advise this routinely
  - Dermoscopy: 23% use it
  - Eye exams: 60% advise it for at least some of their patients
Ocular Melanoma

- Melanoma of the eye
  - Melanocytes are found in the eye
    - In the pigmented layer called the uvea
      - Iris (colored part of the eye) – 20%
      - Choroid (back of the eye, near the retina) – 80%
    - These tumors are quite rare
      - About 6 cases per million person-years
      - More common in those with dysplastic nevus syndrome
        - About 1 in 200 lifetime risk
  - Survival depends on location
    - 95% 10-year survival for iris location
    - 50-70% for choroid location (tend to metastasize early)
Summary

- The relevance of dysplastic nevi to underwriting is almost entirely due to the increased risk for melanoma
- The terms “dysplastic” and “dysplastic nevus syndrome” are frequently used imprecisely by clinicians
- Family history is a crucial differentiator between “acceptable” risks and others
- The number of lesions, the degree of dysplasia and the history and quality of dermatological care can help fine-tune the risk assessment
- Please protect yourself from the sun and tanning lights
References
