SKIN NEOPLASMS

This 2009 lecture is far superior to the lecture delivered in 2011. However, streaming videos and VAP's may not match. Dr. H

-the goal of the first skin lecture was to learn the vocabulary
-now we should focus on learning "clues for detection"

APPROVED

Maria Angelica Selim, MD
Director Dermatopathology Unit
Duke University Medical Center
neoplasms may arise from any of these skin components
we will use this diagram to examine each

Normal Anatomy
-we will see examples of neoplasms that are...

Normal Anatomy
-let's start w/ the most superficial layer: the epidermis

Normal Anatomy
- the epidermis is mostly composed of keratinocytes, so we'll start w/ benign lesions of these
- Seborrheic keratosis = a benign proliferation of keratinocytes
- See a brown, irregular plaque
- Has hyperkeratosis, where white areas represent the thickened stratum corneum
- Common benign lesion, most frequently occurring in older adults
- Need to distinguish from melanoma—The evidence of the expanded stratum corneum in seborrheic keratosis is key
- appear "stuck on"
- can be peeled off (not recommended!) due to flat connection to the underlying dermis
-note the thickening of the epidermis at the plaque

-at higher power, the cells appear small and equal in size and shape, indicating a benign lesion

-small keratin-filled cysts (horn cysts) are characteristic features

-inspection by the clinician with a hand lens will usually reveal small, round, pore-like ostia impacted with keratin, a feature helpful in differentiating these pigmented lesions from melanomas
-now done w/ the benign and onto things that can evolve...

In between

Normal Anatomy
Actinic Keratosis

- Actinic keratosis = a premalignant condition of thick, scaly, or crusty patches of skin
- See a white plaque w/ an erythematous border
- Again, white = expanded stratum corneum
Actinic Keratosis

-rough plaques, due to expanded stratum corneum
-some lesions may produce so much keratin that a "cutaneous horn" develops -such horns may become so prominent that they actually resemble the horns of animals!

-looking at h&e, keratinocytes show signs of dysplasia (enlarged, hyperchromatic nuclei w/ prominent nucleoli)

-there is a progressive loss of normal epidermal polarization -nuclei in the stratum corneum are often retained, a pattern termed parakeratosis -most of the atypia is seen in the lowermost layers of the epidermis, which distinguishes from a full-thickness malignancy
-next up: two types of malignancies arising from keratinocytes

1. some keratinocytes will recapitulate the basal layer = basal cell carcinoma

2. other keratinocytes will recapitulate more the spinous layer = squamous cell carcinoma

Normal Anatomy
Squamous Cell Carcinoma

- as w/ all these epidermal lesions, exposure to sunlight is the major predisposing factor for squamous cell carcinoma
- here you see/feel on the lip a single, erythematous, indurated plaque w/ superficial ulceration
- also shows white areas associated w/ keratin production
-more advanced lesions are nodular, show variable keratin production appreciated clinically as hyperkeratosis, and ulcerate as seen here
- Looking at h& e, you can see the keratinocytes taking on the appearance of the mid-epidermis.
  - They are pink due to keratin production.
  - Here the cells are infiltrating into the dermis, making this an invasive squamous cell carcinoma (see vocab lesson below).

**VOCABULARY**

+ Actinic keratosis: cytologic atypia limited to the lowermost layers of the epidermis.
+ SCC in situ: progression to full-thickness nuclear atypia, but bound by the basement membrane of the dermoepidermal junction.
+ Invasive SCC: crossing the basement membrane into the dermis.

- These distinctions are important for prognosis; once the dermis is invaded, there is metastatic potential due to vascular access.
Squamous Cell Carcinoma

- Large zones of keratinization, indicating the keratinocyte origin of this tumor.
- These tumors may become so poorly differentiated that they reach a point of dyskeratosis, making it difficult to definitively establish cell lineage.

- See pleomorphic, enlarged nuclei with prominent nucleoli.
the tumor can travel through the nerve, meaning that even a surgical resection w/ "clean margins" may leave more distal tumor along the nerves
Squamous Cell Carcinoma

- Here you see lymphatic invasion. These tumors can invade the vasculature and lymphatics, allowing for metastasis.
- The second (and the most common) epidermal malignancy is basal cell carcinoma.
- BCC recapitulates the basal layer of the epidermis.
- It can present clinically as a more superficial or deep erythematous appearance.

Basal Cell Carcinoma
1. On histologic examination, tumor cells resemble those in the normal basal cell layer of the epidermis. They appear basophilic with hyperchromatic nuclei.

2. The cells forming the periphery of the tumor cell islands tend to be arranged radially with their long axes in approximately parallel alignment (palisading). The stroma shrinks away from the epithelial tumor nests, creating clefts or separation artifacts that are diagnostic for BCC.

3. The tumor is often surrounded by many fibroblasts and lymphocytes, demonstrating a significant stromal reaction.
-this advanced plaque appears raised and eaten in the center, explaining the term "rodent ulcer"
- this is the classic presentation of BCC
- a pearly papule containing prominent, dilated blood vessels (telangiectasias)

- Basal Cell Carcinoma

- tumor cell nests

- telangiectasia

- palisading

- retraction

- stromal reaction
-usually BCC presents as a localized lesion that can be excised (such as the superficial and nodular variants)
-this is the **infiltrative** variant, which can grow deeper and deeper when untreated
-most of the time
BCC presents as a small, pearly papule
-if you let it grow, you can get these kinds of problems
-entire L orbit is replaced by tumor
-this should shock you and remind you that no tumor should be ignored

Basal Cell Carcinoma
Basal Cell Carcinoma
- A nevus is a type of hamartoma (a benign mass of tissue of disproportionate size and distribution but composed of the normal tissue of the region) - here the benign proliferation is of melanocytes, so a mole is properly called a "melanocytic nevus"
- Junctional nevus: when the melanocytic proliferation is located in the epidermis along the junction with the underlying dermis.
Intradermal Nevus

- Intradermal nevus: when melanocytic proliferation takes place only in the dermis.

Normal Anatomy
Compound Nevus:

When melanocytic proliferation is occurring both in the dermis and in the epidermis.
A junctional nevus originates in the epidermis and is flat.
- Junctional nevi are characterized by rounded nests of melanocytes originating at the tips of rete ridges (inward projections of the epidermis into the dermis).
-intradermal nevi are raised due to proliferation in the underlying dermis
Intradermal Nevus

Upon biopsy, see benign proliferation of melanocytes in the dermis.
-progressive growth of melanocytes from the dermoeidermal junction into the underlying dermis is accompanied by a process termed maturation
-whereas less mature, more superficial melanocytes are larger and tend to produce melanin, deeper melanocytes seen here are smaller and produce little or no pigment
Compound nevi have both flat and raised components.
Compound Nevus

- See both nests in the epidermis and mature melanocytes in the dermis.
- In a halo nevus, there is a host immune response against the nevus.
- When the lymphocytes kill off the melanocytes, this white ring remains.
-lymphocytic infiltrate
-this may represent a response to either benign or malignant lesions
-we’re now moving into the malignant proliferation of melanocytes = melanoma
-features include: irregular border, nodular, pigmented w/ multiple colors, asymmetrical, growing

Melanoma
-here are the ABCDE's of melanoma

**ASYMMETRY** is in shape—one half unlike the other.

**BORDER** is irregular—edges irregularly scalloped.

**COLOR** is mottled—haphazard display of colors: shades of brown, black, gray, red, and white.

**DIAMETER** is usually large—greater than the tip of a pencil eraser (6.0 mm), nevi usually 4-5mm.

**ENLARGEMENT**—a history of an increase in the size of lesion is perhaps one of the most important signs of malignant melanoma.
dr. selim here applied the ABCDE's to these two lesions. "if you take anything from this lecture, take the recognition of melanoma." -stream @ 28:48
-the distinction between the nevi and melanoma is "easy" at this stage— you need to catch melanoma early, when the nevi first start to change.
<table>
<thead>
<tr>
<th>Type of melanoma</th>
<th>Frequency (%)</th>
<th>Site</th>
<th>Radial growth</th>
<th>Special features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superficial spreading melanoma</td>
<td>60–70</td>
<td>Any site, preference for lower extremities (female), trunk (male)</td>
<td>Yes</td>
<td>More pagetoid, less solar elastosis</td>
</tr>
<tr>
<td>Nodular melanoma</td>
<td>15–30</td>
<td>Any site, preference for trunk, head, neck</td>
<td>No</td>
<td>Nodule with vertical growth</td>
</tr>
<tr>
<td>Lentigo maligna melanoma</td>
<td>5–15</td>
<td>Face, especially nose and cheeks</td>
<td>Yes</td>
<td>Slower growth over years on sun-damaged skin</td>
</tr>
<tr>
<td>Acral lentiginous melanoma</td>
<td>5–10</td>
<td>Palms, soles, subungual</td>
<td>Yes</td>
<td>Most common melanoma in patients with darker skin types</td>
</tr>
</tbody>
</table>

- Superficial spreading is most common
- Pagetoid = upward spread through the epidermis
- Acral lentiginous shows up on the foot and is more common in pts w/ darker skin
- Typical presentation of lentigo maligna is an older pt w/ a flat, brown lesion in a sun-exposed area that suddenly starts to change after yrs
- these cells proliferate as poorly formed nests or as individual cells at all levels of the epidermis, traveling up into the granular layer here.

- In the dermis, the melanocytes fail to mature, remaining large and melanin-producing.
- "Look at how pleomorphic they can be..."
-this is lentigo maligna
-typical presentation of an older pt w/ darkening in a sun-exposed area that has developed over time

-lentigo maligna (seen here) is composed of individual malignant melanocytes limited to the epidermis; it is a melanoma *in situ*
-lentigo maligna melanoma occurs when melanocytes of lentigo maligna-type turn invasive
-this terminology is confusing but important for proper communication
HISTOPATHOLOGICAL REPORTING OF CUTANEOUS MELANOMA

- In addition to reporting a diagnosis, the pathologist is able to predict behavior based on these features:

<table>
<thead>
<tr>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thickness (Breslow depth)</td>
</tr>
<tr>
<td>Mitoses/mm²</td>
</tr>
<tr>
<td>Level of invasion (Clark)</td>
</tr>
<tr>
<td>Regression, tumor infiltrating lymphocytes, presence of plasma cells</td>
</tr>
<tr>
<td>Ulceration</td>
</tr>
<tr>
<td>Vascular invasion</td>
</tr>
<tr>
<td>Microscopic satellites</td>
</tr>
<tr>
<td>Associated nevus</td>
</tr>
<tr>
<td>Margins</td>
</tr>
</tbody>
</table>
-vascular invasion is a bad sign, because it provides systemic access
**Breslow Depth** is a direct measurement (0.5-5mm) of tumor thickness.

**Clark Level** is a related system describing the anatomic level of invasion:
- Clark Level 1 in epidermis
- Clark Level 2 in pap derm w/o distention
- Clark Level 3 in pap dermis w/ distention
- Clark Level 4 in reticular dermis
- Clark Level 5 in subcutaneous fat
## MELANOMA TNM CLASSIFICATION

<table>
<thead>
<tr>
<th>T classification</th>
<th>Thickness</th>
<th>Ulceration status</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>1.0 mm</td>
<td>a: Without ulceration and level II/III</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b: With ulceration or level IV/V</td>
</tr>
<tr>
<td>T2</td>
<td>1.01–2.0 mm</td>
<td>a: Without ulceration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b: With ulceration</td>
</tr>
<tr>
<td>T3</td>
<td>2.01–4.0 mm</td>
<td>a: Without ulceration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b: With ulceration</td>
</tr>
<tr>
<td>T4</td>
<td>&gt; 4.0 mm</td>
<td>a: Without ulceration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b: With ulceration</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N classification</th>
<th>Number of metastatic nodes</th>
<th>Nodal metastatic mass</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1</td>
<td>1 node</td>
<td>a: Micrometastasis*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b: Macrometastasis</td>
</tr>
<tr>
<td>N2</td>
<td>2–3 nodes</td>
<td>a: Micrometastasis*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b: Macrometastasis†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>c: In transit met(s)/satellite(s) without metastatic node(s)</td>
</tr>
<tr>
<td>N3</td>
<td>4 or more metastatic nodes, or matted nodes, or in transit met(s)/satellite(s) with metastatic node(s)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>M classification</th>
<th>Site</th>
<th>Serum lactate dehydrogenase</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1a</td>
<td>Distant skin, subcutaneous, or nodal mets</td>
<td>Normal</td>
</tr>
<tr>
<td>M1b</td>
<td>Lung metastases</td>
<td>Normal</td>
</tr>
<tr>
<td>M1c</td>
<td>All other visceral metastases</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>Any distant metastasis</td>
<td>Elevated</td>
</tr>
</tbody>
</table>
### Proposed Stage Groupings for Cutaneous Melanoma

<table>
<thead>
<tr>
<th>Stage</th>
<th>Survival (%)*</th>
<th>Clinical staging†</th>
<th>Pathologic staging‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T</td>
<td>N</td>
<td>M</td>
</tr>
<tr>
<td>0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IA</td>
<td>95</td>
<td>T1a</td>
<td>M0</td>
</tr>
<tr>
<td>IB</td>
<td>90</td>
<td>T1b, T2a</td>
<td>N0</td>
</tr>
<tr>
<td>IIA</td>
<td>78</td>
<td>T2b, T3a</td>
<td>N0</td>
</tr>
<tr>
<td>IIB</td>
<td>65</td>
<td>T3b, T4a</td>
<td>N0</td>
</tr>
<tr>
<td>IIC</td>
<td>45</td>
<td>T4b</td>
<td>N0</td>
</tr>
<tr>
<td>III#</td>
<td>Any T</td>
<td>N1, N2, N3</td>
<td>M0</td>
</tr>
<tr>
<td>IIIA</td>
<td>66</td>
<td>T1-4a, T1-4a</td>
<td>N1a, N2a</td>
</tr>
<tr>
<td>IIIB</td>
<td>52</td>
<td>T1-4b, T1-4b, T1-4a, T1-4a/b</td>
<td>N1a, N2a, N1b, N2b, N2c</td>
</tr>
<tr>
<td>IIIC</td>
<td>26</td>
<td>T1-4b, T1-4b, Any T</td>
<td>N1b, N2b, N3</td>
</tr>
<tr>
<td>IV</td>
<td>7.5–11</td>
<td>Any T, Any N, Any M1</td>
<td>Any T, Any N, Any M1</td>
</tr>
</tbody>
</table>

*a: Survival at 10 years
†: Clinical staging
‡: Pathologic staging

-“don’t look at all this; it’s too much information.”
-the point is that stage is predictive of survival, so try to catch early while localized (IA)

-terrible survival at Stage IV
COMPARISON OF SURVIVAL CURVES IN FOUR STAGES OF MELANOMA

Proportion surviving vs. Survival (years)

- Stage I (n=9175)
- Stage II (n=5739)
- Stage III (n=1528)
- Stage IV (n=1158)
# SURGICAL TREATMENT OF PRIMARY MELANOMA

<table>
<thead>
<tr>
<th>Thickness</th>
<th>Excision margins (cm)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>In situ</td>
<td>0.5</td>
<td>No randomized studies, lentigo maligna of the face might be treated with radiotherapy in specialized centers&lt;sup&gt;93&lt;/sup&gt;</td>
</tr>
<tr>
<td>&lt;1 mm</td>
<td>1.0</td>
<td>AAD task force suggests 1 cm margin for melanoma &lt;2 mm&lt;sup&gt;67&lt;/sup&gt;</td>
</tr>
<tr>
<td>1–4 mm</td>
<td>2.0</td>
<td>AAD task force suggests 2 cm margin for melanoma ≥2 mm&lt;sup&gt;67&lt;/sup&gt;</td>
</tr>
<tr>
<td>&gt;4 mm</td>
<td>2.0–3.0</td>
<td>No randomized studies</td>
</tr>
</tbody>
</table>

-Breslow Depth also determines excision margins in surgery
- pts w/ dysplastic nevus syndrome have hundreds of irregular lesions on the body surface
- dysplastic nevi are associated w/ an increased risk of developing melanoma
- these fall somewhere between benign melanocytic nevi and malignant melanoma
- Dysplastic nevi show both architectural and cytologic evidence of abnormal growth.
- Nest within the epidermis may be enlarged and exhibit abnormal fusion or coalescence with adjacent nests.
- Melanocytes are still maturing as they descend into the dermis, meaning that they are not becoming malignant.
- This process is between benign and malignant.
-finally finished lesions arising from the epidermis
-now let's look at blood vessels in the dermis...
Hemangioma

- Hemangioma = a benign vascular neoplasm
- Can tell it's vascular by its red color
- When a child presents with a cutaneous lesion of vascular origin, most of the time it is benign
Hemangioma

- See back-to-back proliferation of vessels in the dermis - the endothelial lining appears benign.
-with laser, you can burn out the vessels and treat superficial lesions if they appear in cosmetically significant areas
Angiosarcoma

- angiosarcoma = a malignant endothelial neoplasm
- see irregularity, ulceration, bleeding, masses being formed
-plump, anaplastic endothelial cells piling up around vascular channels

Angiosarcoma
-now we'll focus on connective tissue in the dermis...
-Keloid = a benign overgrowth of collagen that forms a hypertrophic scar in response to trauma.
-Note the very thick bundles of collagen deposition in the dermis -totally benign; only a cosmetic issue
-increased collagen w/ increased fibroblasts

Keloid
Dermatofibroma

-dermatofibroma = a benign dermal neoplasm of fibroblasts
-usually seen in adults, and often occur on the legs of young to middle-aged women
-many cases have a history of antecedent trauma, suggesting an abnormal response to injury and inflammation
-these neoplasms are firm, tan to brown papules
-dimple inward on lateral compression, which is helpful for distinguishing w/o biopsy
Dermatofibroma

- Increased fibroblasts and collagen in dermis
-note the tendency of fibroblasts to surround individual collagen bundles in a dermatofibroma
Dermatofibrosarcoma protuberans is best regarded as a well-differentiated, primary fibrosarcoma of the skin. These tumors are slow growing, and although they are locally aggressive, they rarely metastasize; thus, this is an "in between" lesion called "protuberans," because it develops as aggregated protuberant nodules.
-very cellular
-deep extension from the dermis into subcutaneous fat, producing a characteristic "honeycomb" pattern
Normal Anatomy

-also have adnexal (appendage) tumors
Sebaceous Hyperplasia

- generally affects older pts
- benign papules, mainly on facial skin (the forehead, nose and cheeks)
-note an increased number of sebaceous glands around the hair follicle.
Sebaceous Carcinoma is an aggressive, uncommon, cutaneous tumor, thought to arise from sebaceous glands.
-can still identify certain cells as being sebocytes, due to the foamy cytoplasm -other cells appear more classically neoplastic

-what is important about sebaceous carcinoma is that it can indicate a systemic disorder: Muir-Torre Syndrome -individuals w/ Muir-Torre are also prone to develop cancers of the gi and gu tracts
Lastly, we'll look at lesions of the subcutaneous fat.
Lipomas = benign tumors of fat
- they are soft, mobile, and generally painless nodules that can be multiple
see a well-encapsulated mass of mature adipocytes that can vary considerably in size
at higher power, you can verify that a benign lipoma consists of mature white fat cells with no pleomorphism
Liposarcoma - can also have bad malignancies arising from fat cells.

- They usually occur in the deep soft tissues of the proximal extremities (such as the thigh) and in the retroperitoneum.

- Requires surgical excision, not biopsy.
-to diagnose liposarcoma, look for lipoblasts
-they mimic fetal fat cells and contain round, clear cytoplasmic vacuoles of lipid that scallop the nucleus
THANK YOU

-the remaining slides contain 3 cases which served as an end-of-lecture "quiz"
-a nodular, ulcerative lesion w/ hyperkeratosis
-dx: nodular basal cell carcinoma

-palisading

-retraction

-stromal reaction
- A benign junctional nevus (flat and brown)

- A benign dermal nevus (raised)
- Does NOT meet the ABCDE's
- This lesion is symmetric, has regular borders, uniform color, normal diameter (4-5mm or less), and should not be enlarging
-dx: melanoma

-again, note the ABCDE's
-you need to catch this and confirm w/ biopsy to prevent metastasis