NEVOID MELANOMA

Variants Of Melanoma
Which Mimic A Nevus:
A Clinico-Pathologic Analysis

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NMM: Clinical Data

- 24 Cases
  - All patients Caucasian, 16 male, 8 female
  - Age at initial presentation ranged from 16 to 78, with an average of 43
  - Sites of presentation variable, although back/thorax most common in men and the arm or leg most frequently involved in women
  - Clinical diagnoses varied, but were usually “atypical nevus v. melanoma”, and in younger patients also included “rule out congenital nevus”
  - 10 cases represented routinely processed specimens; 14 cases represented referrals
NMM: Follow-up

- Only 14 cases with a greater than 3-year follow-up
- 8 of the 14 cases have metastasized to lymph nodes (more than one node); 4 with additional systemic metastases
- Two patients died of metastatic melanoma less than three years after diagnosis at ages 35 and 66
- 5 of 8 patients with metastasizing tumors were men, as were the two patients who died with widespread systemic metastases
- All tumors treated initially with wide local re-excision; 20 of the 24 cases had sentinel lymph node sampling and/or lymph node dissection. One patient who died had a positive sentinel node (axillary); the other patient had a negative sentinel node

NMM: Histopathologic Features

- Two major growth patterns:
  - Nodular - resembling intradermal nevus
  - Verrucous - resembling congenital nevus
- Tumors averaged approximately 2 mm in thickness
  - range from 0.5 mm to 4.0 mm
- No ulceration noted
Histologic Features of “Nodular” Nevoid Melanomas

- Pagetoid spread often not conspicuous
- Hypercellularity with loss of the “nested” growth pattern – coalescence of nests and “consumption” of the epidermis are common findings
- Often demonstrate expansile irregular shaped nests at junction and in the dermis – expansile large nests often asymmetrically dispersed in dermis – usually represent invasive melanoma

Histologic Features of “Nodular” Nevoid Melanomas

- Often demonstrate “pseudomaturation” at scanning magnification with melanocytes toward the base appearing smaller than melanocytes at the junction or in the superficial papillary dermis
- However cytologic examination usually reveals atypia even of smallest melanocytes toward the base
  - Nucleoli sometimes evident
  - Irregular nuclear membranes
  - Mitoses
Histologic Features of “Nodular” Nevoid Melanomas

- Usually asymmetric and may demonstrate “shouldering”/radial growth at edges
- Asymmetry of pigment deposition and inflammatory infiltrates sometimes exhibited
- Presence on sun-damaged skin a helpful clue for melanoma
- Sometimes associated with benign nevus components

Histologic Features of “Nodular” Nevoid Melanomas

- Cytologic features
  - Melanoma cells usually atypical – may show marked cytologic atypia or occasionally only mild atypia
  - Mitoses identified in all cases (ranging from 1-2 to 5-7 mm²)
  - Although mitoses were identified in the deeper portions of the tumors in all cases, only rare atypical mitoses were observed
  - Occasionally the task of diagnosis is made easier by the identification of bizarre tumor cells or by multiple mitoses in a single HPF in an adult patient
Nevoid Melanomas resembling “Congenital” Nevi

- Usually young patients, often females, often on head and neck/scalp
- Papillomatous/verrucous architecture
- Overlying thinned epidermis with a focal junctional lentiginous or nested component
- Mild decrease in cell size with increasing depth, representing “pseudomaturation”
- Deep margin occasionally shows infiltrative growth pattern with insinuation between dermal collagen bundles
- Coalescent sheets of tumor cells and hypercellularity typical
- Focal nuclear atypia with occasional prominent nucleoli; hyperchromasia less striking than in nodular variant
- Conspicuous dermal mitotic activity with deep mitoses usually observed
- Atypical mitoses very rare
Histologic Differences: Nevoid Melanoma and “Congenital” Nevus

- More than 3 mitoses present in dermis (in adult), unless patient is undergoing hormonal therapy or is pregnant favors melanoma
- Nucleoli visible at base favors melanoma
- Sometimes maturation with depth not apparent or focal “pseudo-maturation” observed

According to...

- NS McNutt
  - Immunohistochemistry
    - Nevoid melanoma generally HMB-45 positive at base
    - Nevi generally HMB-45 negative at base
    - Nevoid melanoma generally MIB-1/Ki-67 positive at base
    - Nevi generally MIB-1/Ki-67 negative at base

- A. Zembowicz, et al
  - Local recurrence rate is 50%
    - high recurrence rate reflects the fact that many of the primary biopsies were misdiagnosed as benign melanocytic nevi, resulting in insufficient local treatment
  - Overall mortality in nevoid melanomas is comparable to that of classical melanoma of similar tumor thickness
  - These tumors do NOT behave better than other melanomas
Take Home Lessons / Bottom line

- Study the cytology of melanocytic lesions as carefully as you study the architecture
- Hypercellularity, asymmetry, marked nest size variation, solar damage, and mitoses/atypical mitoses may prevent you from making serious mistakes
Molecular Studies

Useful to identify high-risk lesions

High Risk:
- homozygous 9p21 deletions
- 6p25 gains
- 11q13 gains

Low Risk:
- BRAF<sup>V600E</sup>/BAP1<sup>loss</sup> mutations
- HRAS mutations
- isolated 6q23 deletions
- no copy number aberrations
References


References (cont.)

Atypical Lentiginous Melanocytic Proliferations

Occurring on

Sun-Damaged Skin / “Solar” Melanoma

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“Solar Melanoma”

- Lentiginous lesions on severely sun damaged skin may be challenging
  - Lentiginous melanocytic proliferations show a “skip” pattern of involvement of the skin/multifocal growth pattern
  - Sampling is a vexing problem – clinical considerations/limitations may affect histologic diagnosis
  - Patients with chronically sun damaged skin may show a “field effect” of solar activated melanocytes - how much margin is sufficient?
  - Lentiginous melanocytic proliferations require multiple levels for optimal evaluation

“Solar Melanoma”

- Lentigo maligna = Melanoma in situ on sun-damaged skin demonstrating a prominent lentiginous growth pattern
  - Strictly a clinical term, but often used to describe a common growth pattern of melanoma in situ on severely sun damaged skin
“Solar Melanoma”

For lesions judged to fall short of melanoma in situ we use the following terms

- **Low Grade** (mildly to moderately)
  - Mildly atypical lentiginous melanocytic proliferation/atypical lentigo – rarely use this diagnosis
  - Solar lentigo usually demonstrates some club-shaped elongation of the rete ridge epidermal growth pattern
  - Moderately atypical lentiginous melanocytic proliferation/nevus

- **High Grade** (severely/MIS)
  - Severely atypical lentiginous melanocytic proliferation – should be treated like melanoma in situ

“Solar Melanoma”

- These proliferations demonstrate
  - Atypical melanocytes dispersed in a “back-to-back” growth pattern along the DEJ
  - Atypical single melanocytes predominate over nests
  - In high-grade lesions, nests are often irregular in size and shape, and are usually composed of cytologically atypical melanocytes
  - Most of these lesions show atrophy of the epidermis with effacement of the normal rete ridge pattern and associated severe solar elastosis
“Solar Melanoma”

- Normally one melanocyte/5 keratinocytes or so
- Mildly atypical lentiginous melanocytic proliferation
  - Increased numbers of atypical melanocytes but not dispersed in a “back-to-back” growth pattern, usually no nests
  - Usually effacement of the normal rete ridge growth pattern in contrast to mere solar lentigo
  - Lesion small; may have abundant accompanying pigment incontinence
Mildly Atypical

“Solar Melanoma”

- Moderately atypical lentiginous melanocytic proliferation
  - Increased numbers of atypical melanocytes with occasional irregular-shaped nests
  - Some lateral/radial growth, but not extensive – fairly well circumscribed
  - Effacement of rete ridge pattern and severe solar elastosis
  - Usually less than 6 mm in size*
  - No significant adnexal involvement or pagetoid spread
“Solar Melanoma”

- Severely atypical lentiginous melanocytic proliferation
  - “Back-to-back” growth pattern of atypical melanocytes and irregular-shaped nests
  - Lateral/radial growth prominent – poorly circumscribed
  - Effacement of rete ridge pattern, severe solar elastosis, and often a lichenoid and/or perivascular inflammatory host response
  - May be > 6 mm, usually smaller than MIS*
  - No deeply infiltrative adnexal involvement and minimal pagetoid spread
  - Few if any atypical nevus giant cells along the DE junction
“Solar Melanoma”

- Melanoma in situ (lentigo maligna)
  - Large, confluent junctional nests but single atypical cells predominate
  - Generally hypercellular lesions
  - Prominent adnexal involvement
  - Pagetoid spread noted and may be prominent
  - Atypical nevus giant cells dispersed along DE junction
  - Conspicuous inflammatory host response (often with plasma cells)
  - Often large size (usually > 6 mm, may be 10 mm or more) – may be clinically unimpressive
  - Usually high grade cytologic atypia
“Solar Melanoma”

- Most important features of melanoma in situ
  - Cellular lesions
  - Prominent adnexal infiltration
  - More than incidental pagetoid spread
  - High grade cytologic atypia
  - Atypical nevus giant cells noted
  - Discohesion of atypical melanocytes may be noted along the junction; “clefting” at junction may be prominent
  - Large clinical size
“Solar Melanoma”

- Lentigo malignas/MIS often show “skip areas” and may be multifocal in a background of severely sun-damaged skin
“Solar Melanoma”

- Practical Uses for Immunohistochemistry
  - HMB-45, tyrosinase and SOX-10 may be helpful in determining the number and location of melanocytes in equivocal cases
  - MART-1/Melan A not as useful because they may stain pigmented keratinocytes as well as melanocytes and thus may overestimate/exaggerate the lesion
  - Melanocyte markers may aid in cases of equivocal invasion, especially in the absence of inflammation
  - S-100 stain rarely useful because of background staining (dendritic cells/LH cells, etc.)
  - Ki-67 and p16 may be helpful in distinguishing invasive melanoma from accompanying benign nevus
“Solar Melanoma”

- Invasion
  - May be difficult to recognize because of extensive involvement of adnexae*
  - Marked inflammatory infiltrates may obscure individual invasive tumor cells
  - Invasive component may be cytologically bland/nevoid and thus difficult to distinguish from a benign nevus
  - Cellularity of severely sun damaged dermis may mimic invasion
“Solar Melanoma”

- Margin status may be difficult to evaluate in cases of MIS, lentigo maligna type, and this is a frequent source of concern for both clinicians and pathologists.
Solar Melanoma

- “Field Effect” of Activated Melanocytes and Effects on Treatment Decisions
  - In cosmetically sensitive areas (face particularly) may be impossible to obtain 5 mm – 1 cm tumor free margins
  - 2-3 mm margins with close clinical follow-up may have to suffice
  - Narrower margins may be preferable to cosmetic disfigurement particularly in non-invasive lesions (natural history of lentigo maligna important consideration)
    - Topical agents may be useful in the treatment of MIS
    - Staged excisions using rapid permanent section protocol +/- tyrosinase/SOX-10 staining preferable to Mohs technique alone
Clinical Photos

“Solar Melanoma”

- Bibliography