Unusual variants of melanoma

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Melanomas that don’t follow the rules

- Desmoplastic melanoma
- Nevoid melanoma/minimal deviation melanoma
- Melanoma with atypical immunohistochemical features
- Melanoma in non-cutaneous sites
- Animal-type melanoma
- Malignant blue nevus
- Melanoma with metaplastic change
- Signet ring cell melanoma
- Rhabdoid melanoma
- Myxoid melanoma
- Small cell melanoma
Rule-breaking melanomas

**Prognostically significant**
- Desmoplastic melanoma
- Mucosal melanoma
- Animal-type melanoma

**Cool variants with no prognostic significance**
- Atypical immunohistochemical features
- Nevoid melanoma
- Malignant blue nevus
- Metaplastic melanoma
- Signet ring cell melanoma
- Rhabdoid melanoma
- Myxoid melanoma
- Small cell melanoma
58 year old female with history of "dysplastic nevus" of gingiva 2016

Melanoma in situ of gingiva
Melanoma in non-cutaneous sites

- Mucosal melanoma
  - 1-2% of all melanomas
  - Median age 70
  - No racial predilection
  - M:F = 0.5
  - Only head and neck melanoma has staging system
  - Advanced disease at presentation: 6-25% nodal, 10% distant metastasis

Mucosal melanoma
Pathogenesis and diagnosis

- KIT amplification/activation in 14-39%
- NF1 mutation in 20% anorectal melanoma
- 10-fold lower mutational burden than conventional melanoma but copy number alterations common
- Diagnostic pitfall: can be S-100 negative, but Melan-A and HMB-45 usually positive
- In lesions without melanoma in situ, always consider metastatic clear cell sarcoma

Mutation distribution in 16 female genital tract melanomas

- 12/16 cases had mutations identified
  - 3 of 4 negative cases were MIS
- **TP53, KIT** in 25% each
  - mutually exclusive
  - no difference between vulvar and vaginal frequency
- **BRAF** in 19%, p.V600E (2) and p.G466V (1), all vulvar
- **NRAS** 13%, p.G13D and pG12S--mutually exclusive with **BRAF**, all vulvar

Mutated vulvar melanomas

BRAF mutant

KIT mutant

ATRX/P53 mutant

NRAS mutant
Rapidly growing scalp nodule in 33 year old male
Rapidly growing scalp nodule in 33 year old male
Animal-type (pigment-synthesizing) melanoma

- Systematic review of 190 reported cases
- Marked overlap with pigmented epithelioid melanocytoma
- Average age 27 years, median Breslow 3.6 mm
- SLN involvement in 40%
- Only 5 deaths reported (short followup)
- Rare melanoma subset with better prognosis than melanoma of similar depth

Unusual melanoma variants with prognosis similar to conventional melanoma
Melanomas with atypical IHC

• Aberrant marker positivity and complete loss of all melanoma markers more common in metastases

• However, molecular alterations are frequently stable, can be exploited in diagnostically difficult cases

• 1630 benign and malignant soft tissue tumors in 6 studies: BRAFv600e found in 1 MPNST, 4 schwannomas, and 3.5% of clear cell sarcomas

## Lineage-divergent IHC markers in melanoma

<table>
<thead>
<tr>
<th>Aberrant markers</th>
<th>Incidence (no cases tested)</th>
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<tbody>
<tr>
<td>FLI-1</td>
<td>5% (107)(^1)</td>
</tr>
<tr>
<td>Cytokeratin AE1/3</td>
<td>12% (70)(^2)</td>
</tr>
<tr>
<td>CAM 5.2</td>
<td>2-10% (&gt;100, various)(^3)</td>
</tr>
<tr>
<td>EMA</td>
<td>24% (70)(^4)</td>
</tr>
<tr>
<td>Desmin</td>
<td>Isolated cases, esp H&amp;N</td>
</tr>
<tr>
<td>CD34</td>
<td>30% (30)</td>
</tr>
</tbody>
</table>

Too nonspecific to be useful (positive in >30% of cases): WT-1, CD31, CD68, CEA, CD10, bcl-2, Factor XIIa, CD138, CD99, MDM2

\(^1\) Ramani N et al. *J Cutan Pathol*. 2017 Sep;44(9):790-793
\(^3\) Ben-Izhak O et al. *Am J Dermatopathol* 16(3): 241-6
89 year old with desmoplastic melanoma scalp, treated with excision and radiation.
Recurrent nodule, s/p XRT

Sox10
S-100
MiTF
Right thigh melanoma 2005 with multiple local recurrences and XRT
Undifferentiated/dedifferentiated melanoma

• 26 reported cases
  – 2/3 have complete loss of melanoma markers
  – 1/3 have heterologous differentiation (most often rhabdomyosarcoma)

• Consider before diagnosing undifferentiated pleomorphic sarcoma in lymph node

• In my experience, occurs after multiple treatments, especially radiation
Nevoid melanoma vs. minimal deviation melanoma

• **Nevoid melanoma**: Schmoekel C, 1985: “primary cutaneous melanoma with features suggestive of benign nevi”
  – Prognosis same as conventional melanoma

• **Minimal deviation melanoma**: Reed RJ, 1988: nodular melanoma with cytology intermediate between nevus and melanoma (small cell, Spitz, spindle, desmoplastic variants)
  – Conflicting data on prognosis
Workup of suspected nevoid melanoma

• IHC: Ki-67, HMB-45, p16
• FISH is helpful: amplification of 6p25 in 49% and 8q24 in 27% (especially lesions with nevoid histology)

Yélamos O et al. J Cutan Pathol. 2015 Nov;42(11):796-806
Nevoid melanoma

- ~3% of melanomas
- Non-uniform criteria
  - 55% plaque-like: parallel theques
  - 45% polypoid: resemble compound nevi
  - “pseudomaturation”: cell size shrinks, but nucleus remains same
  - DE junction most helpful
  - Deep mitoses

Idriss et al. JAAD 2015 Nov; 73(5):836-42
59 year old female with lesion on medial foot noted by podiatrist

Diagnosis: Nevoid melanoma, 0.6 mm in depth
Rapidly changing nodule on scalp of 65 year old male
Melanoma arising in blue nevus (malignant blue nevus)

- Systematic review, 91 reported cases
  - Slight male predominance, mean age 45
  - 20% metastatic at time of diagnosis
  - Scalp > face > back location

- Genomic alterations, 12 cases:
  - GNA11 33%, GNAQ 25%, BRAFV600E 25%
  - SF3B1 and BAP1 mutations noted in 3 and 1 lesions harboring GNAQ or GNA11

Griewank KG et al. Mod Pathol. 2017 Jul;30(7):928-939
MABN with loss of BAP1 (case 1). A, Dense, nodular dermal infiltration. B, Packed nest of atypical melanocytes, mitotic figures (*). C, Patches of common BN (N) adjacent to melanoma nests (M). D, Same area as C; positive HMB45 staining in nevi and melanoma cells. E, Same area as C; nuclear expression of BAP1 is positive in BN, negative in melanoma nests (BAP1 IHC).
65 year old male with large desmoplastic melanoma of scalp
Melanoma with (osteo)sarcomatous differentiation
Metaplastic melanoma

- Divergent differentiation: fibroblastic, myofibroblastic, Schwannian, smooth muscle, rhabdomyosarcoma, osteosarcoma, chondrosarcoma, ganglioneuroblastic, neuroendocrine, epithelial
- Most frequent in melanomas of acral or desmoplastic origin
- Melanoma markers frequently lost in metaplastic region, which express markers of divergent differentiation

Metaplastic melanoma

• Metaplastic melanoma may express MyoD1, desmin, actin, FLI-1, ERG
• When patient with history of melanoma presents with a possible sarcoma, consider this diagnosis
• Comparison with prior tumor, especially molecular, paramount
Signet ring cell melanoma

- 23 reported cases, 50% metastatic
- EM: accumulation of vimentin filaments
- S-100, Melan-A and melanoma cocktail+

73 year old male presents with hemorrhagic temporal lobe lesion.
Metastatic balloon cell melanoma

S-100

MCK

MiTF

PAX2, PAX8, CAIX, CD10, CK7, CK20, EMA all negative
Balloon cell melanoma

- Accumulation of degenerating melanosomes leads to ballooned clear cytoplasm
- May be PAS+
- Cytology may be deceptive/similar to balloon cell nevus
- Differential diagnosis: clear cell carcinoma, atypical fibroxanthoma, liposarcoma, chondrosarcoma, clear cell sarcoma, PEComa, myoepithelial carcinoma, germ cell tumor
60 year male with 0.7 mm acral lentiginous melanoma right plantar foot and satellite nodule
Myxoid melanoma

- Abundant myxoid matrix thought to be stromal in origin
- IHC features usually typical of melanoma
- Small series do not show differences in clinicopathological features or outcome

Myxoid melanoma
Small cell melanoma

• More common in melanoma arising in congenital nevi
• Overlap with so-called minimal deviation melanoma, small cell variant
• However, others suggest more rapid growth/aggressive course

Rapidly growing flank nodule in 55 year old male
Myogenin, actin negative
INI-1 and EMA retained
Rhabdoid melanoma

• Distinct from melanoma with rhabdomyosarcomatous differentiation (however, often used interchangeably)
• Melanoma with rhabdoid appearance, typically expresses melanoma markers
• This case unusual with keratin expression

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Summary

• Know which zebras are truly different from conventional melanoma (mucosa, nevoid, animal-type melanoma)

• When confronted with atypical staining in a lesion suspected of melanoma, comparison with original paramount, examine entire lesion

• Immunohistochemical markers may change or disappear with recurrence, but molecular alterations typically stable
Aloha and
SAFE TRAVELS