Practical Use of Staining & Immunohistochemistry in the Diagnosis of Melanocytic Lesions

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Desmoplastic Malignant Melanoma
Desmoplastic Malignant Melanoma

- Arise most often in setting of chronically sun-exposed skin
- Patients usually aged 60 and over; head and neck most common
- Painless indurated plaque or scar-like thickening; some begin as small papule or nodule
- Pigmentation usually related to associated lentigo maligna
Desmoplastic Melanoma - Microscopic

- Dermal spindle cell proliferation, resembling fibroblasts with varying degrees of atypia and usually non-pigmented
- Embedded in fibrous or fibromyxoid stroma
- Lymphocytic aggregates
- Sometimes neurotropism, or formation of nerve-like structures
- Junctional changes minimal to absent in ½ of cases; can be features of lentigo maligna
- May be “pure” (≥ 90%) desmoplastic or mixed with non-desmoplastic foci
- IHC positive for S100, SOX10, NGFR; negative for melanosome markers except in combined types
Desmoplastic Malignant Melanoma

- Typical clinical setting
- Frequent junctional changes
- Lack of symmetry
- Lack of maturation
- Mitoses
- Prominent lymphocytic infiltrate
- Immunohistochemistry
Desmoplastic Malignant Melanoma – Differential Dx

- Desmoplastic Spitz nevus
- Sclerosing cellular blue nevi (diffusely HMB45+)
- Immature scars
- Dermatofibroma, atypical fibroxanthoma, sarcomatoid carcinoma, leiomyosarcoma
- Neurofibroma (Husain and Silvers, J Cutan Pathol, 2013)
Desmoplastic Malignant Melanoma - Prognosis

• High recurrence rate
  – Neurotropism may play a role here, as well as diagnostic problems
• Up to 1/3 of these lesions metastasize
• Behave more like sarcoma; regional lymph node involvement less common (especially in “pure” desmoplastic melanomas)
Unusual Melanocytic Tumors

1. Squamo-melanocytic tumor
2. Neurocristic hamartoma
Squamo-Melanocytic Tumor

• Reported in 1999 by Pool, Manieei, Clark and Harrist
• Purple-black nodule on face of middle-aged or older persons
• Recurrence, metastasis not reported; however, outcome of other, non-reported cases is uncertain
Squamo-Melanocytic Tumor

- Atypical epithelial cells with admixed epithelioid to spindled cells and pigment production.
- Atypical keratinocytes are cytokeratin positive; melanocytes express S100 and HMB45
Squamo-Melanocytic Tumor

- An 83 year old man underwent FNA of a cervical lymph node, showing melanoma.
- Biopsy of preauricular skin showed these changes:
- Parotidectomy showed metastatic melanoma in intraparotid node.
Neurocristic Hamartoma

- Controversial “entity”
- Relationships to patch and plaque-like blue nevi
- “Schwannian” elements may represent differentiation within a nevus rather than composite tumor
- Variant: pilar neurocristic hamartoma
- Relationship to “animal melanoma”
Melan-A

Ki-67
Metastatic Melanoma

• Skin is most common site of melanoma metastasis (56%)

• Local, regional, or distant extension by lymphatic, hematogenous, angiotropism, or perineural routes

• One study: 8.3% of patients presented with skin metastasis as only manifestation of disease

• Leg>scalp>arm>face
Metastatic Melanoma

- Solitary pigmented nodule most common, but also zosteriform, blue nevus-like, erysipelas-like, sclerodermiform, purpuric lesions
- Satellite metastasis: within 2 cm of primary site
- In-transit metastasis: >2 cm from primary site but not reaching ipsilateral regional lymph nodes
Metastatic Melanoma - Microscopic

- Well-circumscribed dermal nodule, composed of epithelioid cells, with little inflammation but surrounding fibrosis
- Epidermotropism in ≤ 5% of cases
- Angiolympathic invasion in 5%
- Melanocytic differentiation indicated by fine cytoplasmic melanin granules
Metastatic Melanoma- IHC

- S100: highly sensitive but not specific
- Melan-A and HMB45: more specific but negative in $\leq 15\%$ of metastatic melanoma cells
- Tyrosinase is sensitive but staining may be seen in Schwann cells
- SOX10 highly sensitive, useful in distinguishing melanocytes from melanophages
- Ki-67 useful in nevoid cases
- PDL1 stain: may be helpful to assess for susceptibility to immune checkpoint blockade therapy
Metastatic Melanoma – Differentiation from Primary Melanoma

- Primary melanoma losing junctional component due to trauma or prior biopsy
- Primary dermal melanoma
  - Has lower levels of staining for p53, Ki-67, cyclin D1 than nodular or metastatic
Metastatic Melanoma – Differentiation from Primary Melanoma

• Epidermotropic metastatic melanoma
  – Dermal component broader than the junctional component favors metastatic
  – Accompanying benign nevus favors primary
  – Sheet-like growth, disturbance of surrounding stroma, mitotic activity
  – Elevated N:C ratio
Regression in Malignant Melanoma
Regression in Malignant Melanoma

- Three phases: inflammatory, reduction in tumor with early fibrosis; extensive fibrosis with telangiectasia
- Controversy regarding role in prognosis
- Extensive regression with involution of the primary tumor probably has adverse prognosis
Presentations of Completely Regressed Melanoma

- Vitiligo-like
- Lichenoid
- Tumoral melanosis
Special Staining
Tyrosinase
Ki-67
A p16-Ki-67-HMB45 immunohistochemistry scoring system as an ancillary diagnostic tool in the diagnosis of melanoma

Arnaud Uguen, Matthieu Talagas, Sebastian Costa, Sandrine Duigou, Stéphanie Bouvier, Marc De Braekeleer, and Pascale Marcorelles
Scoring System

Ki-67
- 0: <2%; 1: 2-5%; 2: 6-10%; 3: 11-20%; 4: >20%

P16
- 0: >50%; 1: 11-50%; 2: 1-10%; 3: 0%

HMB45
- 0: gradient present; 1: doubtful/inconclusive gradient; 2: gradient absent

Total score 0-9; nevi: score <4; primary melanoma: score ≥ 4
Desmoplastic Melanoma

“New” Markers:

• P75 nerve growth factor receptor
  – All spindle cell melanomas express in at least 10% of cells
• KBA.62 (recognizes an unknown antigen expressed by melanomas)
  – About ¾ stain with this marker; average of 39% of cells stain
• SOX10 (a transcription factor important in nervous system development)
  – In one study, strongly stained all desmoplastic melanomas
  – Less likely to stain fibrocytes and histiocytes
  – Its gene expression may be regulated by MiTF, but MiTF is weak or negative in desmoplastic melanomas
Plaza et al: Diagnostic Pathology

Performed an immunohistochemical analysis of desmoplastic melanoma using 14 antibodies; they conclude that a panel of S-100p, WT-1, SOX-10, p75 and nestin may be optimal for diagnosis.
Melan-A positive dermal cells in malignant melanoma *in situ*

Mary Elizabeth Danga, Ron Yaar, Jag Bhawan

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ALK Fusion Spitz Tumor
BAP-Inactivated Spitzoid Nevus
PRAME Expression in Melanocytic Tumors.

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PRAME

- Preferentially Expressed Antigen in Melanoma
- Diffusely expressed in several types of melanoma (35% of desmoplastic melanomas)
- 86.4% of melanocytic nevi completely negative
  - Positivity seen – usually in a minor subpopulation – in 13.6% of common, traumatized, dysplastic, and Spitz nevi
Desmoplastic Spitz Nevus
ALK-1
Superficial Spreading Melanoma
HMB45
Ki-67
Problems with Biopsies

- Thin shave biopsies are undesirable; small, partial biopsies may not be representative of the entire lesion
- Compression or crush may give false impression of maturation
- Tangential sectioning may give false impression of confluence
- Tissue artifacts
- Definitive diagnosis may not be possible
Conclusion