Morphologic Considerations in the Diagnosis of Melanoma

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Congenital Nevus

- Present at birth or appears during the first year of life
- 1% of newborns have a small congenital nevus
- Large congenital nevus has frequency of 5-15 cases/100,000 births
- Giant (bathing trunk) nevus has frequency of 5 cases/100,000 births
Congenital Nevus

In adults:
Small: < 1.5 cm
Intermediate: 1.5 - 20 cm
Giant: > 20 cm
Large nevi on scalp or back (especially those with satellite nevi) can involve the CNS

Congenital Nevus - Microscopic

- Large diameter, involve reticular dermis or subcutis
- Splaying of collagen
- Organized around adnexal structures or neurovascular plexuses
- Atypical features: pagetoid migration or confluence of junctional nests, proliferative nodules
Congenital Nevus – Proliferative Nodules

- Essentially new nevi developing in the dermal component of a congenital nevus; can develop at birth or later in life
- Become smaller and regress over time
- Predilection for nevi on the trunk
- Epithelioid, spindled, or small (melanoblasts)
- Some sharply demarcated; others blend with surrounding nevus cells
- Very young patients may have high cellularity and striking atypia; atypical proliferative nodules have striking atypia, sharp circumscription, and pushing borders
Proliferative Nodule vs Melanoma

- Melanoma favored by expansive pattern, necrosis, obvious cytologic atypia (pleomorphism, nuclear enlargement and hyperchromasia, numerous and atypical mitoses)
- However, numerous mitoses have been reported in lesions with the biologic “behavior” of proliferative nodule
Blue Nevus and Cellular Blue Nevus

- Traditional, dendritic blue nevus develops in adults, most often < 40 years
- Usually dorsal extremities and face
- Well demarcated, slightly raised papules

Cellular Blue Nevus

- Duration months to years prior to diagnosis; sometimes present at birth
- Typically scalp, back, buttocks
- Nodules varying from a few millimeters to several centimeters in size
Blue Nevus - Pathology

- Non-circumscribed dermal lesions composed mainly of dendritic melanocytes
- Collagen is sclerotic; markedly sclerotic lesions referred to as sclerosing blue nevus
- Cells bipolar and spindle shaped
- Scattered melanophages, no cytologic atypia, typically no mitotic figures
- Positive for HMB45, SOX10, melan-A; may be S100 negative
Cellular Blue Nevus - Pathology

- Well-circumscribed nodular tumors; plaque-like variant occurs
- Most pigment in melanophages
- Bulbous extension into subcutis
- Well-defined nests of ovoid to fusiform cells; they are usually oriented parallel to long axis of nests
- Lack crowding, pleomorphism, nuclear atypia, hyperchromasia
- Sheets or fascicles of spindled to ovoid cells
- Necrosis usually absent; mitoses absent or low numbers (< 1/mm²)
- May involve capsule or trabeculae of lymph nodes
Blue Nevus – Differential Diagnosis

- Hypopigmented blue nevi can resemble other non-melanocytic spindle cell proliferations, including amelanotic melanoma
- Differentiation can be achieved by clinical correlation, examination of morphology and immunohistochemistry
- Rarely mimicked by a blue nevus-like melanoma, or by a blue-nevus-like metastatic melanoma, including an ocular melanoma metastasizing to the skin
- Clinical history is essential in these cases
- Molecular differences in malignant lesions include BAP1 inactivating mutations
Cellular Blue Nevus – Distinction from Melanoma

CBN is composed of large spindled or epithelioid cells, extends deeply, lacks maturation descent, may feature an occasional mitotic figure.

Features favoring melanoma:
- Cell necrosis
- Large pleomorphic epithelioid cells
- Crowding, associated with increased N:C ratios
- Atypia, pleomorphism
- Frequent mitoses (> 2 mm²)
- Infiltrative growth

But: there are exceptions (may need immunostaining for BAP1, FISH analysis to detect copy number changes of chromosomes 3,6,8).
Malignant Blue Melanoma

• May arise in a pre-existing blue nevus, at the site of a previously excised blue nevus, or de novo with a resemblance to cellular blue nevus
• Scalp is most common site
• Presents as a rapidly growing nodule
Malignant Blue Melanoma - Microscopic

- Dense dermal sheets of large spindled and epithelioid melanocytes
- Severe atypia and high mitotic activity
- Loss of BAP1 expression supports malignancy even with low mitotic activity
- Central areas of tumor necrosis
- Changes of pre-existing blue nevus @ periphery
- Ki-67 proliferation index often > 20%
Spindle and Epithelioid Cell Nevus (Spitz Nevus)

- Most common in younger individuals
- Often pink or flesh-colored, but may be pigmented
- May evolve somewhat rapidly
- Display symmetry, circumscription

Spitz Nevus

- Symmetry and circumscription
- Spindled and/or epithelioid melanocytes in discrete nests along junctional zone; transepidermal elimination occurs
- Kamino bodies
- Edema and telangiectasia
- Maturation descent
Pigmented Spindle Cell Nevus of Reed

- Well circumscribed, uniformly pigmented, dark brown-black
- Typically extremities (particularly thigh), young adults, predominantly women
- Atypical pigmented spindle cell tumors (APSCT) are larger, asymmetrical, with irregular borders and color variation

Pigmented Spindle Cell Nevus - Microscopic

- Small, well circumscribed, symmetrical
- Plate-like acanthosis
- Compact fascicles of uniform, slender spindle cells at junction
- Pagetoid changes limited to lower ½ of epidermis
- May involve papillary dermis and appendages
- May have pigmented Kamino bodies
- APSCTs have diameter > 6 mm, poor circumscription, asymmetry, epidermal effacement, ulceration, single cell melanocytic hyperplasia, pagetoid change, mitoses, cytologic atypia
11P and/or HRAS-Mutated Spitz Nevus

- Represents a subset of Spitz tumors
- Many previously described as desmoplastic nevus
  - Angiomatoid Spitz nevus is a histologic variant of desmoplastic nevus
- Clinically, these lesions can be mistaken for fibrohistiocytic lesions (dermatofibroma or epithelioid cell histiocytoma)

11P and/or HRAS-Mutated Spitz Nevus - Microscopic

- Spitz nevi have characteristic histology
- Typically intradermal, but may be compound
- Small nests and single cells embedded in a desmoplastic or sclerotic stroma; single cells predominate at the base
- Nuclei enlarged; often have nuclear pseudoinclusions
- Express melan-A, SOX10, S100; HMB45 stratification, low proliferative index
- HRAS mutations are rare in melanoma
Kinase Fusion Spitz Tumors

- Occur in younger patients as compared to fusion-negative Spitz tumors
- ALK-fusion Spitz tumor (ALKoma)
  - May be same as plexiform Spitz nevus, accounting for 10% of Spitz tumors
  - Adolescents, solitary dome-shaped lesions on extremities, usually amelanotic
  - Most ultimately classified as atypical Spitz tumor (<50%), spitzoid melanoma accounting for < 10%
  - Overexpression of ALK in melanoma usually not due to ALK kinase fusions but by other mechanisms
  - FISH panels usually negative for copy number gains or losses in ALK-fusion Spitz tumors
  - Lymph nodes can be involved; distant metastases not reported to date

ALK Fusion Spitz Tumor - Microscopic

- Compound or mainly intradermal
- Cells arranged in plexiform pattern with sweeping fascicles
- Melanocytes fusiform and amelanotic
- No overt pleomorphism; mitoses present but superficial
- ALK IHC is positive, correlating with presence of a kinase fusion that can also be detected by FISH
NTRK1 and BRAF-Fusion Spitz Tumors

NTRK1
- Accounts for 10-15% of Spitz tumors
- No age or site predilection
- Often verrucous or plaque-like
- Most in Spitz nevus or atypical Spitz tumor categories, but have been a few spitzoid melanomas

BRAF
- Accounts for 5% of Spitz tumors
- One report: 17% positive for melanoma FISH assay but were apparently not diagnostic of melanoma
(Other tumors involve ROS1, RET, MET, NTRK3)
**NTRK1 and BRAF-Fusion Spitz Tumors - Microscopic**

**NTRK1**
- Epidermal hyperplasia and Kamino bodies

**BRAF**
- Two distinct patterns
  - Sheet-like growth with large, atypical epithelioid cells having nuclear atypia
  - Dysplastic nevus-like with moderately atypical melanocytes; often epidermal hyperplasia, no Kamino bodies

IHC can be used for these Spitz tumors as a surrogate for the translocation.

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**BAP1-Inactivated Spitzoid Nevus (BAPoma)**

- May be the same lesions previously described as ‘halo Spitz nevus
- Sporadic or in context of BAP1 hereditary cancer predisposition syndrome
- 5-10 mm tan-red, dome shaped lesions, on sun-exposed skin
- Sporadic and hereditary lesions carry the BRAF<sup>v600E</sup> mutation, lack HRAS mutations
  - In combined lesions with common melanocytes, all cells have BRAF mutations but only the epithelioid cells have BAP1 inactivation
- The spitzoid nevi have benign course, but BAP1 inactivation can occur in unequivocal melanoma

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**BAP1-Inactivated Spitzoid Nevus - Microscopic**

- Dermal nodule of large atypical epithelioid cells
- Pink to amphophilic cytoplasm, sharp borders
- Moderate pleomorphism, vesicular nuclei, prominent nucleoli
- May be second population of ‘common’ melanocytes
- Mitoses often present but not prominent
- Often inflammatory component
- Lack of features of other Spitz tumors (acanthosis, Kamino bodies)
Metastasizing Spitzoid Tumors of Childhood
Childhood Melanoma

- Clinical features and prognosis similar to adults
- Association with congenital nevi, atypical nevus phenotype, some patients with lichen sclerosus
- But there may be a better outcome than expected in infantile melanoma, “Spitz nevi” with regional nodal metastasis
Differential Diagnosis of Spitz Nevus – Findings Favoring Melanoma:

- Asymmetry, lack of maturation, pagetoid growth with lateral extension
- Pleomorphism, high mitotic rate and atypical mitoses
- In teenagers: fine dusty cytoplasm, marginal or abnormal mitoses, epithelioid intraepidermal melanocytes below parakeratosis, dermal nests larger than junctional nests, mitotic rate > 2/mm², mitoses within 0.25 mm of deep border
- High risk of metastases: age older than 10 years, diameter > 10 mm, ulceration, involvement of subcutis, mitotic rate ≥ 6/mm²
Immunohistochemical Findings Favoring Spitz Nevus over Melanoma:

- HMB45 may be expressed throughout the tumor similar to melanoma, but still less intense staining deep than in superficial cells
- Spitz nevi retain p16 expression; many ASTs and melanomas lose expression (p16 often correlates with CDKN2A loss by FISH)
- Ki-67 <3% in nevi, >15% in melanomas
- Cyclin D1 stratifies in Spitz nevus
- PCNA weak or absent in Spitz
- P53 weak or absent in Spitz
- P27 (cell cycle regulator) increased in Spitz compared to melanoma
- CD99 <5% positive in Spitz
- Neuropilin-2 weak or absent in Spitz
- Osteopontin low in Spitz

Pigmented Epithelioid Melanocytoma

- Melanocytic lesion composed of heavily pigmented epithelioid and dendritic cells
- Metastases limited to regional lymph nodes
- Sporadic or part of Carney’s complex
- Predilection for young people, but can occur in any age group
- Generalized distribution
- Slow-growing pigmented papule or nodule

Pigmented Epithelioid Melanocytoma - Microscopic

- Pure or part of combined nevus
- Heavily pigmented, predominantly dermal (small junctional nests in 30%)
- May be epidermal hyperplasia
- More cellular in center with infiltrative borders
- Epithelioid and dendritic cells with melanophages
- Dendritic cells have vesicular nuclei with prominent nucleoli
- Mitotic activity low
- Large lesions may have ulceration or tumor necrosis
- Some show loss of expression of protein product of PRKAR1A, mutated in many families with Carney complex
Acral lentiginous melanoma

Problems with terminology

Four groups:
- Dome-shaped or polypoid
- Verrucous
- Resembling lentiginous melanocytic nevus
- Predominantly intraepidermal nesting

Nevoid Melanoma

Clinical
- All ages, most in 5th decade (40 years for papillomatous form, 56 years for maturing nevoid type)
- Sexes equally affected
- Arise anywhere on body surface
- No distinctive clinical features; may be papillomatous (or not), small cell, or verrucous, or melanoma with paradoxical maturation
- Papillomatous form resembles nodular intradermal nevus, with moderate pigment and small macular component
- Maturing small cell variant resembles dysplastic nevus
Nevoid Melanoma - Microscopic

- Low-power resemblance to ordinary nevus
- Overall symmetry
- Sharp circumscription
- Limited intraepidermal component
- Monomorphous population of cells

Nevoid Melanoma-Microscopic

- Dermal mitoses
- Monotonous cells in aggregates of high density
- Lack of maturation and subtle cytologic atypia (preserved nucleoli in deep component)
- Patchy dermal inflammation
Nevoid Melanoma – Papillomatous Variant

- Long thin strands of epidermis separate the melanocytes into compartments
- Crowded, hyperchromatic nuclei, scant cytoplasm
- Always mitoses
- Only minor junctional component, giving low-power impression of an IDN

Nevoid Melanoma – “Maturing” Small Cell Variant

- Superficial changes qualify as invasive melanoma
- Merges with small but atypical melanocytes in mid- to deep dermis
- Small hyperchromatic nevoid cells are usually nested, surrounded by dense fibrous stroma