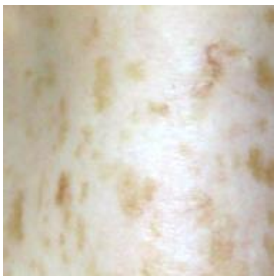
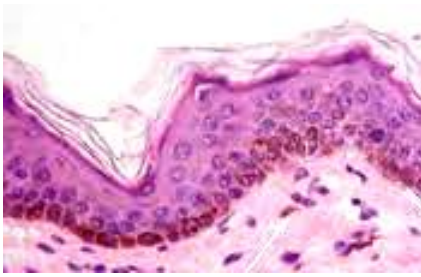
Melanocytic Tumors

IHC: Melanocytes stain with (+) S100, SOX10, HMB45, Melan-A (MART-1), MITF,
However, beware, these are not necessarily specific in isolation. For example, S100 also stains nerves and Langerhans cells, HMB45 and Melan-A can stain pigment in Keratinocytes, and MITF can get histiocytes.

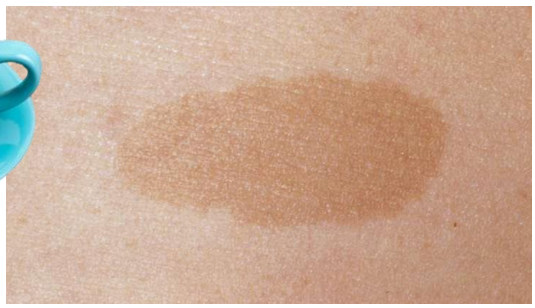
Benign Lesions

Freckles *aka Ephelides*

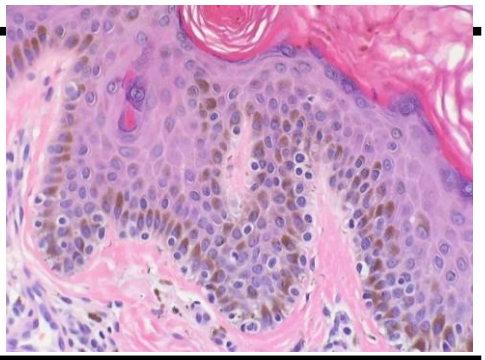
Clinical: clusters of small **Red-brown macules** in sun exposed areas
Micro: Increased melanin in basal layer (normal melanocytes). *No* elongation of rete ridges or nesting.
Extremely common in fair skinned individuals
Lesions darken with sun exposure

Café-au-lait spot/macule

French for "coffee with milk"
Clinical: *Large*, light brown macule
Micro: Increased melanin in basal layer, but otherwise normal (similar to freckles histologically)
Relatively common (~10% population).
Sometimes associated with **NF1**.
If have irregular, jagged borders (like the "coast of Maine"), consider McCune–Albright syndrome with associated polyostotic fibrous dysplasia

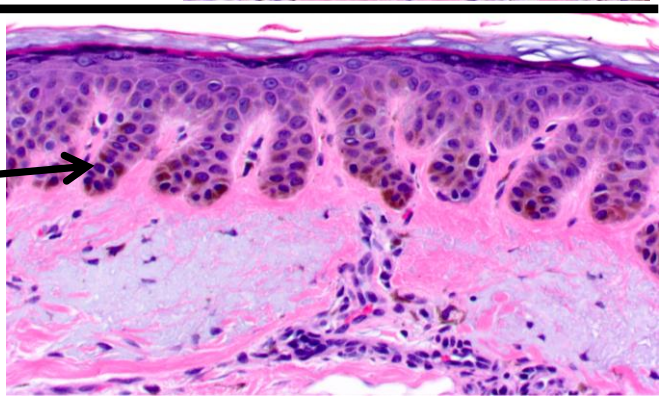
Lentigo simplex



Clinical: Common. Small brown macule(<5mm), Esp. dorsal forearms. Onset in children/adolescence. *NOT* related to sun exposure.

Micro: Hyperpigmented, often elongated rete ridges, usually with increased melanocytes. NO melanocyte nests. NO solar elastosis.
If nests→ Junctional Melanocytic Nevus

Solar Lentigo



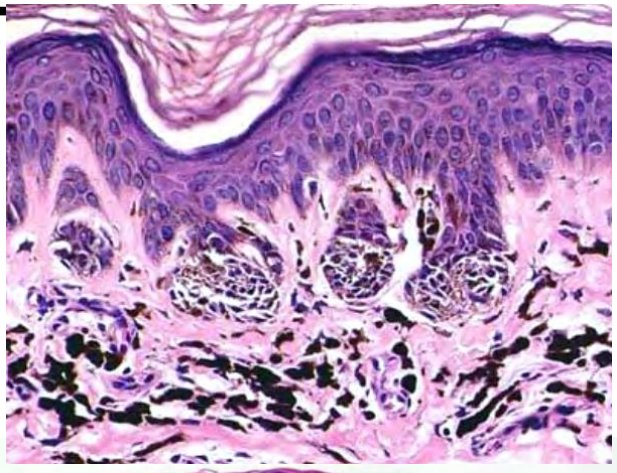
Clinical: Very common brown macule. Due to sun damage. Esp. on face and dorsal hands.

Micro: Hyperpigmented basal layer, often with elongated, clubbed rete ridges. Usually ↑ melanocytes, but not nests. Solar elastosis.
Think ***"Dirty Feet"*** →

Melanocytic Nevus

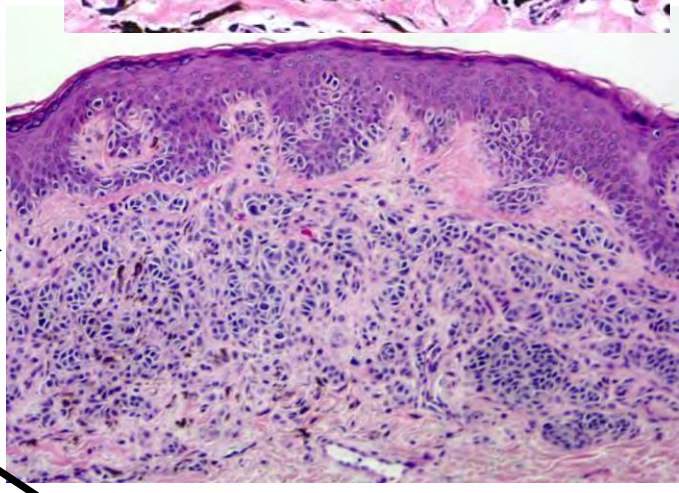
Benign localized proliferations of nevus cells (a type of melanocyte). Defined by the presence of **nests**/theques (clusters of at least 3 cells).

Clinically small (usu. <5 mm), well-circumscribed, symmetrical, evenly colored. All over body, esp. the Trunk.
"Acquired" and grow/accrue during childhood.
Most common with light skin.
Clinical: Light brown macules/papules.
Frequent BRAF (esp. V600E) mutations.



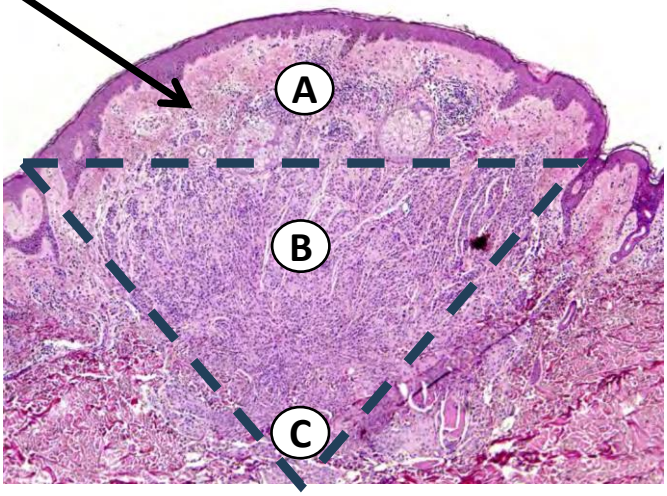
Junctional Nevus
Nests of melanocytes at DEJ only

Compound Nevus
Nests at DEJ *and* in papillary dermis

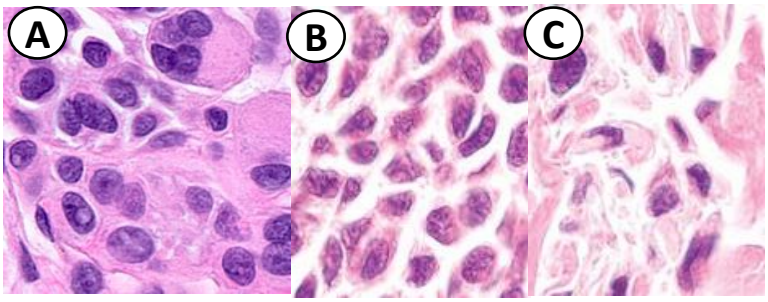


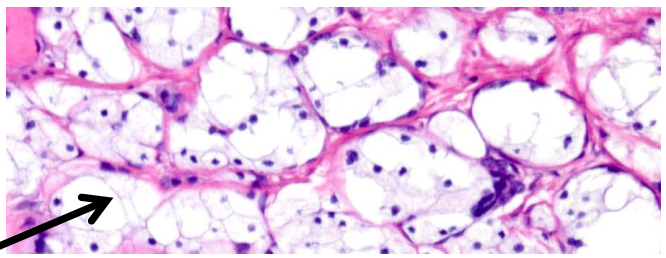
Intradermal Nevus (IDN)
No junctional component (dermis only)

Reassuring histologic features of a *Benign* nevus:
Small size (usually <5mm), Symmetrical, Well-circumscribed, Nested at DEJ, Regular Size & Distribution of nests, Bland cytology, No dermal mitoses.

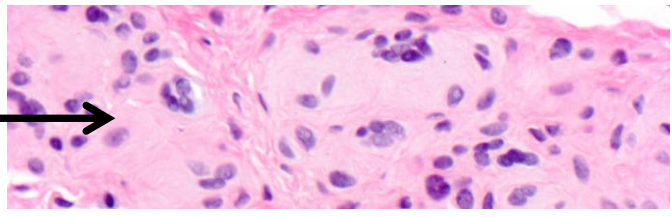


There should be "maturation" from top to bottom:
A cells: Epithelioid upper nevus cells
B cell: Lymphocyte-like mid cells
C cells: Spindled, neural-like lower cells



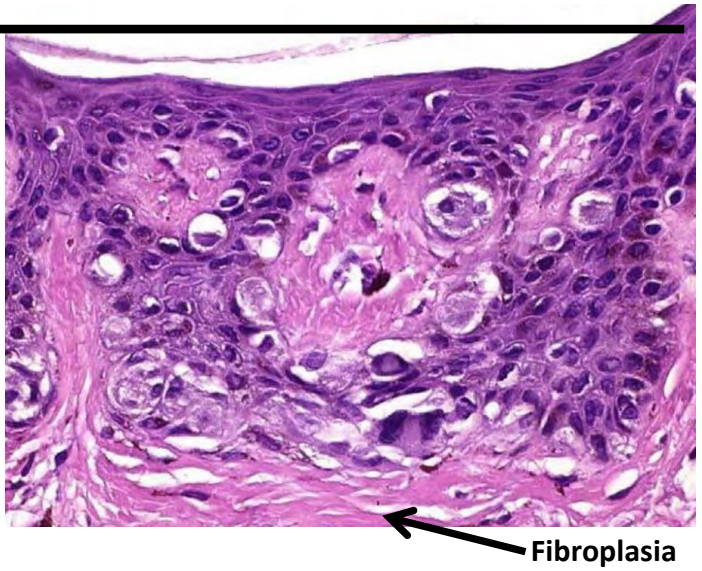


Special variants to know:
Balloon cell nevus—abundant clear/foamy cytoplasm with small central nucleus.



Neural (Neurotized) nevus—Type C cells predominate. May resemble a neurofibroma

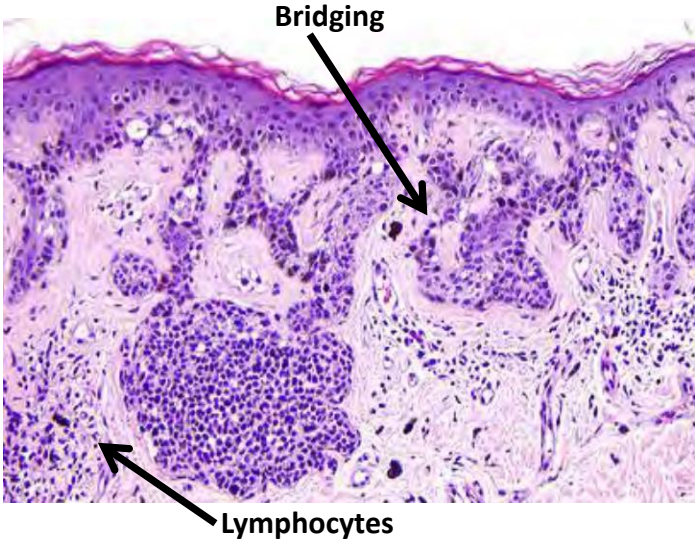
Dysplastic Nevus



Benign melanocytic naevus that is clinically atypical and characterized histologically by **architectural disorder and cytologic atypia** (i.e., it has *some* features of melanoma, but is still benign)

Risk factor for melanoma (benign though)
Term coined in the context of familial cases.

Architectural changes:
(deviation from usual Junctional nevus growth)
- Larger size (>4mm)
- Lateral extension of junctional component beyond dermal component (shoulder)
- Lentiginous hyperplasia of melanocytes
- Bridging of adjacent rete ridges by horizontal nests
- Concentric and lamellar fibroplasia around elongated rete ridges
- Patchy lymphocytic infiltrate



Cytologic Atypia
Nuclear enlargement (compared to resting basal keratinocyte), Hyperchromasia, Prominent nucleoli, and Abundant cytoplasm with "dusty" melanin.

IHC/Molecular: There are no *specific* additional diagnostic tests, given the spectrum on disease with melanoma. Frequent BRAF mutations in both nevi and melanoma. One can try to use the stains below to help support a difficult case as either a nevus or melanoma, but only in the context of each case.

IHC stain	Nevi	Melanoma
Ki67	<2%	>10%
HMB45	Confined to superficial layer	Throughout tumor
P16	Intact	Lost
PRAME	Negative/Focal	Diffuse

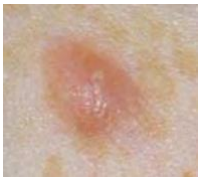
When clinically evaluating a pigmented lesion for melanoma, remember **ABCDE:**
A-Asymmetry (Melanoma is asymmetrical)
B-Border (Melanoma has uneven edges)
C-Color (Melanoma has multiple shades) and/or
Circumscription (Melanoma is poorly circumscribed)
D-Diameter (Melanoma is >6mm usually)
E-Evolution (Melanoma is often changing)

(A suspicious mole ;-)

		No Atypia to Mild	Low-grade Dysplasia (Moderate)	High-grade Dysplasia (Severe)	Melanoma
Architecture	Diameter	Any size, usually <4mm	≥ 4mm	≥ 4mm	Any size
	Symmetry	Good	Good	Usually flawed	Rare
	Lateral Circumscription	Sharp	Moderate	Moderate	Poor
	Junctional proliferation	Slight	Usual	Usual	Extensive
	Rete ridge distortion	Occasional	Usual	Always	Occasional
	Fibrosis	None or slight	Usual (concentric & lamellar)	Usual (concentric & lamellar)	Usual (diffuse)
	Pagetoid spread	Occasional, central	Occasional, central	Occasional	Often extensive
	Nests distribution	Evenly dispersed	Bridging	Bringing and some confluence	Confluent
	Maturation in dermis	Present	Present	May be incomplete	Absent
Atypia	Nucleus size compared to basal cell	1x	1-1.5x	>1.5x	>1.5x
	Distribution of atypia	None	Minority of cells (random)	Usually, >10%, but <50%	Majority of cells
	Nuclear shape	Regular	Irregular, polyhedral	Irregular, often angulated	Irregular
	Chromatin pattern	May be hyperchromatic	Densely hyperchromatic or dispersed	Hyperchromatic, coarse granular, or peripheral condensation	Hyperchromatic, coarse granular, or peripheral condensation
	Nucleoli	Small or absent	Small or absent	Prominent	Prominent, often lavender
	Nuclear membrane irregularity	Minimal	Subset of cells markedly irregular (“Random atypia”)	Prominent	Prominent
	Cytoplasm	Scant	Dusty, melanized	Variable (pale or pigmented)	Markedly variable
	Junctional/dermal mitoses	None	None or very rare	Rare and concerning	May be numerous

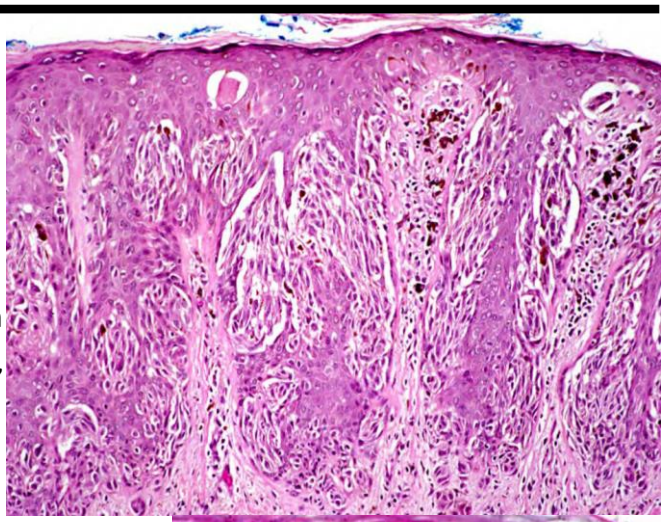
Modified from: WHO Classification of Tumours of the Skin

Spitz Nevus/Tumor



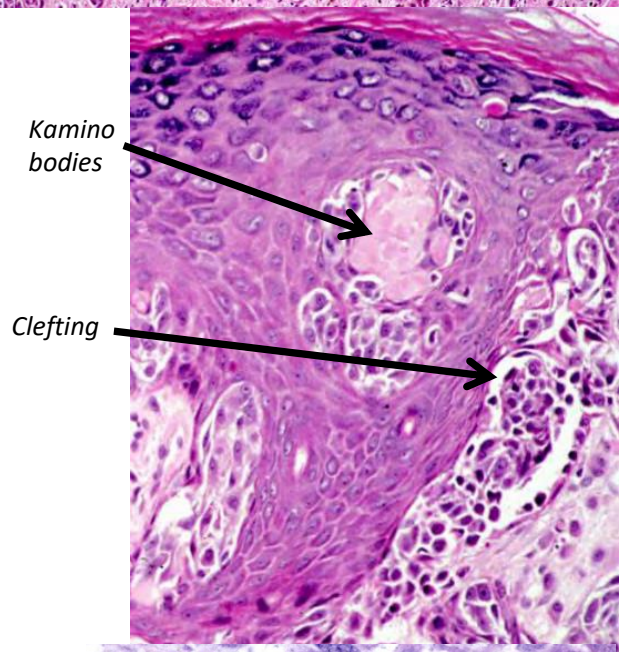
***Warning*: classic mimic of melanoma!**

Usually less than 6 mm. Often **Young**.
Tan papule on upper body/head.



Enlarged epithelioid and/or spindled melanocytes with limited or no architectural aberration, cytological atypia, or deep mitoses.

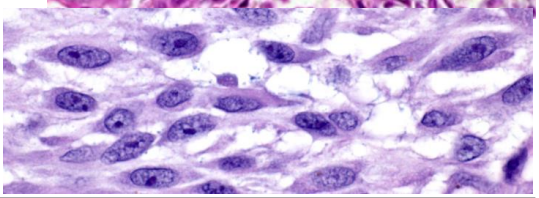
Symmetrical, "**clefting**" about junctional nests, **epidermal hyperplasia** with vertical "**raining down**" appearance of melanocytes, **maturation** of dermal melanocytes, wedge- or V-shaped dermal configuration, and absence of deep/marginal mitoses.
Kamino bodies (eosinophilic globules)
May have focal pagetoid spread centrally.
Multiple specific patterns.



IHC: Retention of p16 expression (lost in melanoma)
HMB45 only in upper dermis (throughout in melanoma)
Ki67 <5-10% (higher in melanoma)

Molecular: usually HRAS mutations or receptor kinase fusions.

Be very suspicious for melanoma if: Patient is older, the lesion is larger than 10mm, there are mitoses, ulceration, fat invasion, asymmetry, poor circumscription, diminished maturation, or diffuse pagetoid spread.



A brief word on challenging melanocytic lesions:

As a general surgical pathologist, I personally find many of these melanocytic lesions extremely challenging, particularly the borderline/dysplastic lesions given the spectrum of disease. So, I would urge those non-dermatopathologists among you to:

1) Have a low threshold for seeking expert opinion
2) Liberally show your colleagues these cases ("always carpool to court")

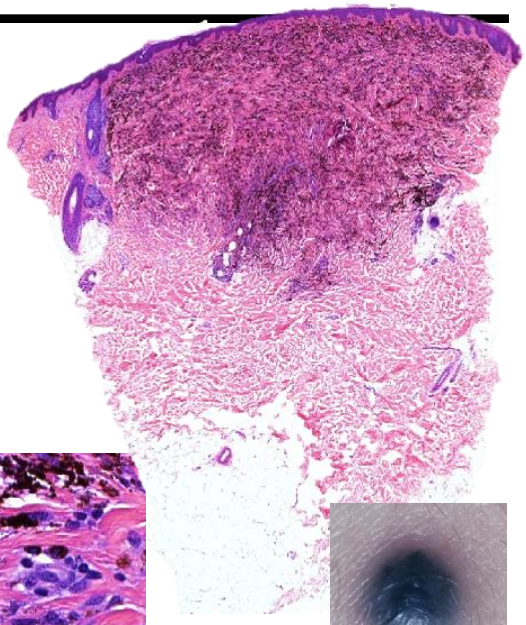
Also, it should be noted, that even experts can have trouble with these lesions with there being some interobserver variability and that the threshold for what is called "melanoma" seems to have shifted over time (PMID: 33406334).

In some circumstances, given differing diagnostic thresholds, one could consider diagnosing a lesion as, "'melanocytic tumor of uncertain malignant potential (MELTUMP)" or "intraepidermal atypical melanocytic proliferation of uncertain significance (IAMPUS)."

	Spitz nevus	Spitz melanocytoma (Atypical Spitz tumor)	Spitz melanoma
Clinical	Usually young (mean 21yr) Upper body Pink or reddish nodule.	Can occur at any age; More common in younger patients Color variegation	Older Virtually always > 10 years, often > 40 years Asymmetrical Enlarged plaque or nodule Color variegation, Changing
Micro	< 6 mm Symmetrical Well circumscribed Epidermal hyperplasia Vertically oriented nests with clefting Central focal pagetoid spread (if any) Often wedge-shaped Maturation of dermal component Few or no dermal mitoses (0–2 / mm^2)	Often > 5 to 10 mm Symmetrical or asymmetrical Well or poorly circumscribed Ulceration possible Irregular nesting Increased cellularity Greater pagetoid spread Deeper dermal extension Maturation may be partial or absent 2–6 or more dermal mitoses / mm^2 Deep mitoses Possible necrosis	> 5 mm; often > 10 mm Often asymmetrical Often poorly circumscribed Irregular and confluent nesting Pagetoid spread may be extensive Ulceration Effacement of epidermis Lack of maturation Invasion of deep dermis or subcutis Often > 6 dermal mitoses / mm^2 Deep / marginal or atypical mitoses Necrosis
Cytology	Enlarged epithelioid / spindle cells Little or no nuclear pleomorphism No high-grade cytological atypia	Enlarged epithelioid / spindle cells Nuclear enlargement, pleomorphism, and hyperchromasia	Enlarged epithelioid / spindle cells High-grade cytological atypia
IHC	HMB45 and Ki-67 staining diminished with depth Low Ki-67 proliferation index (< 5%) Retention of p16 PRAME negative	HMB45 and Ki-67 staining diminished or variable with depth Low to intermediate Ki-67 proliferation index (5–15%) Retention or loss of p16 PRAME usually negative	HMB45 and Ki-67 deep staining common Elevated Ki-67 proliferation index (> 20%) p16 expression may be diminished PRAME may be positive
Molecular	Isolated gains of 7p and 11q, tetraploidy Activating *HRAS* mutations Kinase fusions	Often ≥ 1 chromosomal abnormality Kinase fusions *HRAS* mutations *PTEN* mutations Heterozygous or homozygous loss of CDKN2A may occur	> 1 chromosomal abnormality Kinase fusions *HRAS* mutations *BRAF* and *NRAS* mutations rare or absent *PTEN* mutations Homozygous loss of CDKN2A often *TERT* promoter mutations
Prognosis	Very low risk of progression	Low risk of progression Almost always indolent May recur	Malignant. Can metastasize

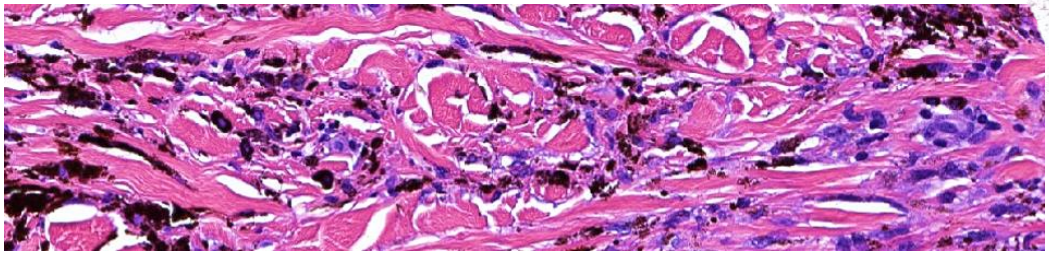
Modified from: WHO Classification of Tumours of the Skin

Blue Nevus

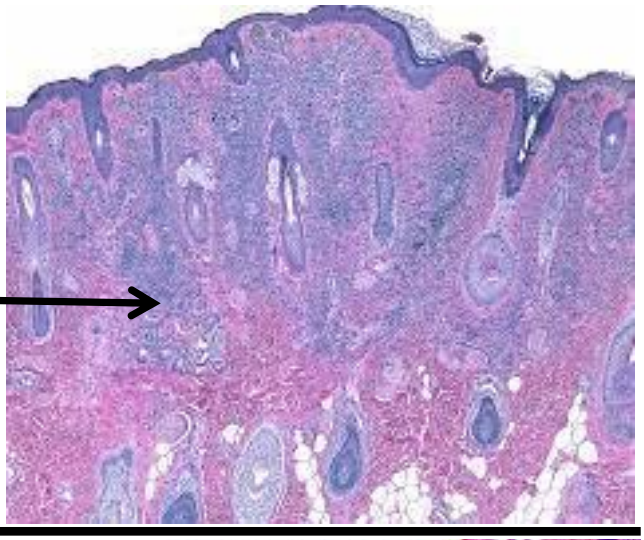


Dermal proliferation of dendritic, **spindle**, and/or ovoid melanocytes associated with **melanin pigment**, in melanocytes and melanophages, with stromal **sclerosis**.
***Clinically*: bluish-black color**

Cellular Blue Nevi—well-circumscribed, cellular, bulbous, vertical extension of the lesion into the subcutaneous adipose tissue. Pigment in mostly melanophages.



Congenital Melanocytic Nevus



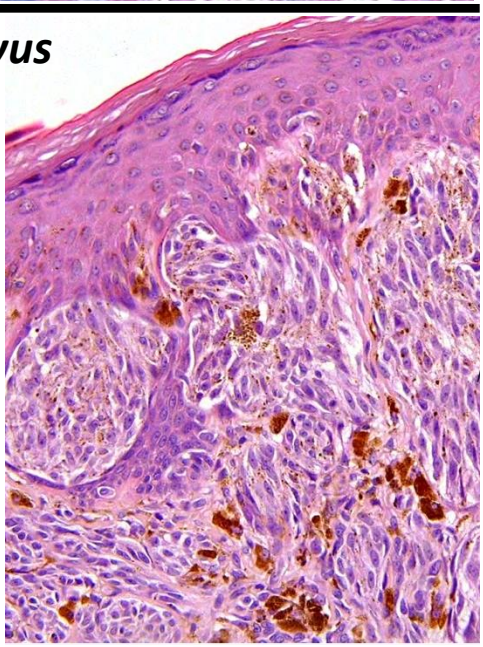
Present at birth or appearing in first year.
Can be quite **large**.

Characteristic **deep** reticular dermal involvement, splaying of collagen, angiotropism, and **infiltration of appendageal structures** by naevus cells

Molecular: Most have NRAS mutations

Can develop "proliferative nodule" (expansile proliferation of melanocytes) and even, rarely, melanoma.

Pigmented Spindle Cell Nevus ***aka Reed Nevus***



A subtype of spitz nevus.

Heavily pigmented spindled melanocytes involving the epidermis or epidermis and superficial dermis.
Epidermal hyperplasia and clefting spaces.
Pagetoid spread is common, usually in lower, central epidermis. Many melanophages.
Should be symmetrical with lateral circumscription.

Usually a small, dark macule/papule (~3 mm).
Usually **younger, often female** on lower body.

Molecular: activating kinase fusions, most commonly involving NTRK3

Special Site Nevus

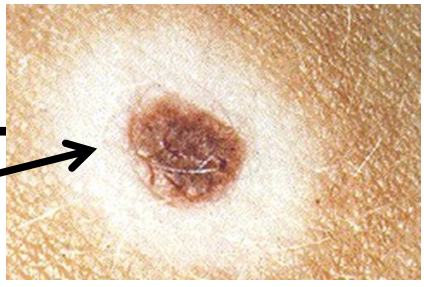
Benign nevi occurring on specific anatomical sites (the breast, axilla and other flexural sites, scalp, ear, umbilicus, genital skin, and acral skin) and showing **atypical or unusual histopathological features** (cytologic/architectural atypia) that **make reliable distinction from melanoma difficult.**

Unclear why this atypia exists in these sites: may be **trauma/friction**, hormones, UV, etc.

Main diagnostic importance is to **recognize site** and **allow more leniency with atypia** before diagnosing a lesion as melanoma to **avoid over treatment.**

Atypical histologic findings include: asymmetry, architectural disorder with an irregular arrangement of the junctional melanocytic nests, cytological atypia, pagetoid spread, dermal fibroplasia, and a lymphocytic infiltrate.

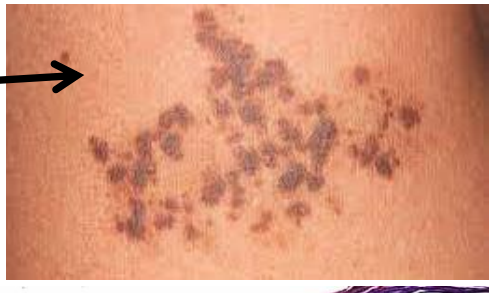
Do NOT show: increased mitoses, individual necrotic melanocytes. There is preserved maturation with descent into the dermis.



Other Nevi

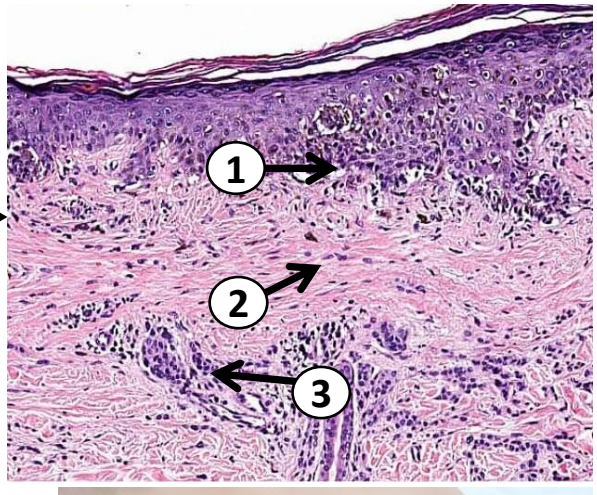
Halo Nevus: Nevus with circumferential depigmentation clinically, often associated with a brisk lymphocytic infiltrate histologically.

Nevus Spilus: Nevus presenting as a patch of hyperpigmented skin containing a variable number of darkly pigmented macules and papules.



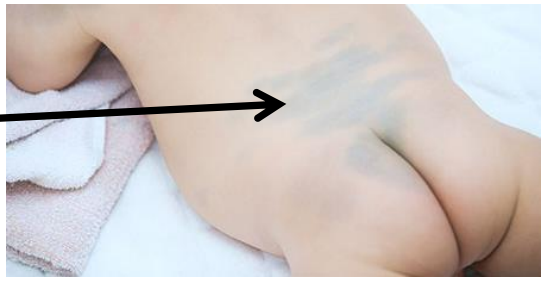
Meyerson Nevus: Nevus with superimposed eczematous dermatitis, characterized histologically by spongiosis. Associated superficial perivascular chronic inflammation, acanthosis,

Recurrent Nevus: Nevus that recurs after incomplete removal. Usually see: 1) Junctional melanocyte proliferation overlying a 2) scar with 3) underneath bland dermal melanocytes.



Nevus of Ito/Ota: Dermal melanocytosis on the shoulders and arms, or on the face, respectively.

Mongolian Spot (Congenital dermal melanocytosis): Bluish patches on lumbosacral skin and other parts of the body. On histology, single pigmented dendritic melanocytes haphazardly dispersed in the dermis. Often regress.

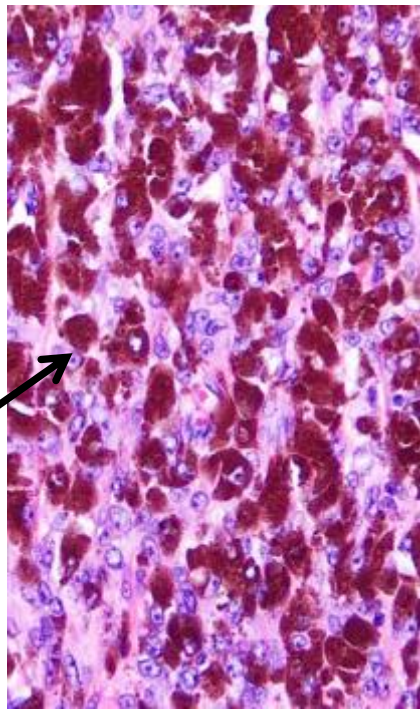


Melanocytomas

All very **Rare**, and therefore low-yield for boards, but worth knowing about at least in general concept.

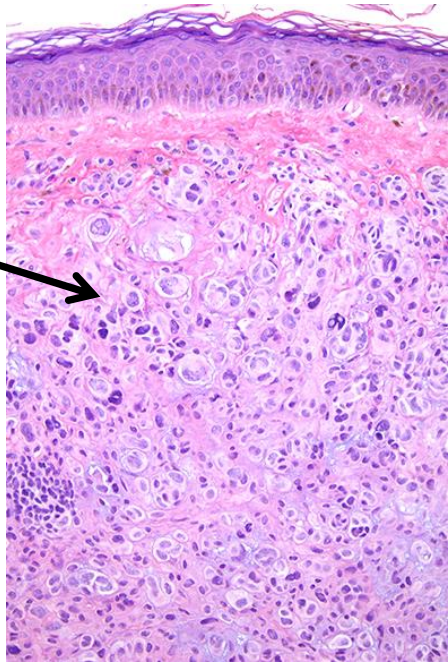
Uncertain malignant potential, but *usually* Benign. Occur in intermittently sun-exposed skin. Genetically intermediate lesions containing more than one driver mutation.

Spitz melanocytoma (Atypical Spitz Nevus/Tumor): Morphologically and genetically "intermediate" between Spitz naevus and melanoma. May be larger, more deeply invasive, and show greater cellular atypia, compared to Spitz nevi (see prior table).



WNT-activated deep penetrating/plexiform melanocytoma: Spindled and/or epithelioid melanocytes and melanophages, arranged in a wedge-shaped, fascicular or plexiform pattern that frequently extends into the deep reticular dermis. It is caused by the combined activation of the MAP-kinase and WNT signaling pathways→ (+) LEF1, Nuclear β-catenin in some melanocytes (and throughout lesion, unlike usual decrease in dermis).

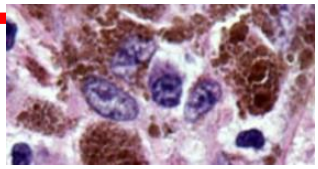
Pigmented epithelioid melanocytoma: Composed of heavily pigmented epithelioid melanocytes (and melanophages), characterized by combined activation of the protein kinase A (PKA) pathway and genetic changes defining other lineages of melanocytic proliferations such as activation of the mitogen-activated kinase (MAP) kinase pathway or presence of a kinase fusion. PRKAR1A inactivation in majority of cases. Old name, "Animal-type melanoma."



BAP1-inactivated melanocytoma: BAP1 (BRCA1-associated protein-1) -inactivated melanocytoma is characterized histologically by large epithelioid, unpigmented melanocytes, often adjacent to a conventional naevus, and genetically by inactivation of the BAP1 gene. It can occur sporadically or in association with the BAP1 tumor predisposition syndrome

MITF pathway-activated melanocytic tumors:
Dermally based melanocytic neoplasms composed of clear cells with specific translocations. Includes:
Clear Cell Tumor with Melanocytic Differentiation and ACTIN::MITF Translocation (CCTMAM)
Clear Cell Tumor with Melanocytic Differentiation and MITF::CREM Translocation (CCTMMC)

Melanoma (Malignant melanocytic tumors)



Defined by cytologically atypical melanocytes and/or architectural abnormalities

Atypical melanocytes: Large nuclei, prominent nucleoli, irregular clumped or dense chromatin, and eosinophilic or lightly pigmented cytoplasm.

Architectural abnormalities: Asymmetrical, Poorly-defined borders (…. Just …. Keep …. Going…), Lack of maturation with dermal descent (top cells look like bottom cells), Deep mitoses, Pagetoid spread (especially if extensive), Epidermal consumption, Lack of dermal nesting (just sheets).

Melanoma In Situ (MIS)—confined to epidermis and DEJ. Includes some Superficial Spreading and Lentigo Maligna.

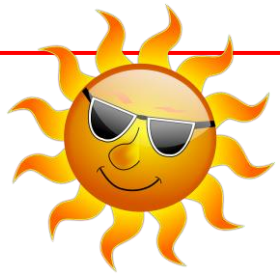
Invasive melanoma—proliferation extends into dermis

Two growth phases:

1) Radial Growth Phase (RGP): Expand horizontally in the epidermis and superficial dermis
Better prognosis at this stage. Includes Superficial spreading melanoma and Lentigo maligna.

2) Vertical Growth Phase (VGP): Deeper/thicker expansile invasion of dermis→ Nodular melanoma → worse prognosis.

Development pathways:



Melanoma arising in sun-exposed skin:

Low Cumulative Sun Damage (Low-CSD)

Intermittent sun exposure. Younger age. Tanning is a risk factor.
Nevi and dysplastic nevi are precursors/risk factors.
Frequent **BRAF V600E mutations.** High mutation burden (Esp. C>T point mutations, "UV signature")
Give rise to **Superficial spreading melanoma** and a subset of **nodular melanoma**.

High-Cumulative Sun Damage (High-CSD)

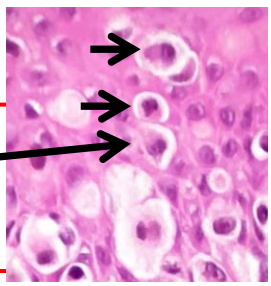
Chronic sun exposure. Older age. Originate from melanoma in situ.
Mutually exclusive NF1, NRAS, KIT and non-V600E BRAF mutations. *Very* high mutation burden.
Give rise to **Lentigo maligna melanoma, Desmoplastic melanoma,** and a subset of **nodular melanoma**

Melanoma arising in sun-shielded skin (No UV association)

Malignant Spitz tumor, Acral melanoma, Mucosal melanoma, Uveal melanoma, Melanoma arising in congenital or blue nevi. Lower mutation burden.

Other genes frequently mutated: TERT promoter, CDKN2A

Special patterns of growth:

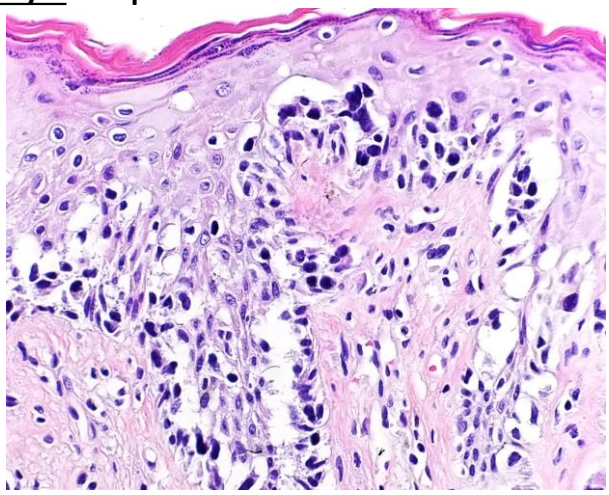


Pagetoid pattern—Individual cells in epidermis with nests at the DEJ.
Lentiginous pattern—Growth along DEJ. No pagetoid scatter, fewer nests.

Prognosis depends on: Depth of invasion (most important), Ulceration, Mitoses, LVI,
Depth usually measured by Breslow thickness (from granular layer to deepest point) in mm.

Superficial Spreading Melanoma *Low-CSD Melanoma*

Pagetoid and/or lentiginous intraepidermal atypical melanocyte components



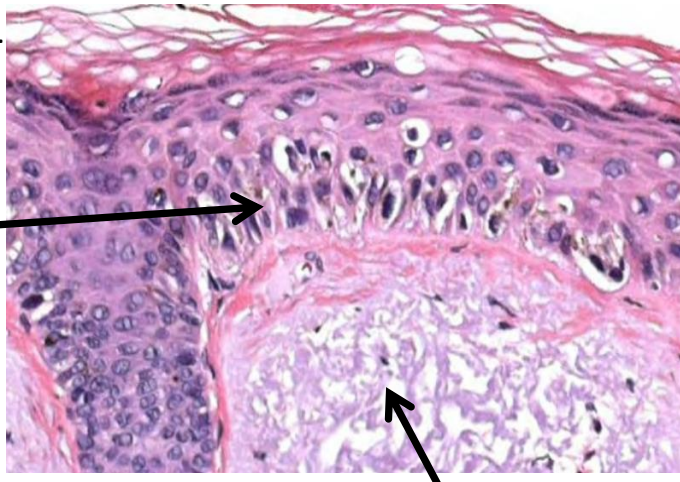
Skin with low cumulative sun damage (low solar elastosis)
Usually still in radial growth phase (RGP)
If confined to epidermis/DEJ→ Melanoma in situ (MIS)
If extends to dermis→ Invasive melanoma
Intraepidermal component often extends >3 rete ridges beyond the invasive component (i.e., superficial spreads… hence the name)

Intermittent sun exposure, including childhood sunburns & tanning. Frequent BRAF V600E mutations.
Associated benign nevus in ~1/2 of cases.
Cannot be on palmar/plantar surfaces.

Lentigo Maligna Melanoma *High-CSD Melanoma*

Skin with a high degree of cumulative sun damage (CSD).
→ Severe **solar elastosis**
Frequently head/neck area of elderly.

Lentiginous proliferation of mostly single (NOT nested) **atypical melanocytes along the base of the epidermis**
Less pagetoid spread, nesting, and pigment.
No precursor nevus majority of the time.
Epidermis often thin/atrophic.
Can extend down adnexal structures.
High mutational burden (from UV).



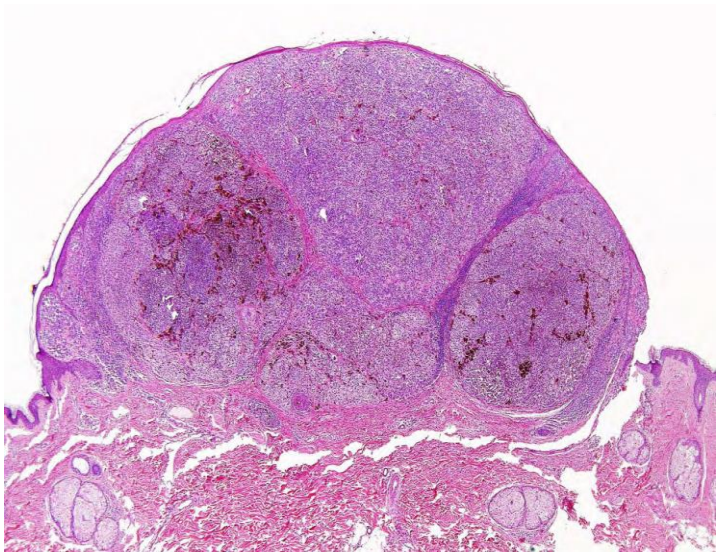
Often extended Radial Growth Phase (RGP)/in situ latency period before developing invasion/metastasis (less aggressive, more indolent).

Nodular Melanoma

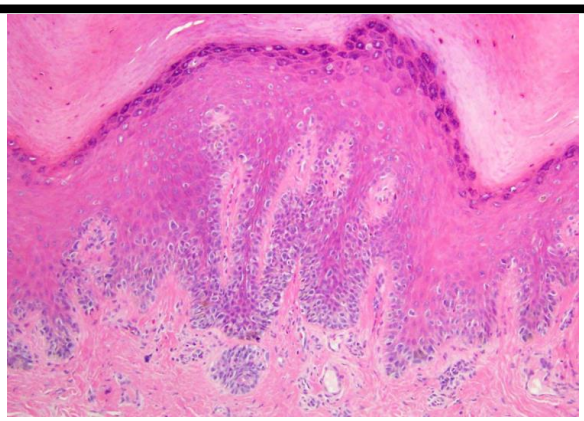
Melanoma in **vertical growth phase** (VGP) without an appreciable radial-growth-phase (RGP)
No evidence of regression in the flanking skin
No evidence of melanoma metastasis (clinically, histologically)

Not a distinct entity, but a manifestation of an accelerated progression of melanomas of multiple pathways, including low- and high-CSD, and acral melanoma.

Often grow rapidly. Can ulcerate and bleed.



Acral Melanoma

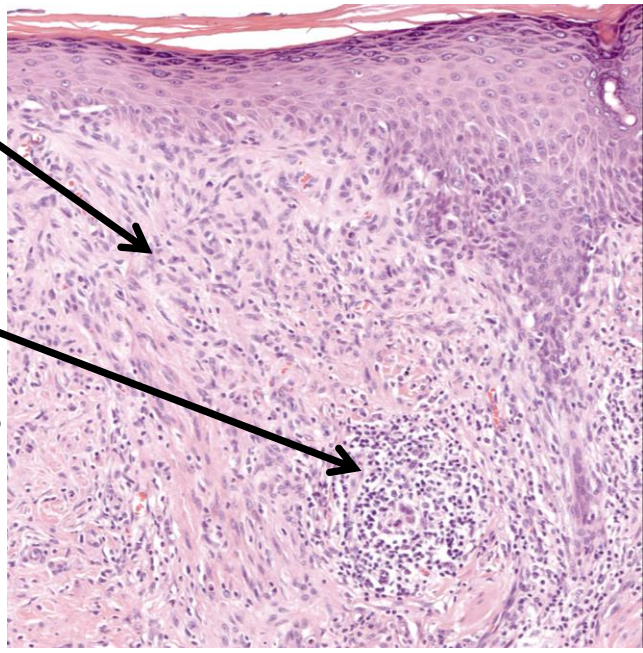


Most common subtype is Acral Lentiginous Melanoma
Not UV-mediated→ low tumor mutation burden

Most common melanoma in people with darker skin types.

Worse prognosis than similar stage tumors at other sites.

Desmoplastic Melanoma

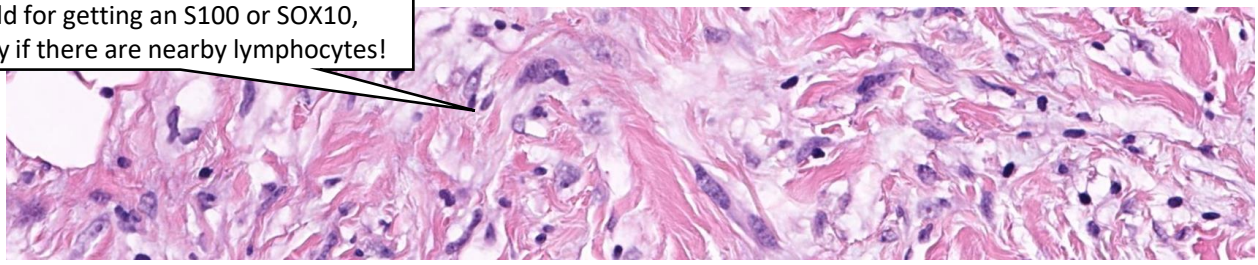


Warning:** Very sneaky/subtle!!
Spindled melanocytes (resembling fibroblasts) **between collagen fibers**. Often deceptively bland.
Often adjacent severe solar elastosis and atrophic/thin epidermis. Can have adjacent Lentigo Maligna.
Characteristic adjacent "cannon ball" lymphocytes or plasma cells. Frequent **neurotropism**.

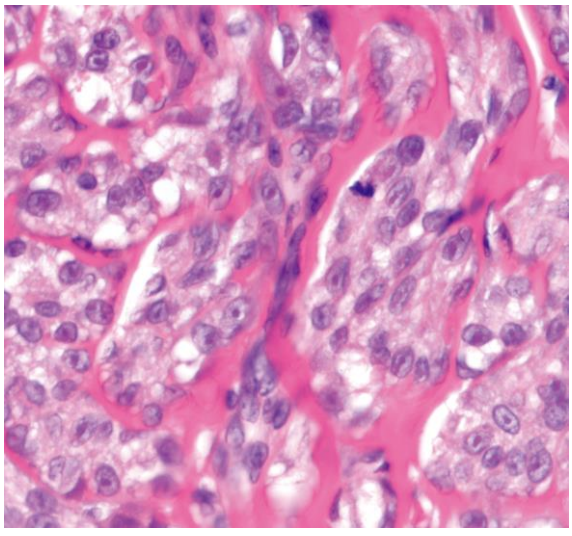
IHC: (+) S100 & SOX10; but usu. *Neg* for MelanA, HMB45

High-CSD→ head and neck of elderly
→ Very high mutation burden.
Clinically, often appear as indurated plaque.

Given how bland they look, have a low threshold for getting an S100 or SOX10, particularly if there are nearby lymphocytes!



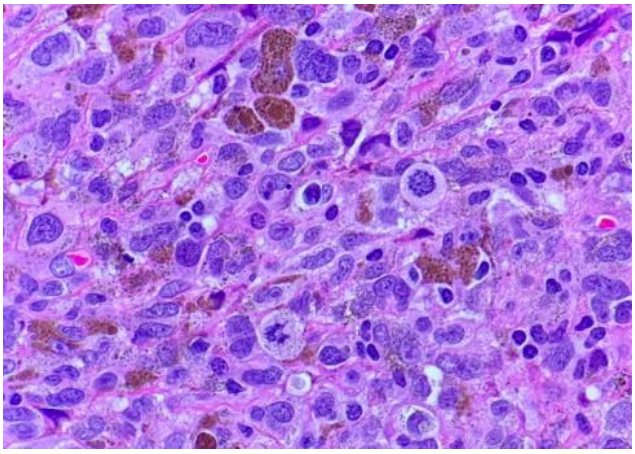
Spitz Melanoma



Melanoma with a genomic alteration characteristic of Spitz nevus (SN). Criteria for malignancy or distinction from Spitz melanocytoma (Atypical Spitz Tumor) is challenging and may be based on a combination of clinical, histopathologic, and molecular features (see prior table).

High grade nuclear atypia
Highly expansile or sheet-like growth patterns
High mitotic activity, with atypical mitoses

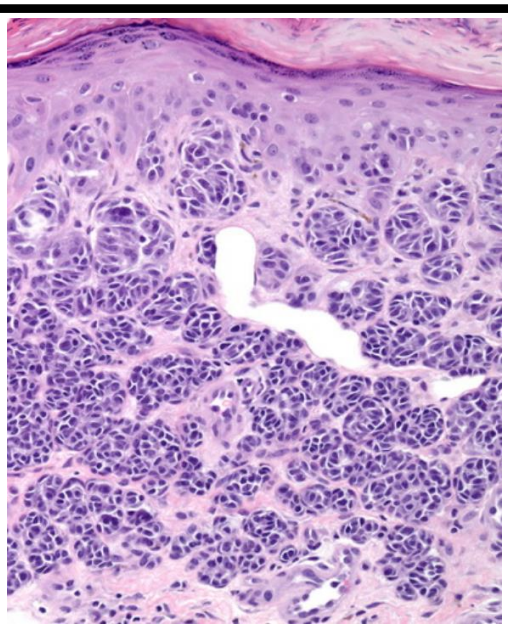
Mucosal Melanoma



Arise in **mucosal sites**, including **anogenital**, **oral**, and **sinonasal** mucosa.
Especially in the GI-tract, one must exclude a metastasis from a cutaneous melanoma.
An in situ/lentiginous component may be present and support a mucosal primary.

Generally **aggressive**.

Nevoid Melanoma

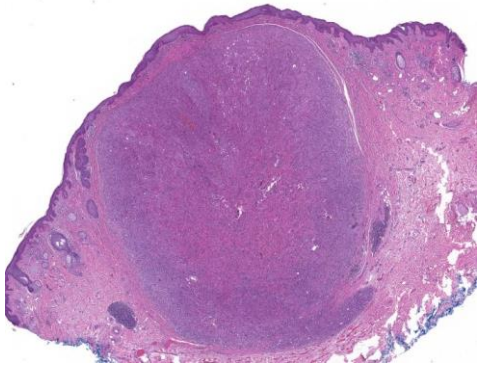


Not a distinct molecular entity→ primary melanoma which resembles a melanocytic nevus (making diagnosis challenging!)

Look for atypia and mitoses (esp. deep) at high power.
Often nests running horizontal to surface.

Often requires supportive immunohistochemical staining (e.g. loss of p16 staining, PRAME positivity) and/or
Supportive molecular data (e.g. evidence of copy number variation, CDKN2A loss, TERT promoter mutation)

Dermal Melanoma



Rare. Primary melanoma limited to the dermis and subcutis *without* intraepidermal involvement.

Diagnosis of exclusion: No ulceration or regression (evidence of a possible prior epidermal component). No nevus precursor. Absence of prior history of melanoma and exclusion of clinically suspected melanoma at another site.
Better prognosis than melanomas with a similar depth.

Metastatic Melanoma to the Skin

Spread from a primary melanoma to the skin. Primary may be occult and/or regressed.
Can involve epidermis (epidermotropism)→ simulate an in situ lesion and/or new primary
Most common presentation: solitary pigmented dermal nodule.
Satellite metastasis: within 2 cm of primary
In-transit metastasis: greater than 2 cm from primary, en route to the regional lymph node basin.