Melanoma and Mimickers

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Disclosures

- No relevant financial disclosures

Objectives

- Recognize common benign melanocytic and non-melanocytic lesions that may mimic melanoma
- Know when to be concerned about nail pigmentation or dystrophy
- Understand the limitations of biopsies of melanocytic lesions and how to biopsy suspicious lesions
- Identify when to refer patients to a specialist and who to refer to

Epidemiology

- Lifetime incidence of melanoma: 1 in 49*
- Incidence has increased 5-7 fold over the past four decades, primarily in Caucasian population
- Mortality rates continue to increase in Caucasian males but are stable in females
- Leads to >90% of skin cancer deaths
- Median age at diagnosis: 61 years
- 82-85% present with localized disease, 10-13% with regional disease, 2-5% with metastatic disease

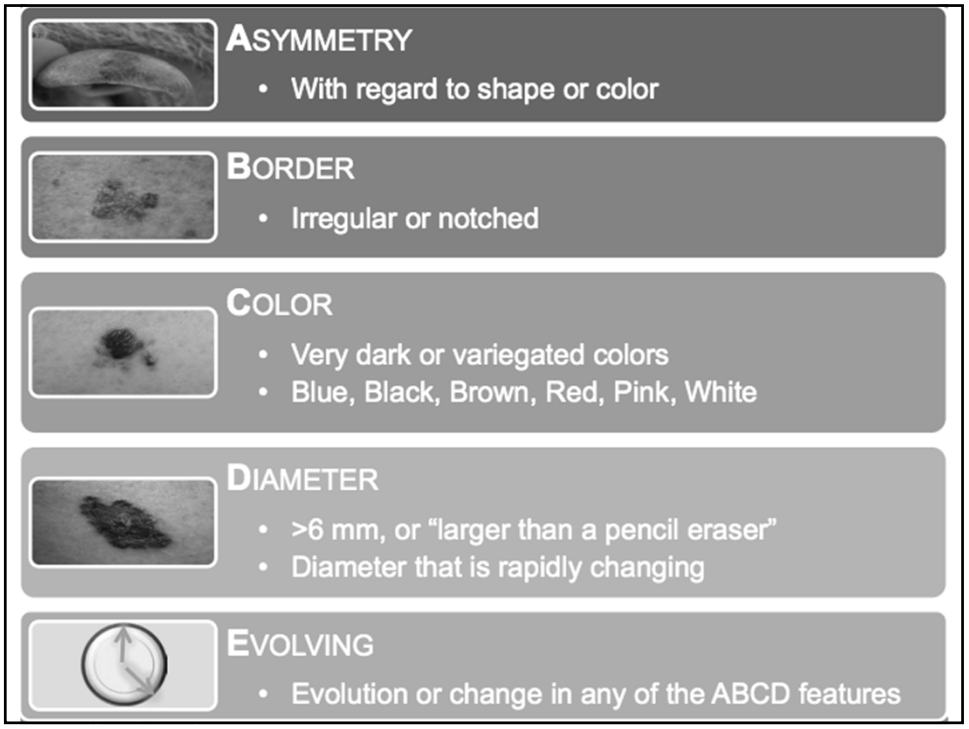
*NCI SEER Database; NCCN melanoma guidelines, 2013
www.cdc.gov/cancer/dcpc/research/articles/cancer_2020_incidence.htm

Risk Factors for Melanoma

Genetic Factors	Environmental Factors	Phenotypic expressions of gene/environment interactions
Family history of cutaneous melanoma	Intense intermittent sun exposure	>100 acquired melanocytic nevi (8- 10x increased relative risk)
Lightly pigmented skin	Chronic sun exposure	>5 atypical nevi (4-6x increased relative risk)
Tend to burn, unable to tan	Residence near equator	Multiple solar lentigines (3-4x increased relative risk)
Red hair color	PUVA (possible)	Personal history of cutaneous melanoma
DNA repair defects (eg. XP)	Tanning bed (esp <35 yo)	
Giant congenital nevus	Immunosuppression	

Diagnosis

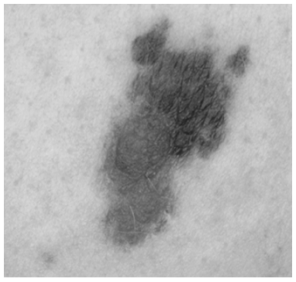
- Early detection key in improving survival
- Clinical diagnosis based on visual inspection and dermoscopy
- In high risk patients, dermoscopic image storing and lesional or total body photography helpful
- Histopathology remains the gold standard for melanoma diagnosis
- Diagnostically difficult lesions may require additional molecular studies such as comparative genomic hypridization (CGH), fluorescence *in situ* hybridization (FISH) or gene expression profiling (GEP)

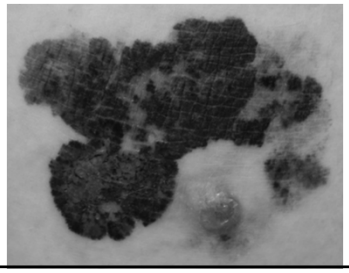


Types of Melanoma

DIFFERENT TYPES OF PRIMARY CUTANEOUS MELANOMA			
Clinico-histopathologic subtype	**Abbreviation**	**Percentage**	**Median age**
Superficial spreading melanoma	SSM	57.4%	51 years
Nodular melanoma	NM	21.4%	56 years
Lentigo maligna melanoma	LMM	8.8%	68 years
Acral lentiginous melanoma	ALM	4%	63 years
Unclassifiable melanoma	UCM	3.5%	54 years
Others		5%	54 years

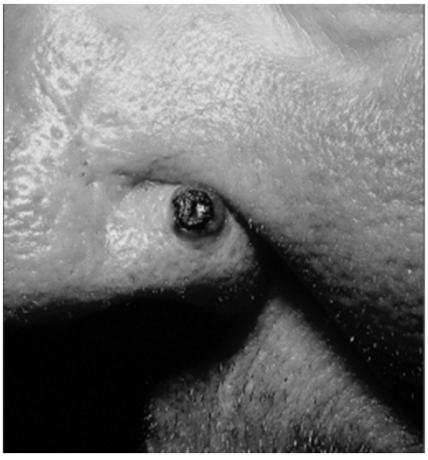
Superficial spreading melanoma





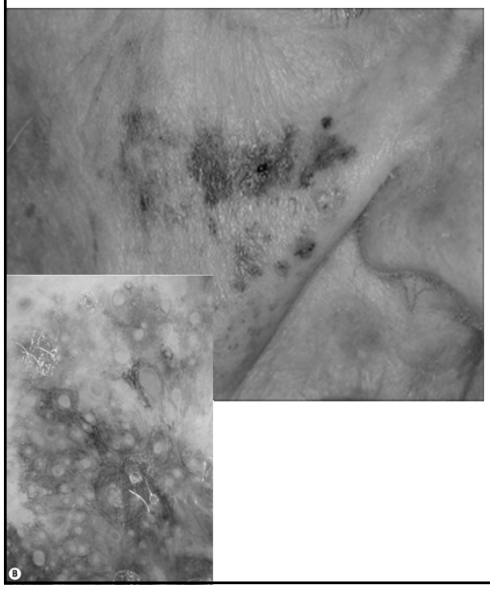
- 60-70% of melanomas
- Females- lower extremities/upper back
- Males- upper back
- ~50% arise in a pre-existing nevus
- BRAF mutations common
- Most common variant in young individuals
- Mean age of diagnosis- 5th decade

Nodular melanoma



- 15-30% of melanomas
- Mean age: 6th decade
- Most commonly on trunk, head and neck
- Men>women
- No radial growth phase
- Rapid progression
- Poor prognosis

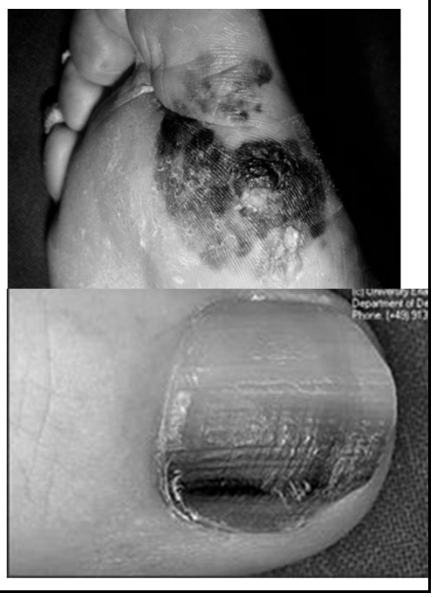
Lentigo maligna melanoma



- 10% of melanomas
- Older individuals (7th decade), M=F
- cKIT mutations (17%)
- Chronically sun damaged skin (face, dorsal hands)
- 5-20 year radial growth phase
- Lentigo maligna is precursor lesion: 5% progress to invasive melanoma

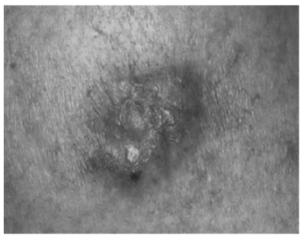
Acral lentiginous melanoma

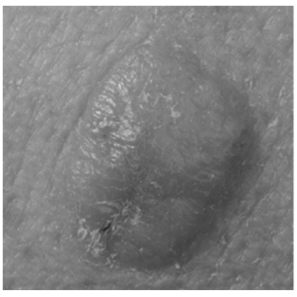
- 5% of melanomas
- Most in 7th decade of life
- cKIT mutations (>20%)
- Palms, soles, nails
- Most common type of MM in blacks and Asians (b/c low frequency of others)
- Incidence similar across all ethnic groups
- Diagnosed at advanced stage



MELANOMA VARIANTS

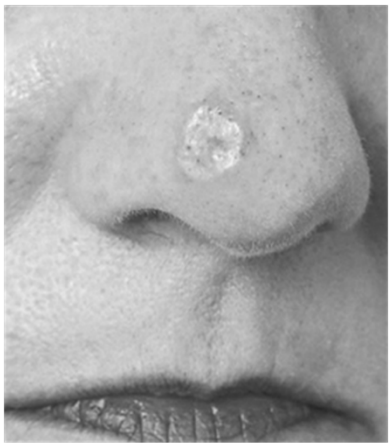
Amelanotic melanoma





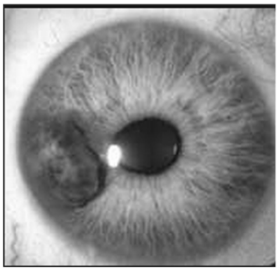
- Amelanotic variants for all melanoma subtypes
- Prognosis and therapy do not differ from pigmented subtypes
- Diagnosis often delayed
- More commonly seen in patients with OCA

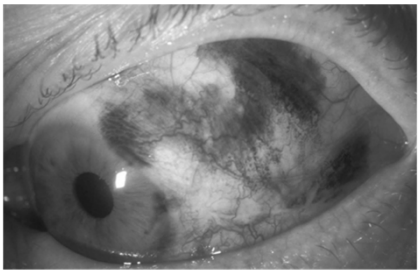
Desmoplastic melanoma



- AKA spindled or neurotropic melanoma
- Skin colored, red, brown plaque
- Often occurs within lentigo maligna, acral lentiginous or mucosal melanoma
- Deep biopsy necessary
- Locally aggressive but mets are uncommon

Ocular Melanoma





• Conjunctival or Uveal melanoma

•5% of all melanomas

• Most common primary intraocular tumor in adults

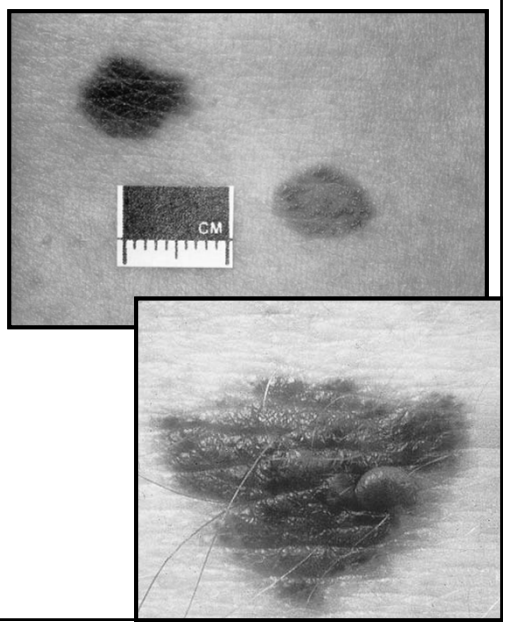
• Uveal – activating mutations in GNA11 or GNAQ

•Increased risk in nevus of Ota (esp Caucasians)

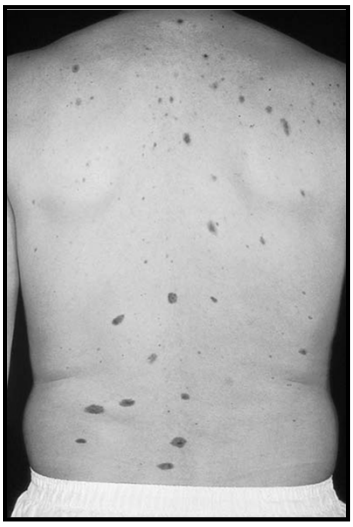
Melanocytic mimickers

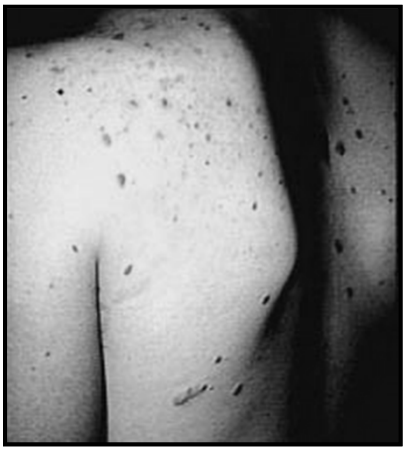
Dysplastic nevi

- Clinically and histologically distinctive
- May occur sporadically or in a familial form
- Patients with multiple dysplastic nevi have increased risk of melanoma
- Clinically larger than acquired nevi, irregular in shape and uneven in color
- Important to document clinical stability
- Often have a benign dermoscopic pattern



Dysplastic nevus syndrome





Dysplastic Nevus Syndrome

Familial Atypical Melanotic Mole Melanoma (FAMMM)

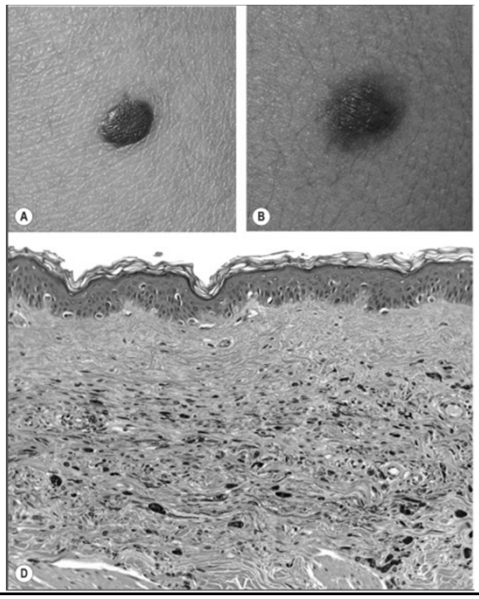
All of the following criteria:

1. Malignant melanoma in one or more first- or second-degree relatives
2. High total body nevi count (often >50) including some of which are clinically atypical
3. Nevi with certain histologic features on microscopy

25-40% with *CDKN2A* mutation	60-75% without *CDKN2A* mutation
60-90% melanoma by age 80 17% pancreatic cancer by age 75	Cancer risks unclear

van der Rhee et al (2011)

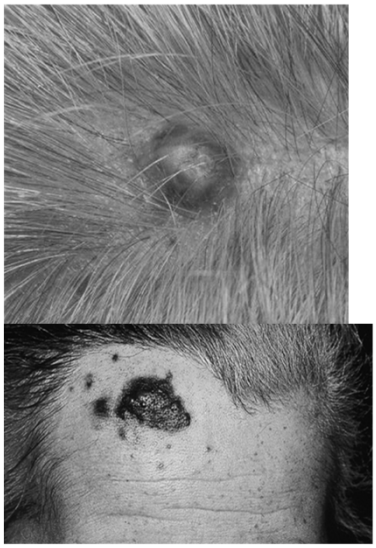
Blue nevi



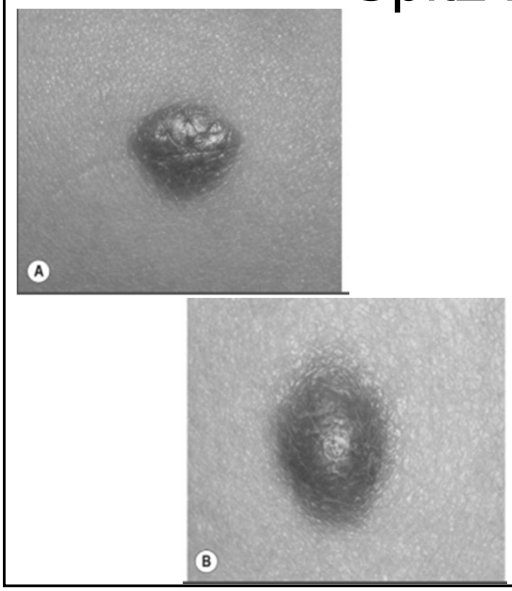
- Blue to blue-black, firm papule, nodule or plaque
- Small and well-circumscribed, rarely larger than 1 cm
- Most common on dorsal aspects of hands and feet, face and scalp
- Often onset during childhood or adolescence
- Lesions that are clinically stable, small and in typical location can be monitored

Malignant Blue Nevus

- Rare tumor of dermal melanocytes
- Most commonly arise in a cellular blue nevus; also within nevus of Ota or Ito, or de novo
- Scalp most common site
- >1cm
- High rate of recurrence and metastasis (LNs and lungs)
- Biopsy lesions that appear de novo, are multinodular or plaque like or have changed



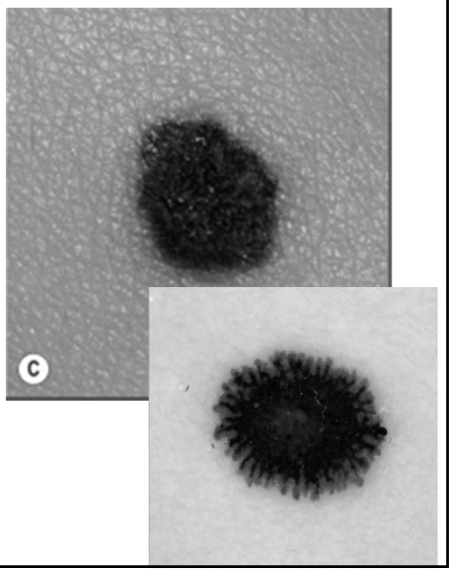
Spitz nevi



- Red or pigmented papule or nodule, avg 8mm
- Can mimic melanoma clinically and histologically
- Generally homogenous color and well defined margins with smooth or verrucous surface
- Most common on lower extremities and head/neck region
- Usually in children or young adults; rare beyond 40-50 years

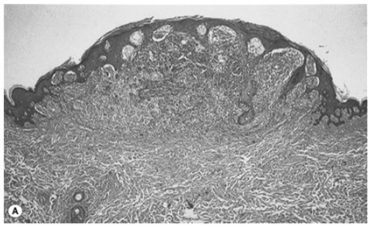
Pigmented spindle cell nevus

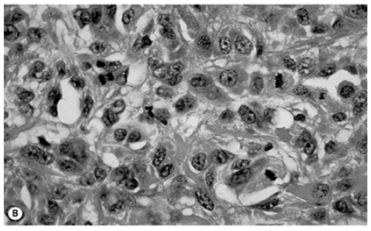
- Spindle cell variant of spitz nevus
- Dark brown to black macule or papule, usually <6mm
- Found in children or young adults
- Most common on extremities, esp thigh of young women
- Rare transformation to melanoma
- Rarely recur unless incompletely excised



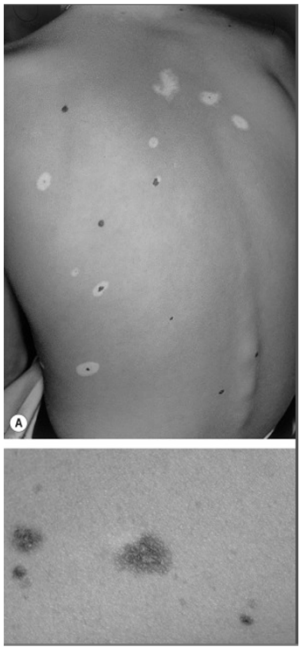
Atypical spitz tumors and spitzoid melanoma

- Some shared histologic features of a Spitz nevus but more atypia, expansile growth, mitotic activity
- Can do FISH for diagnosis and/or prognostication



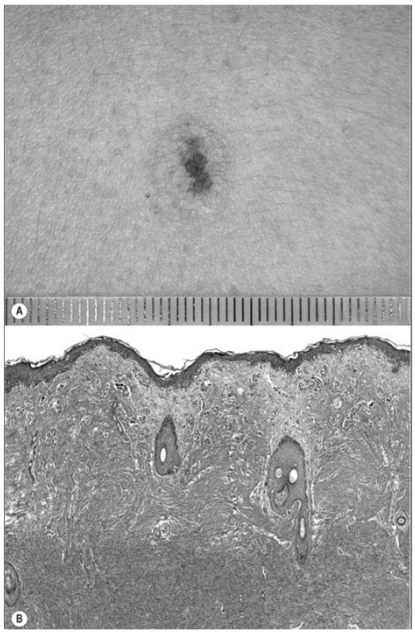


COMPARISON OF SPITZ NEVUS AND MELANOMA		
Parameter	Spitz nevus	Melanoma
Age	Young age, especially prepubertal, favors a benign process	Exceedingly rare in pre-pubertal children; outnumber Spitz nevi in patients >30 years of age
Anatomic site	May occur anywhere, but favor the lower extremities and particularly in children the head and neck region	Most often on the trunk (back) in men and distal lower extremities in women; favor intermittently sun-exposed skin, but may occur anywhere
Size	Often <5–6 mm, usually <10 mm	Often >6 mm, but early lesions may be smaller; large size favors melanoma
Symmetry	Usually symmetric	Increasing asymmetry favors melanoma



Halo nevi

- White halo around a nevus; nevus may be flat or raised and have surface scale or crusting
- Usually preceding erythema; lesions regress over months to years
- Most common on trunk in teenagers with increased number of nevi; up to 50% will have two or more
- Histologically lymphocytes infiltrate nevus
- Most often benign dermoscopic pattern
- ~20% of pts with halo nevi have vitiligo
- New onset of multiple halo nevi can be a sign of an ocular melanoma or cutaneous melanoma elsewhere, esp in older adults
- May appear following immunotherapy for melanoma, eg imatinib, tocilizumab, nivolumab



Recurrent nevi

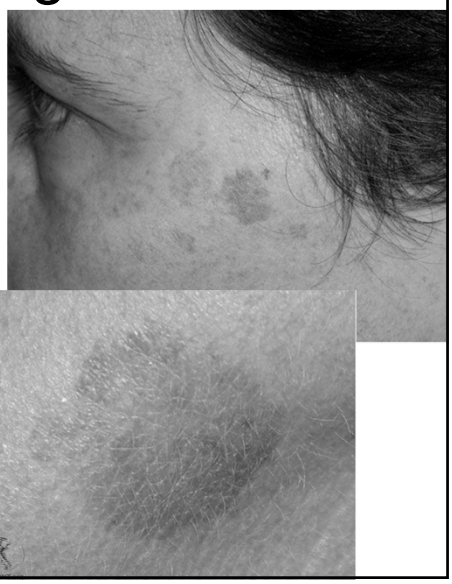
- Fairly common following shave biopsy
- May clinically and histologically resemble melanoma
- Most common on trunk of young females
- Often within 6 mos
- Pigment confined to area of scar and stable over yrs
- Concerning dermoscopic features
- Repeat biopsy if progressive enlargement, extension beyond scar or longer time interval before recurrence*

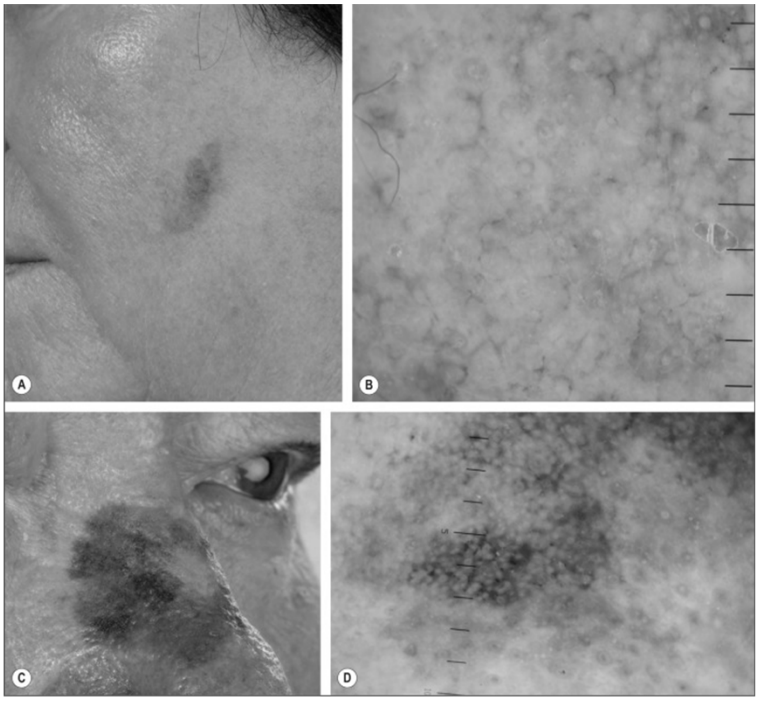
Melanoma with regression

- Usually asymmetric white areas or irregular halo as compared with halo nevi

Solar lentigines

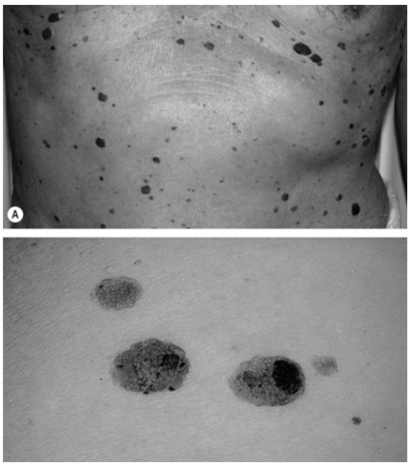
- Well-circumscribed, round to oval, brown to black macules; 3mm-2cm
- Homogenous pigment or mottled appearance
- Almost always multiple; sun exposed sites
- Indicates chronic UV exposure and risk for cutaneous carcinomas
- Lentigo maligna shows greater pigment variation, irregular borders, atypical dermoscopic features





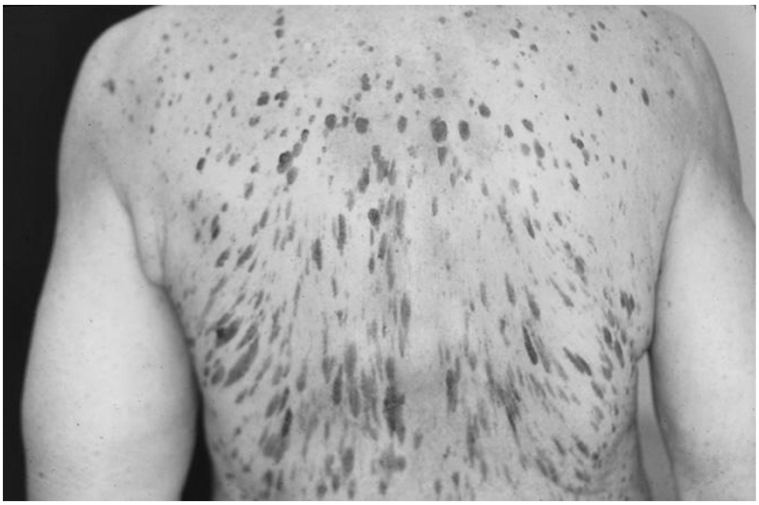
Non-melanocytic mimickers

Seborrheic keratoses



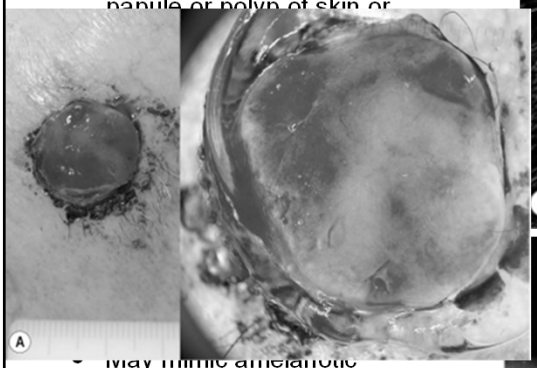
- Appear 4th decade of life
- Can be anywhere excepth mucous membranes, palms and soles
- Tan to black, macular, papular or verrucous lesions; waxy “stuck-on” appearance
- Some lesions difficult or impossible to differentiate clinically from melanoma
- Can usually differentiate with dermoscopy
- Can have collision tumors

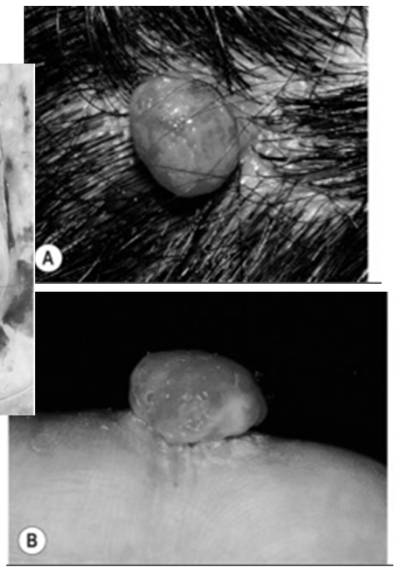
Sign of Leser-Trelát



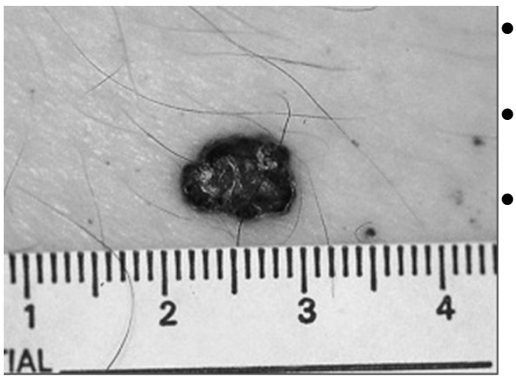
Pyogenic granuloma

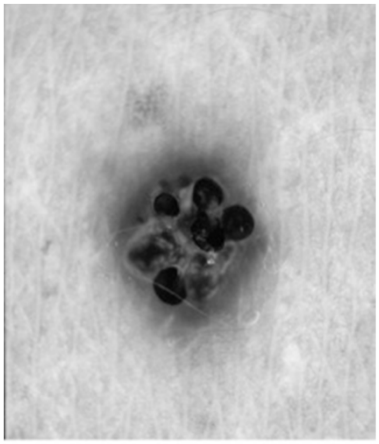
- Rapidly growing, friable red papule or polyp of skin or
- May mimic amelanotic melanoma





Angiokeratoma

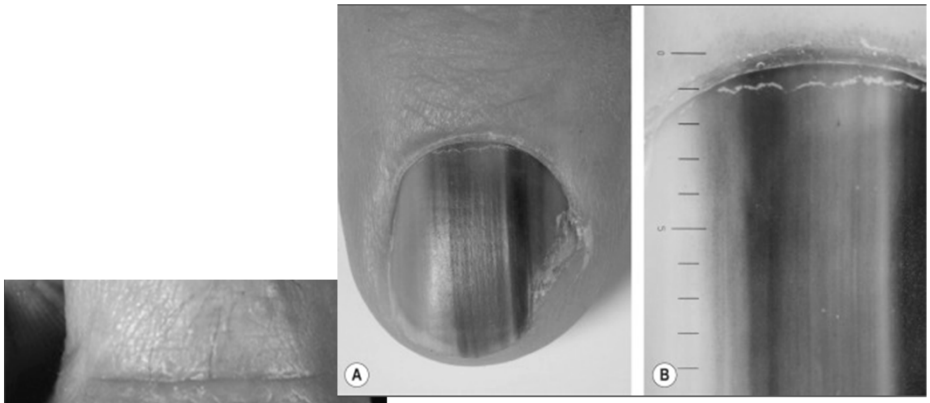




Nail lesions

Nail melanoma

- Nail melanoma most commonly presents with longitudinal melanonychia
- In ~25 % of pts, the lesion is amelanotic
- Most frequently involves the thumb, index finger and great toe
- Diagnosis often delayed and 5 yr survival only 15%
- Peak incidence 5^{th}-7^{th} decades
- Africans, Asians and native americans up to 1/3 of cases
- Width of band usually greater than 3 mm and may have Hutchinson's sign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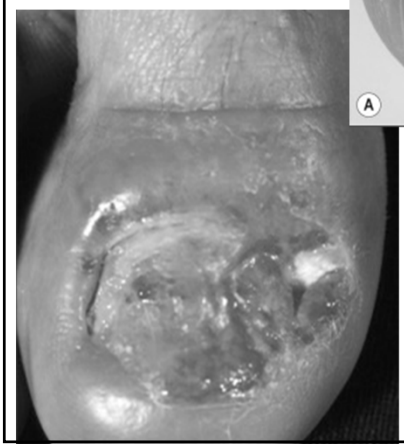

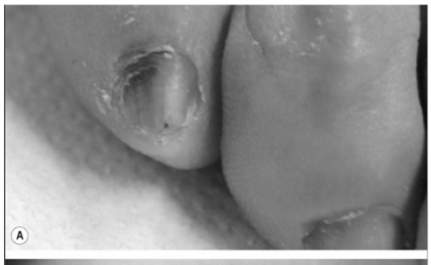
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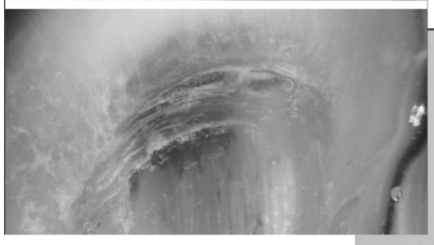
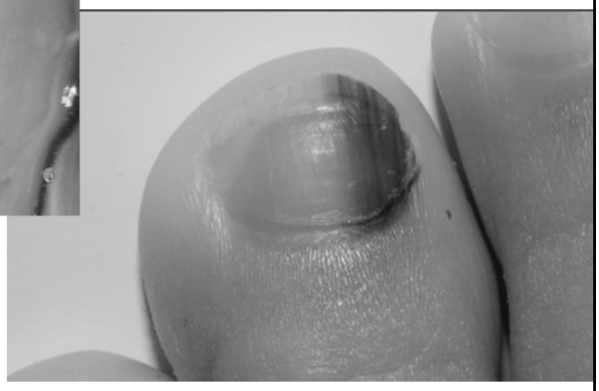




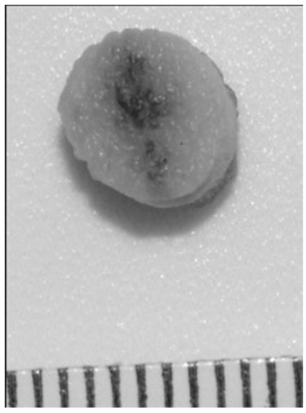
In general…

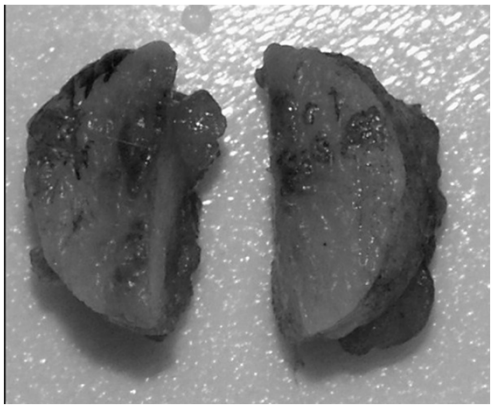
- Rule out exogenous pigment
  - Fungal, hematoma, pyocyanin
- Only one nail affected in an adult (even if amelanotic) → biopsy
  - In child usually due to nevus; if rapidly enlarging or whole nail involved need to biopsy
- Many nails
  - Drugs
  - Racial melanonychia
  - Medications
  - Inflammatory

Evaluation of patient with suspected melanoma

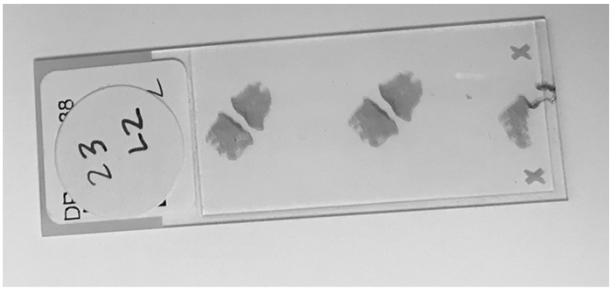
- Medical history
  - Risk factors
  - History of lesion
  - ROS
- TBSE and lymph node exam
- If suspect melanoma
  - Excisional biospy with narrow margins recommended (1-2mm)
  - Deep saucerization many be used for flat lesions or low suspicion for melanoma
- Thoroughly document site of biopsy
- Communicate size of lesion and type of biopsy to the pathologist

The gold standard

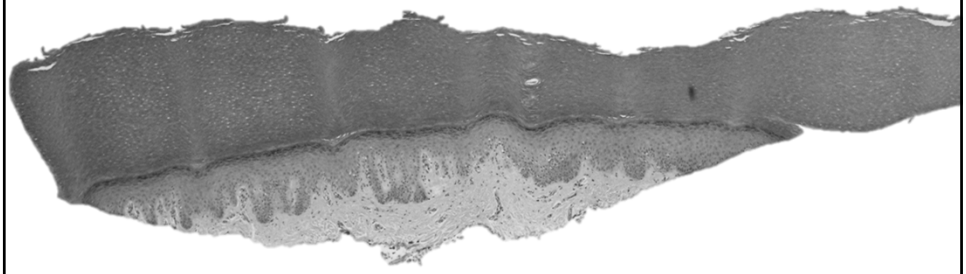


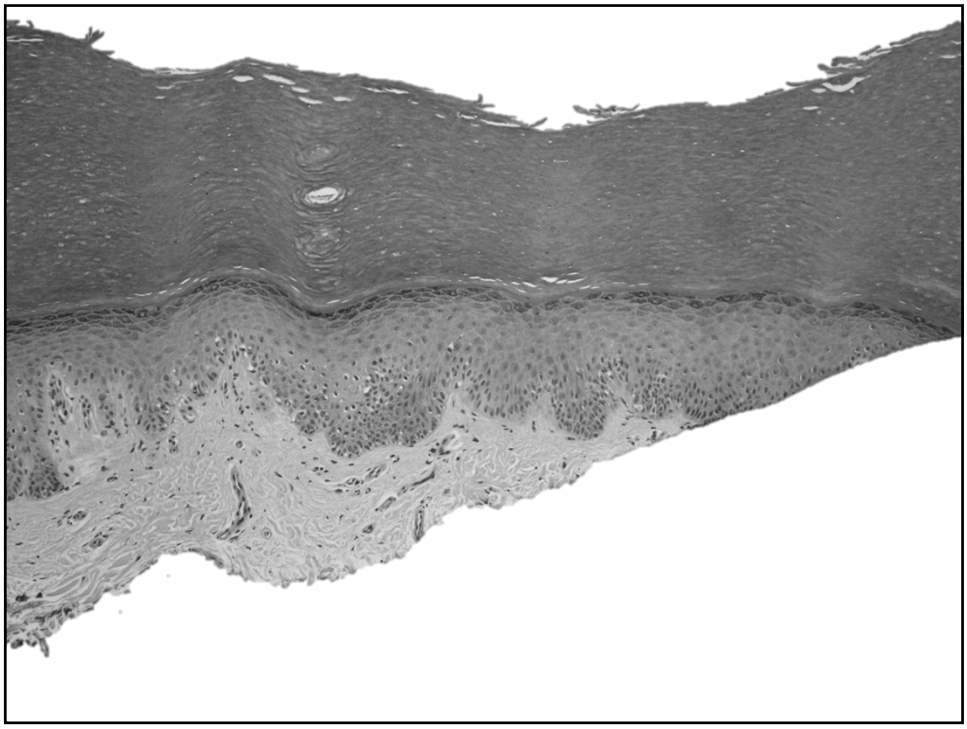


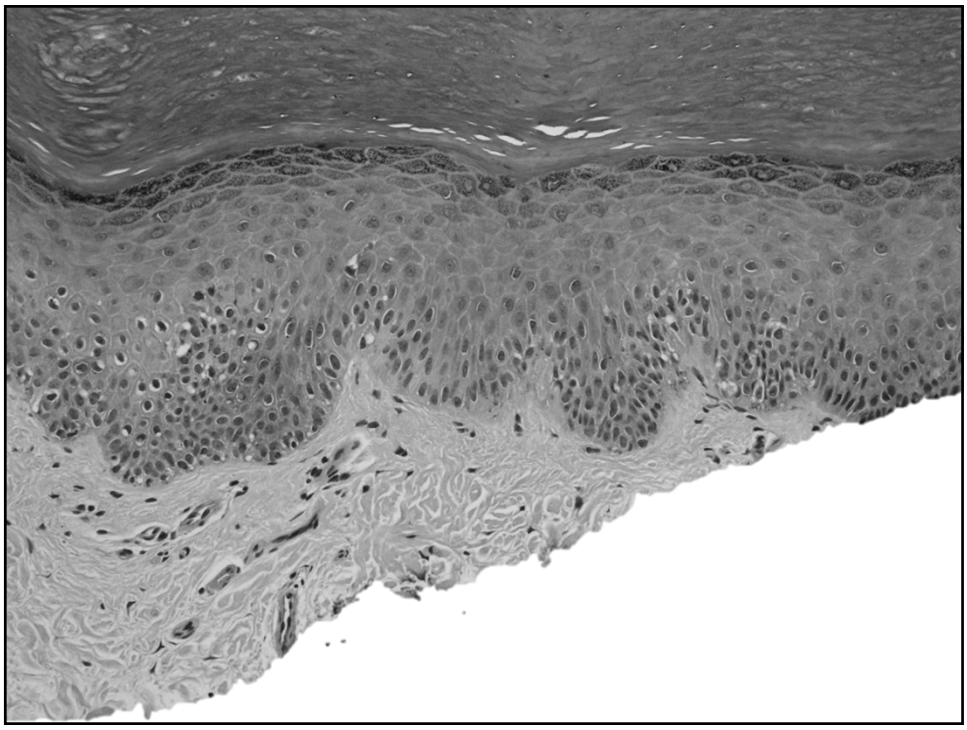
The gold standard

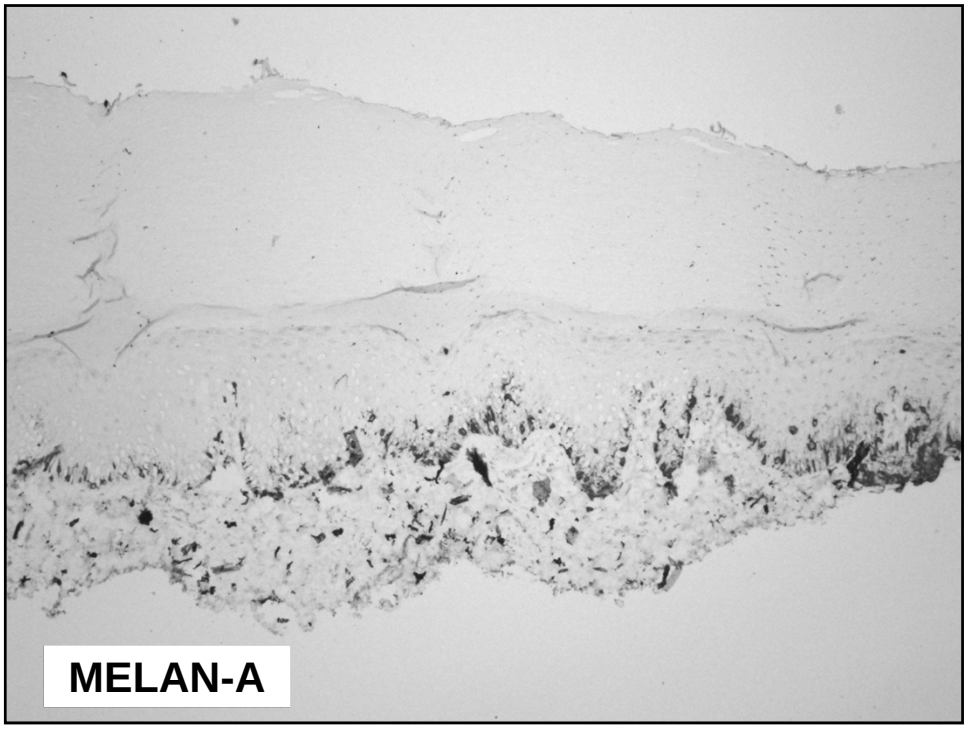


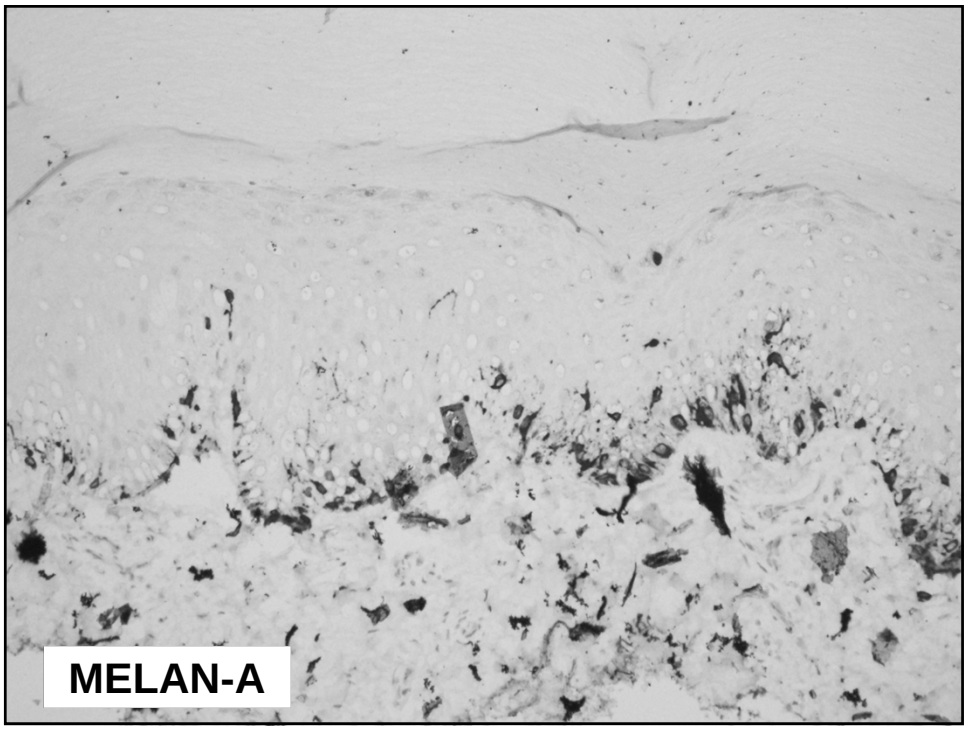
Lesion A



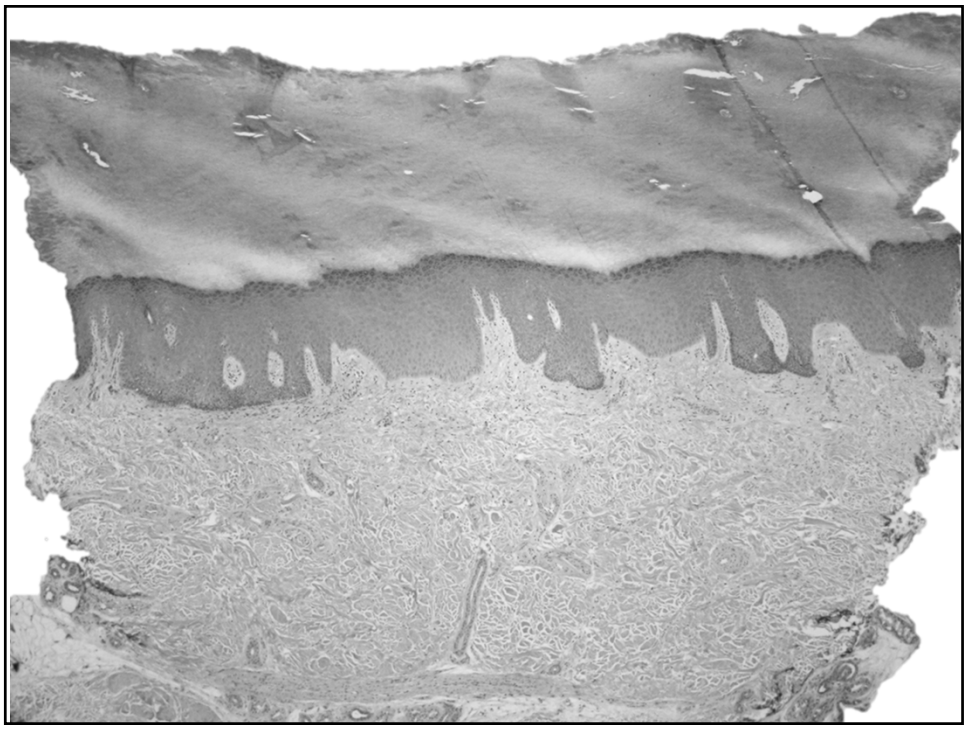


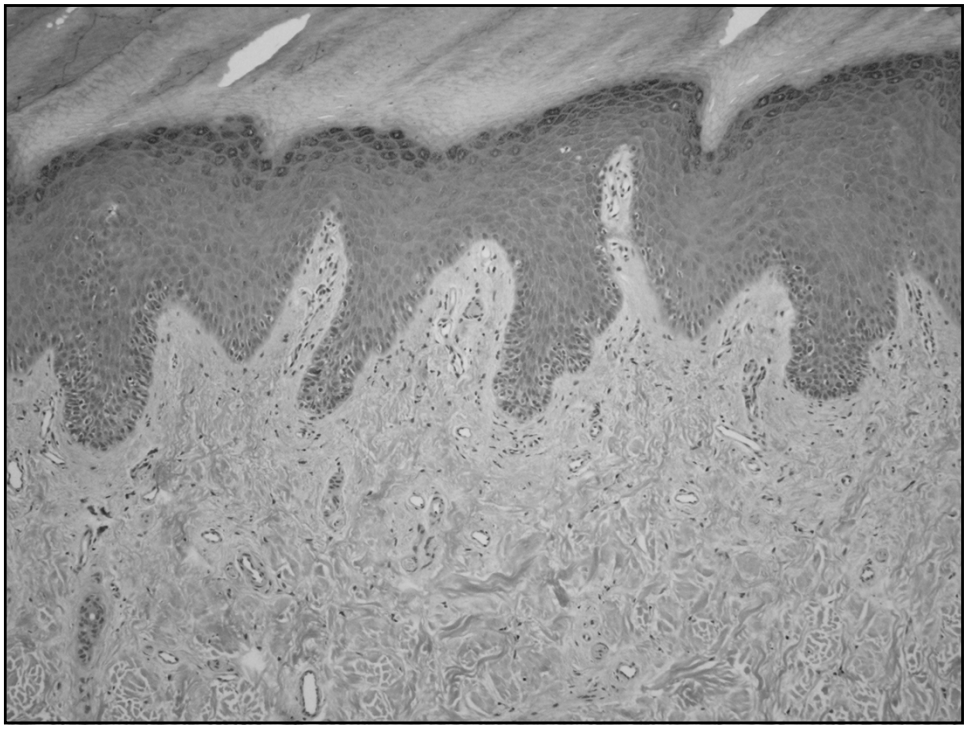


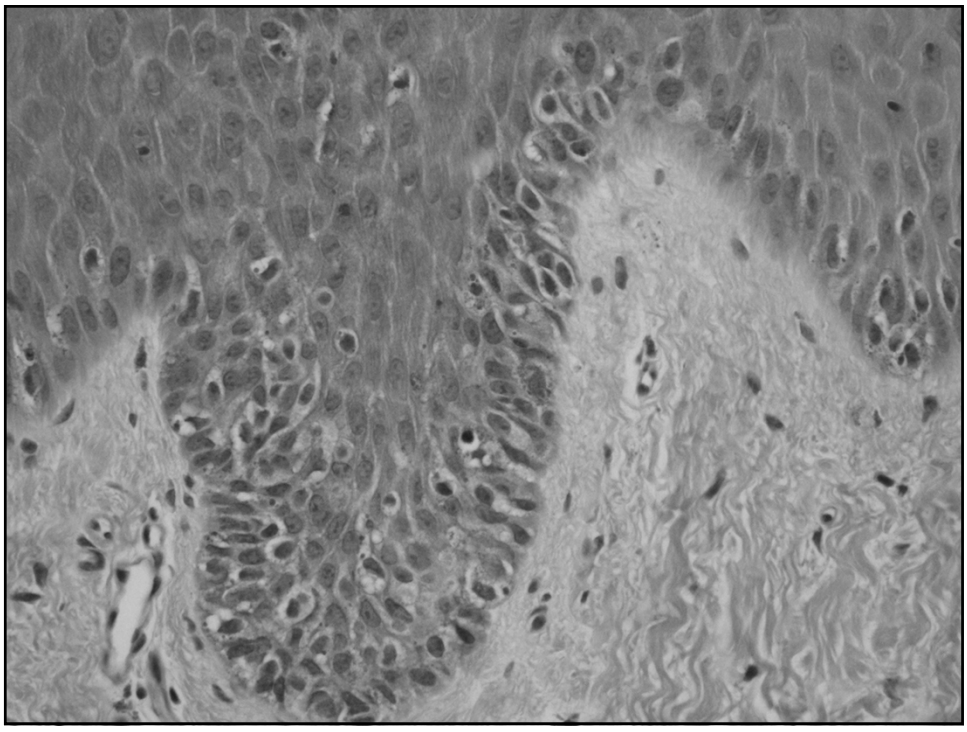

MELAN-A


MELAN-A

Lesion B

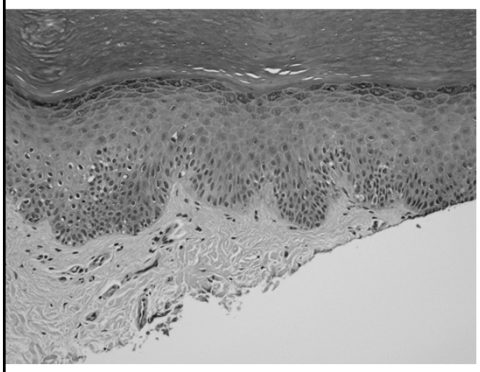




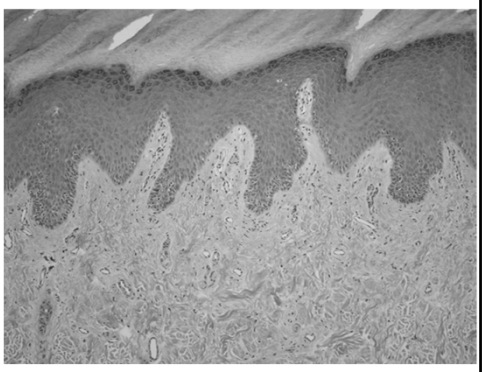


Which is the melanoma?

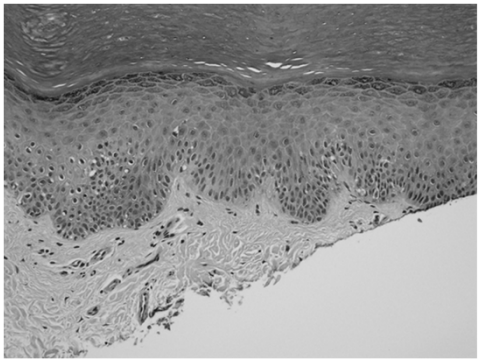
A



B



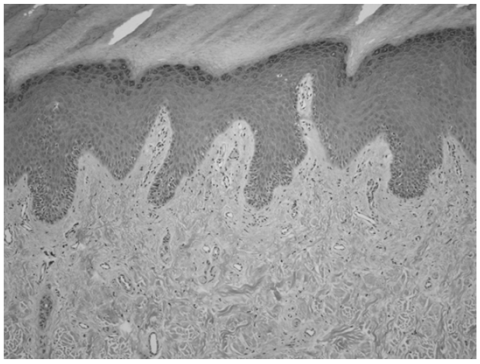
Lesion A

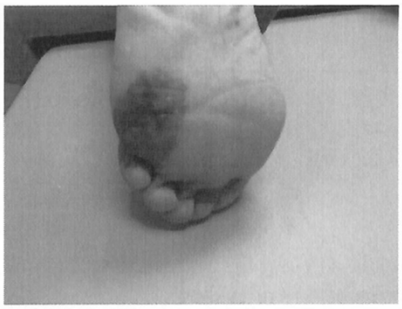


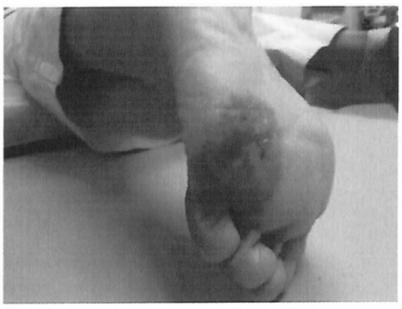
- Further clinical history obtained from the clinician
- Lesion 3 mm in size
- Present for years, stable in size but possibly darker per patient

Lesion B

- Spoke to clinician's office
- Offered to email photo







Treatment

Staging of Melanoma

- American Joint Committee on Cancer (AJCC)
- New guidelines (version 8) to take effect Jan 1, 2018

Staging- TNM

Melanoma TNM staging AJCC UICC 2017

Primary tumor (T)		
T category	**Thickness**	**Ulceration status**
TX: Primary tumor thickness cannot be assessed (eg, diagnosis by curettage)	Not applicable	Not applicable
T0: No evidence of primary tumor (eg, unknown primary or completely regressed melanoma)	Not applicable	Not applicable
Tis (melanoma *in situ*)	Not applicable	Not applicable
T1	≤1.0 mm	Unknown or unspecified
T1a	<0.8 mm	Without ulceration
T1b	<0.8 mm	With ulceration
	0.8 to 1 mm	With or without ulceration
T2	>1 to 2 mm	Unknown or unspecified
T2a	>1 to 2 mm	Without ulceration
T2b	>1 to 2 mm	With ulceration
T3	>2 to 4 mm	Unknown or unspecified
T3a	>2 to 4 mm	Without ulceration
T3b	>2 to 4 mm	With ulceration
T4	>4 mm	Unknown or unspecified
T4a	>4 mm	Without ulceration
T4b	>4 mm	With ulceration

N

category	Extent of regional lymph node and/or lymphatic metastasis	
	Number of tumor-involved regional lymph node	**Presence of in-transit, satellite, and/or microsatellite**
NX	Regional nodes not assessed (eg, SLN biopsy not performed, regional nodes previously removed for another reason). **Exception:** Pathological N category is not required for T1 melanomas, use cN.	No
N0	No regional metastases detected	No
N1	One tumor-involved node or in-transit, satellite, and/or microsatellite metastases with no tumor-involved nodes	
N1a	One clinically occult (ie, detected by SLN biopsy)	No
N1b	One clinically detected	No
N1c	No regional lymph node disease	Yes
N2	Two or three tumor-involved nodes or in-transit, satellite, and/or microsatellite metastases with one tumor-involved node	
N2a	Two or three clinically occult (ie, detected by SLN biopsy)	No
N2b	Two or three, at least one of which was clinically detected	No
N2c	One clinically occult or clinically detected	Yes
N3	Four or more tumor-involved nodes or in-transit, satellite, and/or microsatellite metastases with two or more tumor-involved nodes, or any number of matted nodes without or with in-transit, satellite, and/or microsatellite metastases	
N3a	Four or more clinically occult (ie, detected by SLN biopsy)	No
N3b	Four or more, at least one of which was clinically detected, or presence of any number of matted nodes	No
N3c	Two or more clinically occult or clinically detected and/or presence of any number of matted nodes	Yes

M

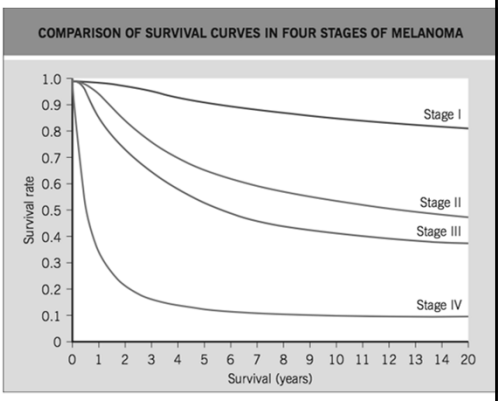
Distant metastasis (M)		
M category	**M criteria**	
	Anatomic site	**LDH level**
M0	No evidence of distant metastasis	Not applicable
M1	Evidence of distant metastasis	See below
M1a	Distant metastasis to skin, soft tissue including muscle, and/or nonregional lymph node	Not recorded or unspecified
M1a(0)		Not elevated
M1a(1)		Elevated
M1b	Distant metastasis to lung with or without M1a sites of disease	Not recorded or unspecified
M1b(0)		Not elevated
M1b(1)		Elevated
M1c	Distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease	Not recorded or unspecified
M1c(0)		Not elevated
M1c(1)		Elevated
M1d	Distant metastasis to CNS with or without M1a, M1b, or M1c sites of disease	Not recorded or unspecified
M1d(0)		Normal
M1d(1)		Elevated

Clinical Staging Melanoma AJCC

T	N	M	Stage
T1a	N0	M0	IA
T1b	N0	M0	IB
T2a	N0	M0	IB
T2b	N0	M0	IIA
T3a	N0	M0	IIA
T3b	N0	M0	IIB
T4a	N0	M0	IIB
T4b	N0	M0	IIC
Any T	>/= N1	M0	III
Any T	Any N	M1	IV

Prognosis (5 year survival)

- Stage IA/B (T1a-T2a/N0/M0)- >90%
- Stage IIA (T2b-T3a/N0/M0)-78%
- Stage IIB (T3b-T4a/No/Mo)- 65%
- Stage IIC (T4b/No/Mo)-45%
- Stage III A (T1-4a/N1a-N2a/M0)- 66%
- Stage III B(T1-4B/N1a or N2a/Mo OR T1-4a/N1b or N2b)- 52%
- Stage III C (T1-4b/N1b or N2b/Mo OR any T and N3)- 26%
- Stage IV- any T/N with M1- 6-18%



Management of Melanoma

- National Comprehensive Cancer Network (NCCN guidelines): 2016 version

Surgical management for primary melanoma

Tumor Thickness	Recommended Margins
In situ	0.5 cm
≤ 1 mm	1.0 cm
1.01 mm- 2mm	1-2 cm
2.01-4 mm	2.0 cm
>4 mm	2.0 cm

--Margins may be modified to accommodate individual anatomic or functional considerations.
--Excision recommendations are based on clinical margins taken at the time of surgery and not gross or histologic margins, as measured by the pathologist

Sentinel Lymph Node Biopsy

- Sentinel node = 1st to receive metastases
- Identifies patients with subclinical nodal metastases, at high risk for recurrence, who should receive CLND and adjuvant therapy
- Useful for staging
- Impact on overall survival has not been proven
- 5-30% patients with Stage I-II are upstaged to Stage III after SLNB

Sentinel Lymph Node Biopsy

- 2013 NCCN recommendations/ASCO
  - Indicated for melanomas >1mm thick
  - <1mm Breslow, risk of regional node mets is 5%
    - SLNB recommended if high risk features (ulceration, mitoses)
- Clinically apparent regional lymph nodes
  - Surgical lymphadenectomy

Management of Melanoma

- Stage 0 in situ- wide excision
- Stage Ia: WLE
- Stage Ib (≤0.75mm, ±ulceration, ±mitotic rate >1/mm2)- wide excision, consider SLNB, CT/PET/MRI only if symptomatic
- Stage IIa (0.76mm-1mm, no ulceration, mitotic rate< 1/mm2)- wide excision, consider SLNB, CT/PET/MRI only if symptomatic

Melanoma Surveillance

- No standard guidelines
- Risk of secondary primary cutaneous melanomas
- Risk of local recurrence (4%, greatest in first 2-5 years)
- Risk of late recurrence (>15 years)
- Risk of other cutaneous and noncutaneous malignancies
- Most recommend 4x/year visit with derm for 2 years then Q6-12 months for life

Summary

- Diagnostic accuracy for clinical diagnosis of melanoma does not exceed 75%, may be increased to 90% with expert use of dermoscopy
- History of change in color, size or shape of pigmented lesion most sensitive clinical sign; clinical context important
- If one pigmented or dystrophic nail in adult → biopsy
- When possible, excisional biopsy is the preferred method for sampling lesions concerning for melanoma; communicate with dermatopathologist
- Patients with dysplastic nevus syndrome and/or high risk for melanoma should be referred to dermatology for close dermatologic surveillance

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