Mihm Cutaneous Pathology Consultative Service

BRIGHAM AND WOMEN'S HOSPITAL

Spindle Cell Melanocytic Tumors

Martin C. Mihm M.D.

Director – Mihm Cutaneous Pathology Consultative Service (MCPCS)
Brigham and Women's Hospital

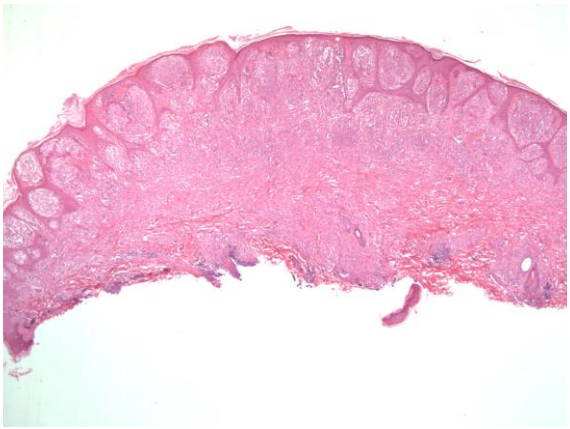
Director – Melanoma Program
Brigham and Women's Hospital and Harvard Medical School

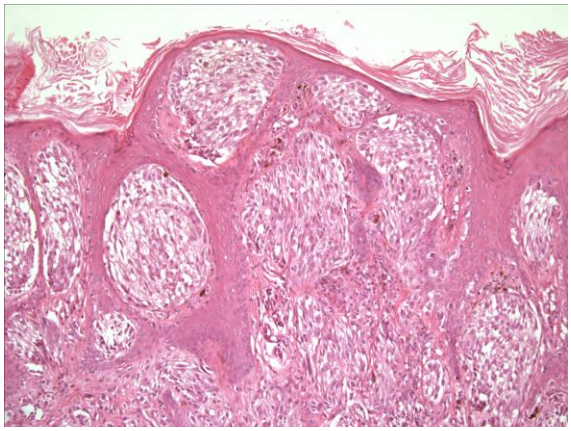
Co-Director – Melanoma Program
Dana-Farber Cancer Institute and Harvard Medical School
European Organization for the Research and Treatment of Cancer (EORTC)

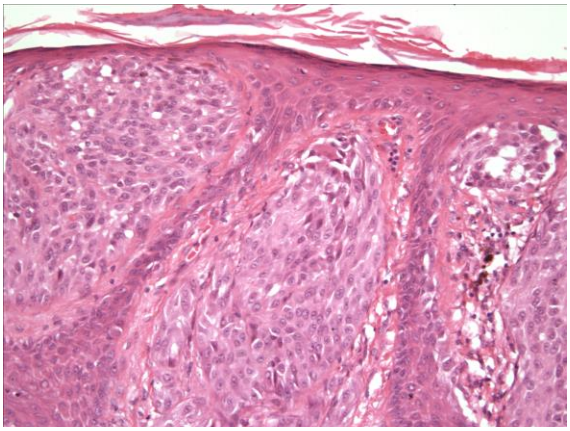
HARVARD MEDICAL SCHOOL

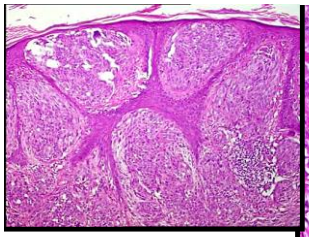
Conflicts of Interest

- Chairman Scientific Advisory Board – Caliber I.D. Inc.
- Member Scientific Advisory Board – MELA Sciences Inc.
- Consultant – Novartis
- Consultant – Alnylam

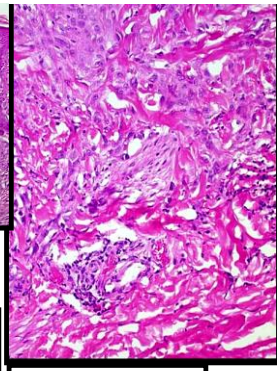






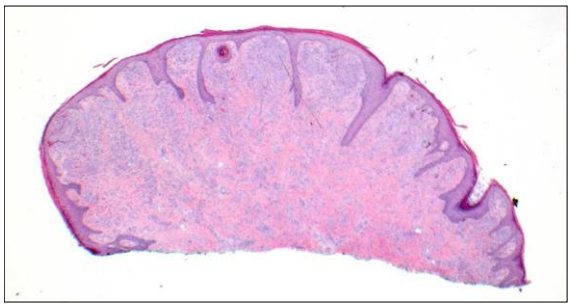


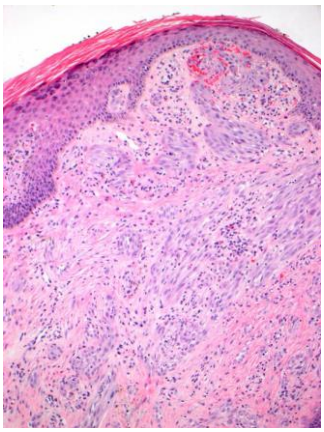
Top of the lesion

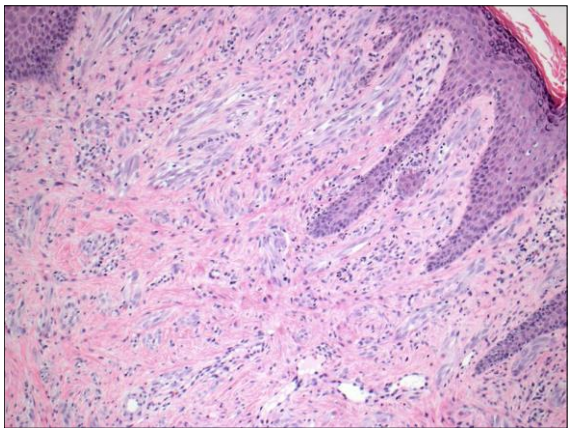


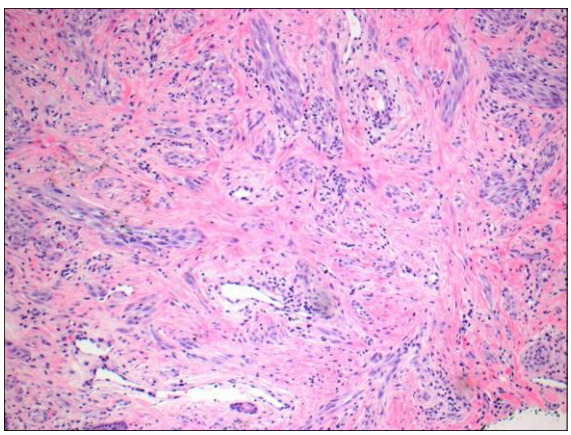
Bottom of the lesion

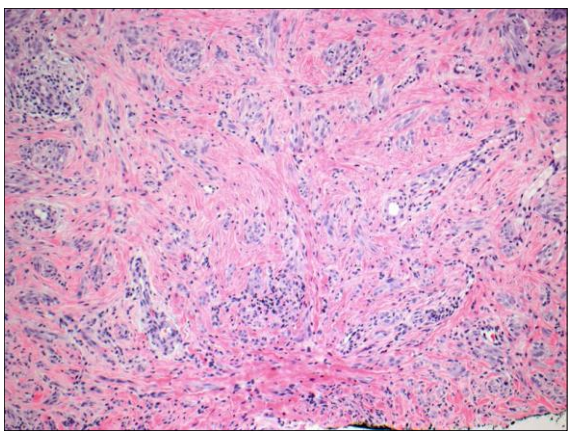
Maturation:
Reduction in nest size and cell size as base is approached

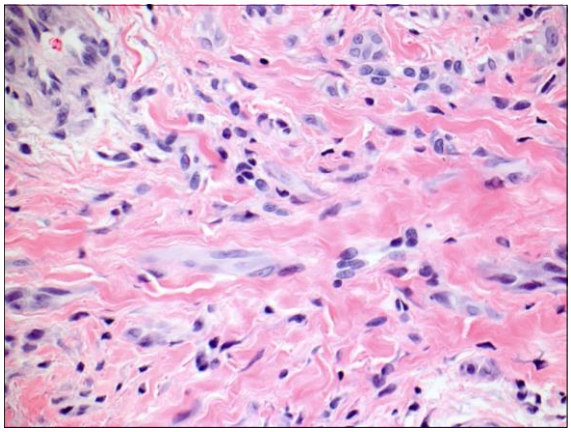












Classical Spitz nevus : clinical morphology

- characteristically on the face of a child
- recent onset and rapid growth
- dome-shaped papule or nodule
- pink-tan or reddish color
  - becomes brown with diascopy
- epiluminescence microscopy:
  - large globules in light tan background
  - radial streaming in a starburst array

Spitz nevus

- Darier and Civatte (1910) : noted that some pigmented childhood lesions were indolent
- Spitz (1948) : defined giant cells as predictive of benign outcome in “juvenile melanoma”
- McGovern(1967) : coined the term “Spitz nevus”
- other appellations :
  - spindle cell nevus : (Helwig, 1954)
  - epithelioid cell nevus : (Kernan and Ackerman, 1960
  - spindle and/or epithelioid cell nevus (Paniago-Periera and Maize, 1978)

Spitz nevus : histology

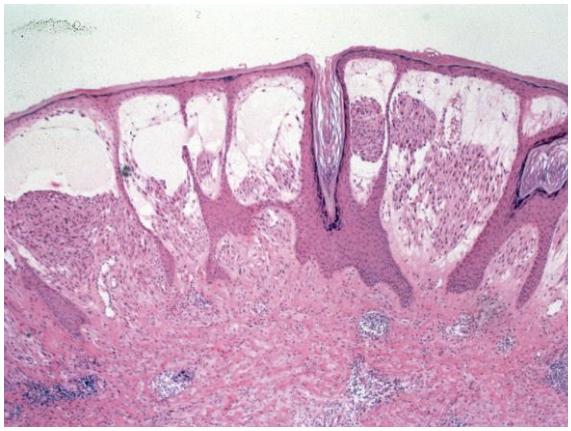
- compound Spitz nevi : 65%
- junctional Spitz nevi : 10%
- dermal Spitz nevi : 25%
  - mainly seen in adults

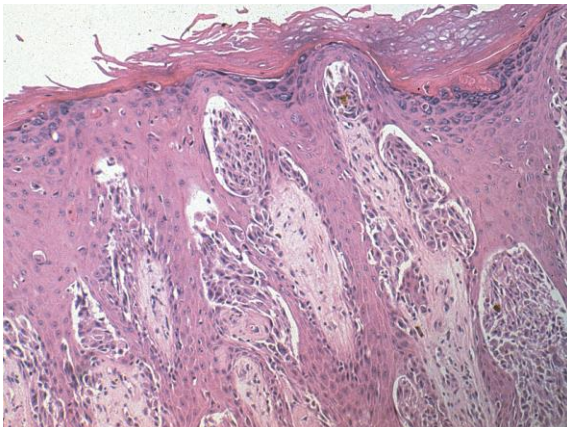
Spitz nevus : histomorphology

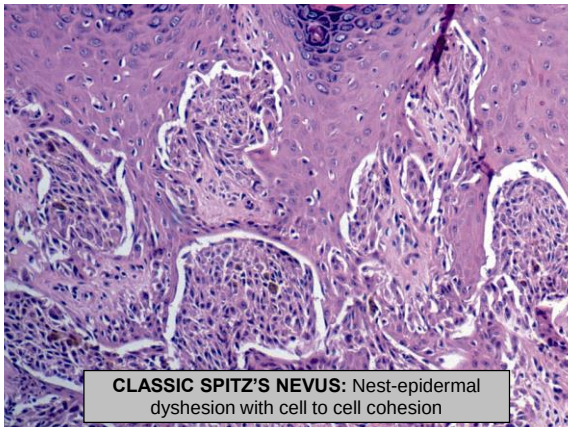
- Architecture :
  - sharply circumscribed dermoepidermal melanocytic proliferation
  - an inverted cone with base parallel to epidermis and apex in reticular dermis
  - large junctional theques separated by cleft-like spaces from hyperplastic epidermis
    - “raining-down” vertical spindled fasicles

Spitz Nevus : Histology

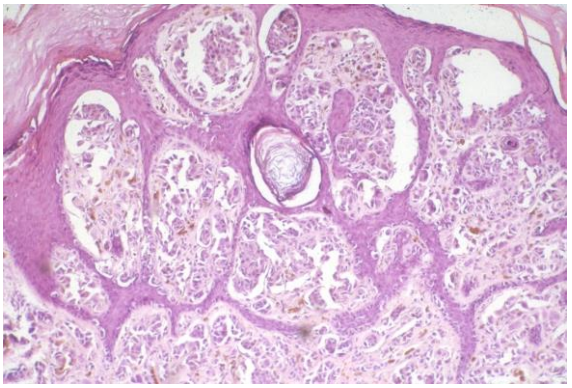
- More common childhood features (especially in first 2 years of life):
  - edema
  - telangiectasia
  - epithelioid cell predominance
  - papillomatosis
  - abrupt maturation – ie – one or two layers at base – common in infancy

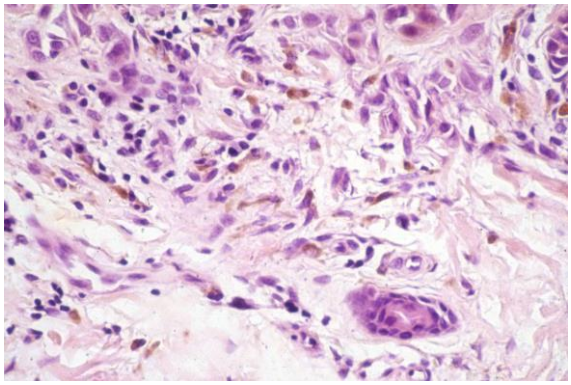






CLASSIC SPITZ'S NEVUS: Nest-epidermal dyshesion with cell to cell cohesion

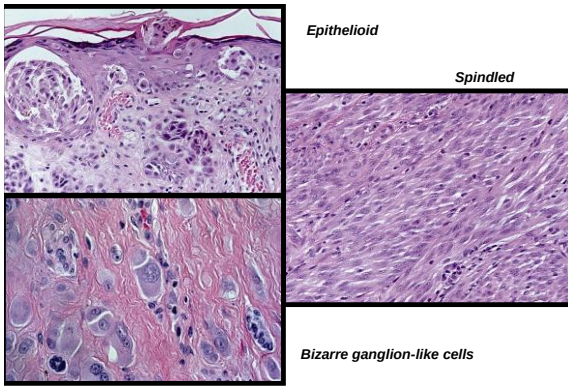




Spitz nevus : cytomorphology

3 cell types:

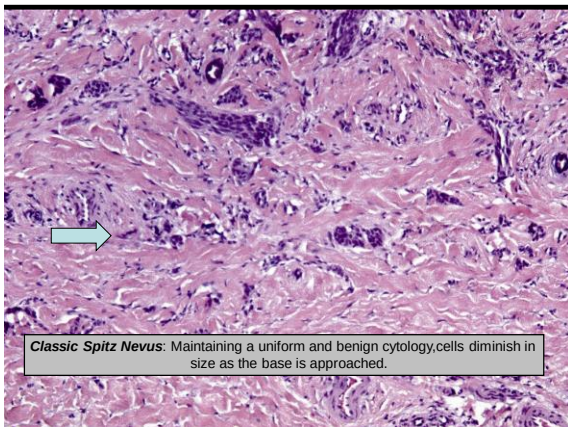
- ganglion cell
- epithelioid melanocytes:
  - large smooth-contoured nuclei with prominent nucleoli, evenly-distributed chromatin, chromatinic rims of uniform thickness; low N/C ratio
  - abundant eosinophilic cytoplasm; spherical shape
- spindled melanocytes:
  - similar nuclei but fusiform clear to variably pigmented cytoplasms



THE CHARACTERISTIC CYTOMORPHOLOGY OF THE SPITZ'S NEVUS

Spitz nevus : histomorphology

- cytology : maturation phenomenon
  - nest and cell sizes diminish towards depth of biopsy, where nests break up into single cells with an infiltrative pattern
    - morphometry confirms diminishing nuclear sizes (Steiner et al., 1994*; Bergman et al., 1996)
    - careful 40X magnification to assess for even scattered small nuclei at base is warranted
    - 500 cubic microns vs 775 in melanoma*
  - maturation absent in some cases



Classic Spitz Nevus: Maintaining a uniform and benign cytology,cells diminish in size as the base is approached.

Spitz nevus : histomorphology

- mitotic figures
  - present in 20% of cases
    - superficial and junctional areas
    - marginal mitoses (ie within 0.25 mm of lesional edge) prompt concern (McCarthy 1994)
  - >5 per mm^2 should prompt concern
- intravascular proliferations
  - seen in 14% of childhood Spitz nevi (Howatt and Variend, 1985)

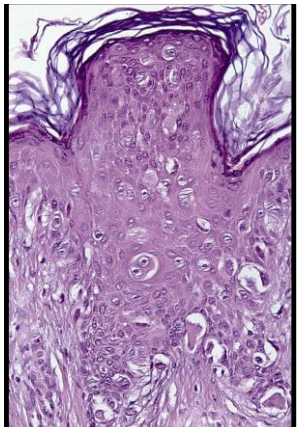
Spitz nevus : Pagetoid spread

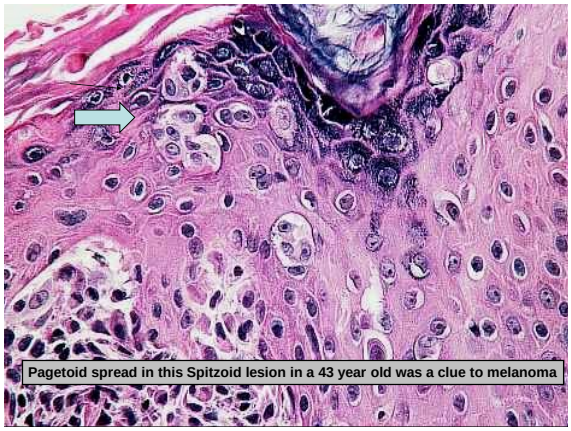
- Present to some degree in most cases
  - prominence in children>adults and in acral>other sites
  - most prominent centrally near maximal nested junctional component
  - does not extend at lateral edges past nested component
  - single cell and nested pattern
  - may involve eccrine/follicular adnexae

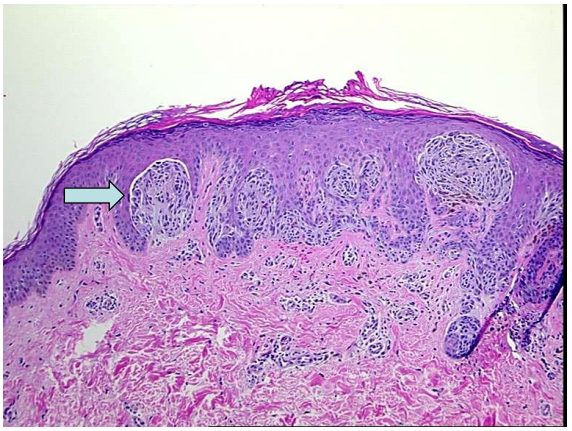
Prominent Pagetoid infiltration with Epithelioid Cytology:

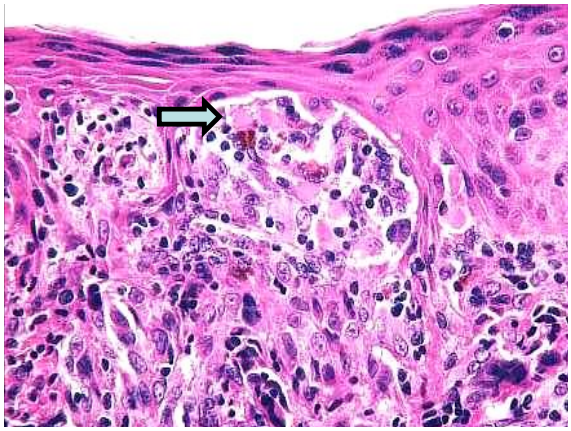
Confined mainly to center of Lesion

Practice point:
The epithelioid cytology is more common in childhood but is unusual in adults and may point to a melanoma when present



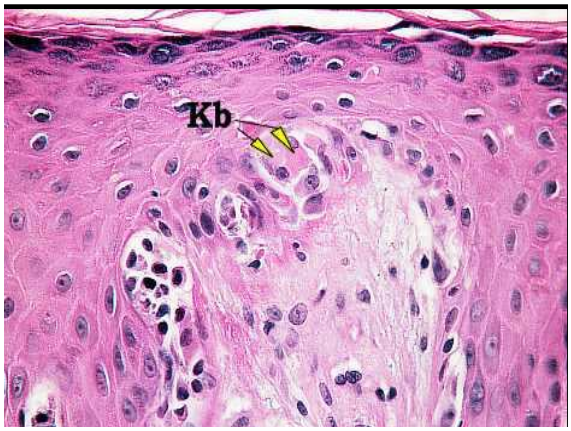






Spitz nevus : histomorphology

- Kamino bodies: (Kamino et al., 1979)
  - seen in 60% of all types of Spitz nevi
  - eosinophilic hyalin bodies 30-40 microns
    - PAS-D-positive/trichrome-positive
  - bundles of filaments and basement membrane components derive from either keratinocyte or melanocyte cytosolic shell
  - coalescence/smaller size variably held to suggest melanoma (Weedon, 1984) or benignancy (McCarthy et al., 1994)

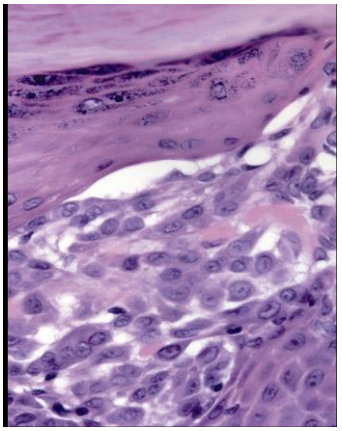


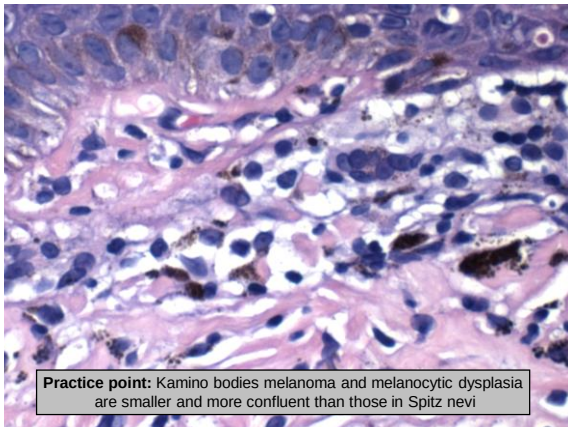
Classic Spitz's nevus

Kamino Bodies:

extracellular filament bundles

trichrome and PAS +





Practice point: Kamino bodies melanoma and melanocytic dysplasia are smaller and more confluent than those in Spitz nevi

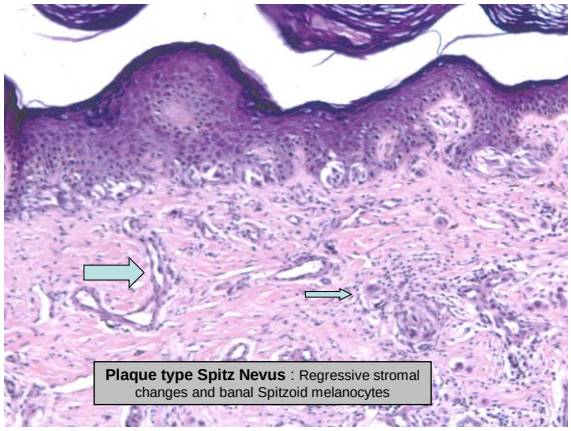
Variants of The Spitz's Nevus

Plaque-like Spitz nevus

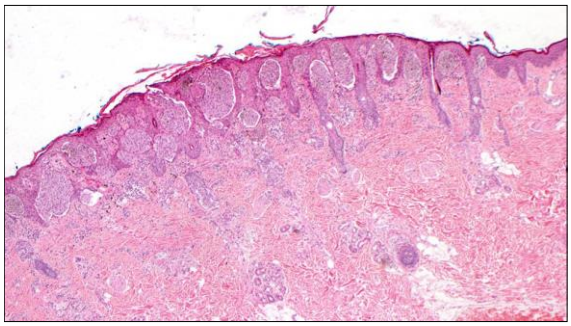
- Most commonly on thighs of women from 20 to 40 years of age.
- Clinically a plaque up to 1.0 cm in size.
- Color variable, pink, brown to black, or flesh colored.
- Clinical diagnosis usually nevus,? Atypia; if pink or fles colored, lichenoid dermatitis or flat wart, respectively.

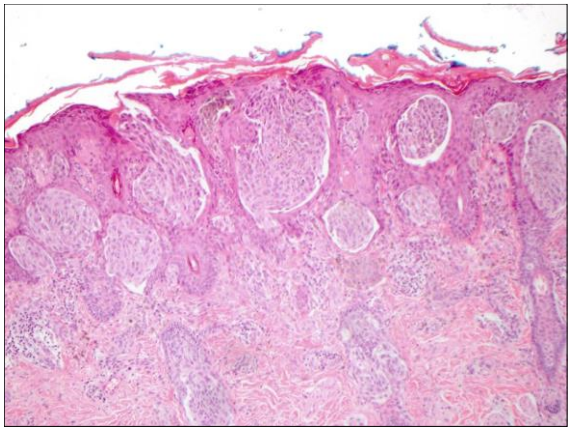
Plaque-like Spitz nevus

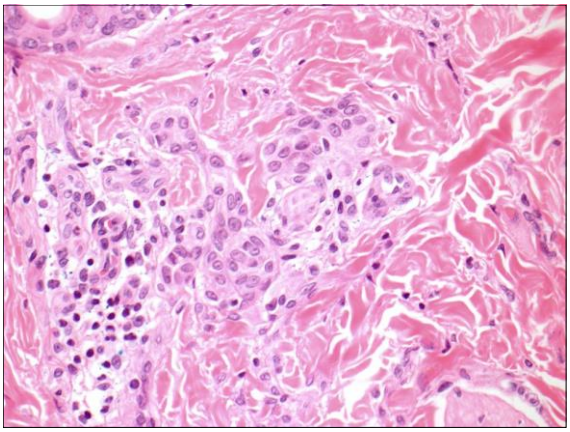
- Normal to slightly hyperplastic epidermis
- Prominent intraepidermal nests with sometimes often pagetoid spread.
- Single and small nested melanocytes in dermis of same morphology as in epidermis- mitoses rare.
- Dermal fibrosis common with prominent vessels.
- Minimal melanophages.



Plaque type Spitz Nevus : Regressive stromal changes and banal Spitzoid melanocytes







Pagetoid Spitz nevus

Busam and Barnhill (1995)

- clinical features :
  - pigmented macule< 0.4 cm in young adult
- histopathology :
  - single cell>nested Pagetoid array of epithelioid cells showing sharp circumscription
    - cells lack angular nuclei
    - abundant cytoplasm with uniform melanization
    - no dominant dermal nodule

Pagets spread phenomenon

Melanoma

Carcinoma

- •Paget's disease
- •Bowen's disease
- •Sebaceous carcinoma
- •Merkel cell carcinoma

Kohler S, Rouse RV, Smoller BR, Mod Pathol 11 (1), 1998
Leboit PE, Crutcher WA, Shapiro PE, AM J Surg Pathol 16 (6), 1992

Frequency of Pagetoid Melanocytosis

	Percent	No. of cases
Melanoma	96	25
Spitz Nevus	38	47
Nerves of palms and soles	61	18
Pigmented spindle cell nerves	20	10
Recurrent nevus	60	10
Vulvar nevus	80	5
Nevus of infancy and childhood	100*	3
Ordinarily acquired nevus	none	3

*cases predicted for pagetoid melanocytosis

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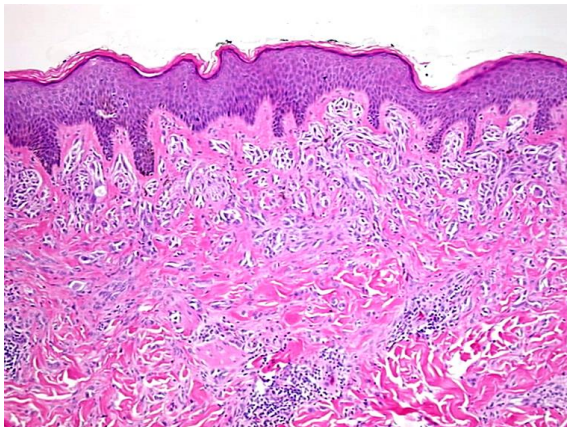
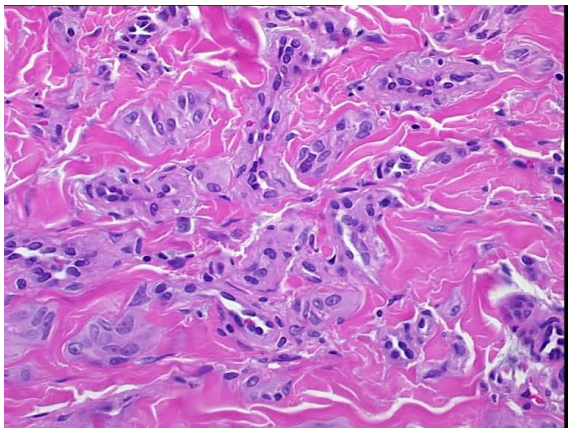
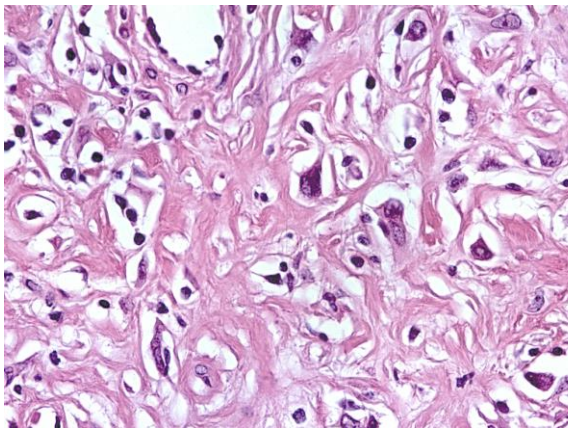
Desmoplastic Spitz nevus

- Clinical features (Reed et al; 1975) :
  - presents in adult life as tan or flesh colored nodule <1.0cm
  - extremities, trunk; duration >3 years
    - spares palms and soles
  - differential diagnosis :
    - scar, dermatofibroma, appendage tumor, or desmoplastic melanoma







Desmoplastic Spitz nevus

- Differential diagnosis :
  - other forms of sclerosing nevus, ie :
    - desmoplastic type A nevus
    - desmoplastic combined nevus
  - sclerosing fibrohistiocytic lesion
  - desmoplastic melanoma

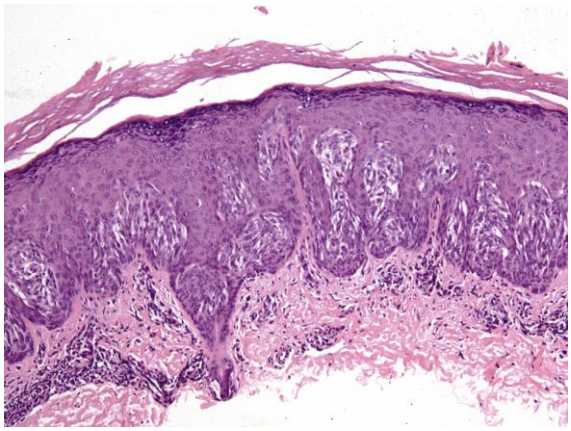
Spindle cell nevus

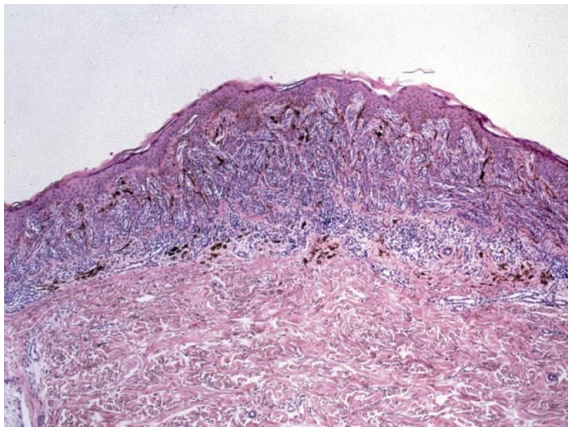
(Reed et al., 1975)

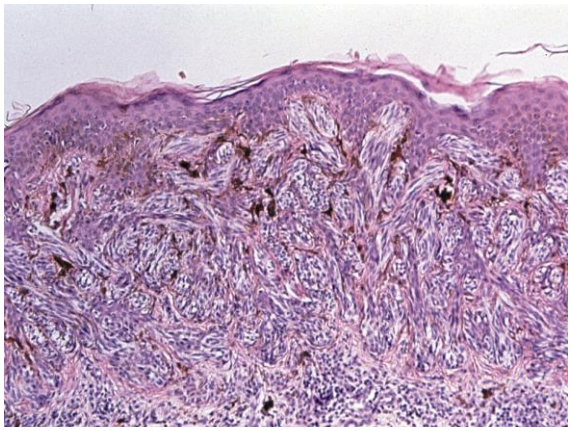
- Clinical features :
  - black or dark dome shaped lesion
  - 2-6 mm in diameter
  - located on proximal extremities or trunk
  - classically young woman (second decade)
  - preferentially on knees + elbows in children
  - 50% on thigh or arm in 1 series **(Sagebiel, 1984)**

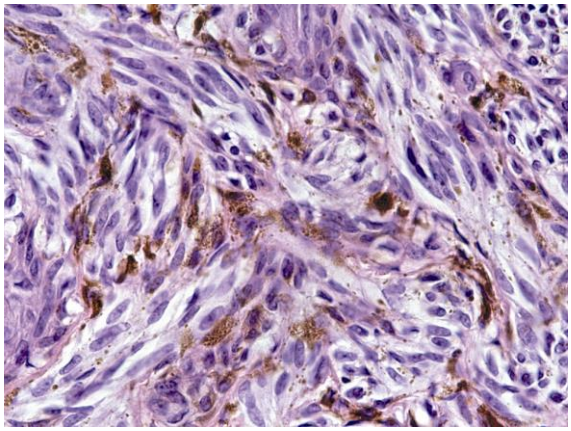
Spindle cell nevus
(Reed et al., 1975)

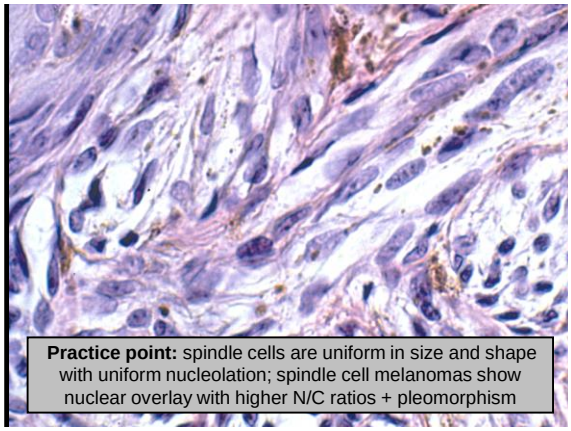
- Histological features : architecture
  - a superficial plaque-like growth involving epidermis+/-dermis (2/3 compound)
  - vertically oriented spindled cells in retia; horizontal disposition when fused
  - fine papillary dermal collagen present; lamellar fibroplasia usually absent
  - Pagetoid spread common; whole nests classic
  - Inflammation frequent but regression rare







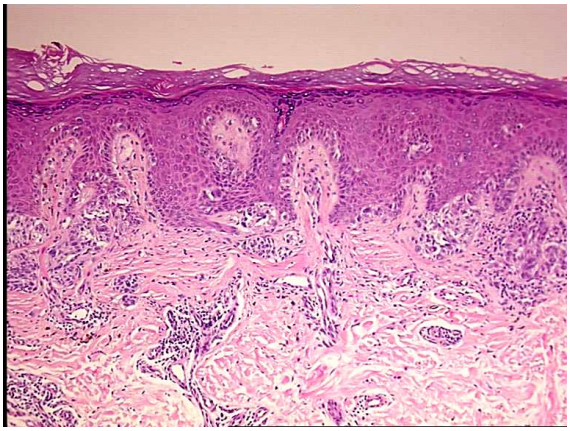


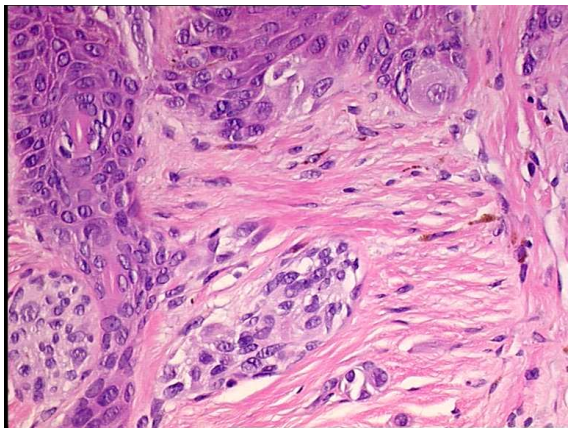


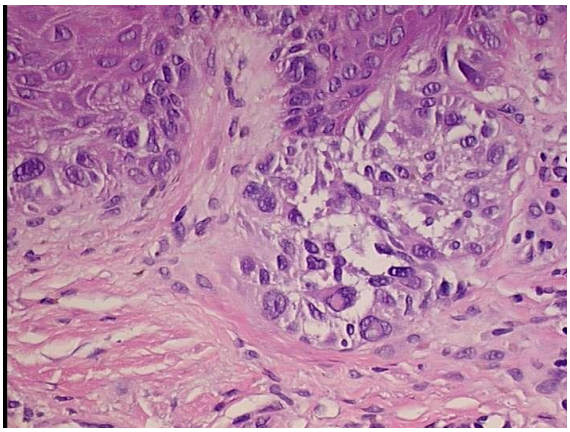
Practice point: spindle cells are uniform in size and shape with uniform nucleolation; spindle cell melanomas show nuclear overlay with higher N/C ratios + pleomorphism

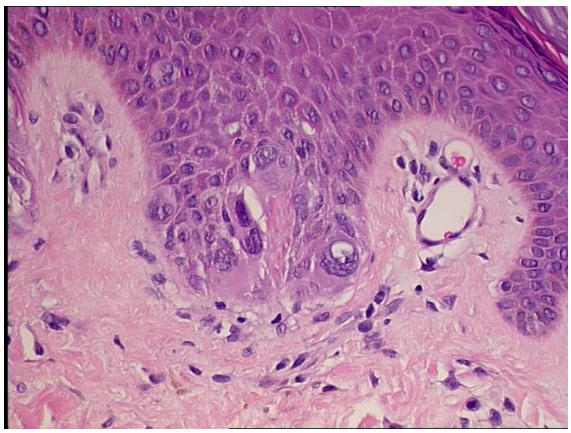
Dysplastic variant of a Spitz's nevus

- There are atypical nevomelanocytic proliferations which manifest overlap features between a Spitz's nevus and a dysplastic nevus.
- The cardinal features are a cytomorphology defining that encountered in the Spitz's nevus in concert with an architecture typical for a dysplastic nevus.
- ***The designation***: Dysplastic nevus with overlap cytomorphologic features with a Spitz's nevus/dysplastic Spitz's nevus









Spindle / Epithelioid Cell Nevus

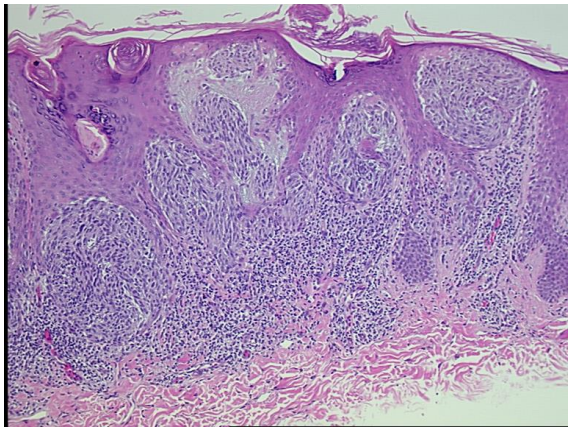
Typical

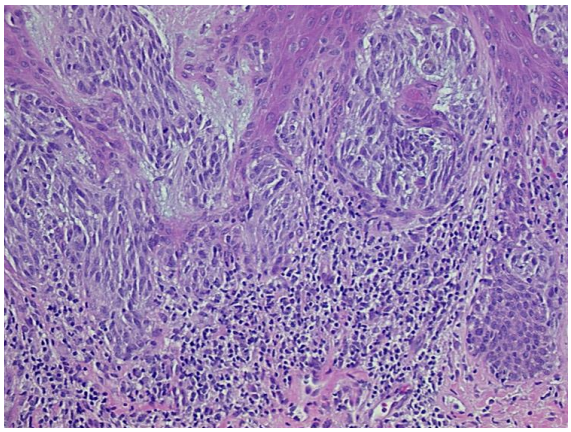
Atypical

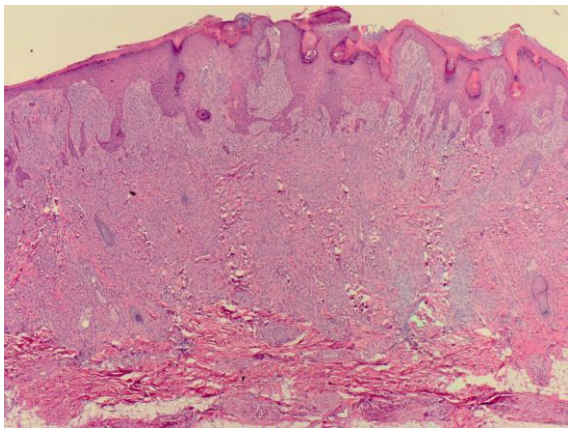
Atypical Spitz Nevus

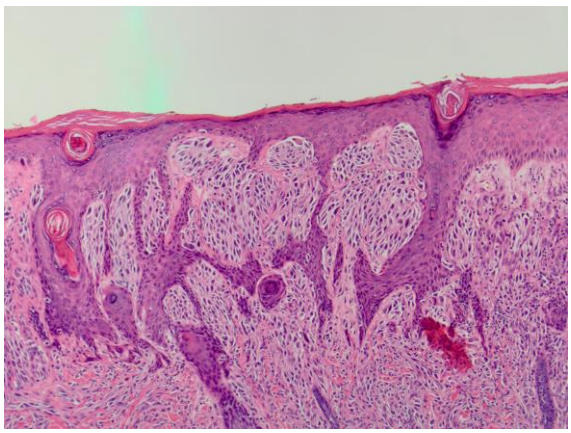
- Superficial expansile nodules
- Asymmetry
- Impaired maturation
- Rare dermal mitosis, especially deep in adults

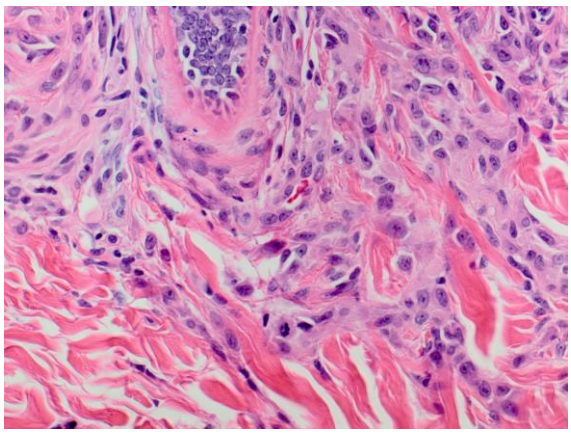
- These are changes that, as single features, would prompt the diagnosis of “Atypical Spitz Nevus”









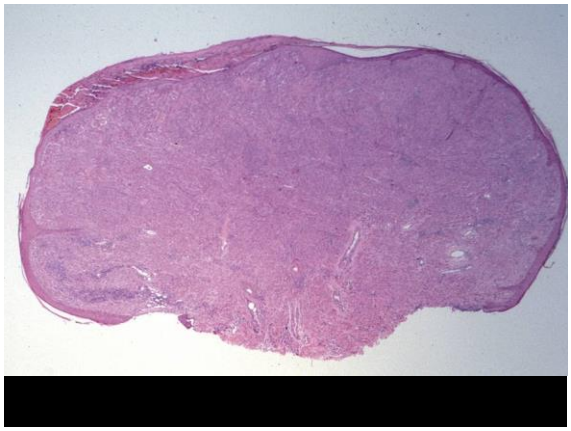


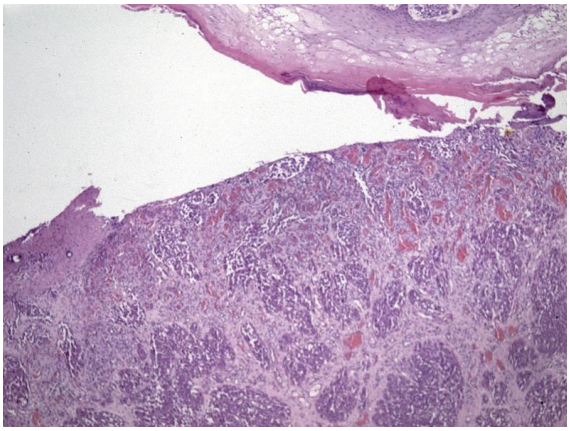
Atypical Spitz's tumor
(Barnhill et al., 1999)

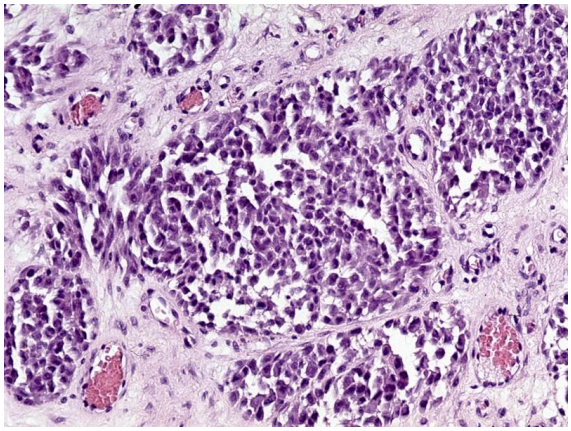
- Subset of Spitzoid melanocytic proliferations with a worrisome histology but indeterminate biologic behaviour
  - architecture resembles VGP melanoma
  - cytology resembles conventional Spitz
  - metastases, when present, tend to confine to regional lymph nodes
- often larger than usual Spitz nevus: >2cm
- clinical appearances otherwise similar to common Spitz's nevi

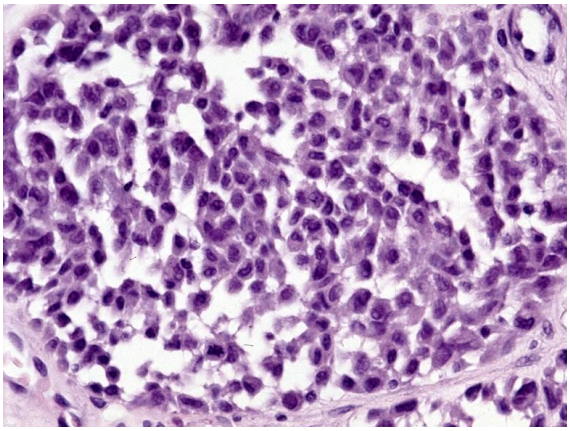
Atypical Spitz's tumor
(Spatz et al, Arch Dermatol 1999)

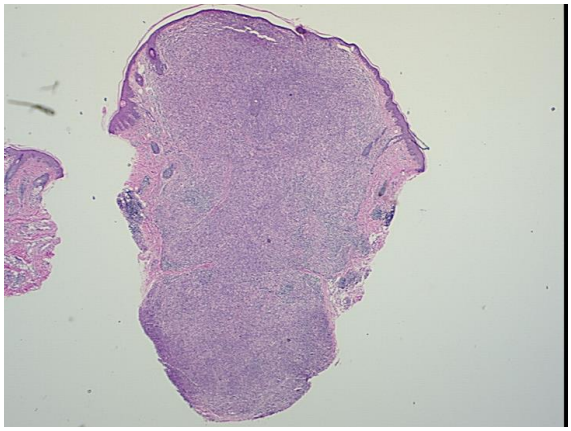
- Histomorphology divided by a scoring system into low/intermediate and high risk
- Conclusion of study: the only independent prognostic variables were:
  - age > 10 years
  - ulceration
  - involvement of subcutis
  - mitotic rate >6 per square mm

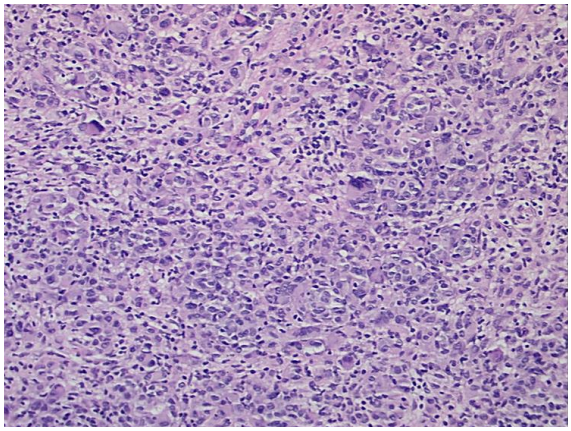


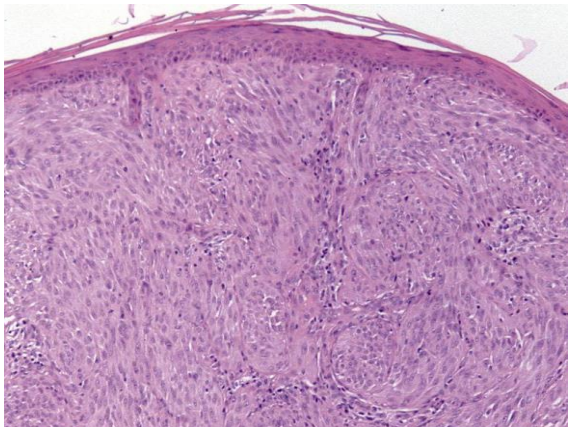


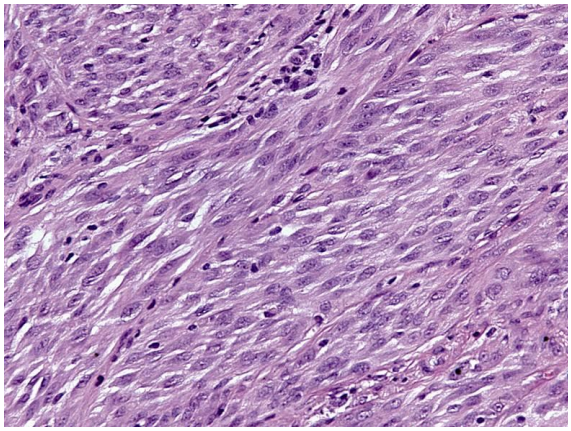










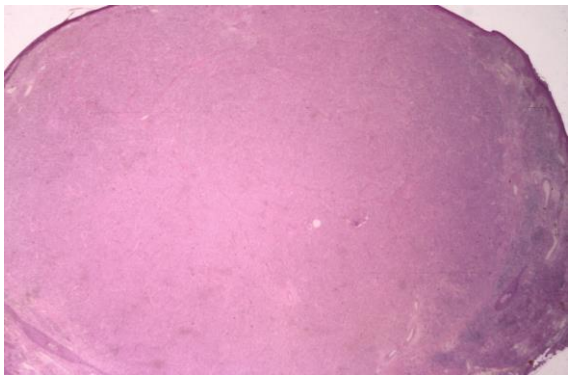


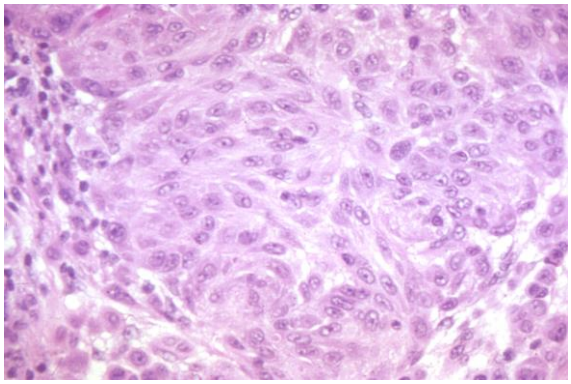
Atypical Spitz's tumor

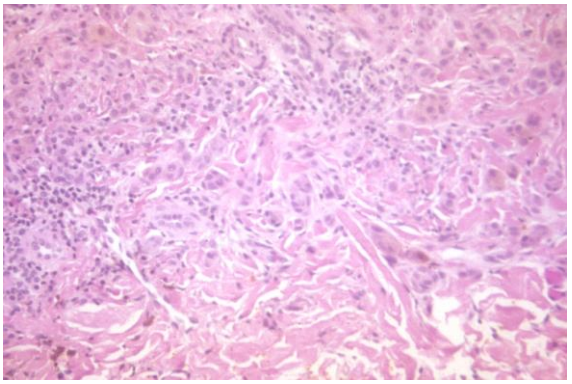
(Busam and Barnhill, 1995)

- **Classical Spitz**
- Size : <1 cm
- symmetrical
- sharp demarcation
- regular nesting
- absent deep extent
- absent expansile nodule

- **Atypical Spitz**
- Size : >1 cm
- asymmetrical
- sharp demarcation-ve
- irregular nesting
- deep extension
- expansile nodule present







Criteria to Distinguish Spitz Nevus From Malignant Melanoma

Table derived from:

Spitz Nevus versus Spitzoid Malignant Melanoma: An Evaluation Of the Current Distinguishing Histopathologic Criteris

Walsh N, Crotty K Palmer A, McCarthy S. Human Pathol 29: 1105-1112

Malignant

- **Breslow thickness (thicker than 2.0mm)**
- **Diameter greater than 1.0 cm**
- **Asymmetrical**
- **Marked pagetoid spread, especially in teenagers, of epitheliod cells**
- **Ulceration (childhood)**
- **Dermal nests larger then intraepidermal nests**
- **Marked nuclear hyperchromasia**
- **Dermal mitosis > 5 mm ^{2} (childhood)**

Malignant (cont)

- Mitosis in papillary dermis $\geq$ 4 mm ^{2}
- Atypical mitosis
- Marginal mitosis
- Large pigment granules especially in deep nests
- Large distinctly more pleomorphic deep dermal nests

Benign

- Symmetry
- < 1.0cm in diameter
- Sharp circumscription of epidermal components
- Epidermal hyperplasia
- Nests relatively uniform in size and shape
- Small uniform nests toward base

Benign (con't)

•Single cells at base

•Cells uniform from side to side

•Predominance of spindle cells

•Rare or no mitosis in lower third

•No mitosis at base

•Maturation (diffuse)

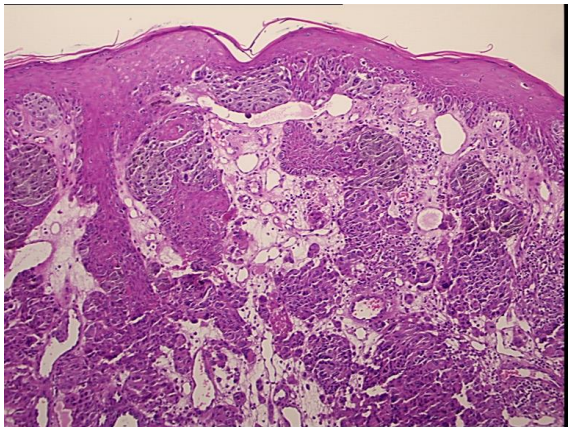
•No regression

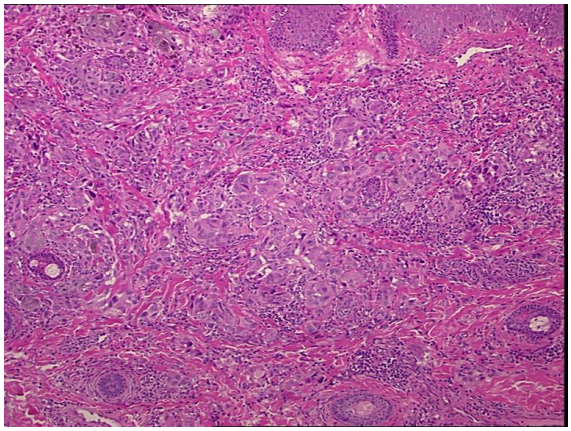
Spitzoid Melanoma

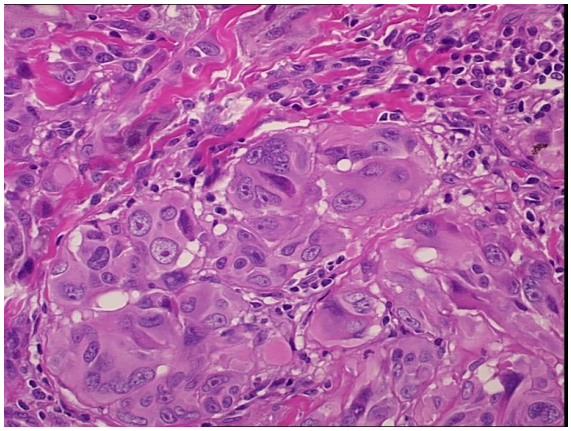
- the classic S*pitzoid melanoma* is seen mainly in the pediatric population most commonly in the head and neck
- the differential diagnosis is primarily the high risk atypical Spitz tumor
- the consensus is that biological behavior is unpredictable
- longer term follow up may reveal a clinical course no different from other types of melanoma

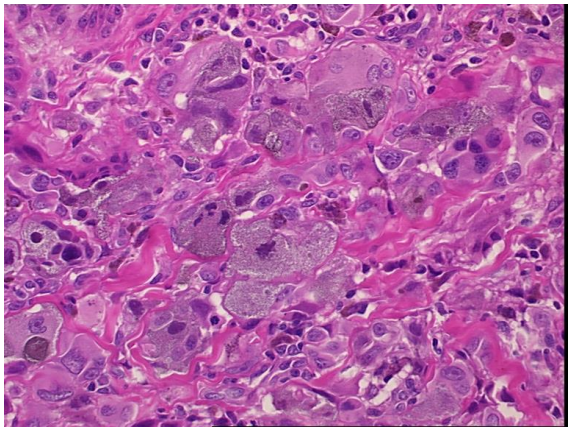
Spitzoid Melanoma

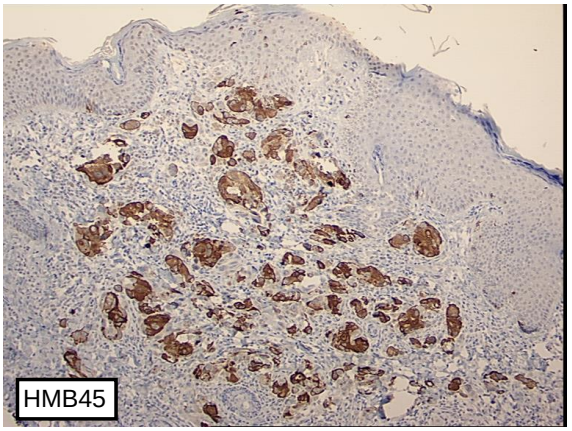
- ***Architecture***: Dominantly dermal based expansile nodule with variable permeation of the subcutis
- Numerous bizarre appearing giant cells similar to those described in the Spitz nevus but with greater pleomorphism and striking nuclear atypia; the cells assume a confluent sheet like disposition.

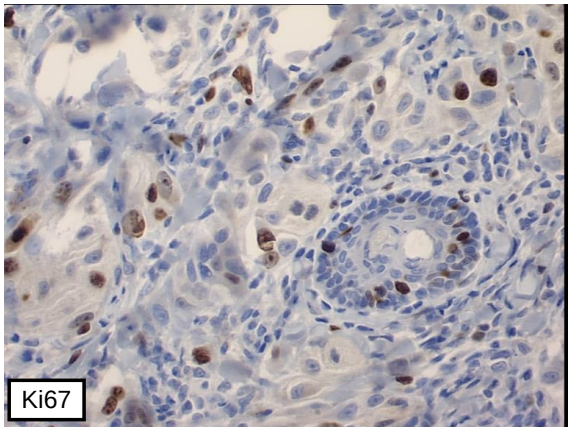


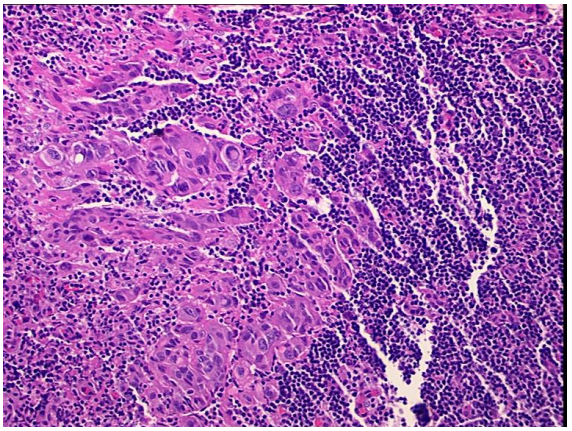












Treatment

- ***Spitz nevi and variants***: complete excision with minimal morbidity
- ***Atypical Spitz's tumors***: excision with current melanoma margins. Narrow margins would be indadequate; sentinel node biopsy with high risk lesions greater than 1 mm.
- ***Spitzoid melanoma***: conventional melanoma therapy with sentinel node biopsy for lesions greater than 1 mm.

Childhood Melanoma

Sites of involvement: Head and neck. Especially scalp when arising in congenital nevi

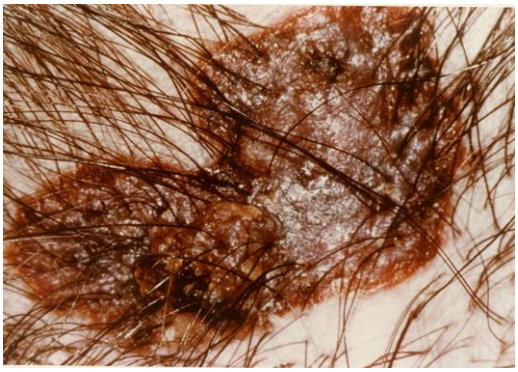
Dorsal surface favored for lesions arising in congenital nevi

For all types: Head and neck > extremities> trunk > generalized skin

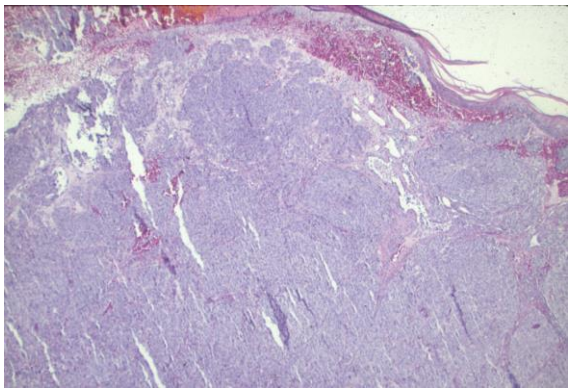
A B

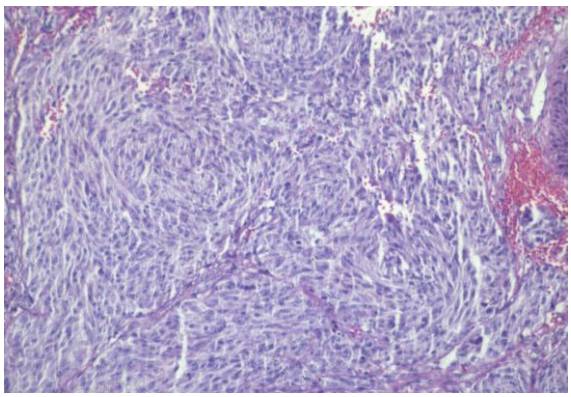
Figure 1. Primary Malignant Melanomas in Two Children.
Shown are a primary malignant melanoma arising in a congenital nevus on the chest of a six-month-old child (Panel A; courtesy of Dr. G. Ibarra-Duran, Mexico) and a primary nodular malignant melanoma on the back of a fair-skinned 14-year-old boy, arising in sun-damaged skin (Panel B).

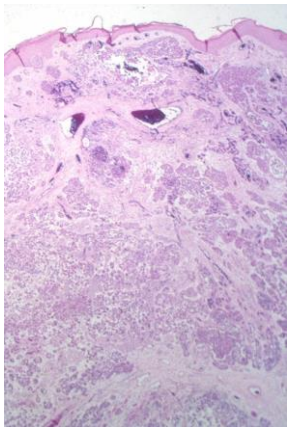
Ceballos et al. NEJM, 1995

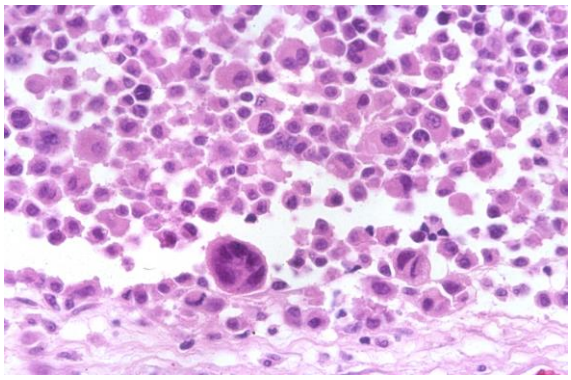


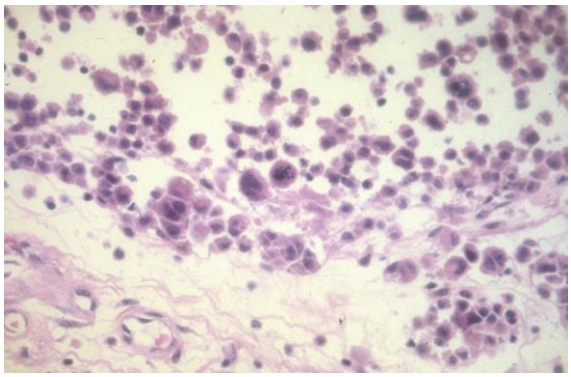
10 year-old girl, scalp, Mihm et al. NEJM, 1973

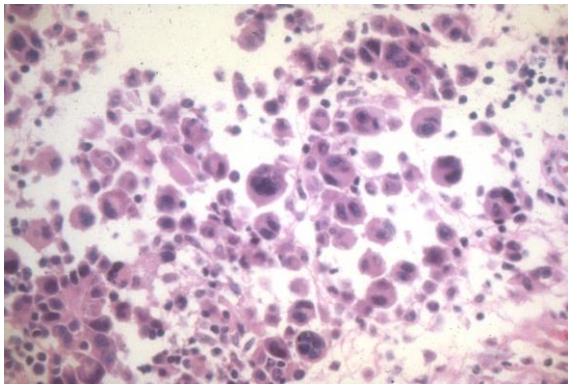


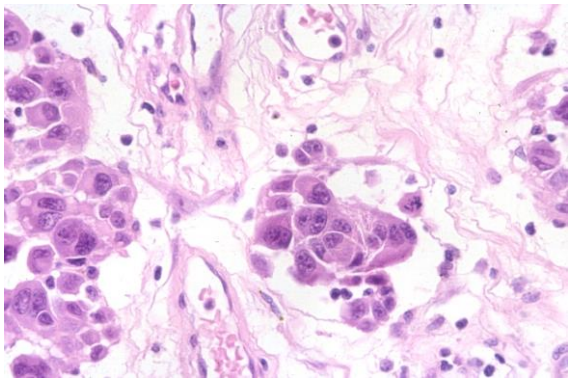


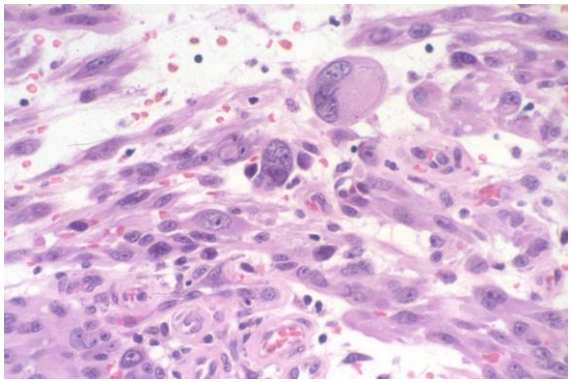


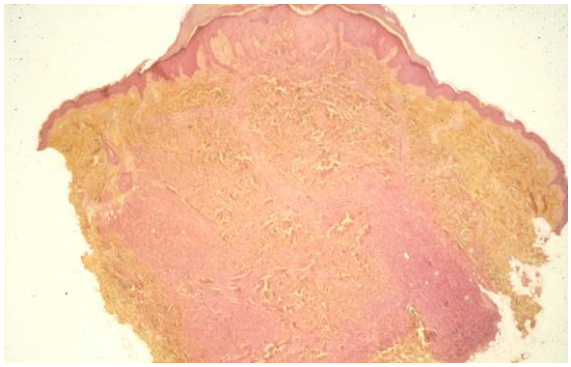


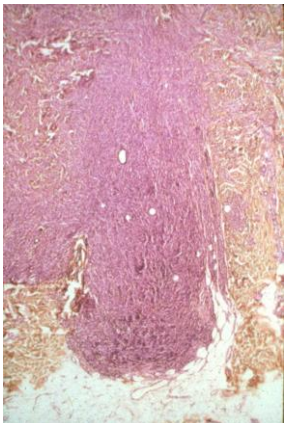


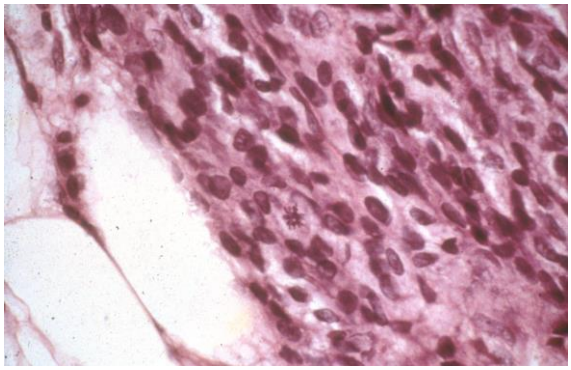








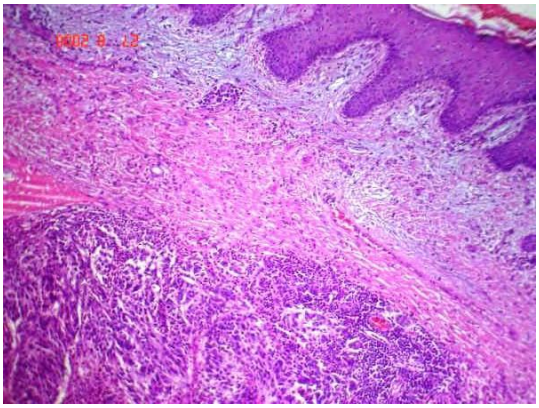


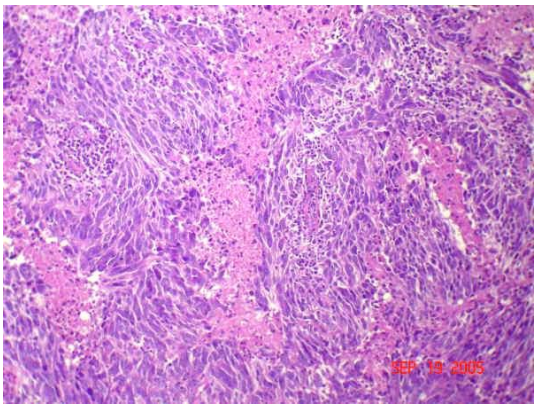


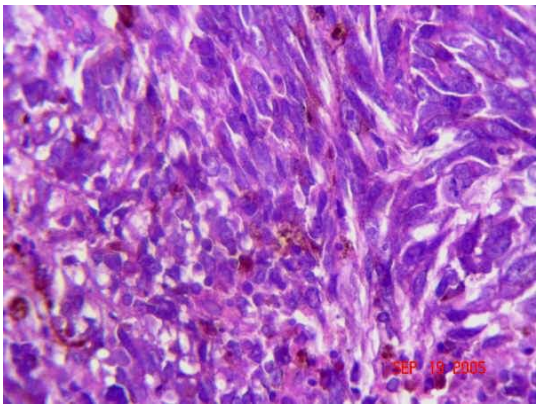
Case:

- 13 year old boy with a “bump” on the scalp for some time that suddenly grew rapidly and ulcerated.
- Clinical Diagnosis: Atypical nevus Vs. Melanoma Vs. Other
- Died within 2 years

13 year-old child, Paraguay

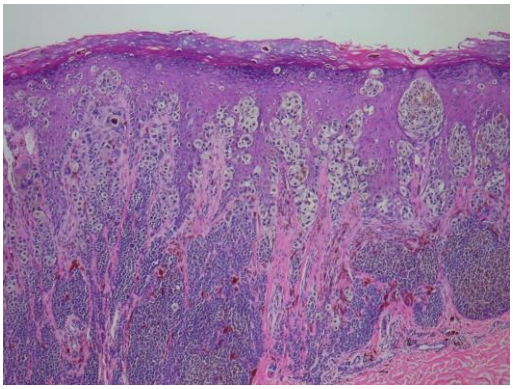


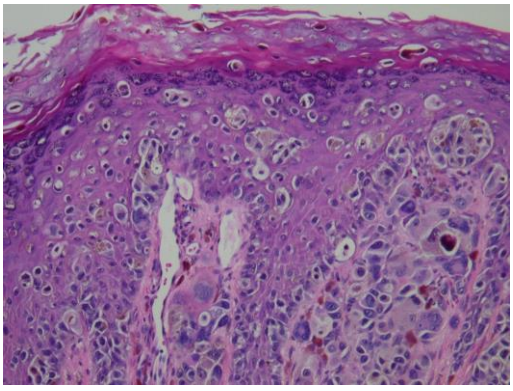


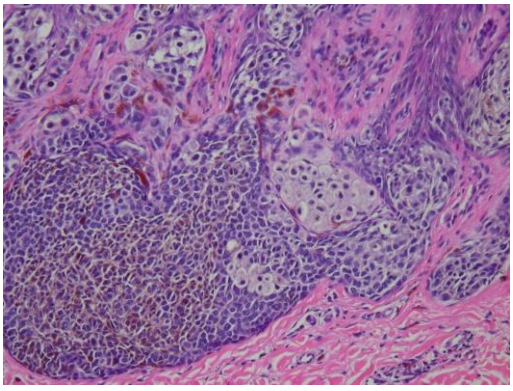


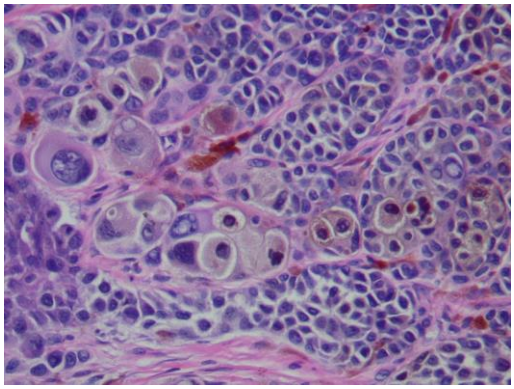
Case:

- 13 years-old, female.
- Primary tumor was 2.2 mm thick (Clark level IV, ulcerated, with a mitotic rate of 3 mit./mm2) and located on the foot. Her lymph node was positive at the time of excision.
- Died of metastatic melanoma 2 years later.









Atypical Spindle/ Epitheliod Cell Nevus Resembling Childhood Melanoma

Clues for the diagnosis of Melanoma

Pleomorphism from one area to another at some level

Deep expansile nodule with monomorphic cells

Multiple deep and marginal atypical mitosis

Lack of maturation with individual cell necrosis

Fine pigment in deep cells

Childhood Melanoma Survival

All patients with metastatic melanoma arising in giant nevi dead within 5 years in study of Trozak et al in 1974

Patients with melanoma arising de novo or in other lesions, including small congenital nevi had 34% survival at 5 years according to Melnick et al

Survival of congenital melanoma poor, > 40% dead within 18 months

SPINDLE CELL MELANOCYTIC NEOPLASMS

BIOLOGICAL CONSIDERATIONS

Spitz nevi versus melanoma

Bastian, LeBoit + Finkel. Am J Pathol 2000

- 102 Spitz nevi studied for 11p copy number increases by FISH; 11p is site of hRAS gene
- 11.8% had at least 3X copy number ↑
- Tumors with 11p copy number larger, more often dermal with desmoplasia, characteristic cytology and an invasive growth pattern
- Sequence analysis of hRAS showed oncogenic mutations in 67% of cases with 11p copy number ↑ **vs** only 5% of tumors with no copy number ↑

Spitz nevus vs melanoma

Bastian et al. J Invest Dermatol 1999;113:1065

- Comparative genomic hybridization of 17 Spitz nevi versus melanoma
- 13 Spitz nevi had no chromosomal anomalies
- 3 Spitz nevi had gains of 11p
- 1 Spitz nevus had a gain of 7q21
- Melanomas had deletions of 9p (92%), 10q (63%), 6q (28%), + 8p (22%); gains of chromosomes 7 (50%), 8 (34%), 6p (28%), 1q (25%)

Molecular Diagnosis in Nevi and Melanoma

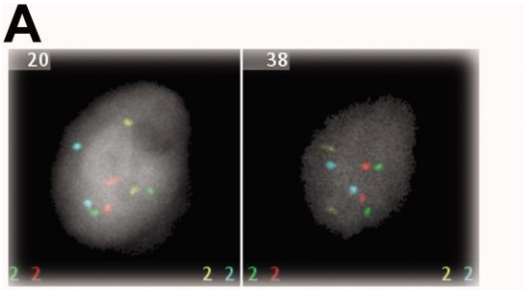
- Fluorescent In Situ Hibridization (FISH)
- Comparative Genomic Hybridization (CGH)

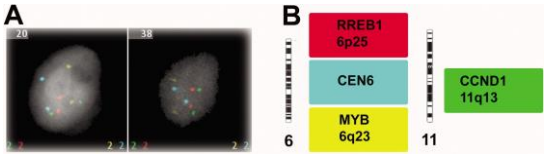
Fluorescence in Situ Hybridization

- Identifies chromosomal copy number aberrations
- Fish probes (short DNA fragments)
- Slide containing 5µm thick paraffin embedded section of tumor (test sample)

Fish probes

- **RREB1, 6p25**: Ras responsive element binding protein 1
- **CEN6**: Centromere 6
- **MYB, 6q23**: v-myb myeloblastosis viral oncogene homologue
- **CCND1, 11q13**: cyclin D1





4 Fish Criteria for Melanoma diagnosis

1 More than 38% of enumerated cells contain >2 signals for CCND1, or
2 More than 55% of nuclei contain more signals for 6p25 than for centromere 6, or
3 More than 40% of nuclei contain fewer signals for MYB than for centromere 6, or
4 More than 29% of cells have >2 RREB1 signals

Gerami & Zembowicz, Arch Pathol Lab Med; 2011

FISH

- These probes and the diagnostic criteria were developed based on the CGH data of Bastian *et al* at UCSF
- Validation studies were performed at Northwestern
- Analysis of 86 nevi and 83 melanomas rendered a sensitivity of 86.7% and a specificity of 95.4%

FISH in ambiguous melanocytic lesions

Gaiser *et al,* Modern Pathol;2010

- FISH/Clinical Behavior►60% sensitivity
  50% specificity

A Highly Specific and Discriminatory FISH Assay for Distinguishing Between Benign and Malignant Melanocytic Neoplasms

Pedram Gerami, MD,*w Gu Li, PhD,z Pedram Pouryazdanparast, MD,* Beth Blondin, BSc,z Beth Beilfuss, BS,* Carl Slenk, MSc,z Jing Du, MSc,z Joan Guitart, MD,*w Susan Jewell, PhD,z and Katerina Pestova, PhD, MBAz

Am J Surg Pathol 2012;36:808–817

Improved FISH

- 322 tumors, including 152 melanomas and 170 nevi
- A more discriminatory probe set:
  9p21, 6p25, 11q13, and 8q24
- Sensitivity of 94%
- Specificity of 98%

Risk Assessment for Atypical Melanocytic Neoplasm

- 75 Atypical Spitz tumors (US & Aus.)
- 64: benign behavior (5 year f/u)
- 11 with metastasis and/or death (3)
- Greater risk: homozygous 9p21 deletion
- High risk: 6p25 or 11q13 gains

Risk Assessment for Atypical Melanocytic Neoplasm

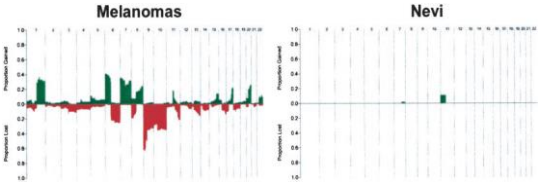
- *6 cases with isolated 6q23 loss showed no evidence of met or death (96 month f/u)
- 64 cases with benign behavior: 23.4% has a positive FISH result

Gerami *et al,* American Journal of Surgical Pathol, 2013.

Comparative Genomic Hybridization (CGH)

- Chromosomal CGH: when the test and normal DNA is hybridized to metaphase chromosomes
- Array CGH: hybridization to DNA microarrays
- CGH represents the first efficient approach to scanning the entire genome for variations in DNA copy numbers

CGH



Bastian *et al. Am J Pathol. 2003.*

Comparative Genomic Hybridization (CGH)

- Bastian *et al.* Classifying melanocytic tumors based on copy number changes. *Am J Pathol, 2003*
- 96% of 132 melanomas had chromosomal copy number aberrations

  -Gains in 6p, 1q, 7p, 7q, 8q, 17q, 11q, and 20q

  -Losses in 9p, 9q, 10p, 10q, and 6q
- 13% of all nevi evaluated (54) showed the same gain in 11p ►Spitz nevi

FISH and CGH in ambiguous melanocytic lesions

Gaiser *et al,* Modern Pathol;2010

- Fish results compared with CGH and long-term clinical follow up in 22 melanocytic proliferations, 12 of which were ambiguous lesions.
- FISH/Clinical Behavior►60% sensitivity
  50% specificity
- CGH/Clinical Behavior►Lesions that metastasized showed significantly more chromosomal aberrations

Molecular tests in Pigmented Lesions: Conclusion

"Correlation between precise molecular attributes and exacting histomorphology is in its infancy"

Tim McCalmont *et al*
J Cutan Pathol,2011

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MIHM CUTANEOUS PATHOLOOGY CONSULTATIVE SERVICE:

- Adriano Piris, MD
- Labib Zakka, MA, MD

Thank you for your kind attention