



Spitzoid Melanoctytic Neoplasms: State of the Uncertainty

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State of the Uncertainty

Lack of concordance and uncertainty exists across the spectrum of Spitz and “spitzoid” tumors

- Spitz nevus
- Atypical Spitz tumor/melanocytoma
- Spitz melanoma
- Typical and atypical “spitzoid” tumors and melanomas – spitzoid cytomorphology: BRAF, NRAS, BAP1 mutations, non MAPK, etc.
- Conventional melanoma

Ongoing Problems

- Spitz nevus/tumor vs melanoma
- Overdiagnosis of atypical Spitz tumor
- Overdiagnosis of Spitz/spitzoid melanoma!
 - The role of ancillary/molecular testing
 - Failure to consider biological outcome
- Terminology: Spitz vs “spitzoid”
 - Morphological distinction often not possible
 - Specific gene fusions may not have any predictive value
 - The natural history may be similar across these lesions but requires more definitive study

WHO Classification 5th Edition 2024

- I. Spitz Nevus
- II. Atypical Spitz Tumor,
Spitz Melanocytoma
- III. Spitz Melanoma

Defining the True Spitz Phenotype?

- Clinical
- Histomorphology
 - Architecture
 - Cytology
- Molecular
 - activating HRAS mutations
 - gene fusions, increasing in number
 - absence of particular genetic alterations

I. Spitz Nevus

What are the criteria
for a Spitz nevus?

Objective Diagnostic Criteria Spitz Nevus

- Children, adolescents, any age
- Diameter usually < 5 mm
- No ulceration
- No aberrant growth or significant atypia
- No subcutaneous fat involvement
- Mitotic rate $\leq 2/\text{mm}^2$
- Usually one genetic alteration:
 - activating HRAS mutation or
 - gene fusion
 - other ?

Spitz Nevus

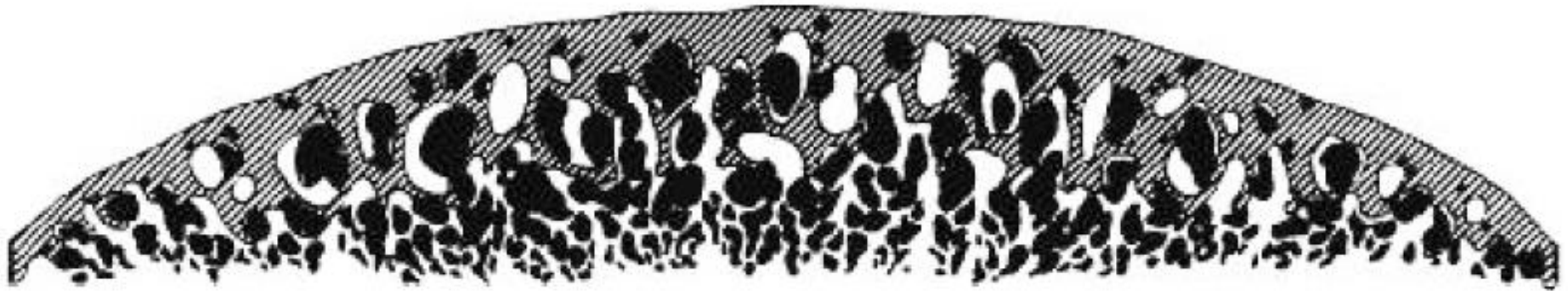
Clinical Criteria

Clinical Diagnosis: Only 20%



Spitz Nevus

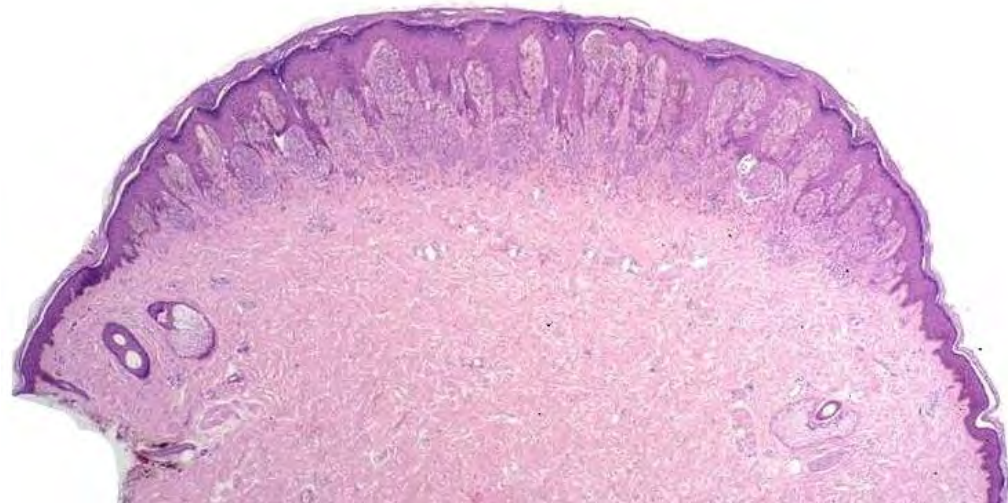
Architecture



Spitz Nevus

Architecture

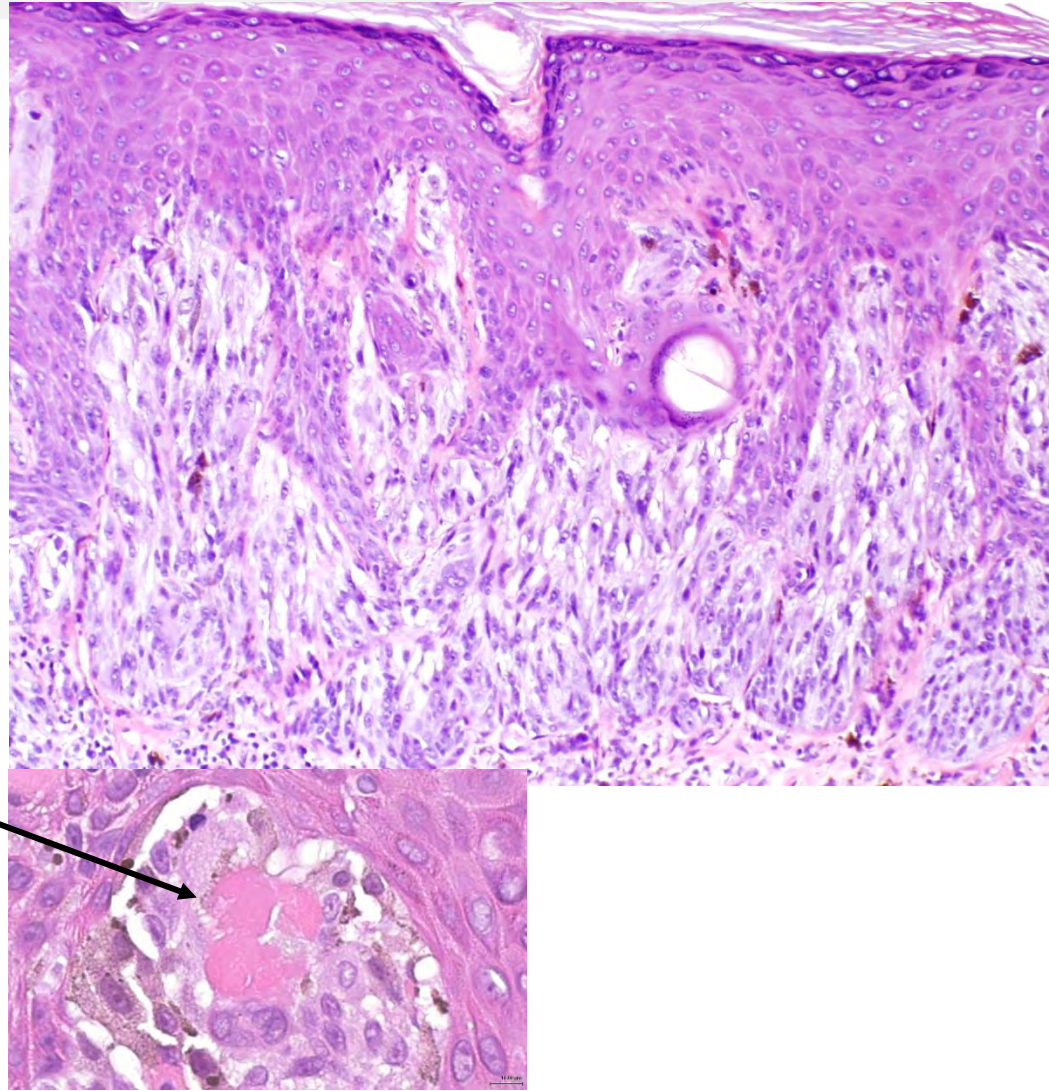
- $< 5 \text{ mm}$ ($< 1 \text{ cm}$)
- Symmetry
- Sharp circumscription
- Maturation
- Polypoid, dome-shaped or plaque-like
- Epidermal hyperplasia
- Vertically-oriented fascicles/nests



Spitz Nevus

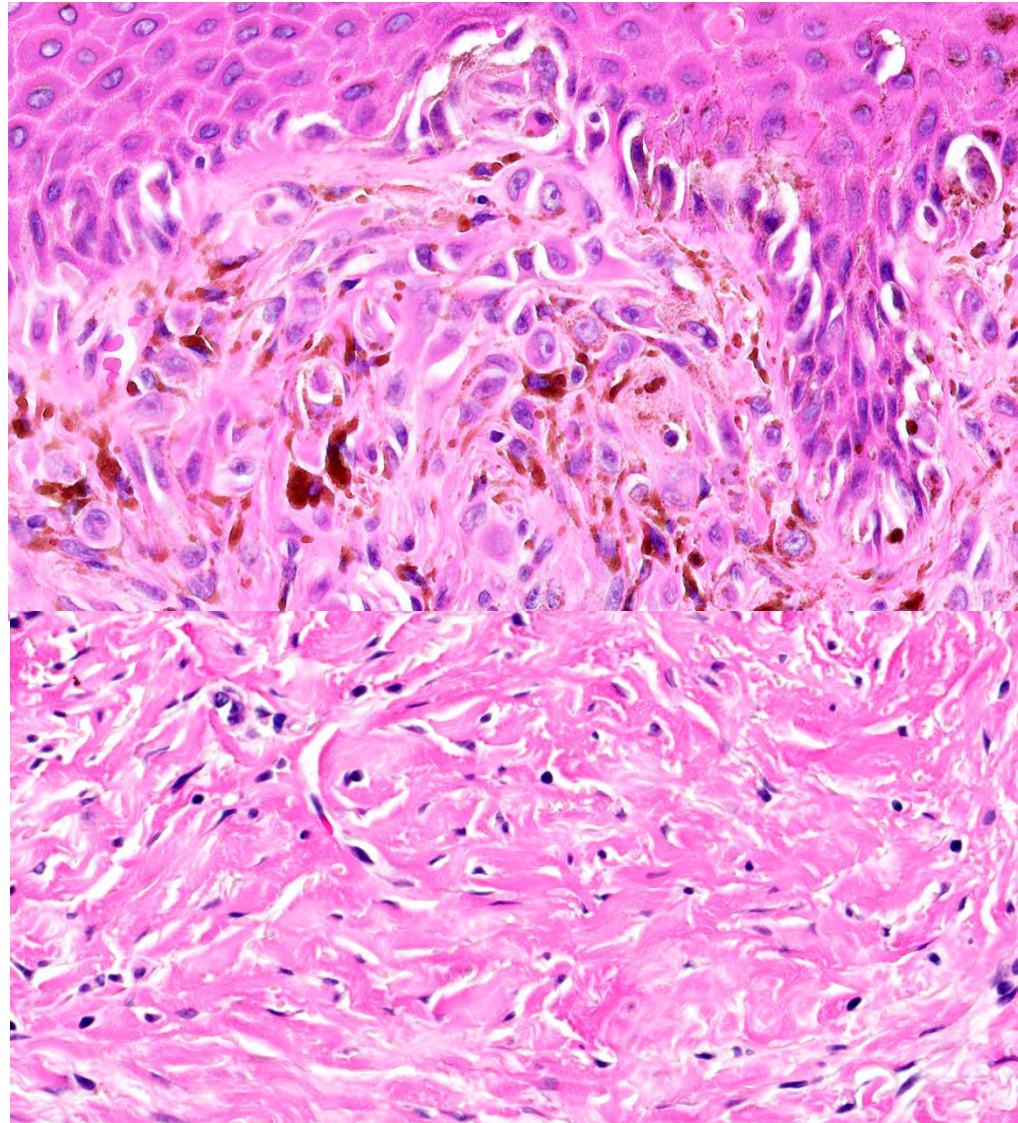
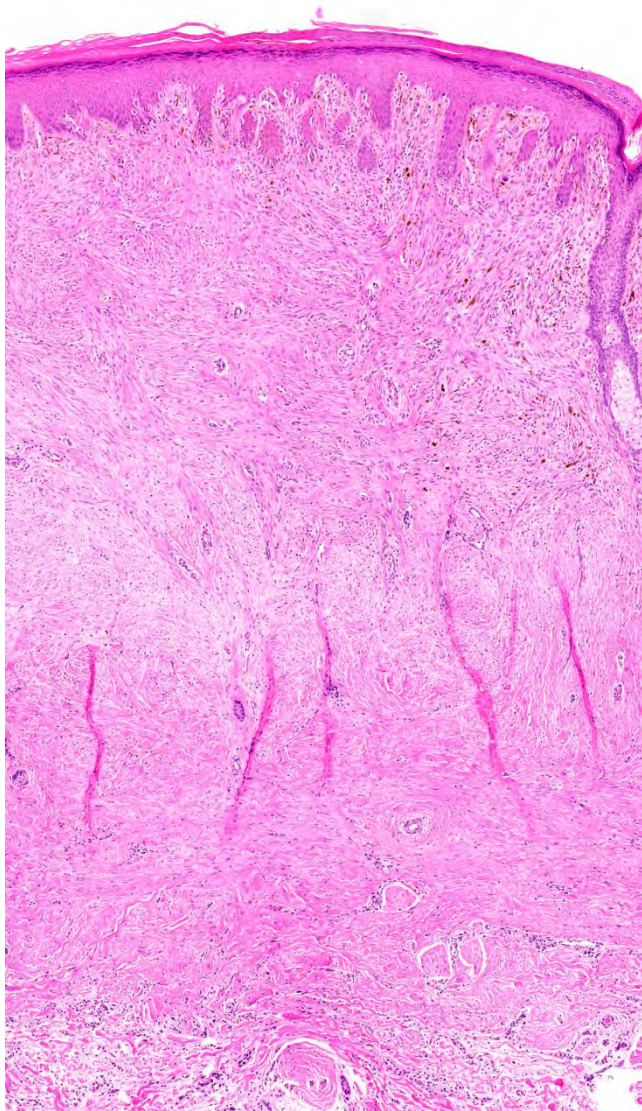
Histopathological Features

- Epidermal hyperplasia, irregular
- Junctional nests with clefting
- Vertical “raining down”
- Eosinophilic (Kamino) bodies



Spitz Nevus

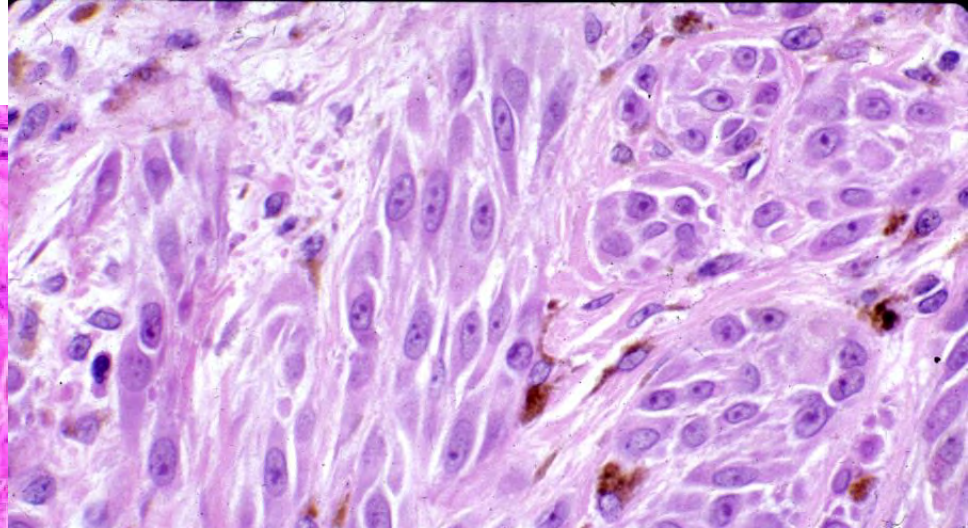
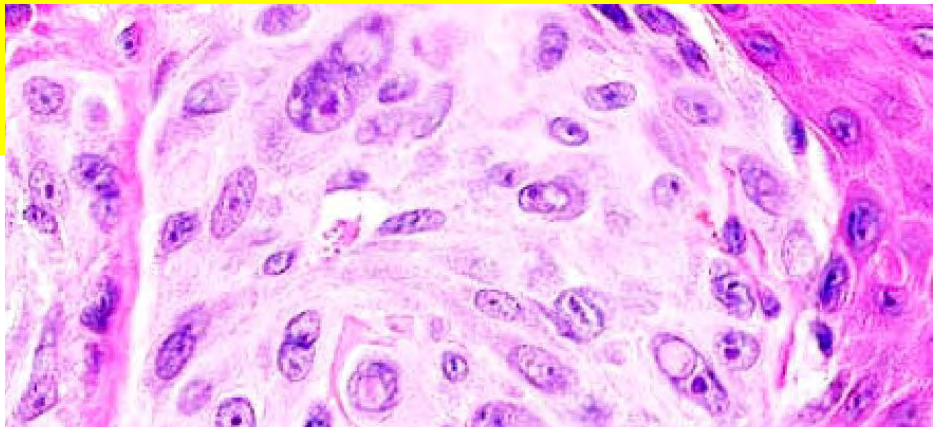
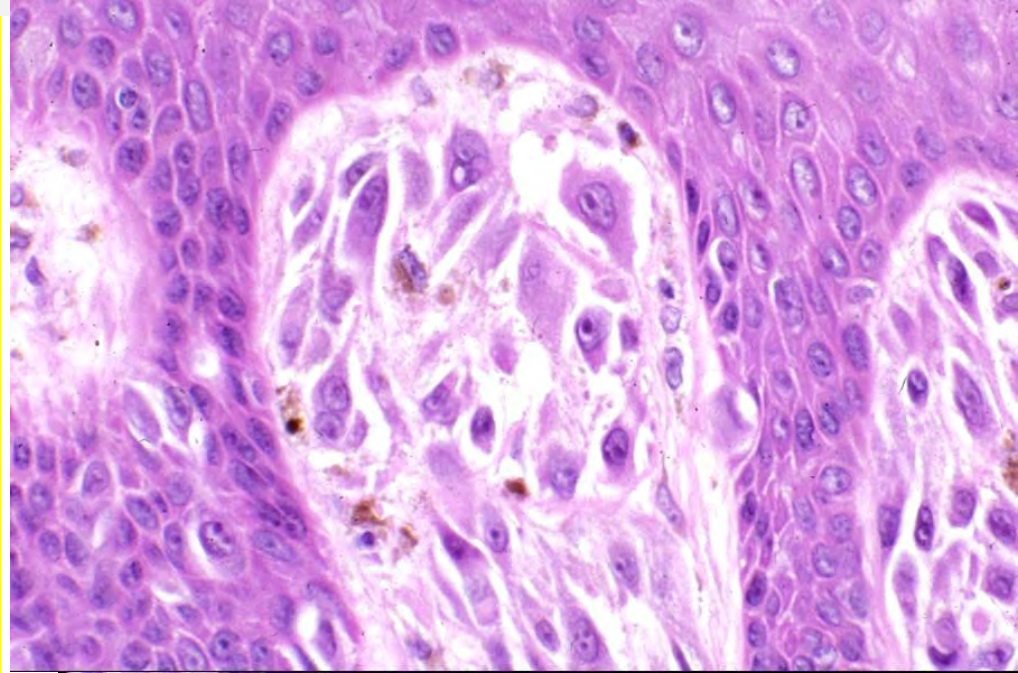
Maturation



Spitz Nevus

Cytology:

- Enlarged epithelioid/spindle cells
- Nuclei: dispersed chromatin, nucleoli



Spitz Nevus

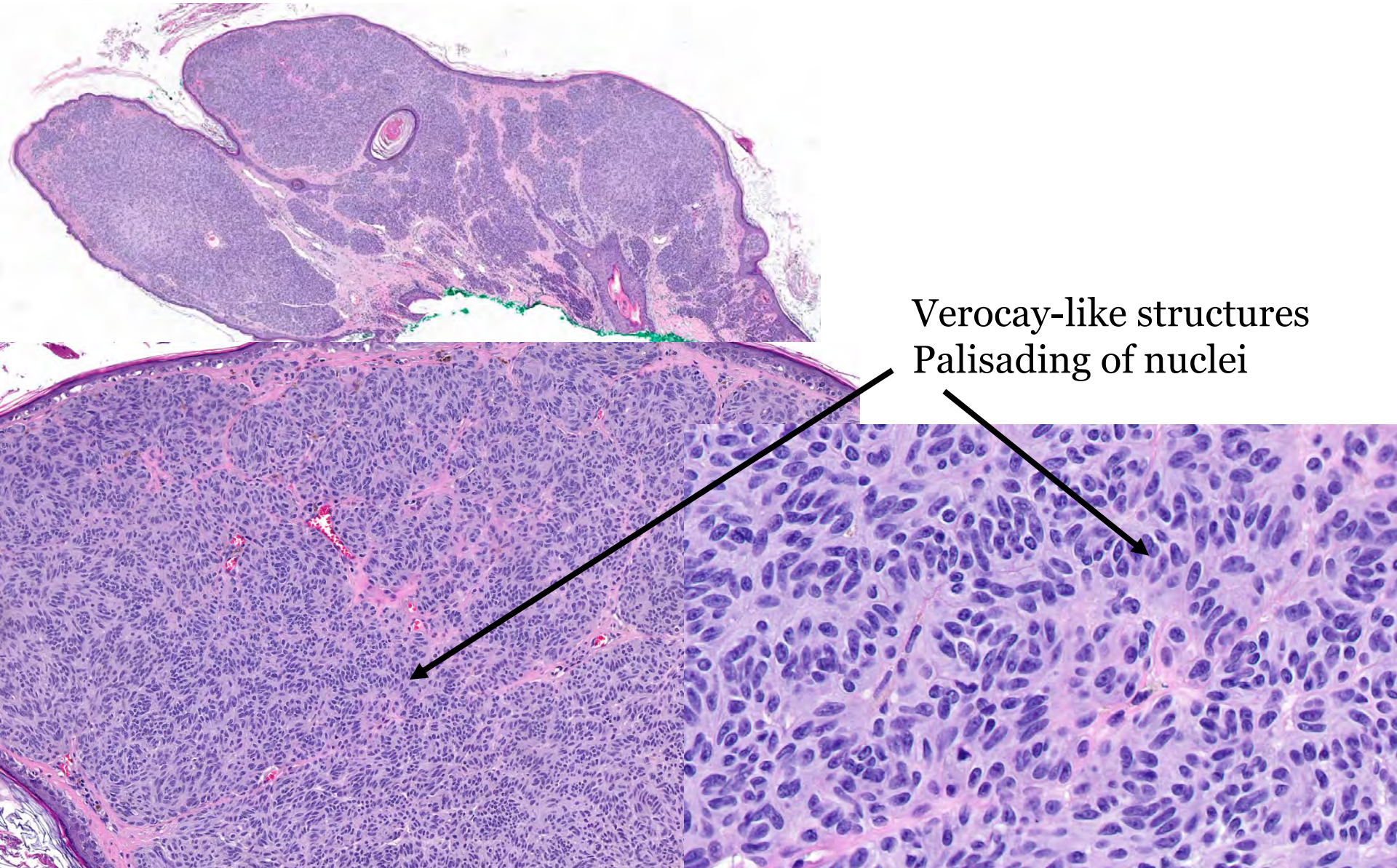
WHO 5th Edition

Molecular criterion – a single genetic alteration

- activating HRAS mutation, hot spot
- A gene fusion (translocation)
 - ROS1
 - ALK
 - NTRK1, 2, 3
 - RET
 - MET
 - BRAF
 - MAP3K8
- New gene fusions continue to be reported

Spitz Tumor

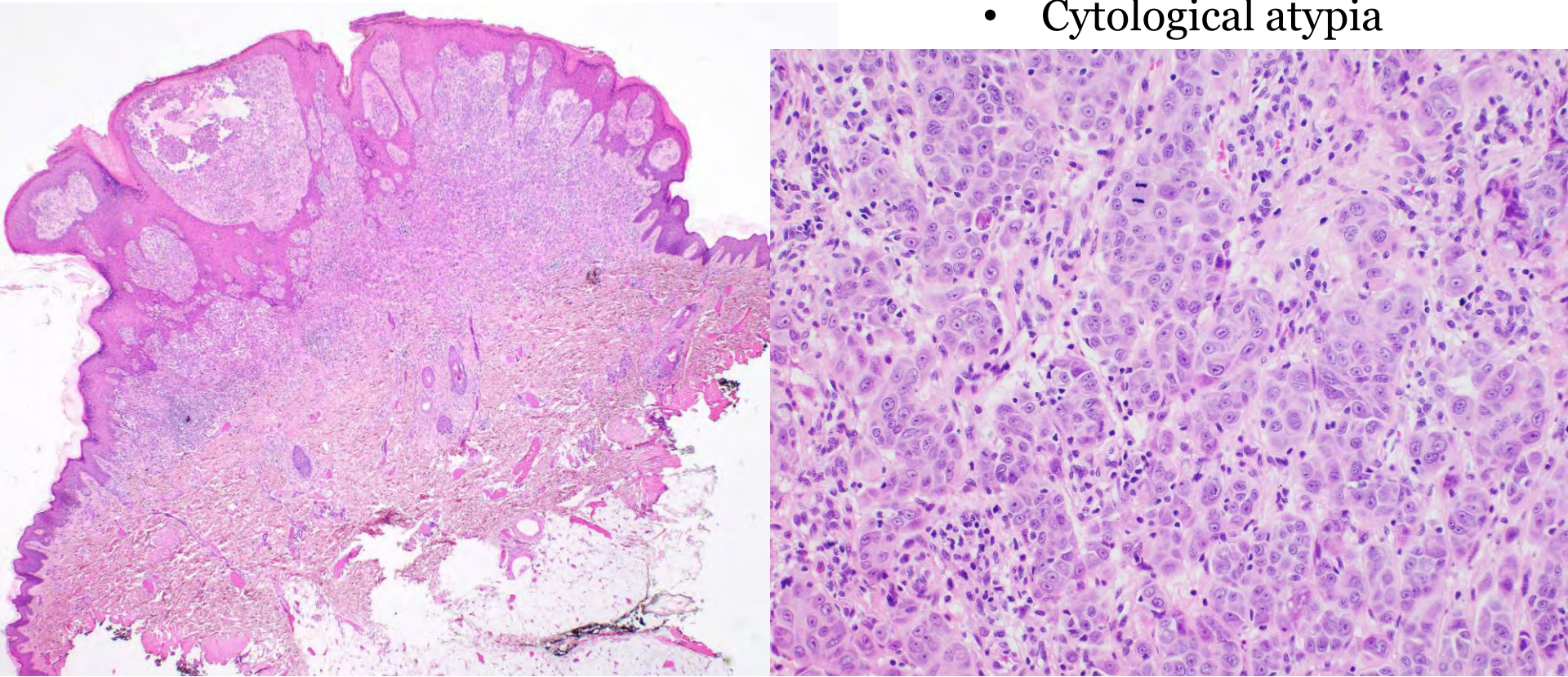
NTRK3 Fusion



Atypical Spitz Tumor

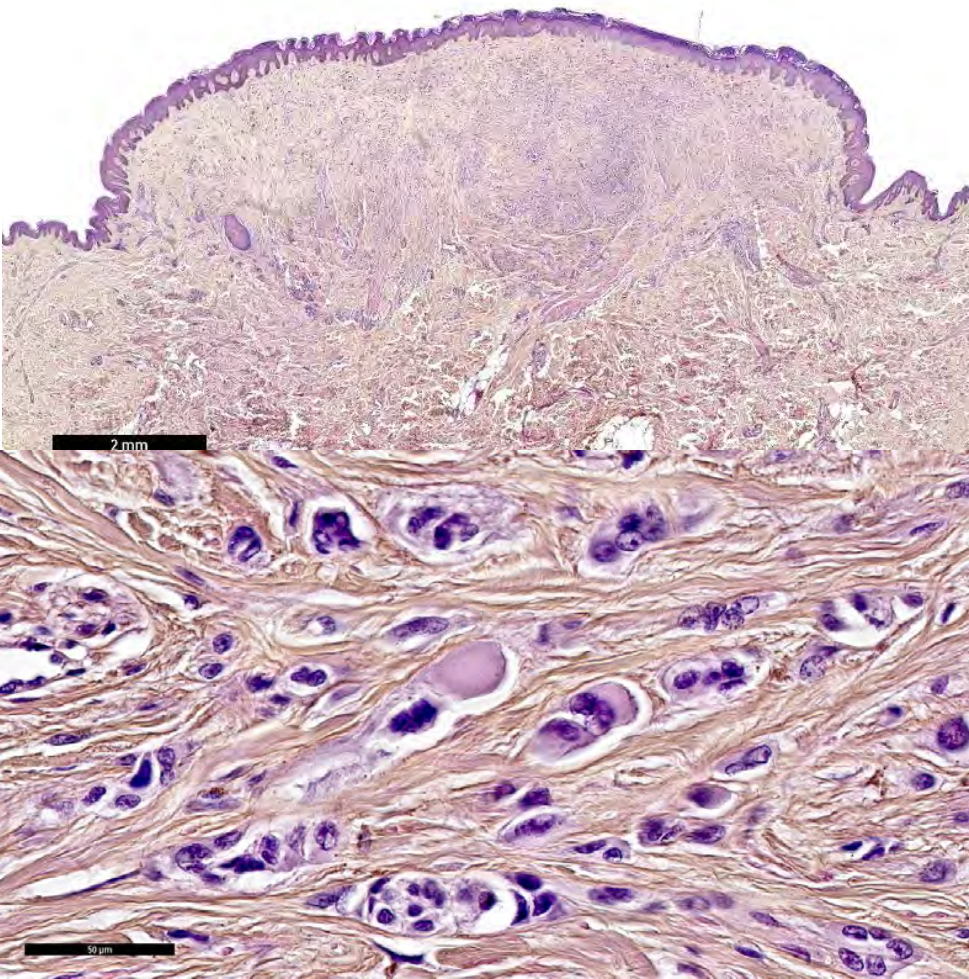
MAP3K8 Fusion

- Large epithelioid cells
- Cytological atypia

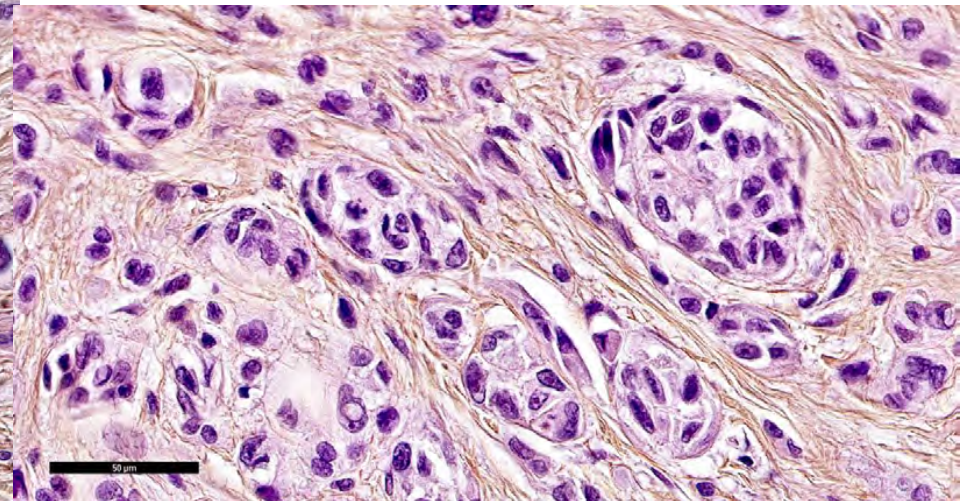


Atypical Spitz Tumor

BRAF Fusion



- Sclerosis of collagen
- Nests and cords of epithelioid melanocytes
- Scattered individual melanocytes
- Cytological atypia



Spitz vs "Spitzoid"

- Spitz is used as both a morphological and a genetic descriptor to denote the true Spitz phenotype
- Spitzoid is used for tumors judged insufficient morphologically and/or genetically
- These distinctions are clouded by the striking heterogeneity, diversity, and overlap in morphology encountered among these true and non-true genetic variants

"Spitzoid" Tumors

- Diverse spectrum of typical and atypical tumors and melanomas such as:
 - BRAF V600E- mutated spitzoid tumors and melanomas
 - NRAS-mutated tumors
 - BAP1-inactivated tumors
 - Melanomas with germline mutations

II.

Atypical Spitz Tumor/ Melanocytoma

What is an Atypical Spitz Tumor?

- Spitz tumor with one or more atypical features
- Spitz tumor with Uncertainty
 - ✓ One has difficulty interpreting the lesion as either benign or malignant
 - ✓ Uncertain malignant potential



What are the Criteria for an
Atypical Spitz Tumor?

Atypical Spitz Tumor

Clinical Criteria

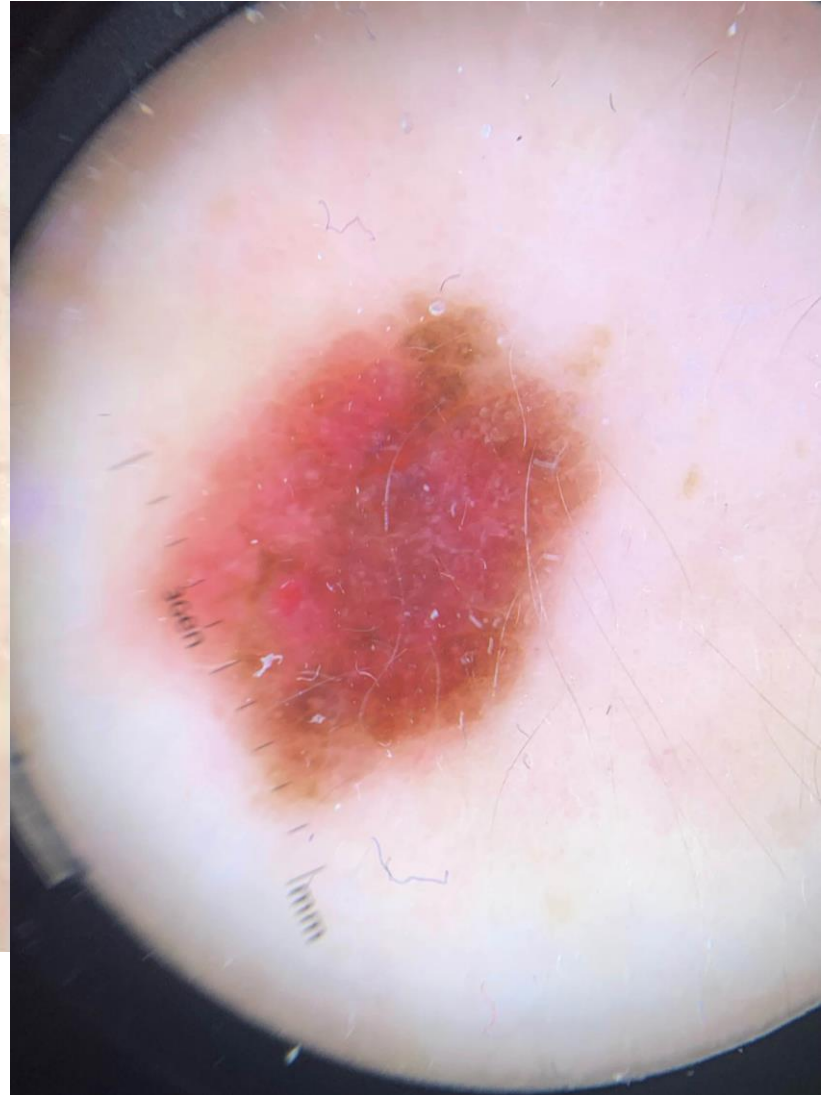
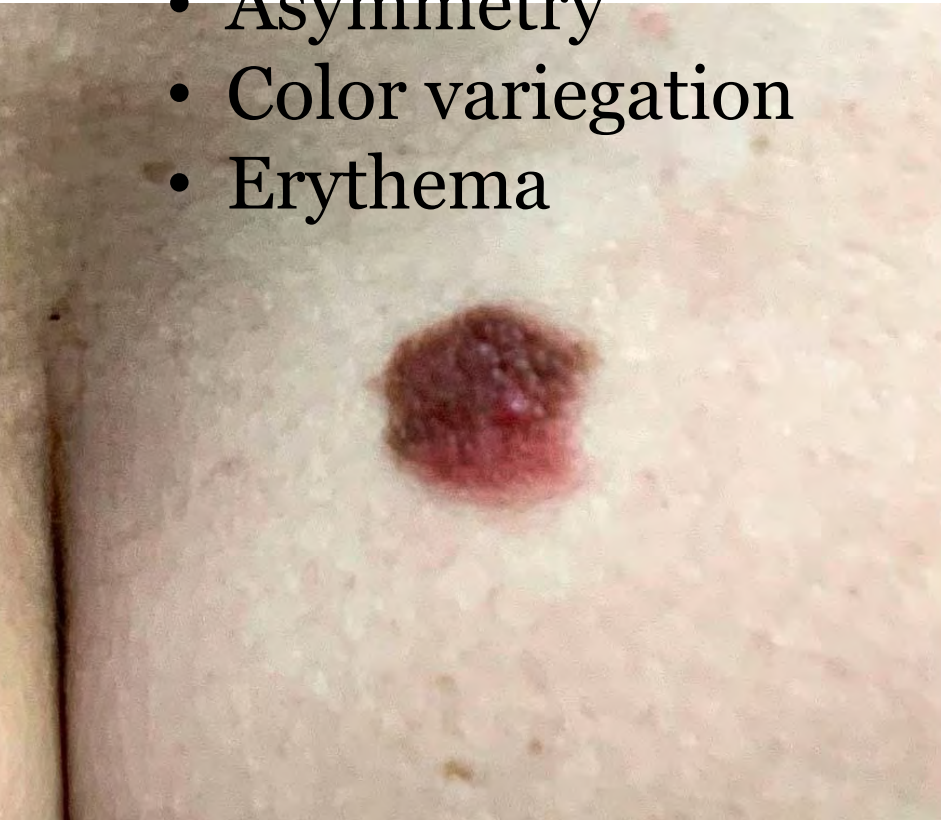
- $> 6 \text{ mm}$ $> 10 \text{ mm}$
- Asymmetry
- Poor circumscription
- Non uniform color



Atypical Spitz Tumor

Clinical Criteria

- Diameter 10 mm
- Asymmetry
- Color variegation
- Erythema



What Are the Histopathologic Criteria for Grading Atypical Spitz Tumors?

- Age \geq 10 years
- Lesional diameter >5 mm, > 1 cm*
- Ulceration*
- Mitotic rate >2 to $6/\text{mm}^2$ or greater
- Involvement of subcutaneous fat

A Grading System for Risk Stratification (Spatz-Barnhill)

- The practical first step in the histopathological evaluation of spitzoid melanocytic tumors and classification as
 - Spitz nevus
 - Atypical Spitz or spitzoid tumor, low risk or
 - Atypical Spitz or spitzoid tumor, high risk with uncertain malignant potential (suspicious for Spitz or spitzoid melanoma)

Spitz Tumors in Children

A Grading System for Risk Stratification

Alain Spatz, MD; Eduardo Calonje, MD; Susan Handfield-Jones, MD; Raymond L. Barnhill, MD

Objective: To describe a grading system for risk stratification of atypical Spitz tumors in children and adolescents. In some circumstances, unequivocal distinction between Spitz nevus and melanoma is practically impossible. It is likely that these lesions for which we lack specific diagnostic criteria represent a broad histological continuum extending from benign to malignant tumors. Therefore, we propose that Spitz tumors be categorized into low-, intermediate-, or high-risk categories based on the accumulation of abnormal features.

Design: Retrospective study.

Settings: Institutional practice.

Patients: We present 30 cases of atypical Spitz tumors in patients younger than 18 years evaluated for at least 3 years or in whom a metastatic event developed during this period.

Intervention: None.

Main Outcome Measure: The grading system was formulated after data collection.

Results: Among the parameters studied, only diagnosis at age greater than 10 years, diameter of the lesion greater than 10 mm, presence of ulceration, involvement of the subcutaneous fat (level V), and mitotic activity of at least 6/mm² carried a likelihood ratio greater than 1.50 and were therefore used for the grading system.

Conclusion: The application of an objective grading system, such as the one described herein for the first time, is the first step in providing useful information for the management of atypical Spitz tumors.

Arch Dermatol. 1999;135:282-285

Assessment of Spitz Tumors in Children and Adolescents for Risk of Metastasis

| Objective Parameter | Score |
|---------------------------|-------|
| ➤ Age (years) | |
| 0-10 | 0 |
| 11-17 | 1 |
| ➤ Diameter (mm) | |
| 0-10 | 0 |
| >10 | 1 |
| ➤ Involvement of subcutis | |
| Absent | 0 |
| Present | 2 |

Assessment of Atypical Spitz Tumors in Children and Adolescents for Risk of Metastasis

| Objective Parameter | Score |
|----------------------------------|-------|
| ➤Ulceration | |
| Absent | 0 |
| Present | 2 |
| ➤Mitotic rate (mm ²) | |
| 0-5 | 0 |
| 6-8 | 2 |
| ≥9 | 5 |

Assessment of Atypical Spitz Tumors in Children and Adolescents for Risk of Metastasis

| Total Score | Risk |
|-------------|------|
| 0-2 | Low |
| 3-4 | |
| 5-11 | High |

SCIENTIFIC REPORTS

OPEN

***TERT* Promoter Mutations Are Predictive of Aggressive Clinical Behavior in Patients with Spitzoid Melanocytic Neoplasms**

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Seungjae Lee¹, Raymond L. Barnhill², Reinhard Dummer³, James Dalton¹, Jianrong Wu⁴, Alberto Pappo⁵ & Armita Bahrami¹

Spitzoid neoplasms constitute a morphologically distinct category of melanocytic tumors, encompassing Spitz nevus (benign), atypical Spitz tumor (intermediate malignant potential), and spitzoid melanoma (fully malignant). Currently, no reliable histopathological criteria or molecular marker is known to distinguish borderline from overtly malignant neoplasms. Because *TERT* promoter (*TERT*-p) mutations are common in inherently aggressive cutaneous conventional melanoma, we sought to evaluate their prognostic significance in spitzoid neoplasms. We analyzed tumors labeled as atypical Spitz tumor or spitzoid melanoma from 56 patients with available follow-up data for the association of *TERT*-p mutations, biallelic *CDKN2A* deletion, biallelic *PTEN*

Atypical Spitz Tumors

Risk for Distant Mets, Death

- TERT-p mutations $p < 0.0001$
- Age ≥ 10 yrs $p < 0.05$
- Ulceration $p < 0.05$
- Mitotic rate > 5 per mm^2 $p < 0.05$
- Lesional diameter > 11 mm $p = 0.054$

What Are the Morphological Criteria for Grading Atypical Spitz Tumors?

- Expansile dermal nodule*
- High-grade cytological atypia*
- Poor circumscription
- Asymmetry
- Pagetoid spread - peripheral
- Absence of maturation

What Are the Genetic Criteria for an Atypical Spitz Tumor?

- At Least Two Genetic Alterations (not always):
 - Activating HRAS mutation, or a kinase fusion (true Spitz phenotype)
 - bi-allelic deletion of CDKN2A, often
 - Other genetic alterations
 - TERT promoter hot-spot mutation***

Atypical Spitz Tumors

Risk for Distant Mets, Death

- 9p21 (bialleleic loss) $p=0.56$
- PTEN (bialleleic loss) $p=1.00$
- Kinase fusions $p=0.62$

ALK, ROS1, NTRK1,2,3, RET, BRAF, etc.

APRIL 2019



APRIL 2024

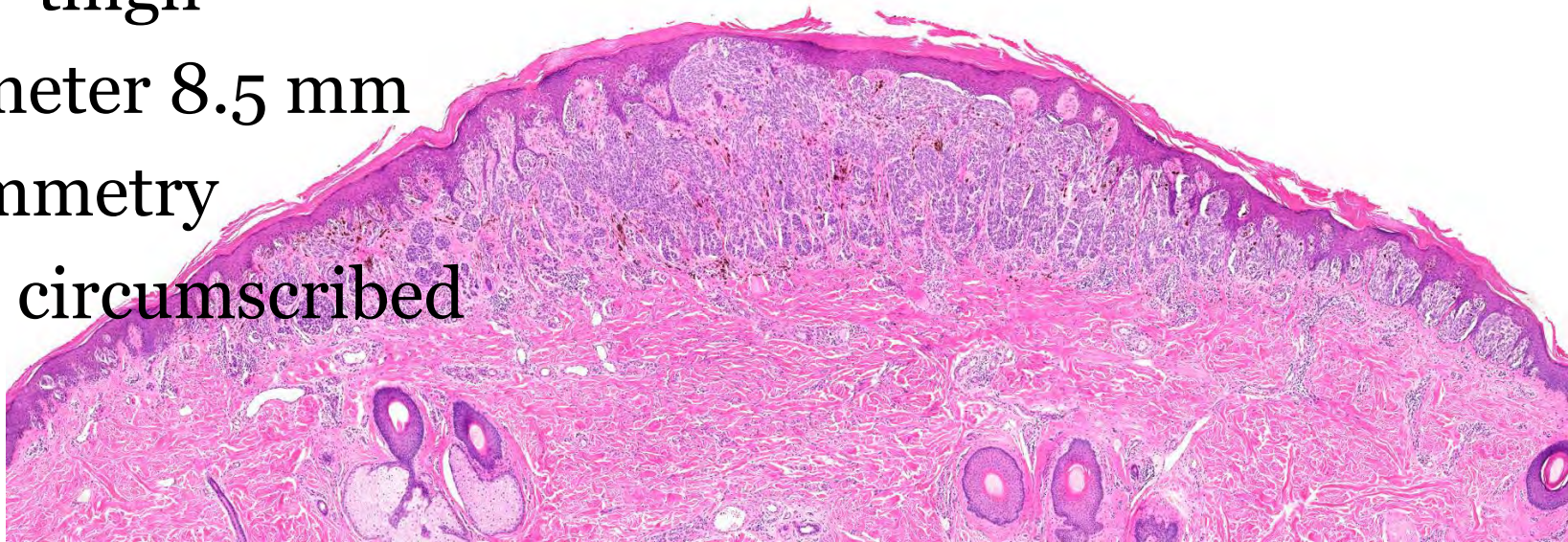


Examples

Spitz Tumor

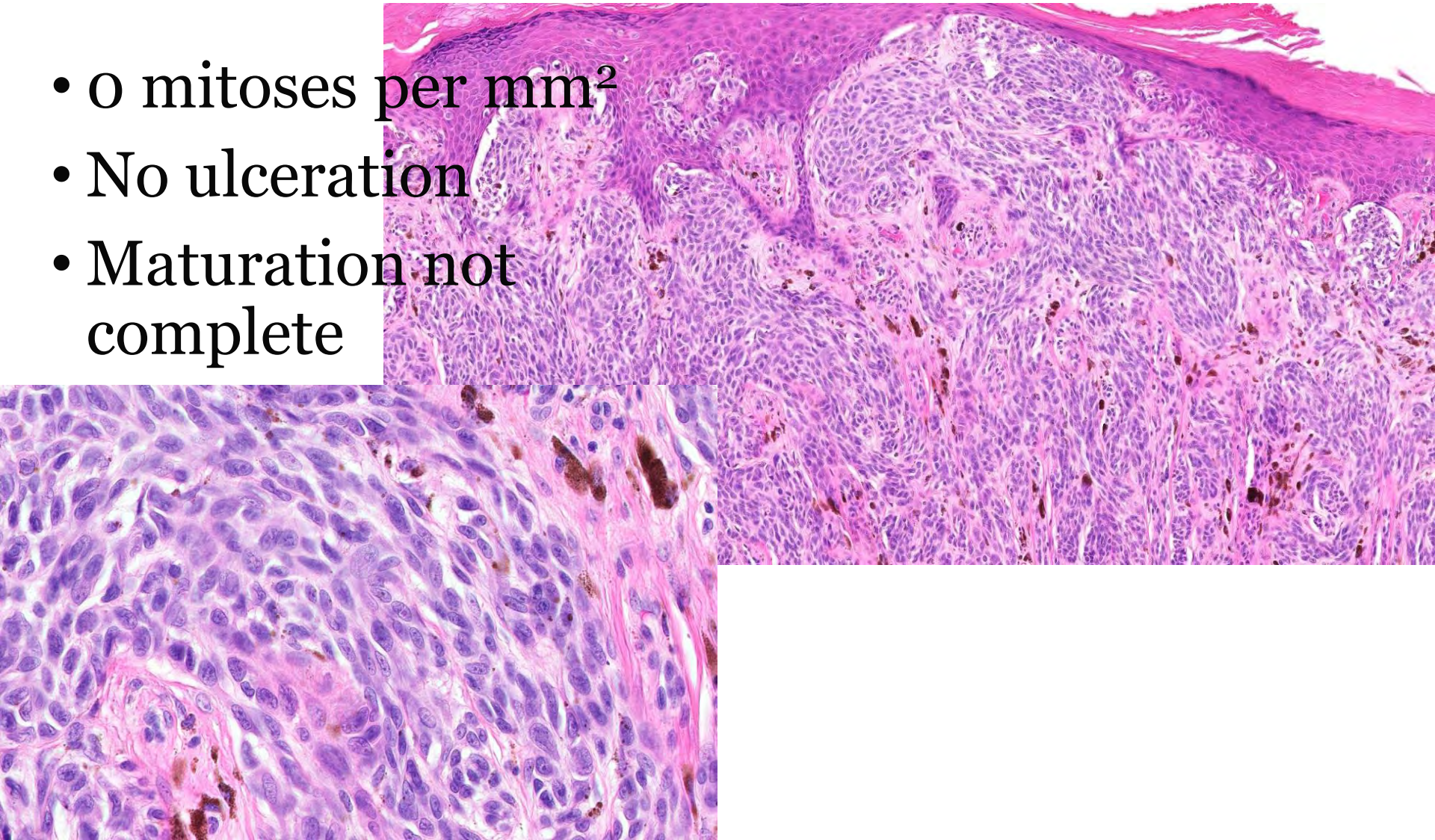


- 25 year old female
- Site - thigh
- Diameter 8.5 mm
- Asymmetry
- Well circumscribed



Spitz Tumor

- 0 mitoses per mm²
- No ulceration
- Maturation not complete

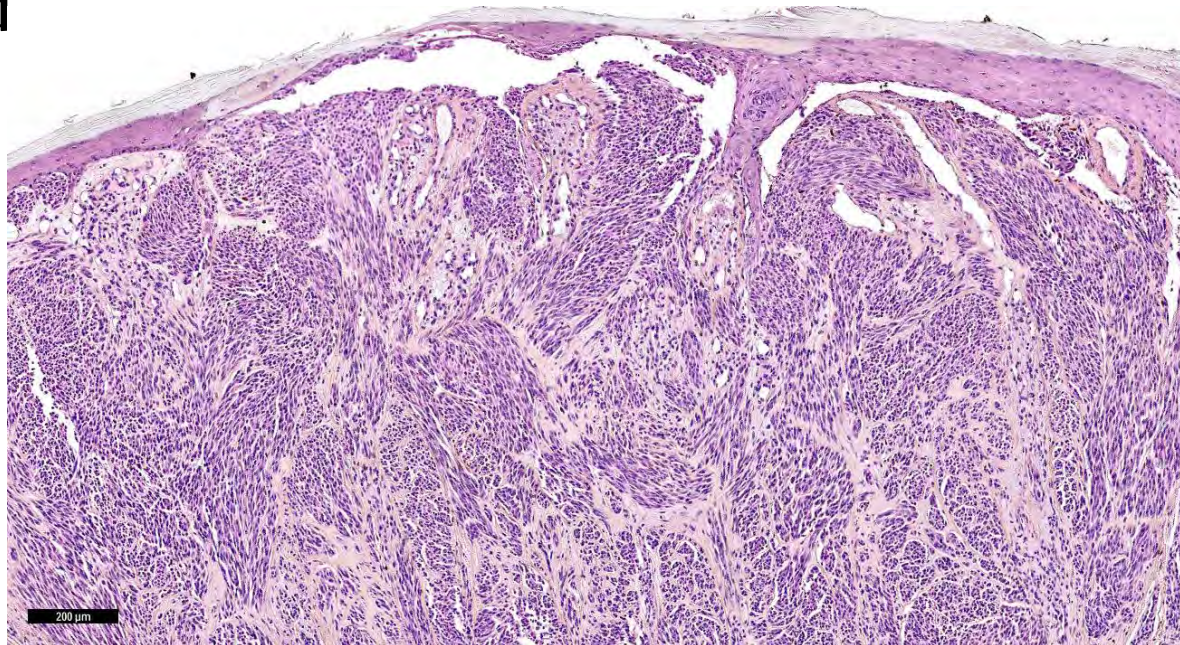
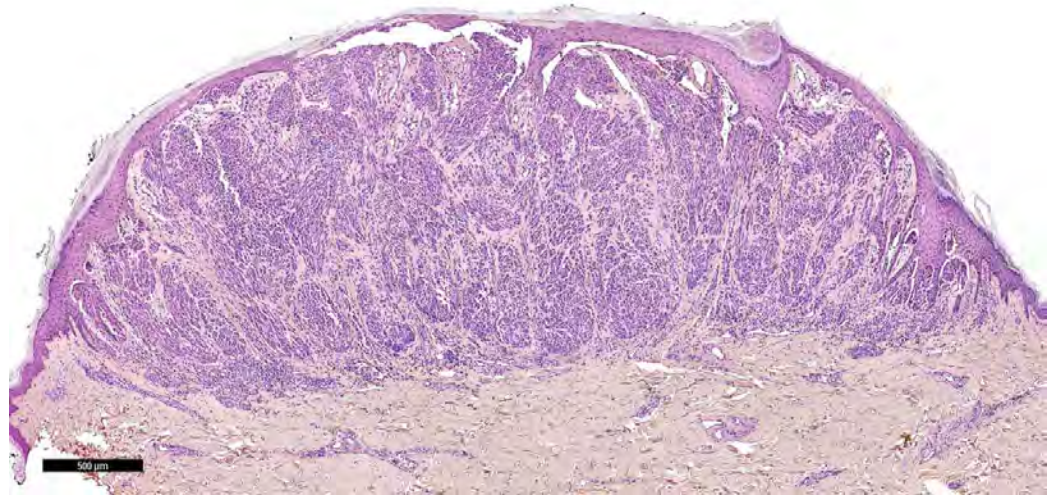


Spitz Tumor

- Conclusion: Score = 0
Spitz tumor with low risk

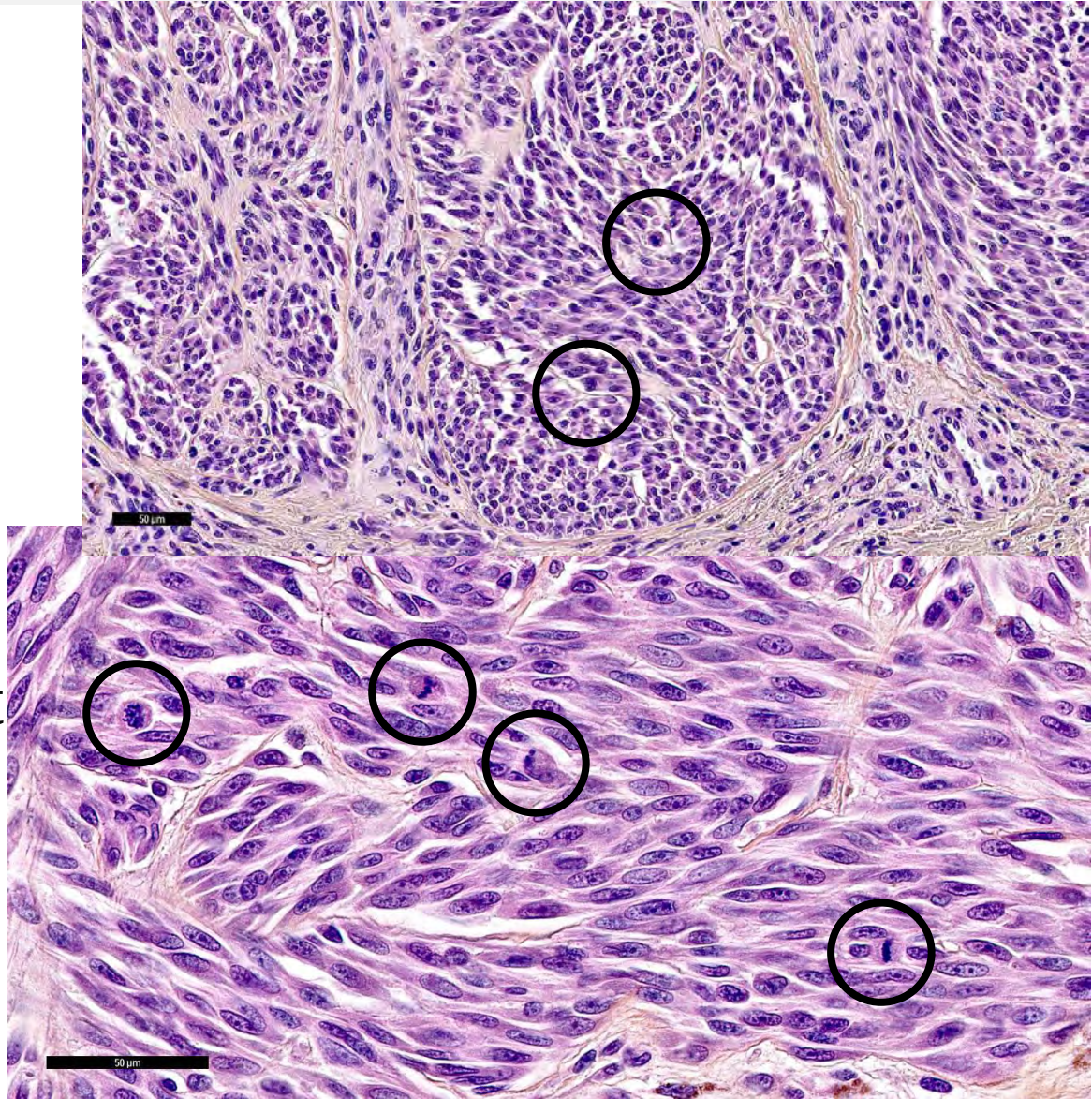
Atypical Spitz Tumor

- 45 year-old male
- Site: right thigh
- Diameter: 4.5 mm
- Well-circumscribed
- Symmetrical
- No ulceration



Atypical Spitz Tumor

- Thickness: 1.6 mm
- 9 mitoses per mm²
- Deep mitoses
- No maturation
- Expansile growth
- No subcutaneous fat involvement
- Cytological atypia



Atypical Spitz Tumor

- Conclusion: Score = 6
- Atypical Spitz tumor with high-risk profile, uncertain malignant potential
- Sentinel lymph node biopsy negative
- No recurrence 7 years

Ancillary Techniques

Immunohistochemistry

- p16
- BRAF V600E
- Consider other:
 - Melan-A/Ki67
 - RAS Q61R (for both HRAS and NRAS), ROS1, ALK, and panTRK

Molecular Testing

- TERT promoter hot spot mutations (c.-124C>T, c.-146C>T, or c.-138/-139 CC>TT)
- If TERT promoter and BRAF V600E are negative, consider next generation sequencing gene fusions and other genetic alterations

Ancillary Testing

- BRAF and MAP3K8 fusions and bi-allelic CDKN2A (p16) deletions suggest possible aggressive disease but are not diagnostic of melanoma.
- Concomitant TERT promoter hot-spot mutations often account for the aggressive phenotype and melanoma.



III.

Spitz Melanoma

State of the Art

- Almost all Spitz melanomas reported in the literature:
 - lack sufficient follow-up and outcome
 - among those with follow-up, there is almost always no evidence of metastases or death from disease

State of the Art

- True Spitz melanomas are virtually nonexistent in children < 10 years of age, and extremely rare in older individuals
- Many atypical Spitz tumors are misclassified as Spitz melanoma
- The gold standard for Spitz melanoma would appear to be metastases and/or death
- Molecular criteria for true Spitz melanoma are in evolution but TERT promoter hot spot mutations strongly suggest melanoma (if sufficient morphological criteria are present).
- The natural history of a few true Spitz melanomas has been definitively characterized.
- It is not clear that »true« Spitz melanoma has a better prognosis than « spitzoid » and conventional melanomas.
- In fact, true Spitz melanomas appear to have an aggressive clinical course.

What are the Criteria for Spitz Melanoma?

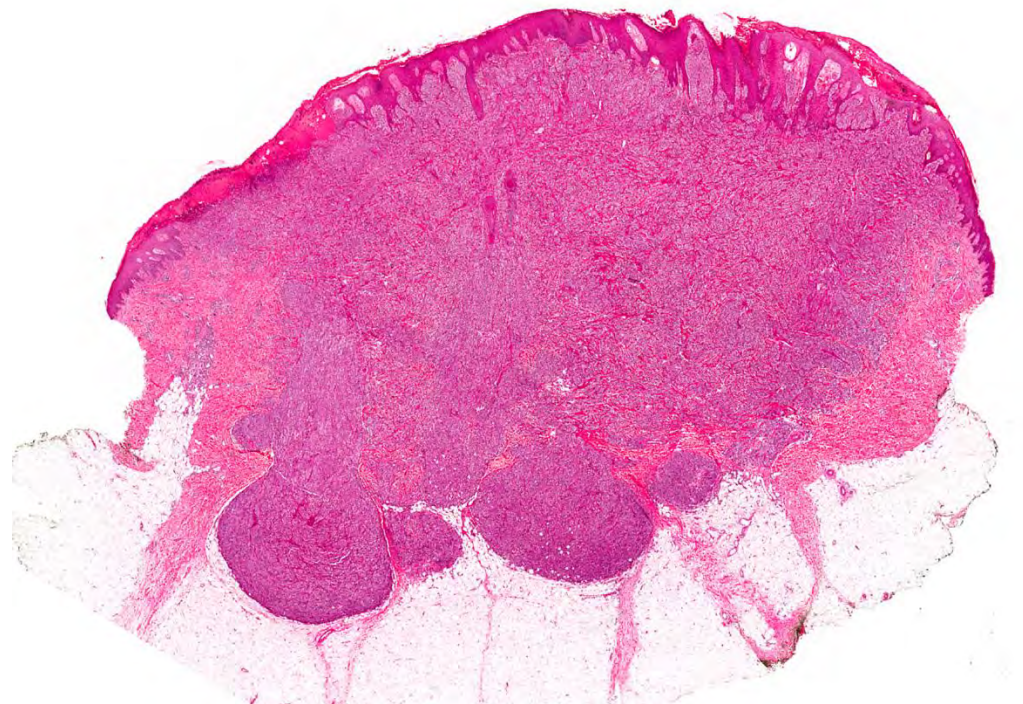
- Age > 10 years
- Size of primary tumor often > 1 cm
- Atypical features as in atypical Spitz tumor
 - Ulceration
 - Involvement of subcutaneous fat
 - Mitotic rate ≥ 5 or 6 or more/mm²
 - High-grade cytological atypia
 - Expansile nodule (vertical growth phase)
- Evidence of distant spread/death

What are the Criteria for Spitz Melanoma?

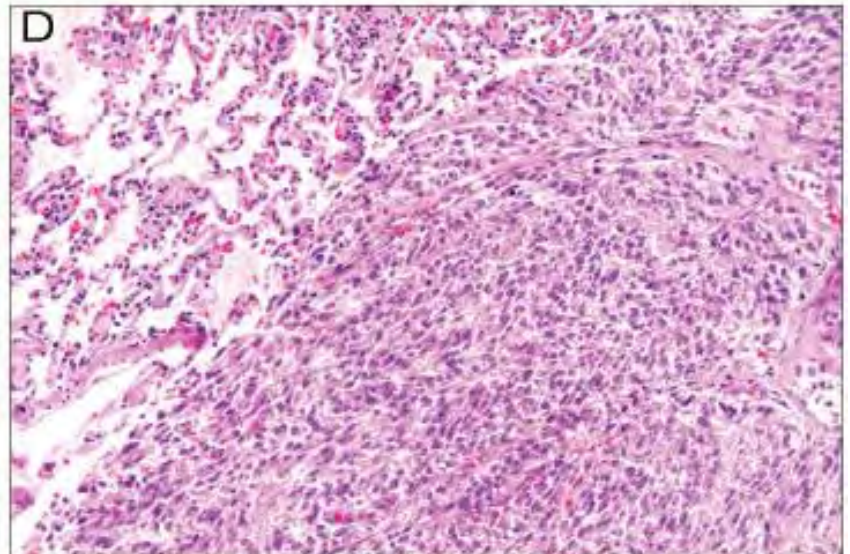
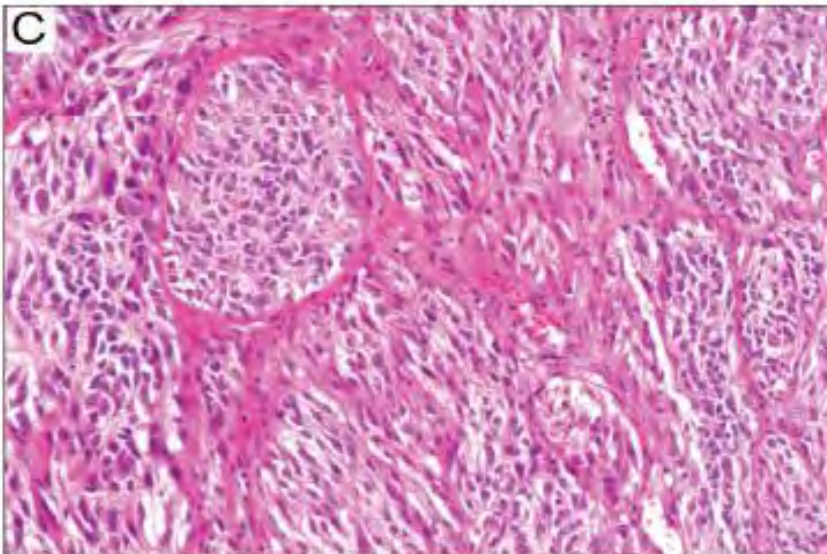
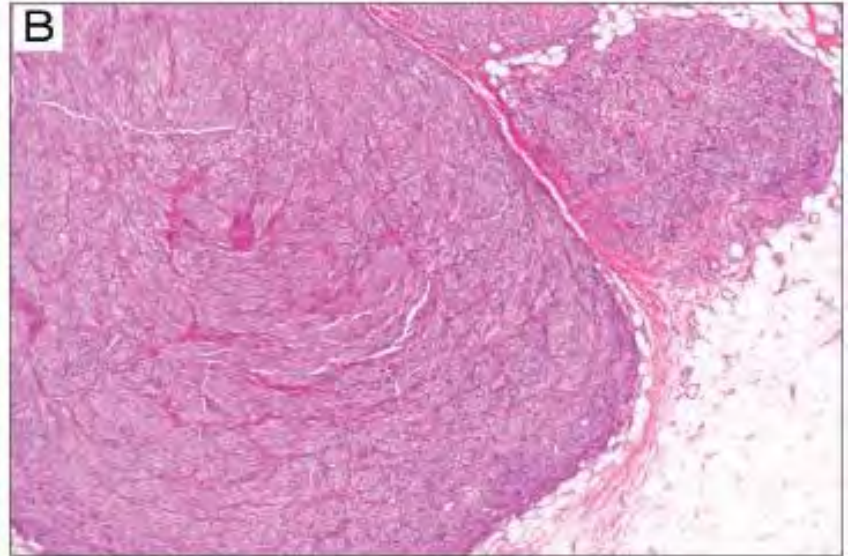
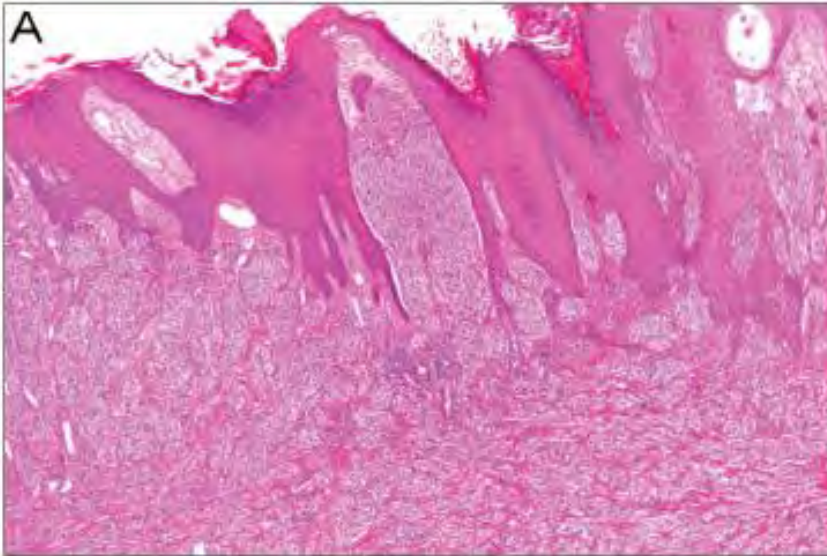
- Molecular studies:
 - Gene fusions or HRAS mutations
 - TERT promoter hot-spot mutations***

Spitz Tumor

- 11 year-old female
- Site: thigh
- Diameter: 1.2 cm
- Ulceration
- 7 mitoses per mm²
- Involvement of subcutaneous fat
- 7 mm thickness
- No maturation



Spitz Tumor



Spitz Tumor

- Conclusion: Score = 8 (high risk)
- Atypical Spitz tumor with high risk and uncertain malignant potential

Molecular Study and Clinical Progression

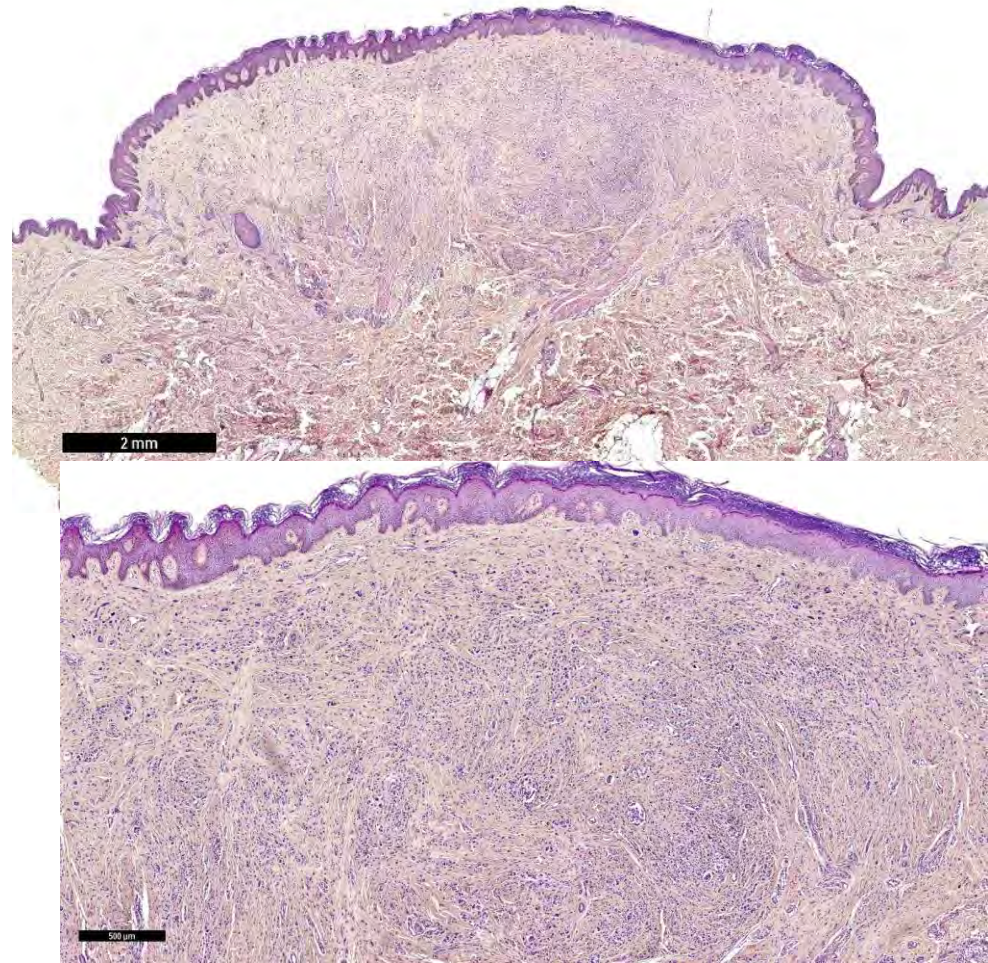
- Kinase fusion
- TERT promoter mutation
- Clinical lymph node metastasis at 6 months
- Distant metastases and death at 24 months

~~Atypical Spitz Tumor~~

- Conclusion: Spitz Melanoma

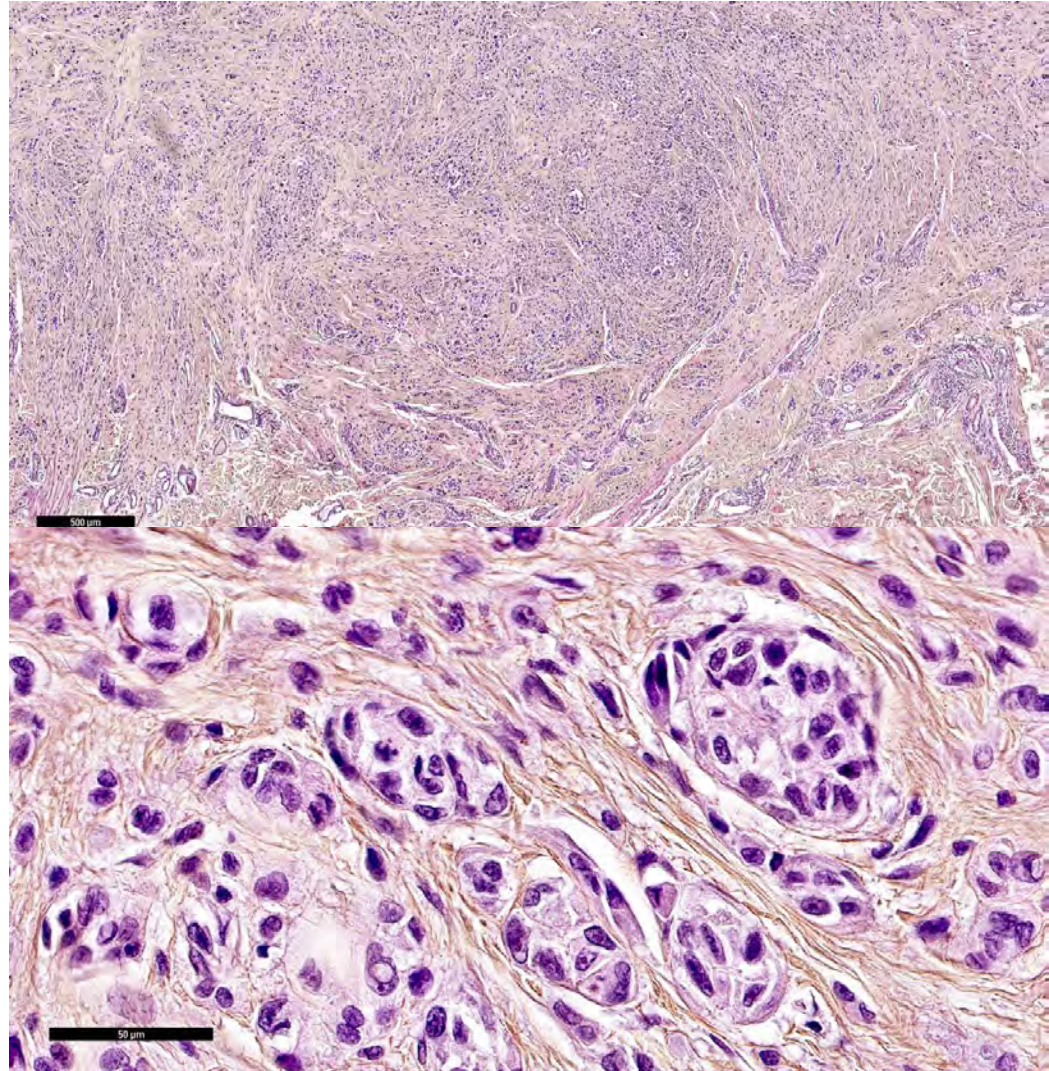
Spitz Tumor

- 28 year-old male
- Site: lower back
- Diameter: 1.1 cm*
- Thickness: 5.1 mm*
- No ulceration
- Well-circumscribed
- Asymmetric



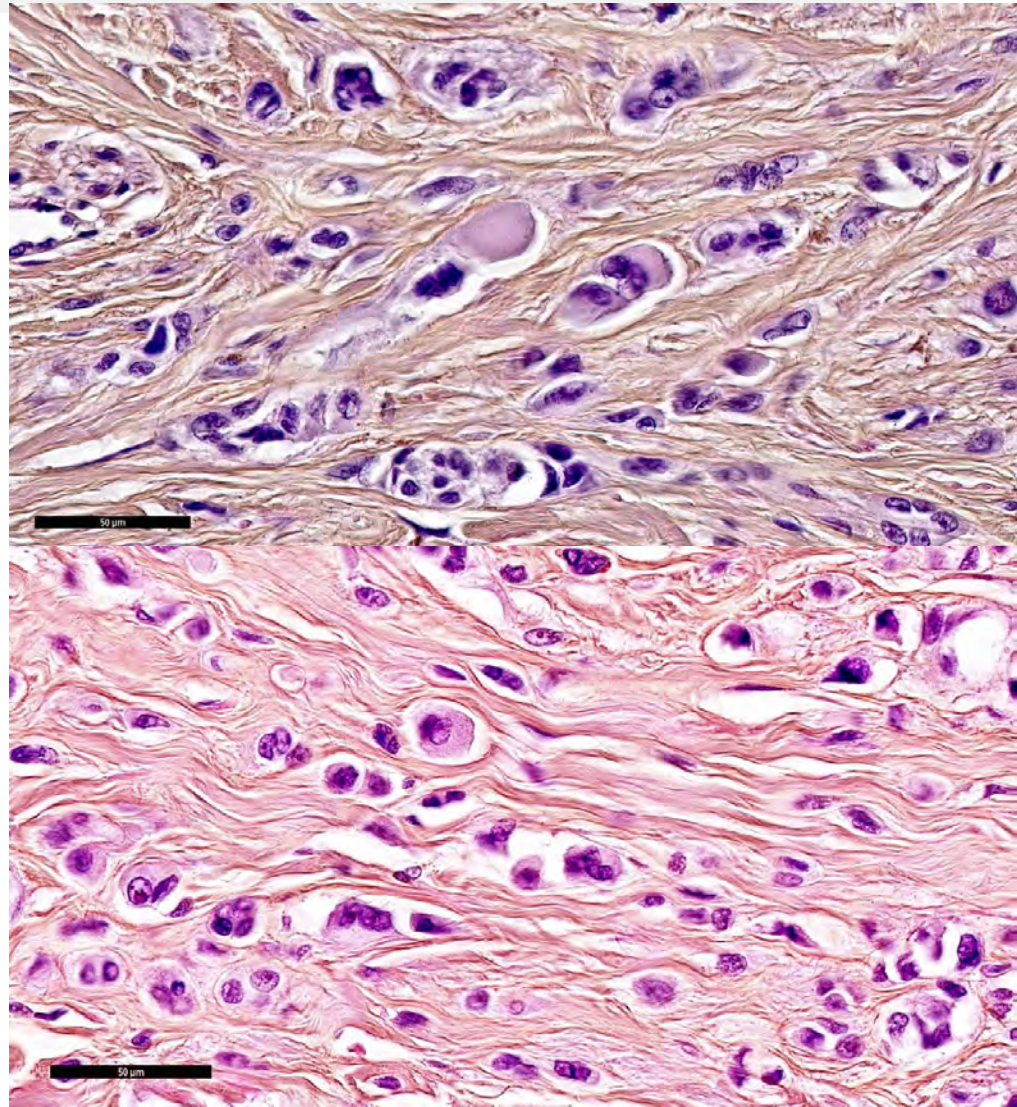
Spitz Tumor

- Subcutaneous fat involvement*
- No maturation
- Epithelioid melanocytes
- High-grade atypia*
- 2 mitoses per mm²
- Neurotropism



Spitz Tumor

- Sclerosis of collagen
- Epithelioid melanocytes
- High-grade atypia
 - Nuclear pleomorphism
 - Hyperchromatism



Atypical Spitz Tumor

- Conclusion: Score = 5
- Atypical Spitz tumor with high risk

Molecular Analysis

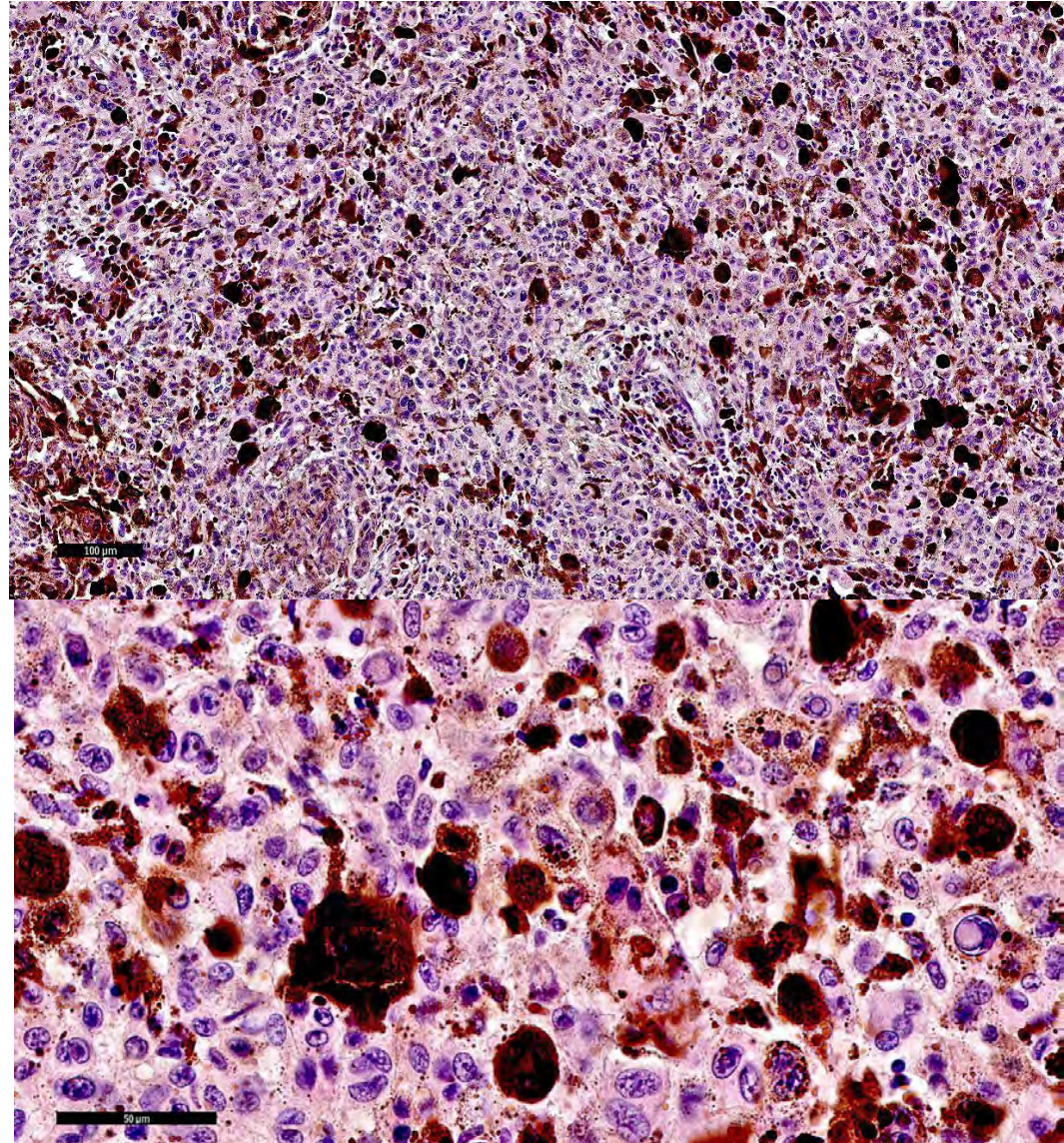
- BRAF kinase fusion
- PTEN monoallelic deletion
- 9p21 biallelic deletion
- ? No apparent TERT promoter mutation

Atypical Spitz Tumor

- Conclusion: Atypical Spitz tumor with high risk and uncertain malignant potential

Progression of Disease

- Development right inguinal lymph node metastasis



Progression of Disease

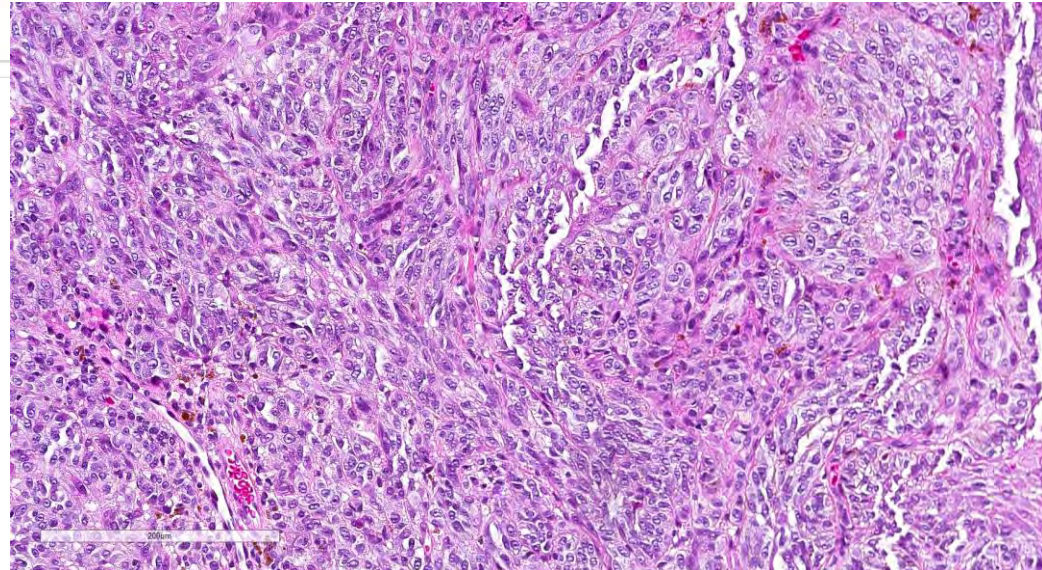
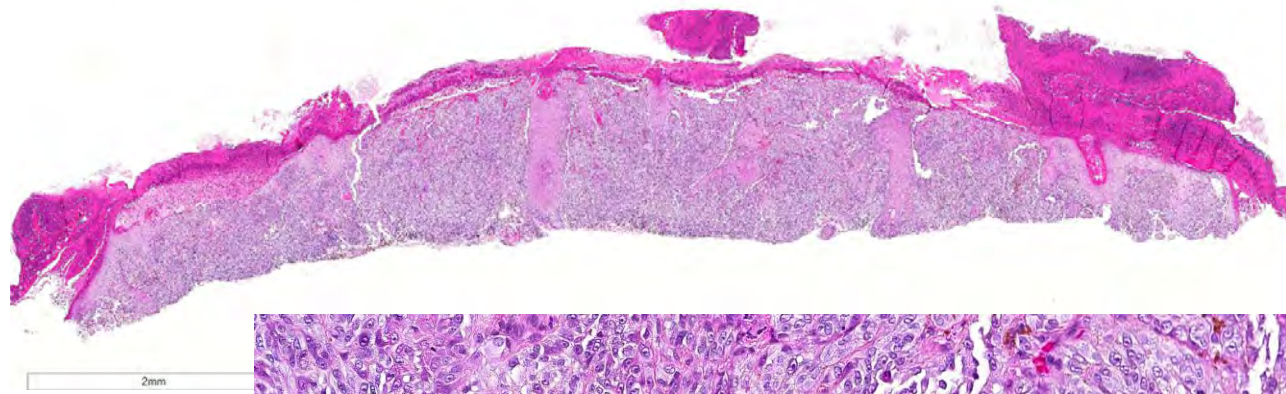
- Months latter: development of new 15 mm imaging defect in liver – consistent with liver metastasis
- Thereafter lost to follow up

~~Atypical Spitz Tumor~~

- Conclusion: Spitz melanoma


Spitz Melanoma

- 14 yo male
- Back
- Diameter: 1.0 cm*
- Thickness: 1.3 mm
- Ulceration*
- Mitotic rate: 5 per mm²*
- Sheets of cells*
- BRAF fusion
- High-grade atypia
- TERT promoter mutation*
- Death 18 months





Clinical features and outcomes of spitzoid proliferations in children and adolescents*

D.W. Bartenstein ^{1,2,3,4} J.M. Fisher,^{1,4} C. Stamoulis,^{1,5} C. Weldon,^{1,6,7} J.T. Huang,^{1,4,7} S.E. Gellis,^{1,4} M.G. Liang,^{1,4} B. Schmidt^{1,8} and E.B. Hawryluk^{1,2,4}

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Linked Editorial: Elder and Barnhill. *Br J Dermatol* 2019; **181**:235.

622 Spitzoid Proliferations in 595 Children and Adolescents from an 18-year Period

| | Median age | n= 622 (%) |
|----------------------|------------|-------------|
| Spitz nevus | 7.4 years | 512 (82.3%) |
| Atypical Spitz tumor | 7.2 | 107 (17.2%) |
| Spitz melanoma | 17.2 | 3 (0.5%) |

Clinical Features and Outcomes of Spitzoid Proliferations in 595 Children and Adolescents

- Ages < 20 years
- Median follow-up – 4.1 years
- 5 recurrences
 - 2 primary tumor with positive margins
 - 2 Spitz nevi
 - 3 atypical Spitz tumors
 - 0 melanomas
- No metastases or death
- All patients with recurrences alive and disease free

Management

- Spitz nevi without atypia in children need not be re-excised for positive margins.
 - Try to examine the entire lesion and to avoid sampling error
- Excise atypical Spitz tumors completely
 - To prevent recurrence and potentially aggressive behavior
- Manage atypical Spitz tumors with high risk/uncertain malignant potential as melanoma in general



Charles Burchard 1908