Spitzoid Melanoctyic Neoplasms: State of the Uncertainty

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Road Map

- Mission of the pathologist
- Classification of Spitz tumors
  - Clinical, histopathological, and molecular criteria
  - Grading system for risk stratification
  - Ancillary techniques
- Boston Children's Hospital Study of 595 patients and their outcome
- Management
- Take home messages

Mission of the Pathologist
Re: Spitzoid Lesions

- Accurate and understandable diagnostic reports for clinicians and patients
  - Prognosis
  - Management, vis-à-vis, surgery,
- Do no harm and due diligence
  - Do not miss melanoma!
  - Do not over-diagnose melanoma!

MPath Study

"Spitzoid lesions are often not classified in any standardized way, evoke uncertainty in diagnosis by pathologists, and elicit variability in treatment recommendations."

Zhao G, Lee KC, Peacock S, Reisch LM, Knezevich SR, Elder DE, Piepkorn MW, Elmore JG, Barnhill RL. The utilization of spitz-related nomenclature in the histological interpretation of cutaneous melanocytic lesions by practicing pathologists:results from the M-Path study. J Cutan Pathol. 2017 Jan;44(1):5-14.

WHO Classification 4th Edition

I. Spitz Nevus
II. Atypical Spitz Tumor
III. Spitz Melanoma

Major Challenges

Lack of concordance and uncertainty exists concerning many Spitz tumors

- Spitz nevus
- Atypical Spitz tumor
- Malignant Spitz tumor/Spitz melanoma
- "Spitzoid melanoma" - other melanomas with spindle and epithelioid cells, BRAF, NRAS, BAP1 mutations, etc.

Defining the True Spitz Phenotype

- Clinical
- Histopathological
- Architecture
- Cytology
- Molecular
- H-RAS,
- kinase fusions
- absence of particular genetic alterations, e.g., BRAF, NRAS, BAP1 mutations

I. Spitz Nevus

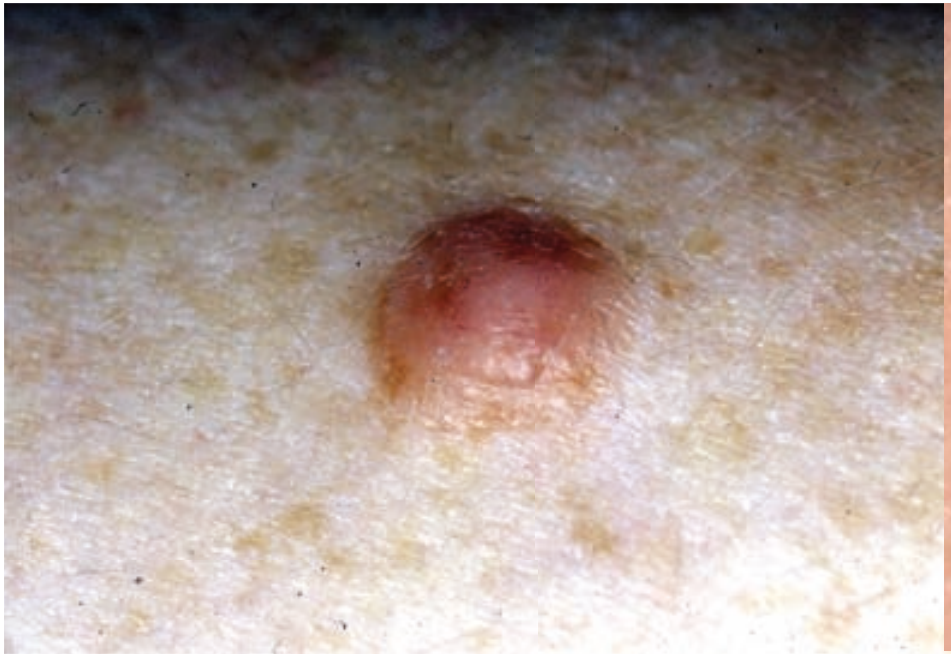
What are the criteria for a Spitz nevus?

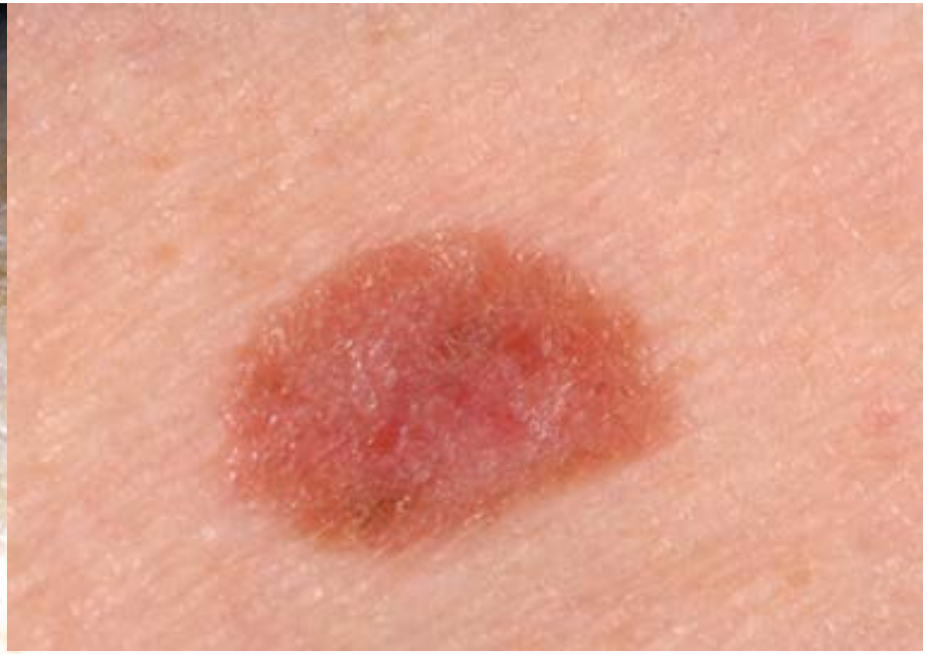
Objective Diagnostic Criteria
Spitz Nevus

- Children, adolescents, any age
- Size of primary tumor, usually < 5 mm
- No ulceration
- No aberrant growth or significant atypia
- Mitotic rate < 2/mm^2
- Usually one genetic alteration:
  - activating H-Ras mutation or
  - kinase fusion
  - other ?

Spitz Nevus
Clinical Criteria

Clinical Diagnosis: Only 20%





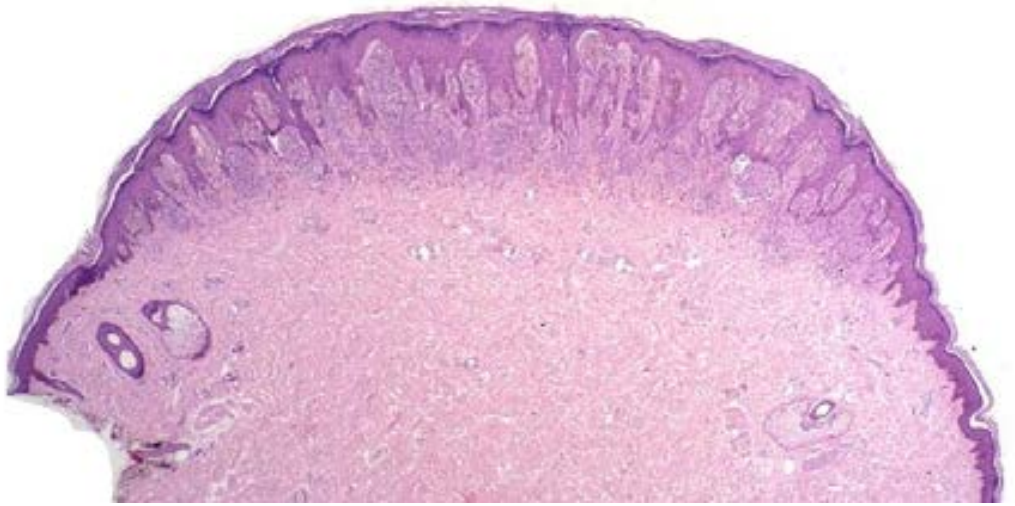
Spitz Nevus

Architecture

Spitz Nevus

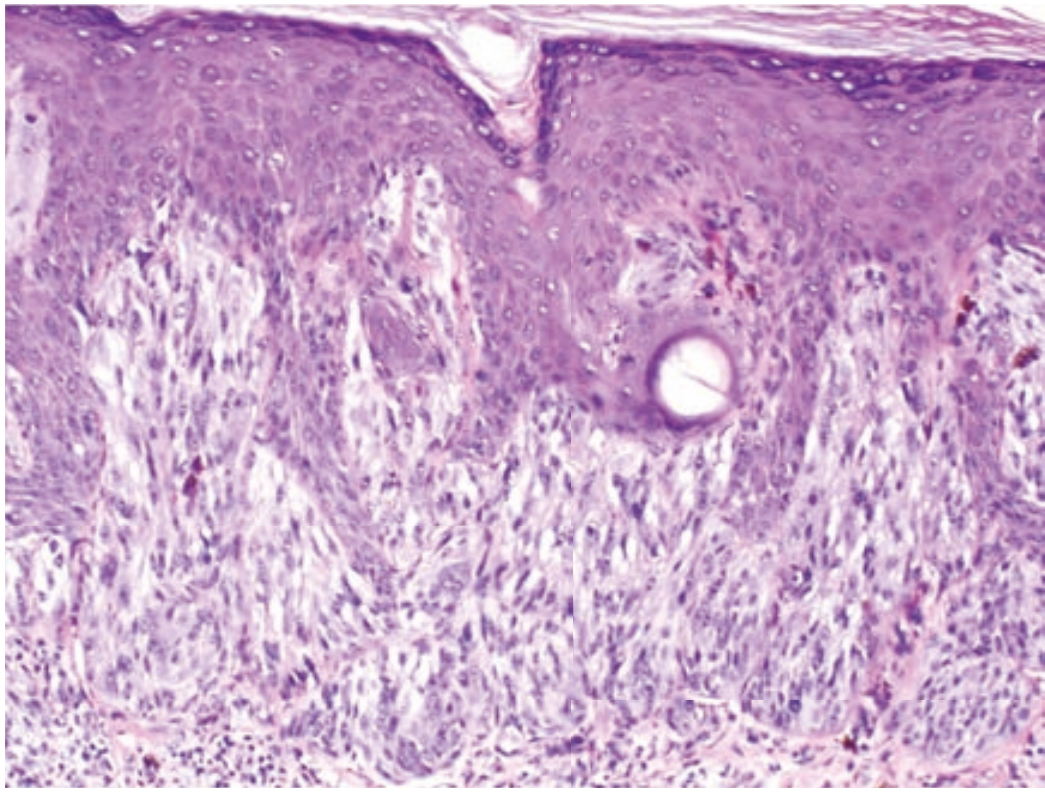
Architecture

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

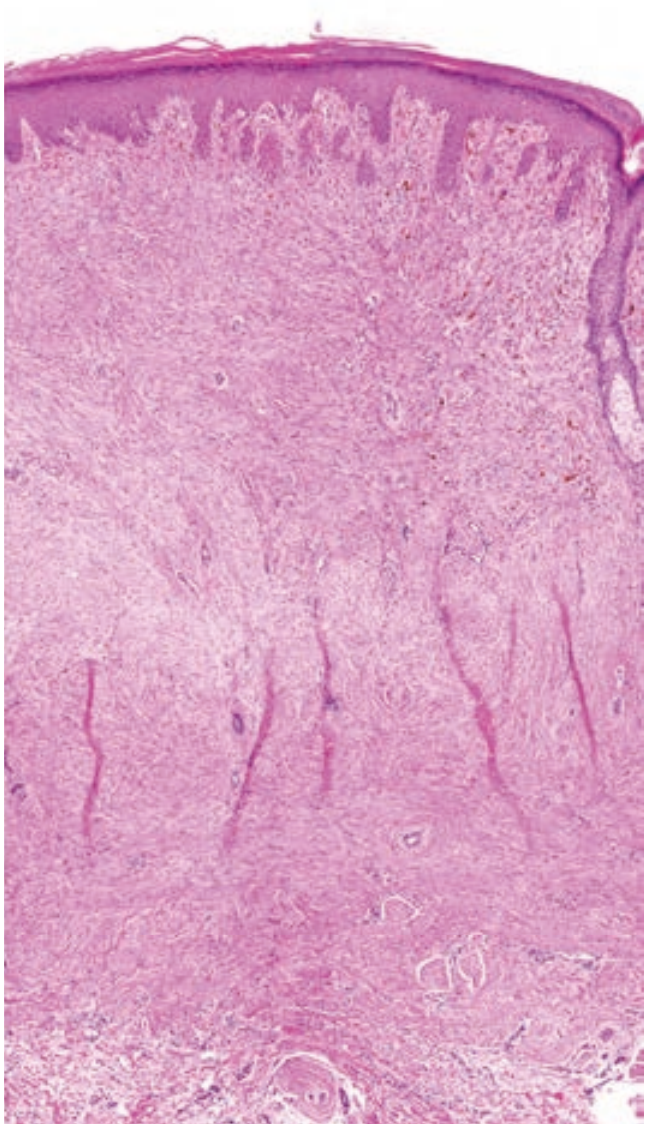


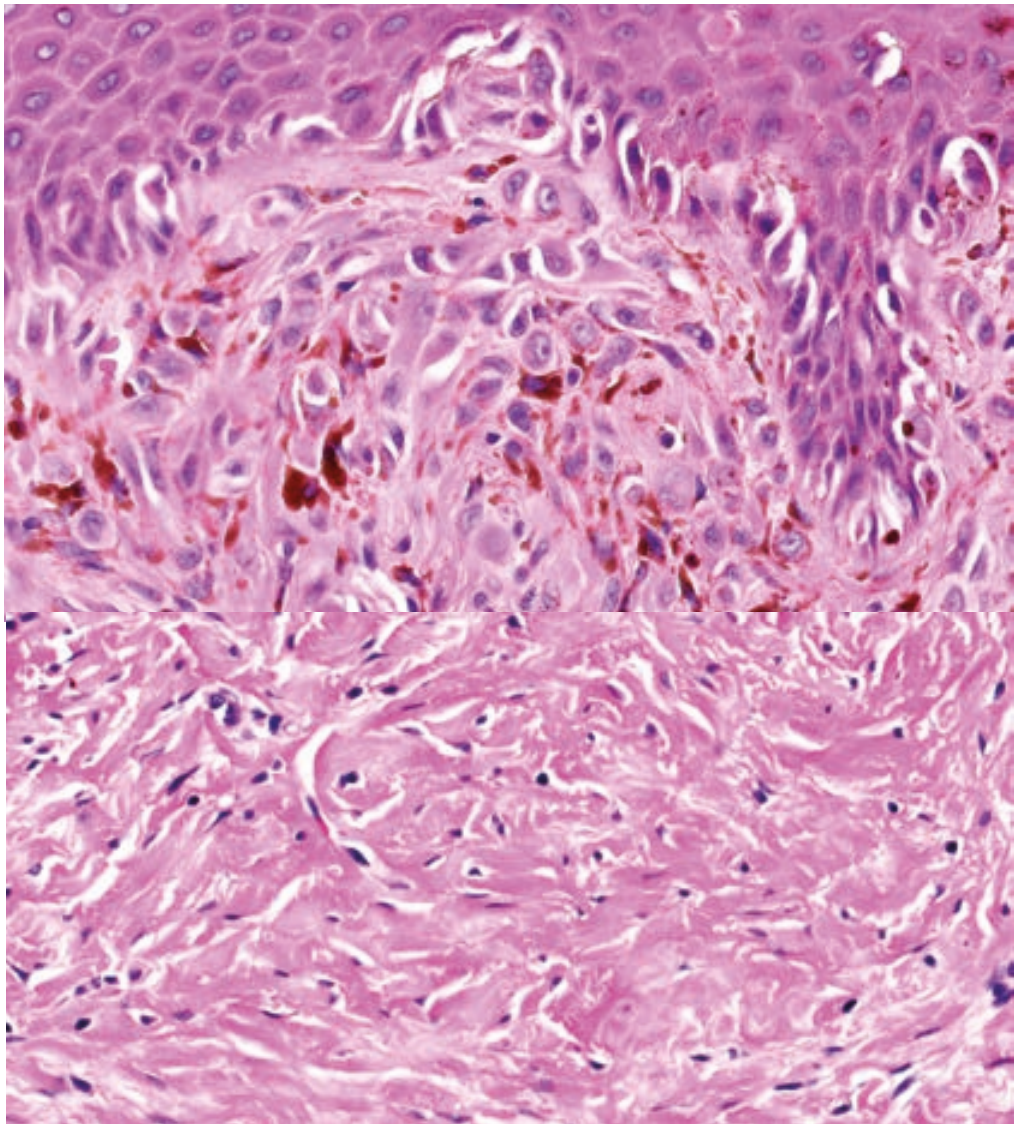
Spitz Nevus
Histopathological Features

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



Spitz Nevus
Maturation

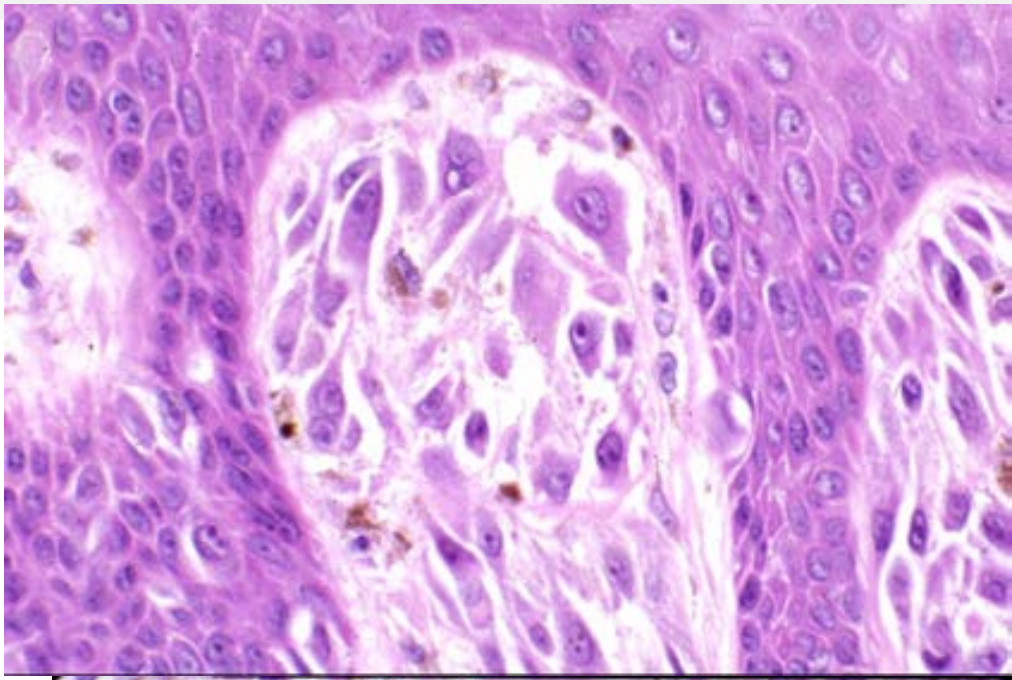


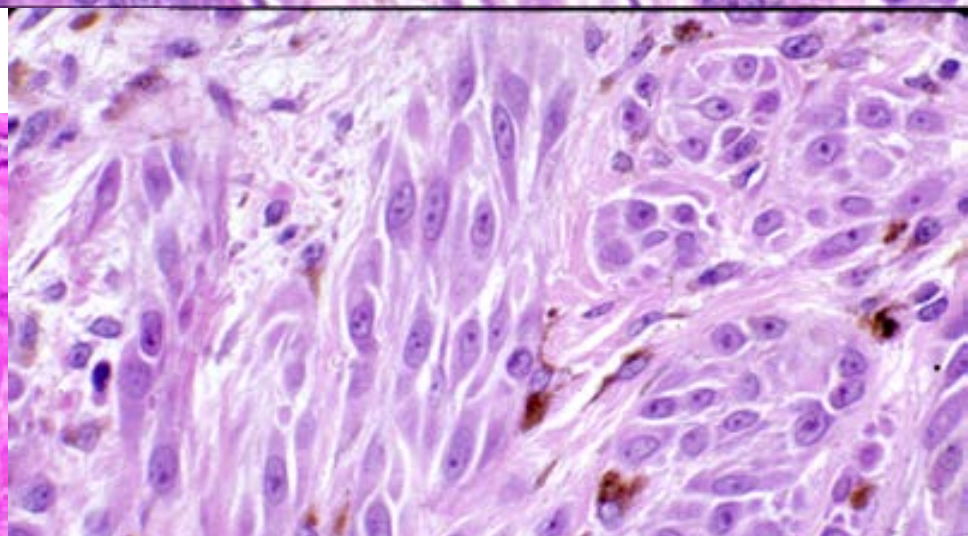


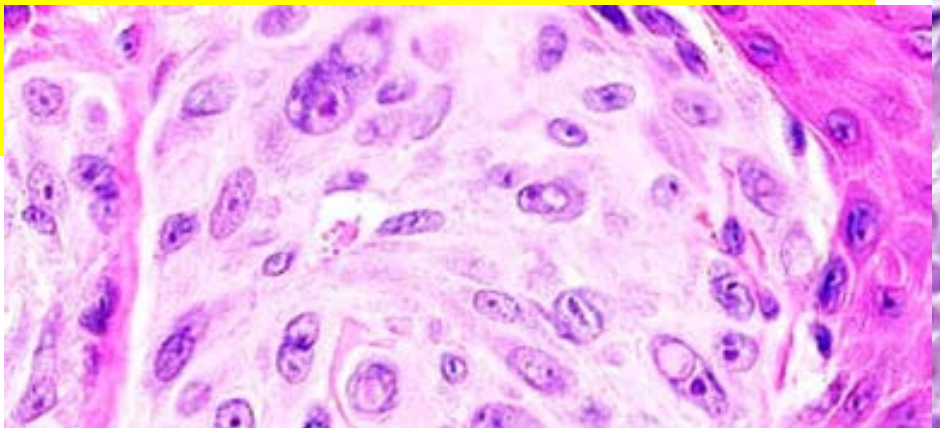
Spitz Nevus

Cytology:

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







Spitz Nevus
WHO 4th Edition

Molecular aspects – a single genetic alteration

- activating HRAS mutation
- A kinase fusion
  - ROS1
  - ALK
  - NTRK1
  - BRAF
  - RET
  - MET
  - MAP3K8
- BUT only ~ 50% of Spitz Nevi/Tumors have kinase fusions !

II.
Atypical Spitz Tumor

What is an Atypical Spitz Tumor?

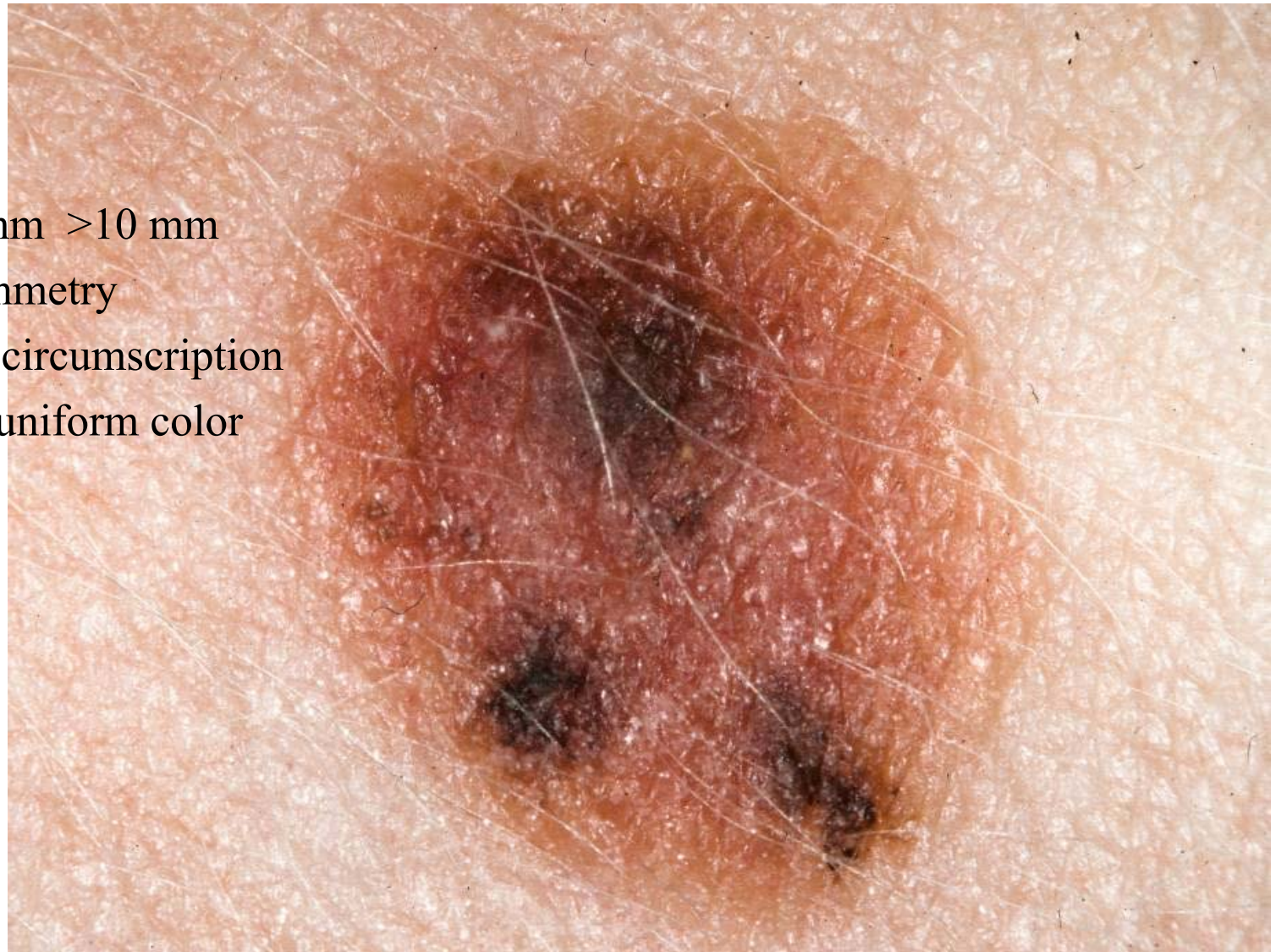
- Spitz tumor with one or more atypical features

- 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 mm >10 mm
- Asymmetry
- Poor circumscription
- Non uniform color



What Are the Histopathologic Criteria for an Atypical Spitz Tumor?

- Lesional diameter > 1 cm*
- Ulceration*
- Mitotic rate >2 to 6/mm^{2*}
- Deep/marginal mitoses
- Involvement of subcutaneous fat*

What Are the Histological Criteria for an Atypical Spitz Tumor?

- Poor circumscription
- Asymmetry
- Pagetoid melanocytosis - peripheral
- Confluence of melanocytes
- Absence of maturation
- Cytological atypia

Use of 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 tumor with low or high risk
- uncertain malignant potential or
- Spitz melanoma

STUDY

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/mm^2 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 Atypical 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

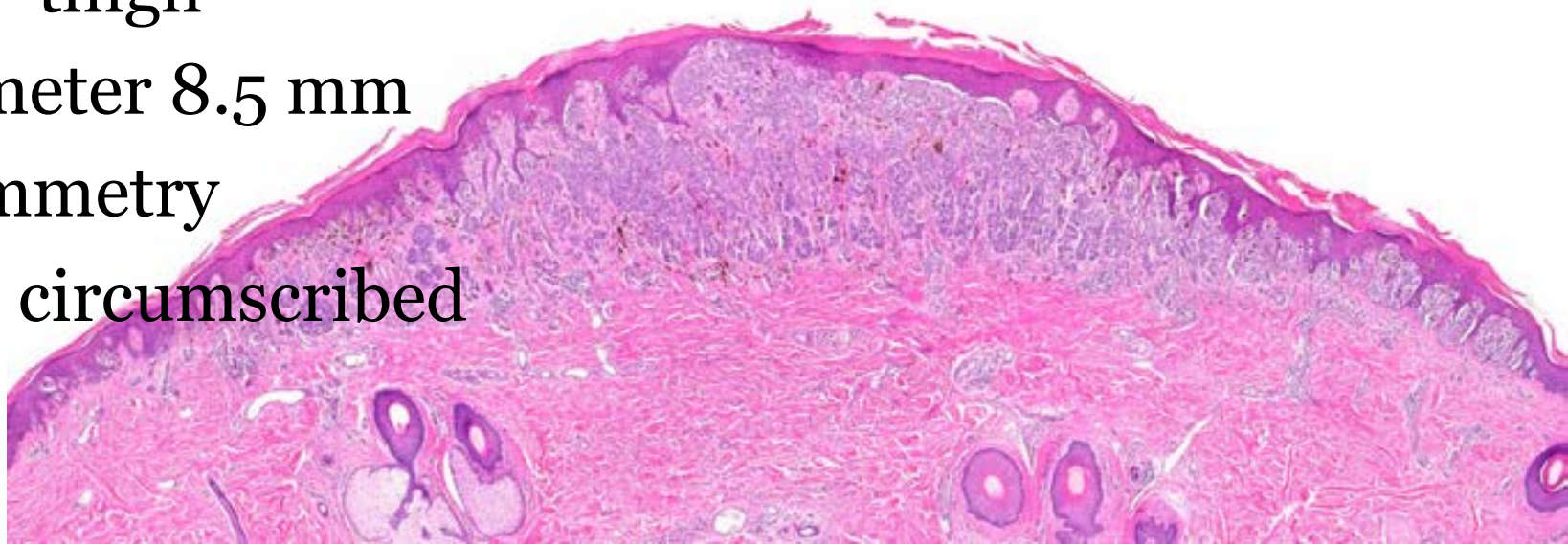
What Are the Genetic Criteria for an Atypical Spitz Tumor?

- At Least Two Genetic Alterations:
  - Activating HRAS mutation, or a kinase fusion
  - p16 loss, bi-allelic deletion of 9p21
  - PTEN, TERT promoter mutation
  - DNA copy number changes

Examples

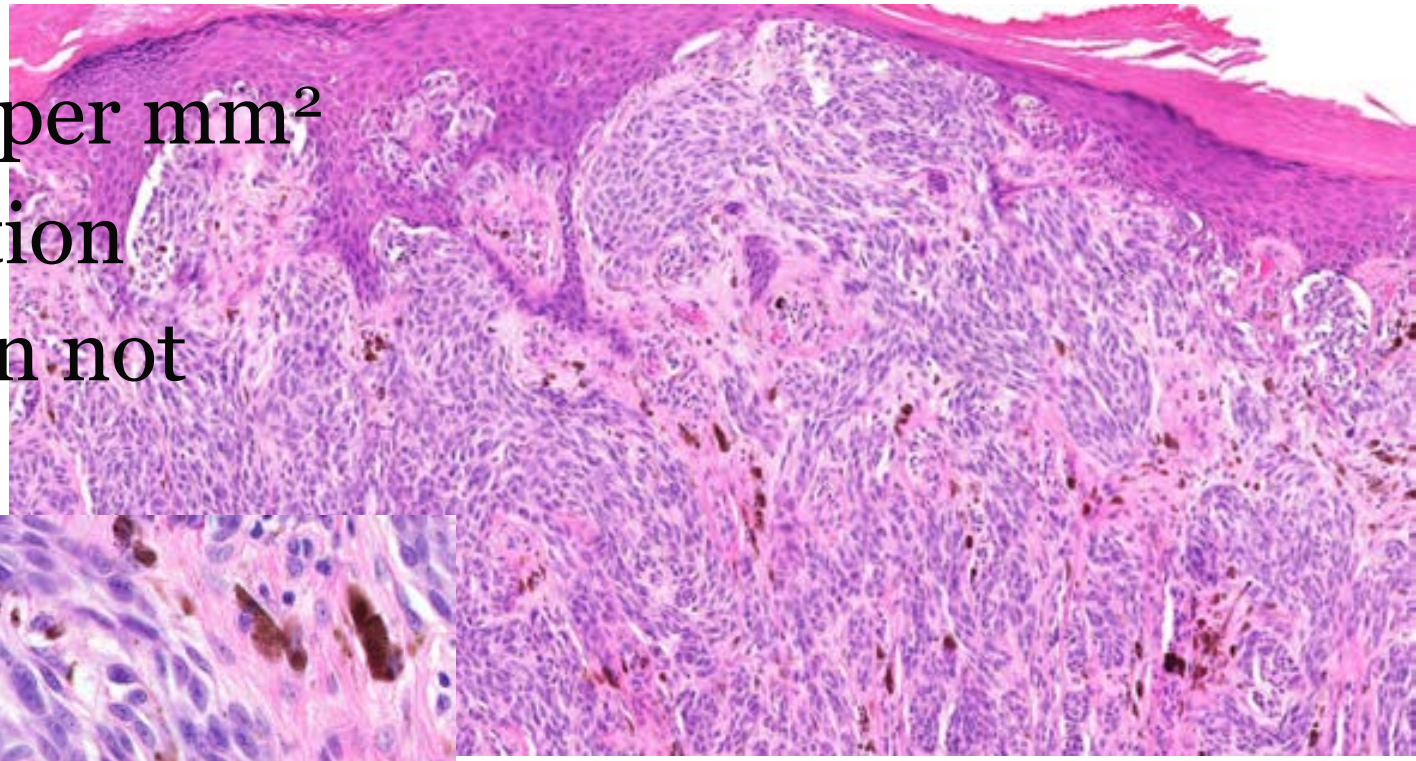
Spitz Tumor

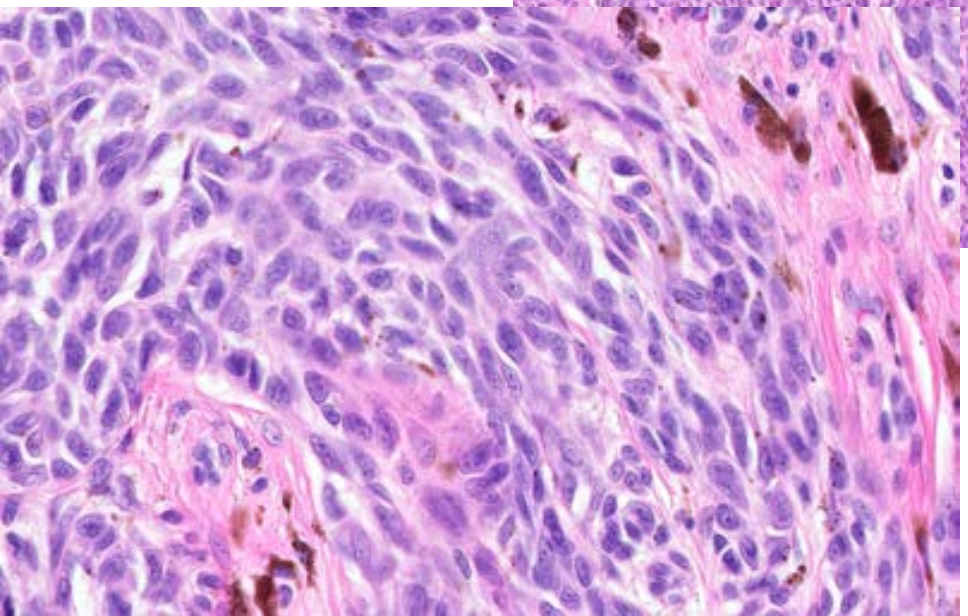
- 25 year old female
- Site - thigh
- Diameter 8.5 mm
- Asymmetry
- Well circumscribed



Spitz Tumor

- 0 mitoses per mm^2
- No ulceration
- Maturation not complete





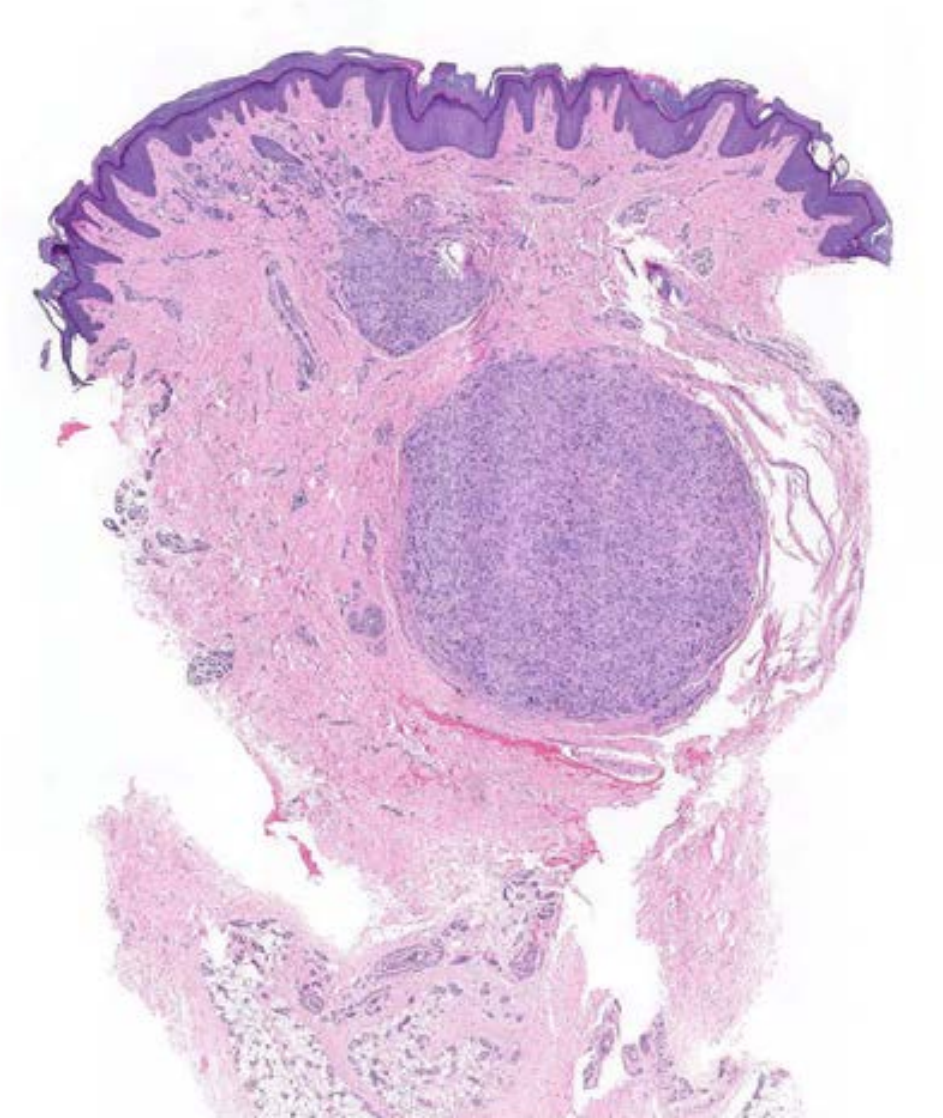
Atypical Spitz Tumor

- Conclusion: Score = 0

Atypical Spitz tumor with low risk

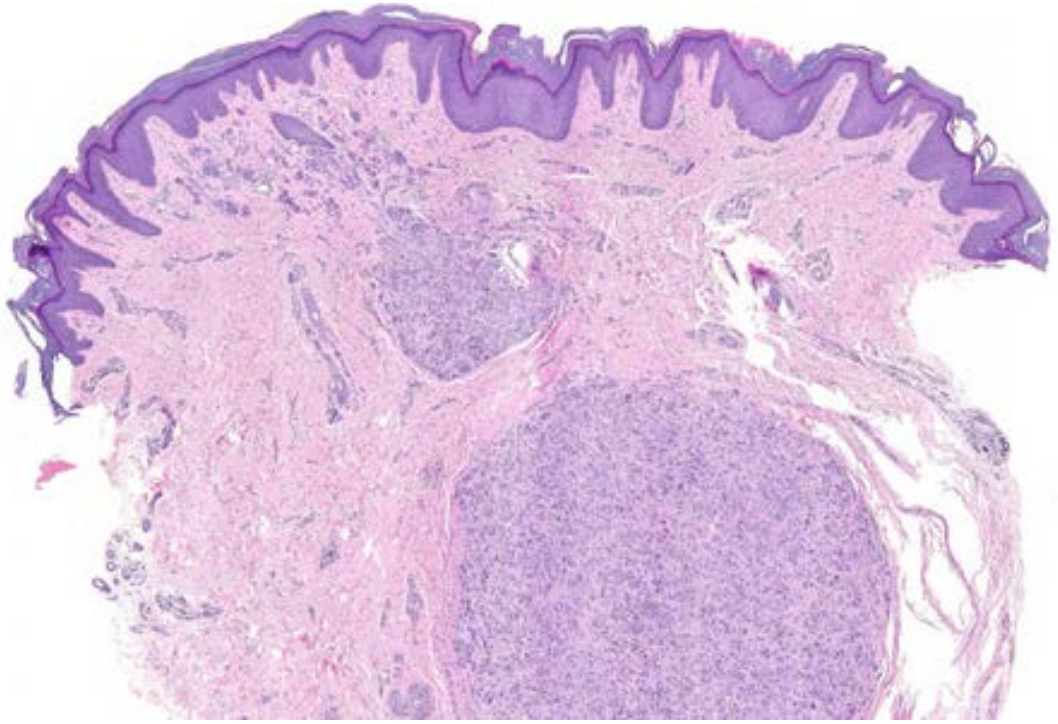
Spitz Tumor

- 9 year-old female
- Site: right knee
- “Cyst ?”
- Diameter: 3.8 mm
- Well-circumscribed
- Symmetrical
- No ulceration
- No maturation

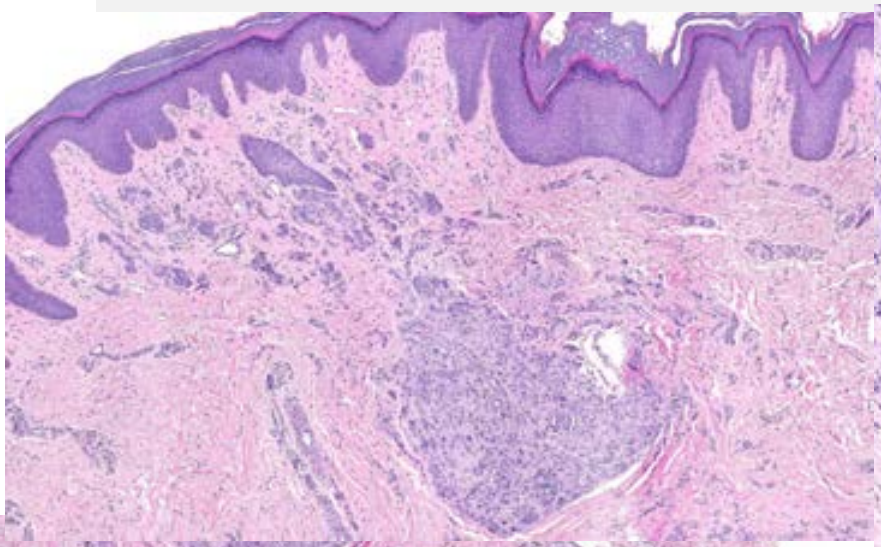


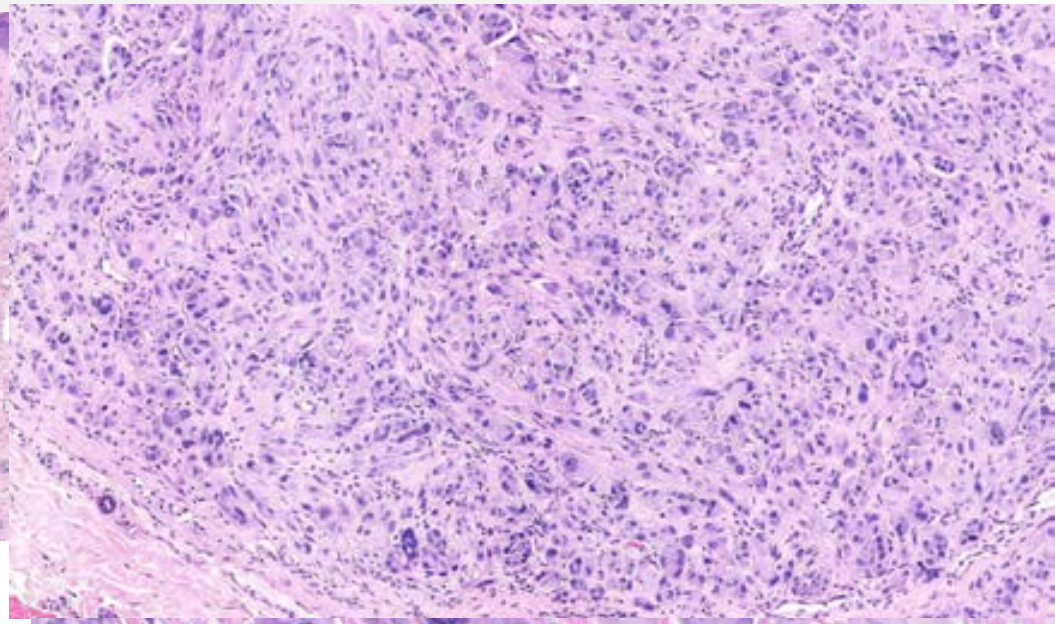
Spitz Tumor

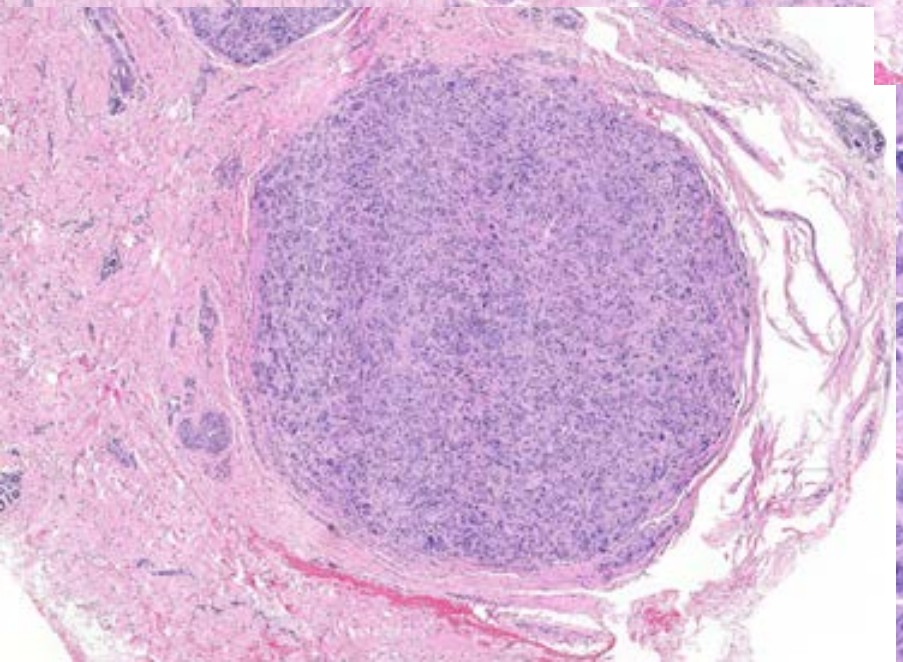
- Thickness: 4 mm
- Nodule: 2.3 mm
- 4 mitoses per mm^2
- Cytological atypia
- Subcutaneous fat involvement

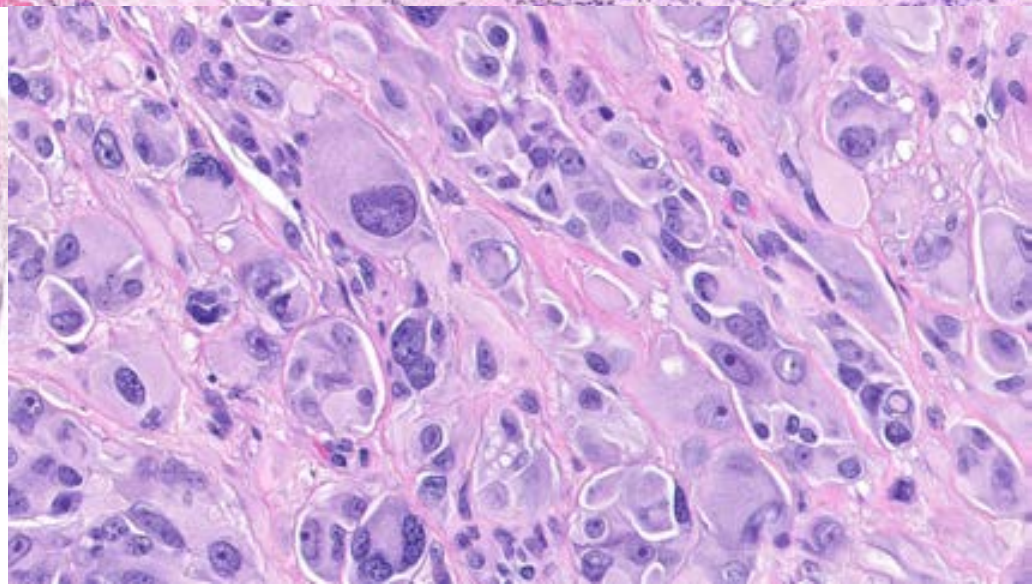


Spitz Tumor









Atypical Spitz Tumor

- Conclusion: Score = 2
- Atypical Spitz tumor with low-risk profile

Atypical Spitz Tumor

- Loss of p16 (IHC)
- Biallelic deletion of 9p21
- No kinase fusions
- No mutations in BRAF, NRAS, BAP1, or TERT promoter

Atypical Spitz Tumor

- Conclusion: Score = 2
- Atypical Spitz tumor with uncertain biological potential

III.
Spitz Melanoma

What is Spitz Melanoma?

- A melanoma with sufficient clinical, histological, and molecular criteria for a Spitz phenotype and evidence for neoplastic progression, distant metastasis, or death
- A diagnosis of exclusion, i.e., exclusion of:
  - ✓Conventional melanomas with spindle and epithelioid cell phenotype
  - ✓BRAF and NRAS-mutated “Spitzoid” melanoma
  - ✓ BAP1-inactivated neoplasms

What are the Criteria for Spitz Melanoma?

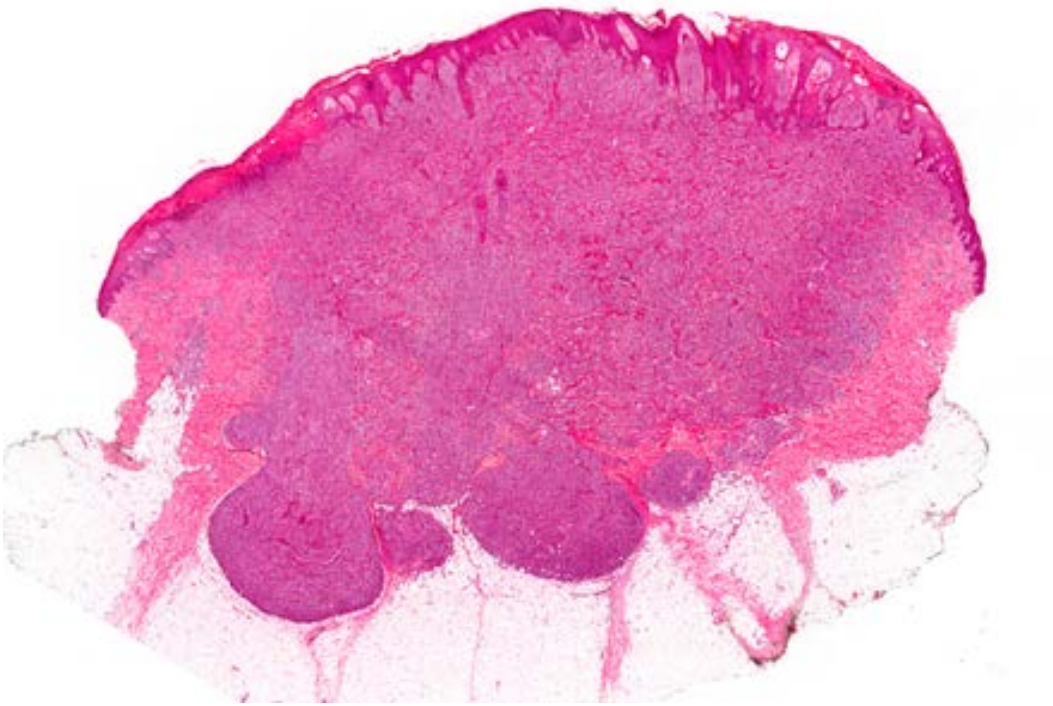
- Age > 10 years
- Size of primary tumor often > 1 cm
- Atypical features as in atypical Spitz tumor
  - Ulceration often
  - Involvement of subcutaneous fat often
  - Mitotic rate >2 to 5, 6 or more/mm^2
- Evidence of regional (palpable lymph node), particularly distant spread, death

What are the Criteria for Spitz Melanoma?

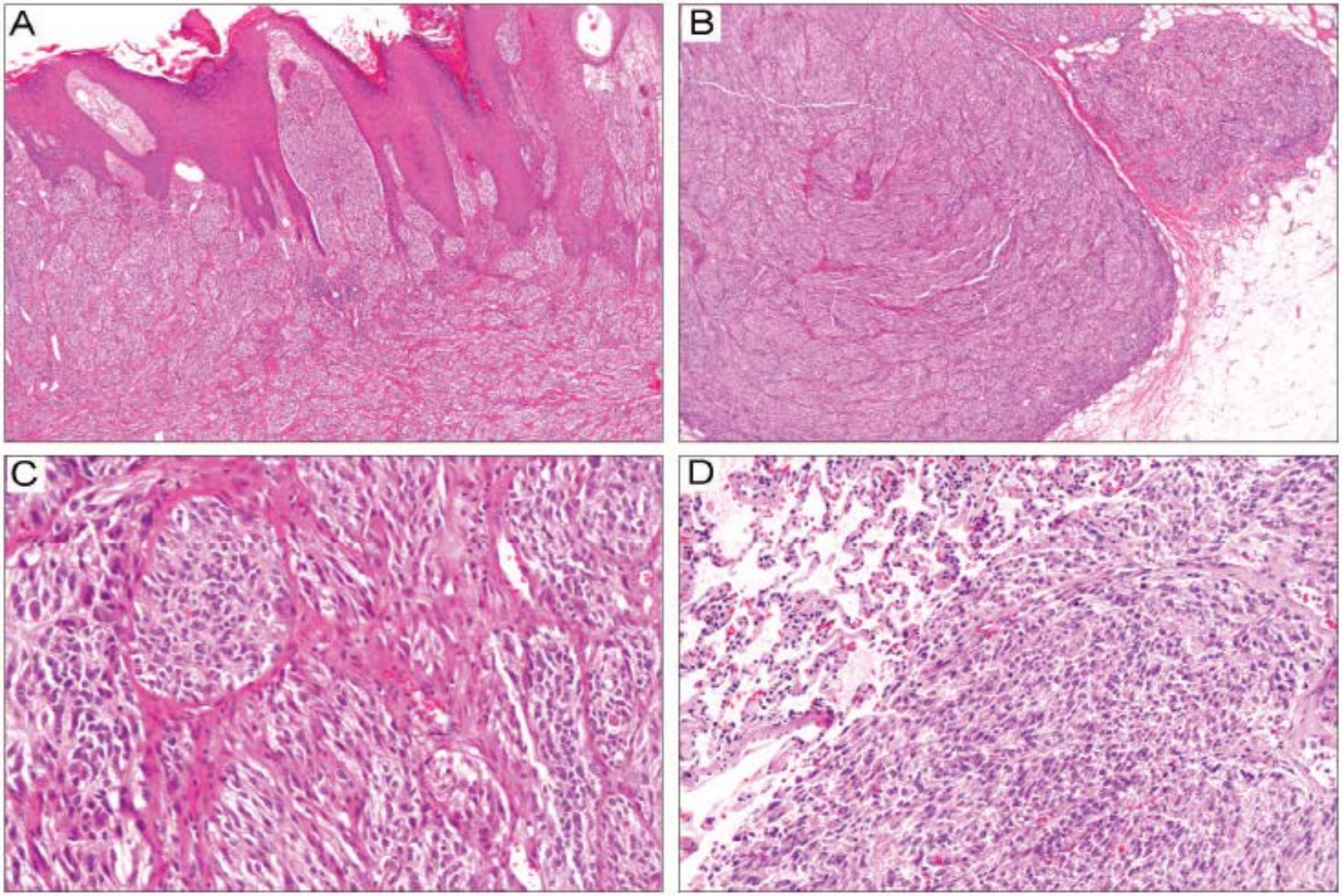
- IHC and molecular studies:
  - Kinase fusions, e.g., fusion, ALK, MAP3k8, etc.
  - p16
  - bi-allelic deletion of 9p21
  - DNA copy number changes
  - PTEN, TERT promoter mutations

Spitz Tumor

- 11 year-old female
- Site: thigh
- Diameter: 1.2 cm
- Ulceration
- 7 mitoses per mm^2
- 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

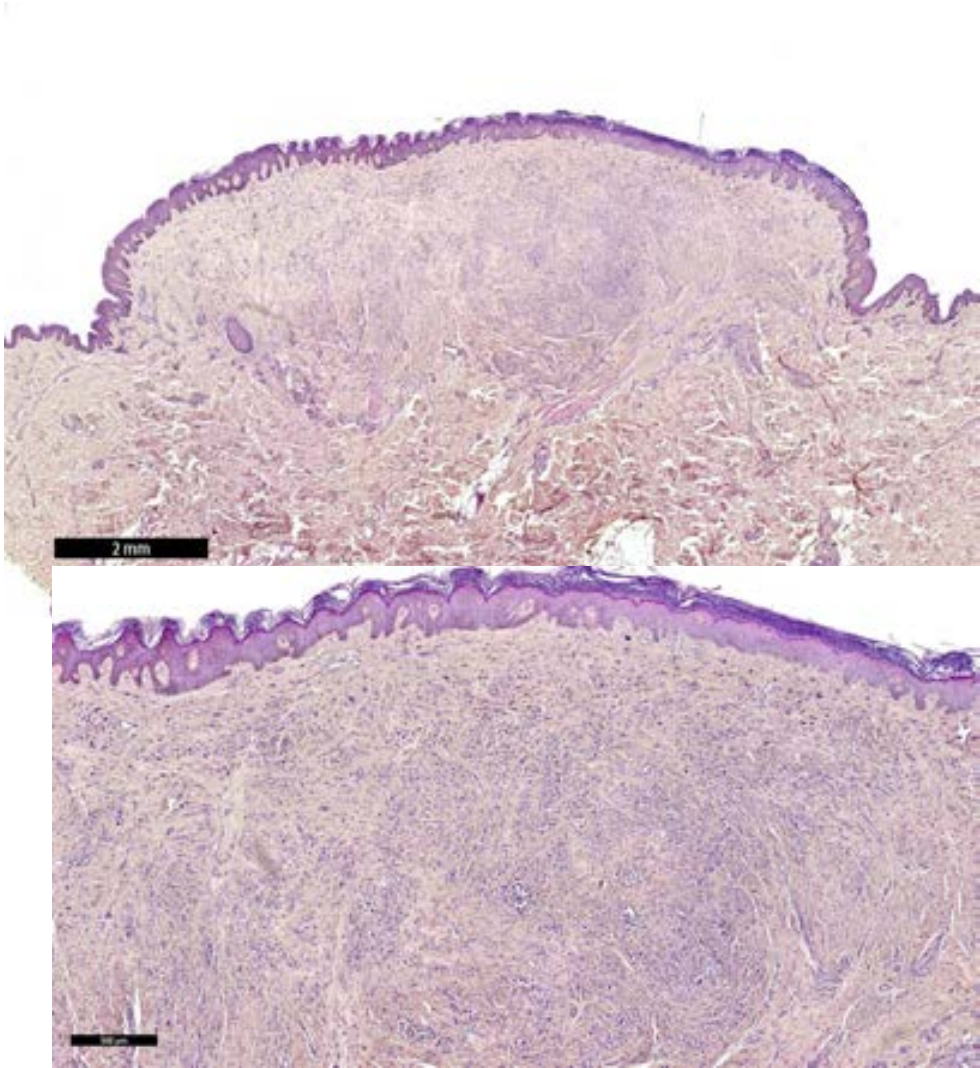
- Kinase fusion
- TERT promoter mutation
- Clinical lymph node metastasis at 6 months
- Distant metastases and death at 24 months

~~Atypical Spitz Tumor~~

- Conclusion: Spitz Melanoma

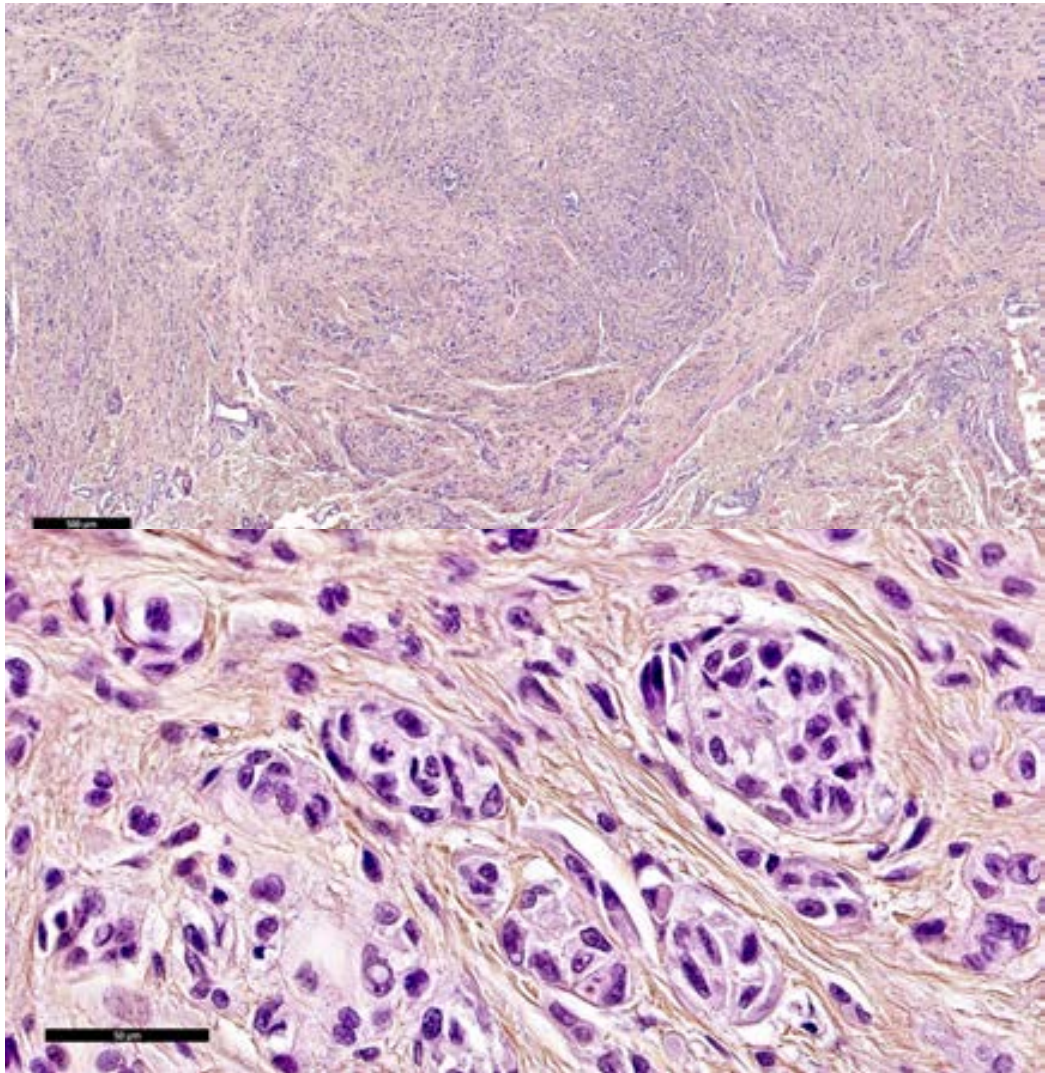
Spitz Tumor

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



Spitz Tumor

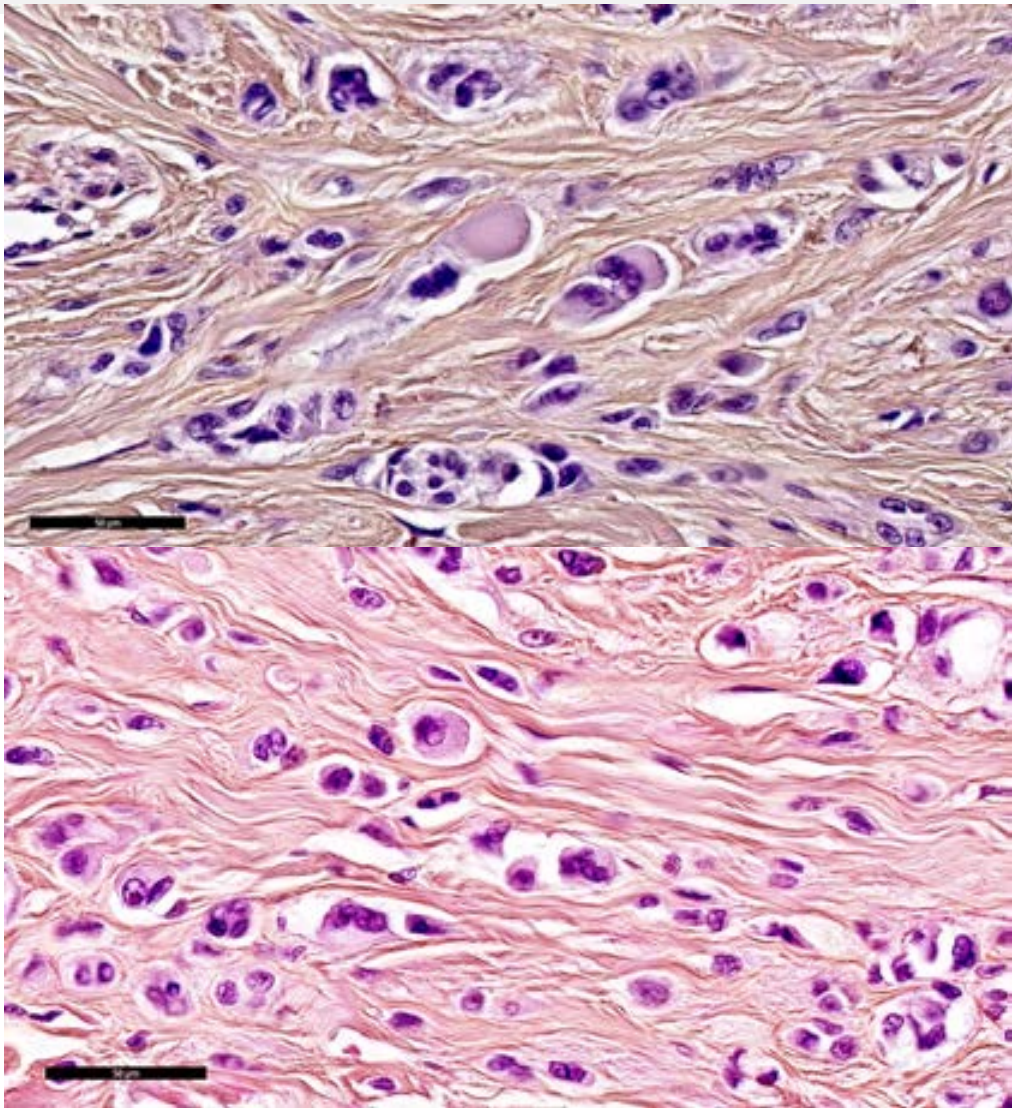
- Subcutaneous fat involvement
- No maturation
- Epithelioid melanocytes
- Cytological atypia
- 2 mitoses per mm^2
- Neurotropism



Spitz Tumor

- Sclerosis of collagen
- Epithelioid melanocytes
- Cytological atypia

- Nuclear pleomorphism
- Hyperchromatism



Atypical Spitz Tumor

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

Molecular Analysis

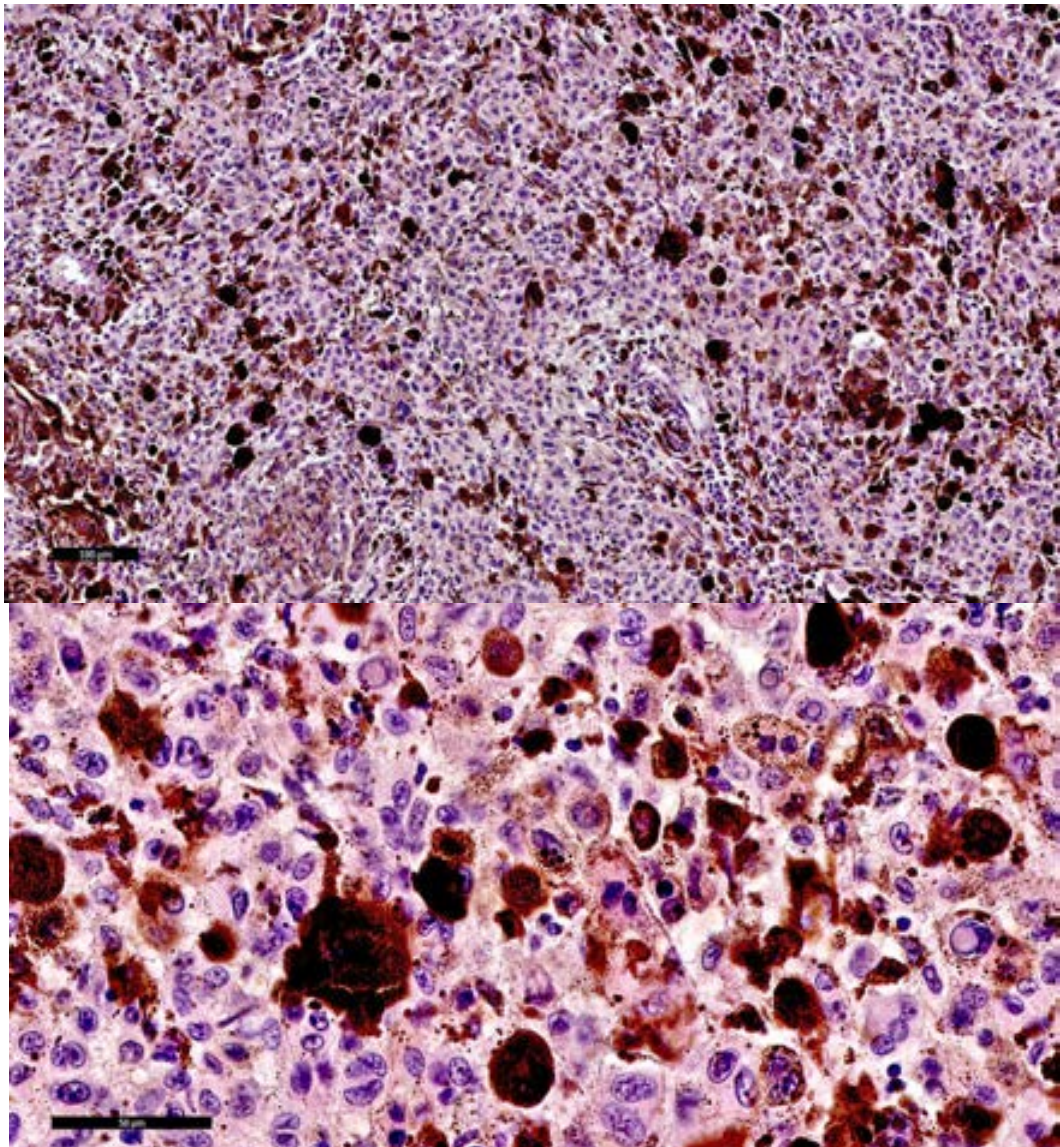
- BRAF kinase fusion
- PTEN monoallelic deletion
- 9p21 biallelic deletion
- No BRAF, NRAS, cKit mutations
- No TERT promoter mutation

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
- BRAF kinase fusion ? indicative of greater risk of aggressive behavior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Ancillary Techniques: Pragmatism and Due Diligence

Ancillary Techniques

- Ki 67
- HMB45
- p16
- array CGH
- Gene signature
- Mutation analysis: BRAF, NRAS, BAP1
- Next generation sequencing
- RNA sequencing

- There is no perfect test.
- Many aspects of the molecular biology of spitzoid lesions remain poorly understood.

Immunohistochemistry

- Ki 67
- HMB45
- p16

- There is no perfect test.
- Low yield information
- Often unreliable

J Cutan Pathol 2012: 39: 1062–1074
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Journal of
Cutaneous Pathology

Expression of p16 alone does not differentiate between Spitz nevi and Spitzoid melanoma

Background: Spitz nevi and Spitzoid melanomas show overlapping histopathologic features, often making the diagnosis challenging. The p16 protein functions as a tumor suppressor and loss of its expression may be seen in some melanomas.

Methods: We evaluated 18 Spitz nevi and 19 Spitzoid melanomas from the Yale Spitzoid Neoplasm Repository for p16 expression. A staining intensity score (SIS) was calculated by multiplying a score for the percentage of stained cells (0–3) by a score for staining intensity (0–3).

Results: Staining with p16 was positive in 15/18 (83%) Spitz nevi and 15/19 (79%) Spitzoid melanomas ($p = 0.73$). Both Spitz nevi and Spitzoid melanomas had a similar SISs, 4.9 and 3.8, respectively ($p = 0.057$). All 19 patients with Spitzoid melanomas had poor outcome with either death (6 patients) or metastases (13 patients) at a median (3 years) and mean (5.4 years) follow up. In contrast, all 18 patients with Spitz nevi had a benign course with no adverse events at a median (4 years) and mean (4 years) follow up.

Conclusions: We found no significant difference in p16 staining in Spitz nevi and Spitzoid melanomas. We conclude that p16 does not

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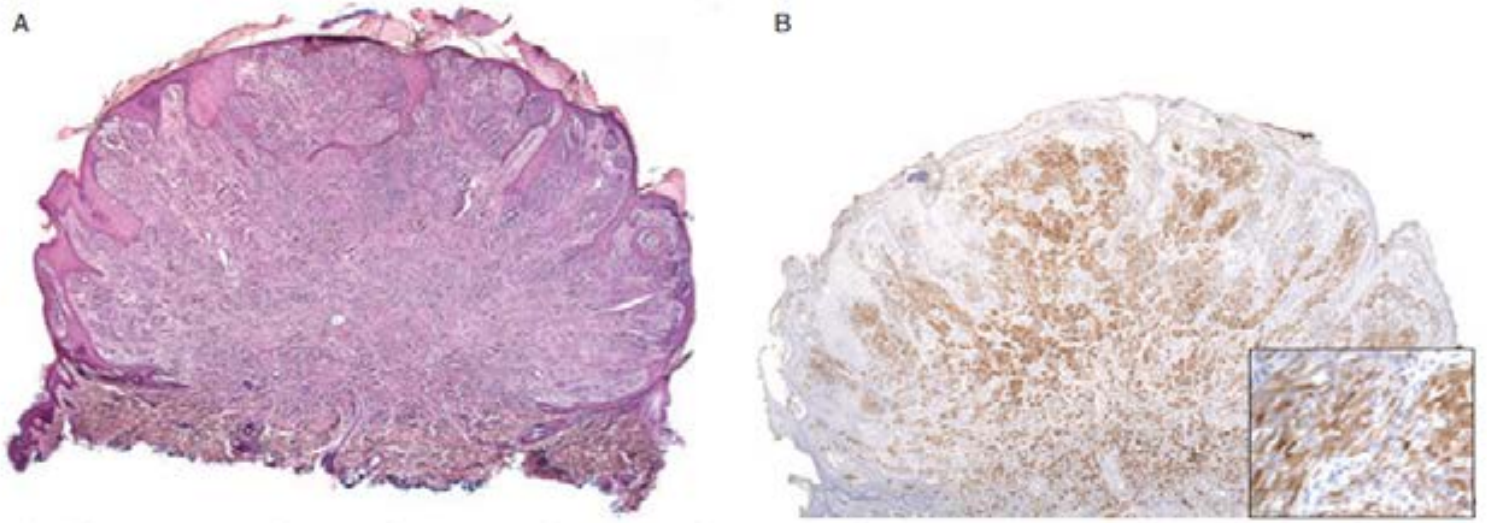

Fig. 1. A) Spitz nevus case 5 is a classic, representative lesion with a symmetric, compound melanocytic proliferation of epithelioid and spindled cells. B) p16 Staining of this Spitz nevus (case 5) shows diffuse staining in the majority of melanocytes. This Spitz nevus scored a 3 for both the percentage of cells staining (67–100% of cells staining) and the intensity of tumoral cells staining (strong). Staining intensity score, the product of the above scores, was 9. Inset: Predominately cytoplasmic staining of melanocytes is seen with p16.

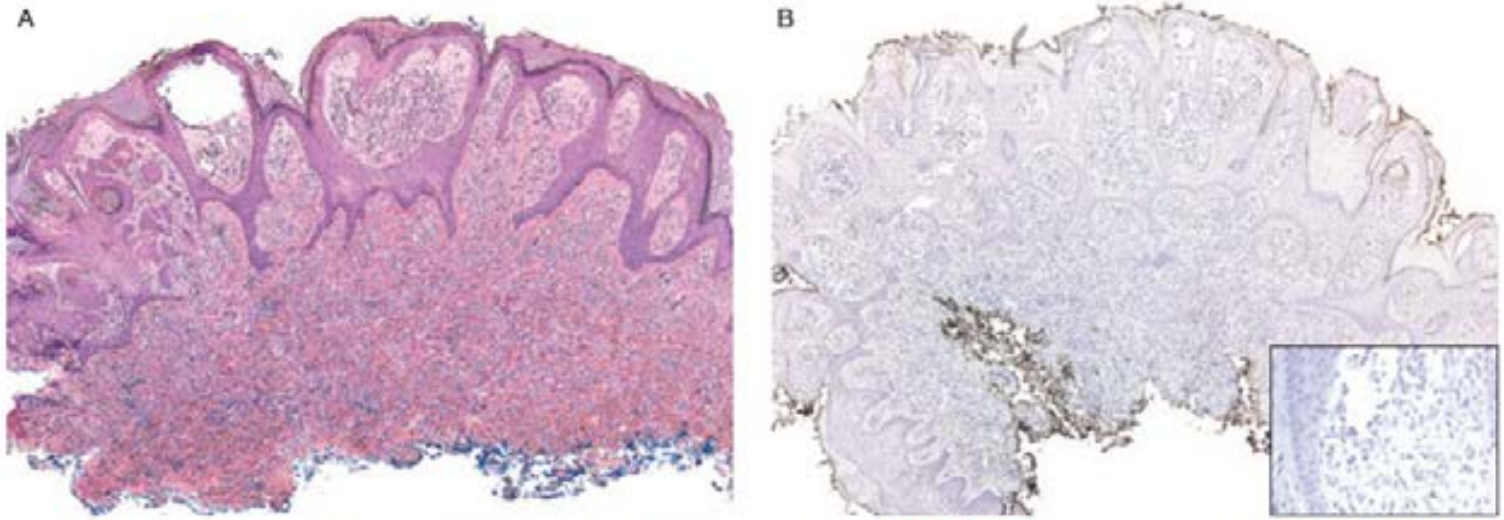

Fig. 2. A) Spitz nevus case 11 is also representative of a classic Spitz nevus. The symmetric, compound melanocytic proliferation is composed of epithelioid and spindled cells. B) Spitz nevus case 11 shows no significant staining with p16. This Spitz nevus scored a zero for both the percentage of cells staining and the intensity of tumoral cells staining. Inset: No significant staining of melanocytes is seen with p16.

Molecular Techniques

	Spitz Nevus	Atypical Spitz Tumor 	Spitz Melanoma
aCGH NGS Mutation analysis	11p (HRAS) Kinase fusion Absence of BRAF, NRAS, BAP1 mutations	11p (HRAS) Kinase fusion 9p21 deletion DNA copy number changes (gains and losses) Absence of BRAF, NRAS, BAP1 mutations	Kinase fusion 9p21 biallelic deletion Multiple DNA copy number changes TERT promoter aberrations

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Kinase fusions are frequent in Spitz tumours and spitzoid melanomas

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Spitzoid neoplasms are a group of melanocytic tumours with distinctive histopathological features. They include benign tumours (Spitz naevi), malignant tumours (spitzoid melanomas) and tumours with borderline histopathological features and uncertain clinical outcome (atypical Spitz tumours). Their genetic underpinnings are poorly understood, and alterations in common melanoma-associated oncogenes are typically absent. Here we show that spitzoid neoplasms harbour kinase fusions of *ROS1* (17%), *NTRK1* (16%), *ALK* (10%), *BRAF* (5%) and

Table 1

Frequency of kinase fusions in spitzoid neoplasms.

Fusion	Spitz nevus (n=75) % (number of cases)	Atypical Spitz tumor (n=32) % (number of cases)	Spitzoid melanoma (n=33) % (number of cases)	Total (n=140) % (number of cases)
ROS1	**25.3%** (19)	**6.3%** (2)	**9.1%** (3)	**17.1%** (24)
ALK	**10.7%** (8)	**15.6%** (5)	**3%** (1)	**10%** (14)
NTRK1	**10.7%** (8)	**25%** (8)	**21.2%** (7)	**16.4%** (23)
BRAF	**5.3%** (4)	**6.3%** (2)	**3%** (1)	**5%** (7)
RET	**2.7%** (2)	**3.1%** (1)	**3%** (1)	**2.9%** (4)
Total	**54.7%** (41)	**56.3%** (18)	**39.4%** (13)	**51.4%** (72)

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

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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*

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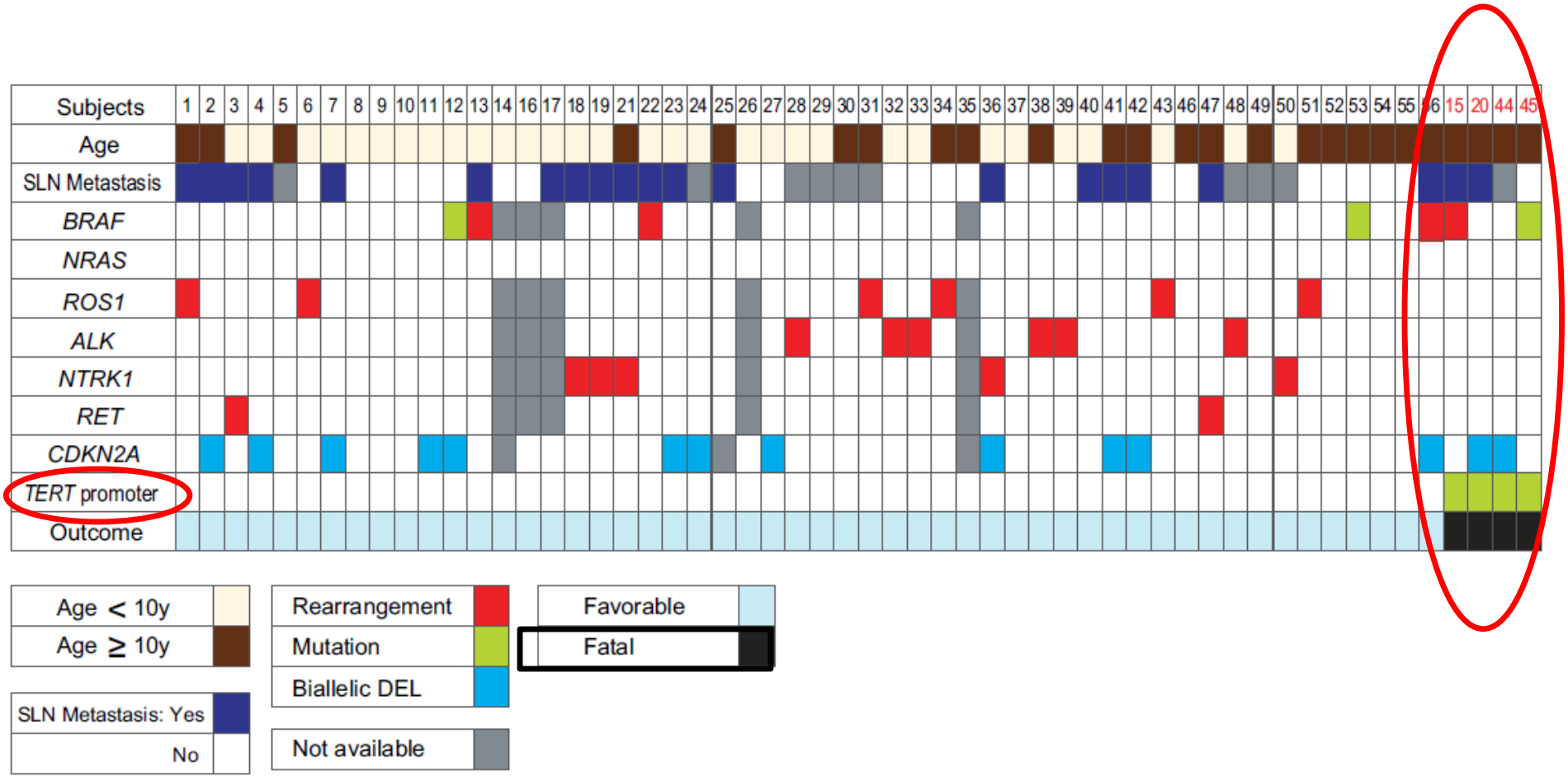

Figure 1. Association of kinase fusions, *BRAF* and *NRAS* mutations, biallelic *CDKN2A* deletion, and *TERT* promoter mutations with outcome in 56 patients with atypical spitzoid melanocytic neoplasm. Subject numbers in black font had a favorable clinical course and subject numbers in red font died of disseminated disease. Abbreviations: SLN, sentinel lymph node; DEL, deletion

Atypical Spitz Tumors
Risk for Distant Mets, Death

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

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, RET, BRAF

What is Spitzoid versus True Spitz Melanoma?

- A melanoma with some criteria for but lacking sufficient clinical, histological, and molecular criteria for a true Spitz phenotype
- Many “Spitzoid” melanomas appear to be Low Cumulative Sun Damage (even some High CSD) melanomas, i.e., with BRAF, NRAS, other mutations which are misclassified as true Spitz melanoma

Over-Diagnosis of Spitz Melanoma

- Spitz melanoma in children < 10 years of age is vanishingly rare to non-existent.
- The use of terms such as ”atypical Spitz tumor with uncertain malignant potential” preferable to melanoma.
- Over-diagnosis of melanoma may result in harm to the patient via overly aggressive intervention and undue psychological burden

GENERAL DERMATOLOGY

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

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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
  - 2/4 (50%) 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

Features of the 3 Spitz Melanomas

	Patient A	Patient B	Patient C
Age (yrs)	17.6 years	17.2	14.7
Assoc medical condition	Metast Ewing sarcoma	Pilocytic astrocytoma	None
Site	R. buttock	L. arm	Perianal
Thickness	0.7 mm	0.7 mm	14 mm
Ulceration	Absent	Absent	Present
Mitotic rate	0 per mm^2	0 per mm^2	3 per mm^2
Sentinel LNB	No	Yes, negative	Yes, negative
Grading Score	Low risk	Low risk	High risk
Recurrence	No	No	No
Death	No	No	No
Follow-up	17.8 years	7.6 years	4.7 years

Management

- Spitz tumors should be completely removed with clear margins with few exceptions

  - To examine the entire lesion and to avoid sampling error

  - To prevent recurrence and potentially aggressive behavior

- Excise atypical Spitz tumors with wider margins
- Manage atypical Spitz tumors with high risk/uncertain malignant potential as melanoma in general

Take Home Messages

1. Substantial uncertainty and lack of concordance continue to be a problem in Spitz melanocytic lesions.

2. The vast vast majority Spitz tumors are indolent.

3. Exercise pragmatism and due diligence and work to avoid over-diagnosis of Spitz melanoma, particularly in children

4. Consider use of a histopathology-based grading system as the first step for classification and risk stratification of Spitz tumors

Take Home Messages

5. However, histopathological criteria have their limits

6. Increasingly, molecular analysis aids in the characterization of Spitz tumors but the molecular biology of Spitz tumors remains poorly understood.