Ancillary Tests for Melanoma Diagnosis

- Immunohistochemistry

- Molecular Tests
II. Immunohistochemistry

• Melanocytic or Not
  • Amelanotic melanocytic tumor vs other
  • Densely inflamed melanocytic tumor
  • SLN analysis

• Surrogate for molecular pathway (e.g., Spitz; BAP1, beta-catenin)

• Targeted therapy (e.g., BRAFV600E)

• Biomarker to help distinguish benign from malignant
What is Your Diagnosis?
What is Your Diagnosis?
What is Your Diagnosis?
Submitted IHC slide
Submitted IHC slide
Changing Lesion; Dual Population of Melanocytes
Diagnostic Support from Ancillary Studies

**FISH TEST POSITIVE**
- Gain of 6p
- Loss of 6q
- Gain of 11q

**FISH TEST NORMAL**
In adjacent nevus

**Final Diagnosis**
FISH evaluation following hybridization revealed BRRM1 (9p22) gain in 50%, neither gain of BRRM1 (9p22)/CEP 9 in 35%, neither loss of MYB (9p22)/CEP 9 in 35%, CCND1 (11q13) gain in 50% and homogenous deletion of CDKN2A (11p15), 9p21) in 40%
**PRAME**

- **PR**eferentially expressed **Antigen** in **Melanoma**
- **Cancer Testis Antigen**

![Image of PRAME expression in tissue](image)
PRAME Expression by IHC

- Metastatic Melanoma (n=100) 87% POS
- Primary Melanoma (n=155) 83% POS
  - Conventional: 88 – 94%
  - Desmoplastic: 35%
- Melanocytic Nevi (n=145) 14% POS

PRAME in Melanocytic Nevi

4/40
(1+)

11/60
(1 – 2+)

1/145
(4+)
Nevus or Melanoma?

**Final Diagnosis**

Right Lateral Inferior Chest, Shave Biopsy:

**Atypical Intradermal Melanocytic Proliferation**

Note: This is a difficult biopsy to interpret. There are sheets of melanocytes with variable nuclear size and few mitotic figures. For these reasons I am concerned this may represent dermal melanoma with a thickness of 1.3mm, Clark's IV.
Nevoid Melanoma

PRAME

SNP Array:
supportive of melanoma
Immunohistochemistry for PRAME

Probably Right, Also Makes Errors

Phil LeBoit
Pitfalls in Using PRAME IHC

• PRAME is not melanoma-specific

• Not all melanomas express PRAME

• Some nevi or non-neoplastic melanocytes express PRAME

• Suboptimal assays

• False interpretation of the results
Utility of PRAME IHC in Clinical Practice

• Nodal Nevus vs metastatic melanoma

• Melanoma in situ vs melanocyte hyperplasia, margins of MIS

• Nevus vs melanoma

• Other
Immunohistochemistry for PRAME in the Distinction of Nodal Nevi From Metastatic Melanoma

Cecilia Lezcano, MD, Melissa Pulitzer, MD, Andrea P. Moy, MD, Travis J. Hollmann, MD, PhD,
Achim A. Jungbluth, MD, and Klaus J. Busam, MD

FIGURE 2. Nodal nevus. Capsular, subcapsular, and intraparenchymal nevus (A, H&E; B, Melan A; C, PRAME) showing no immunoreactivity for PRAME.

Capsular Nodal Melanocytic Nevus
Trabecular Melanocytic Nevus
Capsular and Intranodal Melanocytic Nevus
Capsular and Intranodal Melanocytic Nevus
Capsular and parenchymal nodal nevus
Capsular and parenchymal nodal nevus
PRAME IHC for SLN Analysis

Melan-A

PRAME/Melan-A
Capsular Metastatic Melanoma
Nodal Nevus vs Metastatic Melanoma

• Features typical of nodal nevus
  • Located in fibrous tissue, but may also be surrounded by lymphocytes
  • Cytologically bland
  • Negative for HMB-45 and PRAME

• Features typical of metastatic melanoma
  • Located in nodal parenchyma, but may also involve the fibrous tissue
  • Cytologically atypical
  • Positive for PRAME and/or HMB-45
III. Molecular Tests

- Diagnosis: Cytogenetics, Gene Expression, Gene Fusions, Mutations
- Prognosis: Gene Expression
- Targeted Therapy: Mutation Analysis
Nevus vs Melanoma – Cytogenetic Tests

Melanoma $n=133$

Nevi $n=54$

Bastian et al Am J Pathol 2003
FISHING for Melanoma Diagnosis

Fluorescence In Situ Hybridization (FISH) as an Ancillary Diagnostic Tool in the Diagnosis of Melanoma

Pedram Gerami, MD,* Susan S. Jovell, PhD,† Larry E. Morrison, PhD,‡ Beth Blondin, BS,† John Schulz, BS,‡ Teresa Ruffolo, BS,‡ Paul Matzuk, IV, MS,† Mona Legator, BS,‡ Kristine Jacobson, MS, MAJ,‡ Scott R. Dalton, MD,‡ Susan Charzan, MS,§ Nicholas A. Kolaitis, BS,§ Joan Guittart, MD,* Teruketh Lertscharapa, MD,* Susan Boone, MD,* Philip E. LeBoit, MD,§ and Boris C. Bastian, MD§

Melanoma FISH test

• Advantages
  • Suitable for small biopsies and mixed tumor cell populations
  • FISH technology fairly widely available

• Disadvantages
  • Limitations in test sensitivity and specificity
  • Added cost and time
Spectrum of Blue Tumors

• Blue nevi (e.g., common, sclerosing, cellular)

• Blue nevus-related melanomas

• Metastatic melanoma simulating a blue nevus

• Blue tumors with uncertain diagnosis
Cellular Blue Nevus
Cellular Blue Nevus
Melanoma ex BN vs Atypical Cellular BN

Numerical aberrations of chromosomes 2, 3, 4, 5, 6, 10, 12, 13, 20, 22
Blue Tumors: Features worrisome for melanoma

- Tumor cell overgrowth (loss of background fibrotic dendritic BN)
- Expansile growth of cytologically atypical cells with mitoses
- Tumor necrosis
- Ancillary test results:
  - Loss of BAP1 expression
  - Genomic aberrations
Chromosomal CNA – common in Blue Melanomas

Melanomas Associated With Blue Nevi or Mimicking Cellular Blue Nevi

Clinical, Pathologic, and Molecular Study of 11 Cases Displaying a High Frequency of GNA11 Mutations, BAP1 Expression Loss, and a Predilection for the Scalp

Sebastian Costa, MD,* Michelle Byrne, MBBS† Daniel Pissaloux, PhD,* Veronica Haudal, PharmD,* Sandrine Paindavoine, MSc,* Luc Thomas, MD, PhD,† François Audin, MD, PhD,§ Thierry Lesimple, MD,¶ Florent Grange, MD, PhD,* Béatrice Rombaud, MD,§ Laurent Morrier, MD, PhD,** Christine Mateus, MD,†† Brigitte Demo, MD,‡‡ Brigitte Balme, MD,§ Beatrix Veggler, MD, PhD,** and Arnaud de la Fonchardere, MD, PhD*
CBN or Melanoma?
Epithelioid Atypia and Mitoses
Positive FISH test
Melanoma ex plaque-type blue nevus
Spitz Tumors

• Spitz nevi

• Spitz melanocytoma

• Atypical Spitz tumor with uncertain diagnosis

• Spitz melanoma
Sophie Spitz
“Melanomas of Childhood”; Am J Pathol 1948

• 13 children (18 mo - 12 yrs)

• 12/13 had a benign clinical course

JUVENILE MELANOMA -
different from adult melanomas
Sophie Spitz
Sophie Spitz’s Melanomas  
- Heterogeneous Group of Tumors  
*Am J Pathol* 1948

- 13 children (18 mo -12 yrs)

- All benign except for one:
  - 12 yo girl
  - Tumor on foot
  - Deeply located: plantar fascia

Probable correct diagnosis: **Clear cell sarcoma**
Juvenile Melanoma
Spitz Nevus


• Paniago-Pereira C, Maize JC, Ackerman AB. Nevus of large spindle and/or epithelioid cells (Spitz's nevus). Arch Dermatol. 1978; 114: 1811-23
Spitz Nevus
The Spitz Family Grows


- Polypoid Spitz naevus
- Agminated Spitz naevus
- Pagetoid Spitz naevus
- Dysplastic Spitz tumour
- Desmoplastic Spitz naevus
- Angiomatous Spitz naevus
- Hyalinized Spitz naevus
- Plexiform Spitz naevus
- Halo Spitz naevus
- Pseudogranulomatous Spitz naevus
- Tubular Spitz naevus
- Myxoid Spitz naevus
- Pigmented spindle cell Spitz naevus
- Pigmented epithelioid cell Spitz naevus
- Combined Spitz naevus
- Recurrent/persistent Spitz naevus
Darth Spitz
Report as “Spitz Nevus”
Report as “Spitz Nevus”
Correct diagnosis: Melanoma

6 yrs later: LN Metastasis
The Fog of Spitz
The Fog of Spitz

Atypical Spitz Nevi/Tumors: Lack of Consensus for Diagnosis, Discrimination From Melanoma, and Prediction of Outcome

RAYMOND L. BARNHILL, MD, ZSOLT B. ARGENVI, MD, LYNN FROM, MD, L. FRANK GLASS, MD, JOHN C. MAIZE, MD, MARTIN C. MIHIM, Jr., MD, MICHAEL S. RABKIN, MD, PhD, SALVE G. RONAN, MD, WAIN L. WHITE, MD, AND MICHAEL PIEPKORN, MD, PhD

Hum Pathol 1999; 30: 513

The Spitzoid lesion: rethinking Spitz tumors, atypical variants, ‘Spitzoid melanoma’ and risk assessment

Raymond L. Barnhill
MALIGNANT SPITZ NEVUS

CDR HENRY G. SKELTON III, MC USN,
LTC KATHLEEN J. SMITH, MC USA, CDR THERESA T. HOLLAND, MC USN,
COL MARIA-MAGDALENA TOMASZEWSKI, MC USA, AND COL GEORGE P. LUPTON, MC USA

The patient is a 22-year-old white woman, who was 16 years of age at the time of initial presentation. At that time, a lesion was removed from her left cheek, which was diagnosed as dermatofibrosarcoma protuberans. Four years later, a physical examination of the patient revealed an enlarged lymph node in the lower midline neck area. The lymph node was biopsied and both lesions were sent for further histopathologic examination.

Histopathology: The original lesion was composed of densely cellular fascicles of plump spindle-shaped cells extending into the subcutaneous fat with a pushing not infiltrating margin (Fig. 1). Examination at higher power showed regular fascicles of plump spindle-shaped cells with prominent nucleoli. Occasional mitotic figures were seen, some present deep within the lesion (Fig. 2). The lymph node biopsy showed similar fascicles of spindled cells within the parenchyma surrounded by normal lymphoid tissue (Figs. 3 and 4). Mitotic figures were not found. Between the fascicles were areas of fibrosis. Both the skin and lymph node biopsies showed positive staining with S-100 protein (Chemicon 1:2000; ABC method).

The patient has had no evidence of recurrence or further spread now 5.5 years after excision of the original lesion.

DISCUSSION

Before Dr. Sophie Spitz established criteria for the diagnosis of spindle cell and epithelioid cell nevi (S&E nevi) in 1948, these lesions were considered histologically indistinguishable from malignant melanomas (MM). McWhorter and Woolner confirmed the benign clinical behavior of these lesions after reviewing similar lesions reported by Allen and Spitz, which could be used to differentiate S&E nevi from MM, included (1) features of a compound nevus, (2) edema and telangiectasia in the upper portion of the dermis, (3) nests of cells sharply
Atypical Spitz tumors in patients younger than 18 years

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Francesca Salvianti, PhD,1 Maria Elena Errico, MD,1 Vittoria Donofrio, MD,1 Paola Collini, MD,1
Gabriella Tragani, MD,1 Angela Rita Sementa, MD,1 Franco Ruggioletti, MD,1 Renata Boldrini, MD,1
Andrea Ferrari, MD,1 Claudio Gambini, MD, and Maria Cristina Montesco, MD
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Fig 1. Atypical Spitz tumor in the lower limb of a 8-year-old boy. The lesion measures 6 mm in
thickness. The child is alive, no further evidence of disease after 127 months follow-up. (A and
B, Hematoxylin and eosin stain; original magnifications: A, ×2.5; B, ×40.)

Fig 2. Atypical Spitz tumor in the upper limb of a 3-year-old girl. The lesion is 7.5 mm in
thickness. Sentinel lymph node was negative. Patient was alive with no evidence of disease at
16 months follow-up. (A and B, Hematoxylin and eosin stain; original magnifications: A, ×2.5;
B, ×40.)
Risk Assessment of Spitz Tumors

Spitz Tumors in Children
A Grading System for Risk Stratification
Alain Spitz, MD; Eduardo Calonje, MD; Susan Handfield-Jones, MD; Raymond L. Runnell, MD

Objective: To describe a grading system for risk stratification of atypical Spitz tumors in children and adolescents. In some circumstances, an 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 Measures: 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 1.30 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;135:282-289
FOR DISCUSSION

Sentinel lymph node biopsy as an adjunct to management of histologically difficult to diagnose melanocytic lesions: A proposal

Scott W. Kelley, MD, and Clay J. Cockerell, MD Dallas, Texas

Pediatric Melanoma: Confirming the Diagnosis With Sentinel Node Biopsy

Randall Zuckerman, MD
Joel P. Maier, MD
William B. Guiney, Jr, MD
W. Thomas Huntsman, MD
Eric K. Mooney, MD

Many pediatric melanoma lesions present at a more advanced stage than those in the adult population. Clinical and histological melanoma mimics, including a subset of Spitz nevi, are difficult to discriminate from melanoma. When dealing with a childhood melanoma, the clinician is likely to be faced with a thick lesion, and one in which the actual diagnosis may even be in doubt. There is a paucity of data to guide the physician in his management of melanoma in this age group, particularly with respect to node status and adjuvant therapy. The authors present two cases of pediatric melanoma in which the novel use of sentinel node biopsy helped confirm the diagnosis of melanoma, determined the need for full lymph node dissection, and guided the use of adjuvant interferon therapy.


mimic melanoma histologically, particularly the Spitz nevus. Lastly, there is a paucity of data to guide the surgeon in this age group, particularly with respect to node status and adjuvant therapy. No prospective trials exist and even retrospective studies are rare. In a sense, these factors constitute a “triple threat” of pediatric melanoma:

1. Delayed presentation with thicker lesions
2. Histological ambivalence
3. “Terra incognita” with respect to clinical trials of adjuvant therapy and of node management, particularly in the thick lesions of the childhood age group
Original contribution

Sentinel lymph node metastasis is not predictive of poor outcome in patients with problematic spitzoid melanocytic tumors


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Spitz Nevus with SLN Deposit
Benign Mesothelial Cells in LN
Intranodal Nevus Cells in Lymph node

Incidental finding in an axillary SLN of a patient with breast cancer
Dermal Stroma in LN

Am J Surg Pathol 2010; 34:1492-7
The Brave New Spitz

The Molecularization of Spitz

Mutations and Copy Number Increase of HRAS in Spitz Nevi with Distinctive Histopathological Features

Boris C. Bastian, Philip E. LeBoit, and Daniel Pinkel

debate whether Spitz nevus and melanoma reside at the opposite ends of a biological spectrum or represent two ends of a spectrum. The study examines the role of mutated HRAS in Spitz nevi, which is the first step towards understanding the molecular mechanisms underlying the differentiation between Spitz nevi and melanomas.
Molecular Pathology and Spitz

- Definition of “Spitz” by molecular pathway
  - HRAS aberrations
  - Kinase fusions (Ros1, Alk, Ntrk, Ret, Met, MAP3K8, Braf, other)

- Molecular findings subclassify Spitz
  - Spitz nevus
  - Spitz melanocytoma
  - Spitz melanoma
  - Atypical Spitz tumor of uncertain biologic potential
Spitz Nevus

- Benign clinical findings
- Benign histopathology
- Single genomic aberration typical of Spitz
Spitz Melanoma

- Atypical/malignant pathology

- Spitz pathway aberration and addtl genetic aberrations typical of melanoma

- Example: MAP3K8-SPECC1 fusion plus numerous segmental gains and/or losses
Spitzoid Melanoma

- Melanoma with Spitz-like features
- Non-Spitz pathway (BRAF, NRAS, other)
Melanoma (referred as AST)
Spitzoid Melanocytoma

- Atypical histopathology

- Spitz pathway aberration plus select addtl genomic aberration(s) that are not sufficient for melanoma

- Example: MAP3K8-SVIL fusion plus homozygous deletions of p16
Terminology

- Atypical Spitz tumor
  - Spitz neoplasm with uncertainty as to whether it is benign or malignant

- Spitz Melanocytoma
  - Benign Spitz neoplasm with genetic/genomic aberrations
The Spectrum of Spitz

Benign Spitz

Malignant Spitz
Desmoplastic Melanoma or Not?

- 41 M with nodule on back
- Referred with a diagnosis of desmoplastic melanoma
Desmoplastic Spitz Nevus

Cytogenetics: Isolated gain of 11p
What is Your Diagnosis?
Prelim: “Atypical” Compound Spitzoid Proliferation
Ancillary Test Results = Spitz Nevus

- Negative for BRAFV600E
- Positive for NTRK
Nevus or Melanoma?

DDX: Neoplasm of Uncertain Behavior vs. Dysplastic Nevus

**DIAGNOSIS:**
Left Anterior Distal Thigh (Shave Biopsy):

**MALIGNANT MELANOMA.**
GROWTH TYPE: NODULAR
BRESLOW'S **THICKNESS:** ≥ **1.2 MM.**
MITOSIS PER 1MM: 0/MM2.
LYMPHOID INFILTRATE: NON-BRISK INFLAMMATION
**ULCERATION: FOCAL**
REGRESSION: NOT IDENTIFIED
MARGINS: THE LESION EXTENDS TO THE BASE AND A PERIPHERAL MARGIN.
**PATHOLOGIC STAGE: PT2B**
Diagnosis: Spitz Nevus

Sequence analysis: DCTN1-ALK FUSION

SNP ARRAY:
NO UNBALANCED GENOMIC ABERRATIONS
Spitz Tumors with Alk-Fusions

A

B

C

Melanoma

Losses of: 4p, 6p, 8p, 9, 10p, 10q, 14q
Spitzoid Melanoma

FISH Results:
Gains in CCDN1 (11q13) and RREB1 (6p25) in > 70% of cells

Metastatic melanoma in LN
Nevus vs Melanoma – Cytogenetic Tests
Cytogenetics for Melanocytic Tumors

Often right, but also makes errors
Ordinary Nevus with Positive FISH test

“Positive” FISH Test
Limitations of Cytogenetic Analysis

CGH:
- Loss of 1p and 9p

“Spitzoid Melanoma of Childhood” in 2005
What is Your Diagnosis?

8M, Back

CGH: ↓9p, ↑7q
Fluorescence In Situ Hybridization as an Ancillary Tool in the Diagnosis of Ambiguous Melanocytic Neoplasms
A Review of 804 Cases

Jeffrey P. North, MD,*† Maria C. Garrido, MD,‡ Nicholas A. Kolaitis, MD,‡
Philip E. LeBoit, MD,*‡‡ Timothy H. McCalmont, MD,*‡‡ and Boris C. Bastian, MD*‡‡

FIGURE 5. Blue nevus or blue nevus-like melanoma. Histoplastic image(s) of a 14-year-old boy with a lesion on the foot. This neoplasm has features of a cellular blue nevus with large nests and fascicles of moderately large, oval, and spindled melanocytes extending into the subcutis. However, scattered mitotic figures were present (inset), and a Ki-67 immunostain showed a focus with a mildly elevated proliferation rate. FISH showed no aberrations, and a diagnosis of cellular blue nevus was rendered (hematoxylin and eosin).

FIGURE 3. Acral neoplasms. Histopathologic image(s) of a 70-
Current trends

• NGS more commonly used as main method
  • Molecular pathway
  • Mutation burden
  • Genomic aberrations

• FISH, CGH will likely become less relevant
TERT Promoter Mutations Are Predictive of Aggressive Clinical Behavior in Patients with Spitzoid Melanocytic Neoplasms

Seungjae Lee, Raymond L. Barnhill, Reinhard Dummer, James Dalton, Jianrong Wu, Alberto Pappo & Armita Bahrami
Utility of *TERT* Promoter Mutations for Cutaneous Primary Melanoma Diagnosis

Nancy E. Thomas, MD, PhD,*† Sharon N. Edmiston, BS,*‡ Yihsuang S. Tsai, PhD,* Joel S. Parker, PhD,‡‡ Paul B. Googe, MD,§ Klaus J. Busam, MD,§ Glynis A. Scott, MD,** Daniel C. Zedek, MD,‡§ Eloise A. Parrish, MS;† Honglin Hao,* Nathaniel A. Slater, MD,* Michelle V. Pearlstein, MD,* Jill S. Frank, MS,+++ Fei Fen Kuan, PhD,+++ David W. Ollikka, MD,+++ and Kathleen Conway, PhD+§§

- 86 primary cutaneous melanomas
- 72 melanocytic nevi
- Sensitivity for melanoma: 78%
- Specificity for melanoma: 98%

*Am J Dermatopathol 2019; 41: 264-72*
TERT Mutation in an Ordinary Nevus
Limitations to Molecular Approach to Spitz

• Overlap in mutation profile and genomic aberrations between nevi, melanocytomas and melanomas

• Overlap in genetic and genomic aberrations between Spitz and non-Spitz melanocytic neoplasms
Anal mucosal melanoma with NTRK fusion

NTRK2::TRAF2

Lezcano et al Am J Surg Pathol 2018
Sequence Analysis for Diagnosis

• Melanoma vs soft tissue tumor

• Staging of melanoma

• Subtyping by pathway (e.g. Spitz vs Blue vs Other)

• Ancillary evidence for assessing benign vs malignant (e.g., TERT)
Limitations of Histopathology

Reported as “Metastatic Melanoma”

SEQUENCE ANALYSIS

EWSR1 - CREM FUSION

Revised Diagnosis

Clear cell sarcoma
Limitations of Histopathology: Primary Tumor

CLINICAL INFORMATION:
Melanoma of right great toe.

DIAGNOSIS:
A. Great toe, right (resection):
- Type: Acral lentiginous
- Breslow Depth: 10 mm
- Regression: Absent
- Mitotic count: 3 per 10 high power field
- Tumor infiltrating lymphocytes: Few
- Ulceration: Absent
- Satellite nodules: Absent
- Margin: Negative (skin, soft tissue and bone)

Note: Melanoma is metastatic to a lymph node in a separately submitted specimen.
Primary Tumor: Clear Cell Sarcoma

Specimens Submitted:
1. Great toe, right; resection

DIAGNOSTIC INTERPRETATION:
POSITIVE FOR THE FOLLOWING GENE FUSION IN THE CLINICALLY VALIDATED PANEL:
EWSR1-CREM fusion
Undifferentiated Malignant Tumor

<table>
<thead>
<tr>
<th>Location:</th>
<th>Bone/Soft tissue</th>
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<tr>
<td>Service:</td>
<td>Gastric &amp; Mixed Tumor</td>
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</table>

**Final Diagnosis**

1. Right groin mass, right inguinal lymphadenectomy:
   - High grade primitive sarcoma most consistent with Malignant peripheral nerve sheath tumor. (see Note)
   - Tumor measures 9.0 cm in greatest dimension.
   - Tumor involves superficial soft tissue and shows focal involvement of lymph node.
   - Tumor shows prominent areas of necrosis (50% of tumor).
   - Surgical resection margins are free of tumor.

**Date Signed Out:** 11/14

**Submitting Physician:**

**Primary Pathologist:**
Results from Molecular Studies

- NRASQ61R mutation
- High TMB
- UV signature mutation
Primary Melanoma with NRASQ61R Mutation
What is Your Diagnosis?
CRTC1::TRIM11 Fusion Tumor
Metastasizing CRTC1:TRIM11 Tumor
Metastatic melanoma

History of prior invasive melanoma with pos LNs
Metastatic Melanoma?

Pathology:
- Mass in subcutis
- Multinodular growth
- Necrosis
- No nevus or melanoma in situ
Primary Melanoma

Clinical History
- Lesion present > 10 yrs
- No evidence of melanoma elsewhere

Molecular Findings
- GNAQpQ209L
- Low mutation burden
- No UV signature

Blue Nevus-Related Melanoma
Importance of Clinicopathology Correlation

• Clinicopathologic context important for choice to do NGS

• Clinicopathologic context important to interpret NGS results
The Rise of Melanocytomas

• Pigmented Epithelioid Melanocytoma
• BAP1-Inactivated Melanocytoma
• WNT-Inactivated Melanocytoma
• Spitz Melanocytoma
BAP1-Neg Epithelioid ("Wiesner’s") Nevus

BRCA1-associated protein (BAP1)-inactivated melanocytic tumors

Arianna J. Zhang | Patrick S. Rush | Hensin Tsao | Lyn M. Duncan

FIGURE 3. Cutaneous BAP1-inactivated melanocytic tumor (BMNT). A, This tumor has an overall polypoidal configuration with a biphasic pattern (H&E x200). B, Positive nuclear BAP1 staining in small peripheral melanocytes and epidermis keratinocytes (x200). C, Biphasic proliferation of melanocytes with large epithelial cells (left) and smaller melanocytes with loss of cytoplasm (right) (H&E x400). D, Absent BAP1 nuclear staining in large melanocytes (left) and retained nuclear BAP1 expression small melanocytes (right) (x400). E, F, G, Examples of variable cytoplastic atypia (H&E x400, x100, x400). H, BMNTs showing in both the small nevus population (left) and large epithelioid BAP1-deficient population (bottom) (x200).
MPATH-DX V 2.0

**Table 1. The Melanocytic Pathology Assessment Tool and Hierarchy for Diagnosis Version 2.0**

<table>
<thead>
<tr>
<th>Class</th>
<th>Risk of tumor progression</th>
<th>Probability of progression, No. per population</th>
<th>Treatment recommendation</th>
<th>Examples*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>Consider repeat biopsy</td>
<td>Nondiagnostic or unsatisfactory</td>
</tr>
<tr>
<td>I: low grade</td>
<td>Very low risk for continued proliferation and progression to invasive melanoma</td>
<td>1 in 10 000 to 1 in 100 000</td>
<td>No further treatment¹</td>
<td>Common acquired nevi, no atypia</td>
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<td>Congenital nevi, no atypia</td>
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<td>Atypical and dysplastic nevi, low-grade atypia²</td>
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<td>Common blue nevi</td>
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<tr>
<td>II: high grade</td>
<td>Low risk for progression to invasive melanoma</td>
<td>1 in 100 to 1 in 10000</td>
<td>Re-excision with margins &lt;1 cm²</td>
<td>Atypical and dysplastic nevi, high-grade atypia²</td>
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<td>Spitz nevi, tumors or melanocytomas, and atypical variants</td>
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<td>Cellular blue nevi or melanocytomas and atypical variants</td>
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<td>Plexiform or deep penetrating nevi or melanocytomas</td>
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<td>Lentigo maligna</td>
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<td>Melanoma in situ</td>
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<tr>
<td>III: melanoma pT1a</td>
<td>Relatively low risk for local and regional metastasis</td>
<td>1 in 10 to 1 in 1000</td>
<td>Follow national guidelines (eg, wide excision with 1 cm margins)³</td>
<td>Melanoma AJCC stage pT1a, &lt;0.8 mm Breslow thickness</td>
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<td>Melanoma pT1a (low risk)²</td>
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<td>Melanoma pT1a²</td>
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<tr>
<td>IV: melanoma pT1b</td>
<td>Moderate to increased risk for regional or distant metastasis</td>
<td>1 in 2 to 1 in 10</td>
<td>Follow national guidelines (eg, wide excision with 1-2 cm margins³ and consideration of sentinel lymph node staging and other therapies)</td>
<td>Melanoma AJCC stage pT1b or greater, &gt;0.8 mm Breslow thickness</td>
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</tbody>
</table>

* Examples refer to specific phenotypes or clinical scenarios. Further details required for full understanding.

¹ Further investigation may be warranted.

² Additional risk factors should be considered, such as family history and personal medical history.

³ Margin recommendations vary by jurisdiction and institutional guidelines.
Combined BAP1-Inactivated Nevus
BAP1-Inactivated Melanocytic Tumors

- Histopathology benign: Nevus
- Atypical histo- or molecular path, but still benign: Melanocytoma
- Atypical, but unsure about biology: “atypical tumor”
- Malignant: Melanoma
Ancillary Tests for Melanoma Diagnosis

• Essential for the diagnosis of fusion tumors

• Can help in select cases to reach the correct diagnosis

• Significant limitations in sensitivity and specificity

• Tendency for over-utilization
Acknowledgements and thank you to:

• Colleagues at MSKCC

• Many collaborators at other institutions

• My family
Thank You!

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