Dysplastic Nevi and Pigmented Lesions

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I have no relevant disclosures
NEVUS

(when melanocytes nest together nicely)
MELANOMA
(when good melanocytes go bad)
So, how do we suspect melanoma, clinically and who do we diagnose melanoma histologically?
Interesting tidbits about acquired nevi…

• Eruptive nevi can develop on injured skin after blistering illness (burns, TEN)
• Strong evidence suggests acquired nevi are related to sun-exposure in childhood
  – may explain nevi > in whites than others
  – may explain distribution of nevi upon skin
  – may corroborate observation that use of sunscreen lessens development of nevi

Where do nevi come from?

No one really knows, for sure.
Colorado Study

- N=743 white children (5-6 y/o), 3 years f/u
- Nevus density = boys (36/m²) > girls (31/m²)
- Greatest density upon face, neck, forearms
- Higher # in chronically exposed vs. intermittently exposed skin (P < 0.0001)
- In 2 years, most (69%) had received at least one sunburn, and number of nevi was associated with the number of burns
- Similar findings in Australian study

Dodd et al. 2007; Harrison et al. 2008
Boys – more upon head/neck, chest, back

Girls – more upon arms, thigh and calf (NS)
Clinical Examination

(this is where we **suspect** the diagnosis… at least enough to perform a **biopsy**)

- A – asymmetry
- B – border irregularity
- C – color variegation
- D – diameter > 6 mm
- E – evolution
## Clinical Features of Atypical/Dysplastic Nevi

<table>
<thead>
<tr>
<th>Common Nevi</th>
<th>Dysplastic nevi</th>
</tr>
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<tbody>
<tr>
<td>Absent</td>
<td>Asymmetric elements</td>
</tr>
<tr>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Distinct</td>
<td>Border</td>
</tr>
<tr>
<td>Indistinct (fuzzy)</td>
<td></td>
</tr>
<tr>
<td>Uniform brown</td>
<td>Color</td>
</tr>
<tr>
<td>Variegated (blacks, greys, whites)</td>
<td></td>
</tr>
<tr>
<td>&gt;6 mm</td>
<td>Diameter</td>
</tr>
<tr>
<td>&lt;6 mm</td>
<td></td>
</tr>
<tr>
<td>Usually asymptomatic</td>
<td>Evolution</td>
</tr>
<tr>
<td>Sometimes with symptoms/changing behavior</td>
<td></td>
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</tbody>
</table>
The “Ugly Duckling”

One mole that looks nothing like the other “signature” nevi!
So why do we want to find atypical nevi?

There are two good reasons depending upon what you believe.
Grim Reaper and Atypical Nevi?
Marker of an “At Risk” Person

- **Strong** evidence suggests:

<table>
<thead>
<tr>
<th>Number of Dysplastic Nevi</th>
<th>Risk Above General Population</th>
</tr>
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<tbody>
<tr>
<td>1 to 4</td>
<td>2-3x</td>
</tr>
<tr>
<td>&gt;10</td>
<td>12x</td>
</tr>
<tr>
<td>&gt;50 (w/o family h/o)</td>
<td>184x</td>
</tr>
<tr>
<td>&gt;50 (w family h/o)</td>
<td>500x</td>
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</table>
One of the strongest risk factors for melanoma is the presence of multiple atypical nevi (AMS).

<table>
<thead>
<tr>
<th>Table 1. Risk factors for MM</th>
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<tbody>
<tr>
<td>Specific MM risk factors²</td>
</tr>
<tr>
<td>MN</td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
</tr>
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<tr>
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<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Phenotypic traits</td>
</tr>
<tr>
<td>Freckles³,¹²</td>
</tr>
<tr>
<td>Fair complexion¹³</td>
</tr>
<tr>
<td>Blond hair¹³,¹⁴</td>
</tr>
<tr>
<td>Red hair¹²,¹³</td>
</tr>
<tr>
<td>Tendency to sunburn¹⁵,¹⁶</td>
</tr>
<tr>
<td>Inability to tan¹³,¹⁷</td>
</tr>
<tr>
<td>Blue eyes¹²,¹⁸</td>
</tr>
<tr>
<td>Sun exposure</td>
</tr>
<tr>
<td>Constant¹⁹,²⁰</td>
</tr>
<tr>
<td>Intermittent²¹</td>
</tr>
<tr>
<td>Immunosuppression²²,²³</td>
</tr>
<tr>
<td>History of non-MM skin cancer²⁴,²⁵</td>
</tr>
</tbody>
</table>
Numerous studies from different parts of the world have shown that the relative risk for developing melanoma increases as the number of bland melanocytic nevi increase.
Dysplastic/atypical nevi may also be precursor lesion for melanoma...

- 20-80% of melanoma arises in a nevus
- ? premalignant condition (*controversial*)
- Alternative explanation:
  - we are simply bad at distinguishing atypical nevi from melanoma
Regional Approaches to Atypical Nevi

• Grading
  – usually “mild,” “moderate,” “severe”
  – based on cytology or architecture or both

• No Grading (“allegedly”)
  – nevus, Clark’s nevus, Clark’s nevus – excise

“Everybody’s a critic…“
Benign Nevus
Atypical Nevus – Architectural

Shouldeering
Atypical Nevus - Architectural

Bizarre nest size and arrangement
Atypical Nevus - Architecture

- Lymphocytes
- Melanophages
- Fibrosis
Atypical Nevus – Cytology

Clear cytologic atypia
- large cells
- pleomorphic nuclei
Atypical Nevus Cytology

- Hyperchromasia
- Thick nuclear membrane
- Pleomorphism
- Large nucleolus
Atypical Nevus - Cytology

Poor Vertical Maturation
Atypical Nevus - Cytology
Atypical Nevus - Architecture

Pagetoid extent
Atypical Nevus - Architecture

Pagetoid extent – How much is too
How good is grading?

- **Duncan et al. (1993)**
  - 10 cases of nevi, dysplastic nevi (mild, mod, sev) and melanoma
  - concordance 69-80% for nevus vs dysplastic nevus vs melanoma
  - only 35-58% concordance for grading of dysplasia

- **Piepkorn, et al. (1994)**
  - 149 atypical nevi graded by 6 expert dermatopathologists
  - re-interpreted 6 mos later by same dermatopathologist
  - correlation coefficients 0.5-0.70 (“moderate” to “substantial”)

- **Farmer, et al. (1996)**
  - 37 “classic” pigmented lesions among 8 “expert” dermatopathologists
  - only 13 cases (35%) with complete agreement (8 benign & 5 MM)
The honest truth of the matter...
> 6000 Mutations in Melanoma
Makes for Messy Model
“True” Developmental State of Pigmented Lesion Analysis

Omnipopath LLC
So what can be done to assist us in recognizing melanoma?

Will immunostains help?
Immunostains in Pigmented Lesions - Bottom Line

There is NO single “Melanoma Stain.”
S-100

• In melanocytic neoplasms
  – expressed by 98% of melanomas
  – expressed in 95% of desmoplastic MM
    (often negative for all other markers)
Missed Desmoplastic MM
Melan-A/MART-1

- **Melanocytic-associated Antigen** (A103)
- **Melanoma Antigen Recognized by T cells-1** (M2C107)
- Highly specific, just not as sensitive (particularly for desmoplastic MM)
Malignant melanoma in-situ
or
Lentigo with sun-damaged melanocytes
or
Pigmented actinic keratosis?
The Holy Trinity
- Confluent growth of melanocytes
- Follicular extension
- Nest of > 3 cells
HMB-45

• Benign melanocytic lesions:
  – junctional/superficial component stain
  – normal zonation in the deeper dermis

• Confusing in situations of dusty cells:
  – deeply pigmented nevi
  – deep penetrating nevi
  – clonal nevi
P16


- Studied P16, E-cadherin, cyclin D1 (Spitz and Melanoma)

- Dermal P16 staining was best discriminator:
  - loss of nuclear staining (<25% of cells)
    - 3 fold more likely to be melanoma
  - loss of nuclear and cytoplasmic staining
    - 8 fold more likely to be melanoma
P16- Atypical Spitz Nevus
Combination stains...
KiMart – (MART-1/Ki67)
Other Tests that Might be Employed to Diagnose Melanoma

Comparative Genomic Hybridization (aCGH)

Fluorescent In Situ Hybridization (FISH)

Gene Expression Profiling (GEP)
Comparative Genomic Hybridization

- Assesses entire genome
- Detects only gains or losses in copy number
- >95% of melanoma has gains and losses
- Most benign lesions lack such gains or losses
- Some Spitz nevi may have gain 11p

**FISH for Deletions**

**Figure 1.** Fluorescence in situ hybridization (FISH) analysis of a definitive melanoma with copy number increases of 11q13 (SpectrumGreen) and 6p25 (SpectrumRed), magnification ×1000.

An invasive melanoma is shown on hematoxylin and eosin stain at low power (A), and high power (B). Fluorescence in situ hybridization of a representative melanoma cell demonstrates increased copy numbers of 6p25 (RREB1), 6q23 (MYB) and 11q13 (CCND1). Color of probes: 6p25 - red, 6q23 - gold, CEP6-aqua, 11q13 - green. (From Gerami et al. Fluorescence in situ hybridization for distinguishing nevoid melanomas from mitotically active nevi. *Am J Surg Pathol.* 2009;33:1783-1788. Reproduced with permission from Wolters Kluwer Health.)
- 4 probes with highest diagnostic discrimination:
  - chromosome 6p25, 6 centromere, 6q23, and 11q13
- Correctly classified melanoma with:
  - 86.7% sensitivity
  - 95.4% specificity
- Correctly identified melanoma in 6 of 6 cases with ambiguous pathology but later mets
Only 60% sensitivity and only 60% specificity in ambiguous lesions.
• Acknowledged for difficult Spitzoid lesions “old” probe set only about 70% sensitive
• Proposed new probe set - 6p25, 9p21, 11q13, and 8q24
• Particularly interesting is addition of loss of 9p21 (p16)
• Overall improvement in sensitivity reported to be 94%
New commercial assay for melanoma based upon “genetic signature”

Measures mRNA via qRT-PCR
23 Gene Expression Profiling

- qRT-PCR on FFPE that is microdissected
- Developed and validated on N=400+ nevi/MM

The final gene signature consists of 23 genes (Figure 3).
- Component #1 regulates melanocyte differentiation
- Component #2 is a group of 5 genes that have multiple functions including some immune regulation
- Component #3 represents 8 genes involved in immune signaling
- 9 housekeeper genes are necessary for normalization of gene expression
Validation using N=437 (few Spitz and no desmo MM) Reported Sensitivity = 94%, Specificity = 90%
9% of lesions classified as “Indeterminate”
How might this uncertainty be reflected in the management of atypical/dysplastic nevi?
Management of Atypical Nevi

• 1992 NIH Consensus Panel
  – only attempt at consensus (not achieved)
  – recommend removal of atypical nevi

• Recent papers advocated
  – mildly AN need not be excised
  – Moderately AN may not need to be excised

HOWEVER, THERE IS NO CLEAR CONSENSUS REGARDING THE TOPIC
Points to Consider

• No argument that AN mark a person at increased risk for melanoma
• No argument that melanoma arises in association with AN (although 20-80%)
• Tsao et al. reported a 1:10,000 lifetime risk of AN transforming into MM
• Assuming Tsao et al. is correct a “properly powered” study would be very very LARGE
Favorable long-term outcomes in patients with histologically dysplastic nevi that approach a specimen border

Thomas L. Hocker, MD, a Ali Alikhan, MD, a Nneka I. Comfere, MD, a,b and Margot S. Peters, MD a,b
Rochester, Minnesota

See related letters on pages 682 and 683

Background: Patients with multiple clinically dysplastic nevi are at increased risk for development of melanoma. However, the risk of melanoma arising in a histologically dysplastic nevus (HDN) is unknown.

Objective: We sought to determine the rate of melanoma development in patients with HDNs that approached a microscopic border but were not re-excised.

Methods: We performed a retrospective study of patients evaluated in our dermatology department from January 1, 1980, to December 31, 1989, who had a HDN that extended to within 0.2 mm of a microscopic punch, shave, or excision border and was not re-excised.

Results: The average follow-up in our cohort of 115 patients was 17.4 years (range: 0.0-29.9): 82 patients (71.3%) were followed up for longer than 10 years, 78 (67.8%) longer than 15 years, and 73 (63.4%) had more than 20 years of follow-up; 66 of 115 nevi were mildly dysplastic, 42 moderately dysplastic, and 7 had severe dysplasia. No patient developed metastatic melanoma or melanoma at the site of removal of a HDN.

Limitations: This was a retrospective study performed at 1 large academic medical center.

Conclusion: During a long-term follow-up period, no patient developed melanoma at the site of an incompletely or narrowly removed HDN, providing evidence that routine re-excision of mildly or moderately dysplastic nevi may not be necessary. (J Am Acad Dermatol 2013;68:545-51.)
Hocker et al. paper

- Looked back into Mayo Clinic tissue banks before term “AN” came into play
- Found only 10% BN would be reclassified as AN (N=115)
- Principle finding: none of the AN that “involved or approached (<0.2mm) a margin” went on to be melanoma
Problems with Hocker et al.

- Transformation is only “negative” outcome
- Severely underpowered study (Tsao et al.)
- Why just 10% of all “nevi” in files atypical?
- No information on how many had actual vs. “close” surgical margins.
- How does one know that the grading at MC can be replicated anywhere else?
Hocker Criticism

• Drs. Elston, McNiff and Maize wrote an editorial critical of the Hocker et al. paper
• Would the result matter to even one person who died of their “atypical nevus”?
• For example, varicella zoster vaccine has:
  – NNT=175 prevent one case of zoster ($35,000)
  – NNT = 1087 prevent one case PHN ($217,400)
• Probably won’t save you from a deposition! 😞
Reddy et al. 2013

• Did NOT examine “long term” outcomes in the same manner as Mayo
• Found that higher grade lesions with positive margins were more often excised complete (SOC)
• Found that 4% of moderate-severely atypical nevi were melanoma on re-excision
More critical review of what is said...

- 2936 nevi, of which 871 were atypical
- Precise degree of atypia and margin status unknown
- 85% of re-excisions had no melanocytic process anyway
- Median follow up was just 12 months
Interview with Author

- Author prefers to “saucerize” nevi “…to obtain clear margins…”
- “Isn’t prepared to make blanket recommendations…”
- “[D]on’t think you can make a hard and fast rule… if there are multiple atypical nevi… be a little more cautious and do the excision…”

Dr. Cashman noted that the clinic where this study was conducted tends to do saucerizations to remove the entire mole at biopsy.

"There’s a trend moving toward deeper saucerization biopsy," he explained. "That has caught on a little faster than the concept that we might not need to re-excite moderately atypical moles. We know that deeper saucerization biopsy removes more tissue upfront and raises the likelihood of obtaining clear margins on initial biopsy."

Because many dermatologists base their re-excision decision on margin status, "I believe it does directly affect the need to re-excite," he added.

As for the impact that this study will have on clinical practice, Dr. Cashman said he isn’t prepared to make a blanket recommendation.

"I don’t think I can make a hard and fast rule that moderate atypical moles do not need to be excised. It depends on the patient. If they only have 1 moderately atypical mole, then you could probably follow it instead of doing a re-excision. If they have multiple irregular moles and a history of atypical nevi, then I would be a little more cautious and do the excision. As we continue to do more research to elucidate the biologic behavior of moles, we should be able to come up with reasonable clinical guidelines," he said.

The study is informative, said Delphine Lee, MD, director of the Department of Translational Immunology at the John Wayne Cancer Institute, Saint John’s Health Center, in Santa Monica, California.

"It’s good to have hard data and hard numbers to inform re-excision decisions," she told Medscape Medical News, pointing out that if some procedures aren’t necessary, it could save money and resources.

Still, it might make physicians nervous to forego the re-excision of atypical nevi, on the chance that the patient will be the one who will go on to develop melanoma, no matter how low the odds.

"That’s what you worry about. It’s kind of a controversial thing," said Dr. Lee.

Dr. Cashman and Dr. Lee have disclosed no relevant financial relationships.

Revisiting a question…

“Are we simply bad at distinguishing atypical nevi from melanoma?”
Re-examination of Original

Called compound “moderately” atypical nevus by a well-known Colorado dermatopathologist.

No stains or levels were performed.
Test Result

ORDERING PHYSICIAN
Whitney High MD
UC Denver
12635 E Montview Blvd
Suite 160
Aurora, CO 80045

SPECIMEN
Specimen Type: Tissue Slide
Tissue: Skin
Anatomical Site: Extremities
Biopsy Date: Oct 24, 2014
Accession Date: Nov 17, 2015
Report Date: Nov 23, 2015

PATIENT
Name:
Date of Birth:
Patient ID:
Gender:
Accession #:
Requisition #:

Block(s) Analyzed:

Melanoma Score: 1.0

Melanoma Score Classification

Benign
Indeterminate
Malignant

-16 -14 -12 -10 -8 -6 -4 -2 0 2 4 6 8 10
Do some lesions even have an answer?

Do we know enough to say?
Spitz Nevus
Classic Spitz Nevus
Tale of the “Spitz tumor”...

• 17 year-old girl seen in 2007
• Eruptive lesion on leg
  – only noticed for a “few weeks”
• No personal or FH of melanoma
• Otherwise healthy
Histology
No win situation.

• Overcall and a 17 year-old receives:
  – huge disfiguring scar
  – ruined insurance status
  – chronic leg edema
  – no real hope

• Undercall and there are:
  – medicolegal issues
  – is the patient harmed?
My Report

• “Atypical Spitz Tumor”
  – “lesion of uncertain biologic potential…”
  – “…seen cases like this with nodal involvement…”
  – “…even when SLN deposits are present, the disease often behaves in a manner less aggressive than conventional melanoma.”
Her Sentinel Lymph Node
Survival in sentinel lymph node–positive pediatric melanoma

J. Brent Roaten, David A. Partrick, Denis Bensard, Nathan Pearlman, Rene Gonzalez, James Fitzpatrick, Martin D. McCarter

Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>Age (y)</td>
<td>17 ± 3</td>
</tr>
<tr>
<td>Male</td>
<td>35 (7)</td>
</tr>
<tr>
<td>Preoperative histology</td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td>75 (15/20)</td>
</tr>
<tr>
<td>Atypical nevi</td>
<td>25 (5/20)</td>
</tr>
<tr>
<td>Breslow depth (mm)</td>
<td>3.2 ± 1.0</td>
</tr>
<tr>
<td>Positive sentinel nodes Total</td>
<td>40 (8/20)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>33 (5/15)</td>
</tr>
<tr>
<td>Atypical nevi</td>
<td>60 (3/5)</td>
</tr>
<tr>
<td>CLND</td>
<td>35 (7/8)</td>
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</tbody>
</table>

CU pt survival 100% at 35 months.

Fig. 1 Disease-free survival for SLN-positive adults (ages 21–86) and pediatric patients (ages 12–20) (P = .01).
BACKGROUND: Atypical Spitz tumors (AST) are rare spitzoid melanocytic proliferations with an uncertain malignant potential. ASTs have overlapping features of both Spitz nevi and spitzoid melanoma, and consequently generate controversy with diagnosis and management. Sentinel lymph node biopsy (SLNB) has been proposed as a possible means to gain additional insight into the true biologic potential of these tumors; however, previous reports on the use of SLNB in ASTs have been limited by small numbers of patients and short durations of follow-up. METHODS: The authors extracted data from their institution's prospective melanoma database, collected between 1994 and 2007, for all patients with ASTs of uncertain biologic potential. They reviewed the clinical features of these patients, including the sentinel lymph node status, and the histological features of the tumors. RESULTS: A total of 67 patients with ASTs were identified, with a median age of 23.7 years. The mean depth was 2.4 mm. Of these, 57 had a SLNB performed, with 27 (47%) having a positive sentinel lymph node. SLNB-positive cases had a significantly lower mean age than SLNB-negative cases (17.9 vs 28.7 years; P = .013); however, no other significant differences were observed. All 27 patients with a positive SLNB were alive and disease free with median follow-up of 43.8 months. One patient who did not receive a SLNB developed recurrent disease with regional and distant metastases. CONCLUSIONS: ASTs do not appear to behave like conventional melanoma. There is a high incidence of microscopic lymph node deposits in SLNBs, but despite this finding, patients have a favorable prognosis. Our findings raise several questions regarding the malignant potential of ASTs, and the role of SLNB in their management. Cancer 2009;115:631-41. © 2009 American Cancer Society.

KEY WORDS: atypical Spitz tumor, Spitz nevus, melanoma, sentinel lymph node biopsy.
Sentinel node biopsy in atypical melanocytic neoplasms in childhood: a single institution experience in 24 patients

Introduction: Sentinel lymph node biopsy (SLNB) is a controversial but frequently used adjunct to wide excision of difficult-to-diagnose melanocytic proliferations of childhood. We herein report our institutional experience with SLNB in pediatric patients with these lesions, hereafter referred to as ‘atypical melanocytic proliferations’.

Methods: Our prospectively collected melanoma database was queried for patients <21 years of age status post-SLN for a diagnosis of atypical melanocytic proliferation in which the diagnosis of melanoma ≥1 mm in depth was considered in the differential diagnosis by one or more expert dermatopathologists and for which no diagnostic consensus could be reached.

Results: Of 24 patients identified over 17 years, 7 patients (29%) had a positive sentinel lymph node (SLN). Six SLN-positive patients underwent complete lymph node dissection, with one (14%) having additional nodal involvement identified. With a median follow-up of 4.1 years (range <0.1 to 14.8 years), all patients showed no evidence of disease.

Conclusions: Despite a significant rate of identification of melanocytes in SLNs of children with atypical melanocytic proliferations, survival appears favorable and controversy surrounding the significance of nodal involvement remains. Further studies with larger numbers of patients and long-term follow-up are needed before the true prognostic value of SLNB in this setting can be determined.

Keywords: atypical melanocytic neoplasm, atypical Spitz nevus, prognosis, sentinel lymph node, spitzoid neoplasm

Mills OL, Marzban S, Zager JS, Sondak VK, Messina JL. Sentinel node biopsy in atypical melanocytic neoplasms in childhood: a single institution experience in 24 patients.


Accepted for publication July 12, 2011
Real case...
The Spitzoid lesion: rethinking Spitz tumors, atypical variants, ‘Spitzoid melanoma’ and risk assessment

Raymond L Barnhill

Departments of Dermatology and Pathology, University of Miami Miller School of Medicine, Miami, FL, USA

Although much remains to be learned about Spitzoid lesions, there is increasing evidence that these tumors may be a type of melanocytic neoplasm distinct from conventional melanocytic nevi and malignant melanoma. In the current communication, the author has attempted to describe accurately the state-of-the-art surrounding these lesions, their nomenclature, and assessment of risk. Acknowledging the peculiar nature of Spitzoid lesions, the author prefers the term Spitz tumor rather than ‘Spitz nevus’ (except perhaps for the most typical lesions) and argues against using the term ‘Spitzoid melanoma’ until more information is available to justify such a term. The author also believes that patients are best served by the comprehensive evaluation of Spitzoid lesions and their classification into three categories: (1) Spitz tumor without significant abnormality, (2) Spitz tumor with one or more atypical features (atypical Spitz tumor), including those judged to have indeterminate biological potential, and (3) malignant melanoma, rather than the two categories of ‘Spitz nevus’ and melanoma. Only rigorous characterization of sufficient numbers of Spitzoid lesions and long-term follow-up of patients will provide truly objective information for the formulation of optimal guidelines for the management of patients with these lesions.

Keywords: Spitz nevus, Spitz tumor, melanoma

Modern Pathology (2006) 19, S21–S33. doi:10.1038/modpathol.3800519
Thoughts?

Signed out as:
“Combined nevus (common nevus and Spitz nevus)”
Patient presented in 2016 with right sided cervical LAD and was told initially was “mononucleosis.”

Ultimately, she had melanoma in a cervical lymph node, and tumoral nodules in the right lung.
• “Retrospective review… demonstrated that 13% of melanocytic lesions defied diagnosis.”
• “No diagnostic ‘gold-standard’ for Spitz-like lesions has been established.”
• “Accurate classification… of some melanocytic neoplasms remains a challenge, even for experts.”
• “Perhaps [FISH is] not appropriate for the differential diagnosis of spitzoid tumors in children.”

Demarchis et al. 2014; Massi et al. 2015; Dika et al., 2015