Challenging Melanocytic Lesions

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Conflicts of Interest

None
Objectives

• Case-based review of salient features from related melanocytic lesions
• Quick review of molecular methods used in diagnosis of melanocytic lesions
Acknowledgments

• Jane Messina M.D. and Vernon Sondak M.D. – Moffitt Cancer Center
• Maria Auxiliadora Deschaine M.D. – University of Oklahoma
• Julie V. Schaffer M.D. - Hackensack University
Case #1
Case #1- Clinical Features

10 y/o female, rapidly growing lesions

Pictures courtesy of Dr. Jane Messina and Dr. Vernon Sondak
Case #1- Histopathology
Case #1 - Histopathology
Case #1 - Diagnosis

A. Juvenile Xanthogranuloma
B. Dysplastic Nevus
C. Spitz Nevus
D. Melanoma
E. Benign Epithelioid Histiocytoma
Case #1 - Diagnosis

A. Juvenile Xanthogranuloma
B. Dysplastic Nevus
C. Spitz Nevus
D. Melanoma
E. Benign Epithelioid Histiocytoma
Classic Spitz Nevus

- AKA “Spindle and Epithelioid Cell Nevus”
- First known description from Darier and Civatte as early as 1910
- Characterized by Dr. Sophie Spitz in 1948 as “Melanomas of Childhood” in a series of 13 cases from patients aged 18 months to 12 years old
- Only 1 patient died of widely metastatic disease from a primary lesion consisting of an acral spindle cell tumor associated to the fascia (Clear Cell Sarcoma?)

Barnhill RL. Mod Pathol. 2006;19 Suppl 2:S21-33.

Picture courtesy of Dr. Martin C. Mihm
JXG-like

PG-like

Pigmented

Photos courtesy of Dr. Julie Schaffer
Architecture

• Usually compound - predominantly junctional (Reed), dermal (desmoplastic) variants
• Junctional component:
  – Well-circumscribed large nests of cells in a “raining down” pattern
  – Epidermal hyperplasia
  – Kamino bodies
• Dermal component:
  • Symmetrical, imparting a dome shape to the lesion
  • Inverted triangle shape with evident maturation (“zonation”)

Cytology

• Epithelioid and spindle cells with:
  – Pink/“hyalinized” cytoplasm
  – Large, often pleomorphic nuclei with vesicular chromatin and prominent nucleoli
  – Bizarre forms and giant cells can be seen
• Pagetoid spread is common (Pagetoid variant)
• Mitoses are commonly seen (rapid growth) (less than 6 per mm²)

Barnhill RL. Mod Pathol. 2006;19 Suppl 2:S21-33.
Case #1 – Which of these stains will be helpful in problematic cases?

A. S100 and Sox10
B. Tyrosinase and Mart-1
C. HMB45 and p16
D. Trichrome and PAS
Case #1 – Which of these stains will be helpful in problematic cases?

A. S100 and Sox10
B. Tyrosinase and Mart-1
C. HMB45 and p16
D. Trichrome and PAS
HBM45: Melanosome associated antigen

p16: product of the CDKN2A gene (9p21.3)

Ki-67 and Mart-1 cocktail
Case #2
20 y/o female, lower leg pigmented lesion
Case #2 – Histopathology
Case #2 - Diagnosis

A. Common Acquired Nevus
B. Dysplastic Nevus
C. Spindle Cell Melanoma
D. Pigmented Spindle Cell Nevus of Reed
E. Atypical Spitz Tumor
Case #2 - Diagnosis

A. Common Acquired Nevus
B. Dysplastic Nevus
C. Spindle Cell Melanoma
D. Pigmented Spindle Cell Nevus of Reed
E. Atypical Spitz Tumor
Pigmented Spindle Cell Nevus of Reed

• AKA “Pigmented Spindle Cell Tumor of Reed”
• First described by Dr. Richard J. Reed in 1975
• “Dark brown-black macular or papular dome-shaped lesion appearing in the lower limbs of females in the first 4 decades of life”

Pigmented Spindle Cell Nevus of Reed
Case #2 – How would you treat these lesions (Classic Spitz and PSCN) (2 might be correct)

A. Observe and re-excise upon recurrence
B. Conservative (narrow margin) re-excision
C. Wide local excision with 5-10 mm margin
D. Wide local excision with 10 mm margin and sentinel lymph node biopsy
E. Cryotherapy
Case #2 – How would you treat these lesions (Classic Spitz and PSCN) (2 might be correct)

A. Observe and re-excise upon recurrence
B. Conservative (narrow margin) re-excision
C. Wide local excision with 5-10 mm margin
D. Wide local excision with 10 mm margin and sentinel lymph node biopsy
E. Cryotherapy
Case #3
Case #3 – Clinical Features

14 y/o female, right arm lesion

Pictures courtesy of Dr. Ma. Auxiliadora Deschaine and Dr. Jane Messina
Case #3 – Histopathology

Pictures courtesy of Dr. Ma. Auxiliadora Deschaine and Dr. Jane Messina
Case #3 – Histopathology

Pictures courtesy of Dr. Ma. Auxiliadora Deschaine and Dr. Jane Messina
Case #3 - Diagnosis

A. Intradermal melanocytic nevus
B. Classic Spitz Nevus
C. Spitzoid Melanoma
D. Desmoplastic Spitz Nevus
E. Benign Epithelioid Histiocytoma
Case #3 - Diagnosis

A. Intradermal melanocytic nevus
B. Classic Spitz Nevus
C. Spitzoid Melanoma
**D. Desmoplastic Spitz Nevus**
E. Benign Epithelioid Histiocytoma
Desmoplastic Spitz Nevus

- Uncommon Spitz variant, usually presents in the extremities as scaly, erythematous, flesh-colored or occasionally pigmented papulonodule
- Affected patients are usually in the third decade of life
- The lesions usually show variable amount of fibrosis/hyalinization and are often dermal-based

Mart -1 positive CD68 positive CD163 positive

Mart -1 negative

McKee PH, Calonje E, Granter SR. Pathology of the skin with clinical correlations. Philadelphia Elsevier Mosby; 2005


Desmoplastic Spitz Nevus

Benign Epithelioid Histiocytoma
Case #3 – Clinical Features

Pictures courtesy of Dr. Ma. Auxiliadora Deschaine and Dr. Jane Messina
Case #3 – Histopathology

Pictures courtesy of Dr. Ma. Auxiliadora Deschaine and Dr. Jane Messina
Case #3 – Histopathology

Pictures courtesy of Dr. Ma. Auxiliadora Deschaine and Dr. Jane Messina
Case #3 – Diagnosis of Background Lesion

A. Lentigo maligna melanoma
B. Ephelides
C. Nevus spilus (Agminated Nevus) (segmental variant)
D. Nevoid Melanoma
E. Nevus spilus (Agminated Nevus)
Case #3 – Diagnosis of Background Lesion

A. Lentigo maligna melanoma
B. Ephelides
C. Nevus spilus (Agminated Nevus) (segmental variant)
D. Nevoid Melanoma
E. Nevus spilus (Agminated Nevus)
Segmental Nevus Spilus

6 months interval between left and right hand image

Common Nevus Spilus

Nevus Spilus

Case #3

Pictures courtesy of Dr. Ma. Auxiliadora Deschaine and Dr. Jane Messina
Case #3 – Which genetic aberration characterizes this type of Spitz nevus (desmoplastic)?

A. BAP1 loss
B. BRAF V600E
C. HRAS amplifications
D. BRAF fusions
E. ALK1 fusions
Case #3 – Which genetic aberration characterizes this type of Spitz nevus (desmoplastic)?

A. *BAP1* loss
B. *BRAF* V600E
C. *HRAS* amplifications
D. *BRAF* fusions
E. *ALK1* fusions
Desmoplastic Spitz Nevus

The majority of Spitz lesions with desmoplastic features will show an activation of *HRAS* (11p15.5), through either:
- Increased copy number of 11p (amplification)
- Activating mutations of *HRAS*


Proline for Arginine in position 13
Alanine for Serine in position 11
Activating HRAS Mutation in Agminated Spitz Nevi Arising in a Nevus Spilus

Kavita Y. Sarin, MD, PhD; Bryan K. Sun, MD, PhD; Charles D. Bangs; Athena Cherry, MD; Susan M. Swetter, MD; Jinah Kim, MD, PhD; Paul A. Khavari, MD, PhD

Figure 1. Clinical and Histopathologic Features of the Agminated Spitz Nevi Arising in a Nevus Spilus

Sarin KY et al JAMA Dermatol. 2013 Sep;149(9):1077-81
Molecular Taxonomy of Melanocytic Lesions

Case #3 – How would you treat/manage this patient (2 might be correct)

A. Observe and excise new lesions
B. Wide local excision with 5-10 mm margin
C. Wide local excision with 10 mm margin and sentinel lymph node biopsy
D. If amenable, re-excision with narrow margins and plastic reconstruction
Case #3 – How would you treat/manage this patient (2 might be correct)

A. Observe and excise new lesions
B. Wide local excision with 5-10 mm margin
C. Wide local excision with 10 mm margin and sentinel lymph node biopsy
D. If amenable, re-excision with narrow margins and plastic reconstruction
Case #4
Case #4 – Clinical/Dermoscopic Features

11 y/o male, chest lesion

Case #4 – Histopathology
Case #4 - Diagnosis

A. Spitzoid Melanoma
B. Spitz Nevus
C. Atypical Spitz Tumor/Nevus
D. Superficial Spreading Melanoma
E. Granular Cell Tumor
Case #4 - Diagnosis

A. Spitzoid Melanoma
B. Spitz Nevus
C. Atypical Spitz Tumor/Nevus
D. Superficial Spreading Melanoma
E. Granular Cell Tumor
Atypical Spitz Nevus/Tumor
Atypical Spitz Nevus/Tumor
Atypical Spitz Nevus/Tumor
Atypical Spitz Nevus/Tumor

MELTUMP: Melanocytic Tumor of Undetermined Malignant Potential
SAMPUS: Superficial Atypical Melanocytic Proliferation of Undetermined Significance

1. 6p25: *RREB1* (Ras-responsive binding protein) > 2 copies
2. 6q23: *MYB* (myeloblastosis viral oncogene) loss*
3. 11q13: *CCDN1* (cyclin-D1 protein) > 2 copies
4. CEP6: centromere of 6
5. 8q24: *MYC* > 2 copies
6. 9p21: *CDKN2A* (p16 protein) loss*
7. CEP9: centromere of 9

Pros: No limit in terms of cellularity, relatively easy to do, quick turnaround time

Cons: Technical difficulties, required thresholds/ratios, narrow view of the potential aberrations, might be hampered by poly/aneuploidy or senescent changes

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**FISH vs. CGH**

**FISH**

Analysis of genomic material of tumor versus normal

Pros: Panoramic, comprehensive view of the genome

Cons: Special equipment is required, limit in thickness 0.4 mm., certain findings are still of undetermined significance

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Modified from Dr. Timothy McCalmont’s ASDP board review lecture
FISH findings and prognosis in Atypical Spitzoid Lesions

• **9p21**: *CDKN2A* (codes for p16\(^{\text{ink4A}}\)) homozygous deletion – associated with “high risk lesions”

• **6q23**: *MYB* (codes for MYB protein) isolated loss – associated with “low risk lesions”

Case #4 – How would you treat these lesions (Atypical Spitz nevus/tumor) (2 might be correct)

A. Observe and re-excise upon recurrence
B. Conservative (narrow margin) re-excision
C. Wide local excision with 5-10 mm margin
D. Wide local excision with 10 mm margin and clinical follow up of lymph node basin(s)
E. Cryotherapy
Case #4 – How would you treat these lesions (Atypical Spitz nevus/tumor) (2 might be correct)

A. Observe and re-excise upon recurrence
B. Conservative (narrow margin) re-excision
C. Wide local excision with 5-10 mm margin
D. Wide local excision with 10 mm margin and clinical follow up of lymph node basin(s)
E. Cryotherapy
The End! Questions?
Thank you very much for your attention/endurance
References


