Challenging Melanocytic Lesions

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Conflicts of Interest

None

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Objectives

• Case-based overview of salient features of commonly and not-so-commonly encountered related melanocytic lesions
• Update in molecular findings
• Quick overview on other related pediatric lesions

Case #1 - Clinical Features

Picture courtesy of Dr. Martin C. Mihm

Case #1 - Histopathology
Case #1 - Diagnosis

A. Juvenile Xanthogranuloma
B. Dysplastic Nevus
C. Spitz Nevus
D. Melanoma
E. Atypical Spitz Tumor

Classic Spitz Nevus

- AKA “Spindle and Epithelioid Cell Nevus”
- First known description from Darier and Civatte back in 1910
- Characterized by Sophie Spitz in 1948 as “Melanomas of Childhood” with a series of 13 cases with 1 patient dying of widely metastatic disease – anticipating problems to come
- Usually arises in the head and neck area (particularly cheeks), trunk and lower limbs as a rapidly growing papule that is either flesh-colored (mimicking DF/JXG) or red/vascular (mimicking PG)
Classic Spitz Nevus

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

Cytology
• Inherently atypical cytomorphology
• Epithelioid and spindle cells with pink/hyalinized cytoplasm and large, often pleomorphic nuclei with vesicular chromatin and prominent nucleoli – bizarre forms and giant cells can be seen
• Pagetoid is often seen (“Pagetoid variant”) – OK as long as it is well-circumscribed and within the lesion
• Grow rapidly: mitoses are commonly seen – OK as long as they are not “marginal”
Junctional component:
- Well-circumscribed large nests of spindle cells on a “raining down” pattern
- Epidermal hyperplasia

HMB45 positivity only in the junctional/superficial dermal components and retention of p16 immunoreactivity, reassuring features

Spitz Nevus

Spitzoid Melanoma
Case #2 – Clinical/Dermoscopic Features

Case #2 – Histopathology

Pictures courtesy of Dr. Martin C. Mihm
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

- Well-demarcated, predominantly junctional/superficial dermal growth pattern with long axis of the lesion parallel to long axis of epidermis
- Spindle cells arranged in nests with frequent cleft artifact between nests and epidermis
- Finely pigmented spindle cells with monomorphic nuclei and small nucleoli
- Usually accompanied by inflammation and dermal melanophages
- Slight dermal fibrosis but no lamellar fibrosis or other features of dysplastic nevi

Reed RJ et al Semin Oncol. 1975 Jun;2(2):119-47
Case #3 – Clinical Features

Pictures courtesy of Dr. Ma. Auxiliadora Franco and Dr. Jane Messina

Case #3 – Histopathology

Pictures courtesy of Dr. Ma. Auxiliadora Franco and Dr. Jane Messina
Case #3 – Clinical Features

Case #3 – Histopathology

Case #3 – Histopathology
Case #3 - Diagnosis

A. Giant Congenital Nevus with Proliferative Nodules
B. Multifocally invasive Lentigo Maligna Melanoma with incidental congenital nevus
C. Multifocal atypical Spitz tumors
D. Agminated desmoplastic Spitz Nevi and Congenital Nevus arising in a background of bilateral segmental Nevus Spilus
E. Melanocytic lesions with BAP1 aberrations arising in a congenital nevus

Desmoplastic Spitz Nevus

- Uncommon Spitz variant, usually presents in the extremities as scaly, erythematous, flesh-colored or occasionly 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
Desmoplastic Spitz Nevus

Following pioneering work by Dr. Bastian’s group, it was found that the majority of the lesions this Spitz variant show an activation of the \textit{HRAS} gene, via increased copy number of 11p (amplification) or via activating mutations of \textit{HRAS}.

\textbf{Bastian BC et al Am J Pathol. 2000 Sep;157(3):967-72.}

\begin{itemize}
  \item \textit{HRAS} \textit{p.G13R}, \textit{p.A11S}
  \end{itemize}

\begin{itemize}
  \item Proline for Arginine in position 13
  \item Alanine for Serine in position 11
\end{itemize}
Nevus Spilus

- Nevus Spilus, AKA speckled lentiginous nevus can be congenital or present in the first decade of life and often affects Caucasians
- Tends to follow Blaschko lines and the segmental variants are associated with malignant degeneration
- Spitz nevi arising in the midst of nevus spilus (agminated Spitz) have reported to harbor HRAS mutations
- Nevus spilus associated with mosaicism syndromes are also associated with HRAS mutations (mosaicism RASopathies)

Sarin KY et al JAMA Dermatol. 2013 Sep;149(9):1077-81
Case #4 – Clinical/Dermoscopic Features

Case #4 – Histopathology

Case #4 – Which Test Will Likely Give Results to Allow You to Sleep at Night?
A. Melan A + Ki-67 Immunohistochemical Cocktail (Mel-Pro/K-Mart)
B. p16 Immunohistochemical stain
C. Comparative Genomic Hybridization (CGH) or 7-Probe FISH
D. SEQUENOM – MassARRAY
E. Next Generation Sequencing (NGS) Platform
Case #4 – Which Test Will Likely Give Results to Allow You to Sleep at Night?

A. Melan A + Ki-67 Immunohistochemical Cocktail (Mel-Pro/K-Mart)
B. p16 Immunohistochemical stain
C. Comparative Genomic Hybridization (CGH) or 7-Probe FISH – FISH Negative
D. SEQUENOM – MassARRAY
E. Next Generation Sequencing (NGS) Platform

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

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

The ambiguity of Spitzoid Lesions

A. Benign Malignant Benign Malignant Malignant Benign
B. Malignant Benign Benign Malignant Malignant Benign
C. Benign Malignant Benign Malignant Benign Benign
D. Malignant Malignant Malignant Malignant Malignant Benign
E. Benign Benign Benign Benign Benign Benign

Atypical Spitz Nevus/Tumor

Benign Spitz Nevus et al
Atypical Spitz Nevus Tumor
SAMPUS MELTUMP (Spitzoid Melanoma)

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

Comparative Genomic Hybridization (CGH)

Fluorescence In Situ Hybridization (FISH)

6p25: RREB1 (Ras-responsive binding protein) > 2 copies
9p21: CDKN2A (p16) loss
9p21: CEP9 centromere of 9
11q13: CCND1 (cyclin-D1) > 2 copies

FISH Vs. CGH

**FISH**
1. 6p25: RREB1 (Ras-responsive binding protein) > 2 copies
2. 6q23: MYB (myeloblastosis viral oncogene) loss
3. 11q13: CCND1 (cyclin-D1) > 2 copies
4. CEP6: centromere of 6
5. 8q24: MYC > 2 copies
6. 9p21: CDKN2A (p16) loss
7. CEP9: centromere of 9

**CGH**
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

Modified from Dr. Timothy McCalmont in ASBP board review lecture

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Molecular Taxonomy of Melanocytic Lesions

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Case #5 – Clinical Features
Case #5 – Histopathology

Case #5
A. Nodular melanoma arising in a giant congenital nevus
B. Atypical proliferative Nodule with Spitzoid Features arising in a giant congenital nevus
C. Collision compound congenital nevus and Spitzoid Melanoma
D. Giant congenital nevus with focal area of hypercellularity

Case #5
• FISH Studies were negative
Case #5

A. Nodular melanoma arising in a giant congenital nevus
B. Atypical proliferative Nodule with Spitzoid Features arising in a giant congenital nevus
C. Collision compound congenital nevus and Spitzoid Melanoma
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Proliferative Nodules in Giant Congenital Nevi

- Giant congenital nevi (GCN, > 20 cm) have an estimated 5-10% risk of malignant transformation, particularly during the first 5 years of life. Nevertheless, melanomas arising in this setting are extremely rare.
- On the other hand, proliferative nodules (PN) are benign neoplasms that typically present as papules or nodules within the dermis of GCN in 2.3% to 19% of GCN according to some series.

The mean age of the 19 patients with PN was 8.1 years (median 5 y) with a range from 1 day to 20 years.
Median follow-up was 49 months with a range from 6 months to 14 years.
One PN showed Spitzoid Features.


Expansile nodules, sheet-like growth pattern and infiltrative borders were noted in most cases (83%).

The majority of the cases (9 cases, 45%) demonstrated classic "adult-type" melanoma epithelioid morphology without outright Spitzoid features.

The overall features of these tumors were almost indistinguishable from "adult-type" melanomas.

18 lethal childhood melanomas, diagnosed over a 41-year period.

12 lethal childhood melanomas, diagnosed over a 41-year period.

Breast cancer, familial melanoma, and Spitzoid tumors are all considered to be part of the same disease spectrum.

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The overall features of these tumors were almost indistinguishable from "adult-type" melanomas.

Brief guide on management of Spitzoid/Pediatric Melanocytic Lesions:

- Benign Spitz nevi: Conservative re-excision or observation for recurrence.
- Atypical Spitz nevus/tumor: Re-excision (5-10 mm margin) and clinical follow up.
- Nevus spilus/Giant congenital nevus with proliferative nodules: Excision if possible, observation and further excisions of new lesions develop.
- Pediatric melanomas: Therapeutic approach similar to melanomas in adults but less aggressively if prepubertal, with sentinel lymph node biopsy and staging procedures.
References


