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Borderline Melanocytic Tumors

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Melanoma or Not Paradigm of Classification of Melanocytic Tumors A.D. 1990’s
Difficult areas in diagnostic pathology

- Differentiation between atypical nevus and early melanoma
- Recognition of early lentigo maligna
- Nevoid melanoma
- Spitzoid melanocytic tumors
- Atypical variants of special nevi
- Atypical proliferative nodules in congenital nevi
“Borderline/indeterminate” (MELTUMP/SAMPUS):
- “difficult to classify”, “with overlapping histological features between benign or malignant”, “challenging”, “controversial”, “equivocal”, etc.

Borderline/intermediate
- distinct nozological category, a specific disease or clinicopathological entity of intermediate malignant potential
Pigmented Epithelioid Melanocytoma
A Low-grade Melanocytic Tumor With Metastatic Potential Indistinguishable From Animal-type Melanoma and Epithelioid Blue Nevus

Artur Zembowicz, MD, PhD,† J. Aidan Carney, † and Martin C. Mihm* [Am J Surg Pathol 2004;28:31-40]

• Mean Breslow thickness = 3.3 mm
• 11/24 patients (46 %) had lymph node metastases

Animal type melanoma (ATM)

Epithelioid blue nevus of Carney Complex

ATM

PEM=EBN
Pigmented Epithelioid Melanocytoma

1. Synonymous with epithelioid blue nevus and includes most cases of previously diagnosed as “animal-type” melanoma
2. Can occur in the context of familiar cancer syndrome (Carney complex) and as a sporadic tumor in patients without the complex
3. Unique borderline melanocytic tumor or indolent melanoma capable of lymph node metastases but with limited potential to spread beyond lymph nodes
Carney Complex

- MULTIPLE ENDOCRINE NEOPLASIA AND SKIN LENTIGINOSIS SYNDROME
  - PIGMENTED SKIN LESIONS:
    - Lentiginies, blue nevi, and epithelioid blue nevi
  - ENDOCRINE TUMORS:
    - Primary pigmented nodular adrenocortical disease
    - GH and PRL producing pituitary adenoma
    - Large-cell calcifying Sertoli cell tumor
    - Thyroid adenoma and carcinoma
    - Ovarian cysts
  - NON-ENDOCRINE TUMORS:
    - Cardiac and cutaneous myxomas
    - Psammomomatous melanotic schwannoma
    - Breast duct adenoma
    - Osteochondromyxoma of the bone
Genetics of Carney Complex

- Autosomal dominant inheritance

- Carney Complex gene:
  Protein Kinase A Regulatory Subunit 1α (R1α) (17q22-24)
  44% of families

PEM arising in a compound nevus

Nevus component

PEM (loss of R1a in 82%)
PEM: Genetic studies

LOH for the 17q22-24 locus:
- present in < 7% of 28 melanomas
- present in 5/7 (71%) PEMs

No mutations of PRKRG1a were detected in 60 melanomas or 7 PEM.

No mutations in GNAQ in 9 PEMs (Dr. Bastian’s Lab)
An important implication of this paper is that it supports a recent paradigm shift occurring in melanocytic pathology, which departs from dichotomous classification of all pigmented lesions as either benign nevus or malignant melanoma. Follow-up data of PEM, its histologic similarity to Carney complex-associated epithelioid blue nevus, and the bland histologic features of some cases all suggest that PEM is a unique melanocytic neoplasm with low probability of systemic spread despite its ability to metastasize to regional lymph nodes.

PEM is not the first example of metastasizing or recurring melanocytic tumor with favorable clinical outcome. Cases of “benign” metastasizing Spitz nevi and spitzoid “neviod” melanomas have been described. However, histologic features of Spitz nevus and PEM are quite different. Therefore, it is possible that additional borderline melanocytic entities exist within a not uncommon group of atypical spindle and epithelioid cell tumors, which can not be definitively classified as Spitz nevi or melanoma according to present histologic criteria.
Pigmented epithelioid melanocytoma (PEM) is a recently described entity encompassing epithelioid blue nevus (of Carney complex) and most tumors earlier considered as so-called “animal-type melanoma”. Loss of expression of a Carney complex gene, cyclic adenosine 3’,5’ monophosphate-dependent protein kinase regulatory subunit 1z, is observed in the majority of PEMs. Initial reports with short-term follow-up have suggested that although PEMs frequently metastasize to lymph nodes, they have a more favorable outcome than conventional melanomas. In this report, we present the results of long-term follow-up in 26 patients with PEMs from North America and Australia. There were 9 males and 17 females, with a median age of 20 years. The tumors involved the trunk (6 cases), extremities (12 cases), genitalia (1 case), and the head and neck region (7 cases) had a median Breslow thickness of 2.2 mm (range 0.80 to 10.0 mm) and a median Clark level of 4. Eight of the patients developed lymph node metastases. After a median follow-up period of 67 months (range 39 to 216 mo), all patients are alive and free of disease. These findings provide further evidence that PEM is a unique low-grade melanocytic tumor with limited metastatic potential (to lymph nodes), but a favorable long-term clinical course.

Key Words: pigmented epithelioid melanocytoma, nevus, melanoma, equine melanotic disease, epithelioid blue nevus, Carney complex, protein kinase A regulatory subunit 1z, pathology, diagnosis

Nevus/Melanocytoma/Melanoma Paradigm

- “borderline/indeterminate” (MELTUMP/SAMPUS):
  - “difficult to classify”, “with overlapping histological features between benign or malignant”, “challenging”, “controversial”, “equivocal”, etc.

Clinicopathological and molecular correlation

- Nevus
- Borderline/intermediate melanocytic tumor (Melanocytoma)
  - distinct nozological category, a specific disease or clinicopathological entity of intermediate malignant potential
- Melanoma

Click here
Other “Melanocytomas”

- BAPoma
- Atypical Spitz Tumor
- Other
BAP1 tumors:
- Uveal melanoma
- Melanocytic BAPoma
- Mesothelioma

Biallelic loss of BAP1 expression (mutations or loss of 3p25)
A Distinct Subset of Atypical Spitz Tumors is Characterized by BRAF Mutation and Loss of BAP1 Expression

BRAFV600E/BAP1neg
Atypical Spitz Tumor

145 cases with Sentinel LN + 25-45%

No deaths with mean 35 months F/U

High risk vs. Low risk
Case vignette 3:

A 68 year old female with a third recurrence of a "melanocytic nevus", previously biopsied in 1997 and 2005.
Malignant melanoma, nevoid type, invasive to 3.5 mm, Clark’s level IV
1995
1995: Diagnosis by Pathologist #1

- Dermal nevus
The lesion recurred as a 1.5 cm asymmetrical nodule and 2 shave biopsies were performed.
2006: Diagnosis by Pathologist

#2

- Dermal nevus, present at margin.
- Nevoid melanoma in 2010
- Favor nevoid melanoma in 2006 and likely in 1995
- MelanoSITE FISH which abnormal (RREB1 amplification) in 2010 and 1995
Nevoid melanoma

McKee: “A melanoma that you diagnosed as a nevus and wish you hadn’t!”
Nevoid melanoma: types

- Verrucous
- Nodular
- (Spitzoid)
Pay attention to:

- Maturation
- Infiltrating growth pattern and “indian filing”
- Sheet-like confluent growth and expansile nesting
- Deep dermal mitotic activity
- Subtle but consistent cytological atypia
  - Pleomorphism, nuclear irregularity, abundant cytoplasm, plasmacytoid appearance
Mitotic Activity in Benign Nevi: More Common Than You Think!
Mitotic activity in benign nevi

- At least 1 mitotic figure present in 19% (HE) and 30-42% (PHH3-phospho-Histone H3 Ser28, MPM2-mitotic phosphoprotein monoclonal antibody 2)
- Mitoses more frequent lesions from younger (<20 year-old) and older (>50 year-old patients)
- 3x more frequent in the upper ½ of the dermal component
- Traumatized, inflamed and Spitz nevi have higher mitotic activity
28 year-old female with changing nevus on the abdomen
Diagnosis

- Atypical nevus of pregnancy
Nevi in pregnancy:

- ↑ mitotic activity (66 % versus 13%)
- ↑ Ki67 proliferation index

Just “look different”
- Superficial micronodules of pregnancy
Melanocytic nevi in pregnancy

Only few studies to date have examined the histologic features of benign nevi during pregnancy. Sanchez et al. examined 22 banal melanocytic nevi (predominantly intradermal) from pregnant women and compared them to age-matched controls. These nevi were examined for the presence of melanocytic hyperplasia, elongation of rete ridges, papillary dermal fibroplasia, inflammatory cell infiltrate, melanocytic maturation with depth, vascular dilation, symmetry, circumscription, and melanocytic atypia (defined by pleomorphism, hyperchromatic nuclei, prominent nucleoli, increased nuclear:cytoplasmic ratio, and mitoses). In contrast...
Soluble adenylate cyclase (sAC)
Objective: To investigate the usefulness of a novel marker for melanocytic proliferations.

Design: Using a novel monoclonal antibody against soluble adenylyl cyclase (sAC), various benign and malignant melanocytic proliferations were immunostained.

Setting: Weill Medical College of Cornell University dermatopathology laboratory.

Main Outcome Measures: The results were qualitative, not quantifiable.

Results: The sAC immunostaining produced distinctive patterns that paralleled melanomagenesis. At one pole of the spectrum were benign nevi, including atypical nevi of special sites and recurrent nevi showing a distinct pattern of dotlike Golgi staining, while at the opposite pole was melanoma, in which many cells demonstrated an intense pannuclear expression pattern, often accompanied by loss of the Golgi expression pattern. Melanomas of lentigo maligna and acral lentiginous subtypes exhibited the most striking pannuclear expression, while nodular melanomas showed the least, although with supervening enhanced diffuse cytoplasmic expression. Loss of the Golgi expression pattern was a feature of malignant melanoma.

Conclusion: The sAC expression pattern is complex but seems discriminatory, with distinctive and variable staining patterns according to the nature of the lesion biopsied.
Lentigo maligna

- Histological differential diagnosis
  - Melanocytic hyperplasia (photoactivation, paracicaticeal)
  - Junctional nevus (dysplastic)
  - Superficial spreading melanoma

- Evaluation of excision margins

Expression of Soluble Adenylyl Cyclase in Lentigo Maligna
Use of Immunohistochemistry With Anti–Soluble Adenylyl Cyclase Antibody (R21) in Diagnosis of Lentigo Maligna and Assessment of Margins

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Lentigo maligna melanoma
Lentigo maligna melanoma
Junctional nevus
Lentiginous junctional melanocytic hyperplasia
Lentiginous junctional melanocytic hyperplasia
R21 nuclear staining

- Lentigo maligna: 88%
- Melanoma (other): 40%
- Nevus: 3%
- Hyperplasia: 29%
R21 (sAC antibody)

2nd generation melanocytic marker