Melanocytic Tumours: Update on Epidemiology and Molecular Biology

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Cutaneous Melanocytic Tumours
-Introduction-

- Wide clinical and morphological spectrum
- Ranging from benign naevi to melanoma
- Majority benign
- Separating benign from malignant poses significant clinical and histological challenge
- Most important: identification of predictors of outcome

Melanocytic Tumours

Naevi
- Common acquired naevi
- Congenital naevi
- Special site naevi
- Dysplastic naevi
- Sclerosing naevi
- Blue Naevi
- DPN

Melanoma
- SSM
- Nodular M
- Acral lentiginous M
- Lentigo maligna M
- Desmoplastic M
- Mucosal M
- Lentiginous M
- Blue naevus like M
- Uveal M

Cutaneous Melanocytic Tumours

Intermediate Malignancy
- Spitzoid melanocytic tumours
- Pigmented epithelioid melanocytoma (Pigment synthesising melanoma)
The 10 Most Commonly Diagnosed Cancers: 2012 Estimates

Total Number and Percentage of New Cases Diagnosed per Year, Worldwide

Melanoma Epidemiology

The 20 Most Common Cancers in 2011
Number of New Cases, UK

Malignant Melanoma (C43): 2009-2011
Average Number of New Cases Per Year and Age-Specific Incidence Rates per 100,000 Population, UK

Anatomical Distribution

Malignant Melanoma (C43)
Percentage Distribution of Cases Diagnosed on Parts of the Body, by Sex, UK, 2008-2010
Risk Factors

- Fair skin
- Sun exposure
  - chronic sun exposure
  - intermittent sun exposure, repeated burns
- Increasing age
- Large number of atypical naevi
- Giant congenital naevi
- Family and personal history of melanoma
- Deficient immune system
- Xeroderma pigmentosum
Malignant Melanoma (C43): 1971-2011
Age-Standardised Five-Year Net Survival, England and Wales

Malignant Melanoma (C43): 2002-2006
Five-Year Relative Survival (%) by Stage, Adults Aged 15-99, Former Anglia Cancer Network

Proportion of Cases Diagnosed at Each Stage, Adults 15-99, Former Anglia Cancer Network

<table>
<thead>
<tr>
<th>Stage</th>
<th>Men</th>
<th>Women</th>
<th>Adults</th>
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<tr>
<td>Stage I</td>
<td>61.4%</td>
<td>71.3%</td>
<td>66.4%</td>
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<td>Stage II</td>
<td>21.0%</td>
<td>17.1%</td>
<td>19.1%</td>
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<td>Stage III</td>
<td>13.7%</td>
<td>8.5%</td>
<td>11.1%</td>
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<tr>
<td>Stage IV</td>
<td>2.0%</td>
<td>0.7%</td>
<td>1.3%</td>
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<tr>
<td>Stage not known</td>
<td>1.9%</td>
<td>2.4%</td>
<td>2.1%</td>
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All stages | 100.0% | 100.0% | 100.0% |
Prognostic Factors

- Tumour thickness
- “Anatomic level”
- Mitotic activity
- Ulceration
- LN Metastasis
- Distant Metastasis

Melanoma Diagnosis

- Clinical presentation
- Histological features
- Immunohistochemistry
- Molecular Biology

Melanoma

-Clinical-

Worrying clinical features:
- Asymmetry
- Irregular Borders
- Colour variation
- Diameter >5mm
- Evolution (any change in appearance, including ulceration and bleeding)

Superficial Spreading Melanoma

- Most frequent subtype of melanoma
- Prognostic information on melanoma is based on SSM
- Caucasians
- Adulthood, increasing incidence with advanced age
- Sites of intermittent sun-exposure
- Extremities and trunk
- Enlarging and changing pigmented lesion
Melanoma
-Morphological Spectrum-

Superficial Spreading Melanoma
Nodular Melanoma
Lentigo Maligna Melanoma

Acral Lentiginous Melanoma
Lentiginous Mucosal Melanoma
Desmoplastic Melanoma
Naevoid Melanoma
Spitzoid Melanoma
Pigment Synthesizing Melanoma
Malignant Blue Naevus

Melanoma Variants

- Clinical setting
- Histological features
- Diagnostic criteria
- Specific differential diagnosis
- Immunohistochemical phenotype
- Genetic profile
- Prognosis and behaviour
Melanoma -Immunohistochemistry-

<table>
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<tr>
<th>Marker</th>
<th>S100</th>
<th>Sox10</th>
<th>MIB1</th>
<th>cyclin D1</th>
<th>p53</th>
<th>bcl2</th>
<th>p16</th>
<th>p21</th>
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<td>Melan A/Mart-1</td>
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<td>HMB45</td>
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<tr>
<td>BRAF, NRAS, CKIT, ALK, ROS, BAP1</td>
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**S100/SOX10**

First line melanocytic marker:
- High Sensitivity for melanocytic tumours
- Expressed in Naevi and Melanoma
- Low specificity, also seen in neural and myoepithelial neoplasms
- Best marker in desmoplastic melanoma
- May be weak and focal in benign and malignant blue naevi

**Melan A**

Second line melanocytic marker:
- Good sensitivity for epithelioid melanocytic tumours
- But often lost in spindle cell melanocytic neoplasms
- Expressed in Naevi and Melanoma
- Relatively high specificity, but also seen in PECOMA
- Useful for evaluation of junctional component
- Often strong and diffuse in benign and malignant blue naevi
HMB-45
Second line melanocytic marker:
- Low sensitivity but high specificity
- Highlights maturation with depth in naevi
- Expression in deep component seen in DPN/blue naevi, melanoma and metastasis
- Useful for evaluation of junctional component

Microphthalmia Transcription Factor
Third line melanocytic marker:
- High sensitivity but low specificity

MIB1/Ki67
Proliferation marker:
- Low expression in naevi
- High expression in deeply invasive and metastatic melanoma
Many pitfalls:
- Interpretation in thin melanoma and intermediate thickness tumours difficult
- Low proliferation index in desmoplastic melanoma
Cyclin D1

Little diagnostic/prognostic value
- Highlights maturation in naevi
- Diffuse expression:
  - Concerning for melanoma but rare phenomenon limited to deeply invasive tumours
  - Also seen in Spitzoid neoplasms

P16

Diffuse expression in naevi, including Spitzoid tumours
Loss of expression:
- In subset of melanoma
- In Spitzoid tumours concerning for more aggressive behaviour

Melanoma Genetics

Rapid progress over past 15 years:
- Genomic instability of melanoma
- Development of diagnostic FISH assay
- Mutational analysis and targeted therapy

**Melanoma Genetics**

**Comparative Genomic Hybridisation**
- Frequent chromosomal aberrations in melanoma (>95%) in contrast to benign naevi
- 13 regions on 8 chromosomes

**Melanoma FISH**

Using CGH data a panel of 4 probes was found most informative:
- Centromere chromosome 6
- Gain of CCND1 (11q13)
- Gain of RREB1 (6p25)
- Loss of MYB (6q23)

Sensitivity of 87% and specificity of 96%

Recent inclusion of probe for 9p21 as marker of prognosis

Technically demanding and expensive

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**Fluorescence In Situ Hybridization as an Ancillary Tool in the Diagnosis of Ambiguous Melanocytic Neoplasms: A Review of 804 Cases.**

North, Jeffrey; Garrido, Maria; Kolaitis, Nicholas; LeBoit, Philip; McCalmon, Timothy; Bastian, Boris


DOI: 10.1097/PAS.0000000000000189

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**Mutational Spectrum in Melanoma**

Whole exome sequencing: numerous (>1,000) gene mutations

Challenge: Driver vs bystander mutations

High rate of mutations in BRAF in 50% (vemurafenib)
NRAS in 20% (MEK inhibitor MEK162)
CKIT in 10% (imatinib)
GNAQ/GNA11
Familial Melanoma

**CDKN2a**

Familial atypical multiple mole melanoma (FAMM)/Dysplastic nevus syndrome

40% of familial melanoma

Autosomal dominant

Multiple atypical naevi and melanoma

Superficial spreading and nodular melanoma

References:


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**Familial Melanoma**

**POT-1**

Recently described

Loss of function mutations in the Protection of telomers-1 (POT-1) gene on chromosome 7q31

4% of familial melanoma

Also linked to chronic lymphocytic leukemia (CLL)

References:


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**Uveal Melanoma**

Mutations in GNAQ and GNA11 gene mutations

Additional BAP1 mutations may predict more aggressive behaviour

GANQ and GNA11 gene mutations also observed in blue naevi and blue naevus-like melanoma ("malignant blue naevus")

References:


Familial Melanoma

**BAP1**

- Tumour suppressor gene mutations in BRCA1-associated protein-1 (BAP1) on chromosome 3q21
- Autosomal-dominant
- Multiple melanocytic tumours with epithelioid cell change
- Uveal and cutaneous melanoma
- Mesothelioma
- Renal cell carcinoma


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Pigment Synthesising Melanoma

**Pigment Synthesizing Melanoma**

- Unusual distinctive melanocytic tumour
- Reminiscent of melanomas in grey horses
- "Animal- / Equine-type Melanoma"
- Significant morphological overlap with epithelioid blue naevus in Carney complex
- "Pigmented Epithelioid Melanocytoma"
- Loss of expression of Protein Kinase A Regulatory Subunit 1a (PRKAR1A) in sporadic PEM and EBN in patients with Carney complex

Pigment Synthesising Melanoma

-Clinical Presentation-

- Deeply pigmented tumours
- Extremities, head & neck, trunk
- Mucosa, genital sites
- Young adults (20-30 yrs)
- Wide age range including congenital onset
- M=F
9 year old boy with a pigmented lesion on the left superior deltoid area

02/06/2015
Pigment Synthesising Melanoma

-Histological Features-
- Deeply pigmented tumours
- Invasion of Level IV or V
- Tumour thickness: 2-3 mm (range: 0.8 – 10 mm)
- Large ovoid to polygonal cells
- Heavily pigmented cytoplasm and vesicular nuclei with prominent nucleoli
- Low mitotic rate
- No or minimal junctional component

-Pigment Synthesising Melanoma

-Clinical Behaviour-
- Overall favourable prognosis
- High rate of LN metastasis (30-50%)
- Rare distant metastasis to liver
- Rare documented mortality (limited follow up)

Spitz Naevus

-Introduction-
- One of the most challenging and controversial aspects of melanocytic tumour pathology to date
- Described by Sophie Spitz in 1948 as ‘juvenile melanoma’
- Favourable outcome despite worrying histological features
- Histological features poor predictor of outcome (disease associated mortality in 1/13 patients)

-Spitz Naevus

-Clinical Presentation-
- Wide age spectrum but most common in childhood and adolescence
- Decreasing frequency with age
- Predilection for Caucasians
- Slight female predominance
- Wide anatomic distribution
  - Face and ear in childhood
  - Trunk and extremities in adulthood
- Non-pigmented, red to skin coloured papule <1cm in diameter
Spitz Naevus

-Problems-

65 years after Sophie Spitz’ publication

- Poor insight into the biology of Spitz tumours
- Difficult to predict behaviour

Classification into

- Spitz Naevus
- Atypical Spitz Tumour/Spitz Tumour of Uncertain Malignant Potential
- Spitzoid Melanoma

Spitz Naevus

-Genetics-

• Lack of mutation in NRAS, KIT, GNAQ, GNA11
• HRAS mutations in ~10% (desmoplastic SN)
• Homozygous loss of BAP1 and BRAF mutation
• Kinase fusions involving ROS1, NTRK1, ALK, BRAF, RET in ~50% Spitz Tumours


Morphological Spectrum of Spitz Naevi

- Pagetoid Spitz
- Acral Spitz
- Desmoplastic Spitz
- Pigmented Spitz and Spindle Cell Naevus (Reed)
- Deep Penetrating Naevus

Atypical Spitz Naevus/Tumour/Stump
Spitzoid Melanoma

Desmoplastic Spitz Naevus

- Brown/erythematous papules
- <1cm
- Adulthood
- F>M
- Extremities
- HRAS mutations
Deep-pentrating naevus

- Wide age range; adolescence and early adulthood
- Face, neck, extremities
- Darkly pigmented to grayish symmetrical papule/nodule <1cm
- Closely related to Spitz Naevi
- Mutations in HRAS, but not GNAQ, GNA11
BAPoma

Characteristic epithelioid melanocytic tumours with Spitzoid features
Loss of BAP1 expression
Additional BRAF mutation
Familial or sporadic
Also seen in AST and cutaneous and uveal melanoma


BRAF BAP1
Atypical Spitz Tumour/Spitzoid Melanoma

- Poorly defined criteria with poor interobserver agreement
- Constellation of features

Spitz Naevus with Kinase Fusion

Atypical Spitz Tumour/Spitzoid Melanoma

- Concerning Features

Architecture:
- Diameter in mm (>10 mm)
- Depth in mm (involvement of subcutaneous fat)
- Uteration
- Poor circumscription
- Diffuse Pagetoid spread
- High cellular density
- Lack of zonation and maturation
- Asymmetry
- Few or no dull pink (Kamino) bodies

Cytology:
- High nuclear to cytoplasmic ratios
- Loss of delicate or dispersed chromatin patterns
- Thickening of nuclear membranes
- Hyperchromatism
- Large nucleoli

Proliferation:
- Significant mitotic rate
- Deep/marginal mitoses
- Increased mib-1 proliferation index

Modified from: Barnhill RL. Modern Pathology. 2006; 19: S21-S33
2 year old girl; right ankle tumour

10 year old female with an enlarging lesion on the left calf present for 8 months
<table>
<thead>
<tr>
<th></th>
<th>Nodular M</th>
<th>Sp M</th>
<th>PSM</th>
<th>SSM</th>
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<tr>
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<td>10</td>
<td>9</td>
<td>16</td>
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<tr>
<td>Site</td>
<td>H&amp;N&gt;E&gt;T</td>
<td>E&gt;H&amp;N&gt;T</td>
<td>H&amp;N</td>
<td>E&gt;T</td>
<td>E&gt;T</td>
</tr>
<tr>
<td>Thickness (mm)</td>
<td>4.0</td>
<td>3.7</td>
<td>3.4</td>
<td>1.0</td>
<td>1.1</td>
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<td>Ulceration</td>
<td>50%</td>
<td>24%</td>
<td>nil</td>
<td>0.8%</td>
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<td>Necrosis</td>
<td>25%</td>
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<td>Mitoses</td>
<td>6.5/mm²</td>
<td>5/mm²</td>
<td>1/mm²</td>
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<td>2.5/mm²</td>
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<td>LN metastasis</td>
<td>57%</td>
<td>24%</td>
<td>100%</td>
<td>nil</td>
<td>39%</td>
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<tr>
<td>Dist metastasis</td>
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<td>Mortality</td>
<td>40%</td>
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AST/Spitzoid Melanoma

-Prognose-

In young children (<10 years):

• Favourable behaviour
• Risk for involvement of loco-regional lymph nodes
• Rare disseminated disease and mortality
• Sentinel lymph node biopsy not helpful and should be avoided


Spitzoid Melanoma

• No firm established diagnostic criteria
• Distinction from Atypical Spitz Tumour largely arbitrary
• Best avoided in young patients

AST/Spitzoid Melanoma

-Genetics-

Homozygous but not heterozygous 9p21 deletion associated with more aggressive behaviour

