A/Prof Fiona Maclean

Special Session ESP & IAP – Case 5

Case 5 – The Case I Will Never Forget
NICE Genital Lesions
21 F presented with acute loin pain 1/12 ago

Clinical Dx AML

MRI → no evidence of fat, ??Dx ??AML ?other → laparoscopic right nephrectomy.

Nephrectomy specimen: brown/black tumour located in the upper pole of the kidney, 85x55x50mm.
Sustained Inattentional Blindness

• 24 Radiologists
• A familiar lung nodule detection test
• 48 x larger than the average nodule size
• 83% did not “see” it
• Eye tracking - most looked directly at it
The Predictive Mind
Mechanisms Steering Consciousness

- Most thoughts/actions arise from an automatic unconscious process
- Our minds work both unconsciously and consciously
- Predictive errors = surprise = consciousness
- The autopilot in our brain – not consciousness – makes us us

Ayan, 2018, Solms and Friston 2018
Attention Span
Mechanisms Steering Consciousness

- Attention span of a goldfish 9s
- Attention span of humans dropped from 12s in 2000 to 8s in 2015
- Increased digitized lifestyle
The next day……

Haemosiderin and melanin
The next day …….
The next day……..

- Melanotic Xp11 translocation carcinoma
  - Renal sinus vascular invasion
  - Penetration of the renal capsule
  - LVI of a branch of the renal vein
  - pT3aNX
Now inversions demonstrated.

Tumour cells with break-apart

With thanks to A/Prof Sandra O'Toole, ACL
The International Society of Urological Pathology (ISUP) Vancouver Classification of Renal Neoplasia

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Rodolfo Montironi, MD,** Satish K. Tickoo, MD,†† Ming Zhou, MD, PhD,‡‡
Pedram Argani, MD,§§ and The ISUP Renal Tumor Panel
Renal cell tumors
  Papillary adenoma
  Oncocytoma
  Clear cell renal cell carcinoma
    Multilocular cystic clear cell renal cell neoplasm of low malignant potential*
  Papillary renal cell carcinoma†
  Chromophobe renal cell carcinoma
    Hybrid oncocytic chromophobe tumor*
  Carcinoma of the collecting ducts of Bellini
  Renal medullary carcinoma
  MiT family translocation renal cell carcinoma*
    Xp11 translocation renal cell carcinoma
    t(6;11) renal cell carcinoma*
  Carcinoma associated with neuroblastoma
  Mucinous tubular and spindle cell carcinoma
  Tubulocystic renal cell carcinoma*
  Acquired cystic disease associated renal cell carcinoma*
  Clear cell (tubulo) papillary renal cell carcinoma*
  Hereditary leiomyomatosis renal cell carcinoma syndrome-associated
    renal cell carcinoma*
  Renal cell carcinoma, unclassified
Urothelial tumours

Metastatic tumours

Other tumours

Metanephric tumors
  Metanephric adenoma
  Metanephric adenofibroma
  Metanephric stromal tumor
Nephroblastic tumors
  Nephrogenic rests
  Nephroblastoma
  Cystic partially differentiated nephroblastoma

Hemangioma
Lymphangioma
Juxtaglomerular cell tumor
Renomedullary interstitial cell tumor
Schwannoma
Solitary fibrous tumor
Anatomical Pathology....

Not a Machine

A Machine
19th Century physicians worried about the effect of people sitting in railway cars for hours watching the world rush by in a stream of images that seem to be detached from real people....

Some physicians went so far as to maintain that the experience of speed and technology caused “neurasthenia, neuralgia, nervous dyspepsia, early tooth decay, and even premature baldness”
Melanotic Xp11 translocation carcinoma

- Very rare, children & young adults
- Distinctive histological appearance:
  - solid sheets of epithelioid cells
  - well-developed branched capillary vasculature
  - cytoplasm was variably clear to finely granular
  - melanin pigment within the cells
- Unique immunoperoxidase staining pattern:
  - + HMB45, Melan A and TFE3
  - - S100, MiTF, epithelial markers, renal tubular markers or muscle markers (incl SMA)
  - TFE3 gene fusions were confirmed by FISH

Argani et al, 2009
Melanotic Xp11 translocation carcinoma

PEComa - phenotype

Translocation Carcinoma - TFE3 positive IPX and FISH

Melanoma - melanin pigment, HMB45 & Melan A positive
MiT Family Translocation Tumours

- A family of transcription factors
  - MiTF, TFE3, TFEB, TFEC
- Homologous basic-helix-loop-helix-leucine-zipper (bHLHzip) DNA binding and dimerization domain
- Bind a common DNA motif, suggesting common downstream targets
- Exposure to cytotoxic chemotherapy a risk factor
  - Topoisomerase II inhibitors
  - Alkylating agents
Microphthalmia transcription factor (MiT) family functions

- Regulation of melanocytes
- Regulation of osteoclasts
- Regulation of lysosome homeostasis
- and involved in other degradation pathways
- Exact underlying oncogenic mechanisms remain unclear

Functions as a policeman
Prevalence

Paediatric and Adolescent

Adults

- MiTF
- Other

Calio 2019
Prevalence

Paediatric and Adolescent

10

MiTF

Other

1,260

Adults

Argani, 2015
Xp11 Translocation RCC

- Initially reported in a younger population
- Now identified in a broad age range
- Variable outcomes
- Female to male ratio 22:6
Xp11 translocation RCC

- Wide spectrum of appearances, including papillary areas
  - Depends on partner gene
- Cells with voluminous clear or eosinophilic cytoplasm
- Psammomatous calcification, giant cells
- Immunostain TFE3 (ubiquitously expressed)
- All show fusion with *TFE3*
Probe Description
The SPEC TFE3 Dual Color Break Apart Probe is a mixture of two direct labeled probes hybridizing to the Xp11.2 band. The orange fluorochrome direct labeled probe hybridizes distal to the TFE3 gene, the green fluorochrome direct labeled probe hybridizes proximal to that gene.

Female XX – 1 fused, 1 breakapart

With thanks, Prof Sandra O'Toole

Male XY – 1 breakapart only
t(6;11) translocation carcinoma

- Only 50 cases reported thus far
- Fusion of TFEB and MALAT1(Alpha)
- Results in over-expression of native TFEB with downstream activation targets
  - similar to those seen in Xp11 translocation RCC
  - also including melanocytic markers
Small cells

Entrapped tubules
t(6;11) translocation carcinoma

- A range of appearances
- Usually have a biphasic pattern
  - nests of larger epithelioid cells
  - together with smaller cells
  - clustered around basement membrane-like material.
- Entrapped normal tubules are often identified at the periphery of the tumour
- At times, can be identical to that of Xp11 translocation RCC
t(6;11) translocation carcinoma

- limited follow up information available
- behave in a more indolent fashion than Xp11 translocation RCC
- Of the 50 cases reported
  - 4 have metastasised
  - with 3 patients dying of disease
<table>
<thead>
<tr>
<th>Associated translocation</th>
<th>Xp11 translocation RCC</th>
<th>t(6;11) translocation RCC</th>
<th>Melanotic Xp11 translocation RCC</th>
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</thead>
<tbody>
<tr>
<td>Gene fusion</td>
<td>TFE3 with:</td>
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<td>TFE3-PSF/SFPQ</td>
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<tr>
<td></td>
<td>ASPSCR1 (ASPL)</td>
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<td>PRCC</td>
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<td>NONO (p54nrb)</td>
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<td>SFPQ (PSF)</td>
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<td>CLTC</td>
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<td>Most common pattern</td>
<td>Papillary</td>
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<td>Melanin pigment</td>
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<td></td>
<td>Psammoma bodies</td>
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<td>Solid nests of epithelioid cells</td>
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<td>Voluminous cytoplasm</td>
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<td>Immunophenotype</td>
<td>PAX 8 +</td>
<td>PAX 8 +</td>
<td>PAX 8 –</td>
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<td>panCK, CK7, EMA -</td>
<td>panCK, CK7, EMA –</td>
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<td>60% Cathepsin K +</td>
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<td>TFE3 +</td>
<td>TFEB +</td>
<td>TFE3 +</td>
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<td>Melan A, HMB45 +</td>
<td>Melan A, HMB45 +</td>
<td>Melan A, HMB45 variable</td>
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<tr>
<td>Ancillary Studies</td>
<td>TFE3 FISH</td>
<td>TFEB FISH</td>
<td>TFE3 FISH</td>
</tr>
</tbody>
</table>
Epithelioid AML / PEComa
Epithelioid AML / PEComa

- A range of sites
- co-express muscle and melanocytic markers
- PAX8 negative
- May be seen in association with tuberous sclerosis complex
- Have malignant potential
- TFE3 translocations in a proportion
PEComa with TFE3 gene fusion

- Subset of PEComa with TFE3 gene fusions
  - ?? Distinct entity
  - Younger age
  - Not associated with TS
  - Alveolar architecture & epithelioid cytology
  - Minimal immunoreactivity for muscle markers
  - TFE3 immunoreactivity

Argani et al 2010
Other Tumours with MiTF Dysregulation

- RCC with *TFEB* Amplification
- Melanoma
- Clear cell sarcoma
  - *EWS-ATF1*-mediated activation of MiTF the probable cause of the melanocytic phenotype
- Alveolar soft part sarcoma
- multiple mechanisms for *MiTF* dysregulation occur, including amplification, translocation and direct targeting

Wyvekens 2019, Sounak 2019
Take Away Messages

- Most cases you encounter will be in adults
- Morphology: variable appearances - papillary, epithelioid, voluminous cytoplasm, psammoma bodies, biphasic, melanin pigment
- Under expression of cytokeratins & CK7-
- Aberrant expression of cathepsin K and/or melanocytic markers
- TFE3/TFEB IHC and TFE3/TFEB FISH: complementary role