When ancillary tests lead you astray - in the diagnosis of renal tumors

Case 6

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Absolute certainty and medicine...

If you want a profession where everything is certain - better give up medicine!

Sir William Osler (1849-1919)
Case 1. 48 y/o female, solid-cystic mass (2.6 cm) 
(Case 6 of this session)
Case 1. 48 y/o female, solid-cystic mass (2.6 cm)  
(Case 6 of this session)
Case 1. Variable patterns, mucinous background
Case 1. Focal ‘metanephric adenoma’ area
## Immunohistochemistry:

<table>
<thead>
<tr>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAX 8</td>
<td>CD117</td>
</tr>
<tr>
<td>Cytokeratin 7</td>
<td>CK20</td>
</tr>
<tr>
<td>CA9 (focal)</td>
<td>Cathepsin K</td>
</tr>
<tr>
<td>CD 10 (focal)</td>
<td>AMACR</td>
</tr>
<tr>
<td>34betaE12</td>
<td>Thyroglobulin</td>
</tr>
<tr>
<td>CK5/6 (focal)</td>
<td>WT-1 (non-MA areas)</td>
</tr>
<tr>
<td>EMA</td>
<td>CD57</td>
</tr>
<tr>
<td><strong>TTF1</strong>??</td>
<td>CEA</td>
</tr>
<tr>
<td>Vimentin</td>
<td>HMB45</td>
</tr>
<tr>
<td>INI1</td>
<td>Melan-A</td>
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<tr>
<td>SDHB and FH (retained)</td>
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</tbody>
</table>

**IHC profile non-specific...even if you throw all you have...’kitchen sink’!**
Immunohistochemistry

AHA!!!!

TTF1

ALK1

AHA!!!!
Immunohistochemistry

‘Metanephric adenoma area’
Two Cases of Renal Cell Carcinoma Harboring a Novel STRN-ALK Fusion Gene

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No metanephric adenoma areas!
Case 1:
- 33 y/o female
- MS into para-aortic nodes 10, 12 and 26 years after nephrectomy
- Solid, papillary, tubular, and mucinous cribriform structures; rhabdoid and signet-ring cells
- Mucin and psammoma bodies
- ALK1, TTF-1 (focal, 1%)

Case 2:
- 38 y/o male (4.5 cm)
- Focal necrosis
- Solid, papillary, tubular, and mucinous cribriform structures; rhabdoid and signet-ring cells
- Mucin and psammoma bodies
- ALK1, TTF-1, thyroglobulin
ALK-rearrangement (associated) RCC!

**STRN-ALK** rearrangement RCC (FISH and NGS)

Lesson: variable morphology, mucinous background - non-specific IHC!
Case 2. 42 y/o male, upper pole mass (4.9 cm)
Case 2. variable patterns, focal inflammatory background
# Immunohistochemistry

**Positive:**
- PAX 8
- Cytokeratin 7
- AMACR
- CD 10 (focal)
- CK5/6
- TTF1 (focal)
- Vimentin
- SDHB and FH (retained)

**Negative:**
- CA9
- CD117
- CK20
- Cathepsin K
- Thyroglobulin
Immunohistochemistry

OK...this is not new!
"This may be due to the focally marked inflammatory background and necrosis in the representative consult block we received for evaluation."

(Dr. Yuan Gao)
ALK-rearrangement associated RCC

**ALK translocation and ALK protein expression**

**ALK break apart probe (FISH)**

**ALK protein expression (IHC)**
ALK-rearrangement RCC

About 30 cases reported!

- Children, young adults, 50-60y

- Prognosis – some good, some not so

- MS at presentation – 6 patients

- 3/18 patients with F/U died

Potential Tx with ALK inhibitors!

**IHC:**
- CK7, 34βE12, AMACR, Vimentin, all + ALK+

**Molecular – different ALK partners:**
- VCL, TPM3, ETL4, STRN HOOK1
- CLIP1, KIF5B, KIAA1217

Kuroda N et al. USCAP 2019
ALK-rearrangement RCC

Renal medullary carcinoma-like morphology (pediatric, sickle cell trait)

VCL-ALK rearrangement RCC

TPM3-ALK rearrangement RCC
ALK-rearrangement RCC

**ALK-ETL4 rearrangement - tubulopapillary morphology – NO mucin!**
Case 3. 54 y/o female, ‘renal pelvic polyp’, 24x18x16 mm
Case 3. Looks kind of like thyroid?

Both RCC and thyroid Ca - PAX8 positive!
Case 3. Looks kind of like thyroid?

PAX 8 positive neoplasms

- Thyroid (including anaplastic)
- Parathyroid
- Gynecologic (ovary, endometrial, endocervical)
- Thymus
- Merkel cell carcinoma
- Pancreatic neuroendocrine
- Nephrogenic adenoma

MS from thyroid ca!

Thyroglobulin

TTF1
Case 3. 54 y/o female, ‘pelvic polyp’, 24 x 18 x 16 mm

Patient does not have a (known) thyroid mass!

...but investigations will be performed!

...ooops, there is a 1 cm ‘thyroid nodule’!

Not all ‘renal pelvic polyps’ are renal!

Ancillary tests do not always lead astray!
Bonus case. ‘Thyroid mass’

Both PAX8 positive!

Not all ‘thyroid’ masses are thyroid!

Ancillary tests do not always lead astray!

Clear cell RCC – MS to the thyroid!
Thyroid-like follicular RCC indeed exists!

Resembles thyroid follicular carcinoma, but doesn’t stain like one (r/o MS!)
Thyroid-like follicular RCC

- About 40 cases reported
- Mostly females, broad age range
- IHC: PAX8+, CK7+
  - Thyroglobulin – /TTF1 –
- Molecular: limited data
  - Variable gains and losses
- Usually non-aggressive, rare cases with MS
Thyroid-like follicular RCC (real one!) with spindle cell/sarcomatoid differentiation
Emerging/provisional renal entities:

ALK translocation RCC

Thyroid-like follicular RCC
Case 4. 40 y/o male, renal mass 9.5 cm

- Mostly cystic
  “adherent to adjacent organs”

- Solid areas
  “fungoid, papillary, friable”
  1-2.5 cm

- Fibrous capsule
  Perirenal fat invasion?

- One perinephric node negative
Case 4. Fumarate hydratase (FH) deficient RCC
Clear cell renal cell carcinoma
Multilocular clear cell renal cell neoplasm of low malignant potential
Papillary renal cell carcinoma
  Type 1
  Type 2
Chromophobe renal cell carcinoma
Collecting duct carcinoma
Renal medullary carcinoma
MiT family translocation renal cell carcinoma
Mucinous tubular and spindle cell carcinoma
Tubulocystic renal cell carcinoma
Acquired cystic disease associated renal cell carcinoma
Clear cell papillary/tubulopapillary renal cell carcinoma
**Hereditary leiomyomatosis and renal cell carcinoma-associated renal cell carcinoma**
Succinate dehydrogenase (SDH) deficient renal carcinoma
Renal cell carcinoma, unclassified
Papillary adenoma
Renal oncocytooma
Hereditary leiomyomatosis associated RCC (HLRCC)
Hereditary leiomyomatosis RCC

Autosomal Dominant

Cutaneous and uterine leiomyomas
(M > F; 70% lifetime risk)

50% hysterectomy (< 35y)

Resembles PRCC “type 2”
or “collecting duct-like” RCC

Fumarate hydratase (FH)
germline mutation (1q42)
Abnormal succination ↑ 2SC

Most aggressive RCC!
up to 50% MS at Dx
30% lifetime risk
FH deficient RCC

FH retained RCC
Architectural patterns (n=40):

- Papillary 25 (63%)
- Tubulo-papillary 8 (20%)
- Tubular 2 (5%)
- Solid 1 (2%)
- Mixed 4 (10%)
“FH deficient RCC”

Compatible morphology with HLRCC-associated RCC

Uncertain clinical/family hx of skin/uterine leiomyomas and RCC

IHC = FH negative, and/or 2SC positive

Unknown genetic status at the time of case sign-out
Histomolecular entity

FH deficient RCC

HLRCC
Many ‘unclassified high-grade’ RCC can be classified as FH-deficient RCC!

FH IHC of “Unclassified RCC” detected 24 (19%) RCC with FH deficiency

Fumarate Hydratase–deficient Renal Cell Carcinoma Is Strongly Correlated With Fumarate Hydratase Mutation and Hereditary Leiomyomatosis and Renal Cell Carcinoma Syndrome

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IHC Screening of “Unclassified RCC” detects FH deficient tumors

TMA detected case
(“papillary type 2, with prominent nucleoli”)
Papillary (74%) + other patterns!

Multiplicity of patterns is the key feature of FH-deficient RCC!
Tubulocystic (41%) and tubular (26%)
Solid (44%) and sarcomatoid (15%)
“FH deficient RCC” previously labelled:

- Unclassified, high grade
- Papillary type 2
- Tubulocystic RCC with dedifferentiated foci
- Collecting duct carcinoma (CDC)

Incorrect interpretation, imperfect knowledge!

Ancillary tests ‘over(mis-)interpreted’!
Tubulocystic Carcinoma of the Kidney With Poorly Differentiated Foci

A Frequent Morphologic Pattern of Fumarate Hydratase-deficient Renal Cell Carcinoma

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IHC by FH and 2SC detected 24/29 (83%) FH deficient RCC
25% (13/51) cases previously diagnosed CDC - reclassified as FH-deficient RCC upon review and IHC for FH and 2SC
FH IHC interpretation can be tricky (e.g. inflammation!)
FH and 2SC IHC interpretation can be tricky!

Possible *FH* missense mutation with dysfunctional FH protein!
"FH deficient RCC"

Summary

Multiple patterns (focal prominent nucleoli)

Negative FH on IHC strongly correlates with:

- FH gene alterations and morphology compatible with HLRCC syndrome
- Aggressive behaviour (but often without the stigmata)

Negative FH IHC - genetic testing for FH mutations (pt + siblings)!

- Lifelong MRI surveillance (30% risk) and immediate resection!
When ancillary tests lead you astray – what can possibly go wrong?

Imperfect ancillary test (preanalytical/analytical error)
  e.g. incorrect FISH or IHC (false positive/false negative)

Incorrect interpretation (analytical error)
  e.g. IHC (false positive/false negative)

Imperfect knowledge (analytical error)
  e.g. poor understanding or ignorance
If you don’t want ancillary tests to lead you astray... use your best tools!

Use primarily at low power

Use primarily at high power
Join us at:
www.gupathsociety.org
Hope you don’t feel like this now!

Questions?

Thank you!