Carcinoma of the collecting ducts of Bellini

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Pathologic Variants of Renal Cell Carcinoma

- 1900-Grawitz tumor- hypernephroma- ccRCC
- 1980 – Papillary RCC (Kovacs)
- 1985- Chromphobe RCC (Theones et al.)
- 1990- collecting duct, medullary RCC, translocation RCC, mucinous tubular and spindle-cell RCC
- 2004 – WHO classification of RCC
- 2013 - the International Society of Urological Pathology (ISUP) Vancouver Consensus Statement added five more epithelial tumor subtype
- Furthermore, three new entities were given a provisional status:
  - thyroid-like follicular RCC
  - succinate dehydrogenase B deficiency-associated RCC
  - and anaplastic lymphoma kinase translocation RCC

The most recent 2013 ISUP renal tumor classification scheme now recognizes >24 subtypes of kidney cancer
Renal cell tumors

**ISUP - Vancouver Modification**

<table>
<thead>
<tr>
<th>Renal cell tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papillary adenoma</td>
</tr>
<tr>
<td>Oncocytoma</td>
</tr>
<tr>
<td>Clear cell RCC</td>
</tr>
<tr>
<td>Multilocular cystic clear cell of low malignant potential</td>
</tr>
<tr>
<td>Papillary RCC (types 1 and 2)</td>
</tr>
<tr>
<td>Chromophobe RCC</td>
</tr>
<tr>
<td>Hybrid oncocytic chromophobe tumor</td>
</tr>
<tr>
<td>Carcinoma of the collecting ducts of Bellini</td>
</tr>
<tr>
<td>Renal medullary carcinoma</td>
</tr>
<tr>
<td>MiT family translocation RCC [Xp11, t(6:11)]</td>
</tr>
<tr>
<td>Carcinoma associated with neuroblastoma</td>
</tr>
<tr>
<td>Mucinous tubular and spindle cell carcinoma</td>
</tr>
<tr>
<td>Clear cell tubulopapillary RCC</td>
</tr>
<tr>
<td>Hereditary leiomyomatosis RCC</td>
</tr>
<tr>
<td>RCC, unclassified</td>
</tr>
</tbody>
</table>

*ISUP = International Society of Urological Pathology; MiT = microphthalmia transcription factor; RCC = renal cell carcinoma; WHO = World Health Organization.*
Each renal tumor originates from a specific part of the nephron.

Non–clear cell histology accounts for approximately 10% of cases of metastatic RCC.
Collecting ducts have cortical and medullary parts, passing through almost the entire volume of the kidney, from the capsule to the papillae.

This is the reason why distal nephron tumors may also be located within the renal cortex in the periphery of the kidney, protruding from the convex surface, mimicking tumors arising from the proximal nephrons.

Both principal and intercalated cells show strong positivity for cytokeratins 7, 8 and 18, pankeratin AE1/AE3, EMA and Ecadherin.

J.I. López et al. / Pathology – Research and Practice 211 (2015) 271–280
# Malignant Potential of RCC

<table>
<thead>
<tr>
<th>Entity</th>
<th>Malignant potential</th>
<th>Treatment of localized tumour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarcomatoid variants of RCC</td>
<td>High</td>
<td>Surgery</td>
</tr>
<tr>
<td>Multilocular clear cell RCC</td>
<td>Low, no metastasis</td>
<td>Surgery, NSS*</td>
</tr>
<tr>
<td>Carcinoma of the collecting ducts of Bellini</td>
<td>High, very aggressive</td>
<td>Surgery, in M+ discussable</td>
</tr>
<tr>
<td>Renal medullary carcinoma</td>
<td>High, very aggressive</td>
<td>Surgery</td>
</tr>
<tr>
<td>Translocation RCC Xp11.2</td>
<td>High</td>
<td>Surgery</td>
</tr>
<tr>
<td>Translocation RCC t(6;11)</td>
<td>Low</td>
<td>Surgery, NSS</td>
</tr>
<tr>
<td>Mucinous tubular and spindle cell carcinoma</td>
<td>Intermediate</td>
<td>Surgery, NSS</td>
</tr>
<tr>
<td>Acquired cystic disease-associated RCC</td>
<td>Low</td>
<td>Surgery</td>
</tr>
<tr>
<td>Clear cell (tubulo) papillary RCC</td>
<td>Low</td>
<td>Surgery, NSS</td>
</tr>
<tr>
<td>Hybrid oncocytic chromophobe tumour</td>
<td>Low</td>
<td>Surgery, NSS</td>
</tr>
<tr>
<td>Metanephric tumours</td>
<td>Benign</td>
<td>Surgery, NSS</td>
</tr>
<tr>
<td>Cystic nephroma/Mixed Epithelial and Stromal Tumour</td>
<td>Low/benign</td>
<td>Surgery, NSS</td>
</tr>
<tr>
<td>Oncocytoma</td>
<td>Benign</td>
<td>Observation (when histologically confirmed)/surgery, NSS</td>
</tr>
<tr>
<td>Hereditary kidney tumours</td>
<td>High</td>
<td>Surgery, NSS</td>
</tr>
<tr>
<td>Angiomyolipoma</td>
<td>Benign</td>
<td>Consider treatment only in very well selected patients</td>
</tr>
<tr>
<td>Unclassified RCC</td>
<td>Variable</td>
<td>Surgery, NSS</td>
</tr>
</tbody>
</table>

Pathologic variants differ not only in disease biology, but also in clinical behavior, prognosis, and response to systemic therapy.
Diagnosis of CDC

• Symptoms
  – Flank pain
  – Haematuria
  – Palpable mass

• Clinical presentation
  – Medullary involvement with focal cortical involvement
  – Reniform contour of the kidney preserved
  – Mostly large tumors
  – Most patients with advanced disease
  – Mean age – 55 years
  – More frequent in men

Clinical presentation 2

- Most patient with advanced disease
- Multiple metastases to the lymph nodes, lung, bone, and liver
- Short median survival 44 wk
- Some long-term survivors
  - CDRCC typically presents with a more advanced and more aggressive stage and grade. Despite the unfavourable presentation, when CDRCC cases are compared to CRCC controls with the same pattern of symptoms, stage, and grade of disease, cause-specific survival is strikingly similar in both groups

- For the majority of patients with metastasis - surgical treatment will not result in a cure

Imaging

- US - nonspecific
- Excretory urography - distortion of the intrarenal collecting system
- CT – solid or complex solid/ cystic lesion
  - Enhancement washout value < 0 is highly specific for Pa-RCC and non-CC-RCC\(^1\)
- MR - nonspecific
  - The percentage SI drop on chemical-shift MRI had high specificity and moderate sensitivity in predicting clear cell RCC over non-clear cell RCC and minimal-fat AML\(^2\)
- Angiography - hypovascular lesions
- 18F-FDG (\(^{18}\)F-fluorodeoxyglucose) PET/CT
  - lymph nodes detection

Macroscopic appearance of CDC

Partially cystic, white-gray appearance
Firm consistency
Often exhibits invasion into the renal sinus and/or renal vein
Microscopic appearance of CDC

- Variable but usually has infiltrative glandular/tubular or papillary architectures.
- Presence of desmoplastic stroma (*In contrast to most RCC*), contains mucinous material
- Inflammatory infiltrate
- High-grade cytology with abundant mitosis.
- "Hobnail" or “Signetb ring” appearance of the cells
Immunohistochemical markers

- Ulex europaeus I (UEA-1)
- High molecular weight cytokeratins (HMWCK)
- E-cadherin
- Epithelial membrane antigen (EMA)
- CKβE12 and CK19

PAX8 expressed by normal collecting ducts
  - Member of the PAX gene family of transcription factors that is crucial for lineage commitment in thyroid, Mullerian duct, and metanephron
  - The immunoprofile of PAX8+/p63− supports the diagnosis of CDC with a sensitivity of 85.7% and a specificity of 100%. In contrast, a (PAX8−/p63+) profile supports the diagnosis of UUC with a sensitivity of 88.2% and a specificity of 100%.

**Differential diagnosis - UTCC**

<table>
<thead>
<tr>
<th></th>
<th>CDC</th>
<th>Urothelial (TCC)</th>
<th>Conventional (Clear Cell) RCC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Macroscopic</strong></td>
<td>Centered on renal medulla, usually infiltrative</td>
<td>Centered on pelvicalyceal system</td>
<td>Usually cortical</td>
</tr>
<tr>
<td><strong>Microscopy</strong></td>
<td>Tubulopapillary or papillary, usually multinodular, with extensive desmoplasia, often with admixed neutrophils</td>
<td>Usually papillary, or solid</td>
<td>Solid alveolar/sheet-like with intricate vascularity</td>
</tr>
<tr>
<td><strong>architecture</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cytology</strong></td>
<td>Usually eosinophilic cytoplasm, high-grade nuclei.</td>
<td>Amphophilic or eosinophilic cytoplasm, nuclear grade variable</td>
<td>Clear or eosinophilic cytoplasm, nuclear grade variable</td>
</tr>
<tr>
<td><strong>Mucin stains</strong></td>
<td>Often positive</td>
<td>Focal positivity in up to 40%, more common in high-grade tumors</td>
<td>Absent</td>
</tr>
<tr>
<td><strong>Tubular dysplasia</strong></td>
<td>Present</td>
<td>Tumor extension along tubules, resembling tubular dysplasia</td>
<td>Absent</td>
</tr>
<tr>
<td><strong>Urothelial carcinoma in situ</strong></td>
<td>Absent</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td><strong>Immunohistochemistry</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ulex Europeus</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Peanut agglutinin</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>HMWCK</td>
<td>Positive</td>
<td>Positive</td>
<td>Usually negative</td>
</tr>
<tr>
<td><strong>Molecular genetics</strong></td>
<td>Monosomies 1, 6, 14, 15, and 22 LOH of 1q, 8p, 9p, and 13q c-erb B-2 amplification</td>
<td>LOH 8p, 9 p53, Rb mutations c-erb B-2 amplification</td>
<td>Chromosome 3p abnormalities (e.g., losses, von Hippel-Lindau gene mutations etc.)</td>
</tr>
</tbody>
</table>

CDC: collecting (Bellini) duct carcinoma; TCC: transitional cell carcinoma; RCC: clear cell renal cell carcinoma; HMWCK: high molecular weight cytokerin; LOH: loss of heterozygosity.

Immunohistologic and molecular analyses indicate that CDC more closely resembles transitional cell carcinoma than renal cell carcinoma.

Differential diagnosis- renal medullary carcinoma

• Renal medullary carcinoma (RMC) detected almost exclusively in individuals with sickle cell trait or anaemia.
• This tumour shares many histologic features with CDC
• Some consider it a subtype of CDC or at least a closely related tumour, although the relationship between these two entities still remains controversial
• Both CDC and RMC are considered to be somewhat similar to poorly differentiated urothelial carcinoma.
• The extremely poor prognosis and ongoing clinical trials with specific therapeutic protocols argue for their accurate distinction from other renal cell carcinoma subtypes.

Eur Urol, 2011; 60:634-643
Am J Surg Pathol. 2012 Sep;36(9):1265-78
Overview of the systematic review searches

3 studies relevant to the management of CDC that included a total of 72 patients.

Current standard of care for metastatic CDC is a gemcitabine-cisplatin regimen.

Current Oncology, Vol 20, No 3, (2013)
Immuno therapy- cytokines

• Metastatic non-clear-cell RCC is characterized by a resistance to systemic immunotherapy and poor survival, with the survival for patients with chromophobe tumors longer than that for patients with metastatic collecting duct or papillary RCC.

• Median OS 9.4 months. Only 1 PR.

• The survival was longer for patients with chromophobe tumors compared with collecting duct or papillary histology

Chemotherapy

- Histology of collecting duct carcinoma is similar to that of urothelial carcinoma
- Gemcitabine + Cysplatine or Carboplatine
- 1 CR and 5 PR
- OS 10.5 mts
- Toxicity - mainly hematological with grade 3-4 neutropenia and thrombocytopenia in 50% of pts
- Cisplatin, gemcitabine and bevacizumab in patients with metastatic collecting duct carcinoma can result in long term disease control

Oudard et al, J Urol. 2007 May;177(5):1698-702
Metastatic ncc RCC – Target therapy

The International mRCC Database Consortium (IMDC) predictors of poor survival
• Karnofsky performance status (KPS) <80%
• Time from diagnosis to treatment interval <1 year,
• Anemia
• Hypercalcemia
• Neutrophilia
• Thrombocytosis

With Targeted therapy OS inferior in pts with ncRCC comparing with ccRCC

The IMDC prognostic model reliably predicts OS and Time to Treatment Failure in nccRCC and ccRCC patients

Genomic profiling of CDC

- Recurrent clinically relevant genetic alterations (CRGAs) were detected in CDC
- The most common GAs were in NF2 (5/17, 29%), SETD2 (4/17, 24%), SMARCB1 (3/17, 18%), and CDKN2A (2/17, 12%)
- Average - 0.7 CRGAs per case
- CRGAs suggest a possible benefit from targeted therapy.
- In particular, mTOR inhibitors may be of interest in patients with NF2 alterations.

Eur Urol. published online sept 2015
Conclusion

• CDC is a highly aggressive tumor
• It is a disease hybrid between renal cell carcinoma and upper transitional cell carcinoma
• Seems to respond to TCC chemotherapy
• Role of targeted therapy still unclear
Thank you

for your attention!

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