Houston Society of Clinical Pathologists’ 58th Annual Spring Symposium

Case Discussion
Vijayalakshmi Padmanabhan MBBS, MD, MPH
Associate Professor
Director, Cytopathology Fellowship Program
Department of Pathology and Immunology
Baylor College of Medicine
Director, Anatomic Pathology (for Cytology)
Medical Director of Cytopathology
Ben Taub General Hospital
Houston, TX
47 AA male with obesity (BMI 45.9) and history of hypertension, initially presented to an outside facility with right flank pain

CT scan detected a right renal mass
<table>
<thead>
<tr>
<th>CBC/DIFFERENTIAL</th>
<th>Clear</th>
<th>Clear</th>
<th>Clear</th>
<th>Clear</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>6.1</td>
<td>8.0</td>
<td>6.5</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>12.0</td>
<td>13.2</td>
<td>13.0</td>
<td></td>
</tr>
<tr>
<td>Hematocrit</td>
<td>38.6</td>
<td>41.5</td>
<td>40.4</td>
<td></td>
</tr>
<tr>
<td>MCV</td>
<td>93</td>
<td>90</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>Platelet</td>
<td>335</td>
<td>345</td>
<td>317</td>
<td></td>
</tr>
<tr>
<td>RBC</td>
<td>4.14</td>
<td>4.63</td>
<td>4.57</td>
<td></td>
</tr>
<tr>
<td>MCH</td>
<td>29.0</td>
<td>28.5</td>
<td>28.4</td>
<td></td>
</tr>
<tr>
<td>MCHC</td>
<td>31.1</td>
<td>31.8</td>
<td>32.2</td>
<td></td>
</tr>
<tr>
<td>RDW</td>
<td>49.3</td>
<td>45.1</td>
<td>48.1</td>
<td></td>
</tr>
<tr>
<td>Neutrophil</td>
<td>78.1</td>
<td>68.9</td>
<td>71.7</td>
<td></td>
</tr>
<tr>
<td>Neutrophil, Abs</td>
<td>4.78</td>
<td>5.33</td>
<td>4.69</td>
<td></td>
</tr>
<tr>
<td>Lymphocyte</td>
<td>18.6</td>
<td>22.3</td>
<td>22.5</td>
<td></td>
</tr>
<tr>
<td>Lymphocyte, Abs</td>
<td>1.14</td>
<td>1.78</td>
<td>1.47</td>
<td></td>
</tr>
<tr>
<td>Monocyte</td>
<td>2.0</td>
<td>5.6</td>
<td>4.1</td>
<td></td>
</tr>
<tr>
<td>Monocyte, Abs</td>
<td>0.12</td>
<td>0.45</td>
<td>0.27</td>
<td></td>
</tr>
<tr>
<td>Basophil</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Basophil, Abs</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>Eosinophil</td>
<td>0.8</td>
<td>4.9</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>Eosinophil, Abs</td>
<td>0.05</td>
<td>0.79</td>
<td>0.09</td>
<td></td>
</tr>
</tbody>
</table>

| UACHEM                |       |       |       |       |
| Clarity               | Clear | Clear | Clear | Clear |
| Color                 | Yellow| Yellow| Yellow| Yellow|
| Spec Gravity          | 1.015 | 1.020 | 1.020 | 1.014 |
| pH                    | 6.0   | 6.0   | 7.8   | 5.0   |
| Protein               | Negative| Negative| Negative| Negative|
| Glucose               | Negative| Negative| Negative| Negative|
| Ketone                | Negative| Trace | Negative| Negative|
| Blood                 | Negative| Negative| Negative| Negative|
| Bilirubin             | Negative| Negative| Negative| Negative|
| Unbiliogen            | 0.2   | <1.0  | <1.0  | <1.0  |
| Leukocyte             | Negative| Negative| Negative| Negative|
| Nitrate               | Negative| Negative| Negative| Negative|

| CHEMISTRY/MISC.       |       |       |       |       |
| Iron                  | 41    |       |       |       |
| % Iron Sat            | 9     |       |       |       |
| TBG                   | 437   |       |       |       |

| NUCLEAR MEDICINE LAB  |       |       |       |       |
| Fetuin                | 17.10 |       |       |       |

| ROUTINE CHEMSTRIES    |       |       |       |       |
| Sodium                | 140   |       |       |       |
| Potassium             | 4.7   |       |       |       |
| Chloride              | 102   |       |       |       |
| CO2                   | 28.5  |       |       |       |
| Urea Nitrogen         | 12    | 10    | 10    |       |
| Creatinine            | 1.2   | 1.2   | 1.2   |       |
| Glucose               | 95    |       |       |       |
| GFR, Estim, All-Az    | >60   | >60   | >60   |       |
| GFR, Estimated        | >60   | >60   | >60   |       |
| Anion Gap             | 9.5   |       |       |       |
| Calcium               | 8.9   |       |       |       |
4 cm mass in right kidney, thickening of bladder wall and nephrolithiasis
Cytologic Evaluation

- Cellular smears, three dimensional clusters, vague gland-like appearance
- Monotonous appearance, minimal anisonucleosis
- Medium sized cells, some with plasmacytoid appearance
- Abundant extracellular material
Cytologic Evaluation

• Focal spindling of cells, especially at the edges of large cell clusters
• Not appreciated on DQ-stained slides
Cell Block, Needle Core Biopsies

• Bland tubular structures, some transition to oval-spindle cells
• Monotonous cell-type
• Cuboidal shaped cells with eosinophilic cytoplasm
• Low grade nuclei
• No mitotic figures
• No clear cells, foam cells, necrosis, hemorrhage
• Abundant bubbly basophilic stroma
• Immunostains CK7, AMACR positive, WT-1 negative
Mucinous Tubular and Spindle Cell Carcinoma (MTSCC)
Cytology of MTSCC

• Letter to the editor Ortega, 2006 (Spain):
  73 year old female,
  Location: upper pole, right kidney
  Size: 6cm, 7 cm
  Pre-operative/ FNA diagnosis: likely Renal Cell Carcinoma (RCC)
  Diagnosed as MTSCC after reviewing histology on nephrectomy specimen
  Well circumscribed, solid tumor limited to kidney

  Ortega, 2006
Case Report 1

- Abundant cellularity

- Branched and interconnected epithelial aggregates intermingled with amorphous, metachromatic stroma (vaguely resembling a pleomorphic adenoma)

- Well-defined honey-combed cytoplasm in Pap stain, ill defined/microvesiculated cytoplasm on Diff-Quik stain

- Spindle cell pattern resembling “school of fish”

- Bland, low-grade nuclei

Ortega, 2006
Case Report 2

54 year old female
History of lymphoma, incidentally detected renal mass during staging
FNA with cell block diagnosis:
Renal cell carcinoma with features of a low grade myxoid neoplasm
Partial nephrectomy performed

Sun et al, 2005
Cytologic Features

- Loosely cohesive clusters often associated with a capillary network
- Relatively uniform, medium-sized tumor cells with moderate amounts of finely vacuolated or wispy cytoplasm and indistinct cell border
- The nuclei were primarily round with coarse chromatin and had prominent nucleoli
- EM (on nephrectomy specimen): cuboidal cords of cells with occasional lumens. The cells often lacked a brush border on the surface and had sparse, short microvilli. Nuclei were irregular and cytoplasm contained moderate amounts of mitochondria, some glycogen and lipid droplets

Sun et al, 2005
Case Report 3

54 year old female

Presentation: Flank pain, ARF secondary to rhabdomyolysis after a fall

Location: left kidney

Size: 5.2 cm, 4.5 cm

Pre-operative/ FNA diagnosis: atypical appearing epithelial proliferation consistent with RCC

Diagnosed as MTSCC on review after nephrectomy

4.5 cm non encapsulated, well demarcated white nodular mass confined to kidney

Owens, 2007
Cytologic Features

• Branching pseudo papillae
• Abundant metachromatic stroma
• Bland nuclei
• Focally cells showed moderate nuclear pleomorphism with prominent nucleoli
• Scattered foam cells

Owens, 2007
Report of 2 Cases (Cases 4, 5), Case Report 4

Case 1
- 51 year old male
- H/o lung cancer, s/p lobectomy
- 2.7 cm solid mass, mid-pole Right
- FNA diagnosis: RCC with clear cell features
- Diagnosed as MTSCC after nephrectomy

Case 2
- 54 year old male
- H/o nephrolithiasis
- 5 cm solid mass, lower pole Left
- FNA diagnosis: RCC
- Diagnosed as MTSCC after nephrectomy

Marks-Jones, 2009
Cytologic Features

• Cellular, loosely cohesive, oval to spindle cells in sheets, branching clusters/ pseudo papillae
• Abundant metachromatic substance intermingled with tumor
• Immunohistochemistry on cell-block sections:
  - Positive: CK7, CK19, CD10, vimentin, E-cadherin, alpha-methyl CoA racemase (AMACR/ P504S) + (1 case) EMA, carbonic anhydrase IX (CA-9)
  - Negative: CK20, CK903

Marks-Jones, 2009
Case Report 5

67 year old female
Presentation: flank pain
Location: right kidney
Size: 6.5 cm, 7 cm
Pre-operative/ FNA diagnosis: epithelial tumor consistent with RCC
Diagnosed as MTSCC on review after nephrectomy

Chrysikos, 2012
Cytologic Features

- Well circumscribed
- Positive stains: EMA, CK7
- Negative: CD10 and Vimentin
- Differential diagnosis: metanephric adenoma

Chrysikos, 2012
Case Report 6

67 year old male
Presentation: abdominal pain with metastatic colon cancer
Location: right kidney
Size: 6.5 cm, 7 cm
Pre-operative/ FNA diagnosis: MTSCC on FNA and core biopsies
Mass: stable, not resected

Huimaiiao et al, 2015
Differential Diagnosis

• Conventional RCC- vacuolated cytoplasm and perivascular nesting of tumor cells

• Papillary RCC: more foam cells, true vascular cores

• Sarcomatoid RCC: expect some atypia, anisonucleosis

• Metanephric adenoma: highly cellular, composed of small, uniform embryonic-looking cells

M/E: arranged in tightly packed small acini, long tubular structures with inconspicuous to loose edematous stroma

Immunohistochemistry:

- Positive WT-1, CD57, CK7 (+/- focal)

- Negative: AMACR, EMA, desmin
Dr. George Farrow and his colleagues presented eight tumors at a meeting of the United States and Canadian Academy of Pathology (USCAP) and described them in an abstract in 1994, observing that the tumors were large, well-circumscribed, noninfiltrative, and were solid or extensively cystic.

All tumors were composed of “well-differentiated tubules with little or no tubulopapillary or papillary component” The morphologic, immunohistochemical, and ultrastructural properties of the tumors were consistent with origin from collecting tubules.

The features of these tumors were considered to be in marked contrast to those of classic collecting duct carcinoma (CDC), which typically is clinically aggressive, poorly circumscribed, highly infiltrative, and composed of tubulopapillary or papillary elements that infiltrate a desmoplastic stroma.
Dr. Farrow’s findings were published in 1997
The series included 13 patients
Mean age was 61 years (Range: 39 to 74 years)
In two cases, the tumor was found incidentally at autopsy; the other 11 patients underwent surgical excision
In nearly half of the cases, no symptoms or physical findings were attributable to the tumor

MacLennan, 1997
Gross Description

• Tumors were well-circumscribed
• Mean size: 6 cm (Range: 2 cm to 17 cm in diameter,)
• Some were entirely cystic, some were solid/cystic, but most were solid
• Necrosis was evident in three tumors, hemorrhage was noted in two tumors, and gross extension of tumor into perirenal fat was evident in two cases
• No involvement of renal vein, adrenal, or regional lymph nodes was noted, and no patient had clinical evidence of metastases at the time of tumor discovery
Microscopic Findings

• Microscopically, the tumors demonstrated two architectural patterns.
• Some tumors were composed of ductlike or cystic tubules with little or no mucin production, whereas others were composed of complex anastomosing irregular tubular structures with abundant mucin production.
• Mitotic activity was minimal in all cases.
• Fuhrman nuclear grade was 1 or 2 in all cases.
Reclassification of Original 13 tumors

• Five of the tumors were reclassified as MTSCC
  -These were the subset of tumors that consisted of complex anastomosing irregular tubular structures with abundant mucin production

• The other eight tumors were examples of “tubulocystic renal cell carcinoma”
  -These were the tumors that were composed of ductlike or cystic tubules with little or no mucin production and were immunoreactive to antibodies against UEA-1 or 34βE12
• Reported 4 cases with distinctive morphology and immunophenotype characterized by noninfiltrative borders, basophilic and often “bubbly” myxoid stroma that stained intensely for Alcian blue, elongated tubular and cordlike architecture, low-grade cytology, and immunoreactivity for high–molecular weight keratin

• Each case showed areas where tumor cells were spindled focally

• All tumors were strongly immunoreactive for 34βE12, and negative for UEA-1

• Ultrastructural findings were believed to be indicative of distal nephron differentiation

• All tumors were confined to the kidney

• All patients were female and had benign clinical courses during a mean follow-up of 45 months  

  Parwani, 2001
• *Srigley et al* reported their findings in 20 cases at the 2002 meeting of the USCAP; they confirmed that their light and electron microscopic findings suggested a possible histogenetic relationship to the loop of Henle

• Seven additional tumors from five patients were reported in 2002 by *Rakozy et al*

By comparative genomic hybridization, these investigators found multiple genetic alterations that included consistent losses of chromosomes 1, 4, 6, 8, 9, 13, 14, 15, and 22

They concluded that their immunohistochemical and genetic findings strongly supported an origin from collecting duct epithelium

*Srigley et al, 2002*

*Rakozy et al, 2002*
MTSCC Overview

• Over 100 cases in the literature
• Tumors account for <1% of all renal neoplasms
• Mean age 58 years (Range: 13-81 years)
• Female predilection (female-to-male ration 3:1)
• Site: cortex, medulla
• Some tumors occur in association with nephrolithiasis
MTSCC

• Immunohistochemistry:
  Positive: CK7, PAX2, AMACR

• Genetic profile:
  CGH- Multiple chromosome losses including 1, 4, 6, 8, 9, 13, 14, 15, and 22

Cytogenetic analysis of one high-grade tumor with sarcomatoid differentiation showed losses of chromosome 14 and 15, and gains of chromosomes 2, 5, 7, 9, 10, 12, 17, 19, 20, 22, and X
MTSCC Prognosis

- Indolent course
- Recurrence rare
- Metastasis to lymph nodes reported (even in tumor with typical bland morphology)
- Distant metastasis possible in tumors with high grade transformation
References:


21. WHO Classification of Tumours of the Urinary System and Male Genital Organs WHO/IARC Classification of Tumours, 4th Edition, Volume 8 Edited by Moch H, Humphrey PA, Ulbright TM, Reuter VE.
A very special thanks to my cytology fellows

• Dr Hongxia Sun
• Dr. Malek Alshaikhmohamed
• Dr. Melissa Hardin