RENAL CELL CANCER (RCC) WITH UNUSUAL PRESENTATION: A CASE STUDY

BY

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Introduction

- **Renal cell carcinoma (RCC)** is the commonest cancer in the kidney
- Accounts for 3% of all adult malignancies
- Notorious for:
  - Lack of early warning signs ***
  - Diverse clinical manifestations ***
- ~ 25% present with distance metastasis or advanced disease

(Atkins, 2009).
Importance of Topic

- PCPs responsibilities to improve outcome:
  - Early recognition of presentations ***
  - Early diagnosis
  - Well directed work-up
  - Adequate treatment/referrals
  - Screening high risk individuals

- Missing early clues = late diagnosis, morbidity, mortality, unnecessary health care cost.
Importance of Topic cont.

- This presentation will describe:
  - Case of RCC with an unusual presentation
  - Quick overview of RCC:
    - Epidemiology
    - risk factors
    - clinical presentations
    - differentials
    - diagnostic evaluations
    - management
    - screening
    - follow-up.
Case presentation

• **HPI:**
  - 64-year-old Caucasian female with RCC with unusual presentation. Patient noted lesion in between her teeth on the lower left mandible.
  - She went to dentist
  - Referred to oral surgeon
  - Mandibular gingival lesion excisional biopsy was performed 11/30/10
**Case presentation cont.**

- **Pathology** = clear cell carcinoma.

- Result sent to Baylor College of Dentistry for consultation

- Confirmed histologic features = clear cell carcinoma, highly suggestive of metastatic renal cell carcinoma *(unusual!!)*
CT abdomen 12/2/10 revealed: complex mass within right kidney involving mid to upper pole, measuring 5 x 6 cm in size transversely and 6-7 cm in length. No enlarged retroperitoneal lymph nodes.
MRI of the pelvis 12/2/10 = Multifocal lesions within the sacrum, iliac bone, and left femur most consistent with widespread metastatic disease. There was a soft tissue in the adnexal region probably the ovaries.
Case presentation cont.

- **Referred to surgeon** (Urologist)
- Open right **nephrectomy**
- **Pathology:**
  - Multifocal RCC, clear cell type, 5.8 cm greatest dimension (5.8 cm - mid upper pole and 0.8 cm - lower pole),
  - Fuhrman grade 3 of 4, focal extension into perinephric fat, extension into segmental renal vein, negative resection margins.
Case presentation cont.

Past medical History
Peripheral arterial disease (PAD)

Past Surgical History
Two back surgeries (any connection?)
Aortobifemoral bypass on 11/08/06.
Resection of mandibular gingival lesion on 11/30/10 (metastatic lesion)
Case presentation cont.

- Social History
- Married
- Five children
- Remote history of smoking cigarette (risk factor).
- Alcohol use - minimal (~ a glass of wine per month)
- No illicit drug use.
Case presentation cont.

- **Family History**
  - Father had lung cancer and had surgery. Father died of heart attack.
  - Maternal grandmother died of stomach cancer.
  
  (FH: some risk factor).

- **Health Maintenance:**
  - Never had a colonoscopy

  (wake up PCP!!)
Case presentation cont.

Allergies
- Demerol, Codeine, Penicillin, and Sulfa

Medications
- Aspirin
- Calcium citrate
- Furosemide
- Isosorbide mononitrate
- Levothyroxine
- Metoprolol tartrate
- Morphine
- Ramipril
- Simvastatin
- Spironolactone
- Vitamin D-3 with Aloe
Case presentation cont.

- **Review of Systems**
  - Notable for occasional mild nausea, constipation, and back pain
  - ** Negative genitourinary symptoms

- **Vitals**
  - Height=66in, Weight=173.2lb, BMI = 28.0 Temp=98.0, Pulse=71, Resp =16, BP 149/97
Case presentation cont.

• Physical Exam

• General: Well developed, well-nourished, anxious looking, no obvious respiratory distress.

• Abdomen revealed a well healed oblique scar located in the right flank.

• Oral exam reveals no notable lesion.
• **Laboratory Data**
  - Normal Complete blood count (CBC) with differentials
  - Normal Comprehensive metabolic panel (CMP)

• **Assessment**
  - Clear cell carcinoma of the kidney metastatic to gingiva and bone
  - Status post right radical nephrectomy and resection of mandibular gingival metastatic lesion.
Case presentation cont.

**Plan:**

- Patient was started on a cytokine plus VEGF inhibitor.
  
  - The cytokine is alpha-interferon subcutaneous injection 9 million units three times a week.
  
  - The VEGF inhibitor is Bevacizumab 15 mg/kg intravenous infusion over 1 hour every 2 weeks.
Pathophysiology

• The proximal renal tubular epithelium is the tissue of origin for renal cell carcinoma (RCC). RCC occurs in sporadic (nonhereditary) and hereditary forms.

• Both forms are associated with structural alterations of the short arm of chromosome 3 (3p).
• Genetic studies led to cloning of genes whose alteration results in tumor formation. These genes are either tumor suppressors (VHL, TSC) or oncogenes (MET) (Curti & Harris, 2011)
Molecular pathogenesis
Model for the oxygen sensor mechanism of erythropoiesis.

• Source: http://www.uptodate.com
4 hereditary syndromes associated with RCC:

- a. Von Hippel-Lindau (VHL) syndrome,
- b. Hereditary papillary renal carcinoma (HPRC),
- c. Familial renal oncocytoma (FRO) associated with Birt-Hogg-Dube syndrome (BHDS),
- d. Hereditary renal carcinoma (HRC) (Curti & Harris, 2011)
Hereditary syndromes

Von Hippel-Lindau syndrome

- autosomal dominant syndrome
- 40% of patients develop RCC
- RCC is major cause of death among VHL patients.
- Deletions of 3p occur commonly in RCC associated with VHL
- The \textit{VHL} (tumor suppressor) gene mutation (Curti & Harris, 2011)
• **Hereditary syndromes cont.**

• **Hereditary papillary renal carcinoma**
  inherited disorder with an autosomal dominant inheritance pattern

• **Familial renal oncocytoma** is characterized by development of bilateral, multifocal oncocytoma or oncocytic neoplasms in the kidney

(Curti & Harris, 2011)
• Hereditary syndromes

• **Birth-Hogg-Dube syndrome:** hereditary cutaneous syndrome with benign tumors of the hair follicle

• **Hereditary renal carcinoma:** an inherited medical condition characterized by an increased tendency to develop oncocytomas - benign kidney tumors with low malignant potential.

  (Curti & Harris, 2011)
### Epidemiology

- No significant difference between Whites and Blacks in USA
- **Mortality**
  - Survival rate increased from 34% (1954) to 69% (2002)
- **Gender:** men > women
- **Age:** Older > younger
  - median age ~ 64
- Uncommon in < age 40
- Rare rare in children
  
  (Atkins & Choeiri, 2011; Curti & Harris, 2011)
RISK FACTORS FOR RENAL CELL CANCER

- Smoking:
- Obesity
- Hypertension
- Exposure to toxic compounds
- Von Hippel-Lindau (VHL) disease
- Analgesic abuse nephropathy
- Acquired cystic disease
- Alcohol:
- Chronic hepatitis C
- Cytotoxic Chemotherapy
Clinical Presentations for RCC

- Occult
- Hematuria
- Abdominal or flank mass
- Scrotal Varicocele
- Symptoms associated with metastasis to brain, liver, bone, lymph nodes, and the lungs
- Inferior vena cava involvement
- Paraneoplastic syndromes: erythrocythosis and hypercalcemia
- Anemia
- Hepatic dysfunction
- Fever,
- Thrombocytosis

(Curti & Harris, 2011)
<table>
<thead>
<tr>
<th>Differential Diagnosis</th>
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<tbody>
<tr>
<td>• Abscess</td>
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<tr>
<td>• Angiomyolipoma (benign)</td>
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<tr>
<td>• Acute pyelonephritis</td>
</tr>
<tr>
<td>• Chronic Pyelonephritis</td>
</tr>
<tr>
<td>• Distant primary lesion metastasis</td>
</tr>
<tr>
<td>• Non-Hodgkin’s lymphoma</td>
</tr>
<tr>
<td>• Metastasis from melanoma</td>
</tr>
<tr>
<td>• Oncocytoma (benign)</td>
</tr>
<tr>
<td>• Renal adenoma (benign)</td>
</tr>
<tr>
<td>• Renal cyst</td>
</tr>
<tr>
<td>• Renal infarction</td>
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<tr>
<td>• Sarcoma</td>
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<td>• Wilms Tumor</td>
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(Curti & Harris, 2011)
DIAGNOSTIC EVALUATION

• **Recommended Tests**
  • CBC with differential
  • Urinalysis (UA)
  • Renal profile
  • Electrolytes
  • Liver function tests (LFTs)
  • Calcium
  • Erythrocyte sedimentation rate (ESR)
  • Prothrombin time (PT)
  • Activated partial thromboplastin time (aPTT) (Curti & Harris, 2011)
### Radiographic testing

- **Ultrasound** - less sensitive but is useful for distinguishing simple benign cysts from more complex cysts or solid tumor.

- **Abdominal and pelvic CT** – useful for patient with unexplained hematuria and other suspicious presentations.

(Atkins, 2009)
TISSUE DIAGNOSIS AND STAGING WORKUP

- Biopsy of metastatic sites
- Tissue also obtained for histology and treatment from Nephrectomy or partial nephrectomy

Metastatic work-up
- Abdominal CT
- Bone scan
- CT of the chest
- MRI
- Position-emission tomography (PET) scan

(Curti & Harris, 2011)
# Staging of RCC and 5-Year Survival Rates

<table>
<thead>
<tr>
<th>Description of Disease Extent</th>
<th>American Joint Committee on Cancer (AJCC) Equivalent</th>
<th>5-Year Survival (%)</th>
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</thead>
<tbody>
<tr>
<td>Confined to renal capsule</td>
<td>I</td>
<td>65 - 85</td>
</tr>
<tr>
<td>Equal or less than 7cm</td>
<td>II</td>
<td></td>
</tr>
<tr>
<td>More than 7cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extends through renal capsule</td>
<td>III</td>
<td>45 – 80</td>
</tr>
<tr>
<td>but not through Gerota’s fascia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal vein, inferior vena cava (IVC), or regional nodal involvement</td>
<td>III</td>
<td>15 – 50</td>
</tr>
<tr>
<td>Extends through Gerota’s fascia, more than 1 lymph node, or distant metastases</td>
<td>IV</td>
<td>0 - 10</td>
</tr>
</tbody>
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MANAGEMENT

- **Surgery**
  - For stages I, II, and III RCCs.
  - Partial nephrectomy, Radical nephrectomy
  - conventional approach or by laparoscopy

- **Active surveillance**
  - observation/periodic reevaluation e.g. elderly and those not candidates for surgery

- **Adjuvant therapy**: either immunotherapy or molecularly targeted agents
Management cont.

- **Adjuvant therapy** (post-op management)
  - **Cytokines**: interferon

- **Adjuvant/salvage** (for metastatic disease)
  - **Cytokines** (designed to boost patient’s immune system to fight the cancer cells, thus called immunotherapy)
    - a. Interferon (for stage III)
      - (Patient is treated by this)
    
  - or

    - b. Interlukin (if metastatic)
Management cont.

**Molecularly targeted Therapy**

**Action:**

- Designed to disrupt the signaling pathway through which the cancer supports and perpetuates itself.

- Cells have life spans which ends through programmed cell death (apoptosis). Cancer cells try making anti-apoptotic proteins.
Management cont.

- **Molecularly targeted Therapy examples.**

- Agents that disrupt vascular endothelial growth factor (VEGF) e.g Bevacizumab (*Patient is currently on this*)

- Agents that disrupt vascular endothelial growth factor receptor (VEGFR) - tyrosine kinase inhibitors (TKI) e.g sunitinib,

- Agents that disrupt mTOR e.g. temsirolimus
High risk individuals need periodic monitoring with ultrasound, MRI, CT

Examples:

- VHL syndrome
- end stage renal disease
- prior kidney irradiation
- strong family history of RCC

• **No recommendation** to screen asymptomatic individuals without risk for RCC

(Atkins, 2009).
**Long-Term Follow up and Monitoring**

- **Active surveillance**
- **Counseling** about active surveillance, frank discussion of cancer progression and limitations of treatments if metastasis occur.

(Curti & Harris, 2011)
• For Stage I and II RCC

Follow up Q 6 months x 2 years, then yearly x 5 years (complete history and physical exam, chest radiographs, LFTs, blood urea nitrogen [BUN], creatinine levels, and calcium levels)

(Curti & Harris, 2011)
• For metastatic disease
• Abdominal CT between 4th and 6th month after treatment, then prn
• Close observation prn for asymptomatic patients with metastatic disease
• CT scan/MRI recommended for surveillance in cases of end-stage renal disease
  (Curti & Harris, 2011)
**Discussion**

<table>
<thead>
<tr>
<th>What risk factors for RCC did this patient have?</th>
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<tr>
<td>How could patient’s risks be lowered by PCP?</td>
</tr>
<tr>
<td>How could the PCP have contributed to earlier diagnosis of patient’s disease?</td>
</tr>
<tr>
<td>Who needs to be screened for RCC?</td>
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</table>
References

References

  Lippincott Williams & Wilkins.