Renal Cell Carcinoma with Unusual Presentation: A Case Study

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Renal cell carcinoma (RCC) is the commonest type of kidney cancer accounting for about 90% of malignant kidney tumors and 3% of all adult malignancies, and amongst the most lethal of the urologic cancers (Curti & Harris, 2011; Newton, Hickey, & Marrs, 2009). Renal or kidney cancers have different histologic features, disease courses, and are caused by different genetic abnormalities (Linehan, Rini, & Yang, 2008). Of the kidney cancers 5% to 10% are transitional cell carcinoma; 5% to 6% are Wilms’ tumors (mainly found in children), and less than 1% are classified as renal sarcomas (Newton, Hickey, & Marrs, 2009). Two percent of renal cancers result from inherited syndromes (Newton, Hickey, & Marrs, 2009). About twenty to thirty percent of patients are diagnosed with metastases, and the most common metastatic sites are brain, bone, lung, liver and distant lymph nodes (Newton, Hickey, & Marrs, 2009).

**Subjective**

**Selection of Case**

This case of RCC was selected because of the unusual presentation of the disease and because of the need for advanced practice nurses to understand the risk factors and recognize early warning signs of RCC in order to diagnose RCC and make appropriate referrals for therapy, thus improving patient outcomes.

The prognosis for RCC is based on the grade and stage of the disease (Newton, Hickey, & Marrs, 2009). RCC can often be cured if it is diagnosed early in the disease process when the cancer is localized to the kidney and immediate surrounding tissue (Newton, Hickey, & Marrs, 2009). RCC has an overall 40% survival at 5 years following diagnosis. When diagnosed early when the disease is still confined to the kidney, the 5-year survival rate is about 90%; when
locally advanced, the survival rate is 60%; with distant metastases, the survival rate is 5% (Newton, Hickey, & Marrs, 2009).

The primary care provider has a responsibility in detecting early signs and symptoms, which will lead to early diagnosis, well-directed work-up of the disease, adequate referrals, and adequate treatment. Adequate screening of high risk individuals in the primary care setting will also accomplish early diagnosis and promote better outcomes among those who have RCC. Missing early signs and clues to the disease can lead to late diagnosis, increased morbidity, high mortality, and unnecessary health care costs.

This case study presents an overview of RCC with respect to epidemiology, risk factors, clinical presentations, differential diagnosis, and describes a case of RCC with an unusual presentation, the metastatic work-up/diagnostic evaluations, management, recommended follow-up and screening.

**History of Present Illness**

The patient in this case study is a 64-year-old very pleasant Caucasian female who presented in January 2011 in a Texas cancer center because she was referred to the oncologist for treatment of RCC with unusual presentation. The patient’s experience with the symptoms leading to the diagnosis of RCC began in the middle of November 2010, while in her usual state of good health. She reported a past medical history of peripheral arterial disease, hypothyroidism, hyperlipidemia, and hypertension. She did not have a past history of cancer or kidney disease. The patient reported that while she was brushing her teeth, she found a small, painless lesion in-between her teeth on the lower left mandible. She watched the lesion for a while and the lesion persisted without any significant changes in size or appearance for about
two weeks. She saw her dentist because she was concerned with the concern about this lesion, and the dentist referred her to an oral surgeon for evaluation.

On November 30, 2010, a mandibular gingival lesion excisional biopsy was performed by the oral surgeon. Pathology analysis revealed clear cell carcinoma. This pathology was sent to Baylor College of Dentistry for consultation by dental pathologist who reported that the histologic features are those of clear cell carcinoma, highly suggestive of metastatic renal cell carcinoma.

**Past Medical History**

The patient’s past medical history was significant for peripheral arterial disease (PAD), hypothyroidism, hyperlipidemia, and hypertension. There was no past history of cancer or renal symptoms.

**Past Surgical History**

The patient had a history of two back surgeries as an adult. She also reported having total hysterectomy in her middle 30s for excessive uterine bleeding. Patient also experienced aortobifemoral bypass in November 2006 for her PAD. She underwent surgery for resection of metastatic mandibular gingival lesion on November 30, 2011.

**Social History**

The patient is married and has five adult children, three daughters and two sons. The patient lives with her spouse. She reports quitting smoking more than 10 years ago after having smoked for more than 15 years. She reports minimal alcohol use; she drinks about a glass of wine once a month. She denies any illicit drug use.

**Family History**
The patient’s father had lung cancer and was treated with surgery. However, he died in his 60s of a heart attack. The patient’s maternal grandmother died of stomach cancer.

**Health Maintenance:**

She has never had a colonoscopy.

**Allergies**

Patient reports allergy to Demerol, Codeine, Penicillin, and Sulfa. She broke out in hives when she took these medications. The severity of allergy was worse with penicillin.

**Current Medications**

- Aspirin
- Calcium citrate
- Furosemide
- Isosorbide mononitrate
- Levothyroxine
- Metoprolol tartrate
- Morphine
- Ramipril
- Simvastatin
- Spironolactone
- Vitamin D-3 with aloe

**Review of Systems**
General. The patient has no weight loss, fatigue, loss of appetite, night sweats, fever, or chills.

Eyes. The patient reports no blurred vision and no double vision.

Ears. The patient has no report of ear pain, hearing loss, or ringing in ears.

Nose. The patient reports no nasal congestion, nasal drainage, or nose bleeding.

Mouth and Throat. The patient has no sore throat, problem with swallowing or hoarseness of voice. She has no soreness of mouth.

Cardiovascular. The patient has no chest pain, heart palpitations, light headedness, swelling in legs, or episodes of passing out.

Respiratory. The patient has no cough, sputum production, hemoptysis, and shortness of breath. She has no orthopnea or paroxysmal nocturnal dyspnea.

Gastrointestinal. The patient reports no vomiting, heartburn, diarrhea, abdominal pain, rectal bleeding, and bowel incontinence. She reports occasional nausea and constipation.

Genito-Urinary. The patient reports no burning on urination, pain with urination, blood in urine, frequent urination, and urinary incontinence.

Musculoskeletal. The patient reports no muscle pain, stiffness of muscles, joint pain, or joint swelling. She reported occasional low back pain.

Skin. Patient has no itching, rashes, or skin lesions.

Neurological. The patient has no headaches, seizures, dizziness, or loss of balance. She has no weakness of limbs, loss of sensation, tingling sensations, memory loss, or thinking difficulty.

Psychiatric. The patient has no problem of being nervous, depressed, or restless. She denies difficulty with sleeping.
Hematologic. The patient denies bruising or abnormal bleeding.

Lymphatic/Immunologic. She has no lumps in her armpits, neck, and groin.

Overview of RCC

Epidemiology

Although the incidence of RCC is lower in African countries, the difference in incidence between White populations and Blacks populations in United States is not significantly different (Atkins & Choeiri, 2011; Curti & Harris, 2011)

Mortality

Over the past 50 years, the survival rate following diagnosis of kidney cancer has increased from 34% in 1954 to 69% in 2002; however, the incidence of RCC has increased at three times rate the mortality rate (Atkins & Choeiri, 2011). Improved survival rates are attributed to earlier diagnosis and potential earlier surgical intervention (Atkins & Choeiri, 2011)

Gender. RCC occurs more in men than in women (Atkins & Choeiri, 2011; Curti & Harris, 2011)

Age. RCC occurs more in older ages and is most common during the 6th to 8th decades of life, with median age of around 64 years (Atkins & Choeiri, 2011; Curti & Harris, 2011). RCC is unusual with people who are below the age of 40 and rare in children (Atkins & Choeiri, 2011)

Risk Factors for RCC

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

Pathophysiology and Molecular Pathogenesis

The proximal renal tubular epithelium is the tissue of origin for renal cell carcinoma (RCC). RCC occurs in a sporadic (nonhereditary) and a hereditary form, and both forms are associated with structural alterations of the short arm of chromosome 3 (3p). Genetic studies of the families at high risk for developing renal cancer led to the cloning of genes whose alteration resulted in tumor formation (Curti & Harris, 2011).

The Von Hippel-Lindau (VHL) gene is located on chromosome 3p; its gene product, PVHL, functions as a tumor suppressor and is involved in cellular homeostasis by targeting several proteins for ubiquitination and proteosomal degradation, thereby, regulating their levels within the cell. One such protein regulated by PVHL is hypoxia inducible factor 1 alfa (HIF – 1 alfa), which is sensitive to oxygen tension and is a substrate for PVHL protein complex (Curti & Harris, 2011). Under normal oxygen tension (normoxia), HIF- I alfa is enzymatically hydroxylated, then bound by the PVHL protein complex, linked to ubiquitin, and then degraded by 26 S proteasome (Curti & Harris, 2011). Under hypoxic condition, hydroxylation does not occur and this leads to the accumulation of HIF-I alfa, which translocate to the nucleus promoting the transcription of growth stimulating genes such as vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF), transforming growth factor (TGF- alfa), and erythropoietin (EPO) (Curti & Harris, 2011).
Similarly in renal cell cancer with clear cell histology, VHL is lost or mutated causing HIF-I alfa to accumulate (Curti & Harris, 2011). This then translocates to the nucleus of the cell where HIF-I stimulates growth factor expression that promotes angiogenesis and tumor cell growth (Curti & Harris, 2011).

**Clinical Presentations for RCC**

**Occult.** RCC can present in a variety of ways. The disease could also remain clinically occult until the cancer has advanced (Atkins, 2009; Curti & Harris, 2011).

**The classic triad.** The most common presentations include hematuria, flank pain and a palpable flank or abdominal mass. These symptoms are the classic triad for diagnosis of renal cell carcinoma, but occur in only 10% of patients and in many cases indicate advanced disease (Curti & Harris, 2011).

Hematuria is a sign of tumor invasion of the collecting tubules, and the presence of clots indicates severe bleeding and “colicky” abdominal pain (Atkins, 2011)

Abdominal or flank masses tend to be nontender, firm, and homogenous. The mass moves with respiration and is easier to palpate in thin patients. The presence of a flank mass is associated with lower pole tumors (Atkins, 2009)

**Scrotal Varicocele. Men may have a scrotal varicocele which** fails to empty when the patient is recumbent (and usually left-sided). These findings should arouse suspicion for a renal tumor that has obstructed the gonadal vein where it enters the renal vein (Atkins, 2011)

**Symptoms associated with metastasis.** Patients with disseminated disease will experience variety of signs and symptoms due to metastases. The most common sites involved in metastases are the brain, liver, bone, lymph nodes, and the lungs (Atkins, 2011).
Inferior vena cava involvement. Clinical manifestations, including lower extremity edema, ascites, hepatic dysfunction, and pulmonary emboli are indications of inferior vena cava involvement (Atkins, 2011).

Paraneoplastic. These syndromes are rare but include erythrocythosis and hypercalcemia from overproduction of erythropoietin and parathyroid hormone–related peptide (rPTH) respectively (Atkins, 2011).

Anemia. The anemia associated with RCC may be severe and could be normocytic or microcytic (Atkins, 2011).

Hepatic dysfunction and other Symptoms. Hepatic dysfunction in the absence of liver metastasis (Stauffer syndrome) is indicated by elevated liver enzymes. Both fever and thrombocytosis can be found in patients with RCC (Curti & Harris, 2011).

Objective Data/Exam

Physical Examination

Vital Signs. Temperature 98.0, Pulse 71, Respiration 16, Blood pressure 149/97, Height 66in, Weight 173.2lb, and BMI 28.0.

General. The patient is Well developed, well-nourished, anxious looking but in no obvious respiratory distress. She appears her stated age.

Skin/Hair/Nails. She has no bruises, petechiae, rash, or any abnormal skin lesions.

Eyes. Her pupils are equal, round, and reacts to light and accommodation. Extra ocular muscles are intact; no jaundice or pallor noted. There is no redness or drainage in the conjunctivae.
**Ears.** Her ear canal is normal in caliber, no excessive cerumen, no drainage. Inspection reveals a normal tympanic membrane. Her hearing is grossly intact

**Nose.** Her external nose is unremarkable; she has normal teeth and gum. No tonsillar hypertrophy or exudates noted, and no pharyngeal erythema, exudates or mucosal lesions.

**Mouth and Throat.** No lesions in mouth and oropharyngeal region.

**Neck/Lymph.** Trachea is midline. No jugular vein distension or lymphadenopathy present. Thyroid is midline and not enlarged. Neck is supple.

**Chest/Lungs.** Lungs are clear to auscultation with no rales, rhonchi, or added sounds noted. Percussion and palpation of chest walls are normal.

**Cardiovascular.** She has no murmurs gallop or rub, S1 and S2 is normal with regular rate and rhythm.

**Gastrointestinal.** Abdomen is soft, non-distended, and without masses. There were no ascites present, no hepatosplenomegaly palpated, and no hernia present. Bowel sounds are present in all 4 quadrants. Right upper quadrant, epigastric region and left upper quadrant were "uncomfortable" to palpation

**GU.** No supra-pubic tenderness noted.

**Musculoskeletal.** Her dorsalis pedis pulses are normal. She has normal range of motion, muscle strength and stability in all extremities with no pain on palpation. She has normal gait and station

**Extremities.** She has no edema, cyanosis, digital clubbing, or discoloration.
Neurological. Her memory is intact. Her gait is steady. She has no hemiplegia or hemiparesis. Her cranial nerves are intact. There are no sensory or motor deficits present.

Psychological. The patient is oriented to time, place and situation. She has normal insight and exhibits normal judgment. The patient demonstrates the appropriate mood and affect.

Assessment

Patient’s Diagnosis

Clear cell carcinoma of the kidney metastatic to gingiva, status post resection of mandibular gingival metastatic lesion (ICD 9 code: 189.0)

Laboratory Data

Complete blood count (CBC) with differentials:

- WBC 9.4
- Hemoglobin 14.3
- Hematocrit 42.4
- MCV 88.2
- Platelets 229
- Neutrophils 62%
- Lymphocytes 26%
- Monocytes 10%
- Eosinophil 2%
- Basophils 1%

Comprehensive metabolic panel (CMP):

- Na+ 140
- CI- 104
- K+ 4.6
- C02 26
- Glucose 94
- BUN 17
- Creatinine 1.0
- Calcium 9.7
- Total Protein 7.2
- Albumin 4.5
- Total Bilirubin 1.4
- Alkaline phosphatase 47
- AST 14
- ALT 10
- LDH 129

**Differential Diagnoses**

- Abscess
- Angiomyolipoma (benign)
- Acute pyelonephritis
- Chronic Pyelonephritis
- Distant primary lesion metastasis
- Non-Hodgkin’s lymphoma
- Metastasis from melanoma
- Oncocytoma (benign)
- Renal adenoma (benign)
- Renal cyst
- Renal infarction
- Sarcoma
- Wilms Tumor

**Acute Diagnosis**

189.0 Renal cell carcinoma
724.2 Low back pain.
564.0 Constipation
787.02 Nausea

**Treatment Plan and Rational**

**Metastatic Work-up for RCC**

The metastatic work-up was initiated and included a computed tomography (CT) scan of the abdomen. The CT scan of the abdomen was done on December 2, 2010 and result revealed a complex mass within the right kidney involving the mid to upper pole, measuring at least 5 x 6 cm in size in the transverse plane and 6-7 cm in length. There were no enlarged retroperitoneal lymph nodes noted. The National Comprehensive Cancer Network (NCCN) version 2.2011 guidelines for kidney cancer recommend abdominal and pelvic CT, with and without contrast, for initial imaging workup of RCC cases (Atkins, 2009).

A Magnetic Resonance Imaging (MRI) of the pelvis was also done on the same day - December 2, 2010, and the results demonstrated multifocal lesions within the sacrum, iliac bone, and left femur, most consistent with widespread metastatic disease. The results of the MRI indicated soft tissue in the adnexal region probably the ovaries, although the patient thought that
she had her ovaries removed when she had hysterectomy in the past. The patient was not very sure however.

**Staging**

The stage of the disease is the most important prognostic factor for patients with RCC (Wood, 2009). The primary tumor, regional lymph node involvement, and distant metastasis is what the tumor, node, metastasis (TNM) staging system uses to assign a stage, which is correlated with prognosis (Wood, 2009).

<table>
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<tr>
<th>Staging of RCC and 5-Year Survival Rates</th>
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<tr>
<td>Description of Disease Extent</td>
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<tr>
<td>Confined to renal capsule Equal or less than 7cm</td>
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<tr>
<td>More than 7cm</td>
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<tr>
<td>Extends through renal capsule but not through Gerota’s fascia</td>
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<tr>
<td>Renal vein, inferior vena cava (IVC), or regional nodal involvement</td>
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<tr>
<td>Extends through Gerota’s fascia, more than 1 lymph node, or distant metastases</td>
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Plan/Management

Surgery:

Surgery is recommended for stages I, II, and III RCCs. The types of surgeries done for RCC include partial nephrectomy or radical nephrectomy depending on extent of disease; the surgical approach could be the conventional approach or by laparoscopy (Atkins, 2011).

The oncologist referred this patient to a surgeon (urologist) who performed an open right nephrectomy on Feb 14, 2011 (02/14/11). The pathology results from that surgery indicated the presence of a multifocal renal cell carcinoma, clear cell type, with the greatest tumor dimension being 5.8 cm; Fuhrman grade 3 of 4, focal extension into perinephric fat, tumor extension into segmental renal vein, and negative resection margins.

Treatment

The treatment of RCC requires use of cytokines and molecularly targeted therapy (Thompson, 2009). Cytokines are designed to boost patient’s immune system to fight the cancer cells, thus called immunotherapy e.g. interferon.

Two cytokines approved by FDA for treatment of RCC depending on the stage are:

a. Interferon (for stage III)

b. Interleukin (for metastatic disease or stage IV) (Thompson, 2009).

Molecularly targeted therapy are designed to disrupt the signaling pathway through which the cancer supports and perpetuates itself (Thompson, 2009). Examples of molecularly targeted therapy are:

- Agents that disrupt VEGF (VEGF inhibitor) e.g Bevacizumab
- Agents that disrupt the vascular endothelial growth factor receptor called tyrosine kinase inhibitors (TKI) e.g Sunitinib, Sorafenib, Pazopanib

- Agents that disrupt mammalian target of Rapamicin (mTOR) e.g. Temsirolimus (intravenously), Everilimus (orally)

The patient was started on a cytokine plus VEGF inhibitor and is currently being treated with Alpha-interferon (a cytokine) subcutaneous injection 9 million units three times a week and Bevacizumab (VEGF inhibitor), 15 mg/kg intravenous infusion over 1 hour every 2 weeks.

**Continuity of Care/ Follow-up**

**Long Term Follow up and Monitoring**

RCC patients with stage I and II RCC are followed up every 6 months for 2 years and then yearly for 5 years. The check-up should include a complete history, physical examination, chest radiographs, LFTs, blood urea nitrogen (BUN), creatinine levels, and calcium levels (Curti & Harris, 2011)

Abdominal CT is recommended once between the fourth and sixth month after treatment completion and then as indicated (Curti & Harris, 2011)

Close observation is recommended as indicated for asymptomatic patients with metastatic disease (Curti & Harris, 2011)

CT scan and MRI is recommended for surveillance in cases of patients with end-stage renal disease (Curti & Harris, 2011)

*Active surveillance* is recommended for localized renal masses and for those who are high risk for intervention (Curti & Harris, 2011).
For patients who are candidates for intervention, counseling about active surveillance should include frank discussion about risk of cancer progression and limitations of treatments if metastasis occurs (Curti & Harris, 2011).

**Screening**

Individuals at high risk for RCC such as those with inherited conditions associated with increased risk of RCC (e.g. VHL syndrome), end stage renal disease, prior kidney irradiation, and a strong family history of RCC need to undergo periodic monitoring with ultrasound, MRI and CT to detect early disease (Atkins, 2011). There is no recommendation to screen asymptomatic individuals with no risk for RCC (Atkins, 2011).
References


