Educational Case: Renal Cell and Urothelial Carcinoma

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.

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Primary Objective
UTK1.1 Renal Cell Carcinoma. Compare and contrast the 3 major types of renal cell carcinoma (clear cell, papillary, and chromophobe) in terms of clinical presentation, diagnostic morphologic features, and molecular pathogenesis.

Secondary Objectives
UTK1.2 Urothelial and Renal Cell Carcinoma. Compare and contrast pelvic urothelial malignancies with renal cell carcinomas in relation to risk factors, microscopic appearance, and biologic behavior.

Patient Presentation
A 63-year-old man presents with a chief complaint of intermittent “pink urine” over the preceding 2 months. He also describes chronic pain and discomfort of the left abdomen and flank area with no preceding trauma over the same time frame. He has no significant past medical history. The social history reveals a 42 pack-year history of cigarette smoking.

Diagnostic Findings, Part 1
Physical examination reveals a well-developed man in no acute distress. Vital signs are as follows: height 6 ft 0 in, weight 165 pounds, temperature 98.6°F, heart rate 65 beats per minute, respiratory rate 18 per minute, and blood pressure of 120/75 mm Hg. A 20-pound weight loss since his last office visit 2 years ago is noted, and the patient reports this is unintentional. On palpation of the abdomen, a deep-seated left flank mass is identified. The remaining examination is within normal limits.

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Question/Discussion Points, Part 1

What Is the Differential Diagnosis for a Flank Mass, and What Additional Testing Might Be Helpful?

The differential diagnosis for a flank mass includes a variety of benign and malignant entities, such as superficial lesions including lipoma, hematoma, and epidermal inclusion cyst; however, the deep-seated nature of the lesion on examination makes these considerations unlikely. A deep soft tissue tumor or a variety of renal lesions could produce a deep-seated flank mass such as a lipoma, various sarcomas, renal cyst, angiomylipoma, oncocytoma, lymphoma, infection (pyelonephritis or abscess), renal cell carcinoma (RCC), or urothelial carcinoma (UC). The pink urine suggests an intrinsic renal tract process; however, a soft tissue tumor invading the kidney could also produce hematuria.

Diagnostic Findings, Part 2

An in-office dipstick confirms hematuria, and a computed tomography (CT) scan is performed to better evaluate the flank mass. The CT revealed an 8-cm enhancing mass of the left kidney, and the patient is referred to a urologic surgeon who recommended and performed a radical nephrectomy. The gross and microscopic pathology findings are shown (Figures 1 and 2).

Questions/Discussion Points, Part 2

Describe the Gross and Histologic Findings, Based on This What Is the Most Likely Diagnosis?

The gross tumor cut surface appears solid and is bright golden yellow. Areas of hemorrhage, necrosis, and fibrosis appear red, brown, and white-gray, respectively. The tumor grossly distends and pushes the native renal capsule, but the invasion of the renal capsule or perinephric fat is not seen. A fibrous pseudocapsule typically separates the tumor from native kidney.

Microscopic sections show a background of delicate thin-walled vascularized stroma interspersed with epithelial cells with well-defined cell membranes and clear cytoplasm. The cytoplasmic clearing is due to intracellular accumulation of cholesterol, phospholipids, and neutral lipids which are dissolved by the organic solvents used during tissue processing. The intracellular lipid accumulation in tumor cells is responsible for the bright golden yellow color on gross examination.

What Is the Classic Clinical Presentation of Renal Cell Carcinoma?

Classic presenting symptoms for RCC include hematuria, flank or abdominal pain, and a flank or abdominal mass. Other symptoms that may occur are fever, weight loss, anemia, and left-sided varicocele. However, most RCCs are found incidentally when a patient receives a radiograph for another reason. Para-neoplastic syndromes including erythrocytosis, hypercalcemia, Stauffer syndrome (absence of liver metastasis, hypoalbuminemia, hypergammaglobulinemia, high alkaline phosphatase, prolonged prothrombin time, and reversal on removing the tumor), and acquired dysfibrinogenemia also have been associated and been the presenting symptoms in certain cases.

What Are the 3 Subtypes of Renal Cell Carcinoma? What Are the Typical Gross and Histologic Features of Each Type?

The major histologic subtypes of RCC in order of frequency include ccRCC (70%-80%), papillary RCC (pRCC, ~10%-15%), and chromophobe RCC (chRCC, ~5%). Histologically, ccRCC (Figure 2) cells have clear cytoplasm and well-visualized...
cell membranes. They can develop from any portion of the kidney but usually arise from the proximal tubule epithelium. They are often unifocal. Grossly, ccRCCs appear bright yellow due to the high concentration of lipid in the cells, and when large expand and distort the normal renal outline.

Histology of pRCC (Figures 3) shows papillary formations of cuboidal or low columnar cells. Foam cells are often present in the interstitium of the papillary cores and can sometimes be more apparent than the epithelial component (Figure 4). These carcinomas arise from the distal convoluted tubule epithelium. They are more likely to be multifocal and bilateral when compared to other RCC subtypes.

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What Is the Prognostic Significance of Renal Cell Carcinoma Histologic Subtypes?

Studies have shown that the histologic subtypes of RCC have an important prognostic impact. In one large study including 2357 cases of these 3 main RCC subtypes, cancer-specific survival rates at 5 years were 68.9% for ccRCC, 87.4% for...
pRCC, and 86.7% for chRCC. The difference was independent of nuclear grade and stage on further stratification.5

**How Is Renal Cell Carcinoma Graded?**

The grading system used for RCC is the World Health Organization/International Society of Urologic Pathology system based on nucleolar prominence. The histologic features are grade 1 with inconspicuous or absent nucleoli, grade 2 with nucleoli apparent at ×400 (×40 objective), grade 3 with nucleoli conspicuous at ×100 (×10 objective), and grade 4 with extreme pleomorphism, rhabdoid, or sarcomatoid differentiation.

**What Is the Molecular Basis of the 3 Major Renal Cell Carcinoma Subtypes?**

Molecular alterations associated with ccRCC include 3p chromosome deletions involving the von Hippel-Lindau (VHL) gene. These deletions can be hereditary (~5%); however, most are sporadic (95%). Inactivation of VHL in ccRCC is typically from a combination of allelic deletion and mutation, or allelic deletion and hypermethylation (less common). The VHL gene encodes a tumor suppressor protein, part of a ubiquitin ligase complex. This complex regulates transcription of hypoxia-inducible factor 1 (HIF-1). The concentration of HIF-1 remains high and cell growth is stimulated, in part due to increased expression of angiogenesis-promoting proteins such as VEGF.2 Other genes involved are PBRM1, SETD2, and BAP1. All are involved in chromatin remodeling or histone methylation. BAP1 mutations are associated with a shorter survival in RCC.3

Tumors of pRCC show common chromosomal copy number abnormalities, such as loss of Y and trisomy of chromosome 7 and 17. Associated mutations can also be hereditary or sporadic. The most common sporadic mutation in MET, a tyrosine kinase receptor for hepatocyte growth factor, is implicated in type 1 pRCC. NFR2-antioxidant response element changes are implicated in type 2 pRCC.2,3 Genetic changes in chRCC include one copy loss of chromosomes (1, 2, 6, 10, 13, 17, and 21) in about 81% of cases resulting in hypodiploidy. Mutations in TP53 and PTEN account for the most common single-gene alterations in chRCC.2,3

**What Are the Familial Forms of Renal Cell Carcinoma?**

A variety of inherited susceptibilities to RCC exist. Familial ccRCC is associated with VHL disease as well as chromosome 3 translocations, PTEN hamartomatous syndrome, mutations in BAP1, or the succinate dehydrogenase complex (SDHB/C/D). Familial type 1 pRCC is seen in association with germ line MET mutations, while type 2 pRCC as part of the hereditary leiomyomatosis and renal cell cancer due to mutations of FH. In addition, patients with Birt-Hogg-Dubé cancer susceptibility syndrome, due to germ line FLCN mutations, are at increased risk of renal cell neoplasia in which 70% are of the chromophobe, oncocytoma, or combined chromophobe–oncocytoma histology.6

**What Are the Gross Features of Urothelial Carcinoma of the Kidney, and How Are They Different From Renal Cell Carcinoma?**

The tumor (Figure 7) is a papillary white mass filling and distending the superior calyx. In contrast to RCC which arises in the renal parenchyma, UC arises in the collecting system. Urothelial carcinoma is commonly multifocal, and small foci are present in the inferior calyx and renal pelvis in addition to the main lesion (Figure 7). Luminal blood is apparent in the larger mass in the superior calyx, correlating with the more common presentation of hematuria in UC as compared to RCC. The tumor appears to have grown into the adjacent renal parenchyma as a pale white area replacing portions of the adjacent superior cortex. Unlike RCC, which is centered in the renal parenchyma, UC is centered in the collecting system calyces and renal pelvis. Urothelial carcinoma also lacks the characteristic yellow color of the most common ccRCC and can show
What Is the Histology of Urothelial Carcinoma, and How It Is Distinguished From Renal Cell Carcinoma?

Stained sections (Figures 8-10) show a papillary exophytic growth of cells arising within the urothelium of the collecting system, filling and dilating the lumen. Within the solid tumor nodule (Figure 8), well-formed fibrovascular cores can be seen which define the papillary growth. The individual cells (Figure 10) show an increased nucleus to cytoplasmic ratio. Furthermore, the hyperchromatic nuclei are pleomorphic with prominent nucleoli. The lack of cytoplasmic clearing or distinct granularity helps distinguish UC from the ccRCC (Figure 2) and chRCC (Figure 5), respectively. The papillary UC has many layers of cells surrounding the fibrovascular core, while the pRCC (Figure 3) typically has a single layer and possibly ribbon-like growth not seen in UC. 

How Do Risk Factors for Renal Pelvis Urothelial Carcinoma Differ From Risk Factors for Renal Cell Carcinoma?

Risk factors for RCC include being male, smoking, and obesity. Risk factors for UC are being male, smoking, and toxic exposures to aromatic amines. These include benzidine and beta-naphthylamine, polycyclic aromatic hydrocarbons, and combustion products. Exposure to certain chemicals used to produce rubber, leather, and paint has also been associated with UC. There are different genetic risk factors between RCC and UC. Lynch syndrome, involving errors in mismatch DNA repair, is commonly associated with urothelial cancer, particularly of the upper collecting tract, but is not associated with RCC. Finally, exposure to aristolochic acid, used frequently in traditional Chinese medicine, has been identified as a risk factor for upper urothelial tract carcinoma.

What Is the Biologic Behavior of Urothelial Carcinoma? How Does It Differ From Renal Cell Carcinoma?

Urothelial carcinoma can manifest as two different clinical phenotypes. The first is a low-grade papillary tumor that recurs but does not commonly metastasize, and the second is a high-grade tumor that leads to metastatic disease after early invasion. There are common chromosomal abnormalities associated with both of these UC clinical presentations which include loss of 9q and 9p chromosome portions, consistent with an early event in tumorigenesis. The low-grade subtype has been linked to the activation of FGFR3 altering the RAS/RAF pathway. The high-grade type is characterized by mutations in TP53, RB1, and CDH1 as well as increased VEF2. As mentioned previously, Lynch syndrome is also implicated in upper urothelial tract carcinomas due to mutations in MLH1, MSH2, and MSH6, which are not typical of RCC. Because UC arises in the collecting system, hematuria is a more common...
presentation than in RCC. Also, shed tumor cells are more likely to be recognized on urine cytology, which may assist in the diagnosis.

Diagnostic Findings, Part 3

The patient returns 5 years later for a cough and hemoptysis. A peripheral 2 cm pulmonary nodule is found. Positron emission tomography scan shows mild hypermetabolism in the nodule, but no other foci of abnormal uptake. The nodule is surgically removed with a laparoscopic approach (Figure 11).

Questions/Discussion Points, Part 3
Describe the Histologic Findings in the Lung Nodule. What Is the Diagnosis and How Does This Impact the Patient Stage?

The histology of the nodule is a clear cell carcinoma and is essentially the same as that of the primary tumor in the kidney (Figure 2). This is diagnostic of metastatic RCC. Renal cell carcinoma is pathologically staged using the tumor, node, metastasis (TNM) system. Pathologic tumor stage 1 is 7 cm or less and confined to the kidney, while a stage 2 tumor is greater than 7 cm and confined to the kidney. A stage 3 tumor extends beyond the kidney into major veins or perinephric fat but is contained within Gerota’s fascia. A stage 4 tumor extends beyond Gerota’s fascia or involves the ipsilateral adrenal gland. Stage groups I and II are pT1 and pT2 without regional node involvement and no distant metastasis. Stage group III is pT3 N0 or pT1-3 N1, and stage group 4 is pT4 with any N or any tumor with distant metastasis (M1). Survival is impacted as localized disease patients have a 93% 5-year survival, while with regional involvement and distant disease the 5-year survival falls to 70% and 12%, respectively. Thus, the patient’s lung metastasis, which qualifies as distant disease, significantly impacts his prognosis.4

Teaching Points
Renal Cell Carcinoma
- Clear cell renal cell carcinoma is the most common subtype (70% of cases), followed by pRCC (10%) and chRCC (5%).
- Clear cell renal cell carcinoma is characterized by clear cytoplasm, pRCC shows papillary growth and eosinophilic cytoplasm, and chRCC shows eosinophilic granular cytoplasm with perinuclear clearing.
- Histologic type of RCC is an important prognostic factor, with clear cell type having a worse prognosis than papillary or chromophobe types, even when stratified by stage.
- Most cases of RCC are sporadic (95%), but familial forms occur.
- Smoking and obesity are the major risk factors for RCC.
- Familial clear cell renal cell carcinoma is associated with VHL syndrome, an autosomal dominant disorder.
- Familial chRCC is associated with Birt-Hogg-Dubé syndrome, a rare autosomal dominant genetic disorder.
- The classic triad for the presentation of RCC is hematuria, palpable mass, and flank pain, with hematuria the most common of the 3 features. However, the 3 symptoms rarely occur together, and most cases are discovered during imaging for unrelated reasons.
- Stage is an important factor for the prognosis of patients with RCC.

Urothelial Carcinoma
- Urothelial carcinoma is the most common urinary tract malignant tumor and arises from the urothelial lining of the upper (renal calyx, renal pelvis, ureter) and lower (bladder or urethra) urinary tract.
- Upper and lower tract UCs are histologically similar.
- Cigarette smoke is a major risk factor, and additional risk factors include chemical exposures (napthylamine, azo dyes, and extended cyclophosphamide or phenacetin use).
- The most common presentation is painless hematuria in older adults.
- There are two distinct pathways in which urothelial tumors arise.
- Flat tumors develop as a high-grade carcinoma in situ with subsequent invasion. The genetic cause is early p53 mutations.
- Exophytic papillary tumors develop as a low-grade tumor, which then becomes a high-grade tumor with subsequent invasion. This pathway is not associated with early p53 mutations.
- Renal pelvis UC is often multifocal, recurs frequently, and may be associated with Lynch syndrome.

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