Acquired Cystic Disease-Associated Renal Cell Carcinoma Arising in a Patient After Fifteen Years of Hemodialysis

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Introduction

Acquired cystic disease-associated renal cell carcinoma (ACD- RCC) was recently recognized by the World Health Organization (WHO) as a subtype of renal cell carcinoma (RCC) occurring exclusively in acquired cystic kidney disease (ACKD). ACD-RCC is the most common RCC subtype developing in ACKD. ACKD occurs in 80% of patients with end stage renal disease (ESRD) after 10 to 20 years of hemodialysis. The risk of developing ACD-RCC is directly proportional to length of dialysis, ranging from 1.8% to 8%. ACD-RCC develops from proximal renal tubule epithelial cells, and several hypotheses regarding the etiology and pathogenesis of ACKD and ACD-RCC have been developed. Studies have concluded that uremia, an altered renal chemical microenvironment, and oxidative stress present in ESRD may play a role in the development of ACKD and carcinoma. The proto-oncogene c-Jun and tumorigenesis contributors c-MET receptor tyrosine kinase (c-MET) and its ligand, hepatocyte growth factor (HGF), have been detected in ACKD and ACD-RCC, respectively. ACD-RCC is most commonly incidentally detected as a small, low stage mass during imaging or gross examination of a nephrectomy specimen for other indications. If symptomatic, it is most common for patients to report flank pain and hematuria.

Patient Case

The patient presented as a 71-year-old male with a history of ESRD due to hypertension, 15 years of hemodialysis, prostate cancer, and left colon polyp carcinoma. The patient presented to the emergency department anuric with gross hematuria lasting one month, but denied dysuria, hematuria, pain, fever, chills, nausea, vomiting, and a CT scan revealed multiple, bilateral renal cysts. This and the patient’s history of ESRD and dialysis are compatible with ACKD. A right retrograde pyelogram indicated a displaced collecting system, likely due to renal cysts. The patient underwent an elective right nephrectomy.

Materials and Methods

The grossing procedure followed by the pathologist’s assistant was in accordance with the College of American Pathologists (CAP) Protocol of Macroscopic Examination Guidelines for the Examination of Specimens from Patients with Invasive Carcinoma of Renal Tubular Origin, with the following not included:8,9

- Presence of Gerota’s fascia
- Three-dimensional kidney size without perirenal fat, length, and diameter of the renal artery and vein
- Measurements to the renal sinus, renal vein, arterial, and arterial margins
- Sections of renal sinus fat

Formalin fixed, paraffin embedded sections of tumor nodules were stained with CK7, CD10, CD10, and racemase (p504s) immunostains to determine the subtype(s) of RCC present. All slides were stained with hematoxylin and eosin (H&E). Slides were examined with light and polarizing microscopy to assess cellular morphology and calcium oxalate crystal presence.

Results

Microscopic Examination

The 455 gram, 15.0 x 8.5 x 7.0 cm right radical nephrectomy consisted of attached perinephric fat, kidney, renal vein, renal artery, one accessory vessel, and 2.0 x 0.5 cm uter. The specimen surface appeared markedly cystic with several disrupted areas. The specimen was bisected to reveal multiple smooth-walled cysts occupying the entire renal parenchyma, consistent with ACKD. Papillary smooth-walled cysts of the renal cortex were not identified. The cysts contained serosanguinous fluid, gelatinous material, and clotted blood. Three small, thick-walled nodules were confined within the kidney parenchyma. 1.2 x 0.8 x 0.8 cm and 0.8 x 0.8 x 0.7 cm tan, firm nodules located in the superior pole and central kidney, respectively. 0.8 x 0.4 x 0.2 cm golden yellow and dark brown nodule located in the inferior pole. Invasion of the renal artery, renal vein, and perinephric fat was not grossly identified. Macroscopic images were not available for this case, see Image 1.

Microscopic Examination

H&E stained sections of the superior pole nodule exhibited tumor cells with eosinophilic cytoplasm with the most distinct borders and uniform nuclei, consistent with an oncocyteoma. The remaining two nodules exhibited papillary, micropapillary, solid, or mixed solid tubular morphologic features, see Image 2. Tumor cells with moderate to abundant eosinophilic cytoplasm and Fuhrman Nuclear Grade 3 nuclei were present, see Image 2B. The nodules stained strongly and diffusely positive for CD10 and racemase (p504s) and scattered positive for CK7, see Image 2C. Intratumoral calcium oxalate crystals were identified with polarizing microscopy, see Image 2D. The morphology and IHC are consistent with ACD-RCC. The kidney parenchyma exhibited cystic structures and glomerulosclerosis, consistent with ESRD and ACKD. All three tumor nodules were microscopically confirmed as confined to the kidney without sarcomatoid features, margin involvement, tumor necrosis, or lymphovascular invasion. The ACD-RCC was staged as ptT1b, pNx, pM0.

Discussion

Microscopic & Morphologic Morphology: ACD-RCC nephrocytic specimens are atrophic or normal in size with the renal cortex and medulla obliterated by multiple, small, sporadic cysts. ACD-RCC is solitary or multifocal and typically around 5.0 cm in greatest dimension, well-circumscribed, firm, and arising within a cyst. The cut surface is yellow-white, white, or brown and may demonstrate focal hemorrhage or necrosis. Cystids may exhibit papillary changes. Microscopic tumor architecture can be papillary, tubulolymphatic, microacinar, cystic, solid, or cribriform; papillary and tubulolymphatic being most common. The tumor cells are large with granular eosinophilic cytoplasm, ill-defined membrane borders, and Fuhrman Nuclear Grade 3 nuclei.2,7,9,10 Polarity, birefringent intratumoral calcium oxalate crystals are extracellular within the tumor and kidney parenchyma. Intratumoral calcium oxalate deposition is exclusive to ACD-RCC but is not always present, thus, it is not pathognomonic.2,10

Ancillary Testing: ACD-RCC tumor cells exhibit a unique immunophenotype.27 Positive immunohistochemistry (IHC) results for CD10, renal cell carcinoma marker, and racemase (p504s) prove a proximal renal tubule phenotype.2,7,10 In this case, CD10, CK7, and racemase (p504s) confirmed the diagnosis of ACD-RCC. The use of IHC as a diagnostic tool for ACD-RCC is limited as the immunophenotype is not definitively known; however, IHC is useful for differentiation from clear cell renal cell carcinoma (CCRC). ACD-RCC commonly exhibits gains of chromosomes 3, 7, and 16.52 Chromosomal losses are less common, but may occur with chromosomes 2, 3, 16, and Y. Molecular studies can be used to rule out papillary renal cell carcinoma (PRCC), as PRCC will exhibit a gain of chromosome 14 and no loss of chromosomes 3 and X.

Staging, Prognosis, & Treatment: ACD-RCC staging falls under the American Joint Committee on Cancer (AJCC) kidney cancer staging system in the eighth edition of the AJCC Cancer Staging Manual. Staging depends on tumor size, extent of invasion, extension into vascular, regional lymph node metastasis, and distant metastasis. The bone, liver, lung, brain, adrenal glands, and distant lymph nodes are common metastatic sites. Renal vein extension is a concern when evaluating RCC, as inferior vena cava and right atrium involvement may occur. Compared to sporadic RCC, ACD-RCC is less aggressive with a good prognosis.27,40,41 Surgical differentiation and histological characteristics indicate a more aggressive cancer and poorer prognosis.1,2,42 The RCC five-year survival rate is 70% with metastases, 80% with no metastases, and 60% with perinephric fat invasion. ACD-RCC tumors are discovered at a lower stage and grade due to ESRD patient management. First-line treatment is partial or total nephrectomy. Radiographic surveillance of high risk ESRD patients has been suggested to diagnose ACD-RCC at an early stage.

Future Implications

An important avenue of research for future treatment is the carcinogenesis of ACD-RCC.27 Once understood, targeted therapy can be more effectively utilized.27 Pten and c-MET are IHC positive in ACD-RCC and are promising prospects for targeted therapy. In addition, increasing the understanding of the immunophenotype of ACD-RCC will assist in the differentiation from CCRC and PRCC with the use of IHC. Further research into these aspects of ACD-RCC will improve diagnosis and treatment of the disease.

Acknowledgments

The author would like to extend her appreciation to Dr. Dongping Shi and Dr. Eman Abdultaha for their contributions. Their help in acquiring the patient case and microphotographs as well as interpretation of the clinical data is greatly appreciated.