Clear cell renal cell carcinoma with osseous metaplasia: a case report

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Introduction: *Osseous metaplasia is a rare histologic feature not often associated with renal cell carcinoma; there are only 14 reported cases and just four associated with the clear cell variant. We report the case of a 48-year-old female who presented with diffuse abdominal pain.*
Materials and methods: *We reviewed the case of woman who underwent a robotic assisted partial nephrectomy for an enhancing renal mass. Histologic analyses and immunostains were reviewed by multiple pathologists.*
Results: *CT imaging revealed a 1.8 cm irregular enhancing exophytic mass with calcifications. The patient subsequently underwent robotic assisted laparoscopic partial nephrectomy. The final pathologic diagnosis was clear cell carcinoma with metaplastic bone formation.*
Conclusion: *While the prognostic significance of bone metaplasia occurrence in renal cell carcinoma is controversial, such that can safely be managed with partial nephrectomy.*

Key Words: dystrophic calcification, osseous metaplasia, clear cell carcinoma

Background

Renal cell carcinoma (RCC) originates in the renal cortex and accounts for 2% of all human malignancies. The clear cell form represents the most common histologic subtype, with a frequency ranging from 65% to 80% in adult renal neoplasms.[1,2] Microscopically, the clear cell type is composed of cells with clearly defined borders, small nuclei and abundant cytoplasm set in a delicate vasculature. Macroscopically, however, hemorrhage, necrosis, fibrosis, hyalinization, cystic changes, and calcification all contribute to the mottled appearance of RCC.[3]

In 1905, Albrecht reported the first case of calcified RCC.[4] Since then, radiographic evidence and histologic confirmation of calcifications have been described in association with numerous renal neoplasms, including RCCs, oncocytomas, metanephric adenomas, simple cysts and dermoid cysts.[5]

Radiographically calcified renal masses in adolescents are of utmost concern for renal cell carcinoma.[6] Calcification is seen on computed tomography (CT) in 33% of pediatric RCC cases versus 5%-10% in adults.[7,8] Calcified masses have also been reported in vascular, infectious and cystic masses as well as Wilm's tumors, mixed epithelial stromal tumors (MEST), neuroblastomas, and sarcomas.[9,10] The distribution of calcium within a mass – central, circumferential, curvilinear, stippled - does not have predictive oncologic value.[11] Likewise, uniform, radiographic calcification in a mass does not necessarily imply ossification, as homogeneously calcified fluid filled cysts have also been reported.[12]

Dystrophic calcification is an inflammatory or ischemic event that can cause degenerative or necrotic material to accumulate in tissue in quantities that exceed the capability of macrophage elimination. The process of calcification has two major phases:

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initiation and propagation. These may occur either intracellularly or extracellularly.[13] In the context of RCC, calcification is believed to occur extracellularly, where matrix vesicles containing pyrophosphates and ATPases are derived from degenerating cortical cells. It has been suggested that calcium permeates and collects in theses vesicles when calcium ions bind to phosphate groups; a cycle of binding is repeated, producing a deposit near the membrane. In rare cases, such calcium foci are transformed into bone.

Case report

A 48-year-old female initially presented to her primary care physician's office after 2 days of severe, diffuse abdominal pain. She denied any recent history of fever, dysuria, hematuria, urgency, vaginal symptoms, or bowel problems. Her only medications included ferrous sulfate for a history of mild anemia, and NSAIDs for joint pains. Her medical history was significant for an episode of thrombophlebitis at the age of 18, and a surgical history of tubal ligation, cesarean section, and arthroscopic surgery on her right knee.

At the time of initial urologic evaluation, physical exam revealed a benign soft, non-tender abdomen, without masses, hernias, or bruits. Despite her recent complaints of abdominal pain, bowel sounds were present and active, and pain was not reproducible on exam. No rebound or guarding was elicited. There were no appreciated flank masses and she was without costovertebral angle tenderness. The patient had an unremarkable comprehensive metabolic panel, notable only for a creatinine of 1.13 mg/dL. Urinalysis was negative and without hematuria.

CT of the abdomen with contrast was subsequently performed and showed a peripherally calcified low density mass in the inferior pole of the right kidney, with evidence suggesting either enhancing septations or fine calcification within the mass, Figure 1. The exophytic calcified lesion seen on CT of the lower pole of the right kidney was not visible sonographically. An MRI was obtained to confirm CT findings.

MRI of the kidneys with and without contrast demonstrated a 1.5 cm x 1.8 cm heterogeneous mass extending from the inferior pole of the right kidney. The mass demonstrated mild enhancement, suspicious for a solid tumor. Treatment options were discussed with the patient, including watchful waiting and partial nephrectomy. A robotic assisted laparoscopic partial nephrectomy was recommended and subsequently performed.

Intraoperatively, the kidney was mobilized laparoscopically and the tumor was easily identified off

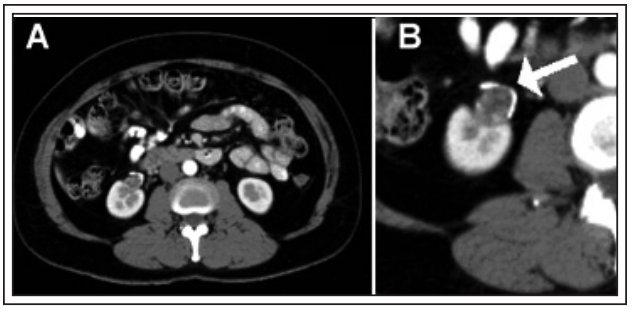

Figure 1. CT scan performed with contrast demonstrating a 1.8 cm irregular exophytic enhancing mass with calcifications. (B) Enlarged image of renal mass showing peripheral enhancement consistent with calcification (arrow).

the inferior pole of the right kidney. One major renal artery and one renal vein were identified entering the kidney. Internally, the gross appearance of the tumor revealed a sharply demarcated edge arising from its inferior border, Figure 2. Intraoperative ultrasound was used to define the tumor margins. The da Vinci robot

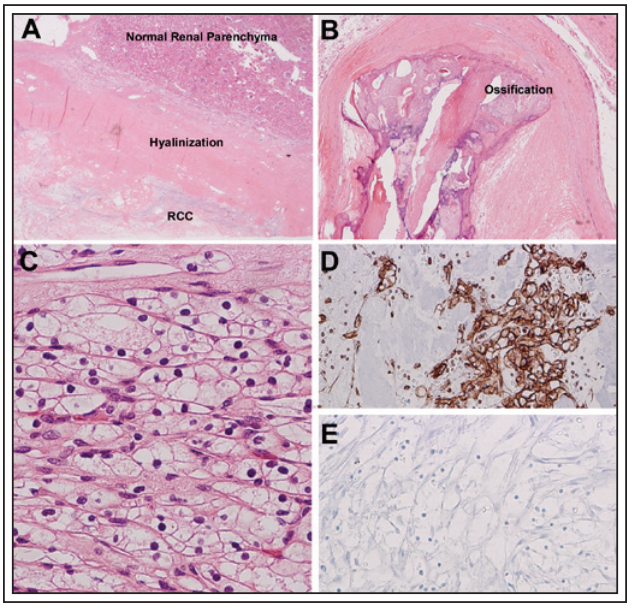

Figure 2. (A) H&E stain of the submitted tumor demonstrating normal kidney tissue, hylanization and a focus of renal cell carcinoma. (B) A different H&E section demonstrating areas of ossification within the tumor. (C) Higher power magnification (60x) demonstrating Furhman grade II, clear cell phenotype. The tumor cells contain irregular nuclei and abundant clear cytoplasm. Immunohistochemistry demonstrates positive vimentin staining (D) and negative Ki-67 staining (E).

(Intuitive Surgical, Inc., Sunnyvale, CA) using a 3 arm technique was used to excise the tumor after the hilum was clamped as previously discussed.[14] Additional deep margins were sent for frozen analysis and confirmed negative. The warm ischemia time was approximately 20 minutes, with an estimated blood loss of 100 cc. The patient subsequently underwent a 2 day uncomplicated hospital course. She has been followed for over 6 months and remains disease/recurrence free.

Histologic analyses were reviewed and agreed upon by multiple pathologists. The submitted pathologic specimen weighed 18 g, and the nodule measured 3.2 cm x 2 cm x 0.5 cm. The nodule appeared calcified. Surgical margins were determined to be grossly free of disease. Serial sections revealed a 1.5 cm x 1.5 cm x 1.5 cm partially cystic tan mass with a calcified rim that abutted adipose tissue. The mass was 0.5 cm away from the renal parenchyma resection margin. The central portion of the mass contained an orange well-circumscribed 0.4 cm nodule.

The tumor was reviewed by a pathologist and determined to be a renal cell carcinoma, Fuhrman grade II of IV associated with extensive areas of hyalinization and focal metaplastic bone formation.

Hematoxylin and eosin stain demonstrated a stratum of normal kidney parenchyma, hyalinization, and foci of renal cell carcinoma, Figure 2. Tumor cells contained slightly irregular nuclei with small nucleoli and abundant pink to clear cytoplasm. Immunohistochemical stains were performed to further characterize the neoplastic cells. The tumor cells stained positive with cytokeratin cocktail (AE1/AE3), vimentin, and CAIX and negative for CD10 and EMA. Further evaluation for proliferating cells using a monoclonal antibody against Ki-67 protein was negative. Positive immunohistochemical staining with both cytokeratin and vimentin together with hematoxylin eosin staining findings of foci of hyalinization, ossification, and clear cell RCC with no significant atypia or mitotic activity support the diagnosis of RCC with osseous metaplasia.

Discussion

Calcifications are present in a variety of renal lesions and are typically considered dystrophic, associated with normal calcemia. The differential diagnosis of a calcified renal mass includes RCC, cystic disease, MEST, xanthogranulomatous pyelonephritis, Wilm's tumor, neuroblastoma, transitional cell carcinoma, osteosarcoma, abscess, schistosomiasis, tuberculosis, hematoma, arteriovenous fistula and arteriovenous malformation.[10] In a 10 year study at the Mayo Clinic,[15] 111 of 2709 renal masses were calcified for an overall incidence of 4.1%. Of 560 RCC, 58 contained focal calcification (10.3%) and nearly 31% of RCCs demonstrate calcification on CT.[16] It has been estimated that approximately 20% of all calcified renal masses are malignant tumors. These tumors generally represent a low pathologic stage and slow growth.[11] The overall 5 year survival rate of 77% in patients with calcified RCC compares favorably with the national 5 year survival rate of 35% for all surgically resected RCCs.[17]

Renal cell carcinoma with osseous metaplasia has rarely been reported. In fact, after performing a MEDLINE analysis from (search terms including calcification, osseous metaplasia, renal, kidney, cancer), only 14 reported cases of osseous metaplasia have been identified to date. To our understanding, the clear cell subtype with metaplastic bone formation has only been reported four times. One report describes a patient with clear cell carcinoma with osseous metaplasia in the context of a multilocular cystic RCC.[18] Similarly, an Italian study reported osseous metaplasia in RCC, clear cell subtype, as a focus in continuity with the main tumor, a giant solitary renal cyst.[19] Two other case reports describe relatively large sized clear cell carcinoma with heterotopic bone formation alone, without a cystic relationship.[20,21] Our report confirms these prior reports and demonstrates that osseous metaplasia can occur as a major feature of small renal tumors, under 2.5 cm.

The pathogenesis for osseous metaplasia in RCC remains unclear and perhaps multifaceted. Current hypotheses include the simple production of bone by tumor cells secondary to ischemia, necrosis, or inflammation in rapidly dividing cells, a reparative response in the tumors or surrounding tissue, or the ossification of preexisting mucin or calcium foci.[17] It has also been suggested that RCC with calcification or osseous metaplasia are often hypovasular and may therefore be predisposed to ischemia and subsequent metaplasia. Bone morphogenic protein 2 (BMP2), an inducer of osteoblastic differentiation from pluripotent cells, has also been implicated in the involvement of ossification in RCC.[22] Additional studies are necessary to determine a common pathway in pathologic ossification.

Although studies have considered ossification a prognostic marker for patients with RCC, the prognostic significance of osseous metaplasia in RCC is controversial. Patients with ossified RCC generally present with early stage disease without invasion beyond gross margins. Therefore, as a tumor marker, it has been suggested that ossification of RCC may represent more favorable prognosis.[6] However, some reports suggest that ossification can also be associated

with high grade tumors and poor prognosis.[23] The low nuclear grade, low tumor stage, and absence of metastatic disease in our patient support the idea that osseous metaplasia may represent a favorable prognostic factor. However, as stated above, osseous metaplasia as a prognostic marker is controversial and the patient's long term outcomes remain to be determined. □

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