CASE REPORT

Clear cell renal cell carcinoma with heterotopic bone formation: A case report and literature review

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ABSTRACT

The phenomenon of heterotopic bone formation (osseous metaplasia) is defined as an abnormal ossification of non-skeletal tissues and does represent a rare occurrence in the renal cell carcinoma (RCC) setting. We describe a case of a 40-year-old man with bilateral renal cell carcinomas of the histological clear cell subtype, with the right-sided renal cell carcinoma demonstrating heterotopic bone formation, as well as the presence of intratumoral adipose tissue. The etiology of bone formation in a renal cell carcinoma is unclear, but possible explanations include a response to tissue ischemia and the expression of Bone Morphogenetic Protein 2. The detection of these rare morphologic variations is of paramount importance, not to be mistaken as sarcomatoid transformation and renal sinus fat invasion, which would advance the pathologic tumor stage and aggressiveness of the disease.

Key Words: Renal cell carcinoma, Clear cell, Heterotopic bone, Osseous metaplasia, Ossification

1. INTRODUCTION

Over 63,000 new cases of kidney cancer are estimated to be reported in the United States annually.[1] While many kidney cancer cases are reported, heterotopic bone formation (osseous metaplasia) in the setting of renal cancer is a rare occurrence with few reported cases.[2] We report the case of a patient with heterotopic bone formation in clear cell renal cell carcinoma (RCC) without sarcomatoid features.

2. CASE PRESENTATION

2.1 Clinical presentation

A 40-year-old male with a past medical history of hypertension and congestive heart failure presented to his primary care provider for routine care and was noted to be thrombocytopenic (platelet count, $70 \times 10^3/\mu$l). Blood calcium level was within normal range, 9.4 mg/dl. Abdominal computed tomography scanning was performed to evaluate for splenic pathology. Imaging incidentally revealed bilateral renal masses: a left upper pole mass (5.2 cm in greatest dimension) and right lower pole mass (4.4 cm in greatest dimension). The patient was referred to a tertiary academic center and subsequently underwent two laparoscopic partial nephrectomies, the right side two months after imaging and the left side three months after imaging.

2.2 Pathologic findings

The right partial nephrectomy specimen revealed a yellow-tan mass (4.2 cm $\times$ 3.7 cm $\times$ 3.4 cm) with calcifications and hemorrhage on gross examination located 0.2 cm from the nearest parenchymal margin. Hematoxylin and eosin stained histologic sections demonstrated nests of well-defined cells with clear cytoplasm and a low nuclear-to-cytoplasmic ratio

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in the background of small thin-walled vessels. The nuclei were small and eccentrically placed with conspicuous nucleoli seen at 400x magnification. The mass was also intermixed with areas of heterotopic bone, fibrosis, and mature adipose tissue (see Figure 1). The heterotopic bone appeared to rim the areas of mature adipose tissue. Sarcomatoid and rhabdoid features were not identified.

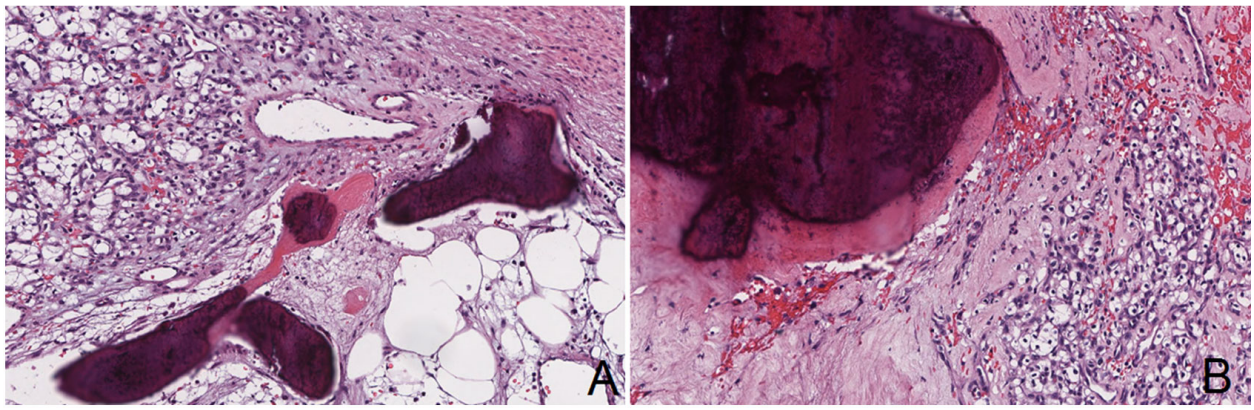

Figure 1. (A) Clear cell renal cell carcinoma with heterotopic bone formation and intratumoral adipose tissue (H&E stain, 100x). (B) Clear cell renal cell carcinoma with heterotopic bone formation and fibrosis (H&E stain, 100x).

The left partial nephrectomy specimen revealed a yellow-tan mass (4.7 cm × 3.4 cm × 2.2 cm) on gross examination located 0.1 cm from the parenchymal margin. Hematoxylin and eosin stained histologic sections demonstrated nests of well-defined cells with abundant clear cytoplasm in the background of small thin-walled vessels. The nuclei were small and eccentrically placed with conspicuous nucleoli at 400x magnification. Heterotopic bone, sarcomatoid, and rhabdoid features were not identified.

The final diagnoses for bilateral partial nephrectomies were RCC, clear cell type, histologic World Health Organization / International Society of Urological Pathology (WHO/ISUP) grade 2, limited to the kidney, American Joint Committee on Cancer (AJCC) 8th Edition primary tumor stage pT1b. In contrast to the conventional clear cell RCC seen in the left kidney, the right kidney mass had heterotopic bone formation. Lymphovascular invasion and necrosis were not identified, and the parenchymal and renal capsule margins were uninvolved by tumor.

The patient's post-operative course was unremarkable, and the patient continues to be monitored by his urologist for management of care. The patient has had one-month follow-up appointments after both partial nephrectomies without complaints or complications. He is scheduled to have a restaging abdominal computed tomography scan six months post operatively.

3. Discussion

Heterotopic bone formation has been described in the context of clear cell, chromophobe, papillary, mucinous tubular, as well as spindle cell RCC, both in the presence and absence of sarcomatoid features.[2–8] The presented case describes heterotopic bone formation and mature adipose tissue associated with clear cell RCC without sarcomatoid differentiation.

Intratumoral adipose tissue in RCC can be associated with ossification.[9] Recognizing osseous metaplasia and intratumoral fat within RCC are crucial for pathologic grading and staging, respectively. Unlike the phenomenon of sarcomatoid transformation, osseous metaplasia shows histologically bland bone formation. Sarcomatoid features would have significant cytologic atypia notable at low power magnifications and would automatically designate the histologic WHO/ISUP grade as 4. According to the AJCC 8th Edition, primary tumor stage is deemed pT3 when the tumor involves renal sinus fat. Therefore, intratumoral fat should be differentiated from renal sinus involvement. In the described case, the right renal tumor was located in the lower pole and did not grossly approach sinus fat. Additionally, rare benign mature adipose cells were seen within the tumor in the heterotopic bone area.

The exact mechanism for the formation of bone in the background of RCC is unclear, but proposed explanations involve a response to tissue ischemia and the expression of Bone Morphogenetic Protein 2 (BMP-2). Previous observations of heterotopic bone in the background of renal cell carcinoma have demonstrated a reduction of vascularity predisposing the tissue to damage including ischemia, necrosis, and inflammation. Osseous metaplasia results secondary to this tissue damage.[2,5] Furthermore, studies involving animal models with human RCC cell lines have shown that BMP-2

limits tumor growth and produces significant bone formation.[10,11] BMP-2 can trigger the process for cartilage and bone formation in tissue.[12] One case report of clear cell RCC with ossification in a 37-year-old woman demonstrated positive cytoplasmic BMP-2 immunohistochemical staining in the tumor cells.[13]

Several authors propose that osseous metaplasia in RCC might represent a favorable prognostic factor. Often, the RCC has a low nuclear grade, low tumor stage, and minimal proliferative activity when benign heterotopic bone formation is present.[2] In contrast, osteosarcomatous heterologous differentiation in RCC portends a poor patient survival, only 1-2 years in many cases.[4] The clinical significance of heterotopic bone features is uncertain. More studies following patient long-term health are needed to determine the relevance of heterotopic bone formation in the setting of RCC.

CONFLICTS OF INTEREST DISCLOSURE

The authors declare that they have no competing interest.

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