Renal cell carcinoma with osseous metaplasia: A case report and literature review

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Abstract
Ossification is rarely seen in renal cell carcinomas. We report a case of a 63-year-old man who was found to have bilateral renal masses on positron emission tomography-computed tomography. One of partial nephrectomy specimens histologically showed a papillary renal cell carcinoma containing bone trabeculae. We also review renal cell carcinoma cases with osseous metaplasia reported in the literature.

Background
Calcifications caused by a plethora of etiologies are found often radiologically in various subtypes of renal cell carcinomas (RCCs) [1]. Sarcomatoid differentiation is also seen in a subset of RCCs and is generally associated with poor patient outcomes. By contrast, metaplastic bone formation with or without bone marrow elements in RCC is extremely rare yet has been reported predominantly in clear cell [2-12] and chromophobe [13-16] subtypes. We here present a case of papillary RCC with osseous metaplasia along with a review of the literature on this unusual condition.

Case report
A 63-year-old Caucasian man with a history of squamous cell carcinoma of the tongue with regional lymph node metastasis, who was status-post chemotherapy and radiotherapy, was found to have bilateral renal masses on positron emission tomography (PET)-computed tomography (CT) (Figure 1). Patient did not have any urinary symptoms at the time, including gross hematuria and flank pain, and was referred to a urology clinic for management. No family history of RCC was noted. A follow-up CT scan of the abdomen/pelvis showed an 8-cm right renal mass located in the lower pole with dense calcification/ossification (Figure 2) and a 5-cm left renal mass located in the lateral border. Both masses were enhancing, raising concern for RCC. In addition, numerous renal cysts and smaller masses were documented bilaterally. Based on these findings, the patient underwent a right partial nephrectomy.

During the surgery, intraoperative ultrasound was utilized to delineate multiple cystic-looking lesions from concerning tumors. Once the more exophytic lesions were located, the more lateral tumors were excised with 2-5 mm margins. One of three partial nephrectomy specimens received for examination grossly showed an 8.5-cm tan-orange to red-brown friable mass that was well encapsulated and contained central areas of calcification. Histologic examination of the tumor revealed a papillary RCC, WHO/ISUP grade 3, with focal areas of bone formation containing adipose tissue without bone marrow elements (Figure 3). This tumor was staged as pT2aNX. The other two partial nephrectomy specimens histologically showed papillary RCCs (1.7 cm and 1.6 cm in their greatest dimensions, respectively) without calcifications or bone formation. All surgical margins were negative for tumor.

The patient underwent partial nephrectomies for left renal masses 2 months after the initial surgery. Two of the specimens again histologically showed organ-confined papillary RCCs (5.3 cm and 2.6 cm in their greatest dimensions, respectively) without ossification, in addition to atypical cysts in other two specimens. He is free from disease 8 months after right partial nephrectomies and is scheduled to undergo surveillance imaging.

Discussion
Calcification found in a variety of tissues refers to the deposition of hydroxyapatite deposition within the tissue and can be seen in RCCs. The patient underwent partial nephrectomies for left renal masses 2 months after the initial surgery. Two of the specimens again histologically showed organ-confined papillary RCCs (5.3 cm and 2.6 cm in their greatest dimensions, respectively) without ossification, in addition to atypical cysts in other two specimens. He is free from disease 8 months after right partial nephrectomies and is scheduled to undergo surveillance imaging.
association with both benign and malignant processes. Osseous metaplasia, however, is a rarer phenomenon. It refers to the presence of mature or immature bone in tissue where bone is not commonly found, while no clear mechanism for ossification has identified. An example of this includes mature bone formation within the endometrial tissue [17]. However, this type of metaplasia is not restricted to the endometrium. As seen primarily in case reports, osseous metaplasia can be present in a number of both benign and malignant lesions in, for instance, the spinal cord and breast, as well as various polyps [18-22], while there appear to be no precise incidence data for osseous metaplasia associated with different types of neoplasms or in different sites.

Osseous metaplasia has also been reported in patients with renal diseases, including less than 20 cases of the major subtypes of RCC [2-16,23-26]. Table 1 summarizes clinicopathologic features of these cases, including the present case, reported in case studies of osseous metaplasia associated with RCC. These patients included 8 males and 11 females with a mean/median age of 52.4/48 years (one case with no information), in contrast to a known male predilection towards RCC and its peak incidence during the sixth and seventh decade of life [27]. Osseous metaplasia has been associated mostly with clear cell RCC (n=11) or chromophobe RCC (n=4), and only one case of papillary RCC has been reported. Accordingly, ours is the second reported case of papillary RCC with associated osseous metaplasia. Histopathologically, these RCCs were organ-confined (pT1 or pT2: n=9) or pT3a (n=3) diseases (unknown: n=8) with a mean/median tumor size of 8.5/6.5 cm. In addition, most of the tumors (10 of 12) exhibited Fuhrman grade of 1 or 2. No lymph node or distant metastasis has been reported in these cases. Meanwhile, bone marrow elements have been identified within bony formation in 4 of 19 cases.

Molecular mechanisms of heterotopic ossification that often occurs following traumatic injury or invasive surgery have been extensively studied, and bone morphogenetic proteins (BMPs) are shown to involve its steps as the primary inducer [28,29]. By contrast, little is known about the histogenesis of intratumoral osseous metaplasia. Hypotheses include osteoblast metaplasia of tumor cells and metaplastic changes of pluripotent stromal cells to osteoblasts by factors secreted by tumor cells [30]. In RCC, osseous metaplasia was suggested to represent secondary changes to ischemia, hemorrhage, necrosis, fibrosis, and/or hyalinization [2,25]. The involvement of BMP2 in ossification of RCC has also been documented [31,32].

The prognostic consequences of osseous metaplasia remain poorly understood. However, most of RCC cases were low-grade organ-confined diseases. Moreover, none has been found to have metastasis at the time of nephrectomy or subsequent disease recurrence or progression. These findings suggest that RCC in most of cases where osseous metaplasia was reported was found during the early stages of disease. Thus, osseous metaplasia may serve as a prognostic factor and implies favorable outcomes in RCC patients. It is also important to distinguish osseous metaplasia from sarcomatoid carcinoma with bone formation (e.g. osteosarcomatous differentiation) that is generally associated with poor prognosis.

In conclusion, papillary RCC associated with osseous metaplasia is a very rare occurrence. It may be worthwhile to further investigate underlying mechanisms for osseous metaplasia within RCC as well as its prognostic significance.
Table 1. Summary of literature review.

| Author, yr [Reference] | Age (yr) / Sex | Laterality | Radical vs. partial nephrectomy | Histologic subtype | Tumor size (cm) | Tumor grade (Fuhrman) | Tumor stage* | Nodal status* | Bone marrow elements | Prognosis |
|------------------------|---------------|------------|--------------------------------|-------------------|----------------|---------------------|--------------|---------------|---------------------|----------|
| Cribbs et al. 1999 [2] | 57 / F         | Right      | Radical                        | CCRCc             | 18             | G2                  | pT3a         | N/A           | N/A                 | N/A      |
| Yokozaki et al. 2000 [13] | 60 / M        | Left       | Partial                         | ChRCC            | 2.7            | N/A                 | N/A          | N/A           | No                  | NED, 2 years |
| Bielsa et al. 2001 [3] | 74 / F         | Bilateral  | Partial (bilateral)             | CCRCc             | N/A            | G1                  | N/A          | N/A           | No                  | NED, 2 years |
| Bloom et al. 2003 [4] | 25 / F         | Right      | Radical                        | CCRCc             | 10.5           | G2                  | pT3a         | pNX           | N/A                 | N/A      |
| Kuroda et al. 2005 [14] | 74 / F         | Left       | Radical                        | ChRCC            | 3.6            | N/A                 | N/A          | Yes           | N/A                 | N/A      |
| Kefeli et al. 2007 [15] | 27 / F         | Right      | Radical                        | ChRCC            | 6.5            | N/A                 | pT1b         | N/A           | Yes                 | NED, 1 year |
| Murugan et al. 2008 [5] | 35 / M         | Right      | Radical                        | CCRCc             | 12.5           | G2                  | pT2b         | N/A           | N/A                 | N/A      |
| Puppa et al. 2008 [6]  | 46 / M         | Left       | Radical                        | CCRCc             | 1.0            | G1                  | pT1a         | N/A           | N/A                 | N/A      |
| Richmond et al. 2010 [7] | 61 / F         | Left       | Radical                        | CCRCc             | N/A            | G2                  | pT2         | N/A           | No                  | N/A      |
| Hartman et al. 2011 [8] | 48 / F         | Unilateral | Partial                        | CCRCc             | N/A            | N/A                 | N/A          | N/A           | No                  | N/A      |
| Hussain et al. 2012 [23] | N/A            | N/A        | N/A                            | MTSCC             | G2             | N/A                 | N/A          | N/A           | N/A                 | N/A      |
| Leung et al. 2012 [24] | 52 / F         | Right      | Radical                        | PRCC              | 8.5            | N/A                 | pT2a         | N/A           | No                  | NED, 2 years |
| Ozkani et al. 2012 [9] | 68 / M         | Left       | Radical                        | ChRCC            | 3.0            | N/A                 | pT1a         | N/A           | Yes                 | NED, 12 months |
| Tanaka et al. 2013 [16] | 77 / F         | Right      | Radical                        | ChRCC            | 28.8           | 3G                  | pT1a         | N/A           | No                  | NED, 3 months |
| Asghar et al. 2015 [25] | 47 / M         | Bilateral  | Radical (left only)            | MTSCC            | 4.0            | G2                  | pT1a         | N/A           | No                  | NED, duration unknown |
| Yun et al. 2015 [26]   | 48 / M         | Unilateral | Partial                        | CCRCc             | 3.0            | G1                  | pT1a         | N/A           | No                  | NED, 14 months |
| Lai et al. 2017 [11]   | 47 / M         | Right      | Radical                        | CCRCc             | N/A            | G1                  | N/A          | N/A           | No                  | N/A      |
| Pan et al. 2017 [12]   | 48 / F         | Right      | Partial                        | CCRCc             | N/A            | N/A                 | N/A          | No            | N/A                 | NED, 1 year |
| Present case           | 63 / M         | Bilateral  | Partial (right only)           | PRCC              | 8.5            | WHO/ISUP G3         | pT2a         | pNX           | No                  | NED, 8 months |

CCRC: Clear Renal Cell Carcinoma, N/A: Not Available or Not Applicable, ChRCC: Chromophobe Renal Cell Carcinoma, MTSCC: Mucinous Tubular And Spindle Cell Carcinoma, PRCC: Papillary Renal Cell Carcinoma, CPRCC: Clear Cell Papillary Renal Cell Carcinoma, NED: No Evidence of Disease.

*We staged tumors according to the AJCC 7th edition cancer staging manual (2010).
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