KJU
Korean Journal of Urology

www.kjurology.org
DOI:10.4111/kju.2010.51.10.729

Case Report

Two Different Renal Cell Carcinomas and Multiple Angiomyolipomas in a Patient with Tuberous Sclerosis

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We report a case of tuberous sclerosis associated with two histologically different renal cell carcinomas (RCCs) and multiple angiomyolipomas (AMLs) in the same kidney. A 43-year-old female was admitted to our hospital with left flank pain and a huge palpable mass in the left flank area. Abdominal computed tomography revealed two concurrent RCCs and multiple AMLs in the left kidney. Because of the clinical suspicion of RCC, the patient underwent left radical nephrectomy. On gross examination, the total size of the resected left kidney was 30.5x17x8 cm. Microscopically, the upper pole tumor features were consistent with chromophobe RCC and the midpole tumor was a clear-cell RCC. The multifocal masses in the remaining remnant parenchyma were AMLs. Six months after surgery, the patient is healthy without signs of tumor recurrence.

Key Words: *Angiomyolipoma; Clear cell renal carcinoma; Renal cell carcinoma; Tuberous sclerosis*

Article History:
received 25 May, 2010
accepted 17 August, 2010

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Renal cell carcinomas (RCCs) are usually categorized on the basis of their histologic, immunohistochemical, and ultrastructural features into clear-cell, papillary, chromophobe, collecting duct, and unclassified carcinomas [1]. The presence of different subtypes of RCC or RCC with other renal neoplasms within the same kidney is extremely unusual. There have been rare reports of the simultaneous occurrence of RCC and a variety of benign and malignant renal neoplasms within the same kidney [2-4]. The most frequently reported combinations are RCC with oncocytoma, angiomyolipoma, and RCC of a dissimilar histological subtype.

The case presented here illustrates the first combination of two dissimilar RCC subtypes: chromophobe carcinoma in the upper pole and clear-cell carcinoma rupture in the midportion of the same kidney. In addition, this case was associated with multiple angiomyolipomas (AMLs) in this patient with tuberous sclerosis (TS).

CASE REPORT

A 43-year-old female who had been clinically diagnosed with TS 12 years previously at another hospital was admitted to our hospital with left flank pain. Laboratory examination revealed her hemoglobin to be 8.5 g/dl, suggesting retroperitoneal hemorrhage, and her serum creatinine was 1.3 mg/dl. Chest computed tomography (CT) revealed multiple small air cysts scattered throughout the lungs, suggestive of lymphangioleiomyomatosis (LAM). An abdominal CT scan showed two mass lesions in the upper pole and the midportion of the left kidney with distinct radiologic appearances (Fig. 1). The upper mass demonstrated a relatively homogeneous enhancement pattern. The lower mass demonstrated a predominantly heterogeneous enhancement pattern. A CT image also showed multiple relatively small fat-containing tumors suggesting AMLs in the kidneys.

The patient underwent left radical nephrectomy. During the operation, a hemorrhage, which was considered to be an RCC rupture, was found around the midpole tumor. Splenectomy was also performed because splenic injury had occurred due to splenic adhesion to the huge left renal mass.

Macroscopically, the mass in the upper pole, measuring

9x7.8 cm across, had a bulging appearance, but was confined within the kidney (Fig. 2). The second mass, in the midportion of the kidney, measured 13x11 cm and its rupture was found beyond the kidney capsule but was confined within the Gerota's fascia. The final stage was T3aN0M0 (stage III). In the remaining renal parenchyma, there were multifocal poorly demarcated yellowish, glistening mass-like lesions. Microscopically, the midportion of the tumor consisted of nests of cells with clear cytoplasm, surrounded by abundant thin-walled blood vessels, which is typical of clear-cell RCC (Fig. 3A). The upper pole tumor was composed of nests of cells with lightly staining abundant cytoplasm, sharply outlined thick cytoplasmic membranes, raisinoid nuclei, and perinuclear halos, which is typical of chromophobe RCC (Fig. 3B). The remaining renal parenchyma had multifocal AMLs, composed of thick-walled blood vessels, admixed with mature fat cells and smooth

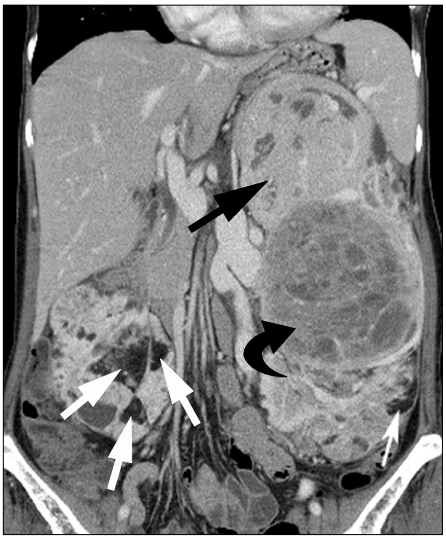

FIG. 1. Coronal reconstruction of a contrast-enhanced CT scan showing two mass lesions in the upper pole and the midportion of the left kidney with distinct radiologic appearances. The upper mass (black arrow), pathologically diagnosed as chromophobe renal cell carcinoma, demonstrates a relatively homogeneous enhancement pattern. The lower mass (curved arrow), pathologically diagnosed as clear-cell renal carcinoma, demonstrates a predominantly heterogeneous enhancement pattern. The CT image also shows relatively small and multiple fat-containing tumors (white arrows) suggesting angiomyolipomas in the kidneys.

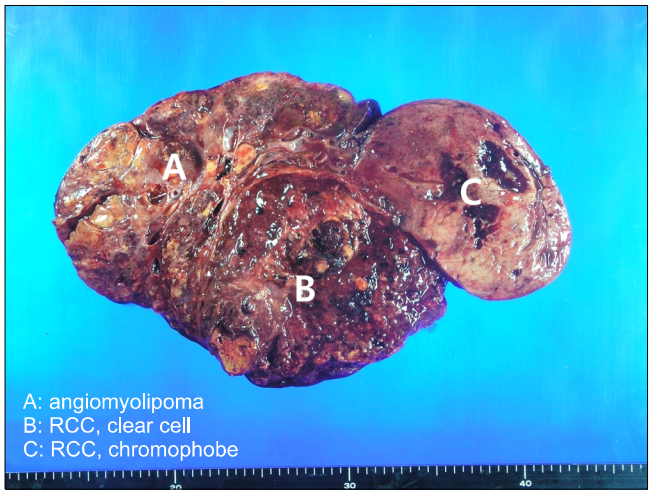

FIG. 2. On gross examination, three different renal masses were found. The cut surface of the largest mass (B) in the midportion had a heterogeneous appearance, composed of hemorrhagic, necrotic, and focal golden yellow soft areas. The cut surface of the smaller mass (C) showed focal hemorrhagic areas in the diffuse yellowish-grayish soft area. In the remaining renal parenchyma, there were multifocal poorly demarcated yellowish, glistening mass-like lesions (A).

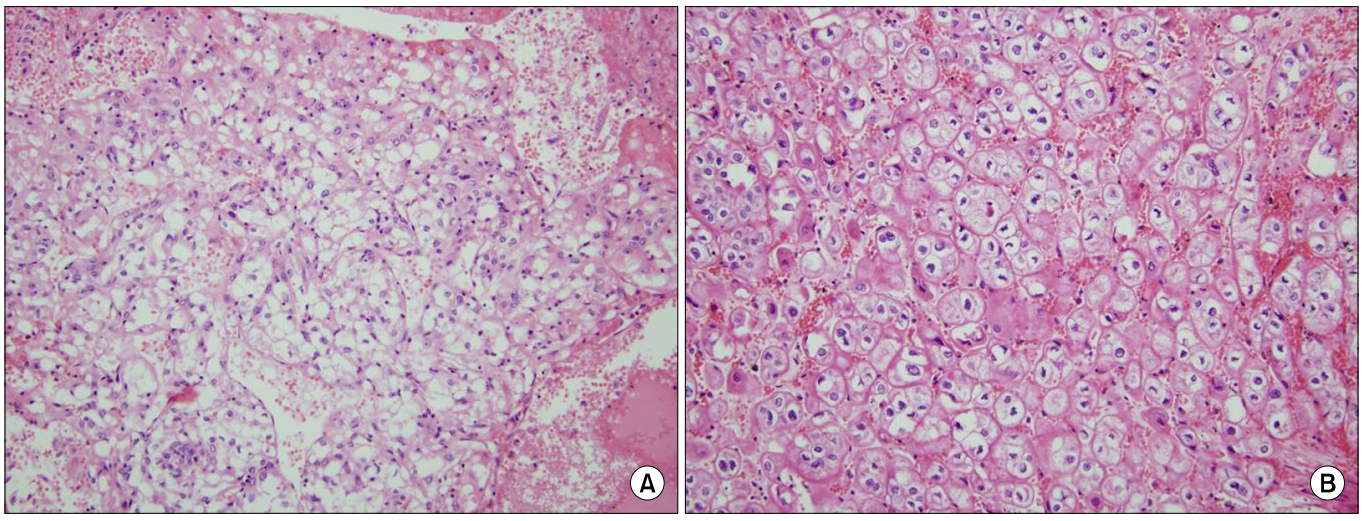

FIG. 3. (A) Renal cell carcinoma (RCC), clear-cell type, composed of nests of cells with clear cytoplasm, surrounded by abundant thin-walled blood vessels. (B) RCC, chromophobe type, composed of nests of cells with abundant cytoplasm, sharply outlined cell membranes, raisinoid nuclei, and perinuclear halos.

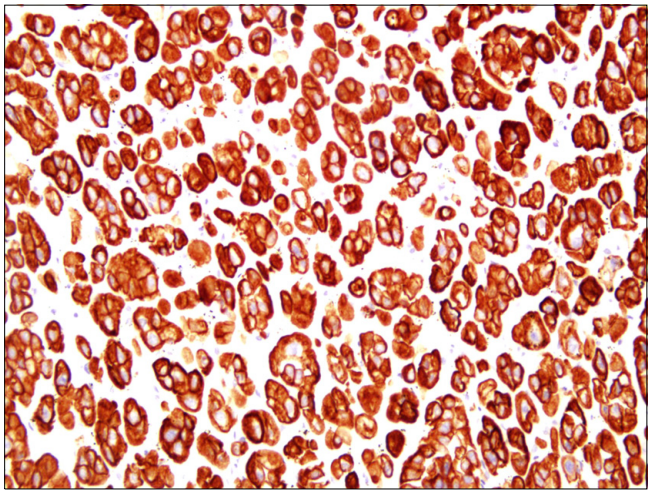

FIG. 4. Renal cell carcinoma (RCC), chromophobe type, showing intense immunoreactivity for cytokeratin 7.

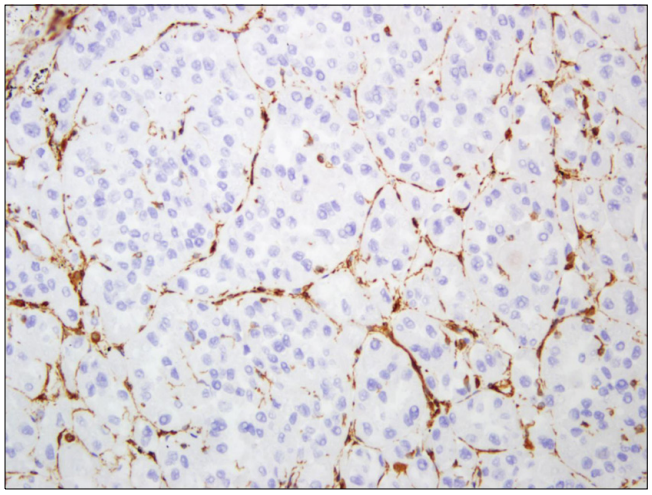

FIG. 5. Renal cell carcinoma (RCC), chromophobe type, showing complete absence of reactivity for vimentin within the tumor cells, except for sinusoidal blood vessels.

muscle cells. Immunohistochemical staining showed the chromophobe RCC was positive for E-cadherin and cytokeratin 7 (Fig. 4), but negative for vimentin (Fig. 5). The spindle cells of the AML were positive for HMB45, vimentin, and smooth muscle actin.

Immediately after surgery, the patient was moved to the intensive care unit because respiratory function can take time to recover due to LAM. Fortunately, her pulmonary function fully recovered 2 days later. After that, the patient had an uneventful postoperative recovery.

DISCUSSION

The coexistence of RCC with other renal neoplasms is only infrequently reported. There have been occasional reports and brief references to the simultaneous occurrence of RCC and a variety of benign and malignant renal neoplasms within a single kidney [2-4]. The majority of these reports consisted of one type of RCC combined with a benign renal tumor, such as oncocytoma or AML, or even an adrenal adenoma [5,6]. Other rare coexisting neoplasms are capsular leiomyoma and hematological malignancy [7].

Reports of concurrent RCCs of different histological types within the same kidney are infrequent and include cases of two spatially separate, histologically different RCCs or a single discrete tumor composed of two types of RCC. Tyritzis et al reported the first combination of two dissimilar RCC subtypes: chromophobe in the upper pole and clear cell in the lower pole of the same kidney [8]. Roehrl et al described the first case of RCC that exhibited the features of both chromophobe and papillary carcinoma within the same tumor [4]. In the context of the aforementioned data, the present case is unique due to the fact that there were two different large RCCs: one was a chromophobe RCC in the upper pole and the second was a clear-cell RCC with rupture in the midportion of the same kidney. In the present case, the chromophobe RCC was a classic form that can easily be archived for diagnosis in routine sections. Immunohistochemically, the tumor cells of chromophobe RCC react with antibodies to cytokeratin 7 and E-cadherin but do not react for vimentin. However, the majority of clear-cell RCCs are positive for vimentin but negative for cytokeratin 7 and E-cadherin. Morphologically, in classic chromophobe RCC, the differentiation from oncocytoma is not problematic. The tumor cells of oncocytoma are uniform in shape and size, with homogeneous granular cytoplasm. Nuclei tend to be central and round with even borders, and mitoses are rare. However, the eosinophilic variant of chromophobe RCC is more problematic because of its close resemblance to oncocytoma. In that case, Hale's colloidal iron stain or ultrastructural study can be helpful. In addition, this patient with TS also had multiple concurrent AMLs in the kidney. AML is a benign neoplasm that most commonly occurs in the kidney. Although no conclusive decision about the association between AML and RCC has been reached, nearly 50 cases of the coexistence of AML and RCC have been reported [2]. Therefore, the possible coexistence of RCC with AML in cases with or without TS must be considered in the management of radiologically diagnosed AML accompanied by other renal masses of an indeterminate nature. Furthermore, the history of TS in the present case could lead to a misdiagnosis of AML rupture. We will follow the contralateral kidney in this patient carefully.

The three different subtypes of renal tumor in our case resulted from completely different genetic abnormalities. Chromosome 3 alterations and VHL mutations are common in conventional (clear-cell) RCC, whereas chromophobe-type RCCs have a loss of multiple chromosomes (most often chromosomes 1, 2, 6, 10, and 21). Angiomyolipomas frequently show a loss of heterozygosity (LOH) at the tuberous sclerosis complex (TSC)2-containing region on chromosome 16p and occasionally at the TSC1 region on

chromosome 9p34 [9]. Recently, the theory of cancer stem cells (CSCs) has become particularly attractive because two or three dissimilar renal tumors could arise from CSCs. Another hypothesis explaining the pathogenesis of the coexistence of different renal tumors might be the evolution of one subtype to another. In addition, patients with TS have been reported to develop RCC with increased frequency. There are now three lines of evidence suggesting that the TS genes are specifically involved in the pathogenesis of RCC [10]. First, at least 30 cases of RCC in TSC patients have been reported since 1980. Most of these reports were of clear-cell carcinoma. Second, a germline mutation in the TSC2 gene has been identified in the Eker rat model of autosomal dominant hereditary renal carcinoma, which was first described in 1954. Third, LOH analysis of sporadic RCCs, in which 14 of 42 tumors showed partial or complete deletion of chromosome 9, suggests that one or more tumor suppressor genes on chromosome 9 are involved in the pathogenesis of RCC. Genetic linkage analysis has shown TSC1 on 9q34 and TSC2 on 16p13 to be responsible genes for TSC.

The present case was also remarkable for an association with LAM. LAM, which is a pulmonary manifestation of TS causing respiratory symptoms related to interstitial or obstructive pulmonary disorders, occurs in up to 34% of patients with TS. When a renal AML is diagnosed in a woman of child-bearing age, recognition of LAM is important, because perioperative pulmonary complications may result. In this case, the patient recovered in the intensive care unit for 2 days because of postoperative pulmonary deterioration, although her recovery was helped by a pulmonary support team who already knew about her condition.

The present case represents an extremely rare manifestation of two concurrent RCCs with AMLs in a TS patient, including a huge tumor burden and an association with LAM. There are several important points to consider in regard to the present case. The occurrence of RCC with AML should be considered in the management of TS. In addition, when a renal AML is diagnosed in a woman of child-bearing age, the possibility of LAM should be considered. Surgeons should cooperate with pulmonologists regarding postoperative complications. Owing to the paucity of reports, the prognosis of this case is difficult to predict. The different subtypes of renal tumors may have an effect on disease-free survival after radical nephrectomy; in particular, rupture of the clear-cell RCC portion may have a less favorable outcome. In addition, the presence of 2 separate and distinct carcinomas in a nephrectomy specimen complicates the assignment of this patient to certain investigational adjuvant therapy protocols. Unusual cases like the one presented herein may serve as tools to further investigate the origin, relatedness, and classification of AML, RCC, and LAM in TS patients.

Conflicts of Interest

The authors have nothing to disclose.

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