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Case Report

Synchronous renal neoplasms: clear cell renal cell carcinoma, papillary renal cell carcinoma, and multilocular cystic renal cell neoplasm of low malignant potential in the same kidney

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Abstract: The simultaneous occurrence of three kinds of primary tumors in the same kidney is extraordinarily rare. Herein we report a case of synchronous clear cell renal cell carcinoma, papillary renal cell carcinoma and multilocular cystic renal cell neoplasm of low malignant potential in a kidney. To our knowledge, this is the first case with synchronous, triple primary renal cell carcinomas thus far.

Keywords: Synchronous neoplasms, clear cell renal cell carcinoma, papillary renal cell carcinoma, multilocular cystic renal cell neoplasm of low malignant potential, kidney

Introduction

The first case of synchronous ipsilateral renal neoplasm was reported by Graves and Templeton in 1921 [1]; however, the combination of three types of malignant renal tumors is rare. The present study reports a case of synchronous clear cell renal cell carcinoma (CCRCC), papillary renal cell carcinoma (PRCC), and multilocular cystic renal cell neoplasm of low malignant potential (mcCRCNLMP) in a kidney.

Case presentation

In June 2017, a 60-year-old male was referred to our hospital with an asymptomatic right kidney tumor mass, which was incidentally identified by computed tomography (CT). He had smoked and drank for 40 years and suffered hypertension for 20 years. He denied having a family history of urologic malignancies or any other genetic diseases. There was no fever, weight loss, or pain in the right renal region, nor was there any hematuria. A physical examination was done, and no palpable abdominal mass was detected. Other routine examinations, such as an X-ray examination of the abdomen, an electrocardiogram, and laboratory tests of the blood and urine, were normal. Abdominal CT showed several hypodense masses in his two kidneys, with the largest mass in the lower pole of the right kidney measuring 11.3×12.6×12.6 cm in size. In addition, another 1.4 cm well-defined solid hypodense nodule was found in the posterior aspect of the upper pole of the right kidney (**Figure 1**). He then underwent a trans-peritoneal laparoscopic right multiple nephron-sparing surgery. During operation, two cystic lesions with a size of 14 cm and 3 cm respectively were found in the inferior pole of the right kidney. Another dusty-red tumor measuring 1.5 cm was observed in the upper pole of the right kidney. In addition, an unexpected yellowish solid nodule measuring 0.5 cm was observed in the middle of the right kidney, which was not identified on the CT images.

Pathologic findings

The resected renal lesions were sent for pathological analysis. The first specimen was a 0.3 cm well-defined solid nodule with a yellowish

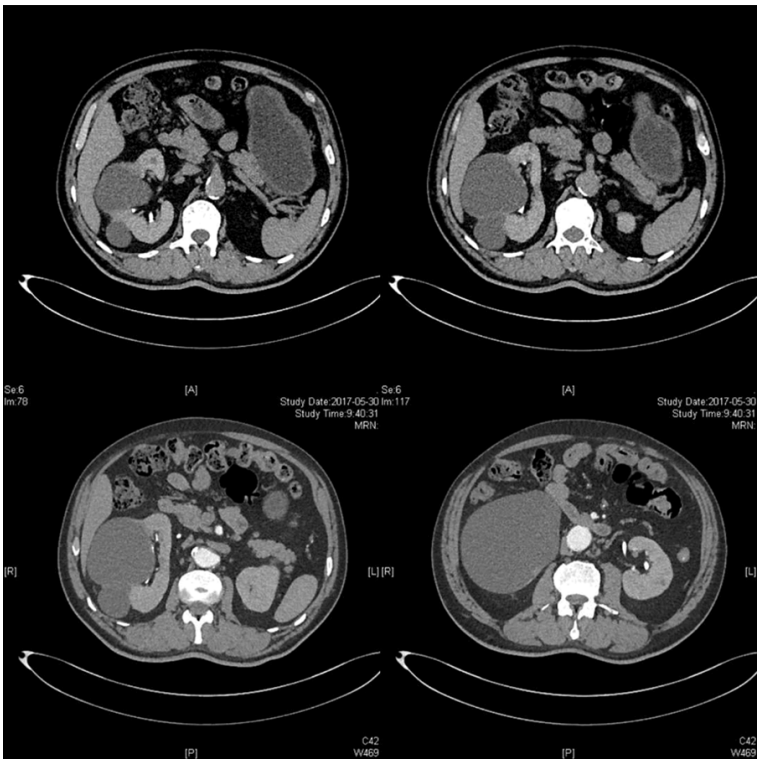

Figure 1. Preoperative abdominal computed tomography (CT). The illustration shows two masses in the right kidney.

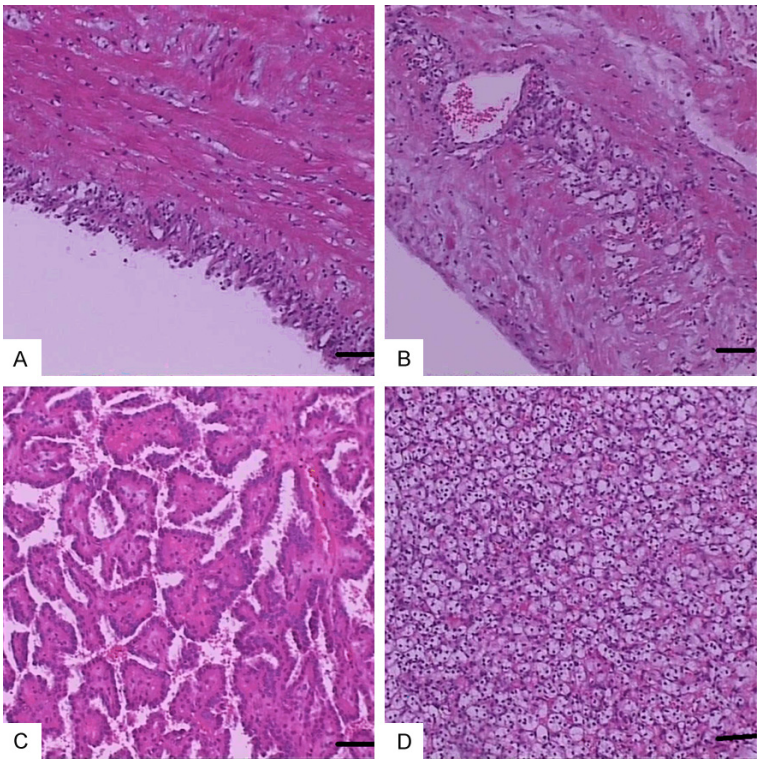

Figure 2. Histopathological observation of synchronous renal neoplasms. A and B: Histological evaluation shows that the mcCRCNLMP tumor tissues are composed of various sizes, separated by thin septa which contain groups of clear cells. The cysts consist of fibrous connective tissue showing hyaline degeneration lined by single or multiple layers of flat to cuboidal epithelia with clear cytoplasms. C: The histological evaluation shows that the PRCC tumor tissues are composed entirely of numerous tightly packed tubulopapillary structures. D: The histological evaluation shows that the CCRCC tumor tissues are characterized by solid sheets of carcinoma cells which have water clear cell cytoplasms surrounded by distinct cell membranes. Bar = 50 μm.

cut surface. The second specimen was measured at 3×1.5×1 cm and contained a 1.5 cm well-defined mass, with a soft and dusty-red color cut surface that did not invade the surrounding tissues. This tumor has no capsule and was adjacent to the surrounding renal tissues. The remaining two renal lesions were measured at 5×4×0.1 cm and 2×1.5×0.1 cm. They were characterized by cysts of various sizes and separated by thin septa filled with serous or gelatinous fluid.

The three specimens were diagnosed as CCRCC, PRCC, and mcCRCNLMP respectively. Histopathologically, areas of CCRCC were characterized by solid sheets of carcinoma cells interspersed by some variably sized cysts. The tumor cells had water clear cell cytoplasms surrounded by a distinct cell membrane and had a World Health Organization (WHO)/International Society of Uropathology (ISUP) nuclear grade 1 morphology (**Figure 2D**). The immunohistochemical staining demonstrated that the tumor cells were positive for vimentin, CA IX, and E-cadherin, focally positive for CD10 and

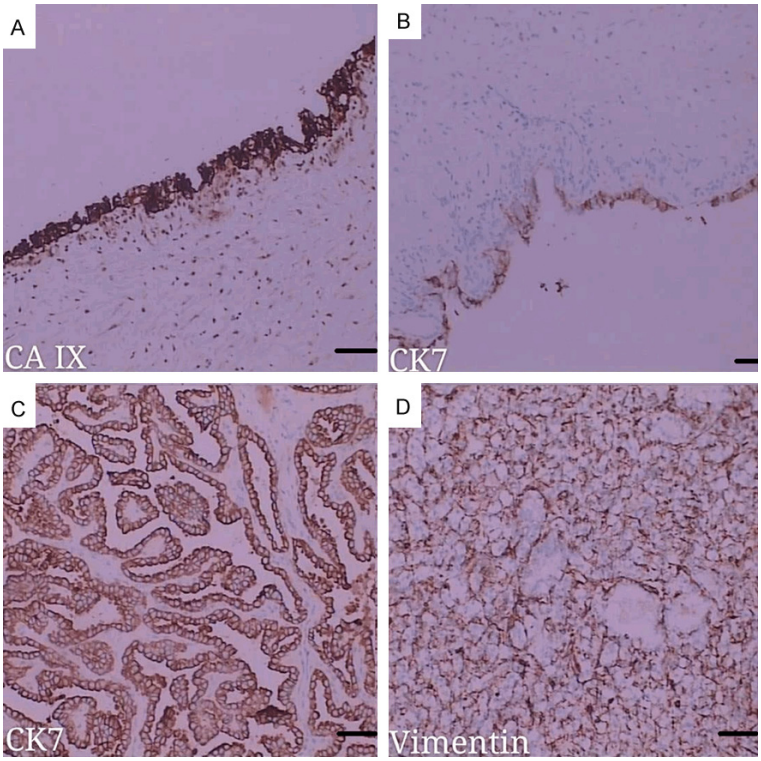

Figure 3. Immunohistochemical staining of the synchronous renal neoplasms. A and B: Immunohistochemical staining of a strong positive for CA IX and CK7 in the mcCRCNLMP tumor tissues. C: Immunohistochemical staining of a strong positive for CK7 in the PRCC tumor tissues. D: Immunohistochemical staining of a strong positive for vimentin in the CCRCC tumor tissues. Bar = 50 μm.

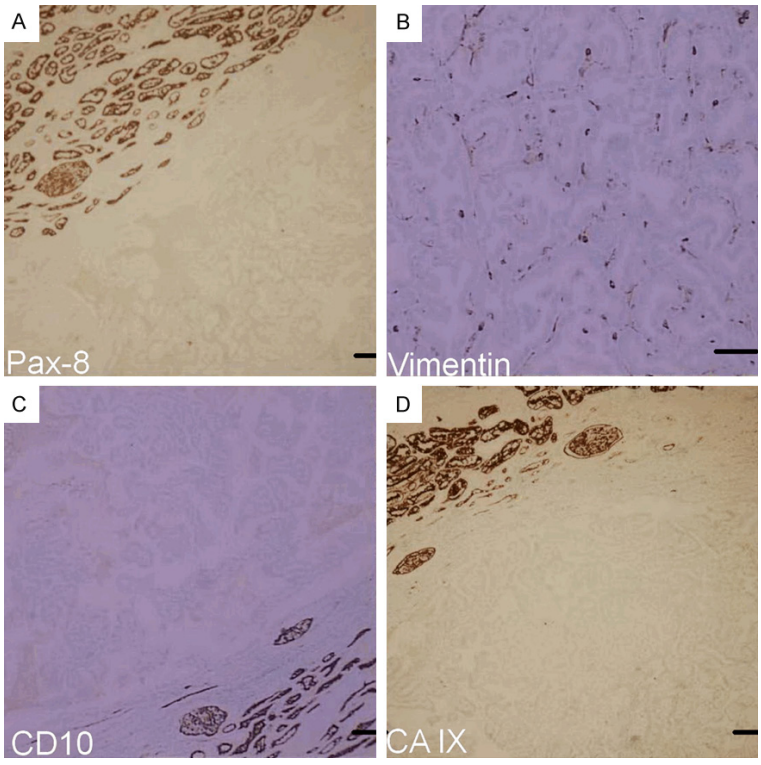

Figure 4. Negative immunohistochemical staining for Pax-8, vimentin, CD10 and CA IX in the PRCC tumor tissues. Bar = 50 μm.

P504S, and negative for CK7, CD117, PAX-8, and TFE3. PRCC (type I) was composed entirely of numerous tightly packed tubulopapillary structures which were lined by a single layer of flat to cuboidal epithelium, with pale eosinophilic cytoplasms, uniform chromatin and small ovoid nuclei with inconspicuous nucleoli. There were fibrovascular stroma in varying quantities in the center of the papillae. In some areas apocrine secretion and hemorrhage could be found. Necrosis was not observed (**Figure 2C**). The tumor cells of the PRCC were positive for CK7, P504S and E-cadherin, but negative for CD10, CD117, vimentin, CA IX, PAX-8, and TFE3 (**Figures 3**, **4**). The areas of mcCRCNLMP were characterized by cysts of various sizes, separated by thin septa containing groups of clear cells with prominent associated vascularity. The cysts consisted of fibrous connective tissue with hyaline degeneration and were lined by single or multiple layers of flat to cuboidal epithelia with clear cytoplasms (**Figure 2A**, **2B**). Immunohistochemically, the tumor cells showed positive immunoreactivity for CK7, vimentin, E-cadherin, CA IX and P504S (**Table 1**).

Discussion

Renal cell carcinoma (RCC) is the most common kidney tumor and accounts for 70% of renal masses [1]. CCRCC, PRCC, and chromophobe RCC are the three most common subtypes and account for 80%,

Table 1. The immunohistochemical staining results of the three tumors

Markers Tumors	CCRCC	PRCC	mcCRCNLMP
CK7	Negative -	Strongly positive 3+	Strongly positive 3+
CD10	Focal positive 2+	Negative -	Negative -
Vimentin	Strongly positive 3+	Negative -	Strongly positive 3+
CA IX	Strongly positive 3+	Negative -	Strongly positive 3+
P504S	Weak positive ±	Strongly positive 2+	Strongly positive 2+
CD117	Negative -	Negative -	Negative -
E-cadherin	Membrane 3+	Strongly positive 3+	Strongly positive 3+
Pax-8	Negative -	Negative -	Strongly positive 1+
TFE3	Negative -	Negative -	Negative -

10%, and 5%, respectively [2]. The 2004 WHO classification of kidney tumors introduced one tumor, multilocular cystic renal cell carcinoma (MCRCC), which was classified as a rare subtype of CCRCC with an excellent prognosis. Microscopy revealed the tumor composed entirely of cysts of various sizes which were lined by occasionally flattened cuboidal clear cells, and the thin septas between the cysts contain groups of clear cells indistinguishable from grade 1 clear cell carcinoma [3]. Owing to the consistently reported indolent behavior of MCRCC, this tumor was recognized as a nonaggressive tumor and has been renamed as multilocular cystic clear cell renal cell neoplasm of low malignant potential (mcCRCNLMP) according to the current 2016 WHO classifications [4]. To the best of our knowledge, despite the immunohistochemical staining, the histological features and genetic analysis regarding the chromosome 3p deletions of the mcCCRCNLMP tumor and of the CCRCC tumor were similar, a different biological behavior could be shown between these two tumors. As a result, the recent classification of renal neoplasms of ISUP [5] recognized them as two different entities and defined mcCCRCNLMP as an indolent neoplasm with a low incidence of recurrence or metastasis if definite nephrectomy was realized. CCRCC coexisting with mcCCRCNLMP in the same kidney is rare. In the present report, the diseased parts, morphological features, and immunohistochemical staining of the mcCCRCNLMP tumor were different from that of the CCRCC tumor, so they were considered tobe two primary malignancies.

The main differential diagnosis with mcCCRCNLMP is low nuclear grade CCRCC with extensive cystic changes. For the histologic diagnosis of mcCCRCNLMP, it is necessary to follow strict criteria such as prominent associated vascularity in some areas [6]. In addition, our case did not display necrosis or solid expansive nodules of the clear cells. The mcCCRCNLMP was composed of numerous cysts which were lined by a single layer of clear cells, compared with the malignant and growing nodules of CCRCC.

Synchronous malignant carcinomas have been reported in many organs with a poor prognosis which were characterized by the coexistence of two or more histologically different malignant neoplasms [7]. To the best of our knowledge, there are only about 50 cases of synchronous renal neoplasms having been reported. Without being exceptional, it is a rare occurrence that a CCRCC, a PRCC, and a mcCCRCNLMP appear together in the same kidney. The Ustuner group [8] has reported a tumor mass with two distinct RCC subtypes (CCRCC and PRCC) occurring synchronously in the right kidney. Likewise, CCRCC and PRCC were the two components of multifocal tumors in our case. Depending on the characteristics, surgical excision (radical nephrectomy or partial nephrectomy) is recommended [9].

Zhang et al. [10] have previously reported that 73% of the renal collision tumor cases presented with hematuria, 37% with flank pain, and 10% without any obvious symptoms. In accordance with their findings, our patient presented none of the common symptoms, and there was no identifiable past medical history be observed. As we all know, CCRCC has a greater malignant potential and metastatic potential than PRCC and mcCCRCNLMP. Research indicates that multiple primary malignancies tend to exhibit poor outcomes [11]. As regards the prognosis, it is known that CCRCC has the greatest malignant potential and a 5-year overall survival rate of 50-60%, but PRCC is associated with less metastatic potential, with a 5-year overall survival rate of 80-90% (references). Furthermore, we have previously reported that mcCCRCNLMP was a low aggressive neoplasm which does not recur or develop metastasis after definite surgical treatment [12-14]. In the present case, a routine follow-up

at 12 months after surgery found that no recurrence or metastasis had developed in the patient up to now.

Lipworth [15] recently found that smoking, obesity, and hypertension are clearly implicated in the etiology of all types of RCC. Among the documented etiological factors that were described above, smoking and hypertension were the etiologic causes in our case. There was a 40-year history of smoking and a 20-year history of hypertension in this case. Many studies have found that CCRCC, PRCC, and mcCCRCNLMP all originated from proximal tubules [16]. Synchronous tumors might arise from the same embryologic processes affected by pathogenic factors such as hormones and carcinogens [17]. All kinds of renal tumors might arise from cancer stem cells that follow varying differentiation pathways regulated by tissue microenvironmental interactions.

In conclusion, we presented an additional case of three or more concurrent, different subtypes of RCC in the same kidney. According to our PubMed searching results, this is the first case report to date which has described CCRCC, PRCC, and mcCCRCNLMP synchronously arising in a single kidney. To the best of our knowledge, there is no sufficient data to compare the different types of renal malignant neoplasms in the same kidney in terms of survival or oncologic survey. Larger numbers of studies are needed to elucidate the etiology of coexisting renal tumors with different histological features.

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Disclosure of conflict of interest

None.

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