Clinical Case Report

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A first case report of primary epithelial myoepithelial carcinoma-like renal tumor showing a perivascular pseudorosette-like pattern

Description of morphologic, immunohistochemical, and genetic features

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Abstract

Rationale: Over the past decade, although several new entities of renal tumors have emerged, a form of renal cell carcinoma (RCC) that morphologically resembles epithelial-myoepithelial carcinoma has not been reported thus far. Herein, we describe a case of an unusual renal tumor that remained unclassified under a current RCC subtype, and briefly present its morphologic, immunophenotypic, and genetic features.

Patient concerns: The patient was an 85-year-old man who presented with hematuria and flank pain. Imaging studies revealed a left renal mass without enlarged lymph nodes. There were no abnormal masses or nodules in other organs.

Diagnoses: The patient underwent no other treatment except the left radical nephrectomy under a clinical diagnosis of invasive urothelial carcinoma and was discharged on the thirteenth day. Histologically, the renal tumor showed biphasic proliferation of epithelial (strongly cytokeratin-positive; P63, P40, and vimentin-negative) and myoepithelial (strongly vimentin-positive; focal P63 and P40-positive; and weakly cytokeratin-positive) cells arranged in a perivascular pseudorosette-like pattern. No mutations were detected in multiple gene tests. According to the pathological structure, the patient was diagnosed as primary epithelial myoepithelial carcinoma-like renal tumor.

Interventions: To the best of our knowledge, the present tumor has not been previously described, and thus, this variant has not been integrated into a known form of PCC. Therefore, we cannot diagnose this type of tumor with other types of kidney tumors.

Outcomes: Three years after primary diagnosis, the patient died of multiple organ failure result from multiple distant metastases.

Lessons: We present the first case of carcinoma of the kidney with EMC-like features and a perivascular pseudorosette-like growth pattern. Clinicians should be aware of the features of this uncommon variant of RCC to avoid diagnostic delays or misdiagnosis and prevent unnecessary or inappropriate treatment.

Abbreviations: CAIX = carbonic anhydrase, EMC = epithelial-myoepithelial carc, PAX-8 = paired box gene 8, RCC = renal cell carcinoma, WHO = World Health Organization.

Keywords: genetic analysis, immunohistochemistry, perivascular pseudorosette-like growth pattern, primary epithelial myoepithelial carcinoma-like tumor

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The informed written consent has been obtained from the other family member of the patient for publication of this case report and accompanying images. Patient has provided informed consent for publication of the case.

The study was approved by the Institute Ethical Committee of Qilu Hospital of Shandong University, Qingdao, China.

The authors have no conflicts of interests to disclose.

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1. Introduction

A recent World Health Organization (WHO) classification system established and introduced new distinctive entities of kidney tumors, such as hereditary leiomyomatosis and renal cell carcinoma (RCC) syndrome-associated RCC, succinate dehydrogenase-deficient RCC, tubulocystic RCC, acquired cystic disease-associated RCC, clear-cell papillary RCC, and microphthalmia transcription factor-family translocation RCC.[1,2] However, most of these tumors have been classified as unclassified RCC in the past. Unclassified RCCs include tumors with a well-defined differential diagnosis but lacking a definitive conclusion of cell type as well as high-grade carcinomas or sarcomatoid carcinomas in which the epithelial element cannot be subclassified. Additionally, carcinomas that produce mucin, demonstrate a mixture of stromal and epithelial elements, or have unrecognizable cell types not otherwise specified are included under this category. However, a form of RCC, which morphologically resembles epithelial-myoepithelial carcinoma (EMC), has not been reported thus far. Herein, we present the first case of carcinoma of the kidney with EMC-like features and a perivascular pseudorosette-like growth pattern with no clinical or radiological evidence of a primary tumor in the salivary gland or other sites. The manuscript has been approved by the Ethics Commottee of Qilu hospital of Shandong University.

2. Case report

An 85-year-old man was referred to our hospital in May 2009 with a history of recurrent episodes of hematuria and left flank pain for the past 2 months. Clinical examination yielded unremarkable findings. A contrast-enhanced computed tomography scan revealed a $6.4 \times 6.2 \times 5$ cm enhancing heterogeneous left renal mass in the upper pole. No metastatic lesions or lymph node enlargement were noted. There were no abnormal enhanced masses or nodules in other organs. The patient underwent on other treatment except the left radical nephrectomy under a clinical diagnosis of invasive urothelial carcinoma and was discharged on the thirteenth day. Three years after the primary diagnosis, the patient died of multiple organ failure caused by multiple distant metastases.

The tissue was fixed in 10% neutral buffered formalin, embedded in paraffin, and stained with hematoxylin and eosin. The nephrectomy specimen revealed a well-circumscribed solid mass measuring 7 cm across the largest diameter, yellow-tan on cross-section, confined to the kidney, and abutting the renal sinus. No extension into the renal vein, ureter, or perinephric fat was identified (Fig. 1A). Microscopic examination showed that the mass was composed of epithelial cells and clear myoepithelial-like cells. The tumor was characterized by a predominately biphenotypic perivascular pseudorosette-like growth pattern, consisting of bilayered cells with an inner layer of myoepithelial-like cells and an outer layer of epithelial-like cells. The perivascular pseudorosette-like structures are composed of tumor cells radially arranged around blood vessels and polarized away from the vascular axis. Some areas demonstrated a diffuse growth pattern, with epithelial-like cells mingled together with myoepithelial-like cells. These myoepithelial-like cells were found to be predominant and contained a clear cytoplasm and distinct cell border. The epithelial-like cells were scattered throughout alongside the myoepithelial-like cells, but were smaller and contained an eosinophilic cytoplasm and indistinct cell borders. Both these cell types had moderate atypical nuclei, irregular nuclear membranes, nuclear grooves, and inconspicuous nucleoli. A few mitotic figures and multiple necrosis were noted. There were a few collapsing glomeruli scattered in the peripheral area of the lesion (Fig. 1B–C).

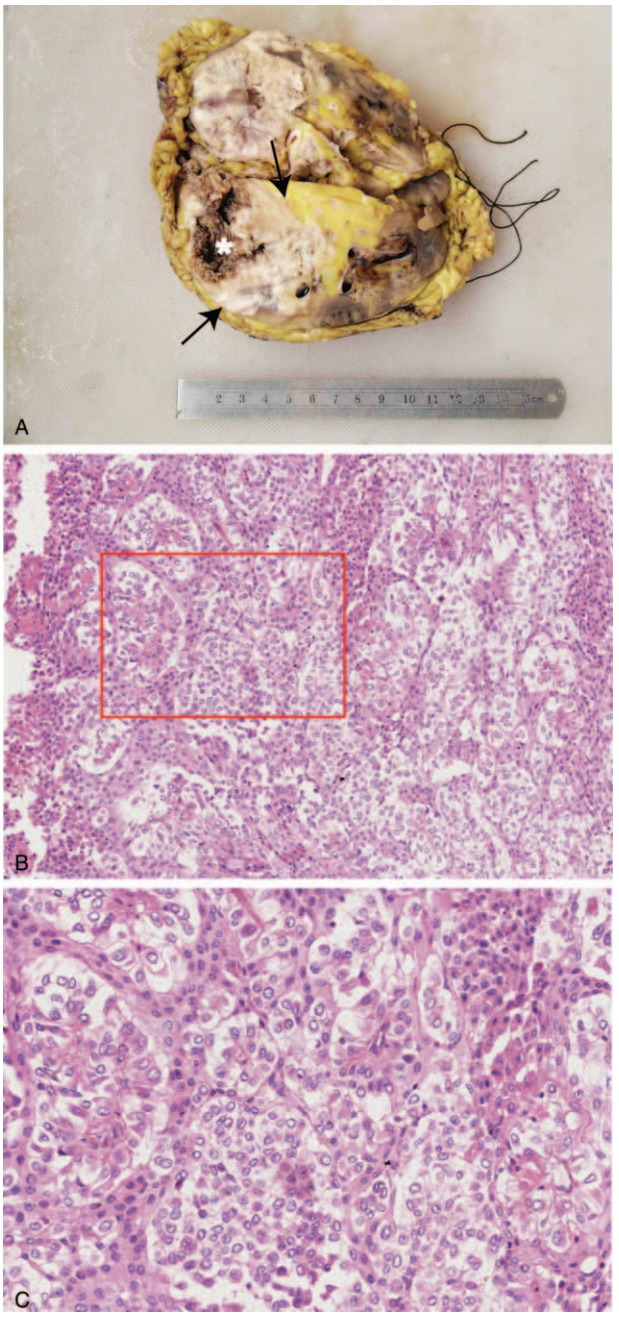

Figure 1. Histologic findings of the tumor. A. A well-circumscribed yellow-tan solid mass (arrow, inset) with hemorrhagic and cystic degeneration (*) in the upper pole of the kidney, confined to the kidney, and abutting the renal sinus. B-C. Hematoxylin and eosin staining showed that the tumor is characterized by a predominately biphenotypic perivascular pseudorosette-like growth pattern, which consisted of bilayered cells with an inner layer of myoepithelial-like cells and an outer layer of epithelial-like cells (B: magnification, ×100; C: magnification, ×200).

Immunohistochemical staining was performed with an automated immunostainer (Roche, Basel, Switzerland) via the avidin-biotin complex technique. The primary antibodies used and their dilutions are listed in Table 1. The epithelial-like cells showed strong immunopositivity for CK7, CK8, CK19, epithelial membrane

Table 1

Antibodies used for immunohistochemical staining and results.

Antibody	Source	Dilution	Result (elc)	Result (mlc)
CK7 (m)	TFS	1: 100	Positive	Weaker positive
CK8 (m)	TFS	1: 100	Positive	Weaker positive
CK19 (m)	TFS	1: 100	Positive	Weaker positive
EMA (m)	TFS	1: 50	Positive	Weaker positive
CAM5.2 (p)	OriGene	1: 100	Positive	Weaker positive
CD10 (m)	TFS	1: 100	Positive	Weaker positive
P63 (m)	TFS	1: 100	Negative	Focal positive
P40 (p)	OriGene	1: 100	Negative	Focal positive
CK5/6 (m)	TFS	1: 50	Negative	Positive
HMW (m)	TFS	1: 100	Negative	Positive
Vimentin (m)	TFS	1: 50	Negative	Focal positive
CAIX (p)	TFS	1: 50	Focal positive	Focal positive
PAX-8 (p)	TFS	1: 50	Focal positive	Focal positive
CK20 (m)	TFS	1: 200	Negative	Negative
RCC (m)	TFS	1: 50	Negative	Negative
S-100 (m)	TFS	1: 100	Negative	Negative
CD117 (m)	TFS	1: 100	Negative	Negative
Calponin (m)	TFS	1: 100	Negative	Negative
PAX-2 (m)	TFS	1: 30	Negative	Negative

elc = epithelial-like cell, EMA = epithelial membrance antigen, m = monoclonal, mlc = myoepithelial-like cell, p = polyclonal antibody, RCC = renal cell carcinoma, TFS = Thermo Fisher Scientific.

antigen, CAM5.2, and CD10. The myoepithelial-like cells stained strongly positive for vimentin, CK5/6, and CK903; focally positive for P63 and P40; and weakly positive for CD10, CK7, CK8, CK19, and CAM5.2. The characteristic cytomorphologic features and immunophenotype of these 2 types of cells indicated a differentiation of epithelial cells and myoepithelial cells, as observed in EMC. The focal immunoreactions observed in these 2 types of cells for the important renal tumor markers, carbonic anhydrase (CAIX) and paired box gene 8 (PAX-8), is consistent with the characteristics of carcinoma of renal origin. Immunostaining of both cells for RCC, S-100, CD117, calponin, PAX-2, and CK20 yielded negative results (Fig. 2). Mutation analysis conducted via PCR and Sanger sequencing by the genetic testing company (SinoMD, Beijing, China) did not reveal any mutations in the C-kit 9, C-kit 11, C-kit 13, C-kit 14, PDGFR14, PDGFR14, and PIK3CA genes (Fig. 3). According to the morphologic and immunophenotypic parameters of the tumor, we diagnosed the tumor as primary epithelial myoepithelial carcinoma-like renal tumor.

3. Discussion

Over the past decade, several new entities of renal tumors have emerged. Therefore, the WHO working group was entrusted

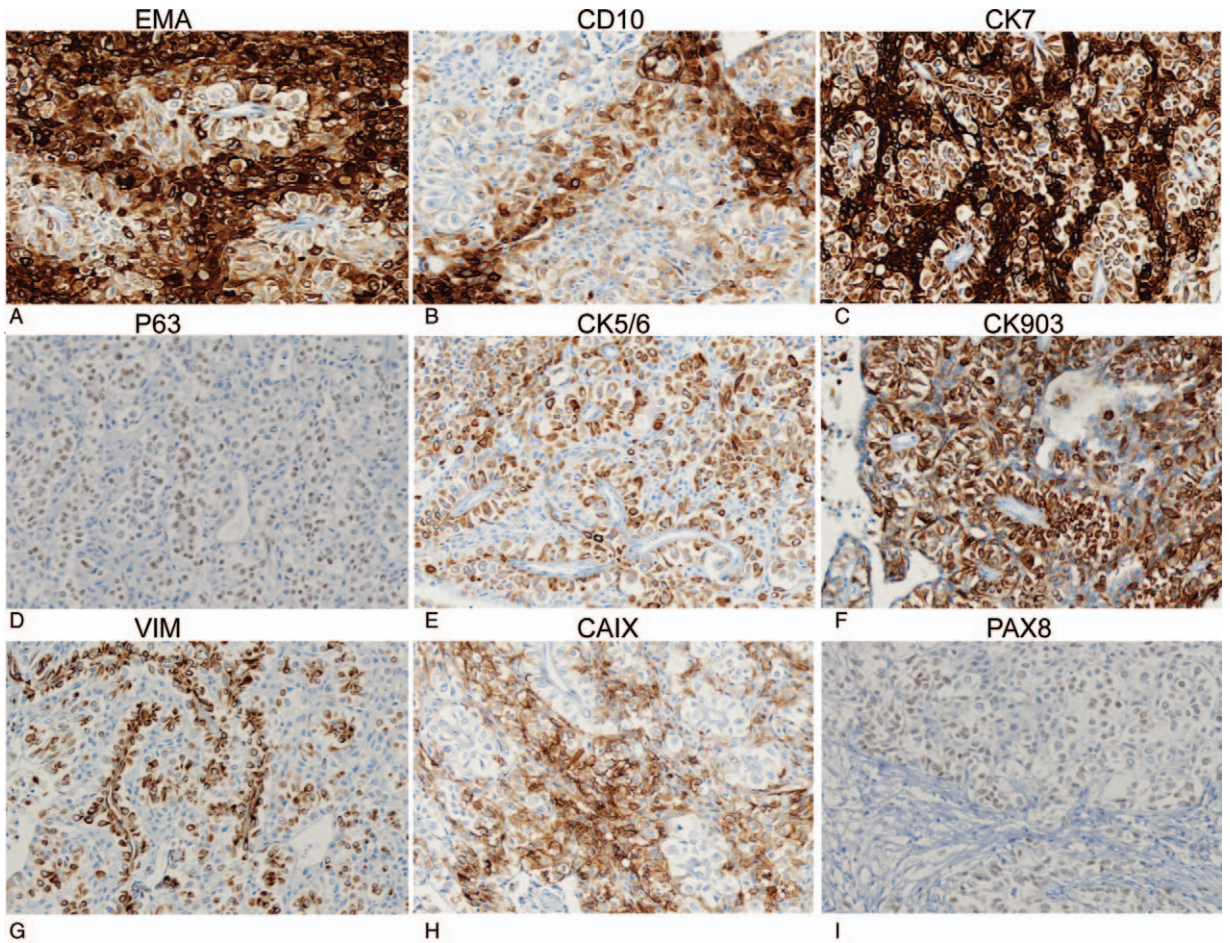

Figure 2. Immunohistochemical staining. Immunohistochemical analysis revealed a strong positive reaction for epithelial membrane antigen, CD10, and CK7 in the epithelial-like cells and a weakly positive reaction in myoepithelial-like cells (A–C, magnification, ×200). The myoepithelial-like cells stained strongly positive for CK5/6, CK903, and vimentin (E–G, magnification, ×200) and focally positive for P63 (D, magnification, ×200). Focal immunoreaction against CAIX and PAX-8 in these 2 types of cells was observed (H-I, magnification, ×200).

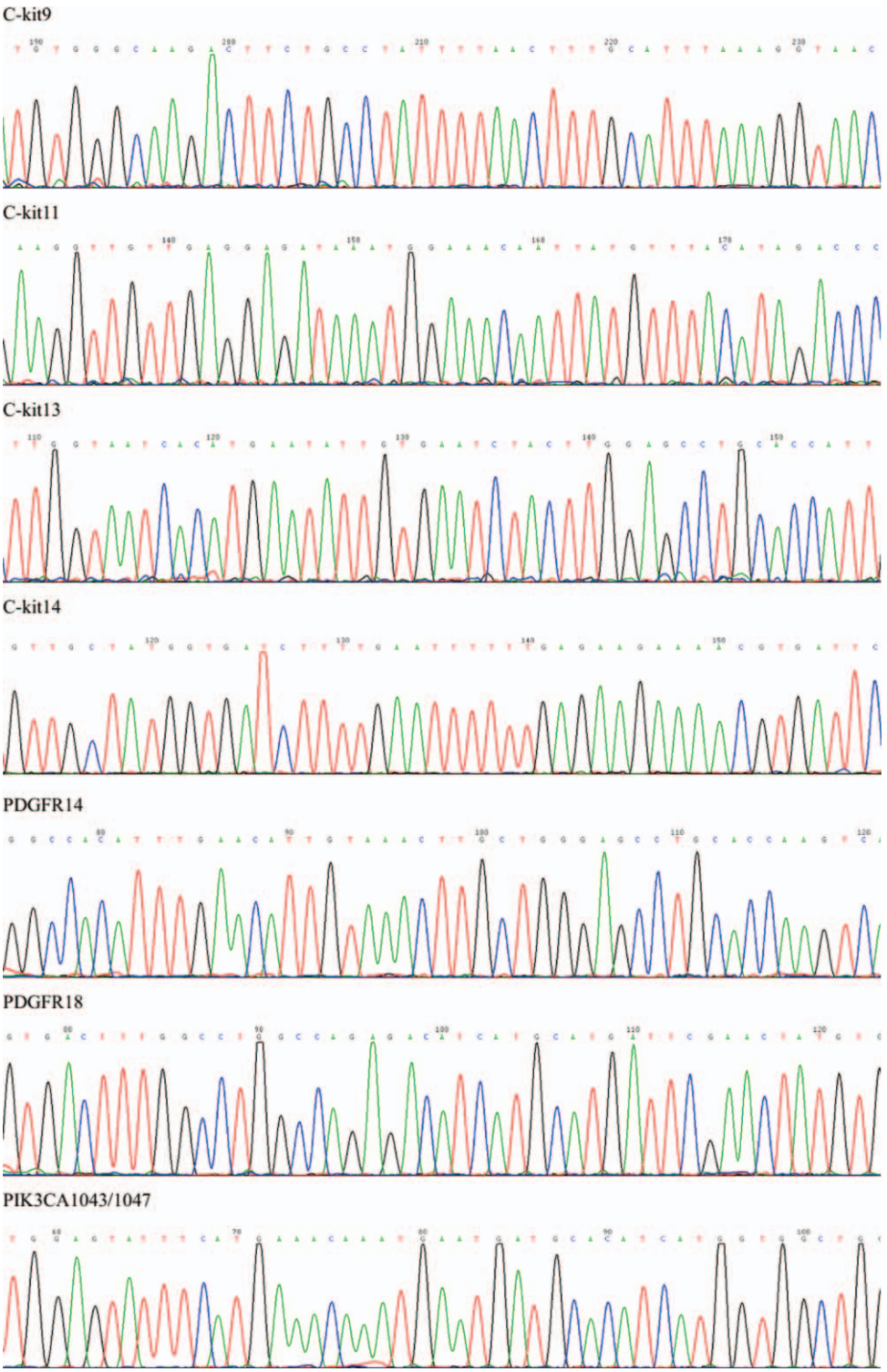

Figure 3. Gene sequencing showed no mutations in the C-kit 9, C-kit11, C-kit 13, C-kit 14, PDGFR14, PDGFR14, and PIK3CA genes.

with the responsibility to decide whether the evidence in support of the molecular clinical follow-up data and pathologic data to justify the recognition of any new distinct tumor entity within the classification system was adequate. Therefore, 3 other entities were added as a provisory in the 2016 WHO classification: anaplastic lymphoma kinase RCC, thyroid-like follicular carcinoma, and oncocytic RCC occurring after neuroblastoma. Much more progress has been made, and new renal tumors are expected to be increasingly recognized.

EMC, first described by Donath et al in 1972,[3] is a rare and unique tumor. EMC accounts for less than 1% of salivary gland tumors, and classically arises from the parotid gland in

Table 2

Summary of cases of salivary gland-type renal cell carcinoma.

Case No.	Age	Sex	Size (cm)	Histological features	TNM stage	prognosis
Case1[9]	48	M	1.0	Warthin's tumor features of the salivary gland	–	DUD 1 months
Case2[9]	64	M	6.0	Warthin's tumor features of the salivary gland	pT3	DOD 9 months
Case3[9]	69	F	3.0	Warthin's tumor features of the salivary gland	pT1	AW 12 months
Case4[9]	76	M	22	Warthin's tumor features of the salivary gland	pT3	DOD 12 months
Case5[9]	45	M	2.8	Warthin's tumor features of the salivary gland	pT1	AW 108 months, then lost to follow
Case6[9]	64	M	14.5	Warthin's tumor features of the salivary gland	pT2	LFU
Case7[9]	14	M	12.5	Warthin's tumor features of the salivary gland	pT2	DOD 36 months
Case8[9]	NA	M	NA	Warthin's tumor features of the salivary gland	NA	LFU
Case9[9]	59	M	2.5	Warthin's tumor features of the salivary gland	pT1	AW 108 months
Case10[9]	74	F	4.2	Warthin's tumor features of the salivary gland	pT1	AW 132 months
Case11[9]	75	F	1.5	Warthin's tumor features of the salivary gland	pT1	AW 10 months
Case12[10]	81	M	3.0	Adenoid cystic carcinoma features of the salivary gland	NA	An indolent fashion
Case13[11]	65	M	5.0	Pleomorphic adenoma of the salivary gland with basaloid features	NA	Low grade
Case14[12]	60	F	4.0	Basaloid and salivary type	NA	Liver metastasis 24 months
Case15 (current)	85	M	7.0	Epithelial myoepithelial carcinoma of the salivary gland with perivascular pseudorosette-like structure	pT1	Death of unknown reason 18 months

AW = alive and well, DOD = death of disease, DUD = death of unrelated disease, LFU = lost to follow up, NA = not available.

females.[4,5] This tumor commonly consists of an inner layer of eosinophilic, duct lining epithelial cells creating a tubular structure, surrounded by an outer layer of clear myoepithelial cells.[6] On immunohistochemical staining, the epithelial cells stain positive for epithelial markers, including cytokeratins and epithelial membrane antigens, but negative for myoepithelial cell markers, for example P63 and vimentin, thus demonstrating their epithelial nature.[7] In contrast, the cells surrounding these duct-forming cells demonstrate antagonistic characteristics; they are positive for myoepithelial cell markers but negative for epithelial cell markers, indicating their myoepithelial nature.[7,8] In our case, the epithelial-like cells were strongly immunoreactive for CK7, CK8, CK19, epithelial membrane antigen, CAM5.2, and CD10, and the myoepithelial-like cells stained strongly positive for vimentin, CK5/6, and CK903, and focally positive for P63 and P40. The immunohistochemical results showed that the tumor demonstrated epithelial and myoepithelial differentiation as can be observed in EMC, which differs from other common RCCs. Thus, the characteristics of the kidney tumor described herein primarily indicated renal metastasis of EMC of the salivary gland. A whole body computed tomography scan could not detect any other primary tumors.

Immunohistochemistry showed that PAX-8 and CAIX were focally positive in both types of tumor cells, suggesting that the tumor originated from the kidney.[2] A review of the literature regarding RCC expressing features of salivary gland tumors revealed a total of 15 cases (Table 2). Patient ages ranged from 14 to 85 years, with a male:female ratio of 11:4. The tumors ranged in size from 40 to 70 mm. Clinically, a few of the patients were asymptomatic, but in our case, the patient presented with recurrent episodes of hematuria and left flank pain.[9–12]

Strikingly, the tumor is characterized by a predominately biphenotypic perivascular pseudorosette-like growth pattern, which is consists of bilayered cells with an inner layer of myoepithelial-like cells and an outer layer of epithelial-like cells, which is not characteristic of EMC and RCC. These tumor cells were radially arranged around blood vessels and were polarized away from the vascular axis resembling the growth pattern of ependymoma. Some areas showed a diffuse growth pattern, wherein epithelial-like cells are mingled with the myoepithelial-like cells. The biphenotypic morphologic features are similar to those of another rare renal tumor, biphasic alveolosquamoid renal carcinoma, which is characterized by a biphasic neoplastic cell population exhibiting a predominantly alveolar architecture and squamoid differentiation among the neoplastic cell populations.[13]

We found that the lesion demonstrated moderate malignant features. It displayed an invasive growth pattern, a few mitotic figures and multiple necrosis, but lacked perineural or angiolymphatic invasion, significant mitotic activity, and a high Ki-67 index (7%).

Moreover, it is well known that the C-kit, PDGFR, and PIK3CA genes play an important role in the development and treatment of various tumors.[14,15] In our case, gene sequencing showed no mutations in C-kit 9, C-kit11, C-kit 13, C-kit 14, PDGFR14, PDGFR14, and PIK3CA. The presence of genetic alterations in the current case is still poorly understood, and further exploration is needed.

In conclusion, we diagnosed the tumor as a primary EMC-like tumor of the kidney showing a perivascular pseudorosette-like pattern. We believe that this tumor shows certain histologic features of the renal tube based on the morphologic and immunophenotypic profiles. Therefore, this tumor should be considered a distinct primary renal neoplasm, although the exact differentiation of the tumor remains to be further investigated. Recognizing this type of primary renal tumor can help avoid misdiagnosis as metastatic malignancy and thus avoid excessive chemoradiotherapy. The pathologic features suggest that the tumor will behave in a moderate malignant fashion. To the best of our knowledge, the present tumor has not been previously described, and thus, this variant has not been integrated into a known form of RCC. Therefore, we cannot diagnose this type of tumor with other types of kidney tumors, because their pathogenesis and treatment may be different, which still needs further study in more cases. Clinicians should be aware of the features of this uncommon variant to avoid diagnostic delays or misdiagnosis and prevent unnecessary or inappropriate treatment.

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Investigation: Zheng Mou.
Methodology: Huifeng Jiang.
Resources: Kun Yang.
Software: Kun Yang.
Writing – original draft: Qiuyao Li.
Writing – review & editing: Huifeng Jiang.

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