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Case report

Clear cell papillary renal cell carcinoma as part of histologically discordant multifocal renal cell carcinoma: A case report and review of literature

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ABSTRACT

Background: Multifocal renal cell carcinoma of different histological subtypes within a single kidney is rare. We report a recently classified clear cell (tubulo) papillary renal cell carcinoma as part of an unusual case of multifocal renal cell carcinoma of discordant histological subtypes.
Results: A 57 year-old-man was found to have multiple renal tumors and cysts on imaging and underwent a laparoscopic left radical nephrectomy. Pathological review showed multifocal renal cell carcinoma (clear cell (tubulo) papillary, clear cell and papillary renal cell carcinomas and papillary adenomas). Morphology of clear cell papillary renal cell carcinoma was supported by immunohistochemical profile (CK7+, HMWK+, CAIX+, AMACR−, CD10−, TFE3−).
Conclusions: This is the first report of clear cell papillary renal cell carcinoma as part of multifocal renal cell carcinoma of different histological subtypes. Related lineage of clear cell renal cell carcinoma and papillary renal cell carcinoma is supported by the highest prevalence of their combination within multifocal renal cell carcinoma of different histological subtypes along with their molecular interconnection. Clear cell papillary renal cell carcinoma may be uniquely placed between clear cell and papillary renal cell carcinomas since it shows morphological features intermediate between clear cell and papillary renal cell carcinoma along with overlapping but unique immunohistochemical profile.

Clear cell papillary renal cell carcinoma may be molecularly related to clear cell and papillary renal cell carcinomas since the tumors overexpress markers of HIF pathway activation with normal/elevated VHL mRNA expression and some tumors show losses of chromosome 3. Due to the overlapping morphology, it is possible that cases of clear cell papillary renal cell carcinoma may have been misclassified as papillary or clear cell renal cell carcinoma in the literature, incorrectly increasing their reported prevalence. Identification of multifocal RCCs may be related to the extent of pathological sampling.

1. Introduction

The frequency of sporadic multifocal renal cell carcinoma (RCC) is reported to be between 4 and 25% in patients undergoing unilateral radical nephrectomy, with clinically occult multifocality representing the majority [1–12]. Most multifocal tumors are of the same histological subtype; however, different histological subtypes are observed in up to 30% of cases of multifocal RCC [2–4]. The majority of cases with discordant tumor subtypes are composed of clear cell renal cell carcinoma (ccRCC) and papillary renal cell carcinoma (pRCC) [5,7,13]. Clear cell (tubulo) papillary renal

Abbreviations: RCC, renal cell carcinoma; pRCC, papillary renal cell carcinoma; ccRCC, clear cell renal cell carcinoma; ccpRCC, clear cell papillary renal cell carcinoma; HIF, hypoxia inducible factors; VHL, Von Hippel–Lindau.

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Table 1
Pathological findings and molecular analysis of tumors.

Diagnosis	Tumor 1 Clear cell RCC	Tumor 2 Papillary RCC	Tumor 3 Clear cell (tubulo) papillary RCC
Macroscopic features	5 cm Solid/cystic Yellow color Hemorrhage, focal	1.2 cm Solid Tan to yellow color Hemorrhage, focal	2 cm Cystic Tan-white color Papillary/granular content
Microscopic findings	Nests and alveoli surrounded by intricate fibrovascular septations. Clear cell cytology.	Fibrovascular cores lined by cells with eosinophilic cytoplasm and nuclear pseudostratification.	Well circumscribed, cystic with focal tubular/acinar features. Cells with clear cytoplasm. Nuclei in linear arrangement away from basal aspect of cells.
Stage Fuhrman nuclear grade Immunohistochemistry	pT1b 2 Positive for CD10, HMWK and focally for CK7. Negative for racemase and TFE3.	pT1a 3 Positive for CK7 and racemase.	pT1a 1 Positive for CK7 (diffuse, strong), CAIX and HMWK (patchy). Negative for CD10, racemase and TFE3.
VHL mutation sequencing 3x (3 fold coverage)	c.585_586delGAinsAT (p.Lys196Ter) 18% mutant allele	Normal	Normal
LOH VHL methylation status (PCR)	LOH present Normal	LOH present Normal	No LOH Normal

Molecular analysis of the background non-tumor kidney tissue showed no molecular changes (normal VHL sequencing, LOH N/A, and normal methylation status). Molecular analysis was performed by Impact Genetics (http://impactgenetics.com). Abbreviations: RCC – renal cell carcinoma; VHL – von-Hippel–Lindau; PCR – polymerase chain reaction; LOH – loss of heterozygosity.

cell carcinoma (ccpRCC) is a new entity that has recently been recognized as a distinct epithelial tumor by the International Society of Urological Pathology (ISUP) Vancouver Classification of Renal Neoplasia [14]. Here we report this novel entity as part of an unusual case of multifocal histologically discordant RCC.

2. Case report

2.1. Clinical history

This 57-year-old man with past medical history of diabetes mellitus, hypercholesterolemia, hypertension, asthma, obstructive sleep apnea, ankylosing spondylitis and morbid obesity was found to have incidental proteinuria. Initial CT scan of the abdomen showed a heterogeneous 6 cm enhancing mass, multiple complex cysts and a staghorn stone within the left kidney. At repeat staging, biphasic CT scan 2 months later showed three masses: a multiseptated exophytic mixed solid and cystic left upper pole mass with minimal eccentric calcification measuring 6.4 cm in maximum diameter; a second solid cortical mass measuring 1.5 cm in maximum diameter and a third ill-defined heterogeneous mass straddling the corticomedullary junction measuring 2.9 cm in maximum diameter. Multiple additional bilateral renal lesions were identified, favored to represent cysts. There was no evidence of extra-renal extension, contralateral renal mass or distal metastasis and the left staghorn stone was still in situ. There was no family or personal history suggestive of a von Hippel–Lindau (VHL) disease or syndrome, specifically, there was no history of hemangioblastomas, pheochromocytomas, multiple cysts in pancreas or kidneys, other than the kidney cysts reported in the imaging studies. The patient underwent a laparoscopic radical nephrectomy.

2.2. Pathological and molecular findings

The resected left kidney had four well circumscribed tumors, multiple simple cysts and a large staghorn and multiple small calculi occupying renal pelvis and calyces. Pathological and molecular findings of the three tumors are presented in Table 1 and Fig. 1. All tumors were confined to the renal parenchyma, none invaded the renal vasculature, ureters or renal sinus fat. None of the tumors had tumor necrosis (gross or microscopic) or sarcomatoid growth. Additional (fourth) tumor described on radiology was a papillary adenoma. On microscopic examination, multiple additional papillary adenomas were found. VHL functional status was assessed by mutational DNA sequencing, loss of heterozygosity (LOH) and VHL promoter methylation. A novel deletion/insertion mutation c.585_586delGAinsAT was identified in 18% of the malignant cells of ccRCC. The mosaic pattern of the mutation and its absence in the normal kidney suggests it is of somatic origin and that it arose later in the tumor progression sequence. There was also detectable LOH by microsatellite analysis in ccRCC. pRCC, despite showing LOH, had no accompanying detectable sequencing abnormalities or VHL promoter methylation. ccpRCC and the background non-tumor kidney parenchyma showed no VHL abnormalities.

3. Discussion

ccpRCC is a relatively recently recognized renal epithelial tumor. Its morphological features are intermediate between ccRCC and pRCC, with an overlapping but unique immunohistochemical profile. The tumor is characterized by variable papillary, tubular/acinar and cystic architecture with clear cells of low nuclear grade and linear arrangement of nuclei away from the basal aspect of cells. Its clinical behavior is that of a low stage, indolent tumor (limited data to date) [14]. It has also been suggested that renal angiomyoadenomatous tumor (RAT) may be related to ccpRCC and some consider these two tumors as a spectrum of a distinct tumor entity [15,16].

VHL alterations are the hallmark of ccRCC. Our findings of a VHL mutation and LOH in the ccRCC are consistent with the literature. Although VHL mutations have been recently described in ccpRCC at frequencies ranging from 15% to 30%, mutational analysis of ccpRCC in our case did not mimic these findings [15,16].