Original Article

Papillary renal neoplasm with reverse polarity: an observational study of histology, immunophenotypes, and molecular variation

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Background: Papillary renal neoplasm with reverse polarity (PRNRP) is a novel entity with unique clinicopathological characteristics, and only a small number of patients with PRNRP have been described.

Methods: We retrospectively analyzed the data for nine patients with PRNRP and evaluated differences in the clinical, histomorphological, immunohistochemical, and molecular features; prognosis; and differential diagnosis of PRNRP from other renal tumors with papillary structure.

Results: There were six males and three females aged 36 to 74 years (mean: 62.33 years; median: 68 years). All the tumors were solitary and ranged from 1 to 3.7 cm (mean: 2.17 cm; median: 2 cm), with three and six tumors arose in the left and right renal tract, respectively. Pathologically, PRNRP is a small, well-circumscribed neoplasm with predominant papillary formations. The lining epithelium is composed of a monolayer of cuboidal to low-columnar cells with low-grade nuclei arranged against the apical pole of the tumor cells. Edema, mucinous degeneration, and hyaline degeneration are found in the fibrovascular cores. Foamy macrophages, psammoma bodies, hemosiderin deposition, and infiltrative tumor boundaries were present in some patients. Immunohistochemically, all tumors showed diffuse positive staining for GATA3. Sanger sequencing confirmed the presence of *KRAS* mutation in seven patients. All patients had a good prognosis after surgery and were relapse free. Positive staining for GATA3 and negative staining for vimentin were the most significant markers for differentiating PRNRP from other renal tumors with analogous structure.

Conclusions: These findings suggested that PRNRP is a distinctive subtype of renal tumor with specific pathological features and indolent behaviors that should be distinguished from other renal tumors, especially papillary renal cell carcinoma. A monolayer of tumor cells with an inverted nuclear pattern, positive staining for *GATA3*, and KRAS mutation are essential for pathological diagnosis. Owing to its satisfactory prognosis, the surveillance and follow-up of patients with PRNRP should be additionally formulated.

Keywords: Papillary renal cell carcinoma (PRCC); renal tumor; GATA3; *KRAS* mutation

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Introduction

Many renal tumors with distinctive histomorphology, combined components or molecular variations have been classified independently in recent years (1). Many of these tumors were once regarded as papillary renal cell carcinoma (PRCC) (2). Due to the poor prognosis of patients with PRCC, it is highly important to continually differentiate the independent entities associated with good clinical outcomes from PRCC.

In 1997, Delahunt and Eble subdivided PRCC into type 1 and type 2 (3), and this concept was recognized in the previous World Health Organization (WHO) classification (4). However, dichotomizing PRCC may be challenging since many tumors frequently harbor mixtures of two types of tumors and because the distributions of type 1 and type 2 tumors do not influence patient outcomes, type 1 and type 2 subtyping of PRCC is not recommended in the new 2022 WHO classification (5). In addition to the above typical PRCCs and some renal cell carcinomas with special molecular mutations and papillary or tubulopapillary architectures, such as MiT family translocation renal cell carcinoma (6) and fumarate hydratase (FH)-deficient renal cell carcinoma (7), there are still many series that are difficult to classify and are provisionally defined as "PRCC, mixed type" (8,9).

Among those tumors, there is a subset with monolayer cells with mild atypical nuclei and rich eosinophilic cytoplasm as well as a good prognosis. These tumors with the same features on a microphotograph had been termed oncocytoid-type PRCC (10,11), PRCC, type 4/oncocytic low grade (12), or renal papillary adenoma, type D (13). However, how to accurately identify the vague features of "eosinophilic rich cytoplasm" and "mild nuclear atypical" without noticeable morphological characteristics or homoplastic immunohistochemical markers makes these terminologies unconvincing. In 2019, Al-Obaidy *et al.* reviewed these reports and noted that there was a subgroup that had distinctively apically located nuclei and coexpressed GATA3 and L1CAM, making this entity easy to identify; on this basis, considering its indolent course, they named it papillary renal neoplasm with reverse polarity (PRNRP) (14). Since then, they found that *KRAS* mutation frequently occurred in this kind of tumor (15), which further verified this peculiar entity.

Given its very recent use as a subclassification tool for renal tumors, few papers have evaluated its clinical features, pathological morphology, immunohistochemistry, molecular characteristics, prognosis, and differential diagnosis. Consequently, we collected the data for nine such patients and compared them with those of other patients with renal tumors and similar architectures to improve the understanding of the disease. We present this article in accordance with the STROBE reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-23-518/rc).

Highlight box

Key findings

- This study reported the clinicopathological characteristics of nine patients with papillary renal neoplasm with reverse polarity (PRNRP).
- This study compared the clinicopathological characteristics of PRNRP with other renal tumors with similar features.

What is known and what is new?

- A monolayer of tumor cells with inverted nuclei, positive staining for *GATA3*, and *KRAS* mutation are essential for the diagnosis of PRNRP.
- This study slightly expanded the morphological spectrum of the entity (one case with psammoma body formation).
- This study used many immunohistochemical markers of molecularly-defined renal tumor that had not been used to characterize PRNRP before.

What is the implication, and what should change now?

- PRNRP is a novel subtype of renal tumor with specific pathological features and indolent behaviors that should be distinguished from other renal tumors.
- Patients with PRNRP are able to adopt a more personalized surveillance and follow-up plan.

Methods

Patient selection

We retrospectively screened nine patients with PRNRP previously treated at Changhai Hospital between August 2017 and November 2021 and collected clinicopathological data. The histomorphological criteria were as follows: (I) the tumor consisted of predominantly thin papillae with or without tubules; (II) the cuboidal to columnar tumor cells were arranged in a single layer lined with the papilla with a finely granular eosinophilic cytoplasm; and (III) the tumor cells had apically located nonoverlapping nuclei (14). In addition, forty PRCCs (twenty type 1 tumors and twenty

Table 1 Information on the primary antibodies

Antigen	Clone	Dilution	Positive localization	Company
GATA3	EP368	Prediluted	Nucleus	Beijing Zhong Shan Goldenbridge Biotech. Co., Ltd
CK7	OV-TL12/30	Prediluted	Cell membrane and cytoplasm	Fuzhou Maixin Biotech. Co., Ltd.
MUC1	EP85	Prediluted	Cell membrane and cytoplasm	Beijing Zhong Shan Goldenbridge Biotech. Co., Ltd
PAX8	EP298	Prediluted	Nucleus	Fuzhou Maixin Biotech. Co., Ltd.
Vimentin	MX034	Prediluted	Cytoplasm	Fuzhou Maixin Biotech. Co., Ltd.
CD10	UMAB235	Prediluted	Cell membrane	Beijing Zhong Shan Goldenbridge Biotech. Co., Ltd
CAIX	H-11	Prediluted	Cell membrane and cytoplasm	Fuzhou Maixin Biotech. Co., Ltd.
CD117	YR145	Prediluted	Cell membrane	Fuzhou Maixin Biotech. Co., Ltd.
P504S	13H4	Prediluted	Cytoplasm	Fuzhou Maixin Biotech. Co., Ltd.
FH	OTI1F10	Prediluted	Cytoplasm	Beijing Zhong Shan Goldenbridge Biotech. Co., Ltd
SDHB	OTI1H6	Prediluted	Cytoplasm	Beijing Zhong Shan Goldenbridge Biotech. Co., Ltd
TFE3	MRQ-37	Prediluted	Nucleus	Fuzhou Maixin Biotech. Co., Ltd.
p53	DO-7	Prediluted	Nucleus	Beijing Zhong Shan Goldenbridge Biotech. Co., Ltd
Ki-67	UMAB107	Prediluted	Nucleus	Beijing Zhong Shan Goldenbridge Biotech. Co., Ltd

type 2 tumors), ten clear cell papillary renal cell tumors (ccPRCTs), and three low-grade oncocytic tumors (LOTs) of the kidney were selected from the archives of Changhai Hospital for comparison with PRNRPs (4). Notably, according to the 5th edition of the WHO classification of renal tumors, PRCC was not subdivided into two types (5); therefore, we compared the clinicopathological characteristics of PRNRPs with those of all PRCCs. All the sections were independently reviewed by two experienced pathologists.

The clinical data for all patients were collected from the electronic records. All tumors were graded according to the WHO/International Society of Urological Pathology (ISUP) grading system (16) and staged based on the eighth edition of the tumor-node-metastasis (TNM) staging system (17). Follow-up data were obtained from the patients' electronic records and telephone interviews. Recurrence-free survival and overall survival were collected to evaluate patient prognosis. The follow-up information was censored through November 2022. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study obtained approval from the Ethics Committee of Changhai Hospital (No. CHEC2021-191). Individual consent for this retrospective analysis was waived.

Immunohistochemical analysis

One 4 μm thick tissue section was cut from formalin-fixed paraffin-embedded (FFPE) tumor tissue sections for immunohistochemical analysis of GATA3, CK7, MUC1, PAX8, vimentin, CD10, CAIX, stem cell factor receptor (CD117), P504S, FH, succinate dehydrogenase complex iron sulfur subunit B (SDHB), Transcription factor E3 (TFE3), p53, and Ki-67. The staining patterns and production information for these primary monoclonal antibodies are shown in *Table 1*. Staining was performed on a Leica Bond-Max autostainer (Leica Microsystems GmbH, Wetzlar, Germany). The extent and intensity of the staining were comprehensively evaluated and recorded as negative (–), weak (+), moderate (++), or strong (+++).

Genetic analysis

We used five to ten 10 μm thick tissue sections cut from FFPE tissues to test alterations in the *KRAS* gene via Sanger sequencing. DNA extraction was performed using an AmoyDx FFPE DNA Kit (AmoyDx, Xiamen, China). Polymerase chain reaction (PCR) was employed using primer pairs covering hot spots corresponding to exons 2, 3 and 4 of *KRAS*. PCR was performed using an automatic

Table 2 Clinical features of PRNRPs

Case	Gender	Age (years)	BMI (kg/m^2)	A history of smoking	Family history of renal tumor	Hypertension	Chronic kidney disease	Symptom	Synchronous tumor	Surgery	Follow-up (months)
1	Male	36	25.86	No	No	No	No	No	No	Partial nephrectomy	63.97
2	Female	39	19.53	No	No	No	No	No	No	Partial nephrectomy	51.60
3	Female	68	25.39	No	No	Yes	No	No	No	Partial nephrectomy	46.07
4	Male	71	26.45	No	No	Yes	No	Lower back pain	PRCC, left kidney	Partial nephrectomy	45.37
5	Male	72	22.84	No	No	Yes	Yes	No	No	Radical nephrectomy	36.97
6	Male	67	21.95	No	No	No	No	No	No	Partial nephrectomy	30.90
7	Male	71	29.76	No	No	Yes	Yes	No	No	Partial nephrectomy	18.83
8	Male	63	24.44	No	No	Yes	No	No	No	Partial nephrectomy	18.47
9	Female	74	26.23	No	No	Yes	No	No	No	Partial nephrectomy	11.53

PRNRP, papillary renal neoplasm with reverse polarity; BMI, body mass index; PRCC, papillary renal cell carcinoma.

thermal cycler (ABI 2720; Applied Biosystems, Waltham, MA, USA). The sequencing results were analyzed with 'Chromas' software (Technelysium Pty Ltd., Brisbane, QLD, Australia).

Statistical analysis

Continuous variables are expressed as the mean ± standard deviation and were analyzed with Student's *t*-test or the Mann-Whitney U test, when appropriate. Categorical variables are expressed as the number of patients (percentages) and were compared with Yates's correction for continuity or Fisher's exact test. All P values were two tailed, and P<0.05 was considered to indicate statistical significance. All the statistical analyses were conducted with SPSS 27.0 (IBM, New York, USA).

Results

Clinical characteristics

The clinical features for nine patients with a history of PRNRP are listed in *Table 2*. There were six males and three females with an average age of 62.33 years (ranging from 36 to 74 years). No patient had a body mass index greater than 30 kg/m^2. No patient had a history of smoking or a family history of renal cancer. Six patients suffered from hypertension. Patients 5 and 7 had been diagnosed with chronic kidney disease before surgery. Eight patients had PRNRPs detected via routine medical physical examination, and the remaining patient 4 was hospitalized for lower back pain. Patient 4 simultaneously had a PRCC in the left kidney with the largest diameter of 3.1 cm.

Pathological characteristics

There were three and six tumors arising in the left and right renal regions, respectively. Grossly, eight tumors appeared as solid masses with a soft to medium consistency (*Figure 1*), and the other tumor presented as a cystic mass with papillae visible on the wall. All lesions were well circumscribed without a pseudocapsule. The tumor size ranged from 1 to 3.7 cm (mean 2.17 cm, median 2 cm). Obvious hemorrhages occurred in the foci of patients 1 and 2. All the resected PRNRPs were staged as pT1a. The gross pathological characteristics of the nine tumors are shown in *Table 3*.

Microscopically, the tumors consisted predominantly of thin filiform papillae formed by the arborizing proliferation of delicate fibrovascular cores (*Figure 2A*). Scattered tubular architectures were detected in patient 9 (*Figure 2B*). There were no complex tertiary branching papillae in any of the tumors, whereas fused papillae were observed in patients 1, 5, and 7 (*Figure 2C*). The tumor cells were monotonous cuboidal or low columnar with a voluminous and eosinophilic finely granular cytoplasm

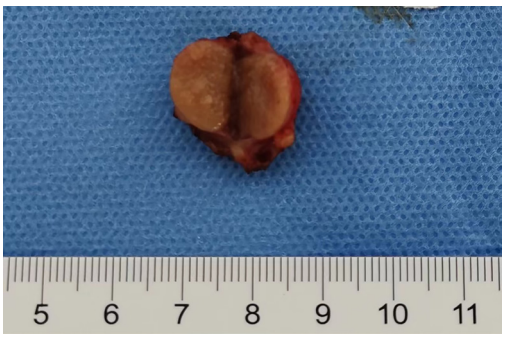

Figure 1 Gross appearance of papillary renal neoplasm with reverse polarity. The cut surface of the tumor was grayish yellow in color, solid to medium in quality, and had a clear boundary with the surrounding renal tissue.

Table 3 Gross pathological features of PRNRPs

Cases	Location	Size (cm)	Number	Texture	T staging
1	Right	1.5	Solitary	Solid	pT1a
2	Right	1.8	Solitary	Solid	pT1a
3	Right	1	Solitary	Solid	pT1a
4	Right	2	Solitary	Solid	pT1a
5	Left	3.7	Solitary	Solid	pT1a
6	Right	3	Solitary	Solid	pT1a
7	Left	2.7	Solitary	Solid	pT1a
8	Left	2.2	Solitary	Cystic	pT1a
9	Right	1.6	Solitary	Solid	pT1a

PRNRP, papillary renal neoplasm with reverse polarity.

arranged in a single layer on the fibrovascular core. The nuclei were characteristically aligned at the apex opposite the basement membrane with smooth overlying luminal borders (*Figure 2D*). The nuclei were nonoverlapping and small with regular contours and inconspicuous nucleoli, leaving all the tumors WHO/ISUP grade 1. Interstitial edema of the papillae was observed in six tumors, hyaline degeneration in five tumors, and mucinous degeneration in five tumors. The peripheral region of three lesions contained a few foamy macrophages (*Figure 2E*), and a sporadic psammoma body was encountered only in patient 6 (*Figure 2F*). Varying hemorrhages were present in all tumors except for patient 9 (*Figure 2G*). Hemosiderin was deposited in five tumors. There were sparse inflammatory cells infiltrating into seven tumors, while the other two tumors exhibited abundant infiltration (*Figure 2H*). All the tumors had a discernible boundary without a pseudocapsule, and some irregular protuberances penetrating into the surrounding kidney parenchyma were observed in patients 7 and 9 (*Figure 2I*). The histological characteristics of the nine PRNRPs are shown in *Table 4*.

Immunohistochemical characteristics

A summary of the immunohistochemical staining is shown in *Table 5*. All nine tumors from the PRNRP cohort showed diffuse strong positive expression of GATA3 (*Figure 3A*). Six tumors were negative for vimentin (*Figure 3B*). Seven and eight tumors showed positive staining for CK7 and MUC1, respectively (*Figure 3C,3D*). PAX8 was positive with moderate to strong staining in all tumors. Four and six tumors showed different degrees of staining of CD10 and CAIX, respectively. P504S showed weak to strong positive expression in seven tumors (patients 3–9, *Figure 3E*). No tumor showed aberrant staining of CD117, FH, SDHB, or TFE3. p53 showed as wild type in all tumors. The Ki-67-positive rate ranged from 1% to 5% (*Figure 3F*).

KRAS mutational analysis

Sanger sequencing of *KRAS* exons 2, 3 and 4 was performed for all tumors. Seven (77.8%) of the nine tumors harbored *KRAS* gene mutations at codon 12 of exon 2. In the aggregate, c.35G>A (G12D) (n=4; patients 1, 5, 7, and 9) and c.35G>T (G12V) (n=3; patients 2, 4, and 6) were identified (*Figure 4*). Two tumors (patients 3 and 8) with typical histomorphology and consistent immunohistochemical staining for GATA3 were positive for the wild-type *KRAS* gene.

Follow-up

Eight patients underwent partial nephrectomy, except for patient 5, who underwent radical nephrectomy. No patients underwent regional lymphadenectomy. All patients recovered well without serious perioperative complications. During the follow-up, all patients achieved a good prognosis without recurrence (range, 11.53–63.97 months, mean 35.97 months, median 36.97 months). However, patient 4 was diagnosed with acinar adenocarcinoma of the prostate two months after nephrectomy.

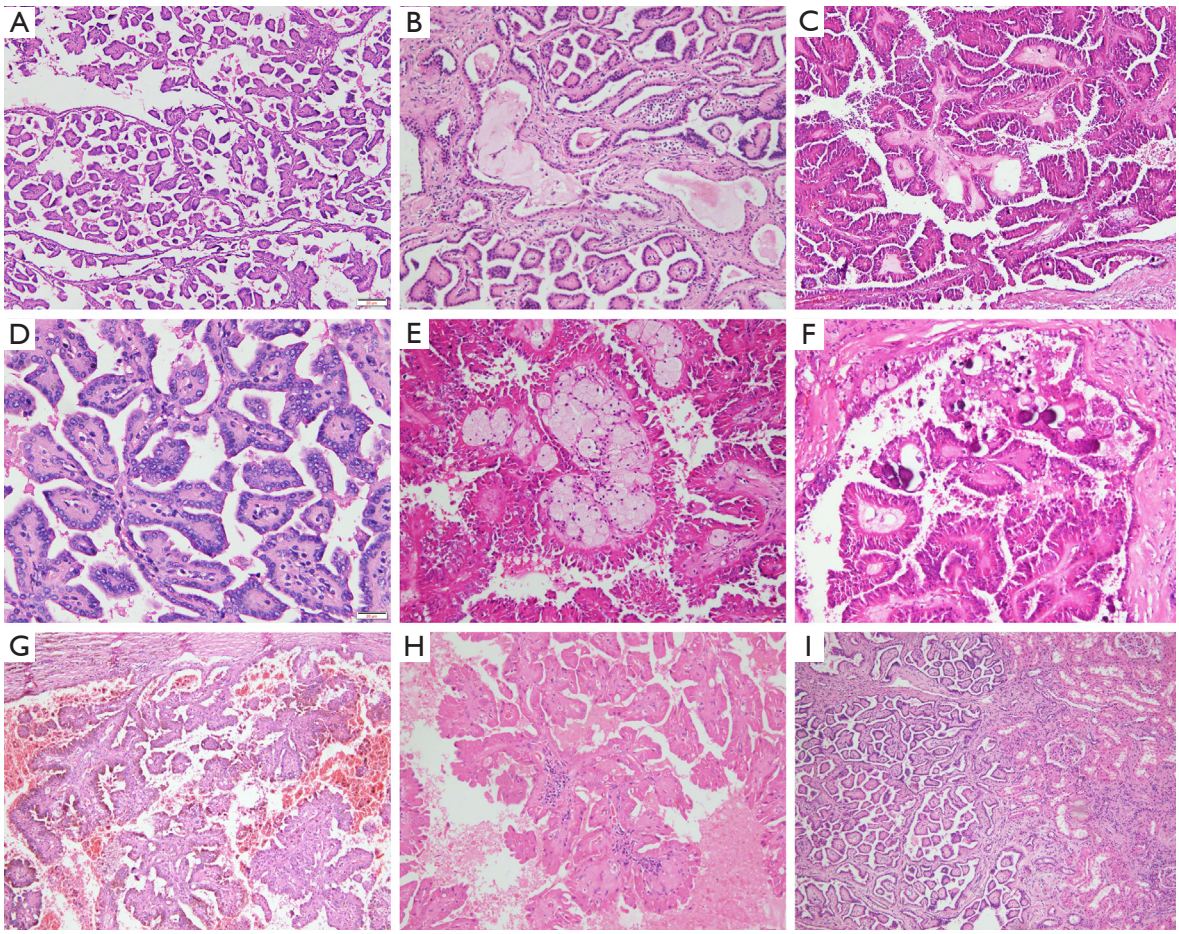

Figure 2 Microscopy images of papillary renal neoplasm with reverse polarity (hematoxylin-eosin staining). (A) Predominantly thin filiform papillae of the tumor (×100); (B) tubular architecture of the tumor (×200); (C) fused papillae structure of the tumor (×100); (D) monolayer of tumor cells with inverted nuclei (×400); (E) foamy macrophages in the tumor (×200); (F) sporadic psammoma in the tumor (×200); (G) hemorrhage in the tumor (×100); (H) a small amount of lymphocyte infiltration in the papillary axis (×200); (I) no pseudocapsule at the tumor boundary (×100).

Table 4 Histopathological features of PRNRPs

Case	Tubular structure	Fused papillary structure	Edema	Mucinous degeneration	Hyaline degeneration	Foamy macrophage	Psammoma body	Inflamation	Hemorrhage	Hemosiderin deposition	Infiltrating growth boundary
1	No	Yes	Yes	Yes	Yes	No	No	Inconspicuous	Prominent	Yes	No
2	No	No	No	Yes	Yes	No	No	Inconspicuous	Prominent	Yes	No
3	No	No	Yes	No	No	No	No	Inconspicuous	Inconspicuous	No	No
4	No	No	Yes	Yes	Yes	No	No	Inconspicuous	Inconspicuous	Yes	No
5	No	Yes	Yes	No	No	A few	No	Prominent	Inconspicuous	Yes	No
6	No	No	Yes	Yes	Yes	A few	A few	Inconspicuous	Inconspicuous	No	No
7	No	Yes	Yes	Yes	Yes	A few	No	Inconspicuous	Inconspicuous	No	Yes
8	No	No	No	No	No	No	No	Inconspicuous	Inconspicuous	Yes	No
9	A few	No	No	No	No	No	No	Prominent	No	No	Yes

PRNRP, papillary renal neoplasm with reverse polarity.

Table 5 Immunohistochemical features of PRNRPs

Case	GATA3	CK7	MUC1	PAX-8	Vimentin	CD10	CAIX	P504S	CD117	FH	SDHB	TFE3	p53	Ki-67
1	+++	+	+++	++	–	++	–	–	–	+++	+++	–	Wild type	5%
2	+++	++	+++	++	++	–	++	–	–	+++	+++	–	Wild type	2%
3	+++	++	+	+++	–	–	++	+	–	+++	+++	–	Wild type	1%
4	+++	+	++	+++	–	–	++	++	–	+++	+++	–	Wild type	2%
5	+++	–	+++	++	–	+++	+	+++	–	+++	+++	–	Wild type	5%
6	+++	+	+++	+++	–	+	+	+++	–	+++	+++	–	Wild type	2%
7	+++	–	–	+++	+++	++	+	+++	–	+++	+++	–	Wild type	5%
8	+++	++	+++	++	+	–	–	++	–	+++	+++	–	Wild type	3%
9	+++	++	+++	+++	–	–	–	++	–	+++	+++	–	Wild type	1%

PRNRP, papillary renal neoplasm with reverse polarity. –, negative expression; +, weak expression; ++, moderate expression; +++, strong expression.

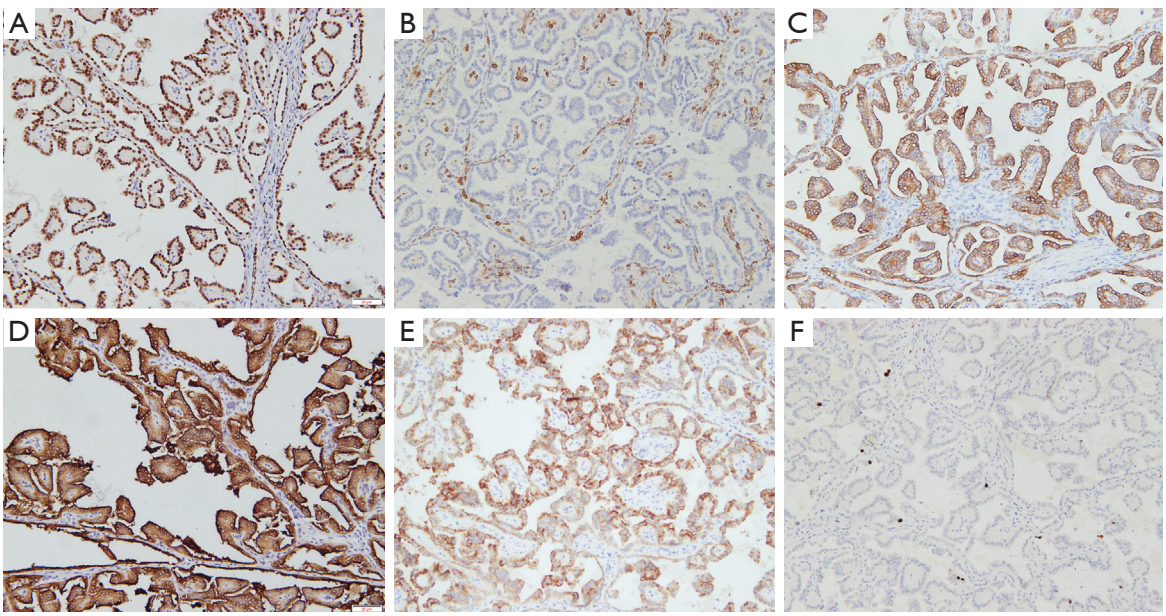

Figure 3 Immunohistochemical images of papillary renal neoplasm with reverse polarity. (A) GATA3-positive cells (×200); (B) vimentin-negative cells (×200); (C) CK7-positive cells (×200); (D) MUC1-positive cells (×200); (E) P504S-positive cells (×200); (F) low percentage of Ki-67-positive cells (×200).

Comparison between PRNRPs and other types of renal tumors

Table 6 shows the basic clinical and immunohistochemical data for patients with PRNRP, PRCC, type 1 PRCC, type 2 PRCC, ccPRCT, and LOT. Positive staining for GATA3 and negative staining for vimentin were the most significant parameters for distinguishing PRNRPs from PRCCs and ccPRCTs. In addition, compared with that of PRCCs but not that of ccPRCTs, the tumor size of PRNRPs was usually smaller. The positive rate of CAIX expression was lower in type 1 PRCCs in contrast to PRNRPs. The positive rate of P504S expression was greater in PRCCs than in PRNRPs, but the difference was not significant in both of subtypes. There were no significantly different clinicopathological

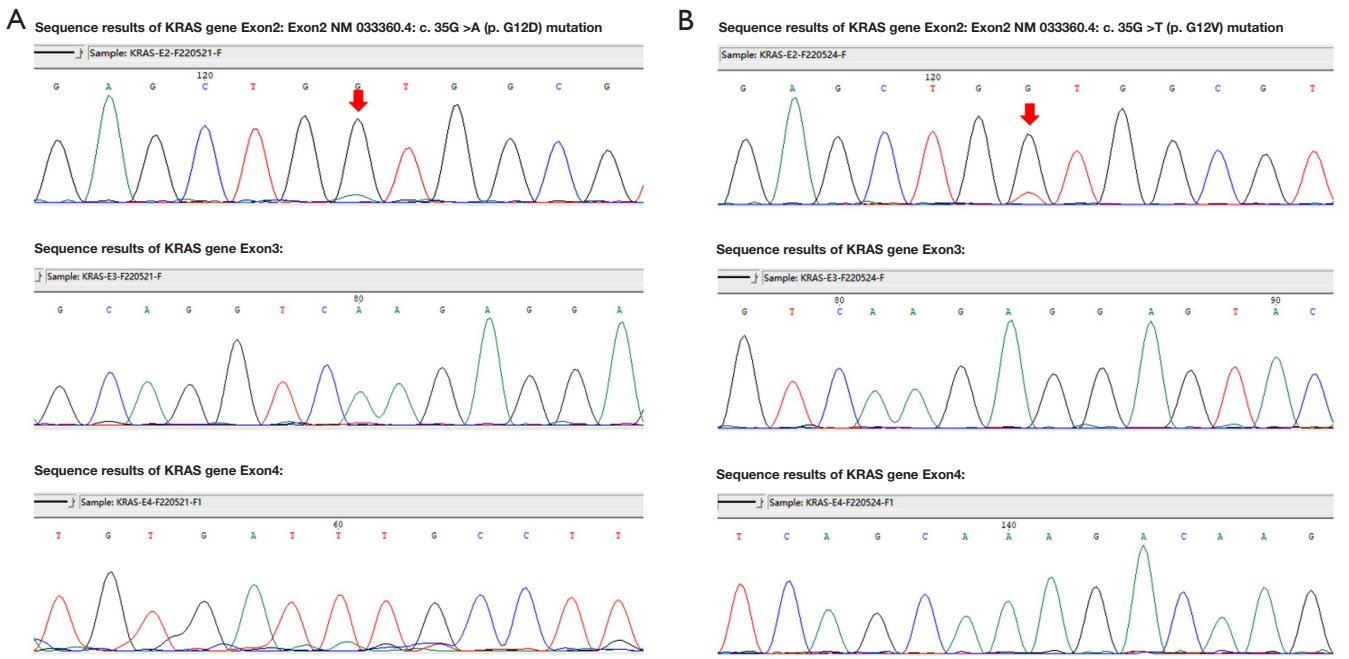

Figure 4 Molecular variation in papillary renal neoplasm with reverse polarity. (A) Representative results of p.G12D; (B) representative results of p.G12V. Arrow: mutation site.

parameters between PRNRPs and LOTs.

Discussion

PRNRP is an extremely rare novel subtype of renal tumor that can morphologically mimic PRCC and papillary adenoma and accounts for 0.49% of renal tumors (18). Due to its unique histological characteristics, immunohistochemical phenotype, molecular changes, and good prognosis, it is necessary to distinguish it from other types of renal tumors, especially PRCC. Based on previous studies, approximately 4–9% of previously diagnosed PRCCs were actually PRNPRs (18,19). Misdiagnosis can cause mental burden and lead to unnecessary therapies for patients with PRNRP. As such, pathologists should be able to fully recognize such tumors in routine work.

In the past two decades, PRNRP has been classified into a wide range of tumor sets and named with various terms based on the different inclusion criteria selected as shown in the varied microscopic images in numerous studies. (I) Oncocytic or oncocytoid PRCC—in the paper published by Allory and his colleagues, four such tumors were identified, and the authors emphasized that the tumor cells of this entity were medium- to large-sized and eosinophilic, with a round regular nucleus and a low nucleus/cytoplasm ratio. The nuclei usually exhibit a conspicuous nucleolus (20). Hes *et al.*, Kunju *et al.*, and Han *et al.* further analyzed the immunohistochemical features of these tumors but obtained inconsistent results (positive rate: CK7 33% *vs.* 100% *vs.* 21%; CD10 83% *vs.* 100% *vs.* 86%) (21-23). The above results indicated that when defining a new subset of renal tumors, merely an eosinophilic cytoplasm might result in overinclusion. (II) Papillary renal tumor with oncocytic cells—given that such tumors often have a good prognosis, some scholars have begun to use "tumor" instead of "carcinoma" (24). (III) Papillary adenoma—according to the WHO classification, papillary adenoma is defined as unencapsulated tumors with papillary or tubular architecture of low WHO/ISUP grade and a diameter of ≤15 mm (5). A study conducted by Chang *et al.* proved that type D papillary adenoma and PRNRP were indistinguishable if the size was unknown. Both entities showed diffuse and strong GATA3 expression and recurrent *KRAS* mutation (19). Therefore, some PRNRPs are diagnosed as a specific subtype of papillary adenoma owing to the small tumor size (13). *KRAS* mutation is likely an early molecular event in the tumorigenesis of PRNRP (19). All the above three archaic terms include partial PRNRPs but without further elaboration of their independent characteristics. In 2009, Park BH and colleagues first proposed that inverted

Table 6 Comparation of PRNRP and other renal tumors

Characteristics	PRNRP	PRCC	P value	PRCC, type 1	P value	PRCC, type 2	P value	ccPRCT	P value	LOT	P value
Number of cases	9	40		20		20		10		3	
Sex			0.672		0.287		>0.99		>0.99		>0.99
Male	6 (66.7)	32 (80.0)		18 (90.0)		14 (70.0)		6 (60.0)		2 (66.7)	
Female	3 (33.3)	8 (20.0)		2 (10.0)		6 (30.0)		4 (40.0)		1 (33.3)	
Age, years	62.33±14.46	54.57±13.41	0.072	54.70±10.63	0.055	54.45±16.01	0.183	58.60±16.11	0.549	66.00±5.57	0.685
Tumor size, cm	2.17±0.84	4.03±2.77	0.003	3.22±1.35	0.049	4.84±3.54	<0.001	1.99±0.69	0.780	2.17±1.19	>0.99
Tumor location			>0.99		0.245		0.339		0.370		>0.99
Left renal	6 (66.7)	25 (62.5)		8 (40.0)		17 (85.0)		4 (40.0)		1 (33.3)	
Right renal	3 (33.3)	15 (37.5)		12 (60.0)		3 (15.0)		6 (60.0)		2 (66.7)	
Surgery			0.758		0.532		0.201		>0.99		>0.99
Partial nephrectomy	8 (88.9)	31 (77.5)		19 (95.0)		12 (60.0)		8 (80.0)		3 (100.0)	
Radical nephrectomy	1 (11.1)	9 (22.5)		1 (5.0)		8 (40.0)		2 (20.0)		0 (0.0)	
GATA3			<0.001		<0.001		<0.001		<0.001		>0.99
Positive	9 (100.0)	0 (0.0)		0 (0.0)		0 (0.0)		0 (0.0)		3 (100.0)	
Negative	0 (0.0)	40 (100.0)		20 (100.0)		20 (100.0)		10 (100.0)		0 (0.0)	
CK7			0.953		0.568		0.234		0.211		>0.99
Positive	7 (77.8)	28 (70.0)		18 (90.0)		10 (50.0)		10 (100.0)		3 (100.0)	
Negative	2 (22.2)	12 (30.0)		2 (10.0)		10 (50.0)		0 (0.0)		0 (0.0)	
MUC1			>0.99		0.532		0.633		0.474		>0.99
Positive	8 (88.9)	34 (85.0)		19 (95.0)		15 (75.0)		10 (100.0)		3 (100.0)	
Negative	1 (11.1)	6 (15.0)		1 (5.0)		5 (25.0)		0 (0.0)		0 (0.0)	
PAX8			>0.99		>0.99		>0.99		>0.99		>0.99
Positive	9 (100.0)	40 (100.0)		20 (100.0)		20 (100.0)		10 (100.0)		3 (100.0)	
Negative	0 (0.0)	0 (0.0)		0 (0.0)		0 (0.0)		0 (0.0)		0 (0.0)	
Vimentin			0.009		0.032		0.010		0.003		0.509
Positive	3 (33.3)	33 (82.5)		16 (80.0)		17 (85.0)		10 (100.0)		0 (0.0)	
Negative	6 (66.7)	7 (17.5)		4 (20.0)		3 (15.0)		0 (0.0)		3 (100.0)	
CD10			0.361		0.237		0.422		>0.99		0.491
Positive	4 (44.4)	27 (67.5)		14 (70.0)		13 (65.0)		4 (40.0)		0 (0.0)	
Negative	5 (55.6)	13 (32.5)		6 (30.0)		7 (35.0)		6 (60.0)		3 (100.0)	
CAIX			0.093		0.010		0.427		0.087		0.182
Positive	6 (66.7)	12 (30.0)		3 (15.0)		9 (45.0)		10 (100.0)		0 (0.0)	
Negative	3 (33.3)	28 (70.0)		17 (85.0)		11 (55.0)		0 (0.0)		3 (100.0)	
P504S			0.031		0.089		0.089		0.170		0.236
Positive	7 (77.8)	40 (100.0)		20 (100.0)		20 (100.0)		4 (40.0)		1 (33.3)	
Negative	2 (22.2)	0 (0.0)		0 (0.0)		0 (0.0)		6 (60.0)		2 (66.7)	

Data are presented as mean ± standard deviation or patients (%). PRNRP, papillary renal neoplasm with reverse polarity; PRCC, papillary renal cell carcinoma; ccPRCT, clear cell papillary renal cell tumor; LOT, low-grade oncocytic tumor.

nuclei could characterize a subset of oncocytic PRCC with an indolent clinical outcome (25). However, they did not find any deterministic immunohistochemical markers or molecular variations; therefore, this terminology was insufficient. In 2019, Al-Obaidy *et al.* proposed the term PRNRP, and its diagnosis could be aided by positive staining for GATA3 and L1CAM along with negative expression of vimentin (14). Furthermore, a subsequent study demonstrated that recurrent *KRAS* mutation emerged in PRNRPs (15). To date, the PRNRP has been widely accepted as a distinct entity and was cited in the 5th edition of the WHO classification (5).

According to a recent literature review, 97 patients with PRNRP exhibited a significant male predominance (male to female: 72.06% *vs.* 27.94%) and a mean age of 63.79 years (26). In our study, there was a clear similarity in both the sex ratio (male to female: 66.67% *vs.* 33.33%) and the mean age of onset (62.33 years) with the above results. The patients in our study generally did not present with common risk factors for renal cell carcinoma, such as a family history of renal tumor, smoking, or obesity (27). Remarkably, two patients (22.2%) had chronic kidney disease, the incidence of which was highly consistent with previous reports (18,19,28). Because of its indolent biological behaviors, the vast majority of patients are diagnosed via physical examination without symptoms or signs (26). In our cohort, there was only one patient with lower back pain, but this pain was more likely associated with contralateral PRCC. All patients survived without recurrence, metastasis or death within 11.53–63.97 months of follow-up. The perfect clinical outcome of patients with PRNRP promotes the separation of this subset from that of patients with PRCC.

In the present study, macroscopically, there were eight tumors with a predominantly solid appearance and one with cystic components. Interestingly, the ratio of solid to cystic texture of PRNRP was quite different according to previous studies (29,30). Intuitively, the histological constitution indicates that PRNRP should be a cystic-solid lesion with dense papilla. The density of the papillary structure leads to a different gross appearance. Furthermore, all the known PRNRPs are well circumscribed and generally have small tumor sizes (26). In our cohort, the minimum and maximum tumor diameters were 1 and 3.7 cm, respectively. To our knowledge, the tumor diameter of reported PRNRPs varies from 0.2 to 8.5 cm (26,29). It is worth discussing whether this kind of tumor should be diagnosed as PRNRP or papillary adenoma if it is less than 1.5 cm. In our opinion, PRNRP is more appropriate under these conditions because both of these terms represent indolent biological behaviors, but PRNRP could imply more accurate morphological characteristics.

Microscopically, PRNRP was formerly considered PRCC, which indicated that this entity was morphologically similar to PRCC. Therefore, it is crucial for pathologists to identify the inverted nuclei of tumors. Moreover, other pathological variations in the parenchyma and mesenchyme, such as predominantly solid and tubular architectures (31), focal clear cytoplasm (28), and edematous papillary cores with floating macrophages, should be highlighted (14). In the cohort of our study, one tumor exhibited a partial tubular structure, and three tumors exhibited a fused papillary structure. Various histological conformations prompted a new consideration as to whether it was optimal to employ 'papillary' to name this kind of tumor. Some alterations in the tumor stroma were also noteworthy. Edema, mucoid degeneration, hyaline degeneration, inflammatory cell infiltration, hemorrhage, and hemosiderin deposition are observed in some tumors and might indicate tumor growth and apoptosis. Interestingly, a psammoma body, a feature of typical PRCC, was detected in patient 6; to our knowledge, this is the first such case reported in a patient with PRNRP. The presence of an infiltrating growth pattern was rare in the PRNRP which was found in only two tumors in our study. These nonbenign pathological findings did not seem to indicate malignant biological behaviors or poor prognosis. In summary, it is very important to keep PRNRP in mind during the differential diagnosis of papillary neoplasms of the kidney, especially when an adequate immunohistochemical panel is not available.

The immunohistochemical expression of the tumors in our cohort resembled that in other studies. CK7, GATA3, and L1CAM are useful markers for diagnosing and differentiating PRNRP from other variants of renal tumors. All these markers were positive in the distal convoluted tubules and collecting system (32-34), which suggests that PRNRPs originate in those renal sites rather than in the proximal tubules. Several other markers of distal convoluted tubules and the collecting system, such as 34βE12 (35) and Claudin7 (36), have also been confirmed to be stably expressed in PRNRPs. In our study, all the tumors showed diffuse and strong staining for GATA3, which confirmed the diagnosis of PRNRP. Notably, 43% of ccPRCTs express GATA3, and the shared features of the papillary structure and low-grade nuclei arranged against the apical pole of the tumor cell in ccPRCTs

and PRNRPs might cause misdiagnosis. Weak or focal staining of GATA3 was more common in ccPRCTs than in PRNRPs (37). Furthermore, LOTs of the kidney are considered to be associated with frequent central stromal degeneration and shared immunohistochemical features (GATA3 and CK7+, CD117–) with PRNRPs; thus, it is prudent in differential diagnosis, especially in core biopsy. As shown in this study, there were no statistically significant differences in clinicopathological parameters between PRNRPs and LOTs. The morphology of LOTs is predominantly solid, with strands of tumor cells in edematous stroma as well as focal tubular architecture, while the morphology of PRNRPs is predominantly papillary or tubulopapillary architecture. Perinuclear clearing is appreciable in LOTs at high magnification. Furthermore, LOTs exhibit frequent mutations in the genes that regulate the mammalian target of rapamycin (mTOR) pathway, namely, *MTOR*, *TSC1*, and *TSC2* (38,39). Unexpectedly, CK7 was not expressed in two tumors. We speculated that perhaps not all PRNRPs originate from the distal convoluted tubule or collecting system and still need further exploration. The lack of vimentin expression was another pragmatic indication of PRNRP because almost all PRCCs express this marker (14). Additionally, several diagnostic markers for certain types of renal tumors, such as CD117, FH, SDHB, and TFE3, were also not abnormally expressed in the PRNRPs in our study; these findings are meaningful for differential diagnosis. It should also be noted that some PRNRPs express CD10, CAIX, and P504S and are occasionally confused with other renal tumors. According to our study, the positive rate of P504S expression in PRNRPs was significantly lower than that in PRCCs, but this was not the case when the tumors were classified into one of two subtypes. Therefore, for renal tumors with papillary structure, negative P504S expression is a prudently meaningful indicator for the diagnosis of PRNRP (30). In brief, accurately determining the morphological characteristics of inverted nuclei and routinely applying GATA3 for diagnosis were the most critical keys to identifying PRNRPs.

For molecular variation, missense mutations in the *KRAS* gene are an important feature of PRNRPs (15,40) and are found in approximately 80% of all reported cases (26). The mutation frequencies from high to low were G12V, G12D, and G12R according to the published literature (26). In our cohort, three and four patients had G12V and G12D, respectively, and the other two patients lacked *KRAS* mutation. According to The Cancer Genome Atlas database, the mutation rate in *KRAS* in PRCC was only 0.7% (2/279), which was much lower than that in PRNRP (31). Although *KRAS* mutation is not an indispensable diagnostic criterion for PRNRP, its occurrence could be used to indicate PRNRP, especially for tumors with overlapping histological features of PRCC and PRNRP. One study performed next-generation sequencing of PRNRPs; for tumors with a *KRAS* missense mutation, no additional mutual gene variation was found; for tumors without a *KRAS* missense mutation, mutations, including *BRIP1* nonsense mutation, *RAD50* nonsense mutation, and *BRCA2* nonsense mutation, were found (28). Another study showed that for tumors with *KRAS* mutation, mutations in *TP53*, *BRCA2*, and *BRAF* as well as duplications in *BRCA2* were found (15). Another study showed that for tumors with *KRAS* mutation, concomitant mutations included *MTOR* (missense mutation), *NF1* (nonsense mutation), *POLE* (frameshift insertion), *ARID1A* (missense mutation), and *ARID1B* (missense mutation) (40). All the above studies indicated that although *KRAS* mutation was the most common molecular variation in PRNRP, there were still some independent or common molecules affecting the occurrence of PRNRP. In addition, how genes downstream of *KRAS* affect the oncogenesis of PRNRP has yet to be determined.

This study has several limitations. First, the sample size of our study was small. The tumorigenesis, morphogenesis, and biological behaviors of this novel entity of kidney tumors are still poorly understood. A large-scale multicenter investigation of PRNRPs is needed. Second, the 5th edition of the *WHO Classification of Tumours of the Urinary and Male Genital Organs* eliminated the type 1 and 2 PRCC subcategorization (5). Considering the morphological characteristics, PRNRP should be the primary focus of comparisons of different types of papillary renal tumors; therefore, we chose to use both the fourth and fifth editions of the WHO classification system. Third, this study revealed only the phenomenon of *KRAS* mutation in PRNRP. Exploration of the mechanism by which mutated *KRAS* participates in the pathogenesis of PRNRP is needed.

Conclusions

In this study, we confirmed that PRNRP has distinct histological and immunohistochemical profiles and molecular features. PRNRP should be considered a novel independent renal cell neoplasm and separated from PRCC

due to its indolent biological behavior. A monolayer of tumor cells with an inverted nuclear pattern, positive staining for GATA3, and *KRAS* mutation are essential for pathological diagnosis.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-23-518/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study obtained approval from the Ethics Committee of Changhai Hospital (No. CHEC2021-191). Individual consent for this retrospective analysis was waived.

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