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ORIGINAL ARTICLE

Biphasic papillary (biphasic squamoid alveolar) renal cell carcinoma: a clinicopathologic and molecular study of 17 renal cell carcinomas including 10 papillary adenomas

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Abstract

Biphasic papillary renal cell carcinoma (synonymous with biphasic squamoid alveolar renal cell carcinoma) is considered within the spectrum of papillary renal cell carcinoma (PRCC). With < 70 reported cases of biphasic PRCC, there is limited data on the pathologic spectrum and clinical course. Seventeen biphasic PRCC cases and 10 papillary adenomas with similar biphasic morphology were assessed. The mean age of the biphasic PRCC patients was 62 years (male to female ratio of 1.8:1), from 10 partial nephrectomies, 6 radical nephrectomies, and 1 biopsy. The mean tumor size was 3.6 cm (range 1.6-8 cm), with 24% showing multifocality. Fifteen out of 17 cases were limited to the kidney (one of which was staged as pT2a but had lung metastases at diagnosis) and 2/17 cases were staged as T3a. All tumors showed typical biphasic morphology with an extent of squamoid foci widely variable from 10 to 95%. Emperipolesis was identified in 88% of cases. All biphasic PRCC tested exhibited positivity for PAX8 (16/16), keratin 7 (17/17), EMA (15/15), AMACR (17/17), and vimentin (12/12) in both large and small cells; cyclin D1 was only expressed in the large cells (16/16). The 10 papillary adenomas showed a similar immunoprofile to biphasic PRCC. NGS testing performed on 13 biphasic PRCC revealed 4 (31%) harboring *MET* SNVs. In 1/5 (20%) papillary adenomas, a pathogenic *MET* SNV was identified. Biphasic PRCC is rare with a generally similar immunoprofile to "type 1" PRCC but with notable strong positivity for cyclin D1 in the large cell component. Although most of the biphasic PRCC cases were of small size, low stage, and with an indolent behavior, one patient had metastatic disease and one patient died of the disease.

Keywords Biphasic · Squamoid alveolar · Papillary · RCC · PRCC · Adenoma · *MET*

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Introduction

According to the 5th edition of the World Health Organization (WHO) Classification of renal tumors, the subclassification of papillary renal cell carcinomas (PRCC) into types 1 and 2 is no longer recommended [1]. Currently, based on the Genitourinary Pathology Society (GUPS) consensus and the World Health Organization (WHO) 2022 classification, biphasic papillary (biphasic squamoid alveolar) renal cell carcinoma is considered a morphologic pattern of PRCC [1–3].

In 2016, Hes et al. [4] proposed biphasic squamoid alveolar renal cell carcinoma as a distinctive subtype of PRCC composed of two different cell populations: a population of low-grade small cells with scant cytoplasm arranged in tubulopapillary and alveolar-like structures, and a population of large eosinophilic squamoid-like cells with large nuclei and prominent nucleoli located in the center of alveolar-like structures and showing frequent emperipolesis [4]. The study by Hes et al. [4] described features of 21 cases and was a follow-up of their previous study of two cases of PRCC with the same morphology [5]. Since then, a few case reports and case series of this morphologic pattern of PRCC have been described in the English literature [6–13]. Thus far, the largest cohort of biphasic PRCC compiled by Trpkov et al. [14] in 2018 included 28 cases. More recently, a study carried out by Denize et al. [15] found that alterations of *MET* oncogene may represent a major oncogenic driver gene in biphasic PRCC harboring a higher frequency of *MET* mutations.

With total number of biphasic PRCC cases less than 70, there is limited data to assess its clinical course and pathologic spectrum [16]. Therefore, we conducted a detailed clinicopathologic and molecular study of a large series of biphasic PRCC with relatively long-term follow-up including an aim of estimating the incidence. In addition, we included a series of papillary adenomas (≤ 15 mm) with biphasic morphology and analyzed them separately.

Methods

Patient selection

At the main participant institution, we carried out a retrospective study of 1771 renal tumors from the files of our hospital during a 22-year period (from 2000 to 2021), from which 219 previously diagnosed PRCC were re-reviewed. Of these, those showing morphology consistent with biphasic PRCC, based on the criteria outlined by Hes et al. [4] and Trpkov et al. [14], were selected. In addition, the databases of 5 other pathology departments were queried to identify additional cases of biphasic PRCC. This study was conducted in accordance with the principles of the Helsinki Declaration.

Clinicopathologic features

Clinicopathological information was obtained from the patients' records including patient age, sex, end-stage renal disease, family history of RCC, laterality of the tumor, type of surgery, time of the follow-up, and status at last follow-up. In addition, tumor size, tumor number, presence of a fibrous capsule, extent of squamoid areas, presence of emperipolesis, sarcomatoid differentiation, necrosis, psammoma bodies, and foamy macrophages were evaluated. All tumors were graded according to the World Health Organization/International Society of Urological Pathology (WHO/ISUP) grading system and staged based on the eighth-edition Tumor-Node-Metastasis (TNM) staging system of renal tumors [17, 18].

When available, immunohistochemistry was performed on one formalin-fixed paraffin-embedded whole slide section per case with antibodies against pan keratin AE1/AE3, keratin 7, keratin 20, epithelial membrane antigen (EMA), paired box gene-8 protein (PAX8), CD10, alpha methyacyl CoA racemase (AMACR), vimentin, carbonic anhydrase 9 (CA9), e-cadherin, cyclin D1, and Ki-67. The staining intensity was recorded as negative (–), weak (+), moderate (++), or strong (+++), and the staining extent was recorded as negative (–), focal (< 25%), intermediate (25% to 75%) or diffuse (> 75%), with separate scoring of both small and large cell components.

Additionally, we selected cases of papillary adenomas (measuring ≤ 15 mm with WHO/ISUP grade 1 to 2 nuclei) that were found during the process of case selection and that showed a similar biphasic morphology to biphasic PRCC. The clinicopathologic and immunophenotype of papillary adenomas were compiled together with the biphasic PRCC cases but analyzed separately.

Molecular study

MET genotyping using next generation sequencing (NGS) and data analysis

Targeted DNA-based next generation sequencing (NGS) was conducted to assess genomic alterations in 13 biphasic PRCCs (cases #1, #2, #3, #4, #5, #6, #7, #8, #9, #11, #13, #14, and #15), and 5 papillary adenomas with biphasic features (cases #1, #2, #3, #6, and #10) using different molecular platforms. In biphasic PRCC cases #1, #2, #3, #4, #5, #6, #7, #8, and #9, and in papillary adenomas case #1, a tumor area of formalin-fixed, paraffin-embedded (FFPE) tissue containing of at least 30%

tumoral cells was obtained, if needed after manual dissection. DNA of each biopsy was extracted on the automatic Genexus Purification System instrument using Genexus FFPE DNA and RNA Purification Kit (Thermo Fisher Scientific, MA, USA). Library preparation and sequencing was performed in Genexus Integrated Sequencer using the panel Oncomine Precision Assay (Thermo Fisher Scientific). Variant analysis was performed using Genexus software. In biphasic PRCC cases #11, #13, and #15, and in papillary adenoma cases #2, #3, #6, DNA was extracted from formalin-fixed, paraffin-embedded sections using *QIAamp DNA FFPE Tissue kit* (*Qiagen, Hilden, Germany*). A minimum tumor cellularity of 70% was established for sample acceptance. DNA concentration was determined by fluorometric quantitation using *Qubit 2.0 Fluorimeter (Thermo Fisher Scientific, USA*) with *Qubit DNA HS dsDNA Kit*. Library preparation was carried out from a total of 10 ng input DNA per sample using the *Oncomine™ DNA Kidney, Chef-ready library* panel for *Ion Chef* instrument (*Thermo Fisher Scientific*); library sequencing was conducted on *Ion GeneStudio™ S5 System* with automatic workflow to detect and annotate the somatic variants in *Ion Reporter (Thermo Fisher Scientific)*, following manufacturer's instructions. *Oncomine™ DNA Kidney* panel is validated to analyze the presence of single nucleotide variants (SNVs), insertions and deletions (indels) and copy number variations (CNVs) present in *ATM, BAP1, KDM5C, MET, mTOR, NF2, PBRM1, PIK3CA, PTEN, SETD2, SMARCB1, TP53, TSC1, TSC2* and *VHL* genes. Lastly, in biphasic PRCC case #14, and in papillary adenoma case #10, DNA extraction was realized using the automatic Genexus Purification System instrument using Genexus FFPE DNA and RNA Purification Kit (Thermo Fisher Scientific, MA, USA). Library preparation and sequencing was performed using Custom Solid Tumor Solution (*Sophia Genetics*, *Rolle, Switzerland*) and MiSeq sequencing instrument (*Illumina, San Diego, CA, USA*). The variant analysis was performed using Sophia DDM software (Sophia Genetics).

Results

Clinicopathological findings

A total of 17 cases of biphasic PRCC were included in this study. Nine out of 17 cases were identified at the main participant institution (University Hospital Donostia, San Sebastian, Spain) which represented 4% (9/219) of previously diagnosed PRCC and 0.5% (9/1771) of all renal tumors during the 22-year period. The mean age of the patients was 62 years (range 45 – 75 years). Eleven patients were male, and 6 were female (ratio 1.8:1). Four out of 17 (24%) patients had end-stage renal disease and none of the cases had family history of RCC. The specimens included 10 (59%) partial nephrectomies, 6 (35%) radical nephrectomies, and 1 (6%) CT-guided needle biopsy. Ten (60%) tumors were located in the left kidney and 7 (41%) tumors in the right kidney. The tumor size ranged from 1.6 to 8 cm (mean 3.6 cm) and multifocality was found in 4/17 (24%) cases. Fifteen out of 17 (88%) tumors were limited to the kidney [pT1a, 12 cases; pT1b, 2 cases; and pT2a, 1 case (this patient had metastatic lesion to the right lung middle lobe at diagnosis)], and 2/17 (12%) tumors were staged as T3a (one of them was clinically staged as cT3a cN + cM +).

Macroscopically, the tumors were usually well-delineated, soft, and yellowish on cut surface; some of them were also cystic and had heterogeneous surfaces (Fig. 1).

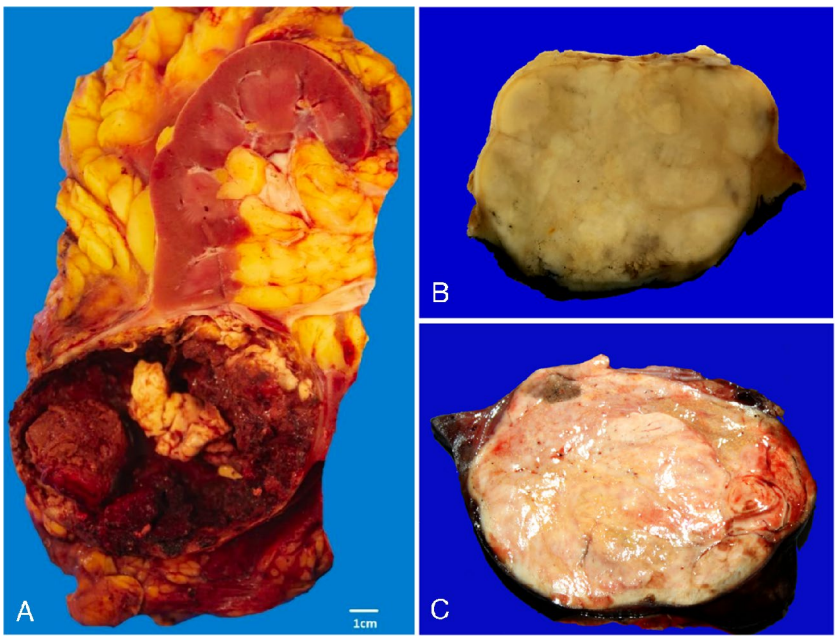

Fig. 1 Representative macroscopic images from 3 cases of biphasic papillary renal cell carcinoma. **A**, Radical nephrectomy specimen showing a circumscribed, friable, hemorrhagic tumor. **B** and **C**, two different partial nephrectomy specimens showing a homogenous, white/tan solid tumor

Microscopically, 7/17 (42%) cases had a thick fibrous capsule with no extracapsular extension. All tumors showed typical biphasic morphology with an extent of the squamoid area widely variable from 10 to 95%. This biphasic morphology was easily recognizable in most of the cases; only 1 case had squamoid areas < 10% of the tumor. All tumors were composed by 2 distinct neoplastic cell populations: a small cell population exhibiting scant amphophilic cytoplasm with round nuclei and inconspicuous nucleoli forming tubular/alveolar structures and a large cell population with abundant eosinophilic cytoplasm and higher-grade nuclei with prominent nucleoli (imparting a squamoid morphology). This larger cell population was arranged in cohesive clusters and located within the alveolar or tubular architecture, mimicking renal glomeruli (Fig. 2). The small cells were graded as WHO/ISUP nuclear grade 1 (13/17 cases; 62%) and grade 2 (4/17 cases; 38%); the large cells were graded as WHO/ISUP nuclear grade 2 (15/17 cases; 83%) and grade 3 (2/17 cases; 17%).

Areas of tumor necrosis were identified in only 1/17 (6%) case, estimated at 60%. Emperipolesis was identified in 15/17 (88%) cases, psammoma bodies were seen in 8/17 (47%) cases, and foamy macrophages were present in 14/17 (82%) cases. No cases demonstrated sarcomatoid or rhabdoid differentiation. Sixteen out of 17 (94%) patients had no evidence of the disease during a mean and median follow-up period of 51 months and 48 months, respectively (range: 1 to 135 months). One patient (case 12) died of the disease during a follow-up time of 3 months.

Immunohistochemically, all biphasic PRCC cases tested exhibited positivity for PAX8 (16/16 cases), keratin (17/17 cases), EMA (15/15 cases), AMACR (17/17 cases), and vimentin (12/12 cases) in both large and small cells. CD10 was positive weakly and focally in 2/15 (13%) cases in the small cells, whereas it was positive in only scattered cells in

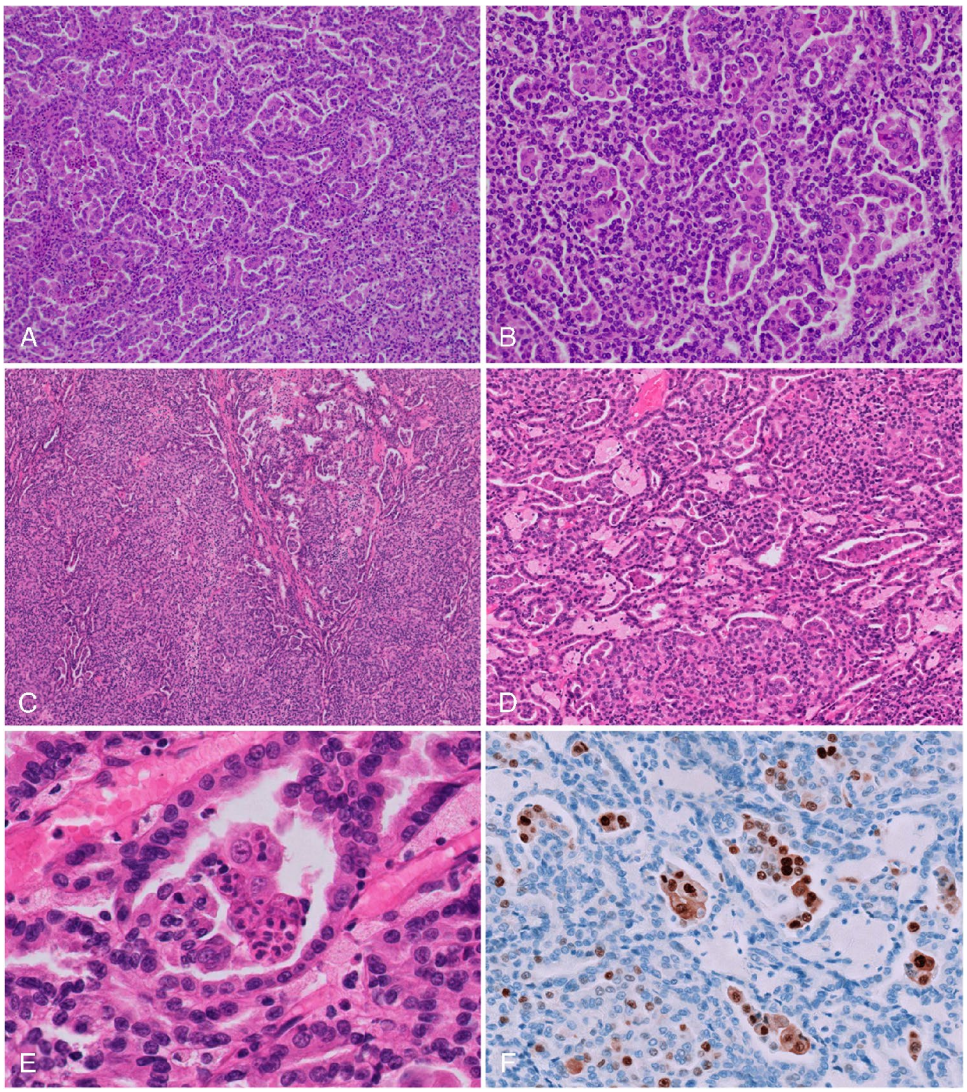

Fig. 2 Representative microscopic images of biphasic papillary renal cell carcinoma. **A**–**D**, two different cases showing the typical biphasic morphology with prominent admixed large squamoid cells. E, higher magnification of a case showing emperipolesis in the squamoid cells. **D**, these large squamoid cells show nuclear positivity for cyclin D1. (**A**–**E**, hematoxylin and eosin; **A** and **C**, 40x; **B** and **D**, 100x; **E**, 400x; **F**, 200× magnification)

9/15 (60%) cases in the large cells. E-cadherin was expressed in 5/15 (33%) cases in the small cells and in 11/15 (73%) cases in the large cells. Cyclin D1 was only expressed in the large cells (16/16). CA9 (10/10) and keratin 20 (5/5) were negative in all cases tested. The Ki-67 proliferative index was low (≤2%) in the small cells and higher (1%-15%) in the large cells.

In addition, 10 papillary adenomas with similar morphology and immunoprofile as biphasic PRCC were included in this study. The mean age of the patients was 62 years (range, 52 to 82 years). Most of the patients (9/10, 90%) were male (male to female ratio 9:1). Half of the patients (5/10; 50%) had end stage renal disease. None of the patients had a family history of RCC. Most of the cases were located in the right kidney (7/10, 70%) and the specimens were mostly radical nephrectomies (6/10; 60%). All papillary adenomas were associated with multiple tumors (3 cases were associated with clear cell RCC; two cases each with oncocytoma and chromophobe RCC; and one case each with traditional pattern PRCC, clear cell papillary renal cell tumor, and urothelial carcinoma). Microscopically, emperipolesis in 6/10 (60%) cases, psammomatous bodies in 2/10 (2/10) cases, and foamy macrophages in 4/10 (40%) cases (Fig. 3). The mean of the squamoid area in papillary adenomas was 42% (range: 10–90%) (See Supplementary Tables 1 and 2).

Molecular findings

Thirteen biphasic PRCC and 5 papillary adenomas with biphasic morphology were successfully sequenced. Analysis was focused on pathogenic single nucleotide variants (SNVs) involving the coding sequences of *MET*.

Among 13 biphasic PRCC, 4 (4/13, 31%) harbored *MET* SNVs, including 3 pathogenic variants and 1 variant of uncertain significance (VUS). The 3 pathogenic SNVs were present at variant allele frequencies (VAF) between 37 and 86% and likely represented a driver event (see Table 1). Given that *MET* is located in chromosome 7, the VAF of 86% of the variant seen in case 15 (*MET* p.V1206L) may indicate the presence of an early somatic event with superimposed gain of chromosome 7 or, alternatively, a germline variant with loss of heterozygosity. This variant has been reported twice in Catalogue of Somatic Mutations in Cancer (COSMIC), once in a PRCC and once in an oncocytoma, with confirmation of its somatic origin [19, 20] The fourth variant, considered a VUS (*MET* p.G1103A, case 11), has not been reported in COSMIC previously and may represent a nonpathogenic germline event. Of note, the latter variant is not annotated in GnomAd.

In papillary adenomas with biphasic morphology, a pathogenic *MET* SNV was identified in only 1 case (1/5; 20%) at a VAF of 61%, suggesting that it may represent an early oncogenic event with superimposed duplication of chromosome 7 or a germline variant with loss-of-heterozygosity. This papillary adenoma had an ipsilateral chromophobe RCC in addition to a contralateral biphasic PRCC (with *MET* mutation; case 11) diagnosed one year later. Pathogenic SNVs involving other genes covered by the sequencing panel were not detected in either biphasic PRCC or papillary adenomas with biphasic morphology.

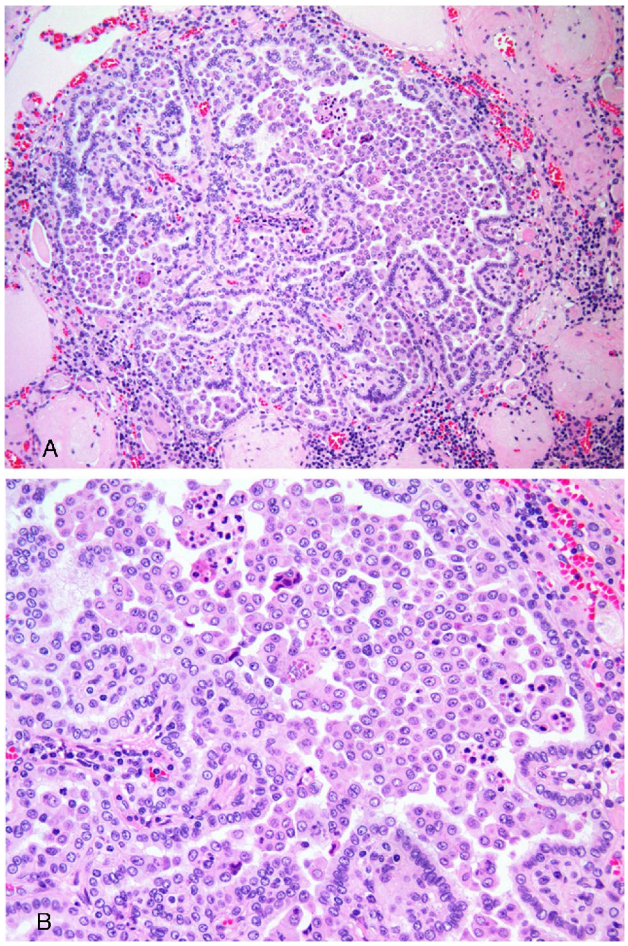

Fig. 3 Representative microscopic images on hematoxylin and eosin of a case of renal papillary adenoma showing biphasic morphology of the tumor and emperipolesis in the large squamoid cells. (**A**, 100x; **B**, 200×magnification)

Discussion

In this study, we provide additional clinicopathologic and molecular information from a relatively large cohort (17 cases) of biphasic PRCC and its counterpart papillary adenomas (10 cases) in order to expand our knowledge about this rare entity. Our findings support that biphasic PRCC shows distinctive biphasic morphology and immunoprofile and is an uncommon pattern of PRCC (incidence of 4% of

Table 1 Results of somatic *MET* genotyping in 4 biphasic papillary RCC and 1 papillary adenoma with biphasic morphology

Case	*MET* alteration	Variant	Protein change	Type	Variant interpretation	Exon	Allelic frequency	Reads	Transcript
11^	Yes	c.3308G > C	p.Gly1103Ala	SNV	Uncertain significance	15	63.3%	1996	NM_001127500.3
13^	Yes	c.3742 T > C	p.Tyr1248His	SNV	Likely pathogenic	19	37.2%	1999	NM_001127500.3
14^	Yes	c.3280C > T	p.His1094Tyr	SNV	Likely pathogenic	NA	38%	639	NM_000245.3
15^	Yes	c.3616G > T	p.Val1206Leu	NA	Pathogenic	18	86%	NA	NM_001127500.2
2*	Yes	c.3736G > A	p.Asp1246Asn	SNV	Pathogenic	19	60.8%	2000	NM_001127500.3

Abbreviations: *SNV* single nucleotide variant, *NA* not available

^Biphasic papillary renal cell carcinoma; *Papillary adenoma with biphasic morphology

previously diagnosed PRCC and 0.5% of all renal tumors). In addition, we have reviewed the literature and identified biphasic papillary renal tumors measuring ≤ 15 mm previously described (10 cases) and analyzed them in conjunction with the papillary adenomas identified in our study (10 cases).

Biphasic PRCC was first reported by Petersson et al. [5] in 2012 from 2 patients with detailed histology, immunohistochemistry, ultrastructure, and molecular analysis highlighting the biphasic nature of these tumors, both composed of a dual-cell population with relatively different immunoprofiles. Subsequently, in 2016 Hes et al. [4] carried out the first large series on this entity including 21 cases, from 12 institutions, and proposed it as a distinctive morphological variant of PRCC. In this series, 9/21 (43%) tumors had a visible transition of the squamoid alveolar and papillary components, with dual morphology comprising 10% to 80% of the total tumor volume and emperipolesis present in all cases [4].

Thus far, the largest cohort of biphasic PRCC has been compiled by Trpkov et al. [14] in 2017 which included 28 cases from 10 institutions. In their study, the dual morphology was variable from 5 to 100% of tumor and emperipolesis was also present in all cases. The unusual biphasic nature of this tumor has been hypothesized to represent various stages in the evolution of the morphology [14]. In our series, this dual cell component (small cell population with scant amphophilic cytoplasm and round nuclei forming alveolar structures and a large cell population with squamoid cytoplasm and higher-grade nuclei) was also widely variable (from 10 to 95%).

As Trpkov et al. [14] highlighted in their study, in the past several studies have reported descriptive terms like 'glomeruloid', 'solid-glomeruloid', and 'micronodular' for morphological variants of PRCC [21–24]. The histologic description of these morphological patterns is very similar to the recently described biphasic PRCC, therefore, all these patterns seem to belong to an identical subgroup [12].

In our series, most biphasic PRCC cases (88%) showed emperipolesis. Notably, emperipolesis was also seen in 60% of our papillary adenomas showing biphasic alveolar squamoid features. While emperipolesis is a generally consistent finding among biphasic PRCC, it should be noted that it is uncommonly encountered in renal tumors, occasionally reported in some clear cell RCC with syncytial type multinucleated tumor cells [25, 26].

While the cases reported by Hes et al. [4] were solitary and unifocal, multifocality (multiple biphasic PRCC or biphasic PRCC plus another tumor type) remains a consistent theme among biphasic PRCC. The series by Trpkov et al. [14] reported multifocality in 32% (8/25) cases, all involving the same kidney [multiple biphasic PRCC in one case, biphasic + PRCC in two cases, biphasic + clear cell RCC in three cases, biphasic + low-grade renal pelvic urothelial carcinoma in one case, and biphasic + chromophobe RCC-like/hybrid tumors (patient had Birt–Hogg–Dubé syndrome) in one case]. Denize et al. [15] also reported multifocality in 35% (6/17) of patients. Similarly, case reports of BSA-RCC with multifocality have been described [7, 11]. In our study, multifocality was identified in 24% (4/17) of the patients with biphasic PRCC (all were biphasic plus another tumor type), none of biphasic PRCC cases had a concurrent papillary adenoma. However, all patients with papillary adenomas included in our study had multiple tumors associated, as they were incidental findings during the pathologic evaluation of the specimen resections for other tumors.

Although the two largest studies carried out to date by Hes et al. [4] and Trpkov et al. [14] described long-term follow-ups, there were differences in the outcomes of patients with biphasic PRCC. Hes et al. [4] found metastatic disease in 36% (5/14) of the patients with available data during a follow-up period ranging from 1 to 96 months. However, Trpkov et al. [14] found the great majority of the tumors were low-stage and indolent during a follow-up period of 1 month to 244 months. In this last study, 83% (19/23) of the patients were alive without disease, 4% (1/23) of the patients had recurrent tumors, and 4% (1/23) of the patients died of the disease. More recently, Denize et al. [15] found that 17% (3/17) of the patients presented with aggressive tumors (two locally advanced tumors and one with sarcomatoid areas).

In our study, however, most of the patients had no evidence of the disease during the follow-up time studied. Only 1 patient had a metastatic lesion to the right lung middle lobe at diagnosis, that was excised and confirmed histologically, and 1 patient died with the disease; this patient was clinically diagnosed with cT3a cN + cM + (diagnosis was later confirmed by a CT-guided biopsy of the renal mass).

Among papillary adenomas with biphasic morphology, 10 tumors measuring ≤ 15 mm have been described and analyzed in conjunction with biphasic PRCC cases in previous studies [4, 6, 14, 15]. All previously reported papillary adenomas shared biphasic morphology, most of them also showing emperipolesis with variable presence of psammoma bodies and/or foamy histiocytes [4, 14, 15]. Notably, among a total of 20 papillary adenoma cases (10 previously described and 10 from current study), none showed adverse behavior during a follow-up period (Table 2). Therefore, the WHO tumor size cut-off of 15 mm for distinguishing papillary adenoma from PRCC [1] may also be appropriate for papillary adenomas with biphasic morphology.

Papillary adenomas with typical morphology usually harbor the same chromosomal gains (7 and 17) seen in papillary RCC [27]. These chromosomal gains are also present in most biphasic PRCC, with concurrent *MET* mutations in a significant subset (~60%) [14, 15]. However, the molecular alterations present in papillary adenomas with biphasic morphology remain poorly understood. In our study, most papillary adenomas with biphasic morphology (4/5) did not demonstrate *MET* variants, with 4/13 BSA-RCC showing *MET* alterations, somewhat less than the 54% reported by Denize et al. [15] In the only biphasic papillary adenoma and in 1/4 biphasic PRCC with *MET* SNVs, the VAF of these variants was > 60%. These findings may indicate that in some papillary renal neoplasms with biphasic morphology *MET* mutations represent an early event that precedes the gain of chromosomes 7 and 17. However, given the absence of paired germline data, a germline event with loss of heterozygosity cannot be excluded. Conversely, in cases with pathogenic *MET* variants present at VAFs < 50%, this may indicate that *MET* mutations are late events that happened after gains of chromosome 7 or, alternatively, that the chromosomal duplications involved a chromosome harboring wild-type copy of the gene. Because copy number data cannot be properly assessed with the platforms used herein, the temporal relationship between gains of chromosome 7 and *MET* mutations in this tumor type requires further clarification. Future studies are needed to assess for possibility that these papillary adenomas showing biphasic squamoid alveolar morphology represent precursor lesions to biphasic PRCC. Additionally, as this was a retrospective study without limited tissue blocks available for further testing, it may be of interest to compare MET expression

Table 2 Clinicopathologic features of 20 papillary adenomas with biphasic morphology in the literature and the present study

Reference	Age(years)/Sex	Side	Tumor size (mm)	Squamoid area (%)	Emperipolesis	Psammoma bodies	Foamy histiocytes	Follow-up (months)	status
Trpkov et al. [14]	53/M	L	12	100	Yes	NA	NA	26	DWOD
Trpkov et al. [14]	63/M	R	9	10	Yes	NA	NA	35	NED
Trpkov et al. [14]	57/M	R	10	90	Yes	NA	NA	23	DWOD
Trpkov et al. [14]	54/M	L	10	25	Yes	NA	NA	8	NED
Trpkov et al. [14]	39/M	L	14	90	Yes	NA	NA	NA	NA
Trpkov et al. [14]	55/M	R	15	30	Yes	NA	NA	54	NED
Trpkov et al. [14]	55/F	L	12	5	Yes	NA	NA	106	NED
Zhou et al. [6]	36/M	L	10	NA	No	No	No	8	NED
Hes et al. [4]	46/M	R	15	40	Yes	NA	NA	NA	NA
Denize et al. [15]	57/F	R	15	5	Yes	No	Yes	2	NED
Present study	82/F	R	1	60	Yes	No	No	35	NED
Present study	71/M	R	13	75	No	No	No	8	NED
Present study	66/M	L	7	70	No	No	Yes	31	NED
Present study	51/M	L	3	90	Yes	No	No	3	DWOD
Present study	69/M	R	14	40	Yes	Yes	Yes	137	NED
Present study	67/M	R	7	20	Yes	No	Yes	9	NED
Present study	68/M	R	1.2	10	No	No	No	25	NED
Present study	79/M	R	2	10	No	Yes	No	1	DWOD
Present study	72/M	L	5	25	Yes	No	No	84	NED
Present study	52/M	R	10	20	Yes	No	Yes	15	NED

Abbreviations: *M* male, *F* female, *L* left, *R* right, *NA* not available, *DWOD* dead without the disease, *NED* no evidence of disease

by immunohistochemistry [15] in both biphasic PRCC and papillary adenomas showing biphasic morphology.

Previously utilized terminology for the morphologic PRCC pattern described herein include "biphasic squamoid alveolar" RCC, "biphasic alveolosquamoid RCC", "solid PRCC", and more recently "biphasic PRCC" [4, 5, 14, 22]. This variable terminology can create confusion as to whether it represents a separate entity or morphological "variant" of PRCC, when it is now well-recognized that this entity is a morphological pattern of PRCC [1–3]. To avoid confusion, we advocate for "biphasic PRCC" as a uniform, straightforward, and simple diagnostic terminology to describe tumors as described in the current study.

The main limitation of this study is its multi-institutional, retrospective, and descriptive design. Furthermore, the molecular analysis was performed using different molecular platforms depending on availability at each institution.

In conclusion, biphasic PRCC represents a rare morphological pattern of PRCC with a generally similar immunoprofile to traditional ("type 1") PRCC but with notable strong positivity for cyclin D1 in the large cell component of biphasic PRCC. Although most cases were of small size, low stage, and with an indolent behavior, one patient had a metastatic disease at diagnosis and one patient died of the disease. In addition, we describe the clinicopathologic features of 10 papillary adenomas sharing similar biphasic morphology to biphasic PRCC.

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Declarations

Ethics approval/consent to participate Retrospective study not interfering with diagnosis and patient management.

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