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ORIGINAL PAPER

Clinical and morphologic review of 60 hereditary renal tumors from 30 hereditary renal cell carcinoma syndrome patients: lessons from a contemporary single institution series

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Abstract

Hereditary renal cell carcinoma syndromes (HRCCS) are characterized by the presence of pathogenic germline variants that predispose patients to renal cell carcinomas as well as additional extra-renal manifestations. The importance of identifying HRCCS patients cannot be overemphasized, as patients and their families can begin surveillance for syndrome-associated manifestations once identified. The present study is a retrospective clinical and morphologic review of 60 hereditary renal tumors from 30 HRCCS patients treated at our institution with either Von Hippel-Lindau disease (VHL), Birt-Hogg-Dubé syndrome (BHD), tuberous sclerosis complex (TSC), hereditary leiomyomatosis and renal cell cancer syndrome, or succinate dehydrogenase (SDH) deficiency syndrome. Hereditary renal cell carcinoma syndromes kidney tumors often demonstrate specific morphologic features, characteristic background changes in renal parenchyma, and extra-renal manifestations, which, when recognized by the pathologist, can trigger genetic testing referral for specific familial cancer syndromes. Our study demonstrates the majority of tumors were consistent with the anticipated clinicopathologic profile of renal tumors found within HRCCS patients, although we found some unique characteristics within this cohort including a case of clear cell papillary renal cell carcinoma within a VHL patient, and a unique renal tumor with tubulopapillary features present in a patient with a germline *SDHD* mutation. Additionally, although the literature reports the presence of epithelioid angiomyolipoma (AML) as a common occurrence in TSC patients, our cohort of 3 patients with AMLs demonstrated only classic features. The findings we describe facilitate pathologist-based recognition of HRCCS and can prompt genetic evaluation for relevant patients.

Keywords Hereditary renal cell carcinoma · Von hippel-lindau · Birt-hogg-dubé · Tuberous sclerosis complex · Hereditary leiomyomatosis and renal cell carcinoma syndrome · Succinate dehydrogenase deficiency

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Introduction

Renal cell carcinomas (RCCs) accounted for 2.2% of incident cases of cancer worldwide in 2018, with an incidence of 403,262 [1]. Most cases of RCC are sporadic, although as many as 3–8% of cases may be associated with a hereditary renal cell carcinoma syndrome (HRCCS) [2–5]. HRCCSs are characterized by underlying pathogenic germline variants, frequently inherited in an autosomal dominant manner, that predispose affected individuals to developing renal cell carcinomas and/or benign renal neoplasms [3, 6]. Hereditary renal cell tumors are frequently bilateral and/or multifocal, often occur at a young age, and may show morphologic features that suggest a particular HRCCS [2, 7]. Due to the increased risk of RCC, identifying HRCCS is important so that patients and their families can begin surveillance for renal and/or extra-renal tumors [4].

The most common and well-described HRCCSs are Von Hippel-Lindau disease (projected incidence of 1:36,000 individuals), Birt-Hogg-Dubé syndrome (1:200,000), and Tuberous Sclerosis Complex (1:6,000 to 1:10,000) [2, 4]. Von Hippel-Lindau (VHL) syndrome is caused by germline pathogenic variants in the *VHL* tumor suppressor gene located on chromosome 3p25.3 and is typically associated with clear cell renal cell carcinoma (CCRCC). *VHL*-associated CCRCCs are often morphologically indistinguishable from sporadic CCRCC, but tend to be multifocal/bilateral and develop at a younger age. Birt-Hogg-Dubé (BHD) syndrome is characterized by a loss of function mutation of the folliculin (*FLCN*) gene. Renal tumors in BHD patients are generally low-grade and include hybrid oncocytic tumors (HOTs), oncocytomas, and chromophobe renal cell carcinomas (ChRCCs). Tuberous sclerosis complex (TSC), defined by *TSC1* or *TSC2* germline pathogenic variants, is associated with multifocal renal angiomyolipomas (AMLs), and less commonly TSC-associated RCCs. Unlike many familial renal cell cancer syndromes, most *TSC* germline pathogenic variants develop de novo, where 60-70% of cases are sporadic [7, 8].

Hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome, and succinate dehydrogenase (SDH) deficiency syndrome are more recently described HRCCSs that are becoming better recognized. HLRCC syndrome, characterized by pathogenic variants in the fumarate hydratase (*FH*) gene, is unlike many HRCCS in that RCCs have low penetrance (20–30%), and when present are usually unilateral and solitary [9]. HLRCC-associated RCC often demonstrates a distinct morphology with prominent eosinophilic/orangeophilic nucleoli and tends to be aggressive, high-grade tumors. SDH-deficient RCCs, defined by mutations in one of four genes that code for a SDH enzyme, are rare tumors that show characteristic cellular features including vacuolated cytoplasm, and flocculent eosinophilic inclusions. SDH-deficient RCCs can metastasize, especially if aggressive histologic features are present, but can also behave indolently [9]. Other rarer reported HRCCS are hereditary papillary RCC syndrome, hyperparathyroidism-jaw tumor syndrome, and constitutional chromosome 3 translocation RCC [10].

Due to the under recognition and rarity of hereditary renal cell tumors, there are relatively few comprehensive reviews of renal tumor morphology in HRCCS patients. Although afflicted patients are frequently identified through a combination of family history and extra-renal clinical and pathologic findings, recognition of hereditary renal cell tumor morphology is important to identify patients who have a de novo germline mutation where other clinical/pathologic findings are not present or extra-renal clinical findings have not been recognized. The present study is a retrospective review of renal tumor morphology in VHL, BHD, TSC, HLRCC, and SDH deficiency syndrome patients at our institution. In addition, we review renal tumor biopsies performed in these patients to determine the role of renal biopsy in the management of HRCCS patients. Finally, as indicated above, inherited renal neoplasms can demonstrate specific morphologic features, which, when recognized by the pathologist, can trigger genetic counseling and testing referral for specific familial cancer syndromes; this study aims to facilitate such pathologist based recognition and genetic evaluation for the relevant patients.

Materials and methods

Cohort description

This study was approved by the Institutional Review Board at the University of Michigan Medical School. (Patient consent was deemed not necessary as part of the ethical review that was conducted.) With approval by the University of Michigan Institutional Review Board, the University of Michigan surgical pathology and clinical database was searched for HRCCS tumor resections and biopsies, and germline mutations diagnosed between 2000 and 2017 by keyword search of "Von Hippel-Lindau," "VHL," "Birt-Hogg-Dubé," Tuberous Sclerosis Complex," "TSC," "hereditary leiomyomatosis and renal cell carcinoma," "HLRCC," "succinate dehydrogenase deficiency," and "SDH." All patients with a clinical and/or molecular HRCCS diagnosis with a biopsy and/or resection were included in the current cohort. 56 unique tumors sampled by 23 biopsies and 37 resections (total $N = 60$) from 30 patients were interrogated. All available hematoxylin and eosin (H&E)-stained slides with paraffin-embedded blocks were reviewed by two pathologists

(JMK, RM). Tumor morphological characteristics, immunohistochemical findings, tumor size, tumor classification, stage, and grade were recorded through morphologic review and/or pathology reports obtained from the medical record for each case. Additional clinicopathologic information, including clinical management, molecular testing, radiologic information, syndrome-related clinical findings, and clinical follow-up information was obtained from the medical record. Table 1 shows criteria used to establish the clinical diagnosis of specific HRCCS [11–14].

Immunohistochemistry and RNA in situ hybridization

Immunohistochemistry was performed on select cases as necessary. Antibodies used for immunohistochemical labeling employing standard protocols were as follows: CK 7 (catalog number 307 M-96; 1:200 dilution; Cell Marque), CA-IX (catalog number NB100-417; 1:600 dilution; Novus Biologicals), and SDHB (mouse monoclonal antibody, clone 21A11AE7; 1:100 dilution; Abcam, Cambridge, MA).

VSTM2A gene expression was detected on formalin-fixed paraffin-embedded (FFPE) tissue sections using the RNAscope 2.5 HD Brown kit (Advanced Cell Diagnostics, Newark, CA) and the target probe against human *VSTM2A* gene (cat # 492031). RNA quality was evaluated by positive control probe against human low-copy housekeeping gene *PPIB*. Assay background was evaluated by negative control probe targeting bacterial *DapB* gene. FFPE tissue block was cut into 4 µm sections. The tissue sections were baked at 60 °C for an hour, deparaffinized in xylene, and dehydrated in 100% ethanol followed by air dry. After hydrogen peroxide pretreatment and target retrieval in citrate buffer, tissue

Table 1 Clinical criteria for diagnosis of hereditary renal cell carcinoma syndromes [11–14]

Von Hippel Lindau (VHL)

Patients with family history of VHL: One CNS/retinal hemangioblastoma or visceral lesion (e.g., CCRCC, pheochromocytoma)

Patients without family history of VHL: Two hemangioblastomas, or hemangioblastoma and visceral lesion

Birt-Hogg-Dube (BHD)

1 major criteria, or 2 minor criteria required for diagnosis

Major criteria	*Minor criteria*
1. Five fibrofolliculomas or trichodiscomas (one histologically confirmed)	1. Early onset renal cancer (< 50 years), renal cancer multifocal/bilateral, or mixed chromophobe/oncocytic histology
2. FLCN germline mutation	2. Multiple lung cysts with or without spontaneous pneumothorax
	3. First degree relative with BHD

Tuberous sclerosis complex (TSC)

2 major criteria, or one major and two or more minor features required for diagnosis

Major criteria	*Minor criteria*
1. Hypomelanotic macules (≥ 3, at least 5 mm diameter)	1. "Confetti" skin lesions (1 to 2 mm hypomelanotic macules)
2. Angiofibromas (≥ 3)	2. Dental enamel pits (≥ 3)
3. Ungual fibromas (≥ 2)	3. Intraoral fibromas (≥ 2)
4. Shagreen patch	4. Retinal achromic patch
5. Multiple retinal hamartomas	5. Multiple renal cysts
6. Cortical dysplasias (e.g., tubers)	6. Non-renal hamartomas
7. Subependymal nodules	
8. Subependymal giant cell astrocytoma	
9. Cardiac rhabdomyoma	
10. Lymphangioleiomyomatosis (LAM)	
11. Angiomyolipomas (≥ 2)	

Hereditary leiomyomatosis and renal cell carcinoma syndrome (HLRCC)

Criteria to prompt clinical suspicion of HLRCC

1. Multiple cutaneous piloleiomyomas (histologically confirmed)
2. At least two of the following manifestations
   - Surgical removal of symptomatic uterine leiomyomas before age 40
   - Type 2 papillary renal cell carcinoma before age 40
   - First-degree family member who meets one of the above criteria

CCRCC clear cell carcinoma

sections were permeabilized using protease and hybridized with target probe in the HybEZ oven for 2 h at 40 °C, followed by a series of signal amplification steps. Finally, the sections were chromogenically stained with DAB and counterstained with 50% Gill's Hematoxyline I (Fisher Scientific, Rochester, NY).

Targeted next-generation sequencing

Available H&E stained slides were reviewed by an experienced genitourinary pathologist (AMU) to select formalin-fixed paraffin-embedded (FFPE) tissue for sequencing, and multiple 1.5 mm punches were obtained manually from a representative area of tumor with at least 30% tumor cell nuclei. DNA was extracted using the AllPrep DNA/RNA FFPE Kit (80234; Qiagen, Venlo, Netherlands) and quantitated using the Qubit™ dsDNA HS Assay Kit (Q32851; Thermo Fisher Scientific, Waltham, MA). An amplicon library was generated from 20 nanograms of FFPE-extracted DNA by multiplex PCR using the Ion AmpliSeq Library Kit 2.0 (4475345; Thermo Fisher Scientific) and a custom pan-cancer DNA AmpliSeq panel (Oncomine Comprehensive Panel, version 1c), as described [15]. The amplicon library was quantitated using qPCR, and sequencing templates were generated using the Ion PI™ Hi-Q™ OT2 200 Kit (A26434; Thermo Fisher Scientific). The resulting templated library was then pooled with other libraries and sequenced on an Ion Torrent Proton machine using the Ion PI™ Chip Kit v3 (A26771; Thermo Fisher Scientific). Sequence alignment and analysis were performed using Ion Torrent Suite Software (version 5.0.4; Thermo Fisher Scientific), including the variantCaller and coverageAnalysis plugins, and validated in-house bioinformatics pipelines, as described previously [15]. A total of 2,376,208 aligned reads were obtained (on target % = 96.07, mean depth = 942.1, and uniformity % = 95.49). Potential variants and copy number alterations were manually curated by an experienced molecular pathologist (AMU) using previously established criteria [15].

Results

The review of the medical record yielded 23 biopsies and 37 resections from 30 patients with HRCCS, including VHL, BHD, TSC, HLRCC, and SDH deficiency. Thirty tumor resections were available for morphologic review. Tables 2 and 3 summarize the clinical features and renal tumor findings, respectively, for the HRCC syndrome patients in the cohort.

Table 2 Clinical features of hereditary renal cell carcinoma syndrome patients with hereditary renal cell tumors

Clinical characteristics of hereditary renal cell carcinoma patients						
	Average age at 1st resection	Male/female ratio	Germline pathologic variant	CKD	Average age of death	Average age of alive patients (range)
VHL	31.2 (range 19 to 38); N = 10	1:2	42% (5/12)	25% (3/12)	49.0 (range 43 to 60); N = 4	46.1 (38 to 54); N = 7
BHD	55.0 (range 42 to 72); N = 5	100% males	71% (5/7)	29% (2/7)	None reported	61.4 (48 to 76); N = 5
TSC	22.5 (range 7 to 48); N = 4	3:4	14% (1/7)	57% (4/7)	1 patient died at 18 years old	31.5 (11 to 57); N = 4

VHL lesions						
CNS hemangioblastomas	Retinal angiomas	Pheochromocytoma	Pancreatic NET	Pancreatic cysts/cystadenomas	Renal cysts	Other cystic lesions (liver, lung, ovary, fallopian tube)
83% (10/12)	83% (10/12)	33% (4/12)	42% (5/12)	58% (7/12)	100% (12/12)	17% (2/12)

BHD lesions			TSC lesions		
Cutaneous lesions[a]	Lung cysts	Lipomas	Brain tumors[b]	Retinal hamartomas	Cutaneous lesions[c]
86% (6/7)	71% (5/7)	14% (1/7)	71% (5/7)	14% (1/7)	86% (6/7)

VHL Von Hippel-Lindau, *BHD* Birt-Hogg-Dube, *TSC* tuberous sclerosis complex, *CKD* chronic kidney disease, *NET* neuroendocrine tumor

[a]Fibrofolliculomas, trichodiscomas, acrochordons

[b]Cortical tubers, subependymomas, giant cell astrocytoma

[c]Angiofibromas, hypopigmented macules

Table 3 Hereditary renal cell tumor resections: distribution, tumor type, stage, grade, and morphologic features

	# of resections	Available for review	Tumor type	Multifocal	Average # of tumors per resection	Average tumor size	Stage of RCCs	Grade of RCCs (excluding ChRCC)	Morphologic features
VHL	20	19	CCRCC: 95% (19/20)	RCC: 80% (16/20)	RCC: 3.9 (N = 20)	RCC: 2.3 cm (N = 60)	T1: 100% (20/20)	Gr2: 45% (9/20)	Cystic: 95% (18/19 resections available for review)
			CCPRCC: 5% (1/20)					Gr3: 55%	Hyalinization: 47% (9/19 resections available for review)
									CCRCC tumorlets: 44% (4/9 patients with resections available for review)
BHD	8	4	ChRCC: 50% (4/8)	RCC: 0% (0/5)	RCC: 1.0 (N = 5)	RCC: 3.0 cm (N = 5)	T1: 100% (5/5)	Gr2: 100% (1/1)	Oncocytosis: 1 of 3 patients available for review
			CCRCC: 12.5% (1/8)	HOT: 100% (3/3)	HOT: N/A	HOT:3.6 cm (N = 6)			Renal cysts: 0 of 3 patients available for review
			HOT: 37.5% (3/8)						
TSC	5	3	RCC-unclassified: 40% (2/5)	RCC: 50% (2/4)	N/A	RCC: 5.5 cm (N = 4)	T1: 50% (2/4)	Gr2: 50% (2/4)	Background cysts (3 of 3 patients available for review)
			TSC-associated RCC: 20% (1/5)	AML: 100% (4/4)		AML: N/A	T2: 50% (2/4)	Gr3: 25% (1/4)	AML tumorlets (2 of 3 patients available for review)
			CCRCC: 20% (1/5)					Gr4: 25% (1/4)	
			AML: 80% (4/5)						
HLRCC	3	2	HLRCC-associated RCC: (3/3)	0% (0/3)	1	7.5 cm (N = 3)	T1 N0: 33% (1/3)	Gr3: 33% (1/3)	Prominent eosinophilic/orangeophilic nucleoli (2/2 resections available for review)
							T3 N1: 33% (1/3)	Gr4: 66% (2/3)	
							T4 N0: 33% (1/3)		
SDH deficiency	1	0	RCC unclassified, (1/1)	1 of 1	2	2.2 and 1.7 cm (N = 2)	T1 (1/1)	Gr 2 (1/1)	Solid and cystic. Tubulopapillary morphology

VHL Von Hippel-Lindau, *BHD* Birt-Hogg-Dube, *TSC* tuberous sclerosis, *HLRCC* hereditary leiomyomatosis and renal cell carcinoma, *SDH* succinate dehydrogenase, *CCRCC* clear cell renal cell carcinoma, *ChRCC* chromophobe renal cell carcinoma, *CCPRCC* clear cell papillary renal cell carcinoma, *HOT* hybrid oncocytic tumor, *AML* angiomyolipoma, *RCC* renal cell carcinoma, *N/A* not available

Table 4 Syndromic clinical findings and tumors in Von Hippel-Lindau patients

Patient	Age[a]	Sex	Hemangioblastomas	Retinal angiomas	Pheochromocytoma	Pancreatic NET	Pancreatic cystadenoma/cysts	Renal cysts	Other cysts	Other tumors	CKD	Follow-up (age)
1	32	M	Multiple	Y	N	N	Cystadenoma	Y	N	Medullary thyroid carcinoma	Y	DOD (60); renal disease and stroke
2	35	F	Multiple	Y	N	N	Cystadenoma	Y	N	Adrenal gland adenomas	Y	Alive (52)
3	36	F	Multiple	Y	N	N	Serous cystadenoma	Y	N	N	Y	DOD (46), stroke
4	32	F	None	N	Y, bilateral	Y	N	Y	Lung, ovarian, fallopian tube	Pleomorphic adenoma (parotid)	N	DOD (43); Metastatic pancreatic NET
5	36	F	Multiple	Y	N	Y	N	Y	N	Adrenal gland adenoma	N	Alive (47)
6	30	F	Multiple	Y	N	N	Cysts	Y	N	N	N	Lost to followup (33)
7	42	M	Multiple	N	N	N	N	Y	N	Pituitary mass	N	Alive (54)
8	30	F	None	Y	Y, unilateral	Y	N	Y	N	Pituitary adenoma	N	Alive (45)
9	38	F	Multiple	Y	N	Y	N	Y	N	None	N	DOD (47), metastatic CCRCC
10	23	M	Multiple	Y	Y, unilateral	Y	Cystadenoma	Y	N	Endolymphatic sac tumor	N	Alive (38)
11	27	F	Multiple	Y	Y, unilateral	N	Cysts	Y	Liver	N	N	Alive (40)
12	36	M	Multiple	Y	N	N	Cysts, serous cystadenoma	Y	N	N	N	Alive (47)

NET neuroendocrine tumor, *CKD* chronic kidney disease, *DOD* dead of disease, *CCRCC* clear cell renal cell carcinoma

[a]Age at first renal tumor diagnosis

Clinical features of hereditary renal cell carcinoma syndrome patients

Clinical findings in Von Hippel Lindau patients (*N* = 12 patients)

Table 4 details the clinical findings of 12 VHL patients in the cohort, and Tables 2 and 3 summarize the clinical features and renal tumor findings, respectively, for HRCCS (including VHL) patients. Molecular testing established a germline *VHL* pathologic variant in 42% of patients (5/12), while the remainder of patients were diagnosed by family history and clinical syndromic findings (Table 1). The VHL cohort showed a female predominance, with a male/female ratio of 1:2 (*N* = 12). The average age of patients' first renal tumor resection was 31.2 years (range 19 to 38 years; *N* = 10). Clear cell renal cell carcinoma (CCRCC) was the most common renal neoplasm resected (95%; 19/20), while one resection was diagnosed as clear cell papillary renal cell carcinoma (1/20). Ninety-five percent of renal tumors demonstrated cystic changes upon morphological review (18/19).

Review of the medical record revealed that non-renal cystic lesions were common (67%; 8/12 VHL patients) and were identified in the pancreas, lung, and liver. Hemangioblastomas and retinal angiomas were seen in 83% (10/12) of patients. Pancreatic neuroendocrine tumors and pheochromocytomas were diagnosed in 42% (5/12) and 33% (4/12) of patients, respectively. Twenty-five percent (3/12) of patients had chronic kidney disease.

Thirty-three percent (4/12) of patients in our cohort died due to complications of VHL, with the average age of death at 49 years (range 43 to 60). One patient (patient 1) died due to complications of chronic kidney disease and complications of stroke, which was likely related to multiple CNS hemangioblastomas (Table 4). A second patient (patient 3) died of stroke, also likely related to the patient's multiple CNS hemangioblastomas (Table 4). Patients 4 and 9 died of metastatic pancreatic neuroendocrine carcinoma, and metastatic clear cell renal cell carcinoma, respectively (Table 4). The average age of the seven patients alive and not lost to follow-up was 46.1 years (range 38 to 54).

Clinical findings in Birt-Hogg-Dubé patients (*N* = 7 patients)

Table 5 details the clinical findings of the seven individual BHD patients in the cohort, and Tables 2 and 3 summarize the clinical features and renal tumor findings, respectively, for HRCCS (including BHD) patients. Molecular testing established a germline *FLCN* pathogenic variant in 71% (5/7) of patients, while the remainder of the patients were diagnosed based on family history and syndromic clinical findings (Table 1). All patients in our cohort were male (*N* = 7). Chromophobe renal cell carcinoma, hybrid oncocytic tumors, and clear cell renal cell carcinomas made up 50% (4/8), 37.5% (3/8), and 12.5% (1/8) of resected tumors in the cohort, respectively. The average age of first renal tumor resection or biopsy was 55 years (range 42 to 72 years; *N* = 5).

Syndromic cutaneous lesions, including fibrofolliculomas, trichodiscomas, and acrochordons, were present in 86% (6/7) of patients. Lung cysts were present in 71% of patients (5/7). Of patients with lung cysts, 60% (3/5) had an associated pneumothorax (Table 5). One patient (patient 19) had numerous excisions of multifocal subcutaneous lipomas (Table 5). Twenty-nine percent (2/7) of BHD patients had chronic kidney disease. The average age of alive patients at the time of the study was 61.4 (range 48 to 76; *N* = 5). No deaths have been reported in our cohort; however, two patients were lost to follow-up.

Clinical findings in tuberous sclerosis complex patients (*N* = 7)

Table 6 details the clinical findings of individual TSC patients in our cohort, and Tables 2 and 3 summarize the clinical features and renal tumor findings, respectively, for HRCC syndrome (including TSC) patients. All patients were diagnosed based on family history and syndromic clinical

Table 5 Syndromic clinical findings and tumors in Birt-Hogg-Dube patients

Patient	Age[a]	Sex	Skin lesions[b]	Lung cysts	Lipomas	CKD	Follow-up (age)
13	52	M	Y	Y, with pneumothorax	N	N	Alive (57)
14	70	M	Y	Y, with pneumothorax	N	Y	Lost to follow-up (70)
15	42	M	N	Y	N	N	Lost to follow-up (45)
16	72	M	Y	N	N	N	Alive (76)
17	58	M	Y	Y, with pneumothorax	N	Y	Alive (63)
18	47	M	Y	Y	N	N	Alive (63)
19	47	M	Y	N	Y	N	Alive (48)

CKD chronic kidney disease

[a]Age at first resection

[b]Fibrofolliculomas, trichodiscomas, acrochordons

Table 6 Syndromic clinical findings and tumors in tuberous sclerosis complex patients

Patient	Age[a]	Sex	Brain tumors	Retinal hamartomas	Skin lesions	Non-renal AML	PEComas	LAM	CKD	Follow-up (age)
20	26	F	Cortical tubers, subependymomas, giant cell astrocytoma	N	Angiofibromas, hypopigmented macules	N	N	N	N	Lost to follow-up (27)
21	13	F	Giant cell astrocytoma	N	Angiofibromas, hypopigmented macules	N	N	N	Y	DOD (18); Chronic renal failure
22	48	F	N	N	N	N	N	N	Y	Alive (57)
23	13	M	Cortical tubers, subependymomas	N	Angiofibromas	N	N	N	Y	Alive (17)
24	7	F	Cortical tubers, subependymomas, giant cell astrocytoma	Y	Angiofibromas, hypopigmented macules	N	N	N	Y	Alive (11)
25	57	M	N	N	Angiofibromas	N	N	N	N	Lost to follow-up (57)
26	37	M	Giant cell astrocytoma	N	Angiofibromas	N	N	N	N	Alive (41)

CKD chronic kidney disease

[a]Age at first resection

findings (Table 1), with no confirmed germline *TSC1*/*TSC2* pathogenic variants. The male/female ratio of TSC patients was 3:4 ($N=7$). The average age of first tumor biopsy or resection was 22.5 years (range 7–48 years; $N=4$). Eighty percent (4/5) of resections were for renal cell carcinoma, with unclassified type RCC, TSC-associated RCC, and CCRCC were diagnosed in 40% (2/5), 20% (1/5), and 20% (1/5) of resections, respectively. The two cases of RCC, unclassified were not available to us for morphologic review to confirm the morphologic diagnosis. Angiomyolipomas were identified in 80% (4/5) of resection specimens, including 3 of 4 resections (75%) performed for a renal cell carcinoma.

Syndromic brain tumors (cortical tubers, subependymomas, giant cell astrocytomas) were present in 71% (5/7) of patients. Retinal hamartomas were present in one patient (14%; 1/7). Cutaneous lesions (hypopigmented macules, angiofibromas) were common, being present in 86% (6/7) of patients. Fifty-seven percent of patients (5/7) had chronic kidney disease. No patients in our cohort were diagnosed with PEComas or pulmonary lymphangioleiomyomatosis.

One patient in our cohort died at the age of 18 from complications of chronic kidney disease due to multiple kidney resections for RCCs (Table 6). Two patients were lost to follow-up. The remainder of patients were alive at the time of the study, with an average age of 31.5 years (range 11 to 41 years; $N=4$).

Clinical findings in hereditary leiomyomatosis and renal cell carcinoma patients ($N=3$)

Table 7 details the clinical features of each HLRCC patient in our study, and Tables 2 and 3 summarize the clinical features and renal tumor findings, respectively. All patients ($N=3$) had a germline *FH* gene mutation confirmed by molecular testing. Two patients in the study group were male, and one was female. The average age at first resection was 47.3 years (range 28–64 years; $N=3$). All three patients received one resection for a HLRCC-associated renal cell carcinoma. None of the patients had documented cutaneous leiomyomata, but the sole female in the study group had uterine leiomyomata. Two patients are alive with disease at 50 and 68 years of age. One patient was lost to follow-up at age 28.

Clinical findings in succinate dehydrogenase deficiency patients ($N=1$)

There was one 35-year-old male patient in our cohort with SDH deficiency. The patient presented with two renal masses discovered incidentally on imaging, which were

Table 7 Syndromic clinical findings and tumors in hereditary leiomyomatosis renal cell carcinoma syndrome (HLRCC) patients

Patient	Age[a]	Sex	Cutaneous leiomyomas	Uterine leiomyomas	Follow-up (age)
27	64	M	N	NA	AWOD (68)
28	28	F	N	Y	LFU (28). AWOD when LFU
29	50	M	N	NA	AWOD (50). Diagnosis of acute lymphoblastic leukemia

NA not applicable, *AWOD* alive without disease, *LFU* lost to follow-up

[a]Age at first resection

both diagnosed as renal cell carcinoma with tubulopapillary features, morphologically suspicious for mucinous tubular and spindle cell cell carcinoma (MTSCC), on biopsy and resection. Due the presentation of multifocal RCCs at a young age, the patient underwent genetic evaluation for an underlying HRCCS and was found to have a pathogenic germline *SDHD* variant by molecular testing. The patient had no systemic findings, such as pheochromocytomas or paragangliomas, pointing toward a clinical syndrome, but had multiple excisions for cutaneous lipomas. The patient is alive without disease (38 years old) undergoing surveillance imaging.

Biopsy study group (*N* = 23 biopsies)

The biopsy indication, radiologic diagnosis, histologic diagnosis, and subsequent post-biopsy management for each individual patient in the biopsy group, and biopsy summary table are detailed in Tables 8 and 9, respectively. Twenty-three biopsies were performed on 19 HRCCS patients with renal tumors in this cohort. Of the 23 biopsies performed, 7 were in VHL patients, 7 in BHD patients, 6 in TSC patients, 2 in HLRCC patients, and 1 in a SDH deficiency syndrome patient.

Summary of renal tumor biopsy indications, diagnoses, and post-biopsy management

Most of the biopsies were performed on renal masses undergoing surveillance imaging in patients with an established diagnosis of a HRCCS (57%; 13/23). Renal tumor biopsies were also performed on masses found during an initial workup of patients clinically suspected to have a HRCCS (9%; 2/23). Confirmation of effective ablation following radiofrequency or cryoablation (9%; 2/23), incidental discovery of a renal mass on radiologic imaging (17%; 4/23), and the discovery of a renal mass after symptomatic flank pain (9%; 2/23) were additional indications leading to renal mass biopsies. The average radiologic size of all biopsied renal hereditary tumors was 3.5 cm ($N = 14$), with the average mass size for VHL and TSC tumors being 2.1 cm ($N = 6$), and 3.8 cm ($N = 5$), respectively. The radiologic average mass size in BHD patients was not calculated, as many radiologic reports reported "multifocal masses" without giving size measurements.

Forty-three percent (10/23) of biopsied masses resulted in a definitive renal cell carcinoma diagnosis, with masses suspicious for RCC (9%; 2/23), benign neoplasms (43%; 10/23), and necrosis (4%; 1/23) accounting for the remainder of renal mass diagnoses. Surveillance imaging was the most common (39%; 9/23) form of post-biopsy management, followed by partial nephrectomy (35%; 8/23), and radioablation/cryoablation therapy (17%; 4/23). One biopsy (4%) was performed to confirm successful radioablation/cryoablation of a previously biopsied mass. Three biopsies (13%) led to molecular testing for a hereditary renal cell carcinoma cancer syndrome.

Biopsies performed on patients without a pre-biopsy hereditary renal cell carcinoma syndrome diagnosis

Of the 19 patients who received renal biopsies, 14 (74%) had a HRCCS diagnosis prior to biopsy, while 5 patients (26%) had no known HRCCS diagnosis prior to biopsy. Of the 5 patients without a HRCCS diagnosis prior to biopsy, 3 had histologic findings on biopsy that suggested an underlying HRCCS that led to molecular testing. Molecular testing confirmed an underlying HRCCS in all 3 of these cases (2 BHD diagnoses, 1 HLRCC diagnosis).

The two remaining patients (2/5) without a HRCCS diagnosis prior to renal biopsy did not have histologic features on biopsy suggestive of a HRCCS. One of these patients (patient 28; Table 8) was found to have two renal masses after imaging was performed for flank pain. One mass was suspicious for RCC and was not biopsied. The other mass was suspicious for hilar metastasis and was biopsied to confirm malignancy. The biopsied hilar mass was consistent with a paraganglioma (with no features of an underlying HRCCS) and was later conservatively excised. The mass suspicious for RCC (not biopsied) on imaging was partially resected and diagnosed as an RCC, unclassified. Two years post-resection, after clinical

Table 8 Hereditary renal cell tumor biopsies: indications, diagnoses, and post-biopsy management

Patient	Age	Sex	HRCCS	HRCSS Dx prior to Bx	Bx number/side	Bx indication	Radiologic Dx	Pathologic Dx	IHC	Post-Bx management	Dx at resection
1	32	M	VHL	Y	1. L	IS. Mass suspicious for RCC	3 cm cystic mass	CCRCC	N	RA; performed at time of biopsy	N/A
2	35	F	VHL	Y	1. L	IS. Increasing mass size	2 cm cystic mass	CCRCC	N	RA unable to be performed. IS until mass reached 3.2 cm, partial resection 3 years post-bx	CCPRCC
5	36	F	VHL	Y	1. L	IS. Masses consistent with RCC	2.8 cm and 2.2 cm solid masses	CCRCC	N	RA (x2)	N/A
6	30	F	VHL	Y	1.R	IS. Increasing mass size	1.1 cm solid mass	CCRCC	N	RA	N/A
					2.R	Post-RA bx	NA	Suspicious for CCRCC	N	RA	N/A
					3.R	Post-RA bx	NA	Necrotic tissue	N	Confirmed tumor ablation	N/A
7	42	M	VHL	Y	1. R	IS. Increasing mass size	1.5 cm cystic mass	CCRCC	N	IS. RA 6 months post-bx after mass increased to 2.3 cm	N/A
13	52	M	BHD	N	1. R	Mass discovered after clinical suspicion of BHD	4.7 cm solid mass	Oncocytic neoplasm, cannot exclude RCC. Suspect BHD	Vimentin (+), PAX8 (+), CD117 (−), CK7 (−), AMACR (−)	Molecular testing for BHD, resection	CCRCC
14	70	M	BHD	Y	1. R	Mass discovered after IS for prior RCC. Reported history of BHD	3.8 cm solid mass	Oncocytic neoplasm. Favor ChRCC	CK7 (+), CD117 (+), AMACR (−), Vimentin (−)	Partial resection. Outside medical records confirmed BHD	ChRCC
16	72	M	BHD	Y	1. R	IS. Increasing mass size	Bilateral solid masses (x7), 1.4–3.8 cm	HOT	CK7 (focal), CD117 (+), PAX8 (+), CA9 (−)	Partial resections of 4 right renal masses	HOT

Table 8 (continued)

Patient	Age	Sex	HRCCS	HRCSS Dx prior to Bx	Bx number/side	Bx indication	Radiologic Dx	Pathologic Dx	IHC	Post-Bx management	Dx at resection
17	58	M	BHD	N	1. R	Incidental finding on imaging	Bilateral solid masses (x15), 0.8–5.5 cm	Oncocytic neoplasm. Suspect BHD	CK7 (focal), CD117 (+), vimentin (−)	Molecular testing for BHD. IS. Rebx 2 years later	N/A
					2. L	IS. Increasing mass size	Bilateral solid masses (x5), 2.7–5.7 cm	Low-grade oncocytic neoplasm	CK7 (focal), CD117 (+), PAX8 (+), CA9 (−), vimentin (−)	Partial resection	HOT (x9)
18	47	M	BHD	Y	1. R	IS. Masses on initial screen after BHD dx	Bilateral solid masses (x8), 0.6–2.6 cm	HOT	CK7 (patchy), CD117 (+), S100A1 (+), vimentin (−)	IS	No resection to date (4 years post-bx)
19	47	M	BHD	Y	1. L	IS. Rapidly enlarging mass	Bilateral solid masses (x8), 0.5–1.8 cm	HOT	CK7 (patchy), CD117 (+), PAX8 (+), AMACR (focal), CA9 (−)	IS	No resection to date (2 years post-bx)
20	26	F	TSC	Y	1. R	Incidental finding on imaging	3.9 cm and 4.3 cm solid masses	CCRCC	AE1/AE3 (+), EMA (+), PAX2 (+), TFE3 (−)	Partial resection	CCRCC
23	13	M	TSC	Y	1. Horseshoe kidney	Found on imaging for CKD surveillance	2.9 cm mass. Numerous small AMLs	AML	HMB45 (focal), Melan A (focal), PanCK (−), CA9 (−), PAX8 (−), S100 (−)	IS	No resection to date (4 years post-bx)
24	7	F	TSC	Y	1. L	IS. Mass suspicious for RCC	3.0 cm mass. Numerous small AMLs	RCC, unclassified, eosinophilic type	PanCK (+), PAX8 (+), vimentin (focal), CD10 (focal), AMACR (focal), EMA (focal), CK7 (focal), HMB45 (−), MelanA (−), HHF35 (−), CA9 (−)	Partial resection	RCC, unclassified
					2. R	IS	Same imaging as bx #1	AML	N	IS	No resection to date (4 years post-bx)

Table 8 (continued)

Patient	Age	Sex	HRCCS	HRCSS Dx prior to Bx	Bx number/side	Bx indication	Radiologic Dx	Pathologic Dx	IHC	Post-Bx management	Dx at resection
25	57	M	TSC	Y	1. R	IS. Large mass size	Bilateral solid masses (multiple), 1.0–8.0 cm	AML	HMB45 (+)	IS	Lost to follow-up
26	37	M	TSC	Y	1. L	IS. Increasing mass size	5.0 cm solid mass. Multiple bilateral AMLs	AML	N	IS	No resection to date (5 years post-bx)
28	28	F	HLRCC	N	1. L	Imaging for flank pain	5.5 cm cystic mass concerning for RCC (not biopsied). 4.4 cm solid hilar mass suspicious for metastasis (biopsied)	Paraganglioma	N	Partial resection of RCC. Conservative excision of paraganglioma. FH mutation documented and HLRCC diagnosed 2 years post-resection	RCC, unclassified
29	50	M	HLRCC	N	1. L	Imaging for urinary retention	13.0 cm solid mass in left upper pole extending to spleen and left adrenal gland	High-grade carcinoma, most consistent with HLRCC	FH weak +	FH molecular testing. En bloc resection of left kidney and adrenal gland, distal pancreas, spleen, and diaphragm	Poorly differentiated RCC, most consistent with HLRCC
30	35		SDH deficiency	N	1. L	Incidental finding on imaging for abdominal pain	2.2 cm solid mass concerning for RCC. 1.1 cm cyst	RCC with tubulopapillary features (both masses)	CD10–	Partial resections. SDHD mutation detected and SDH deficiency diagnosed 1 month post-resection	RCC with tubulopapillary features (both masses)

HRCCS hereditary renal cell carcinoma syndrome, *bx* biopsy, *dx* diagnosis, *IHC* immunohistochemistry, *VHL* Von Hippel-Lindau, *BHD* Birt-Hogg-Dube, *TSC* tuberous sclerosis complex, *HLRCC* hereditary leiomyomatosis renal cell carcinoma syndrome, *SDH* succinate dehydrogenase, *IS* imaging surveillance, *RA* radioablation, *CKD* chronic kidney disease, *NA* not applicable, *CCRCC* clear cell renal cell carcinoma, *ChRCC* chromophobe renal cell carcinoma, *HOT* hybrid oncocytic tumor, *AML* angiomyolipoma, *RCC* renal cell carcinoma

Table 9 Summary of hereditary renal cell tumor biopsy indications, diagnoses, and post-biopsy management

	VHL	BHD	TSC	HLRCC	SDH deficiency	All hereditary renal tumors
Patients with known HRCCS Dx prior to first Bx	100% (5/5)	67% (4/6)	100% (5/5)	0% (0/2)	0% (0/1)	74% (14/19)
Morphologic Dx suggested hereditary renal cell tumor[a]	N/A	100% (2/2)	N/A	50% (1/2)	0% (0/1)	60% (3/5)
Average size of bx masses (cm)	2.1 ($N=6$)	N/A	3.8 ($N=5$)	7.7 ($N=2$)	2.2 ($N=1$)	3.5 ($N=14$)
Biopsy indication						
Imaging surveillance	71% (5/7)	57% (4/7)	67% (4/6)	0%	0%	57% (13/23)
Post-ablation	29% (2/7)	0%	0%	0%	0%	9% (2/23)
Renal mass screening after clinical suspicion of HRCCS	0%	29% (2/7)	0%	0%	0%	9% (2/23)
Incidental renal mass on imaging	0%	14% (1/7)	33% (2/6)	0%	100% (1/1)	17% (4/23)
Symptomatic mass	0%	0%	0%	100% (2/2)	0%	9% (2/23)
Biopsy diagnosis						
CCRCC	86% (6/7)	0%	17% (1/6)	0%	0%	30% (7/23)
RCC, unclassified	0%	0%	17% (1/6)	0%	0%	4% (1/23)
Oncocytic neoplasm	0%	57% (4/7)[b]	0%	0%	0%	17% (4/23)
HOT	0%	43% (3/7)	0%	0%	0%	13% (3/23)
AML	0%	0%	67% (4/6)	0%	0%	17% (4/23)
HLRCC-associated RCC	0%	0%	0%	50% (1/2)	0%	4% (1/23)
Other neoplasm	0%	0%	0%	50% (1/2)[c]	100% (1/1)[d]	9% (2/23)
Necrosis	14% (1/7)	0%	0%	0%	0%	4% (1/23)
Post-biopsy management						
Imaging surveillance	29% (2/7)	43% (3/7)	67% (4/6)	0%	0%	39% (9/23)
Radioablation/cryoablation	57% (4/7)	0%	0%	0%	0%	17% (4/23)
Confirm successful ablation	14% (1/7)	0%	0%	0%	0%	4% (1/23)
Partial resection	0%	57% (4/7)	33% (2/6)	100% (1/2)	100% (1/1)	35% (8/23)
Total resection	0%	0%	0%	50% (1/2)	0%	4% (1/23)
Molecular testing	0%	29% (2/7)	0%	50% (1/2)	0%	13% (3/23)

VHL Von Hippel-Lindau, *BHD* Birt-Hogg-Dube, *TSC* tuberous sclerosis complex, *HLRCC* hereditary leiomyomatosis renal cell carcinoma syndrome, *SDH* succinate dehydrogenase, *HRCCS* hereditary renal cell carcinoma syndrome, *dx* diagnosis, *bx* biopsy, *CCRCC* clear cell carcinoma, *RCC* renal cell carcinoma, *HOT* hybrid oncocytic tumor, *AML* angiomyolipoma

[a]Patients with no prior familial cancer syndrome diagnosis

[b]Details of BHD oncocytic tumor biopsies: 1. cannot exclude RCC, 2. Favor ChRCC, 3. Oncocytic neoplasm, 4. Low-grade oncocytic neoplasm

[c]Paraganglioma

[d]RCC with tubulopapillary features

suspicion of an underlying HLRCC syndrome, molecular testing confirmed the presence of a germline FH mutation.

The second patient (patient 30; Table 8) without a HRCCS diagnosis prior to renal biopsy that did not have histologic features suggesting a HRCCS presented with two renal masses discovered incidentally on imaging. On biopsy, both of these masses were diagnosed as RCC with tubulopapillary features, suspicious for MTSCC. After resection of the masses, similar diagnoses were rendered. One month post-resection, clinical suspicion of an underlying HRCCS led to molecular testing that identified a *SDHD* germline mutation.

Von Hippel Lindau biopsy study group ($N=7$ biopsies in 5 patients)

Each patient in the VHL biopsy group had a known diagnosis of VHL prior to biopsy. Most biopsies (71%; 5/7) were performed after surveillance imaging revealed an enlarging mass or mass suspicious for RCC. All of the masses ($N=5$) found on surveillance imaging proved to be CCRCC on biopsy. Of the masses biopsied after imaging ($N=5$), 80% (4/5) were ablated after the diagnostic biopsy. One mass was continued on surveillance because ablation was deemed too risky. This was surveilled until it was 3.2 cm 3 years post-biopsy and then was removed by partial nephrectomy. One biopsy (1/7; 14%) was performed to confirm successful tumor ablation.

Birt-Hogg-Dubé (BHD) biopsy study group (*N* = 7 biopsies in 6 patients)

Thirty-three percent of patients (2/6) in the BHD biopsy group did not have a BHD diagnosis prior to the diagnostic biopsy. One of these patients had clinical features suggestive of BHD that initiated radiologic imaging to screen for renal masses, and led to a subsequent biopsy of a renal mass. In the second patient without a BHD diagnosis prior to biopsy, the mass was discovered incidentally and there was no clinical suspicion of BHD. Both patients had histologic features suggestive of BHD on the renal tumor biopsies, which led to molecular testing that confirmed the presence of a germline *FLCN* gene mutation.

Fifty-seven percent (4/7) of biopsies were performed on renal masses followed by surveillance imaging. Twenty-nine percent (2/7) of biopsies were performed on tumors discovered during initial BHD renal mass screening, and one biopsy (1/7) was performed on an incidentally discovered renal mass. Forty-three percent (3/7) of all biopsied masses were hybrid oncocytic tumors (HOT). Two of the HOTs are undergoing surveillance imaging post-biopsy, with no subsequent resections to date, and one HOT was resected along with other un-biopsied masses for symptomatic treatment. The remainder of biopsied masses (4 of 7; 57%) were diagnosed as oncocytic neoplasms, with 2 of the 4 being suspicious for RCC. Both of the biopsies suspicious for RCC led to partial nephrectomies, where the tumors were diagnosed as CCRCC and ChRCC. The other two oncocytic neoplasm biopsy diagnoses occurred in the same patient, with the first biopsy leading to surveillance imaging, and the second biopsy leading to a partial nephrectomy; the resected mass was diagnosed as a HOT.

Tuberous sclerosis complex biopsy study group (*N* = 6 biopsies in 5 patients)

All patients (*N* = 5) in the TSC biopsy study group had an established TSC diagnosis prior to biopsy. Sixty-seven percent (4/6) of biopsies were performed after surveillance imaging demonstrated an enlarging mass or a mass with features suspicious for RCC. Three (3/4) of the surveillance imaging biopsies were diagnosed as angiomyolipoma (AML) with classic features. Surveillance imaging continued on all three of these AMLs (2 of 3 patients have no resection to date, and 1 of 3 patients was lost to follow-up). One (1/4) of the surveillance imaging biopsies was diagnosed as a RCC, unclassified, for which the patient received a partial nephrectomy.

Two biopsies (33%; 2/6) were performed after a renal mass was discovered incidentally on imaging. One mass was diagnosed as a CCRCC on biopsy, which led to a partial nephrectomy. The other biopsied mass was diagnosed as an AML and has continued on surveillance without resection for 4 years post-biopsy.

Resection study group (*N* = 37 resections)

Thirty-seven resections from 23 patients were identified for the study. Of the 37 resections, 28 were available for morphologic review. Table 3 summarizes the tumor classification, stage, grade, distribution, and morphologic characteristics for each HRCCS.

Von Hippel Lindau resection study group (*N* = 20 resections in 12 patients)

Table 10 details the tumor classification, stage, grade, distribution, and morphologic characteristics for each VHL patient. All the tumors in the VHL resection study group were diagnosed as a RCC, with CCRCC being the most common (95%; 19/20), followed by clear cell papillary renal cell (CCPRCC, 5%; 1/20). Eighty percent (16/20) of tumors were multifocal, with an average of 3.9 tumors per resection (*N* = 20). The average RCC tumor size was 2.3 cm (*N* = 60). All RCCs were tumor stage T1, and no lymph node or distant metastases were identified in any of the cases (*N* = 20). Nuclear grade 2 (45%; 9/20) and grade 3 (55%; 11/20) tumors were common.

CCRCC was the most common (95%; 19/20) RCC in the VHL study group. CCRCC in VHL patients of our cohort were often indistinguishable from the morphology of sporadic CCRCC, which shows nests of clear cells with a delicate vascular network (Fig. 1a). Our cohort demonstrated cystic changes in 95% (18/19) of resections available for review (Fig. 1b). The cystic changes ranged from benign cysts with a single layer of bland clear cells, to atypical cysts (Fig. 1c, d) lined by thickened layer of 2 to 3 atypical clear cells that may include focal papillary tufting. Cystic RCC with cysts lined by a layer of > 3 atypical cells (Fig. 1b) with or without associated with a component of solid RCC were present in many cases. Secondary degenerative changes characterized by hyalinization were also frequent, occurring in 47% (9/19) of reviewed resections. Clear cell tumorlets within the background benign renal parenchyma were also a common feature, occurring in 44% (4/9) of patients with tumor resections (Fig. 1e–h). The tumorlets manifested as either solid nests of clear cells (Fig. 1e, f), or clear cell-lined cysts (Fig. 1g, h).

One tumor (5% of resections) in the VHL resection cohort was CCPRCC. Large areas of the tumor had the morphologic appearance of CCRCC with prominent cystic changes, characterized by a prominent tubulopapillary architecture of low-grade clear cells with reverse nuclear polarity (Fig. 2a, b). Immunohistochemical stains demonstrated strong, complete membranous staining for cytokeratin 7 (CK7), and

Table 10 Von Hippel-Lindau patients with renal tumor resections: clinical and pathologic features

Patient	Age[a]	Sex	Confirmed germline pathologic variant	Type of resection (Side)	Indication for resection	Slides for review	Diagnosis	Number of tumors
1	32	M	N	1. Partial (L)	IS. Tumor size increased > 3 cm	Y	CCRCC	3
2	35	F	N	1. Partial (L)	IS. Tumor size increased > 3 cm	Y	CCRCC	Solitary
				2. Partial (R)	IS. Tumor size increased > 3 cm	Y	CCPRCC[c]	2
3	36	F	N	1. Partial (L)	IS. Tumor increased in size to 2 cm	Y	CCRCC	2
				2. Partial (R)	IS. Lesions suspicious for RCC	Y	CCRCC	3
4	32	F	N	1. Partial (R)	Mass found on imaging for flank symptoms	Y	CCRCC	Solitary
5	36	F	Y	1. Total (R)	Mass found on imaging for abdominal symptoms	N	CCRCC	15
6	30	F	N	No resections				
7	42	M	N	No resections				
8	30	F	Y	1. Partial (R)	IS. Two tumors increased in size	Y	CCRCC	Solitary
9	38	F	N	1. Partial (L)	IS. Multiple lesions increased in size	Y	CCRCC	5
				2. Partial (R)	IS. Multiple lesions increased in size	Y	CCRCC	4
10	23	M	Y	1. Total (L)	Renal mass on imaging after new diagnosis of VHL	Y	CCRCC	6
				2. Partial (R)	IS. Multiple lesions increased in size	Y	CCRCC	7
				3. Partial (R)	IS. Mass increased in size	Y	CCRCC	4
11	27	F	Y	1. Partial (L)	IS. Multiple lesions increased in size	Y	CCRCC	3
				2. Partial (R)	IS. Multiple lesions increased in size	Y	CCRCC	4
				3. Partial (R)	IS. Multiple lesions increased in size	Y	CCRCC	Solitary
				4. Partial (L)	IS. Multiple lesions increased in size	Y	CCRCC	3
12	36	M	Y	1. Partial (R)	Renal masses on imaging after new diagnosis of VHL	Y	CCRCC	3
				2. Partial (L)	Renal masses on imaging after new diagnosis of VHL	Y	CCRCC	8
				3. Total (L)	IS. Tumor size increased > 3 cm	Y	CCRCC	2

Patient	Tumor size range (cm)	Stage	Grade[b]	Cystic	Tumorlets	Hyalinization	Follow-up (age)
1	0.2–3.1	T1	3	Y	N	N	DOD (60); Renal disease and stroke
2	1.4	T1	3	Y	N	N	Alive (52)
	3.2	T1	2	Y	N	Y	
3	1.5, 1.6	T1	2	Y	Y	N	DOD (46); Stroke
	1.1–1.8	T1	3	Y	Y	N	
4	3.8	T1	2	Y	N	Y	DOD (43): Metastatic pancreatic NET
5	3.0–6.2	T1	2[d]	NA	NA	NA	Alive (47)
6							Lost to follow-up (33)
7							Alive (54)
8	1.0	T1	3	Y	Y	N	Alive (45)
9	0.8–3.5	T1	3	Y	N	Y	DOD (47); Metastatic CCRCC
	0.6–2.5	T1	2	Y	N	Y	

Table 10 (continued)

Patient	Tumor size range (cm)	Stage	Grade[b]	Cystic	Tumorlets	Hyalinization	Follow-up (age)
10	5.5; other tumor sizes NA	T1	2	Y	Y	N	Alive (38)
	0.6–3.4	T1	3	Y	Y	N	
	1.8–5.5	T1	3	Y	Y	Y	
11	0.6–1.6	T1	3	Y	N	Y	Alive (40)
	0.3–2.5	T1	2	Y	N	N	
	2.3	T1	2	N	N	N	
	2.2–3.7	T1	2	Y	Y	N	
12	1.2–3.8	T1	3	Y	N	Y	Alive (47)
	1.0–4.1	T1	2	Y	N	Y	
	3.0, 4.5	T1	3	Y	N	Y	

IHC immunohistochemistry, *IS* imaging surveillance, *CCRCC* clear cell renal cell carcinoma, *CCPRCC* clear cell papillary renal cell carcinoma, *NET* neuroendocrine tumor, *NA* not available

[a]Age at first renal tumor diagnosis

[b]WHO/International Society of Urological Pathology (ISUP) grading system

[c]IHC CK7+, CA-9 cup-like

[d]Fuhrman grade

membranous cup-like staining for carbonic anhydrase IX (CA-IX), classic for CCPRCC (Fig. 2c, d). Targeted next-generation sequencing confirmed the presence of a germline *VHL* mutation without evidence of chromosome 3p25 loss.

Birt Hogg Dubé resection study group (*N* = 8 resections in 5 patients)

Table 11 details the tumor classification, stage, grade, distribution, and morphologic characteristics for each BHD patient. 62.5% (5/8) of resections in the BHD study group were diagnosed as a RCC, including ChRCC (50%; 4/8) and CCRCC (12.5%; 1/8). The average size of RCC (*N* = 5) was 3.0 cm. All resected RCCs were solitary, pT1 tumors (*N* = 5). Hybrid oncocytic tumors (HOTs) comprised 37.5% (3/8) of resections in the BHD resection study group. All HOTs in our study group were multifocal (*N* = 3), and the average tumor size was 3.6 cm (*N* = 6). Renal oncocytomas were not identified in this cohort.

Morphologically, HOTs demonstrated morphologic features consistent with those described previously, including nests with a mixture of cells resembling oncocytoma (round monomorphic nuclei, prominent nucleoli, and eosinophilic cytoplasm), and cells with relatively clear cytoplasm and minimal to no koilocytic atypia resembling those seen in ChRCC (Fig. 3a, b). One case of ChRCC was available for review and demonstrated features consistent with the eosinophilic variant of ChRCC. The tumor consisted of a solid growth pattern of cells with occasional irregular nuclei, frequent binucleation, some perinuclear halos, and eosinophilic cytoplasm (Fig. 3c, d). Background oncocytosis was present in 1 of 3 resection specimens available for review (Fig. 3e–h), and consisted of nodules, small clusters, and cysts of oncocytic cells within the benign renal parenchyma, morphologically resembling cells which may be seen in oncocytoma and/or ChRCC.

Tuberous sclerosis resection study group (*N* = 5 resections in 4 patients)

Table 12 details the tumor classification, stage, grade, distribution, and morphologic characteristics for each TSC patient. Angiomyolipoma (AML) was common (80%; 4/5) in the TSC resection specimens in our cohort, all of which were multifocal (*N* = 4). Only one resection contained AML alone, while the remainder of resections with AML (*N* = 3) had concurrent RCC. All reviewed AMLs had triphasic morphology; no epithelioid AMLs were identified in this cohort (Figs. 4a, b). One resection showed an AML that was largely cystic, where the cyst walls contained foci of typical AML. AML tumorlets were present within background benign renal parenchyma in 67% (2 of 3) patients with resections available for review (Fig. 4c). All resections available for review showed background cysts with a single layer of eosinophilic cells (*N* = 3).

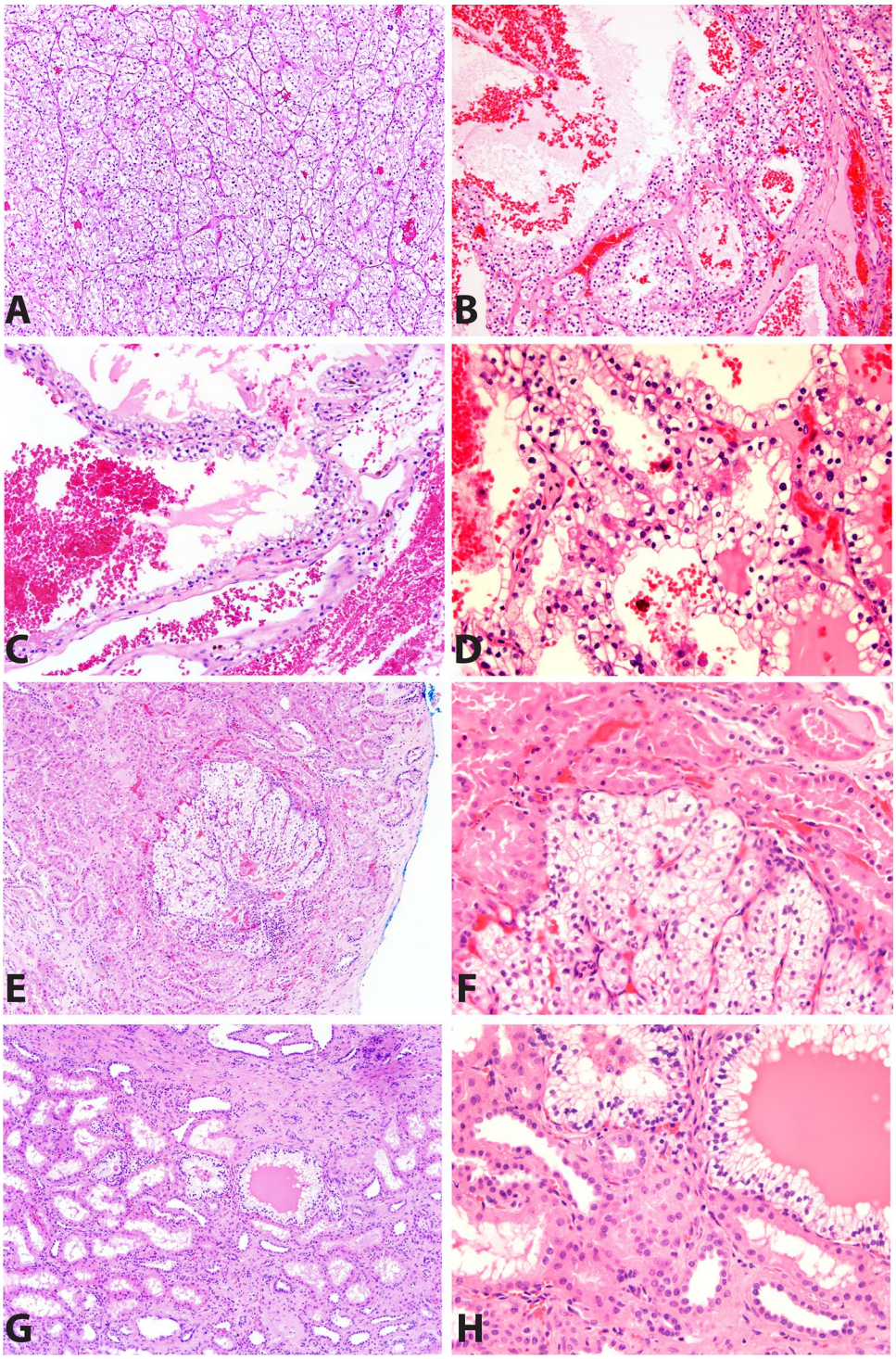

Fig. 1 Morphologic findings in VHL renal tumors. CCRCC in VHL patients often show a similar morphology to sporadic CCRCC (**a**), although cystic CCRCC (**b**) can usually be identified. Atypical cysts (**c**, **d**) lined by a layer of 2-3 clear cells, often with focal papillary tufting, are frequently found in the nearby renal parenchyma uninvolved by RCC. Clear cell tumorlets, a feature unique to VHL, can be seen within benign renal parenchyma as solid nests (**e**, **f**), or cysts (**g**, **h**)

Eighty percent (4/5) of resections in our cohort were performed for RCC. One resection was a solitary classic CCRCC. The remainder of RCCs resected ($N=3$) were initially diagnosed as RCC, unclassified. Of these cases (patient 21, Table 12), one was available for morphologic review and was reclassified as tuberous sclerosis complex-associated RCC (TSC-associated RCC-eosinophilic, granular and macrocystic type; Figs. 4d–h). Numerous foci of AML were present throughout the resection specimen and were frequently intermingled or directly adjacent to the RCC (Fig. 4d). The RCC had variable morphologies, including eosinophilic, granular tumor cells arranged in a papillary architecture (Fig. 4e), and microcysts and macrocysts lined by large cells with voluminous, eosinophilic to clear cytoplasm (Fig. 4f, g). Large

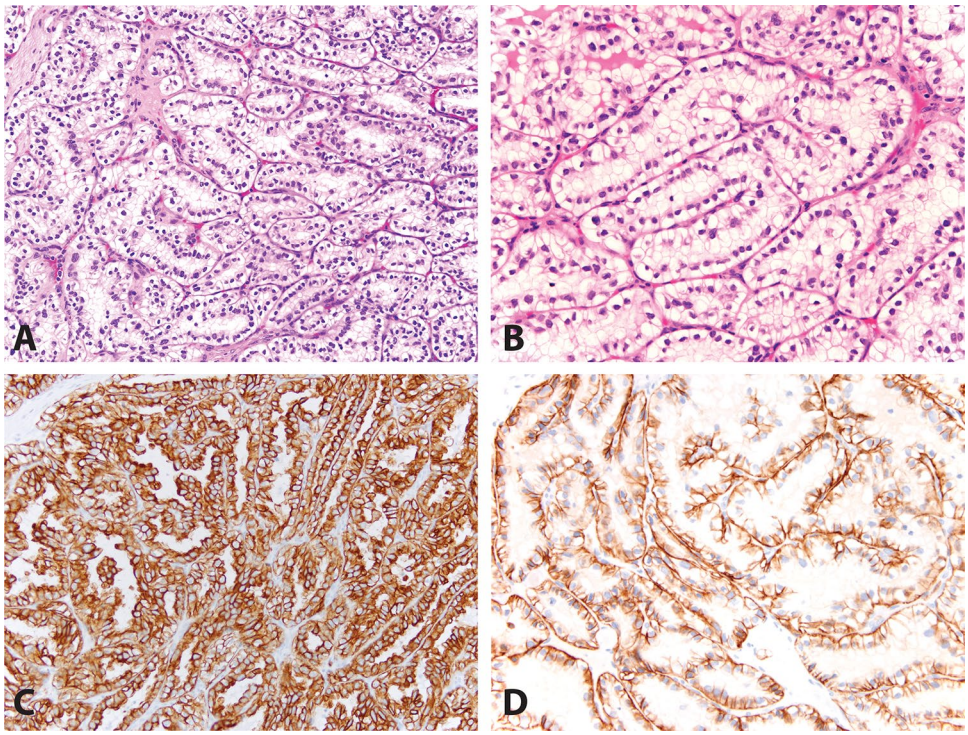

Fig. 2 Clear cell papillary RCC in a VHL patient. Clear cells arranged in a tubulopapillary architecture with reverse nuclear polarity are demonstrated (**a**, **b**). Immunohistochemical stain for cytokeratin 7 (**c**) shows strong, diffuse membranous staining, while carbonic anhydrase-IX immunostain (**d**) demonstrates cup-like membranous staining

portions of the tumor consisted of dyscohesive giant cells with abundant, granular eosinophilic cytoplasm (Fig. 4h).

The average size of resected RCCs was 5.5 cm ($N=4$). Fifty percent (2/4) of RCCs were T1, while the other 50% (2/4) were T2 tumors. Fifty percent (2/4) of RCCs were nuclear grade 2, one was grade 3, and one was grade 4.

Hereditary leiomyomatosis-associated renal cell carcinoma resection study group ($N=3$ resections in 3 patients)

Table 13 details the tumor classification, stage, grade, distribution, and morphologic characteristics for each HLRCC patient. Each of the 3 patients in this HLRCC cohort had a single resection of a HLRCC-associated RCC. All 3 resections contained a solitary tumor, with an average tumor size of 7.5 cm ($N=3$). The HLRCC tumors tended to be a high pT stage, with one pT4 tumor, and one pT3 tumor that also had lymph node metastases (pN1). One tumor was pT1; two tumors were WHO/ISUP grade 4; one tumor was WHO/ISUP grade 2, and per pathology report was consistent with low-grade oncocytic HLRCC-associated RCC. The slides for this case were not available for review.

Both HLRCC-associated RCC tumors available for morphologic review had eosinophilic/orangeophilic nucleoli, although not as prominent as classic RCCs from HLRCC patients (Fig. 5a). One tumor showed predominantly papillary morphology (Fig. 5b), while the other had scattered tubules with cords and small cluster of cells with eosinophilic cytoplasm (Fig. 5c). Immunohistochemistry showed loss of FH expression in the tumor cells, consistent with the known profile of HLRCC-associated RCC (Fig. 5d).

Succinate dehydrogenase deficiency resection study group ($N=1$)

One SDH deficiency patient was included in the study. The patient had a resection for a pT1, grade 2, multifocal renal tumor that was favored to represent a renal cell carcinoma with tubulopapillary features on initial diagnosis. The tumor was solid and cystic with a tubulopapillary architecture, consisting predominately of tightly packed tubules with luminal blue mucin and a focal spindle cell component (Fig. 6a, b). VSTM2A expression, a marker of MTSCC was assessed by RNA ISH for this study, and was negative, which along with other ancillary work up (data not shown), was supportive of this tumor representing a RCC, type unclassified (Fig. 6c) [16]. The tumor retained SDHB by immunohistochemistry (Fig. 6d).

Discussion

Von Hippel Lindau

Clinical and pathologic findings in Von-Hippel Lindau (VHL) patients

VHL is a highly penetrant autosomal dominant syndrome defined by pathogenic germline deletions, missense

Table 11 Birt-Hogg-Dube patients with renal tumor resections: clinical and pathologic features

Patient	Age[a]	Sex	Confirmed pathologic germline variant	Resection (side)	Indication for resection	Slides for review	Diagnosis	Focality (number of tumors)
13	52	M	Y	1. Partial (R)	Mass found on intitial BHD screening showed oncocytic neoplasm, cannot exclude RCC, on biopsy	N	CCRCC	Solitary
				2. Partial (L)	IS. Mass increasing in size	Y	ChRCC, eosinophlic variant	Solitary
14	70	M	N	1. Partial (R)	IS. Mass increasing in size	N	ChRCC	Solitary
15	42	M	Y	1. Partial (R)	NA	Y	ChRCC	Solitary
				2. Partial (L)	IS. Mass increasing in size	N	ChRCC	Solitary
16	72	M	N	1. Partial (R)	IS. Multiple enlarging masses	N	HOT	Multifocal (4)
17	58	M	Y	1. Partial (L)	IS. Multiple enlarging masses	Y	HOT	Multifocal (9)
				2. Partial (R)	IS. Multiple enlarging masses	Y	HOT	Multifocal (NA)
18	47	M	Y	No resection				
19	47	M	Y	No resection				

Patient	Tumor size (cm)	Stage	Grade[b]	Oncocytosis	Cysts	IHC	Follow-up (age)
13	4.6	T1	2[c]	NA	NA	N	Alive (57)
	2.2	T1	Not graded	N	N	CD117 (+), CK7 (patchy), PAX2 (−)	
14	4.4	T1	Not graded	NA	NA	N	Lost to follow-up (70)
15	1.2	T1	Not graded	N	NA	N	Lost to follow-up (45)
	2.5	T1	Not graded	NA	NA	CK7 (+), CD117 (+), E-cadherin (+), CD63 (+), vimentin (−)	
16	1.8–4.3			NA	NA	N	Alive (76)
17	Up to 4.2			N	N	CK7 (patchy), CD117 (+)	Alive (63)
	Up to 6.5			Y	N	N	
18							Alive (63)
19							Alive (48)

IHC immunohistochemistry, *IS* imaging surveillance, *CCRCC* clear cell renal cell carcinoma, *ChRCC* chromophobe renal cell carcinoma, *HOT* hybrid oncocytic tumor, *NA* not available

[a]Age at first renal tumor diagnosis

[b]WHO/International Society of Urological Pathology (ISUP) grading system

[c]Fuhrman grade

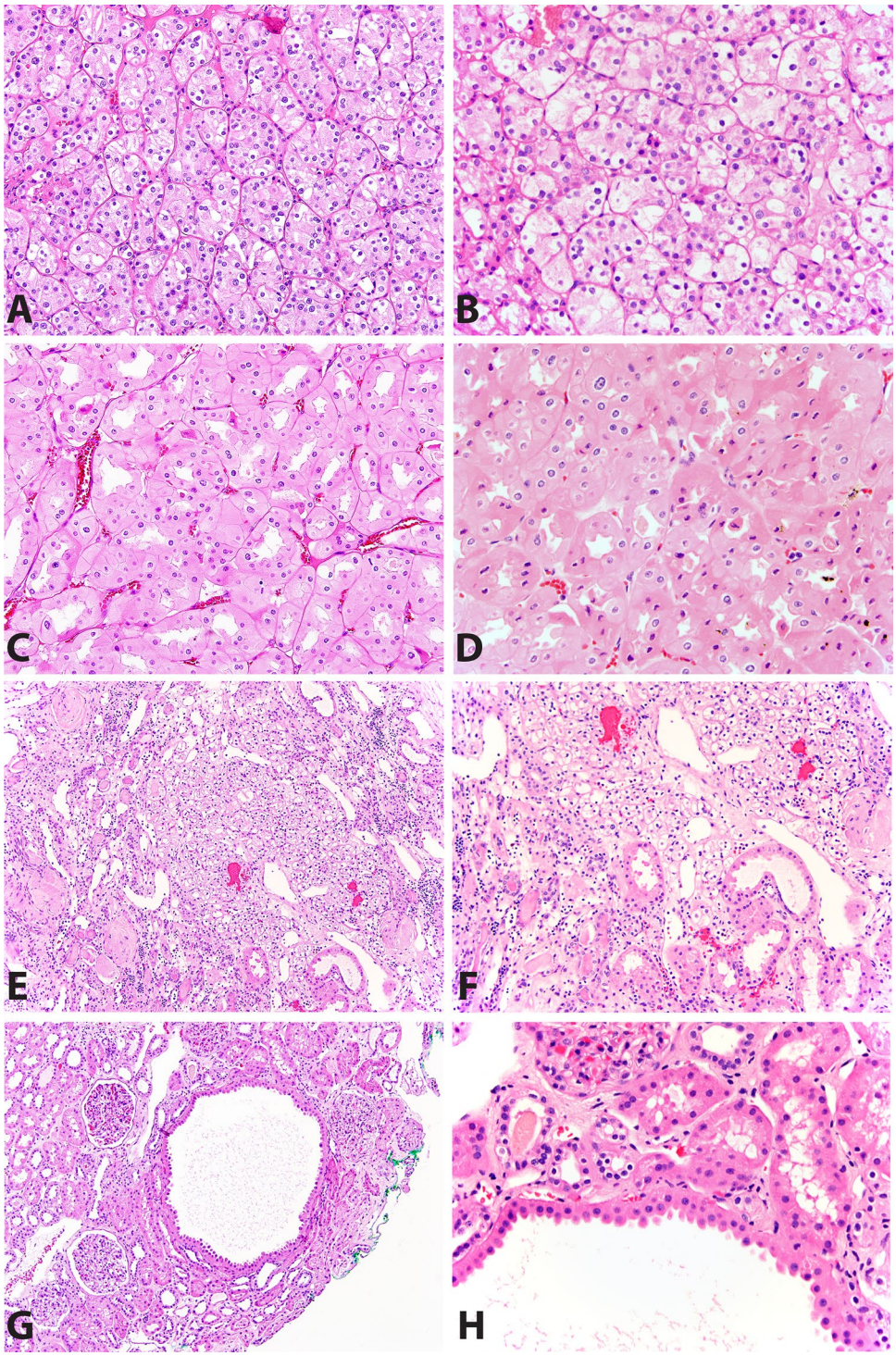

Fig. 3 Morphologic findings in BHD renal tumors. HOTs demonstrate a nested arrangement of cells resembling conventional oncocytomas and ChRCC (**a**, **b**). ChRCCs are the most common RCC and are similar to sporadic ChRCCs, showing a solid growth pattern, irregular nuclei, perinuclear halos, frequent binucleation, and prominent cell membranes. Pictured is an eosinophilic variant of ChRCC (**c**, **d**). Renal oncocytosis is characterized by nests (**e**, **f**) or cysts (**g**, **h**) of oncocytic to clear cells within benign renal parenchyma

mutations, or non-sense mutations in the *VHL* tumor suppressor gene located on chromosome 3p25.3. Most pathogenic germline *VHL* variants are inherited, but as many as 20% arise de novo [17]. A subsequent somatic mutation ("second hit") results in the loss of the VHL protein, ultimately leading to the development of numerous highly vascular tumors including renal clear cell renal cell carcinomas (25–45% of VHL patients), CNS hemangioblastomas (60–80%), retinal hemangioblastomas (25–60%), pheochromocytomas (10–20%), and pancreatic neuroendocrine tumors (8–17%) [7, 17–19]. Benign simple cysts are common in VHL patients, especially in the kidney (50–70%) and pancreas (17–56%), but also in the ovary, fallopian tube, liver, and lungs [17, 19]. Cystadenomas of the epididymis

Table 12 Tuberous sclerosis complex patients with renal tumor resections: clinical and pathologic features

Patient	Age[a]	Sex	Confirmed germline pathologic variant	Resection (side)	Indication for resection	Slides for Review	Diagnosis	Focality
20	26	F	N	1. Partial (R)	Suspicious mass on IS showed CCRCC on biopsy	Y	CCRCC; AMLs	AML—multifocal; CCRCC—solitary
21	13	F	N	1. Total (L)	Mass on imaging screening	N	RCC (clear cell, papillary, and granular cell features); AML	RCC and AML—multifocal
				2. Total (R)	New mass on IS	Y	TSC-associated RCC, eosinophilic, granular and macrocystic type; AML	Multifocal
22	48	F	N	1. Total (L)	New mass on IS	Y	AML (multiple)	Multifocal
23	13	M	N	No resection				
24	7	F	N	1. Partial (L)	Mass found on IS showed CCRCC on biopsy	N	RCC, unclassified	Solitary
25	57	M	N	No resection				
26	37	M	N	No resection				

Patient	Tumor size (cm)	Stage	Grade[b]	Background cysts	Epithelioid AML changes	AML tumorlets	Follow-up (age)
20	CCRCC: 3.7; AML: NA	T1	2	Y	N	Y	Lost to follow-up (27)
21	11.0 (largest mass)	T2	2[c]	NA	NA	NA	DOD (18); Chronic renal failure
	3.8 (largest mass)	T2	4	Y	N	Y	
22	1.3 (largest mass)			Y	N	N	Alive (57)
23							Alive (17)
24	3.5	T1	3[c]	NA	NA	NA	Alive (11)
25							Lost to follow-up (57)
26							Alive (41)

IS radiosurveillance, *CCRCC* clear cell renal cell carcinoma, *AML* angiomyolipoma, *RCC* renal cell carcinoma, *TSC* tuberous sclerosis complex, *NA* not available

[a]Age at first renal tumor diagnosis

[b]WHO/International Society of Urological Pathology (ISUP) grading system

[c]Fuhrman grade

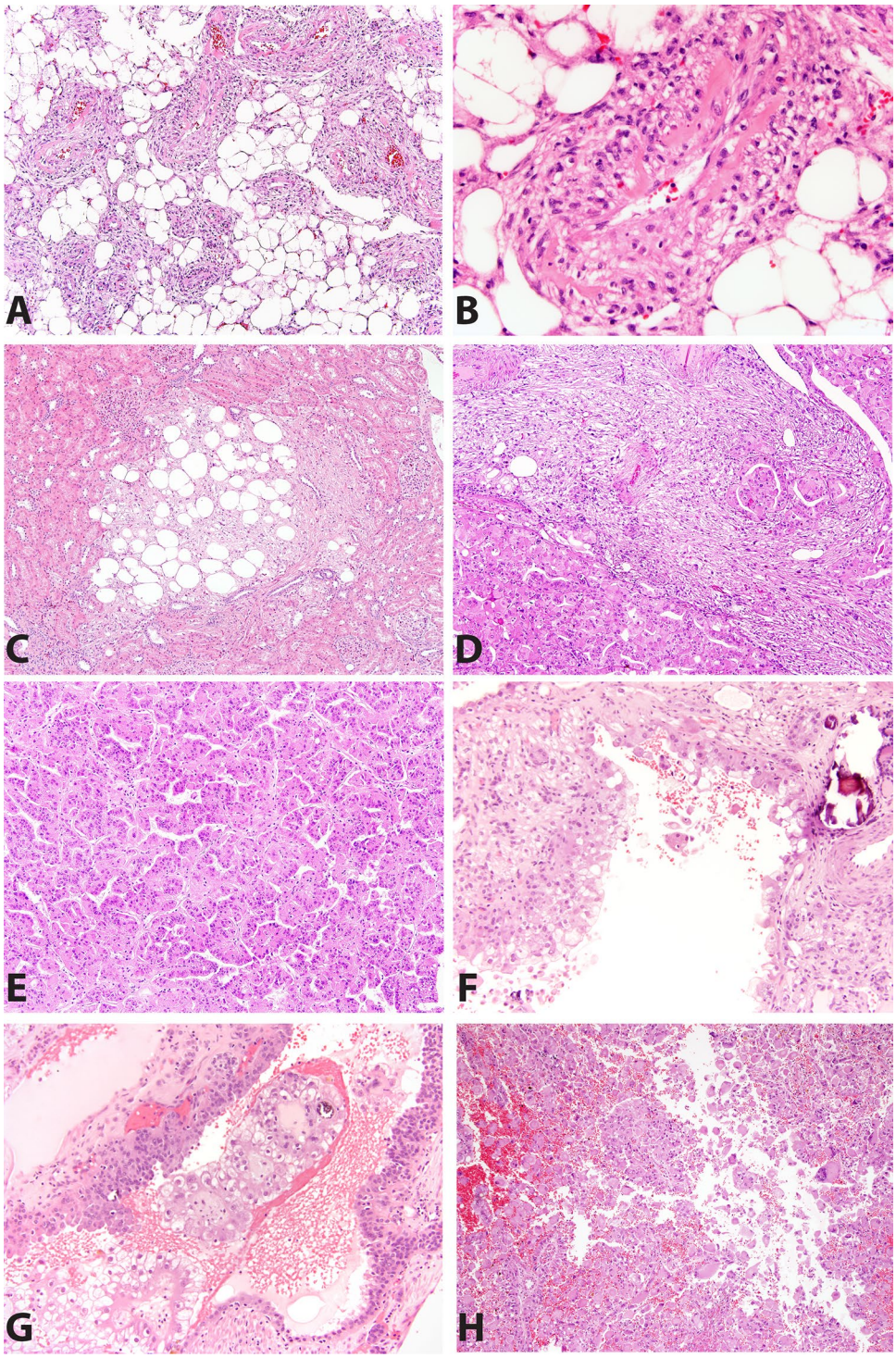

Fig. 4 Morphologic findings in TSC renal tumors. Classic triphasic AML (**a**, **b**) showing a mixture of adipose tissue, spindled or epithelioid smooth muscle cells, and dystrophic vessels. Smooth muscle cells can have clear cell change and often appear to radiate from vessel walls. AML tumorlets (**c**) are often found in the background renal parenchyma. TSC-associated RCCs have variable morphologies and may resemble CCRCCs, ChRCC/HOTs, type-2 PRCCs, or have a renal angiomatous-like stroma. Pictured is a TSC-associated RCC (**d**–**h**), granular eosinophilic-macrocystic type, with a solid tubulopapillary component (**d**, **e**) along with microcysts and macrocysts lined by with large cells with voluminous eosinophilic to clear cytoplasm (**f**, **g**). Portions of the tumor consisted of granular, eosinophilic, multinucleated giant cells (**h**). Numerous foci of AML intermingled or were directly adjacent to the RCC (**d**)

(25–60% of male VHL patients), ovary, and pancreas, as well as inner ear endolymphatic sac tumors (10% of VHL patients) can also be seen [7, 17, 19]. VHL syndromic tumors present at a young age, on average at 25 years for retinal hemangioblastomas, 30 years for CNS hemangioblastomas, and 37 years for CCRCC [17, 19–21]. Metastatic CCRCC is responsible for 35–45% of VHL patient deaths and is historically the leading cause of death in VHL patients, although death due to metastatic CCRCC may have decreased in recent years due to increased surveillance and improved imaging [4, 11].

In our cohort, extra-renal tumors and benign cysts occurred at similar frequencies as reported in the literature (Table 2) [17, 19]. The average age of first renal resection

Table 13 Hereditary leiomyomatosis renal cell carcinoma syndrome patients with renal tumor resections: clinical and pathologic features

Patient	Age[a]	Sex	Confirmed pathologic germline variant	Resection (side)	Indication for resection	Slides for review	Diagnosis	Focality
27	64	M	Y	Total (L)	Imaging for hematuria showed renal mass	Y	Poorly differentiated renal cell carcinoma, consistent with HLRCC	Solitary
28	28	F	Y (2 years post-resection)	Partial (L)	Imaging for flank pain showed renal mass	N	HLRCC-associated RCC; paraganglioma	Solitary
29	50	M	Y	Total (L), en bloc resection of left adrenal gland, distal pancreas, spleen, diaphragm	Imaging for urinary retention revealed renal masses, biopsy showed high-grade carcinoma consistent with HLRCC	Y	Poorly differentiated renal cell carcinoma, consistent with HLRCC	Solitary
Patient	Tumor size (cm)	Solid versus cystic	Stage	Grade[b]	Architecture	Prominent eosinophilic/orangeophilic nucleoli	IHC	Follow-up (age)
27	6.1	Solid	T3, N1	4, with sarcomatoid change	Type 2 papillary	Y	CK (+), PAX8 (+), INI1 (+), p63 (−)	AWOD (68)
28	4.8	Solid and cystic	T1	2	N/A	N/A	EMA (+), Vimentin (+), CK7 (−), AMACR (−), Ckit (−), E-cadherin (−), CAIX (−), CD10 (−)	LFU (28). AWOD when LFU
29	11.7	Solid	T4, N0	4, with sarcomatoid change	Tubular/glandular	Y	FH weak and patchy	AWOD (50). Recent diagnosis of acute lymphoblastic leukemia

IHC immunohistochemistry, *IS* imaging surveillance, *HLRCC* hereditary leiomyomatosis renal cell carcinoma syndrome, *N/A* not available, *AWOD* alive without disease, *LFU* lost to follow-up

[a]Age at first renal tumor diagnosis

[b]WHO/International Society of Urological Pathology (ISUP) grading system

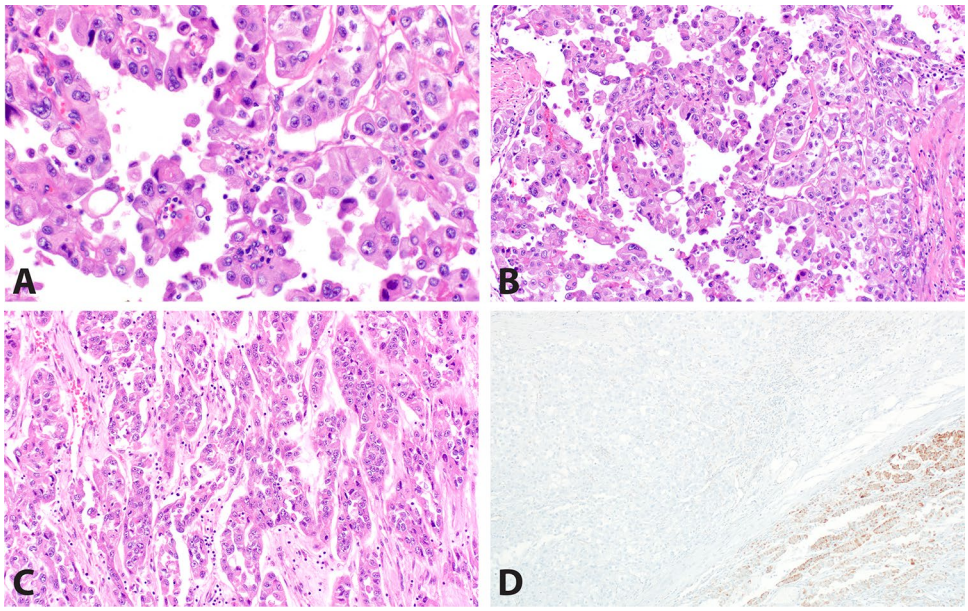

Fig. 5 HLRCC-associated RCCs. The most diagnostic finding in HLRCC-associated RCC is a large nucleus with a prominent eosinophilic/orangeophilic nucleoli (**a**). **b** A case with predominately papillary architecture, and (**c**) a HLRCC-associated RCC with scattered tubules, and cords and small clusters of tumor cells. Loss of FH expression is a characteristic finding in HLRCC-associated RCC (**d**). FH expression is retained in normal renal parenchyma (lower right)

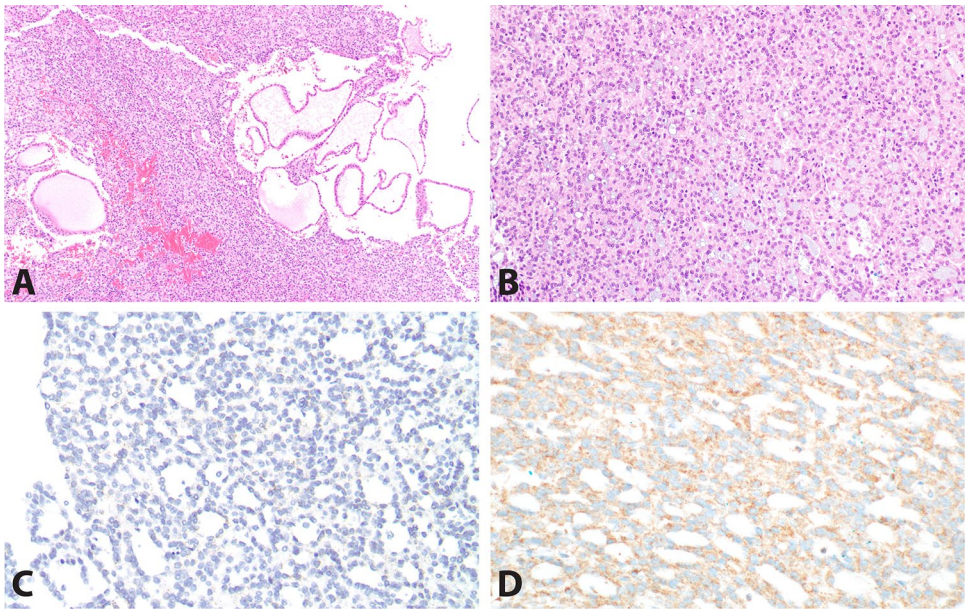

Fig. 6 Renal cell carcinoma, type unclassified, in a patient with a germline *SDHD* mutation. The tumor had a cystic component (**a**), but was predominantly solid with compact tubules filled with blue mucin (**b**). The spindle cell component of the tumor was focal. Expression of VSTM2A by RNA ISH, a marker of mucinous tubular and spindle cell renal cell carcinoma, was negative (**c**). The tumor retained SDHB expression by immunohistochemistry (**d**)

was 31.2 years, compared to the average age of RCC presentation of 37 years reported in the literature [20]. CCRCC was the most common RCC in VHL in our study, a finding also seen in the literature (Table 2). The average resected tumor was 2.3 cm ($N=60$), which is smaller than size threshold (3.0 cm) recommended to prompt tumor resection (Table 3). This finding most likely reflects that the majority of VHL patients adhere to annual surveillance and while resection is triggered by the largest tumor approaching ~ 3 cm, multiple small tumors are usually resected along with the largest tumor (Table 10). Interestingly, 55% of resected tumors in our study were WHO/ISUP grade 3, whereas the literature reports that most resected VHL CCRCCs to be low-grade (WHO/ISUP grade 1 or 2) [2]. All resected CCRCCs in the cohort were T1 tumors, reflecting that most resections (75%) in the study were performed in response to concerning findings discovered during surveillance for renal cell carcinomas (Table 10). There were no patients in our cohort where the first clinical manifestation of VHL was a CCRCC. Only one patient in our cohort died of metastatic CCRCC (Table 4), while the remaining 3 deaths in our cohort were attributed to stroke related to multiple hemangioblastomas, chronic kidney disease from multiple renal resections, and metastatic pancreatic neuroendocrine carcinoma.

The present study demonstrated a high frequency (95%; 18/19) of cysts and/or cystic CCRCC in resection specimens

(Table 3; Fig. 1b, d), and all VHL patients in the study had radiologic evidence of renal cysts (Table 2). Clear cell tumorlets were seen in 44% of VHL patients with a resection in our cohort, although many resections had little renal parenchyma uninvolved by tumor for evaluation. With more thorough sampling of normal renal parenchyma, we suspect a higher frequency of tumorlets would be identified. Clear cell tumorlets within benign renal parenchyma in an undiagnosed patient should raise strong suspicion of an underlying VHL syndrome.

Atypical renal cysts in Von Hippel Lindau (VHL) patients

It has been estimated that over 1000 benign and atypical clear cell-lined cysts can exist in a VHL kidney and that atypical clear cell-lined cysts are the precursor lesion to CCRCC in VHL patients [22–24]. Atypical cysts in VHL patients have been shown to have second-hit *VHL* gene deletions and overexpress CA-IX protein by immunohistochemistry, supporting the notion that atypical cysts are precursor lesions to CCRCC in VHL patients [24]. Benign clear cell cysts and renal tubular epithelial cells in VHL patients have also been shown to harbor the second-hit *VHL* gene deletion and may also represent precursor lesions [23, 24]. Additionally, CCRCCs in VHL patients have demonstrated cytogenetic heterogeneity, supporting the idea that atypical cysts and CCRCCs are multiclonal and arise from de novo genetic events after the initial germline *VHL* gene mutation [25]. It appears that multifocal CCRCCs in VHL patients represent individual primary tumors rather than a single clonal tumor forming multiple metastases.

Atypical clear cell-lined cysts are not unique to VHL patients and can be seen in association with clear cell neoplasms such as multilocular cystic clear cell renal cell neoplasm of low malignant potential, cystic CCRCC with or without regression, and clear cell papillary RCC. Clear cell cysts can also be seen in acquired cystic disease of the kidney (ACDK) and in TSC patients, although eosinophilic cell-lined cysts may be common in these entities [23, 26, 27]. Infrequently, atypical clear cell-lined cysts occur in association with other sporadic renal tumors such as PRCC and oncocytomas [23, 26].

A recent case series by Matoso et al. reviewed morphologic, immunohistochemical, and molecular characteristics of atypical renal cysts [26]. Atypical cysts were classified into three morphologic subtypes: clear cell, eosinophilic stratified, and eosinophilic papillary. Nine cases of atypical clear cell cysts were reviewed and were associated with neoplasms (PRCC, CCRCC, oncocytoma), lithiasis, dialysis, or had no associated lesions or comorbidities. Interestingly, 7 of the 9 cases were positive for both CK7 and CA-IX by immunohistochemistry, with cup-like staining seen in two cases. None of the atypical clear cell-lined cysts demonstrated a 3p deletion. This study highlights that atypical clear cell-lined cysts can arise from etiologies unrelated to *VHL* gene abnormalities and also that atypical clear cell cysts can at least immunophenotypically resemble the profile seen in CCPRCC. Outside of atypical clear cell-lined cysts seen in VHL patients, the role of atypical clear cell-lined cysts as a precursor to malignancy is uncertain. In our cohort, atypical clear cell-lined cysts were a common finding juxtaposed to CCRCC.

Clear cell papillary renal cell carcinoma (CCPRCC) in Von Hippel Lindau (VHL) patients

Clear cell papillary RCC (CCPRCC) is a low-grade RCC that shares a morphologic resemblance to CCRCC, although lacks the molecular alterations, such as *VHL* gene mutation or chromosome 3p deletion, characteristic of CCRCC [28]. Additionally, CCPRCC typically lack trisomy of chromosomes 7 and 17, as well as loss of chromosome Y characteristic of PRCC, although gains of chromosome 7 and 17 have been documented in a few tumors [29]. To date, no consistent molecular aberration has been identified in CCPRCC.

The distinction of CCPRCC from CCRCC is important, as CCPRCC have a good prognosis [29, 30]. Morphologically, CCPRCC consists of clear cells, often with reverse nuclear polarity, arranged in a tubulopapillary architecture. Immunohistochemically, the tumor cells typically show strong membranous expression of CK7, and membranous cup-like CA-IX expression.

Recently, cases with features of clear cell papillary RCC (CCPRCC) have been investigated in VHL patients [31, 32]. Williamson et al. reported morphologic, immunohistochemical, and molecular findings of 14 CCPRCC-like tumors in four VHL patients. Only two tumors demonstrated the characteristic CCPRCC immunohistochemical profile (CK7+ , CA-IX+), and 82% of tumors demonstrated loss of chromosome 3p by FISH, suggesting that the CCPRCC-like tumors in these VHL patients more closely resembled CCRCC [32]. To the contrary, Rao et al. described three CCPRCCs in VHL patients that demonstrated the classic immunohistochemical profile of CCPRCC and lacked 3p deletions [31].

CCPRCC was seen in one VHL patient (patient 2) in our cohort and demonstrated strong membranous expression of CK7 and membranous cup-like CA-IX expression, and lacked chromosome 3p25 loss by targeted next-generation sequencing. These findings are relatively supportive of what is seen in sporadic CCPRCCs, as well as the VHL-related findings of Rao et al.

Birt-Hogg-Dubé

Birt-Hogg-Dubé (BHD) is an autosomal dominant syndrome characterized by a pathogenic germline variant of the

FLCN gene located on chromosome 17p11.2, which codes for protein folliculin. The clinical findings of BHD include cutaneous lesions (fibrofolliculomas, trichodiscomas, and acrochordons), which occur in 90% of BHD patients, and pulmonary cysts (83% of BHD patients) [2, 7, 12, 33, 34]. Pneumothorax is a common complication of pulmonary cysts, occurring in 23–38% of BHD patients, most commonly in patients < 40 years old [7, 12, 33, 35].

Renal tumors occur in 34–49% of BHD patients, presenting at a mean of 50 years, and are frequently multifocal and bilateral [2, 34, 36]. The most common tumor is hybrid oncocytic tumor (HOT), which accounts for 50% of renal tumors [36]. Pure oncocytomas has also been reported. Renal cell carcinomas include chromophobe renal cell carcinoma (ChRCC) and clear cell renal cell carcinoma (CCRCC) making up 34% and 9% of BHD renal tumors, respectively, comparable to the findings in the present study (Table 3) [36]. Papillary renal cell carcinomas can also occur. Metastatic renal cell carcinoma is rare in BHD patients, but have been reported [34]. Although most tumors in BHD patients are benign or low-grade, the potential for the development of RCCs justifies screening BHD patients for RCCs. In our cohort, no cases of RCC led to recurrent or metastatic disease.

Benign renal cysts, often lined by eosinophilic cells, are commonly seen in BHD patients, but their frequency is unknown [2, 12]. Oncocytosis is common and occurs in 58% of BHD patients and is characterized by oncocytic clusters or cysts within the renal parenchyma, or oncocytic change in non-neoplastic tubules (Fig. 3e–h). [36] Oncocytosis frequently occurs in association with ChRCC, HOT, or oncocytoma, tumors commonly seen in BHD [37]. Most cases of oncocytosis are now thought to be related to BHD, although there are rare reports of oncocytosis occurring in patients without BHD [38].

The clinical findings of cutaneous lesions, pulmonary cysts, and pneumothorax in the present study are comparable to what has been reported in the literature (Table 2). In our study, one BHD patient was afflicted with numerous small (< 2 cm) angiolipomas involving the chest, arms, and thighs (Table 5). An association of BHD with multifocal lipomas has been noted in the literature, although only a few cases have been reported [35, 39]. HOTs were seen in 37.5% (3/8) resection specimens in the study, slightly lower than the 50% renal tumor frequency rate in BHD patients reported in the literature (Table 3) [36]. Likewise, ChRCC accounted for 50% (4/8) of resected tumors in our cohort, higher than the 34% reported in the literature (Table 3) [36]. CCRCC was seen in 12.5% of resections (1/8), similar to what is reported in the literature. No renal cysts were seen in BHD resection specimens in our study, and oncocytosis was seen in 1 of 3 resections available for review.

Tuberous sclerosis complex

TSC is an autosomal dominant syndrome with pathogenic germline variants of *TSC1* (located on 9q34) or *TSC2* (located on 16p13.3), which encode hamartin and tuberin, respectively. Hamartin and tuberin are tumor suppressors in the mTOR (mammalian target of rapamycin) signaling pathway. Renal tumors are common, occurring in 70–90% of TSC patients, most of which are angiomyolipomas (AMLs) [4, 40, 41]. Renal failure and hemorrhage due to multifocal AMLs are the leading causes of morbidity and death in TSC patients [4, 41]. Renal cell carcinomas occur in 2–4% of TSC patients, similar to the prevalence of sporadic renal cell carcinomas, although TSC-associated renal cell carcinomas present at a much younger age (average 28 years) and show a female predominance [9, 42]. Concurrent, multifocal angiomyolipomas (56–94%) are frequently seen in association with TSC-associated RCCs [41, 43].

Other clinical manifestations of TSC include brain tumors, including cortical tubers (80% of TSC patients), and subependymal giant cell astrocytomas (10%) [4]. Notably, 57% (4/7) of TSC patients in the present study were diagnosed with giant cell astrocytomas (Table 2). Retinal hamartomas are prevalent, comparable to findings in our study, and skin lesions (angiofibroma, periungual fibroma, hypomelanotic macules) are seen in 90-100% of patients (Table 2) [4]. Tumors from the PEComa family (lymphangioleiomyomatosis, clear cell tumors, and extra-renal angiomyolipomas) can occur at various sites, but were not identified in our study.

Renal angiomyolipomas (AMLs) in tuberous sclerosis complex (TSC) patients

Renal angiomyolipomas most often occur sporadically and have several variant morphologies such as classic triphasic, epithelioid, lipid-rich, sclerosing, and smooth muscle-like with epithelial cysts. Epithelioid AMLs are of particular interest, as they have a reported association with TSC, especially when they are seen in combination with epithelial cysts and microscopic tumorlets, and they may have potential for malignant behavior [2]. Malignant behavior is not as common as previously thought, occurring in only 4.6% of sporadic AMLs in a recent study by He et al. [44–47]. Epithelioid AMLs have variable morphologic patterns [44]. One pattern consists of uniform populations of small clear to eosinophilic epithelioid cells organized as nests, in an alveolar pattern, or as sheets. Another pattern consists of large eosinophilic epithelioid cells with abundant cytoplasm, sometimes with pleomorphic multinucleated giant cells, ganglion-like cells, and atypical nuclear features (vesicular nuclei, prominent nucleoli, and nuclear pleomorphism) [44, 46]. It has been proposed that tumors with > 70% atypical

epithelioid cells, > 2 mitoses per 10 high power fields, atypical mitoses, and necrosis have an increased risk of malignant behavior [48]. No epithelioid AMLs were identified in our cohort.

Tuberous sclerosis complex association renal cell carcinoma (TSC-associated RCC)

TSC-associated RCCs have a large degree of morphologic heterogeneity and may resemble CCRCCs, ChRCC/HOTs, TCEB1-mutated tumors, and type-2 PRCCs, among other growth patterns. Guo et al. organized TSC-associated RCCs into three general categories: 1. Carcinoma resembling renal angiomyoadenomatous tumor (RAT-like)/RCC with smooth muscle stroma. 2. Carcinomas resembling sporadic ChRCC (chromophobe-like). 3. Granular eosinophilic-macrocystic [43]. RAT-like TSC-associated RCCs often resemble sporadic CCRCC with nests of clear cells, although branching tubules and focal papillary architecture can be present. Admixed bundles of smooth muscle are the most characteristic feature. Chromophobe-like TSC-associated RCC shows nests and sheets of clear to eosinophilic cells with hyperchromatic, irregular nuclei with at least focal perinuclear halos, although large areas can exhibit monomorphic nuclei as in oncocytomas. Focal intratumoral cysts are common. The most unique type of TSC-associated RCC is the granular eosinophilic-macrocystic morphology, which is characterized by microcystic and macrocystic cysts lined by granular eosinophilic cells with admixed solid foci of RCC [43, 49]. One case of TSC-associated RCC (patient 21; Table 12) in this study demonstrated a granular eosinophilic-macrocystic morphology, along with large areas resembling type 2 PRCC and focal areas resembling CCRCC (Fig. 4d–h).

Histologic features suggestive of underlying tuberous sclerosis complex (TSC)

In addition to characteristic clinical and morphologic tumor findings, the background uninvolved renal parenchyma can provide additional diagnostic clues that suggest underlying TSC. One such finding is microscopic AML tumorlets, which was seen in two TSC patients in our study (Table 3). Additionally, renal cysts, seen in 30–40% of TSC patients, in benign renal parenchyma are common [23]. They are typically lined by eosinophilic cells and can sometimes show papillary tufting. All TSC patients ($N = 3$) with slides available for morphologic review demonstrated renal cysts in our study (Table 12). If a patient has a combination of AML, eosinophilic renal cysts, and microscopic AML tumorlets, TSC should be suspected [44].

Recognition of renal features suggestive of TSC is of particular importance, as the clinical presentation of TSC is variable and 60–70% of cases arise by de novo mutation without an associated family history [7, 8]. Pathology assessment can play an important role in the diagnosis of TSC patients who are difficult to diagnose clinically.

Hereditary leiomyomatosis and renal cell carcinoma syndrome (HLRCC)

Hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome is an autosomal dominant syndrome characterized by pathogenic germline variants in the *FH* gene, predisposing affected individuals to renal carcinoma, and cutaneous and uterine leiomyomata. Renal cell carcinomas in HLRCC have relatively low penetrance (20–30%), although they present at a young age (median age 39–44 years) and tend be aggressive, high-grade tumors associated with a high mortality [2, 14, 50–53]. Unlike most hereditary syndrome tumors, they tend to be solitary and unilateral. Morphologically, most tumors have papillary or tubulopapillary growth patterns and often resemble type 2 papillary RCC at least focally [9]. Other growth patterns include solid, tubular, or tubulocystic, or resemble collecting duct carcinomas. The most distinctive morphologic feature are large nuclei with perinuclear halos and prominent eosinophilic/orangeophilic nucleoli, although this feature may not be prominent in all cases as demonstrated in one tumor in our cohort (Fig. 5a). Loss of FH expression in tumor cells is often demonstrated by immunohistochemistry. Due to its rarity and challenge to diagnose, HLRCC-associated RCC is likely an under recognized entity. There should be a high degree of suspicion for HLRCC if a young patient presents with a high-grade tumor that demonstrates any morphologic characteristics suggestive of HLRCC-associated RCC.

Similar to what is commonly reported in the literature, all two of the three HLRCC-associated RCCs in the study were solitary, high-grade tumors that tended to present at a high T stage with lymph node metastases in one case. One tumor was a T1, low-grade oncocytic HLRCC-associated RCC. Two patients presented at an older age (50 and 64 years of age) than is typically described in the literature, and one patient presented at 28 years of age. Two patients are alive without disease at 4 and < 1 years of follow-up, and one patient was lost to follow-up.

Succinate dehydrogenase deficiency syndrome (SDH Deficiency)

SDH-deficient RCCs, defined by pathogenic germline variants in one of four genes (*SDHA*, *SDHB*, *SDHC*, *SDHD*) that encode for components of a mitochondrial SDH enzyme, are rare tumors with an incidence of 0.1–0.2% of all RCCs [54]. Patients with SDH deficiency predominately develop pheochromocytomas and paragangliomas. In addition, these

patients may develop renal cell carcinomas, carotid body tumors, and gastrointestinal stromal tumors. SDH mutation involving *SDHB* accounts for the vast majority of RCCs in SDH-deficient patients, although mutations in *SDHA*, *SDHC*, and *SDHD* rarely occur. The estimated risk for development of an RCC by age 60 in *SDHB* pathogenic variant carriers is ~ 5% [55]. The average age of RCC presentation is 37 years, and not uncommonly (26% of tumors) present bilaterally [54]. Most cases of SDH-deficient RCC appear indolent, although metastases have been reported in as high as 21% of cases in one study [54]. Tumors with metastatic disease are frequently ISUP/WHO grade 3 or 4, and were associated with tumor necrosis. Patients have been reported to progress rapidly to metastatic disease, with death resulting within 1 year, although some patients have been reported to develop metastases after a disease-free interval of greater than 10 years [54, 56]. Further studies will be needed to further elucidate the malignant behavior and metastatic potential of SDH-deficient RCCs.

The majority of SDH-deficient RCCs are associated with the mutation of *SDHB* and frequently demonstrate characteristic morphologic findings. Tumors are typically composed of solid nests or tubules of eosinophilic cells, although cystic change may be present. Most cases (72%) have inconspicuous nucleoli and are WHO/ISUP grade 1 or 2 [2]. Vacuolated cytoplasm and cytoplasmic inclusions consisting of pale eosinophilic, flocculent material is the most characteristic finding, and is at least found focally in SDH-deficient tumors with a *SDHB* mutation [54, 57]. In the rare cases with *SDHC* or *SDHD* mutations, RCCs have been suggested to morphologically resemble CCRCCs [58].

There was one patient (patient 30) with SDH deficiency in our cohort with a germline *SDHD* mutation. The patient's renal tumor was initially diagnosed as RCC with tubulopapillary features. Upon re-review of the tumor for this study, a negative RNA ISH for *VSTM2A* expression along with other ancillary work-up (data not shown) supported that this tumor is best categorized as a renal cell carcinoma, type unclassified. The tumor retained SDHB expression by immunohistochemistry. *SDHD* mutations are rarely documented in SDH-deficient RCCs, and have been reported to resemble CCRCCs in the literature [58]. Our cohort demonstrates a unique kind of renal cell carcinoma with tubulopapillary morphology to occur within a patient with germline *SDHD* mutation; apart from the germline defect, we were unable to confirm a somatic loss within this tumor and therefore the true association with the underlying syndrome remains elusive.

Summary

Our study characterizes the clinical trajectory including clinical surveillance, biopsy, and resection information with outcomes for a cohort of patients at a tertiary hospital and cancer center. We were able to confirm the previously known clinical stigmata of HRCCS patients, as well as characterize renal lesions and tumors from a clinical, radiologic and pathologic perspective. While the majority of tumors were consistent with the anticipated clinicopathologic profile of renal tumors found within HRCCS patients, we found some unique characteristics within this cohort. Tumor classification and molecular characterization confirmed a bona fide case of CCPRCC within a VHL patient. Furthermore, while the previous literature reports the presence of epithelioid AML as a common occurrence in TSC patients, the 4 resections (3 patients) with AMLs in our cohort demonstrated only classic features. We ascribe this phenomenon to a better understanding of tumor classification and biologic behavior of relatively enigmatic/uncommon renal entities like epithelioid AML. Finally, we describe a unique renal tumor with tubulopapillary features presenting in a patient with an *SDHD* variant; whether this tumor shows a consistent association with the SDH-deficient realm of HRCCS needs to be determined in a larger series.

Identifying HRCCS patients and their families is important so that appropriate genetic testing and surveillance measures can be taken. The pathologist can play an important role in identifying these patients in renal tumor biopsies. In our study, five of the nineteen (26%) patients with a kidney biopsy had no HRCCS diagnosis prior to biopsy, and in three of these five patients' biopsies the pathologist recognized morphologic features of a hereditary renal tumor that prompted molecular testing and confirmed a HRCCS diagnosis (2 BHD, 1 HLRCC).

In addition to specific morphologic features of HRCCS tumors, tumor multifocality or bilaterality, tumor presentation at a young age, and/or background renal cysts may assist in the recognition of HRCCS renal tumors. Clinical clues such as a family history of renal tumors, and extra-renal syndromic clinical findings are also helpful. In addition to patient care, the identification of HRCCS tumors is important to better understanding their underlying genetics and potential therapeutic targets [59].

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interest.

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