Pathobiology

Research Article

Pathobiology 2023;90:322–332
DOI: 10.1159/000529276

Received: September 28, 2022
Accepted: January 14, 2023
Published online: January 25, 2023

Renal Cell Carcinoma in End-Stage Renal Disease: A Retrospective Study in Patients from Hungary

Dávid Semjén[a] Borbála Dénes[b] Áron Somorácz[b] Attila Fintha[c] Gertrúd Forika[c] Alex Jenei[c] Deján Dobi[d] Tamás Micsik[e] Kornélia Veronika Eizler[e] Nándor Giba[e] Fanni Sánta[f] Anita Sejben[f] Béla Iványi[f] Levente Kuthi[f]

[a]Department of Pathology, Medical School and Clinical Centre, University of Pécs, Pécs, Hungary; [b]MedServ Ltd., Budapest, Hungary; [c]Department of Pathology and Experimental Cancer Research, Semmelweis University, Budapest, Hungary; [d]Department of Pathology, Forensic and Insurance Medicine, Semmelweis University, Budapest, Hungary; [e]Pathology Unit, Fejér County Szent György University Teaching Hospital, Székesfehérvár, Hungary; [f]Department of Pathology, Albert Szent-Györgyi Medical School, University of Szeged, Szeged, Hungary

Keywords
Renal cell carcinoma · End-stage renal disease · Acquired cystic kidney disease

Abstract

Introduction: End-stage renal disease (ESRD) and acquired cystic kidney disease (ACKD) are known risk factors for renal cell carcinoma (RCC). Hereby, the clinicopathological features of RCCs developed in ESRD were investigated. ***Methods:*** A database consisting of 34 tumors from 31 patients with ESRD among 2,566 nephrectomy samples of RCC was built. The demographic, clinical, and follow-up data along with pathological parameters were analyzed. The RCCs were diagnosed according to the current WHO Classification of Urinary and Male Genital Tumors. ***Results:*** Twenty-two tumors developed in men and 12 in women, with a median age of 56 years (range: 27–75 years). The causes of ESRD were glomerulonephritis (n = 7), hypertensive kidney disease (n = 6), autosomal dominant polycystic kidney disease (n = 6), chronic pyelonephritis (n = 4), diabetic nephropathy (n = 3), chemotherapy-induced nephropathy (n = 1), and undetermined (n = 4). ACKD complicated ESRD in 12 patients. The following histological subtypes were identified: clear cell RCC (n = 19), papillary RCC (n = 5), clear cell papillary tumor (n = 5), ACKD RCC (n = 3), and eosinophilic solid and cystic RCC (n = 2). The median tumor size was 31 mm (range: 10–80 mm), and 32 tumors were confined to the kidney (pT1-pT2). There was no tumor-specific death during the period of this study. Progression was registered in 1 patient. ***Conclusion:*** In our cohort, the most common RCC subtype was clear cell RCC (55%), with a frequency that exceeded international data appreciably (14–25%). The incidence of clear cell papillary tumor and ACKD RCC (14.7% and 8.5%) was lower than data reported in the literature (30% and 40%). Our results indicate a favorable prognosis of RCC in ESRD.

karger@karger.com
www.karger.com/pat

Correspondence to:
Levente Kuthi, kuthi.levente@med.u-szeged.hu

Introduction

End-stage renal disease (ESRD) is rapidly increasing worldwide, with the highest incidence rate in well-developed countries [1]. Generally, ESRD is associated with diabetes, hypertension, obesity, and primary glomerular diseases, such as IgA nephropathy [2]. Even though ESRD could be treated by kidney transplantation, the number of available donors is insufficient; therefore, patients with ESRD are maintained by long-term peritoneal or hemodialysis (HD) [3]. Approximately 20% of these patients develop acquired cystic kidney disease (ACKD) as an adverse effect [4]. ACKD is defined as more than 3 cysts per kidney or cysts involving >25% of the renal parenchyma [5]. ESRD and ACKD are well-known risk factors for renal cell carcinoma (RCC) [6]. The pathogenesis of RCC in ESRD is considered a complex process, attributed to the decreased immune surveillance, increased oxidative stress, and hypermethylation of tumor suppressor genes [7]. The estimated risk for RCC in ESRD varies in the literature; still, generally 3–7% of ESRD patients will develop RCC that is much higher compared to healthy individuals (approximately 4–5/100,000) [8]. The time period of hemodialysis determines the extent of ACKD, while the longer duration of dialysis is associated with elevated RCC incidence and dismal clinical events [9, 10]. Furthermore, it must be emphasized that the number of the developed cysts may start to decrease after kidney transplantation. According to histology, all RCC types can be developed in ESRD, but there are some discrepancies between ESRD patients and the general population [11]. First of all, ACKD RCC occurs mutually in ACKD patients [11, 12]. ACKD RCC was primarily defined in the 4th edition of the World Health Organization (WHO) Classification of 2016, based on its unique clinical background, behavior, and morphology [12]. However, clear cell papillary tumor (CCPT) that was earlier designated as clear cell papillary RCC also develops at a higher frequency in ESRD kidneys [11]. The first papers on this entity linked CCPTs directly to ESRD, but later on, CCPTs were proven to occur in otherwise healthy kidneys, as well. Finally, the emerging/provisional entities, including eosinophilic solid and cystic (ESC) RCC and low-grade oncocytic tumor of the kidney, also have a higher prevalence in ESRD patients [13]. The clinical outcome for RCCs in ESRD is yet uncertain. On one hand, these patients more commonly undergo imaging modalities; therefore, there is a higher chance of finding these tumors in an early stage [7]. On the other hand, the longer duration of dialysis is associated with unfavorable risk factors, including advanced tumor stage, sarcomatoid transformation, and rhabdoid morphology [14]. In this retrospective, consecutive study RCCs of Caucasian patients with ESRD were reviewed. We assessed and analyzed the clinical and pathological data, to expand the landscape of these unique tumors.

Materials and Methods

Study Cohort and Review Process

We collected all RCCs with ESRD from 1935 to 2022 of the archive of the Department of Pathology, Albert Szent-Györgyi Medical School, University of Szeged. We enrolled both in-house and consultation cases, although we excluded biopsy samples, and analyzed nephrectomy specimens only. ESRD was defined as either chronic kidney failure stage 5 or chronic kidney failure treated by kidney transplantation or dialysis. Regarding ACKD, the above-mentioned definition was applied. Two pathologists (SD and LK) reviewed all the available hematoxylin-eosin-stained and immunohistochemical slides, while remaining unaware of the previous pathological diagnosis and the clinical outcome. If needed, we ordered additional immunohistochemical stains and molecular studies. Lastly, we established the final diagnosis of the tumors based on the 5th edition of the WHO Classification Urinary and Male Genital Tumors [15].

Clinical and Pathological Data

The main clinical characteristics included were symptoms, age, sex, the underlying cause of ESRD, type, and duration of dialysis. We collected the follow-up data from the electronic patient files and general practitioners. The data on multifocality, laterality, surgical technique, tumor size, and stage were obtained from the original histopathological report; however, the stage was amended according to the 8th edition of the American Joint Committee on Cancer Staging Manual [16] and applied only for carcinomas. For clear cell RCCs and papillary RCCs, the grade was given based on the WHO and International Society of Urological Pathology (WHO/ISUP) criteria during the review process [17]. In addition, we recorded the presence of invasion (renal vein, renal sinus, and fatty capsule) and adverse features (sarcomatoid differentiation, rhabdoid change, and microscopic tumor cell necrosis). Furthermore, we screened the non-tumorous kidney parenchyma for ACKD and papillary adenomas, as well.

Comparison of the Frequencies of ESRD and Non-ESRD RCCs

From the same archive, non-ESRD RCC samples were obtained between 1983 and 2022 and compared the frequency of the investigated RCC subtypes.

Results

Using the inclusion criteria, 34 tumors associated with ESRD among 2,556 nephrectomy samples of RCC were included in this study, revealing that 1.3% of RCCs developed on the basis of ESRD.

Table 1. Clinical features of the patients investigated

Patient	Age, years	Sex	Etiology of ESRD	Type of dialysis	Duration of dialysis[a], months	Tx	Follow-up, months	Status
1	27	F	FSGS	HD	13	Yes	352	NCRD
2	68	M	ND	ND	ND	No	0	NCRD
3	75	F	ND	ND	ND	No	ND	LTF
4	54	M	ADPKD	HD	23	No	26	LTF
5	61	M	HTKD	HD	46	Yes	58	NCRD
6	56	M	ADPKD	HD	24	Yes	85	NCRD
7	46	M	ADPKD	PD + HD	27	Yes	194	NED
8	56	M	IgAN	HD	33	No	57	NCRD
9	64	M	DNP	HD	26	Yes	138	NCRD
10	56	F	FSGS	HD	91	No	144	NED
11	57	M	ADPKD	HD	48	Yes	61	NCRD
12	66	F	ADPKD	HD	51	Yes	26	NCRD
13	66	F	Chemotherapy-induced NP	HD	64	No	60	NCRD
14	47	M	IgAN	PD + HD	204	Yes	96	NED
15	48	M	Chr pyelonephritis	HD	25	No	202	LTF
16	43	M	Chr GN	HD	57	Yes	47	NED
17	47	M	ND	ND	ND	No	ND	LTF
18	41	M	Chr pyelonephritis	ND	ND	No	ND	LTF
19	62	M	HTKD	HD	154	No	6	NCRD
20	64	F	ADPKD	PD	25	Yes	40	AWD
21	58	F	HTKD	HD	53	No	27	NED
22	47	M	IgAN	HD	82	No	11	NED
23	53	M	DNP	PD	48	No	11	NED
24	50	M	ND	HD	16	ND	ND	LTF
25	51	F	Chr pyelonephritis	HD	36	Yes	3	NCRD
26	66	M	IgAN	HD	ND	No	25	NED
27	63	F	HTKD	HD	32	NO	41	NED
28	71	F	HTKD	ND	ND	No	34	NED
29	53	M	Chr pyelonephritis	HD	60	Yes	3	NED
30	74	M	DNP	PD + HD	46	No	2	NED
31	56	M	HTKD	PD	83	Yes	98	NED

ESRD, end-stage renal disease; Tx, kidney transplantation; F, female; M, male; FSGS, focal segmental glomerulosclerosis; ND, no data; ADPKD, autosomal dominant polycystic kidney disease; IgAN, IgA nephropathy; DNP, diabetic nephropathy; chr GN, chronic glomerulonephritis; HTKD, hypertensive kidney disease; HD, hemodialysis; PD, peritoneal dialysis; NCRD, not a cancer-related death, LTF, lost to follow-up; NED, no evidence of disease; AWD, alive with disease. [a]Duration of dialysis was measured from the beginning of dialysis until the nephrectomy.

Clinical Characteristics and Follow-Up

In our cohort, 22 tumors developed in males and 12 in females. A male and female patient had synchronous tumors in both kidneys at the time of the discovery, while in *patient 26*, 2 years after his right-sided renal tumor, another metachronous RCC developed in the contralateral kidney. The median age was 56 years (mean: 56.3 years; range: 27–75 years). Radical nephrectomy was carried out in all 34 patients. Furthermore, surgical removal was ordered because of a clinically detected tumor in every case. Four patients had cancer-related symptoms, and tumors were incidental findings in the remaining cases (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000529276). The causes of ESRD were as follows: hypertensive kidney disease (n = 6), autosomal dominant polycystic kidney disease (n = 6), IgA nephropathy (n = 4), chronic pyelonephritis (n = 4), diabetic nephropathy (n = 3), focal segmental glomerulosclerosis (n = 2), chemotherapy-induced nephropathy (n = 1), and chronic glomerulonephritis (n = 1). In 4 patients, the cause of ESRD remained unknown. In most of the patients, hemodialysis was carried out, and the time interval of dialysis had a median of 47 months (mean: 55 months; range: 13–204 months). Twelve patients were suitable for

Fig. 1. Multifocal renal tumor in end-stage renal disease. The parenchyma is severely damaged with signs of acquired cystic kidney disease and multifocal tumors.

kidney transplantation during the study period. Only 6 patients were lost to follow-up, and the median follow-up time was 41 months (mean, 68.4 months; range: 0–352 months). Twelve patients died of non-cancer-related causes, while 13 patients were alive without any evidence of disease. Regional lymph node metastasis was seen in a single patient that was eradicated along with the renal tumor. Before the nephrectomy, distant metastasis was not detected in any case. Progression was registered only for 1 patient. She had a multifocal primary tumor and developed pancreatic, breast, and hepatic metastases 10 months after her nephrectomy. She has been receiving combined immuno- and tyrosine kinase inhibitor therapy, while her clinical condition remaining stable. The principal clinical data are summarized in Table 1.

Morphological Aspects

Among the tumors studied, in 2 patients, synchronous tumors were present in both kidneys. Also, only one tumor was multifocal. The largest diameter of the tumors ranged from 10 mm to 80 mm, and the median was 31 mm (mean: 35.2 mm). In two cases, the actual size of the tumors was unknown. Grossly, the tumors had a diverse appearance, influenced by the RCC subset. In the kidney parenchyma, papillary adenomas and/or cysts were present (shown in Fig. 1). We identified the following histological subtypes: clear cell RCC ($n = 19$), papillary RCC ($n = 5$), CCPT ($n = 5$), ACKD RCC ($n = 3$), and ESC RCCs ($n = 2$). None of the tumors showed sarcomatoid transformation, rhabdoid change, and microscopic tumor cell necrosis. Thirty-two tumors were organ-confined (pT1+pT2), while 2 tumors had a pT3 stage with the invasion of the renal sinus in 1 tumor, and with the invasion of the renal vein in the other. In the peritumoral parenchyma, severe tubulointerstitial damage was seen along with sclerotic glomeruli and chronic inflammation. In addition, papillary adenomas and ACKD were observed in 7 and 12 cases, respectively. In two ACKD RCCs, both lesions were present. The main pathological parameters in detail are summarized in Table 2, while we listed the immunoprofile and the molecular features in online supplementary Table 2.

Clear Cell RCC

This subtype was the most common, with the frequency of 55.9%. Only 2 tumors had grade 3 nuclear atypia by the WHO/ISUP grading system, and one of these resulted in metastatic disease. In the peritumoral parenchyma, ACKD was seen in 9 cases, but papillary adenoma never occurred alongside clear cell RCC.

Papillary RCC

Among the 5 tumors, 3 were identified as low grade and 2 as high grade. These tumors were built up by either basophilic or eosinophilic cells. Foamy macrophages were present in all tumors, and papillary adenomas were observed in 2 kidneys. ACKD and calcium oxalate crystals were not seen at all.

Clear Cell Papillary Tumor

Along with the papillary RCC, this tumor was the second most common subtype (14.7%). All tumors had a thick, smooth muscle-rich pseudocapsule. The dominant growing pattern was tubular with irregular "shark smile"-like glands, and the papillary architecture was a minor component. A linear arrangement of nuclei away from the basal membrane was present in 4 tumors. In 2 patients, papillary adenomas were located next to the main tumor mass, although ACKD was not detected in these tumors. The immunohistochemistry showed the usual phenotype in all cases, and the molecular tests performed revealed no von Hippel-Lindau (*VHL*) gene anomalies in 2 cases (see online suppl. Table 2). Representative images are shown in Figure 2.

Acquired Cystic Kidney Disease RCC

Three ACKD RCCs were observed, and in our set, these were the largest tumors with a median size of 47 mm. ACKD RCCs were composed of eosinophilic tumor cells with papillary and sieve-like architecture. The characteristic calcium oxalate crystals and ACKD were observed in every case. One tumor produced regional lymph node metastasis. Representative images are shown in Figure 3.

Table 2. Pathological features of the tumors investigated

Patient	Histological subtype	Grade[a]	Stage[b]	Size, mm	Papillary adenoma	ACKD
1	Clear cell RCC	2	pT1a	22	No	No
2	Papillary RCC	1	pT1a	30	No	No
3L	Clear cell RCC	1	pT2b	33	No	No
3R	Clear cell RCC	1	pT2a	70	No	No
4	Papillary RCC	2	pT1a	40	Yes	No
5	Clear cell RCC	3	pT2a	80	No	Yes
6	Clear cell papillary tumor	NA	–	10	No	No
7	Clear cell RCC	1	pT1a	35	No	No
8	Clear cell RCC	1	pT2a	73	No	Yes
9	Clear cell RCC	1	pT1a	19	No	Yes
10	Clear cell RCC	2	pT3a	56	No	Yes
11	Clear cell RCC	1	pT1a	25	No	Yes
12	Clear cell RCC	2	pT3a	35	No	No
13	Clear cell RCC	1	pT1a	25	No	Yes
14	Clear cell papillary tumor	NA	–	19	Yes	No
15	Clear cell RCC	2	pT1a	25	No	No
16R	Clear cell RCC	1	pT1a	45	No	Yes
16L	Clear cell RCC	2	pT1a	19	No	Yes
17	Clear cell RCC	2	pT1a	ND	No	Yes
18	Papillary RCC	2	pT1a	ND	Yes	No
19	ACKD RCC	NA	pT1bN1	60	No	Yes
20	Clear cell RCC	3	pT1b	52	No	No
21	Clear cell papillary tumor	NA	–	25	No	No
22	ACKD RCC	NA	pT1a	47	Yes	Yes
23	Clear cell RCC	2	pT1a	30	No	No
24	ACKD RCC	NA	pT1b	41	Yes	Yes
25	Papillary RCC	3	pT1b	44	No	No
26R	Eosinophilic solid and cystic RCC	NA	pT1a	20	No	No
26L	Papillary RCC	3	pT1a	38	No	No
27	Eosinophilic solid and cystic RCC	NA	pT1a	32	No	No
28	Clear cell RCC	2	pT1a	24	No	No
29	Clear cell papillary tumor	NA	–	23	Yes	No
30	Clear cell papillary tumor	NA	–	11	No	No
31	Clear cell RCC	1	pT1a	19	Yes	No

By definition, the clear cell papillary tumor is in pT1 stage. RCC, renal cell carcinoma; ACKD, acquired cystic kidney disease; L, left; R, right; NA, not applicable; ND, no data. [a]Grade was defined by the World Health Organization and International Society of Urological Pathology Criteria Stage. [b]The removal of the regional lymph nodes was performed solely for patient 19.

Eosinophilic Solid and Cystic RCC

Both cases had been originally diagnosed as unclassified RCCs. These cases had a typically solid and cystic growing pattern. The tumor cells contained coarse cytoplasmic granules and expressed CK20 (see online suppl. Table 2). In one of these tumors, a pathogenic mutation in the tuberous sclerosis 2 (*TSC2*) gene was revealed by whole exome sequencing. In the atrophic kidney parenchyma, neither papillary adenomas nor ACKD was present. Representative images are shown in Figure 4.

Comparison of the Frequencies of ESRD and Non-ESRD RCCs

During the study period, 2,407 RCCs developed in non-ESRD patients and were treated with nephrectomy. Clear cell RCC was the most common subtype in both ESRD (77.7%) and non-ESRD (55.9%) patients. In addition, 25% and 18.5% of our ESC RCC and CCPT tumors occurred in ESRD kidneys, respectively. By definition, no ACKD RCC arose in non-ESRD patients. Table 3 briefly summarizes the frequencies of the tumors observed in ESRD and non-ESRD patients.

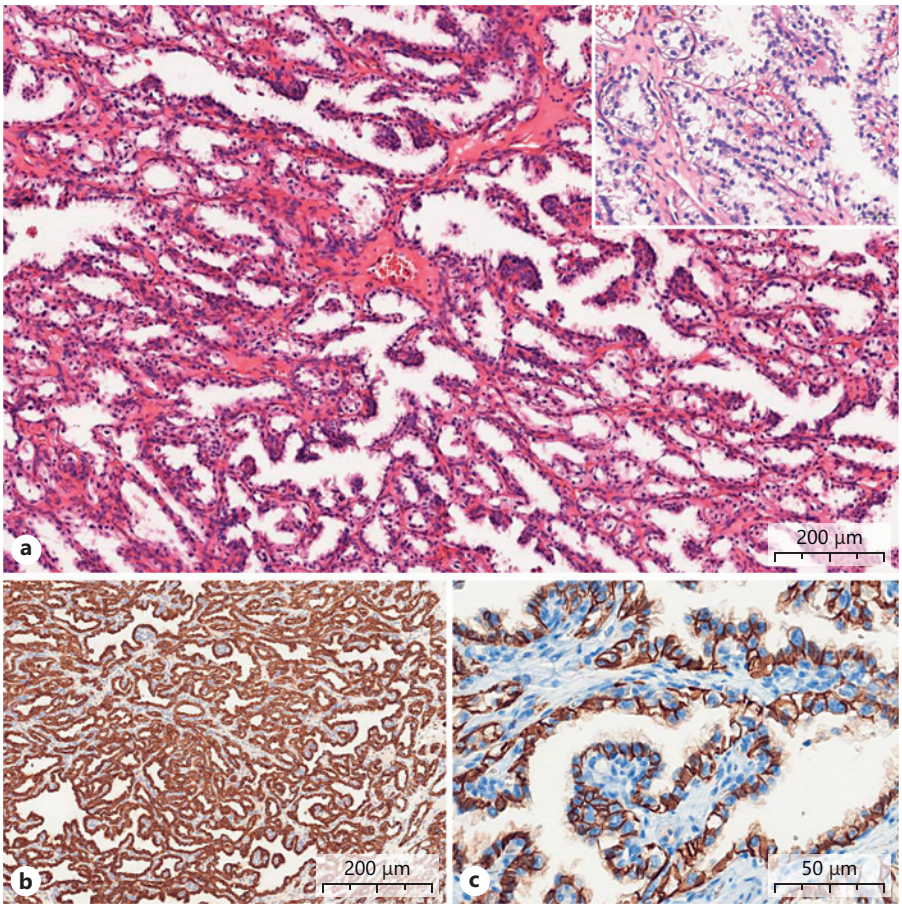

Fig. 2. Clear cell papillary tumor. **a** According to our experience, tumors were composed of clear cytoplasm tumor cells forming primarily atypical glands, and papillary architecture was a minor component. The cytological and nuclear atypia was mild, and a linear arrangement of the nuclei away from the basement membrane was present (insert picture). **b** The cytokeratin 7 immunohistochemistry labeled the tumor cells diffusely and strongly. **c** The carbonic anhydrase 9 stains were less intense and had a characteristic cup-shaped positivity.

Discussion

In the present study, we examined the clinicopathological features of RCCs in ESRD. The incidence of ESRD is increasing, due to the high number of patients with hypertension and diabetes [18]. In our data set, hypertensive kidney disease and autosomal dominant polycystic kidney disease were the most common causes of ESRD. It is a fact that ESRD significantly elevates the risk for RCC [19], and this risk increases proportionally with the period of being on dialysis [20]. Altogether, in the native population, RCC develops when the patients are in their early sixties, yet RCCs in ESRD patients occur earlier [21]. According to our experience, ESRD RCCs were noticed 4–6 years before RCCs in healthy individuals. All RCC subtypes have been reported in ESRD kidneys, and in contrast to the non-ESRD population, papillary RCC, CCPT, and ACKD RCC are the most frequently seen tumors [11, 22].

ACKD is one of the adverse effects of dialysis and develops in 40–90% of patients [23]. It must be emphasized that ACKD RCC never develops without the presence of cysts in the surrounding kidney parenchyma, and it is the most common subset in ESRD patients with ACKD [10]. Despite this, our cohort had a slightly different composition. ACKD was present in 12 tumors, and in most cases, clear cell RCC was the final diagnosis. Literature data are limited on the RCC subsets in ACKD patients, different from ACKD RCC.

It has been proven that the population's genetic features influence the RCC subtype. Papillary RCC is more frequent in black individuals, while clear cell RCC is more common in Caucasians [24, 25]. It has to be noted that our tumor set is smaller than in those fundamental papers that defined ACKD RCC. Still, this alteration is considered a result of the different genetic backgrounds of the investigated patients. In 84% of the patients, the clear cell RCC was organ-confined, and the majority of the tumors belonged to the low-grade group by the WHO/ISUP grading system. In the native population, approximately 30% and 40% of the tumors are high grade and already left the renal parenchyma at the time of the diagnosis, respectively [26]. The lack of adverse prognostic factors can explain the excellent outcome of

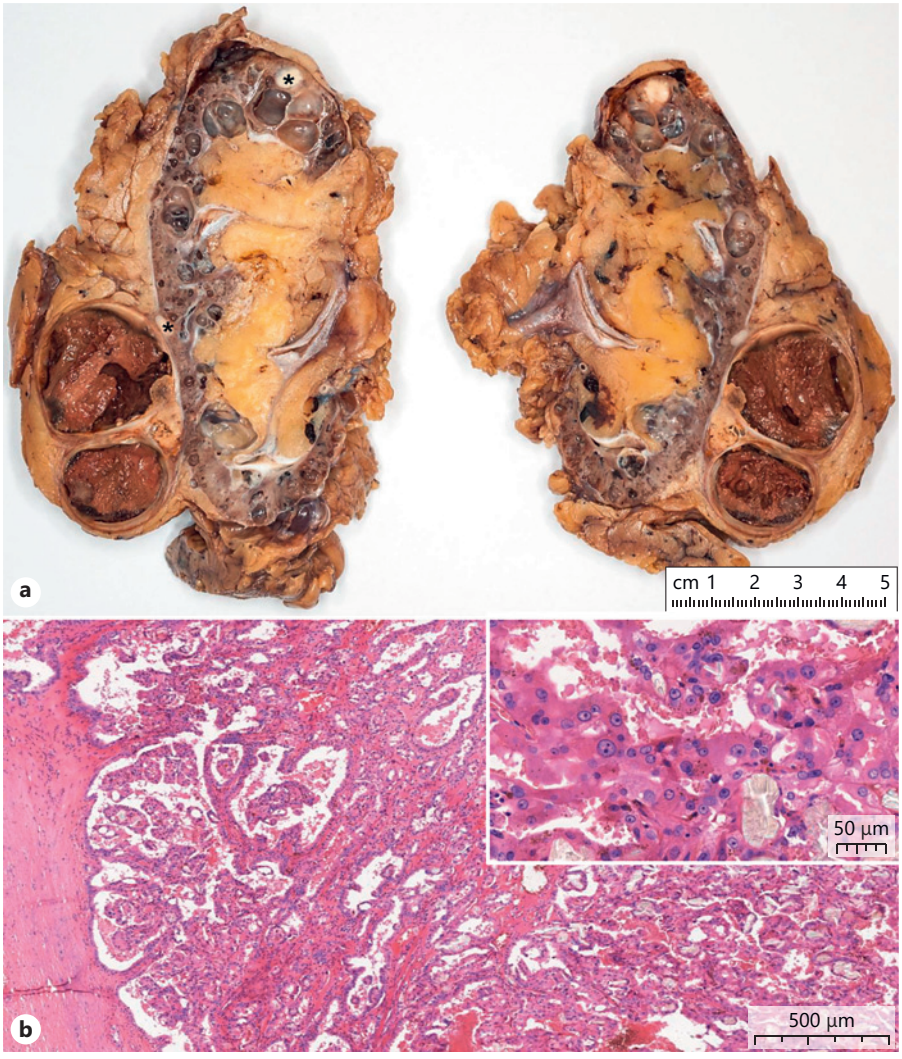

Fig. 3. Acquired cystic kidney disease-associated renal cell carcinoma. **a** Grossly, the tumor was well defined and had a brownish cut surface. Surrounding kidney parenchyma contained a great number of smaller and larger cysts along with two papillary adenomas (asterisk). **b** Histologically, the tumors had a diverse growing pattern with papillary architecture and a sieve-like appearance. The tumor cells had eosinophilic cytoplasm, large nuclei, and prominent nucleoli. Also, among the tumor cells, numerous calcium oxalate crystals were present (inset picture).

the clear cell RCC patients in our study, since progression was registered solely in 1 patient. In addition, at the end of the registration of follow-up data, no cancer-specific death occurred. It must be stated that these patients are under strict surveillance to monitor their kidneys' status or screen them for kidney transplantation. This close follow-up results in earlier tumor discovery and better outcome.

Concerning ESRD (including ACKD), any RCC may arise in these kidneys; however, tumors with a papillary architecture have an increased prevalence [27]. These RCC subtypes include the aforementioned ACKD RCC, papillary RCC, and CCPT. The latter was described as a renal angio-adenomyomatous tumor [28], then later designated as clear cell papillary carcinoma [29]. The 2022 WHO classification retitled it again as CCPT and considered it a renal tumor with an indolent clinical course [15]. CCPT was initially observed in ESRD patients, but later turned out to be able to evolve from native kidneys, as well [30, 31]. In our cohort, its frequency was only 14%, which is significantly lower than those reported by others [32]. Although CCPT is built up by clear cytoplasm tumor cells and expresses CA9, it lacks any chromosome 3-related alterations, including *VHL* mutation, hypermethylation, and deletion [33]. In 2 cases, genetic data supported this observation. In all patients, CCPT followed an indolent clinical course.

ACKD RCC is another subtype with a papillary growing pattern [34]. This tumor is extensively studied and considered the most frequent RCC subset in ACKD kidneys; therefore, it serves as a main differential diagnostic challenge in patients with a clinically diagnosed renal tumor and ACKD [11, 21, 35]. Our cohort only included 3 ACKD RCC cases, and all of these were kidney-confined tumors, although one of these had a regional lymph node metastasis

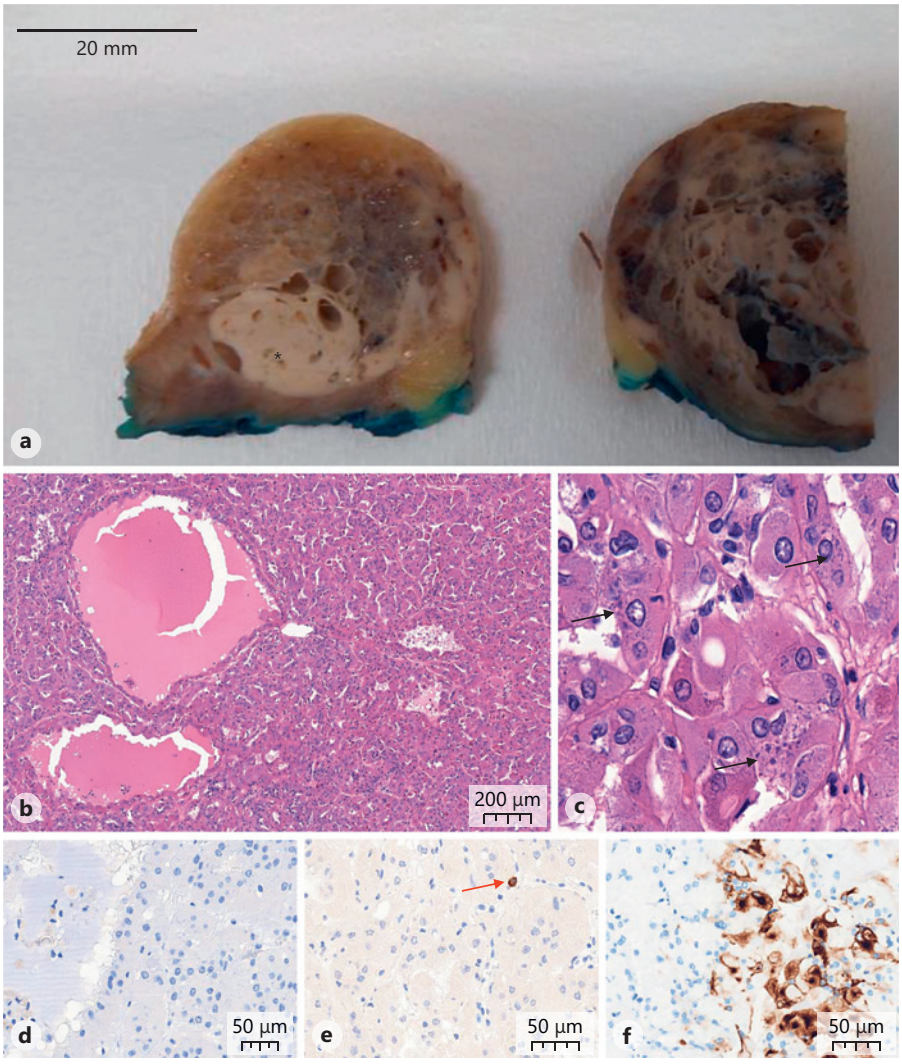

Fig. 4. Eosinophilic solid and cystic renal cell carcinoma. **a** Macroscopically, these tumors had a light-brown color with cystic and solid areas (asterisk). **b** Histologically, eosinophilic tumor cells were observed with the aforementioned cystic and solid growth pattern. **c** The cytoplasm of the tumor cells contained coarse basophilic inclusions (arrows). **d**, **e** These tumors lacked cytokeratin 7 and CD117 expression. The red arrow indicates a mast cell as a positive control for CD117 stain. **f** Characteristically, the tumors were positive with cytokeratin 20.

Table 3. Frequencies of RCCs in ESRD and non-ESRD patients

Histological subtype	ESRD (*n* = 34) (%)	Non-ESRD (*n* = 2,407) (%)
Clear cell RCC	19 (55.9)	1,870 (77.7)
Papillary RCC	5 (14.7)	199 (8.3)
Clear cell papillary tumor	5 (14.7)	22 (0.9)
Eosinophilic solid and cystic RCC	2 (6.5)	6 (0.3)
ACKD RCC	3 (8.8)	–

The non-ESRD group contains 310 other RCC subtypes, but those were not seen among the ESRD patients. ESRD, end-stage renal disease; RCC, renal cell carcinoma; ACKD, acquired cystic kidney disease.

at the time of the nephrectomy. Intriguingly, in the same patient's kidney, a marginal zone lymphoma was identified as well, and the patient died due to the complications of this disease. Generally speaking, the outcome for ACKD RCC is difficult to predict [36]. In the fundamental paper of Tickoo et al. [11], there was 1 patient with cancer-specific death, and another 2 with spread to the regional lymph nodes. In the study of Przybycin et al. [12], 4 patients were found with adverse events, and 1 of them died from the consequences of the tumor. In terms of genetics, frequent gains of

chromosomes 3, 7, 16, and 17 were observed in ACKD RCC, suggesting a relationship between papillary RCC and ACKD RCC [37]. Inoue et al. [38] used array comparative genomic hybridization and found 2 clusters of tumors in ESRD kidneys. One was composed of mainly clear cell RCC, while the other encompassed the RCCs with papillary morphology.

Lastly, ESC RCC was encountered in two cases, that is, a newly recognized entity [15, 39, 40]. ESC RCC may occur either sporadically or be associated with tuberous sclerosis [41]. Our ESC RCCs were sporadic but developed in association with ESRD. Previously, Lerma et al. [42] observed such clinical scenario in their tumor set. We are aware that we had low number of cases, but in our set, 25% of all ESC RCCs appeared in ESRD patients. CK20 positivity is practically seen only in ESC RCC among the RCC subsets, and these tumors harbor mutations of the mTOR pathway [43, 44]. Both of our cases had a patchy CK20 expression, and importantly, they lacked any positivity with CK7 and CD117. Those markers are observed in the well-known eosinophilic tumors of oncocytoma and chromophobe RCC. Also, CK7 and CD117 expressions have a decisive role in diagnosing emerging/provisional entities of eosinophilic vacuolated tumor and low-grade oncocytic tumor of the kidney [45, 46]. In addition, genetic analysis can be particularly useful for the further classification of renal tumors. For one of our ESC RCC cases, a whole exome sequencing was carried out as part of a different study, and pathogenic *TSC2* mutation was described. The patient had no other tumors nor a family history of tuberous sclerosis; therefore, no germline testing was ordered. The clinical course was indolent in these two cases, but in progressive cases, mTOR targeting agents might have a positive therapeutic effect [47].

To conclude, the clinicopathological features of 34 RCCs developed in ESRD patients were examined. Our observations aligned with the earlier findings, although some discrepancies were also noticed. First of all, among ACKD patients, clear cell RCC was the most common subtype. Second, our database included a relatively low number of CCPT and ACKD RCC cases. Third, we observed ESC RCCs in ESRD patients, and ours is the second paper with this phenomenon. Lastly, the outcome of tumors was excellent since there was no cancer-specific death, and progression was registered in only a single case. This fine clinical course might be the consequence of the early discovery and surgical treatment.

Acknowledgments

The authors gratefully acknowledge the assistance of Vivien Sánta and Samir Martin in the language editing of the text.

Statement of Ethics

This retrospective was conducted with the permission of the Regional and Institutional Human Medical Biological Research Ethics Committee, University of Szeged (No. 188/2019-SZTE), and the Scientific and Research Ethical Committee of Hungarian Scientific Council (ETT TUKEB, 49585/2-2019/EKU). Here, the data reviewed were collected from patients as part of the routine standard of care; no diagnostic or therapeutic interventions were performed, and no patient contact was involved. Therefore, patient consent was not required in accordance with local or national guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This research was funded by the University of Szeged, Faculty of Medicine Research Fund-Heténi Géza Grant (Grant No. 5S 340 A202) and the New National Excellence Programme (Grant No. ÚNKP-21-4-SZTE-131, ÚNKP-22-4-SZTE-305).

Author Contributions

D. Semjén reviewed the cases and drafted the paper. B. Dénes, Á. Somorácz, A. Fintha, G. Fórika, A. Jenei, D. Dobi, T. Micsik, K. Eizler, and N. Giba provided the cases with clinical data. F. Sánta and A. Sejben prepared the figures and evaluated the results. B. Iványi edited the draft and constructed the discussion. L. Kuthi coordinated the study and carried out the final supervision of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

References

1 Thurlow JS, Joshi M, Yan G, Norris KC, Agodoa LY, Yuan CM, et al. Global epidemiology of end-stage kidney disease and disparities in kidney replacement therapy. Am J Nephrol. 2021;52(2):98–107.
2 Abbasi MA, Chertow GM, Hall YN. End-stage renal disease. BMJ Clin Evid. 2010;2010:2002.
3 Queeley GL, Campbell ES. Comparing treatment modalities for end-stage renal disease: a meta-analysis. Am Health Drug Benefits. 2018;11(3):118–27.
4 Matson MA, Cohen EP. Acquired cystic kidney disease: occurrence, prevalence, and renal cancers. Medicine. 1990;69(4):217–26.
5 Pope JC, Koch MO, Bluth RF. Renal cell carcinoma in patients with end-stage renal disease: a comparison of clinical significance in patients receiving hemodialysis and those with renal transplants. Urology. 1994;44(4):497–501.
6 Maisonneuve P, Agodoa L, Gellert R, Stewart JH, Buccianti G, Lowenfels AB, et al. Cancer in patients on dialysis for end-stage renal disease: an international collaborative study. Lancet. 1999;354(9173):93–9.
7 El-Zaatari ZM, Truong LD. Renal cell carcinoma in end-stage renal disease: a review and update. Biomedicines. 2022;10(3):657.
8 Denton MD, Magee CC, Ovuworie C, Mauiyyedi S, Pascual M, Colvin RB, et al. Prevalence of renal cell carcinoma in patients with ESRD pre-transplantation: a pathologic analysis. Kidney Int. 2002;61(6):2201–9.
9 Levine E. Acquired cystic kidney disease. Abdom Imaging. 1995;20(6):569–71.
10 Kondo T, Sasa N, Yamada H, Takagi T, Iizuka J, Kobayashi H, et al. Acquired cystic disease-associated renal cell carcinoma is the most common subtype in long-term dialyzed patients: central pathology results according to the 2016 WHO classification in a multi-institutional study. Pathol Int. 2018;68(10):543–9.
11 Tickoo SK, dePeralta-Venturina MN, Harik LR, Worcester HD, Salama ME, Young AN, et al. Spectrum of epithelial neoplasms in end-stage renal disease: an experience from 66 tumor-bearing kidneys with emphasis on histologic patterns distinct from those in sporadic adult renal neoplasia. Am J Surg Pathol. 2006;30(2):141–53.
12 Przybycin CG, Harper HL, Reynolds JP, Magi-Galluzzi C, Nguyen JK, Wu A, et al. Acquired cystic disease-associated renal cell carcinoma (ACD-RCC): a multiinstitutional study of 40 cases with clinical follow-up. Am J Surg Pathol. 2018;42(9):1156–65.
13 Kravtsov O, Gupta S, Cheville JC, Sukov WR, Rowsey R, Herrera-Hernandez LP, et al. Low-grade oncocytic tumor of kidney (CK7-positive, CD117-negative): incidence in a single institutional experience with clinicopathological and molecular characteristics. Hum Pathol. 2021;114:9–18.
14 Kondo T, Sassa N, Yamada H, Takagi T, Iizuka J, Kobayashi H, et al. Comparable survival outcome between acquired cystic disease associated renal cell carcinoma and clear cell carcinoma in patients with end-stage renal disease: a multi-institutional central pathology study. Pathology. 2021;53(6):720–7.
15 WHO Classification of Tumours Editorial Board. Urinary and male genital tumours. Lyon (France): International Agency for Research on Cancer; 2022. (WHO classification of tumours series, 5th ed.; vol. 8).
16 Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, Washington MK, et al, editors. AJCC cancer staging manual: Springer International Publishing: American Joint Commission on Cancer; 2017.
17 Delahunt B, Cheville JC, Martignoni G, Humphrey PA, Magi-Galluzzi C, McKenney J, et al. The International Society of Urological Pathology (ISUP) grading system for renal cell carcinoma and other prognostic parameters. Am J Surg Pathol. 2013;37(10):1490–504.
18 McCullough KP, Morgenstern H, Saran R, Herman WH, Robinson BM. Projecting ESRD incidence and prevalence in the United States through 2030. J Am Soc Nephrol. 2019;30(1):127–35.
19 Tsuzuki T, Iwata H, Murase Y, Takahara T, Ohashi A. Renal tumors in end-stage renal disease: a comprehensive review. Int J Urol. 2018;25(9):780–6.
20 Sassa N, Hattori R, Tsuzuki T, Watarai Y, Fukatsu A, Katsuno S, et al. Renal cell carcinomas in haemodialysis patients: does haemodialysis duration influence pathological cell types and prognosis? Nephrol Dial Transplant. 2011;26(5):1677–82.
21 Cossu-Rocca P, Eble JN, Zhang S, Martignoni G, Brunelli M, Cheng L. Acquired cystic disease-associated renal tumors: an immunohistochemical and fluorescence in situ hybridization study. Mod Pathol. 2006;19(6):780–7.
22 Bhatnagar R, Alexiev BA. Renal-cell carcinomas in end-stage kidneys: a clinicopathological study with emphasis on clear-cell papillary renal-cell carcinoma and acquired cystic kidney disease-associated carcinoma. Int J Surg Pathol. 2012;20(1):19–28.
23 Sun Y, Argani P, Tickoo SK, Epstein JI. Acquired cystic disease-associated renal cell carcinoma (ACKD-RCC)-like cysts. Am J Surg Pathol. 2018;42(10):1396–401.
24 Mafolasire A, Yao X, Nawaf C, Suarez-Sarmiento A, Chow WH, Zhao W, et al. Racial disparities in renal cell carcinoma: a single-payer healthcare experience. Cancer Med. 2016;5(8):2101–8.
25 Sankin A, Cohen J, Wang H, Macchia RJ, Karanikolas N. Rate of renal cell carcinoma subtypes in different races. Int Braz J Urol. 2011;37(1):29–32; discussion 33–4.
26 Kuthi L, Jenei A, Hajdu A, Németh I, Varga Z, Bajory Z, et al. Prognostic factors for renal cell carcinoma subtypes diagnosed according to the 2016 WHO renal tumor classification: a study involving 928 patients. Pathol Oncol Res. 2017;23(3):689–98.
27 Kovacs G. High frequency of papillary renal-cell tumours in end-stage kidneys-Is there a molecular genetic explanation? Nephrol Dial Transplant. 1995;10(5):593–6.
28 Michal M, Hes O, Havlicek F. Benign renal angiomyoadenomatous tumor: a previously unreported renal tumor. Ann Diagn Pathol. 2000;4(5):311–5.
29 Srigley JR, Delahunt B, Eble JN, Egevad L, Epstein JI, Grignon D, et al. The international society of urological pathology (ISUP) vancouver classification of renal neoplasia. Am J Surg Pathol. 2013;37(10):1469–89.
30 Deml KF, Schildhaus HU, Compérat E, von Teichman A, Storz M, Schraml P, et al. Clear cell papillary renal cell carcinoma and renal angiomyoadenomatous tumor: two variants of a morphologic, immunohistochemical, and genetic distinct entity of renal cell carcinoma. Am J Surg Pathol. 2015;39(7):889–901.
31 Aron M, Chang E, Herrera L, Hes O, Hirsch MS, Comperat E, et al. Clear cell-papillary renal cell carcinoma of the kidney not associated with end-stage renal disease: clinicopathologic correlation with expanded immunophenotypic and molecular characterization of a large cohort with emphasis on relationship with renal angiomyoadenomatous tumor. Am J Surg Pathol. 2015;39(7):873–88.
32 Zhou H, Zheng S, Truong LD, Ro JY, Ayala AG, Shen SS. Clear cell papillary renal cell carcinoma is the fourth most common histologic type of renal cell carcinoma in 290 consecutive nephrectomies for renal cell carcinoma. Hum Pathol. 2014;45(1):59–64.
33 Somorácz Á, Kuthi L, Micsik T, Jenei A, Hajdu A, Vrabély B, et al. Renal cell carcinoma with clear cell papillary features: perspectives of a differential diagnosis. Pathol Oncol Res. 2020;26(3):1767–76.
34 Sule N, Yakupoglu U, Shen SS, Krishnan B, Yang G, Lerner S, et al. Calcium oxalate deposition in renal cell carcinoma associated with acquired cystic kidney disease: a comprehensive study. Am J Surg Pathol. 2005;29(4):443–51.
35 Rioux-Leclercq NC, Epstein JI. Renal cell carcinoma with intratumoral calcium oxalate crystal deposition in patients with acquired cystic disease of the kidney. Arch Pathol Lab Med. 2003;127(2):E89–92.
36 Neuzillet Y, Tillou X, Mathieu R, Long JA, Gigante M, Paparel P, et al. Renal cell carcinoma (RCC) in patients with end-stage renal disease exhibits many favourable clinical, pathologic, and outcome features compared with RCC in the general population. Eur Urol. 2011;60(2):366–73.

37 Kuroda N, Shiotsu T, Hes O, Michal M, Shuin T, Lee GH. Acquired cystic disease-associated renal cell carcinoma with gain of chromosomes 3, 7, and 16, gain of chromosome X, and loss of chromosome Y. Med Mol Morphol. 2010;43(4):231–4.
38 Inoue T, Matsuura K, Yoshimoto T, Nguyen LT, Tsukamoto Y, Nakada C, et al. Genomic profiling of renal cell carcinoma in patients with end-stage renal disease. Cancer Sci. 2012;103(3):569–76.
39 Guo J, Tretiakova MS, Troxell ML, Osunkoya AO, Fadare O, Sangoi AR, et al. Tuberous sclerosis-associated renal cell carcinoma: a clinicopathologic study of 57 separate carcinomas in 18 patients. Am J Surg Pathol. 2014;38(11):1457–67.
40 Trpkov K, Hes O, Bonert M, Lopez JI, Bonsib SM, Nesi G, et al. Eosinophilic, solid, and cystic renal cell carcinoma: clinicopathologic study of 16 unique, sporadic neoplasms occurring in women. Am J Surg Pathol. 2016;40(1):60–71.
41 Athanazio DA, Amorim LS, da Cunha IW, Leite KRM, da Paz AR, de Paula Xavier Gomes R, et al. Classification of renal cell tumors – current concepts and use of ancillary tests: recommendations of the Brazilian society of pathology. Surg Exp Pathol. 2021;4(1):4.
42 Lerma LA, Schade GR, Tretiakova MS. Co-existence of ESC-RCC, EVT, and LOT as synchronous and metachronous tumors in six patients with multifocal neoplasia but without clinical features of tuberous sclerosis complex. Hum Pathol. 2021;116:1–11.
43 Mehra R, Vats P, Cao X, Su F, Lee ND, Lonigro R, et al. Somatic bi-allelic loss of tsc genes in eosinophilic solid and cystic renal cell carcinoma. Eur Urol. 2018;74(4):483–6.
44 Pivovarcikova K, Alaghehbandan R, Vanecek T, Ohashi R, Pitra T, Hes O. TSC/mTOR pathway mutation associated eosinophilic/oncocytic renal neoplasms: a heterogeneous group of tumors with distinct morphology, immunohistochemical profile, and similar genetic background. Biomedicines. 2022;10(2):322.
45 Trpkov K, Williamson SR, Gao Y, Martinek P, Cheng L, Sangoi AR, et al. Low-grade oncocytic tumour of kidney (CD117-negative, cytokeratin 7-positive): a distinct entity? Histopathology. 2019;75(2):174–84.
46 He H, Trpkov K, Martinek P, Isikci OT, Maggi-Galuzzi C, Alaghehbandan R, et al. "High-grade oncocytic renal tumor": morphologic, immunohistochemical, and molecular genetic study of 14 cases. Virchows Arch. 2018;473(6):725–38.
47 Argani P. A molecular marker for eosinophilic solid and cystic renal cell carcinoma. Eur Urol. 2018;74(4):487–8.