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Minimally Invasive Surgery-Based Multidisciplinary Clinical Management of Reninoma: A Single-Center Study

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Background: This article presents our experience in managing a rare kidney tumor – reninoma – by analyzing a relatively large series of cases from a single center.


Material/Methods: Nine cases of reninoma were reviewed. Clinical manifestations, imaging examinations, laboratory examinations, perioperative data, and pathological findings were summarized. A 58.8-month follow-up was performed to evaluate patient survival and recrudescence.

Results: The main clinical manifestations were hypertension, hypokalemia, headache, dizziness, nausea, vomiting, palpitation, and sweating. Three patients had hypertensive end-organ damage, including brain hemorrhage, gestation termination, and grade III ocular fundus changes. All patients underwent retroperitoneal laparoscopic partial nephrectomy successfully. The mean warm ischemic time was 23.4 min. The median operation time was 95.1 min, with a median estimated blood loss of 60 ml. The median hospital stay was 6 days. No serious intraoperative or postoperative complications occurred. The histology and electron microscopy findings confirmed the diagnosis of reninoma in all cases. After 58.8 months of follow-up, symptoms involving hypertension were relieved in all patients, and no tumor recurrence or metastasis was detected.

Conclusions: Reninoma may have severe consequences despite being a benign tumor. Retroperitoneal laparoscopic partial nephrectomy is a feasible and effective method for the surgical removal of reninoma. Multidisciplinary cooperation plays an important role in improving the diagnosis and enabling the early surgical treatment of reninoma. Especially in cases of reninoma with moderate and high RENAL scores, an accurate diagnosis of reninoma based on multidisciplinary cooperation facilitates the selection of less invasive surgical approaches.

MeSH Keywords: **Case Management • Renin • Surgical Procedures, Minimally Invasive**

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Background

Reninoma, also known as juxtaglomerular cell tumor, which indicates its origination, is an endocrine tumor that releases renin, hence its name. Excessive renin leads to activation of the renin-angiotensin-aldosterone system. Therefore, reninoma is a possible cause of renin-mediated hypertension and secondary hyperaldosteronism [1]. The hypertension caused by reninoma is often resistant to treatment [2,3]; however, it can be eliminated by surgical removal of the renal tumor. Reninoma tends to occur in young people, at an average age of 25 years. Reninoma was first reported by Robertson in 1967 [4]. Since then, approximately 100 cases of reninoma have been reported by different institutions, mostly as individual case reports [5]. There is a lack of case series from medical centers to provide systemic evidence of the disease. In addition, this rare disease is not well known by many urologists, and failure to recognize it might account for its extremely low reported incidence. Thus, the accumulation of case reports and further discussion of the clinical management of this rare disease are of great importance.

Surgical tumor removal is the only way to cure reninoma, and several surgical methods could potentially be used for the removal of renal tumors like reninoma, which are usually small and benign. Among them, retroperitoneal laparoscopic partial nephrectomy is the most well-taught and prevalent method in our center. Here, we retrospectively summarized the clinical data of the 9 cases of reninoma from this center and analyzed the therapeutic effect of retroperitoneal laparoscopic surgery. Based on these results, we provide suggestions regarding the management of reninoma cases.

Material and Methods

Ethics statement

The study was approved by the Protection of Human Subjects Committee of the Chinese People's Liberation Army (PLA) General Hospital. Written informed consent was obtained from each individual who underwent nephrectomy prior to sample collection.

Patients

Nine patients were diagnosed with reninoma in our hospital from May 2010 to October 2016. The patient characteristics are summarized in Table 1. The age of the patients ranged from 17 to 34 years, with an average of 24.6 years. Five of the patients were male. In 2 cases, the tumor was located in the left kidney. The diagnosis was confirmed histologically in all 9 cases. The clinical diagnosis process and the treatment path in

Table 1. Baseline demographic and clinical characteristics.

Characteristics	Total (n=9)
Age, year, mean (SD)	24.6 (5.6)
Gender, no.	
Male	5
BMI, kg/m ² , mean (SD)	22.6 (3.4)
Tumor site, no.	
Left	2
Tumor size, mean (SD)	3.1 (0.9)
Tumor location, No.	
Upper	5
Middle	2
Lower	2
Hypertension, No.	
Present	8
Family history of hypertension, No.	
Present	3
Complications of hypertension, No.	
Present	5
Hypokalemia	
Present	6
Surgical approach	
LRPN	8
Follow up time, month, mean (SD)	58.8 (22.3)

BMI – body mass index; SD – standard deviation;
LRPN – retroperitoneal laparoscopic partial nephrectomy;
No. – number of cases.

all 9 cases were reviewed. All 9 patients underwent retroperitoneal laparoscopic partial nephrectomy. RENAL scores were calculated and perioperative data were collected.

Imaging and laboratory examinations

All patients underwent an abdominal B-mode ultrasound examination and examination by computed tomography (CT) or/and magnetic resonance imaging (MRI), and the renal and adrenal areas were carefully examined.

Seven out of 9 patients underwent endocrine examinations. Supine-upright tests were conducted, and the plasma renin activity (PRA), angiotensin II (Ang II), and plasma aldosterone (ALD) levels were measured. After patients had been in upright position for 4 h, the PRA and ALD levels were obtained and

compared with the baseline levels. Four patients underwent split renal venous sampling for renin activity assay. The PRA, Ang II, and ALD levels were measured using the chemiluminescence immunoassay (CLIA) method. The normal ranges in the supine and upright positions are <0.79 ng/ml/h and 0.93–6.56 ng/ml/h for PRA, 28.2–52.2 ng/L and 55.3–115.3 ng/L for Ang II, and 163.4–481.9 pmol/L and 180.1–819.9 pmol/L for ALD, respectively. The aldosterone-to-renin ratio (ARR) was calculated by dividing the plasma ALD value (ng/dl, 1 ng/dl=27.7 pmol/L) by the PRA value (ng/ml/h). The cutoff value for screening primary aldosteronism (PA) was ARR >20 [6].

The serum levels of thyroid-stimulating hormone (TSH), free triiodothyronine (FT₃), and free thyroxine (FT₄), as well as the levels of 24-h urinary cortisol, urinary metanephrine, normetanephrine, urinary vanillylmandelic acid (VMA), and urinary free cortisol (USF), were measured in 7 cases. The 1-mg overnight dexamethasone suppression test was carried out in 7 cases.

Immunohistochemical and ultrastructural examinations

Formalin-fixed, paraffin-embedded tumor tissues were subjected to immunohistochemical staining. Antibodies against renin (1: 100, Abcam), CD34 (1: 100, DAKO), Ki-67 (1: 200, DAKO), vimentin (1: 200, BioGenex), Syn (1: 200, Abcam), and CgA (1: 200, Leica) were applied. Gomori's reticulin staining was used for the identification of reticular fibers.

Small pieces of formaldehyde-fixed tumor tissue from 9 cases were postfixed in glutaraldehyde and routinely examined by electron microscopy.

Follow-up

Patients underwent follow-up examinations every 6 months for 1 year postoperatively and annually thereafter in our hospital or a local hospital near their residence. The patients regularly underwent blood pressure examinations and ultrasound examinations of both kidneys. The follow-up time was defined as from the first day postoperatively to September 2018.

Results

Clinical manifestations

The observed clinical manifestations include moderate to severe hypertension and normal potassium levels to profound hypokalemia. All 9 patients exhibited symptoms of hypertension (Table 2); 5 patients had a history of high blood pressure from 9 months to 8 years before the renal tumor was detected. The other 4 patients had been diagnosed with hypertension shortly before the renal mass was detected. Owing to the

mildness of the symptoms, the real time of hypertension onset is untraceable.

Among the 9 patients, 3 patients had severe hypertension end-organ damage. The first of these 3 patients was a pregnant 22-year-old woman who had severe headache, nausea and vomiting, blurred vision, and edema of the lower extremities starting during the 20th week of gestation. Her blood pressure was 210/150 mmHg. In addition, a random quantitative test of the protein in this patient yielded extremely high results. Thus, this patient was diagnosed with severe preeclampsia by her obstetrician and received drug treatment. However, despite the treatment, her fetus stopped growing after 24 weeks of gestation, and her pregnancy had to be terminated. The second patient with severe hypertension end-organ damage was an 18-year-old man whose highest blood pressure was recorded as 220/120 mmHg. This young man suffered from hemorrhage of the left basal ganglia region and brain next to the lateral ventricle, followed by secondary epilepsy. The third patient was a 28-year-old man with a history of blurred vision. At the time of diagnosis, his optic fundi already showed functional arterial stenosis and grade III hypertensive changes.

Hypokalemia was detected in 6 cases. In 3 cases, hypokalemia was accompanied by related symptoms; 2 patients experienced limb numbness, and 1 suffered from attacks of generalized convulsions. The other patients experienced no symptoms of hypokalemia.

Imaging examinations

B-mode ultrasound examinations were performed in 7 cases, all of which revealed the occupying lesions as hyper- or isoechoic. The tumor lesions were round or oval in shape, with thin walls and clear borders. Ultrasound examination of the bilateral renal, iliac, and adrenal arteries was also performed, but no abnormalities were found. All patients underwent CT or contrast-enhanced CT examinations. Moderate- or low-density solid masses were detected in the kidneys without enhancement. Contrast-enhanced CT showed delayed enhancement of the tumor, which differs from the findings of typical renal cell carcinoma (i.e., obvious renal cortical-phase enhancement). The adrenal areas showed no abnormalities on medical imaging in any of the 9 cases. Eight patients underwent MRI, and mild corticomedullary-phase enhancement of the tumor was observed.

Laboratory examinations

In all 9 cases, the serum creatinine and blood urea nitrogen (BUN) levels were normal, and no abnormalities were revealed by the urine analysis (i.e., protein, erythrocyte, and leucocyte levels), thus excluding renal parenchymal diseases. Seven patients underwent endocrine examinations.

Table 2. Blood pressure and symptom.

Case No.	History of hypertension	Previous drug treatment	BP value (mmHg)					Symptom Before operation	
			Highest recorded	During hospital stay	Before operation	During operation	After operation		Follow-up, months
1	3d	None	154/96	120–154/80–96	141/91	140/108	128/84	125/85, 23	None
2	1m	Felodipine Irbesartan	201/147	128–145/82–110	138/108	129/90	119/80	120/80, 73	Dizziness
3	4y	Nifedipine Telmisartan Metoprolol	180/120	120–159/80–120	150/118	117/76	117/79	115/80, 50	Nausea and vomiting; chest distress; the whole body numb and convulsion
4	5y	Metoprolol	170/100	124–162/81–100	140/90	126/84	115/76	125/80, 48	Aortic valve stenosis
5	8y	Metoprolol Enalapril	210/150	140–170/90–110	142/95	160/120	130/93	128/78, 102	Urine protein +++; headache and vomiting; palpitation and sweatiness
6	9m	Enalapril	220/120	120–140/70–100	130/80	122/82	130/90	126/82, 43	Cerebral hemorrhage; secondary epilepsy
7	5d	Nifedipine Terazosin	190/140	110–190/70–140	122/74	145/101	125/89	125/80, 72	None
8	1m	Nifedipine	210/135	160–210/90–135	147/102	130/74	140/92	133/86, 62	None
9	7y	Captopril Nifedipine Metoprolol	240/140	160–190/102–135	158/111	151/89	138/94	130/90, 55	Functional artery stenosis; grade III hypertension fundus change

BP – blood pressure; d – day; m – month; y – year.

Table 3. Results of endocrine examinations.

Case No.	PRA (ng/ml/h)	Ang II (ng/L)	ALD (pmol/L)	ARR	Renal vein and inferior vena PRA (ng/ml/h)
1	NA	NA	NA	NA	NA
2	9.1 (S)/12.0 (U)	111.7 (S)/343.6 (U)	534.1 (S)/880.7 (U)	2.65	13.02 (R)/11.70 (L)/12.8 (I)
3	2.7 (S)/7.7 (U)	501.6 (S)/914.3 (U)	512.9 (S)/702.1 (U)	3.29	NA
4	NA	NA	NA	NA	NA
5	17.0 (S)/12.1 (U)	245.7 (S)/800.0 (U)	447.4 (S)/709.6 (U)	2.13	24.0 (R)/11.75 (L)/23.5 (I)
6	6.6 (S)/6.3 (U)	124.6 (S)/156.6 (U)	386.2 (S)/515.4 (U)	2.95	NA
7	9.8 (S)/12.8 (U)	88.5 (S)/107.6 (U)	483.0 (S)/673.7 (U)	1.90	7.1 (R)/6.8 (L)/6.25 (I)
8	7.8 (S)/12.5 (U)	85.7 (S)/331.1 (U)	713.0 (S)/740.7 (U)	2.14	8.1 (R)/10.2 (L)/8.6 (I)
9	15.9 (S)/16.4 (U)	549.5 (S)/838.1 (U)	925.2 (S)/973.1 (U)	2.14	NA

PRA – plasma aldosterone concentration; Ang II – Angiotensin II; ALD – plasma aldosterone concentration; ARR – aldosterone renin ratio; ARR=ALD (ng/dl)/PRA (ng/ml/h); ALD – 1 ng/dl=27.7 pmol/L; U – upright position; S – supine position; RV – renal vein; IVC – inferior vena cava; NA – not available.

Table 4. Results of perioperative data.

Case No.	Sex/age	Tumor location	Tumor size (cm)	Classification	SP (mmol/L)	Scr (μmol/L)		BUN (mmol/L)		R.E.N.A.L. score	ASA score	Operative time (min)	WIT (min)	EBL (ml)	Drainage (ml)	POHS (day)
						Preoperative	Postoperative	Preoperative	Postoperative							
1	F/34	Right lower	4.5	Typical	3.14	54.8	66.8	3.68	5.67	7	II	120	25	50	173	5
2	F/27	Right upper	2.2	Typical	2.60	48.8	58.9	3.28	6.07	5	II	90	20	50	80	6
3	M/23	Right, middle, CEn	3.3	Typical	2.56	59.7	77.9	3.19	5.75	10	II	125	40	50	13	7
4	M/23	Right, lower	3.5	Atypical	3.88	59.4	82.5	4.99	6.45	6	II	110	30	200	88	8
5	F/22	Right, upper	3.0	Typical	3.07	62.1	75.3	3.56	4.22	5	II	90	17	50	90	8
6	M/18	Right, upper	3.0	Atypical	3.82	58.4	68.4	2.52	3.87	7	II	61	16	20	16	6
7	F/17	Right, middle	2.1	Atypical	3.68	46.5	82.1	2.36	4.22	8	II	90	20	50	95	4
8	M/30	Left, upper	2.0	Typical	2.72	58.0	83.3	2.92	4.12	6	II	90	23	50	95	5
9	M/28	Left, upper	4.5	Typical	3.22	90.3	150.3	5.22	7.99	7	III	80	20	20	37	5

SP – serum potassium, normal range: 3.5–5.5mmol/L; Scr – serum creatinine, normal range 1.8–7.5 μmol/L; BUN – blood urea nitrogen, normal range 30–110 mmol/L; ASA score – American Society of Anesthesiologists Score; I – a normal healthy patient; II – a patient with mild systemic disease; III – a patient with severe systemic disease; WIT – warm ischemia time; EBL – estimated blood loss; CEn – complete endophytic; POHS – post operation hospital stay; NA – not available.

No abnormalities were found in the levels of urinary free metanephrines (normetanephrines and metanephrine) or urinary VMA, and there was no typical image evidence for pheochromocytoma and extra-adrenal sympathetic paraganglioma (PGL), thus excluding these diagnoses. The 24-h urinary free cortisol (UFC) level and 1-mg overnight dexamethasone suppression test were conducted. No abnormal results were found, thus excluding the diagnosis of Cushing’s syndrome. No abnormalities were found in the serum concentrations of TSH, FT₃, or FT₄, thus excluding hyperthyroidism-related secondary hypertension. Endocrine examination data for differential diagnosis are shown in the Supplementary Table 1. The outcomes of the supine-upright tests of 7 patients are shown in Table 3. These 7 patients showed high aldosterone in the upper range or exceeding the upper limit of normal aldosterone. They showed elevated PRA, with median values of 9.8 (range, 2.7–15.9) ng/ml/h and 12.4 (range, 6.3–16.4) ng/ml/h in the supine and upright positions, respectively. The ARR of all 7 patients ranged from 1.9 to 3.29, which is less than 20, thus excluding the diagnosis of primary hyperaldosteronism.

Split renal venous sampling was carried out in 4 cases. No definite renal arterial stenosis was found during the procedure.

In 1 case, the renin level on the tumor side (24.0 μg/l/h) was approximately 2 times higher than on the normal side (11.7 μg/l/h), indicating that the tumor mass could secrete renin. In the remaining 3 cases, while the renin level was higher on the tumor side, the difference was relatively small (Table 3).

Treatment and outcomes

After admission, patients with hypertension were administered antihypertensive agents, including β-receptor blockers, calcium channel blockers (CCBs), angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin II receptor blockers (ARBs). Hypokalemic patients were also treated with supplemental potassium.

All patients underwent retroperitoneal laparoscopic nephron-sparing surgery under general anesthesia. All surgeries were successfully performed without open conversion. The perioperative data are summarized in Table 4. The mean warm ischemic time of partial nephrectomy was 23.4 (16–40) min. The median estimated blood loss during surgery was 60 (20–200) ml. The median operative time was 95.1 (61–125) min. Blood pressure was recorded before, during, and after surgery.

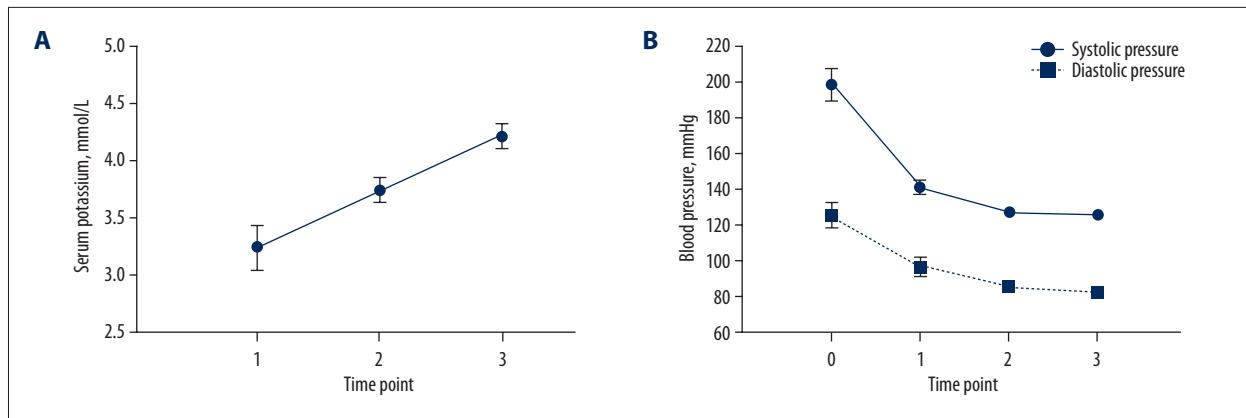


Figure 1. Blood potassium and blood pressure. (A) Postoperative blood potassium returned to normal after surgery. (B) Hypertension resolved after surgery. Time point 0, before hospitalization; time point 1, before surgery; time point 2, 1 day after surgery; time point 3, 6 months after surgery.

No abnormal fluctuations in blood pressure occurred during the operation. The median hospital stay was 6.25 (4–9) days.

After surgery, the blood pressure and serum potassium levels of all patients were remeasured and were found to have returned to normal (Figure 1). The median follow-up time was 58.8 (23–102) months. No abnormalities in the serum potassium, renin, or aldosterone levels were found during follow-up. The patient who had hypertensive disorders during pregnancy before the surgery became pregnant again after the surgery and gave birth naturally 2 years later without experiencing hypertensive disorders during pregnancy. No recurrence or metastasis was detected in any case.

Histology and electron microscopy findings

Histologically, the tumor consists of ovoid or polygonal cells with a granular, eosinophilic cytoplasm arranged in sheets and trabeculae (Figure 2). The results of the immunohistochemical examinations are summarized in Table 5. In all cases, neoplastic cells showed strong immunoreactivity for renin (10/10), CD34 (10/10), and vimentin (10/10). Among the tested cases, 6/6 were negative for CgA, 7/7 were positive for Syn, and tumor cells showed weak immunoreactivity (all less than 15%) for Ki-67, indicating a low degree of malignancy. Gomori's reticulin staining identified reticular fibers in all cases. The tumor morphology and immunohistochemical profile supported the diagnosis of reninoma. Electron microscopy revealed numerous characteristic secretory granules, which help distinguish reninoma from histologically similar hemangiopericytoma (Figure 2).

Discussion

In this study, we report the cases of 9 patients with reninoma diagnosed and treated in our hospital from April 2010 to November 2017. Based on clinical manifestations, Dong et al. reported that reninoma can be classified into 3 types: typical, atypical, and nonfunctioning [7]. According to this classification system, 6 of our reninoma cases were typical, while the other 3 were atypical.

Among these 9 patients, 1 had a history of pregnancy termination due to severe preeclampsia, with the hypertension continuing afterward. In total, 6 cases of reninoma-related gestational hypertension are been reported: 1 patient underwent cesarean section and the newborn infant died after a 4-week complicated course of intensive care [8], 3 patients had miscarriages [9,10], and the other 2 patients went through normal labor and continued to experience hypertension after delivery [11,12]. In these cases, after the tumor was excised, the patients' blood pressure returned to normal. We suggest that for women with a history of hypertension who are preparing for pregnancy, the probability of reninoma should be excluded, as the diagnosis and treatment of reninoma before pregnancy may be life-saving.

As a rare cause of secondary hypertension, reninoma should be differentially diagnosed from other causes of secondary hypertension, especially other causes of hyperaldosteronism. Imaging and endocrine examinations play important roles in this differential diagnosis [13]. Reninoma should be differentiated from PA, which accounts for 20% of resistant hypertension cases and features primary hyperaldosteronism [14]. The major difference between reninoma and PA is the PRA level, which is usually elevated in reninoma in both the supine and upright positions, but is suppressed in PA. However, in some reninoma patients, the increase in PRA may not be

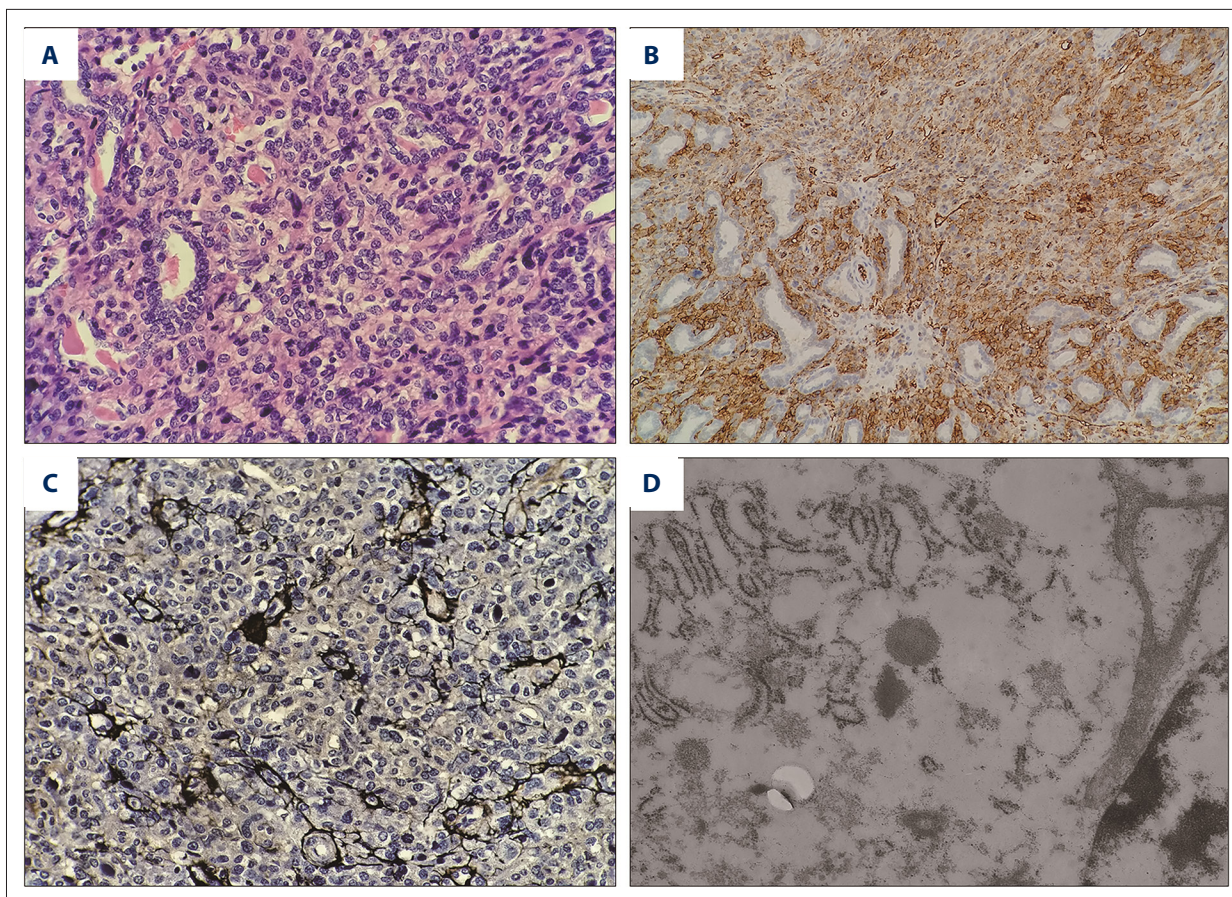


Figure 2. Pathological and ultrastructural findings. (A) Clusters of round or polygonal cells with an eosinophilic cytoplasm were observed. (A1-Hematoxylin-eosin, A2-Hematoxylin eosin 100×). (B) Renin was diffusely distributed throughout the tumor cell cytoplasm (40×). (C) Reticular fibers (black) were identified by Gomori's Reticulin staining. (100×). (D) Electron microscopy revealed rhomboid crystalline protogranules in the tumor cells.

Table 5. Immunohistochemical results of 9 cases of reninoma.

Case No.	Renin	CD34	Vimentin	CgA	Syn	Ki-67	Reticular fibers
1	+++	+	+	NA	+	+(2%)	+
2	+++	+	f, +	NA	NA	+(1-15%)	+
3	+++	+	+	-	+	+($<1\%$)	+
4	+++	+	+	-	+	NA	+
5	+++	+++	+++	-	+	+($<3\%$)	+
6	+++	+	+	-	+	+(3%)	+
7	+++	+	+	-	+	+(1-5%)	+
8	+++	+	+	-	+	NA	+
9	+++	+	f, +	NA	NA	+($<10\%$)	+

F – focal; + – positive; +++ – strongly positive; NA – not analyzable.

significant. Current guidelines recommend using the ARR to screen for PA in “higher risk groups of hypertensive patients and those with hypokalemia, or on incidental finding of an adrenal adenoma” [15]. In our cases, none of the calculated ARRs exceeded the recommended cutoff value of 20 [6].

Renal arterial stenosis is also the cause of secondary hyperaldosteronism, which can be excluded by imaging examinations [16]. In our cases, no signs of renal arterial stenosis were detected by B-mode ultrasound or CT. Four patients underwent split renal venous sampling, and no renal arterial stenosis was found during the procedure. The solid kidney mass also indicated the diagnosis of reninoma rather than renal arterial stenosis.

Cushing’s syndrome as another cause of secondary hypertension and can be excluded by 24-h urinary free cortisol (UFC) and 1-mg overnight dexamethasone suppression tests. Adrenal pheochromocytoma and extra-adrenal sympathetic PGL also need to be excluded when reninoma is suspected. These conditions can be distinguished from reninoma by abnormalities in the blood and urine levels of catecholamines and their metabolites. It is noteworthy that reninoma and MEN2B-related bilateral pheochromocytoma can exist simultaneously in the same patient [17], increasing the difficulty of diagnosis. In our patients, the VMA level was normal, and no patients had family history of MEN2B-related diseases, such as pheochromocytoma, thyroid diseases, and parathyroid diseases. Although the concomitant situation is extremely rare, it serves as a reminder of the importance of postoperative follow-up of reninoma patients. In addition to the abovementioned diseases, other causes of secondary hypertension, including renal parenchymal diseases, obstructive sleep apnea, and thyroid diseases, also need to be excluded. Detailed medical history inquiry and laboratory examinations are required.

Furthermore, as a solid kidney mass, reninoma needs to be differentiated from malignant renal tumors. Kang et al. compared the MRI features of 8 reninoma cases (overlapping with 8 cases in this study) with those of 27 clear cell renal cell carcinoma (ccRCC) cases, and emphasized the usefulness of MRI in distinguishing reninoma from other renal tumors [18].

Split renal venous sampling to determine renin activity is considered helpful for diagnosing reninoma; however, its positive rate was only 62.5% [19]. In the present series, 4 patients underwent this test, but there was a significant difference in renin activity between the 2 renal veins in only 1 patient (25%). Due to the low positive rate and high complexity of this test, it is not recommended.

Briefly, establishing a diagnosis of reninoma depends on the supine-upright test for PRA and ALD in combination with

determination of the ARR value, while the imaging and endocrine examination results can be used to exclude other causes of secondary hypertension. The final diagnosis of reninoma depends on pathological examinations. The features found in these cases by histology and electron microscopy are consistent with previous reports [20,21]. Renin, CD34, and vimentin are positive markers for reninoma. In addition, we found that 7/7 specimens were positive for Syn, indicating the neuroendocrine nature of reninoma. CgA may not be a biomarker for reninoma because none of the tumors were positive for it.

Although drug treatment may relieve the hypertension caused by renin secretion [20], the most effective treatment is complete surgical removal of the tumor. Local recurrence and metastasis are rare but nevertheless possible after surgical treatment [22,23]. Based on previous studies, most tumors are 2–3 cm in diameter [24], but some can reach 9.8 cm [25]. This is consistent with our data, which show that the tumor diameter ranged from 2 cm to 4.5 cm. As reninoma tumors are usually small, nephron-sparing surgery has great advantages over radical nephrectomy for preserving kidney function. The RENAL nephrometry system was used to judge the complexity of partial nephrectomy. According to previous studies, renal masses scored as 4–6, 7–9, and 10–12 are considered low-, moderate-, and high-complexity lesions, respectively [26]. In the present study, the number of patients with low-, moderate- and high-complexity lesions was 4, 4, and 1, respectively. For moderate- and high-complexity lesions, surgical procedures need to be chosen cautiously based on the presurgical diagnosis and the surgeon’s experience. In the present study, we were able to obtain a preliminary clinical diagnosis of reninoma for most (7/9) of the patients before surgery, notably in the complex cases with scores of 8 and 10. The preoperative diagnosis helped us choose partial nephrectomy rather than radical nephrectomy for the maximum protection of renal function. Among the 2 patients who did not have a diagnosis of reninoma before surgery, one had atypical reninoma, while the other had typical reninoma with mild symptoms. In both cases, a renal mass was detected during a physical examination, and the patients visited a urology clinic. Fortunately, we chose partial nephrectomy due to the small size of the renal mass and the benign features observed on imaging. Our work shows that retroperitoneal partial nephrectomy is a feasible and effective the treatment for reninoma, even for a completely endogenous mass.

Compared with transperitoneal laparoscopic nephrectomy, the retroperitoneal approach has the advantages of providing a direct approach to the kidney and making it feasible to dissect the renal artery directly, thereby avoiding vein retraction [27]. Compared with the transperitoneal approach, the retroperitoneal approach also allows faster recovery of bowel function. The choice of a retroperitoneal approach may shorten

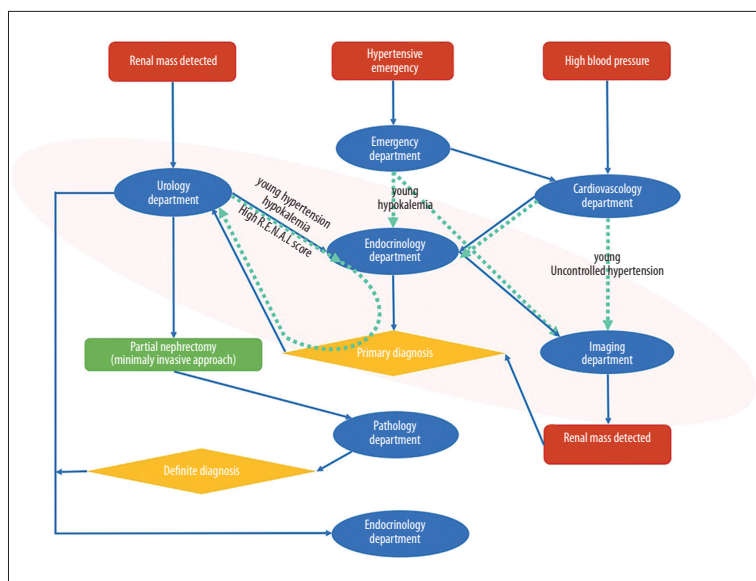


Figure 3. Multidisciplinary management of reninoma. The clinical diagnosis and treatment paths of these patients are demonstrated using solid blue lines and arrows. Suggestions for the management of reninoma patients are indicated by the dotted green lines and arrows. Reninoma patients are usually initially received by the Urology Department due to incidental tumor identification, by the Emergency Department due to hypertensive emergencies, or by the Department of Cardiovascular Disease due to hypertension. The Urology, Endocrinology, and Imaging Departments are the core departments that play an important role in the rapid and accurate diagnosis and management of reninoma patients. We highly recommend that urologists refer patients with suspected reninoma to endocrinologists for preoperative and postoperative endocrine assessments.

the hospital stay and the operative time in the beginning period of the learning curve [28]. Retroperitoneal laparoscopic nephrectomy has become a routine surgical approach in our center. Our abundant experience with retroperitoneal laparoscopic surgery also lays a solid foundation for selection of the retroperitoneal approach.

The potential for hemodynamic fluctuations during the surgical resection of reninoma has not yet been well described. According to our observations, there were no significant fluctuations in blood pressure during the operation in any of the 9 cases, which is consistent with previous reports [29,30].

In all 9 of our cases, the blood pressure and plasma renin levels returned to normal after surgery. However, according to some reports in the literature, approximately 10% of patients remain hypertensive after nephrectomy [31,32]. One explanation for this observation is that these patients have primary hypertension. The postoperative recurrence of hypertension may indicate the possibility of tumor recurrence or metastasis. Some scholars have noted that close postoperative follow-up is warranted in cases of reninoma tumors that are large or invading peripheral tissue and vessels, and in elderly patients [33].

Based on our experience, reninoma patients may seek medical help in 3 different ways, depending on their initial reception department (Figure 3). First, patients may initially be admitted to the Urology Department due to a renal mass detected during a regular medical examination. These patients usually have no significant symptoms, and their reninoma is usually of the nonfunctioning or atypical type. Second, patients may initially be admitted by the Emergency Department due to a hypertensive emergency. After urgent and temporary management, these patients will likely be transferred to the Department of

Cardiovascular Disease. Third, patients may initially be admitted to or followed long-term by the Department of Cardiovascular Disease due to hypertension. In the latter 2 groups of patients, reninoma is usually of the typical type.

Based on this patient category system, several suggestions can be given for the management of reninoma patients. In the first group of patients with an accidentally discovered renal mass, active surveillance is considered an appropriate strategy for the management of renal masses smaller than 4 cm (i.e., small renal masses) [34]. Here, we suggest that if a patient is young and exhibits hypertension or hypokalemia, urologists should cooperate with endocrinologists to investigate the possibility of a benign renal tumor such as reninoma, especially in cases with high RENAL scores. The malignancy of the renal mass influences the surgical options, especially for masses with a high RENAL score. A preoperative diagnosis of reninoma may increase the likelihood of choosing partial nephrectomy, which has advantages in protecting renal function. In the second and third groups of patients, secondary hypertension caused by reninoma should be considered. Failure to consider reninoma will delay surgical treatment and could thus affect the patient's quality of life for years.

Conclusions

Reninoma is a rare tumor on which few studies have been published. The present study adds both clinical data and relevant considerations to the existing body of knowledge regarding

reninoma. Reninoma may have severe consequences despite being a benign tumor. The diagnosis of reninoma relies on multidisciplinary cooperation. Reninoma should be carefully differentially diagnosed from other causes of secondary hypertension, hyperaldosteronism, and malignant renal tumors. Endocrine and imaging examinations play important roles in

this differential diagnosis. Retroperitoneal laparoscopic partial nephrectomy is a feasible and effective treatment for patients with reninoma that allows the maximum preservation of renal function. Multidisciplinary treatment plays an important role in the clinical management of reninoma and therefore increases the rate of diagnosis to enable early surgical intervention.

Supplementary Table

Supplementary Table 1. Endocrine examination data for differential diagnosis.

Case No.	Urinary VMA (mg/24 h)	Urinary metanephrine (µg/24 h)	Urinary Normetanephrine (µg/24 h)	UFC (mmol/24 h)	Plasma cortisol (nmol/L, 1 mg dexamethasone suppression)	TSH (µIU/ml)	FT4 (ng/dl)	FT3 (pg/ml)	Scr (µmol/L)	BUN (mmol/L)
1	NA	NA	NA	NA	NA	NA	NA	NA	54.8	3.68
2	5.3	2.65	66.36	240.1	25.7	2.34	1.64	4.21	48.8	3.28
3	6.8	9.24	65.71	245.2	44.0	1.56	1.23	7.07	59.7	3.19
4	NA	NA	NA	NA	NA	NA	NA	NA	59.4	4.99
5	7.1	6.83	67.43	328.5	29.2	1.21	1.43	4.51	62.1	3.56
6	3.6	5.21	43.53	468.2	35.5	2.04	0.82	4.64	58.4	2.52
7	7.9	11.74	70.59	321.5	25.7	1.34	0.90	3.10	46.5	2.36
8	5.5	6.91	59.33	289.3	32.6	2.42	1.33	3.68	58	2.92
9	5.9	8.56	72.87	333.5	28.9	2.33	1.55	3.38	90.3	5.22

VMA – vanillylmandelic acid, normal range: <8.0 mg/24 h; urinary metanephrine, normal range: 1.52–34.53 µg/24h; urinary normetanephrines, normal range: 22.09–75.36 µg/24 h; UFC – 24 h urinary free cortisol, normal range: 9 8.0–500.1 nmol/24 h; 1 mg dexamethasone suppression test (administration of 1 mg dexamethasone at bedtime, measurement of plasma cortisol concentration the next morning (normal range: <50 nmol/L); TSH – thyroid-stimulating hormone, normal range: 0.4–4.0 mU/L; FT4 – free thyroxine, normal range: 9.0–25.0 pmol/L; FT3 – free triiodothyronine, normal range: 3.5–7.8 pmol/L; Scr – serum creatinine, normal range 1.8–7.5 µmol/L; BUN – blood urea nitrogen, normal range 30–110 mmol/L; NA – not available.

References:

- Trnka P, Orellana L, Walsh M et al: Reninoma: An uncommon cause of Renin-mediated hypertension. *Front Pediatr*, 2014; 2: 89
- Choi JH, Park TH, Kim MH et al: A rare cause of secondary hypertension in a young adult. *Korean Circ J*, 2015; 45: 531–34
- Toricelli FC, Marchini GS, Colombo JR Jr. et al: Nephron-sparing surgery for treatment of reninoma: A rare renin secreting tumor causing secondary hypertension. *Int Braz J Urol*, 2015; 41: 172–76
- Robertson PW, Klidjian A, Harding LK et al: Hypertension due to a renin-secreting renal tumour. *Am J Med*, 1967; 43: 963–76
- Nunes I, Santos T, Tavares J et al: Secondary hypertension due to a juxtaglomerular cell tumor. *J Am Soc Hypertens*, 2018; 12: 637–40
- Funder JW, Carey RM, Mantero F et al: The Management of primary aldosteronism: Case detection, diagnosis, and treatment: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*, 2016; 101: 1889–916
- Dong D, Li H, Yan W, Xu W: Juxtaglomerular cell tumor of the kidney – a new classification scheme. *Urol Oncol*, 2010; 28: 34–38
- Diker-Cohen T, Abraham SB, Rauschecker M et al: Reninoma presenting in pregnancy. *J Clin Endocrinol Metab*, 2014; 99: 2625–26
- Lachvac L, Svajdler M, Valansky L et al: Juxtaglomerular cell tumor, causing fetal demise. *Int Urol Nephrol*, 2011; 43: 365–70
- Lee DB, Zawada ET, Kleeman CR: The pathophysiology and clinical aspects of hypercalcemic disorders. *West J Med*, 1978; 129: 278–320
- Kim HJ, Kim CH, Choi YJ et al: Juxtaglomerular cell tumor of kidney with CD34 and CD117 immunoreactivity: Report of 5 cases. *Arch Pathol Lab Med*, 2006; 130: 707–11
- Shin YS, Cha JS, Kang MJ et al: Newly developed hypertension due to juxtaglomerular cell tumor in pregnancy. *Clin Nephrol*, 2012; 78: 325–27
- Funder JW, Carey RM, Fardella C et al: Case detection, diagnosis, and treatment of patients with primary aldosteronism: An endocrine society clinical practice guideline. *J Clin Endocrinol Metab*, 2008; 93: 3266–81
- Sabbadin C, Fallo F: Hyperaldosteronism: Screening and diagnostic tests. *High Blood Press Cardiovasc Prev*, 2016; 23: 69–72
- O'Shea PM, Griffin TP, Fitzgibbon M: Hypertension: The role of biochemistry in the diagnosis and management. *Clin Chim Acta*, 2017; 465: 131–43
- Niikura S, Komatsu K, Uchibayashi T et al: Juxtaglomerular cell tumor of the kidney treated with nephron-sparing surgery. *Urol Int*, 2000; 65: 160–62
- Paragliola RM, Capoluongo E, Torino F et al: A rare case of juvenile hypertension: coexistence of type 2 multiple endocrine neoplasia-related bilateral pheochromocytoma and reninoma in a young patient with ACE gene polymorphism. *BMC Endocr Disord*, 2015; 15: 30

18. Kang S, Chen F, Zhong Y et al: Preoperative diagnosis of juxtaglomerular cell tumors in eight patients. *J Clin Hypertens (Greenwich)*, 2016; 18: 982–90
19. Haab F, Duclos JM, Guyenne T et al: Renin secreting tumors: Diagnosis, conservative surgical approach and long-term results. *J Urol*, 1995; 153: 1781–84
20. Kuroda N, Gotoda H, Ohe C et al: Review of juxtaglomerular cell tumor with focus on pathobiological aspect. *Diagn Pathol*, 2011; 6: 80
21. Kuroda N, Maris S, Monzon FA et al: Juxtaglomerular cell tumor: A morphological, immunohistochemical and genetic study of six cases. *Hum Pathol*, 2013; 44: 47–54
22. Duan X, Bruneval P, Hammadeh R et al: Metastatic juxtaglomerular cell tumor in a 52-year-old man. *Am J Surg Pathol*, 2004; 28: 1098–102
23. Mendez GP, Klock C, Nose V: Juxtaglomerular cell tumor of the kidney: Case report and differential diagnosis with emphasis on pathologic and cytopathologic features. *Int J Surg Pathol*, 2011; 19: 93–98
24. Dunnick NR, Hartman DS, Ford KK et al: The radiology of juxtaglomerular tumors. *Radiology*, 1983; 147: 321–26
25. Beaudoin J, Perigny M, Tetu B, Lebel M: A patient with a juxtaglomerular cell tumor with histological vascular invasion. *Nat Clin Pract Nephrol*, 2008; 4: 458–62
26. Hou W, Yan W, Ji Z: Anatomic features involved in technical complexity of partial nephrectomy. *Urology*, 2015; 85: 1–7
27. Chen Z, Tang ZY, Liu HT, Chen X: Treatment of juxtaglomerular cell tumor of the kidney by retroperitoneal laparoscopic partial nephrectomy. *Urol J*, 2014; 10: 1160–61
28. Benoit T, Peyronnet B, Roumiguie M et al: Laparoscopic nephrectomy for polycystic kidney: Comparison of the transperitoneal and retroperitoneal approaches. *World J Urol*, 2016; 34: 901–6
29. Gil NS, Han JY, Ok SH et al: Anesthetic management for percutaneous computed tomography-guided radiofrequency ablation of reninoma: A case report. *Korean J Anesthesiol*, 2015; 68: 78–82
30. Nicholson JP, Rayman G, Donaldson P, Driver IK: The anaesthetic management of a patient with a reninoma. *Anaesthesia*, 2003; 58: 466–70
31. Beevers DG, Maheshwari MB, Ryan PG et al: Hypertension due to a renin-secreting juxtaglomerular cell tumor. *Am J Hypertens*, 2008; 21: 1359–61
32. Vidal-Petiot E, Bens M, Choudat L et al: A case report of reninoma: Radiological and pathological features of the tumour and characterization of tumour-derived juxtaglomerular cells in culture. *J Hypertens*, 2015; 33: 1709–15
33. Rubenstein JN, Eggener SE, Pins MR et al: Juxtaglomerular apparatus tumor: A rare, surgically correctable cause of hypertension. *Rev Urol*, 2002; 4: 192–95
34. Uzosike AC, Patel HD, Alam R et al: Growth kinetics of small renal masses on active surveillance: Variability and results from the DISSRM registry. *J Urol*, 2018; 199: 641–48