CASE REPORT

Juxtaglomerular Cell Tumor that was Preoperatively Diagnosed Using Selective Renal Venous Sampling

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Abstract

We herein report the case of a patient with a juxtaglomerular cell tumor (JCT). Dynamic enhanced computed tomography revealed a small nodule on the surface of the lower pole of the right kidney. Selective renal venous sampling showed an elevated level of plasma renin activity (PRA) in the right lower pole renal vein only. We performed right partial nephrectomy and diagnosed the patient with JCT. Making a diagnosis of JCT is often difficult due to the small size of the tumor and the lack of lateralization of the PRA on renal venous sampling. This case highlights the importance of performing selective renal venous sampling for the preoperative diagnosis of JCT.

Key words: juxtaglomerular cell tumor, selective renal venous sampling, hypertension

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Introduction

Juxtaglomerular cell tumors (JCTs) are very rare renin-secreting tumors of the kidneys that were first described by Robertson et al. in 1967 (1). To date, approximately 110 cases of JCT have been reported in the English literature (2-8). Patients with JCT are clinically characterized by hypertension with hyperaldosteronism secondary to excessive renin secretion by the tumor. These characteristics usually normalize following removal of the tumor (9). The preoperative diagnosis of JCT is based on the hormonal and radiological findings observed on computed tomography (CT) and/or magnetic resonance imaging (MRI) and lateralization of the plasma renin activity (PRA) on renal venous sampling. However, patients with JCT are occasionally nondiagnostic due to the small size of the tumor and the lack of lateralization of the PRA on renal venous sampling (9). We herein present a case of JCT that was not diagnosed for 17 years most likely due to the small size of the tumor and/or incomplete imaging procedures. The lesion was ultimately preoperatively diagnosed using selective renal venous sampling.

Case Report

A 34-year-old woman with a family history of hypertension was referred to our hospital for a further examination of persistent hypertension lasting for over 17 years. At 18 years of age, although hypertension (180/120 mmHg) was first noted during an examination for headaches, the patient did not receive any diagnostic examinations or treatment. At 24 years of age, hypertension was again noted during an examination for urinary tract stones. At that time, a diagnostic examination to assess the hypertension was performed. The endocrine examination revealed that the PRA level was elevated (19 ng/mL/hr; normal level, 0.2-2.7 ng/mL/hr); however, the plasma aldosterone concentration (PAC) was normal (130 pg/mL; normal level, 36-240 pg/mL). Non-enhanced CT and MRI of the abdomen showed no abnormal findings, and magnetic resonance angiography (MRA) and Doppler ultrasonography demonstrated no evidence of renal
The patient was diagnosed with primary hypertension with elevated PRA and was administered antihypertensive drugs (benidipine hydrochloride: 4 mg/day and alacepril: 50 mg/day; later, at 30 years of age, they were switched to 80 mg/day of valsartan). Her blood pressure was controlled to between 120/60 and 130/80 mmHg, and she had experienced no cerebrovascular events, such as ischemic heart disease or strokes, prior to admission. On admission, she measured 156 cm in height and 48.3 kg in weight and was asymptomatic. Her blood pressure was 106/80 mmHg under the administration of 80 mg/day of valsartan. Her blood pressure was 120/60 mmHg in the supine position two weeks after switching from valsartan to 80 mg/day of valsartan. Her blood pressure was 120/60 mmHg and controlled to between 120/60 and 130/80 mmHg, and she had experienced no cerebrovascular events, such as ischemic heart disease or strokes, prior to admission.

On admission, she measured 156 cm in height and 48.3 kg in weight and was asymptomatic. Her blood pressure was 106/80 mmHg under the administration of 80 mg/day of valsartan. A physical examination showed no significant findings. Chest radiography and electrocardiography were normal. There was no proteinuria on dipstick testing, and the urinary albumin-to-creatinine ratio was 5.3 mg/gCr. A fundoscopic examination showed no hypertensive or atherosclerotic changes in the retina. Ultrasound echocardiography demonstrated an intraventricular septum thickness and a left ventricular posterior wall thickness of 8 and 7 mm, respectively, while the E/A, E-wave deceleration time and E/e’ were 1.91, 204 msec and 7.2, respectively. These findings suggested a lack of definitive evidence of hypertension-related hypertrophy or diastolic dysfunction of the left ventricle. The serum potassium level was 3.6 mEq/L and the creatinine level was 0.62 mg/dL (eGFR: 86.7 mL/min). The results of other routine laboratory and urine tests were within the normal ranges. An endocrine examination performed in the morning (8:00 AM) after a 30-minute rest in the supine position two weeks after switching from valsartan (80 mg) to amlodipine (10 mg) showed that the levels of PRA and PAC were both elevated (12.9 ng/mL/hr and 356 pg/mL, respectively). The results of other endocrine examinations, including measurement of the levels of serum adrenocorticotropic (ACTH), cortisol, dehydroepiandrosterone-sulfate (DHEA-S), thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxin (FT4), catecholamines, insulin-like growth factor-1 (IGF-1) and 24-hour urinary metanephrine, normetanephrine and cortisol, were all within the normal ranges.

Although non-enhanced CT of the abdomen showed no abnormal findings (Fig. 1A), dynamic contrast-enhanced CT revealed a small, round nodule (6 mm in diameter) without enhancement in the early phase (Fig. 1B), but with slight enhancement in the late phase, on the surface of the lower pole of the right kidney. The tumor exhibited low and high signal intensity on T1- and T2-weighted MRI, respectively (Fig. 2A, B). On the other hand, there was no evidence of renal artery stenosis on renal MRA, and common causes of secondary hypertension with elevated PRA, such as pheochromocytoma, aortitis and malignant hypertension, were ruled out based on the findings of hormonal and imaging tests. In accordance with these findings, we suspected that the hypertension was caused by a JCT on the surface of the lower pole of the right kidney. However, considering the findings of CT and MRI, we could not completely exclude the possibility that the renal tumor was not a JCT, but rather a lesion of angiomylipoma or renal cell carcinoma and that renin was being secreted by an extrarenal tumor. Therefore, we performed selective renal venous sampling to assess the level of direct renin secretion by the tumor in the lower pole of the right kidney. Consequently, the PRA level was 27.2 ng/mL/hr and 8.7 ng/mL/hr in the right lower and upper pole renal veins, respectively, 9.7 ng/mL/hr in the left renal vein and 8.7 ng/mL/hr in the low inferior vena cava (Fig. 3). This indicated that the PRA level in the right lower pole renal vein was 3.1- and 2.8-fold higher than that observed in the right upper pole renal vein and left renal vein, respectively. In addition, these results strongly suggested that renin was directly secreted by the tumor in the lower pole of the right kidney. Subsequently, we conducted renin suppression and stimulation tests to examine the renin secretory profile using a saline infusion test (SIT) (infusion of 2 L of saline between 8 A.M. and 12 A.M.), a furosemide upright test (FUT) (intravenous injection of 40 mg of furosemide followed by two hours of standing) and a captopril challenge test (CCT) (oral administration of 50 mg of captopril). Consequently, the PRA level was not markedly suppressed (from 13.1 ng/mL/hr to 9.6 ng/mL/hr) in the SIT (Fig. 4A) and was not stimulated (from 12.9 ng/mL/hr to 14.8 ng/mL/hr) in the FUT (Fig. 4B), although it was partially stimulated (from 11.2 ng/mL/hr to 19.4 ng/mL/hr) in the CCT (Fig. 4C). These results suggest that the renin secretion from the tumor was autonomous. Taken together, we strongly suspected that the tumor in the lower pole of the right kidney was a JCT.

We performed right partial nephrectomy using the combined laparoscopic/mini-incision approach. Briefly, following complete laparoscopic mobilization of the right kidney and securing of the renal vessels, the right kidney was transferred extracorporeally via a 5-cm sub-11th rib flank incision for tumor resection, which enabled us to locate and identify the entirely endophytic tumor as an elastic hard nodule using palpation, whereas vigilant laparoscopy and echography did not detect the lesion. The surgical procedure
was uneventful, with 14 minutes of renal ischemia. The surgical specimen weighed 890 mg, and the tumor measured 8×6×7 mm in size. The cut surface of the tumor was solid with a whitish color (Fig. 5A). Histologically, the tumor was well encapsulated by a margin of normal renal parenchyma (Fig. 5B). The tumor cells contained eosinophilic cytoplasm and round to polygonal nuclei. No mitotic activity or abnormal mitosis were observed (Fig. 5C). Immunohistochemical staining demonstrated the tumor cells to be positive for anti-renin polyclonal antibodies (Fig. 5D). These polyclonal antibodies (Proteintech, IL, USA) are directed against human, mouse and rat renin, and immunohistochemical staining of renin was performed according to the manufacturer’s data sheet (http://www.ptglab.com/Products/Pictures/pdf/14291-1-AP.pdf). The tumor cells also exhibited positive staining for CD34, CD117 and vimentin, whereas staining for CD31, keratin and HMB-45 was negative (data not shown). The tumor was diagnosed as a JCT of the right kidney.

The level of plasma renin activity promptly decreased to a normal level after surgery (Fig. 6). On the first postoperative day, the patient’s blood pressure decreased to 90/60 mmHg. The postoperative period was uneventful, and the patient’s blood pressure was 112/78 mmHg on the 7th postoperative day without the use of antihypertensive medications. After the 8th postoperative day, we conducted a second round of renin suppression and stimulation tests. In contrast with the results of the first tests performed before surgery, the basal PRA level was slightly suppressed, and the PRA level observed during the SIT was also suppressed (from 0.9 ng/mL/hr to 0.4 ng/mL/hr) (Fig. 4A). On the other hand, the PRA level was not completely stimulated (from 0.2 ng/mL/hr to 1.0 ng/mL/hr) in the FUT (Fig. 4B) and was unchanged (from 0.4 ng/mL/hr to 0.4 ng/mL/hr) in the CCT (Fig. 4C). Six months after surgery, the patient’s blood pressure was 110/82 mmHg without the use of antihypertensive medications, and the PRA level was 0.8 ng/mL/hr.

Discussion

In this report, we presented a case of a small JCT in the kidney that was not diagnosed for 17 years until it was preoperatively diagnosed using selective renal venous sampling. The causes of hypertension with an elevated level of PRA include renovascular disease, pheochromocytoma, malignant hypertension, diuretic therapy and, rarely, renin-secreting tumors (10). JCT, also known as reninoma, is a very rare renin-secreting tumor of the kidneys. This tumor was first described by Robertson et al. in 1967 (1) and was subsequently named “juxtaglomerular cell tumor” by Kihara et al. (11). This type of tumor arises from the modified smooth muscle cells in the wall of the glomerular afferent arterioles, which comprise part of the juxtaglomerular afferent apparatus. Excessive renin secretion by tumor cells leads to hypertension with secondary hyperaldosteronism. The incidence of this tumor is very low. For example, Habb et al. reported only eight cases of JCT among 30,000 hypertensive patients over a 15-year period (12). To date, approximately 110 cases of JCT have been reported in the English litera-
Figure 4. Changes in the PRA level in response to a saline infusion test (SIT) (infusion of 2 L of saline for four hours) (A), a furosemide upright test (FUT) (intravenous injection of 40 mg of furosemide followed by two hours of standing) (B) and a captopril challenge test (CCT) (oral administration of 50 mg of captopril) (C) before (●) and after (○) surgery.

Figure 5. (A) Macroscopic appearance of the JCT with a solid and whitish cut surface (black circle). (B) The tumor was well encapsulated by a margin of normal renal parenchyma (line). (C) Microscopic view of the JCT. The tumor was composed of polygonal or spindle-shaped cells with oval to round nuclei and eosinophilic cytoplasm. (D) An immunohistochemical examination showed positive staining of the tumor cells for renin.
In addition, the presence of renin-secreting extrarenal tumors. Whether an observed tumor is a JCT, however, the radiological findings of JCTs are occasionally confused with those of other tumors, such as lung carcinomas, pancreatic adenocarcinomas and fallopian tube adenocarcinomas, has been reported (19). Therefore, performing renal venous sampling to evaluate direct renin secretion by the tumor is necessary for making a preoperative diagnosis of JCT. In previous reports, renal venous sampling has usually been performed by catheterizing the renal veins (9). However, this procedure shows no definitive lateralization of the PRA in many cases. A previous study of 50 cases of renal venous sampling reported that the sensitivity and specificity was 56% and 94%, respectively, for a lateralization ratio of 1.5, which maximizes specificity while limiting sensitivity (9). Therefore, we performed selective sampling in the right kidney by visualizing the tumor via catheterization of the right upper and lower pole renal veins. Consequently, the PRA level in the right lower pole renal vein was 3.1- and 2.8-fold higher than that observed in the right upper pole renal vein and left renal vein, respectively. These results strongly suggest not only direct renin secretion by the tumor in the lower pole of the right kidney, but also the usefulness of selective renal venous sampling for making a diagnosis and determining the localization of the tumor. Although the detailed reasons for the lack of lateralization of the PRA observed in previously reported cases of renal venous sampling are unclear, one proposed hypothesis is that the tumors are primarily located on the surface of the kidneys and most of the venous blood supply of the tumors is collected into the perivascular veins instead of the main renal vein (12, 15). However, our results showing tumor localization on the surface of the kidneys do not support this hypothesis.

Renin secretion by juxtaglomerular cells is usually regulated by diverse mechanisms via baroreceptors, the macula densa, the sympathetic nervous system and angiotensin II (20). On the other hand, renin secretion by JCTs is usually autonomous and regulated by physiological mechanisms (21). In the present case, the PRA level was not markedly suppressed in the SIT, thereby suppressing renin via mechanisms of baroreceptors and the macula densa, and was not stimulated in the FUT, thereby stimulating renin via mechanisms of baroreceptors, the macula densa and the sympathetic nervous system. On the other hand, the PRA level was partially stimulated in the CCT, thereby stimulating renin via mechanisms of angiotensin II. In addition, after surgery, the basal PRA level was slightly suppressed and was not completely stimulated in renin-stimulating tests, including an FUT and CCT. These results suggest that normal renin secretion by juxtaglomerular cells is partially suppressed, whereas renin secretion by JCTs is primarily autonomous under partial physiological regulation by angiotensin II mechanisms. Although we did not examine the mRNA expression of angiotensin II type 1 receptors in the present case of JCT, Tanabe et al. reported a positive association between the angiotensin II type 1 receptor mRNA expression in JCTs and the renin response in CCTs (21).

Regarding the surgical management of JCTs, laparoscopic tumor resection or partial nephrectomy have recently been recommended because JCTs are not only usually benign and small, but also often located on the surface of the kidneys and can be easily removed (22, 23). However, in our case, the tumor was too small and entirely endophytic to detect its location during laparoscopy. Therefore, we performed a mini-incision and successfully recognized the lesion using palpation, which prevented the need for radical nephrectomy. Interestingly, two malignant cases in which the tumors were large (8 cm and 15 cm in diameter, respectively) were recently reported (4, 14). Therefore, if the tumor is large and malignancy is suspected or the lesion is located deep in the renal parenchyma, the use of radical nephrectomy should be considered. As shown in our case, the blood pressure usually normalizes after surgery in most reported cases of JCT. However, in approximately 10% of cases, hypertension persists after surgery (9).

In conclusion, we herein reported a case of JCT in a young patient in which the tumor was not diagnosed for 17 years, most likely due to the small size of the lesion and/or the use of incomplete imaging procedures, until it was preoperatively diagnosed using selective renal venous sampling. Hypertension in a young patient is uncommon, and, in such cases, the causes of secondary hypertension should be extensively examined. Although making the diagnosis of JCT is
often difficult, conducting detailed examinations, including enhanced CT and MRI and/or selective renal venous sampling, is important for early diagnosis.

The authors state that they have no Conflict of Interest (COI).

Saeko Osawa, Yoshiya Hosokawa, and Tetsuji Soda contributed equally to this work.

References