Case report
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Reninoma: a rare cause of curable hypertension

Ji Hye Kim, MD[1], Ji Hyun Kim, MD[1], Myung Hyun Cho, MD[2], Eujin Park, MD[3], Hye Sun Hyun, MD[4], Yo Han Ahn, MD[5], Hee Gyung Kang, PhD[1,6], Kyung Chul Moon, PhD[7], Il-Soo Ha, PhD[1], Hae Il Cheong, PhD[1,6,8]

[1]Department of Pediatrics, Seoul National University Children's Hospital, Seoul National University College of Medicine, Seoul, [2]Department of Pediatrics, Korea Cancer Center Hospital, Seoul, [3]Department of Pediatrics, Hallym University Kangnam Sacred Heart Hospital, Seoul, [4]Department of Pediatrics, St. Vincent's Hospital, The Catholic University of Korea, Suwon, [5]Department of Pediatrics, Seoul National University Bundang Hospital, Seongnam, [6]Research Coordination Center for Rare Diseases, Seoul National University Hospital, Seoul, [7]Department of Pathology, Seoul National University Hospital, Seoul, [8] Kidney Research Institute, Medical Research Center, Seoul National University College of Medicine, Seoul, Korea

The most common type of refractory hypertension found in children is secondary hypertension, which is a potentially curable disease. Reninoma, a renin-secreting juxtaglomerular cell tumor, is a rare cause of severe hypertension that is usually diagnosed in adolescents and young adults. Surgical resection of the tumor completely cures the hypertension of patients with reninoma. The typical clinical presentation of reninoma includes hypokalemia, metabolic alkalosis, and features secondary to the increased activation of the renin-angiotensin system without renal artery stenosis. We report a case of reninoma in a female adolescent with a typical clinical presentation, in which surgical removal of the tumor completely cured hypertension. We discuss here the clinical features, imaging studies, and immunohistochemical examination of the tumor used to establish the diagnosis of reninoma and for the management of the condition.

Key words: Renal hypertension, Renin, Juxtaglomerular apparatus, Hypokalemia

Corresponding author: Hae Il Cheong, MD
Department of Pediatrics, Seoul National University Children's Hospital, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea
Tel: +82-2-2072-2810
Fax: +82-2-743-3455
E-mail: cheonghi@snu.ac.kr
https://orcid.org/0000-0001-7556-1265

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Introduction

Hypertension in children and adolescents is defined as systolic and/or diastolic blood pressures >95th percentile for age, sex, and height. A child with severe hypertension (blood pressure >99th percentile) or symptomatic hypertension is more likely to present with secondary hypertension caused by renal, vascular, or endocrine disorders.[1)] Identifying the cause of secondary hypertension is essential because secondary hypertension is risky if not managed appropriately, and this type of hypertension is often cured following surgical correction/intervention for the removal of causative factors including renal artery stenosis, coarctation of the aorta, tumors, and/or a few endocrine diseases.

Renin-dependent hypertension caused by excessive renin activity is an important cause of secondary hypertension. It occurs owing to hypoperfusion of renal arterioles, renin-secreting malignant tumors, or the proliferation of renin-producing cells. Patients show clinical features secondary to hyperactivity of the renin-angiotensin-aldosterone system including hypokalemia and metabolic alkalosis in addition to hypertension secondary to peripheral vasoconstriction. Reninoma, a renin-secreting tumor of the juxtaglomerular cells (JGC) causes renin-dependent hypertension, which can be treated by surgical resection of the tumor.[2-4)]

We report a case of a reninoma (also called a juxtaglomerular cell tumor [JCT]) in a female adolescent with a typical clinical presentation, in whom surgical removal of the tumor completely cured hypertension. This study was approved by the Seoul National University Hospital's Institutional Review Board (approval number: H-1808-127-967). As a retrospective case report, written consent was waived.

Case report

A 16-year-old female adolescent was referred to our hospital with severe hypertension (systolic pressure 178 mmHg), which was first detected 7 months prior to presentation during a routine annual physical examination. She complained of intermittent headache for about 1 year, and her previous blood pressure, measured 1 month prior to her detection of hypertension, had been normal. She showed mild hypokalemia (3.4 mmol/L) in a routine blood test, and an additional workup considering secondary hypertension was planned. Despite taking amlodipine (0.1 mg/kg twice a day), her blood pressure remained uncontrolled.

Upon admission to our hospital, her systolic and diastolic blood pressures were 155 mmHg (>99th percentile) and 111 mmHg (>99th percentile) respectively. She was 162.8 cm tall (50th–75th percentile) and weighed 55 kg (50th–75th percentile). Physical examination including ophthalmological examination revealed no abnormality other than hypertension, and her family history was negative for hypertension or renal diseases. Laboratory examination revealed normal levels of hemoglobin (14.4 g/dL), serum creatinine (0.57 mg/dL), serum total cholesterol (144 mg/dL), and normal urinalysis. Serum sodium, potassium, chloride, and total carbon dioxide levels were 134 mmol/L, 3.4 mmol/L, 102 mmol/L, and 27 mmol/L, respectively. Plasma renin activity was 9.83 ng/mL/hr (normal, 0.5–3.3 ng/mL/hr), and serum aldosterone level was 77.3 ng/dL (normal, 4–48 ng/dL). Urinary levels of vanillylmandelic acid, epinephrine, norepinephrine, dopamine, metanephrine, and normetanephrine were normal, and plasma levels of epinephrine, norepinephrine, and dopamine were also normal. Chest radiography, electrocardiography, and echocardiography showed normal findings. Renal Doppler ultrasonography revealed an avascular bilobed cyst in the lower pole of the right kidney (Fig. 1). Abdominal computed tomography (CT) angiography showed bilaterally normal renal arteries and an eccentric soft tissue component at the peripheral aspect of the cystic lesion (Fig. 2). The mass remained unenhanced during the arterial phase, and its margin was indistinguishable from the surrounding

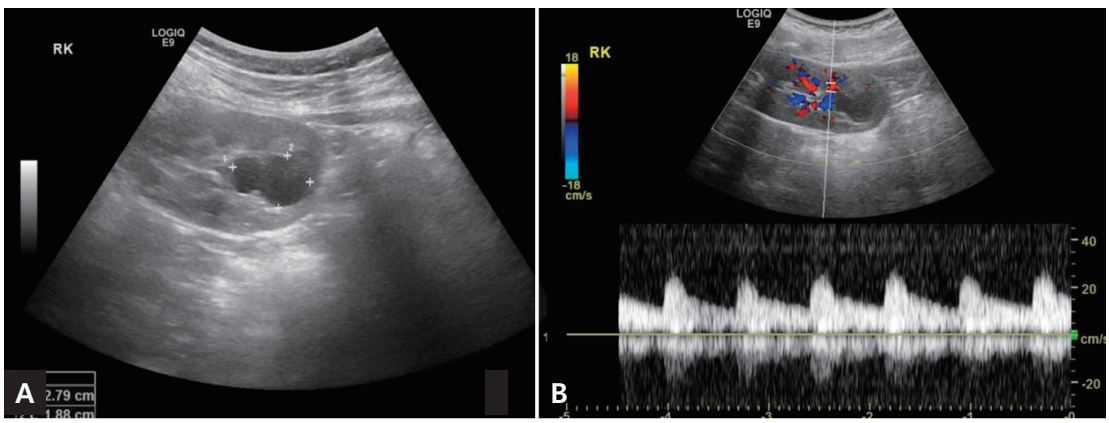

Fig. 1. Renal Doppler ultrasonographic images show: (A) a bilobed cyst measuring 2.79 cm×1.88 cm at the lower pole of the right kidney and (B) that the renal arterial flow is intact.

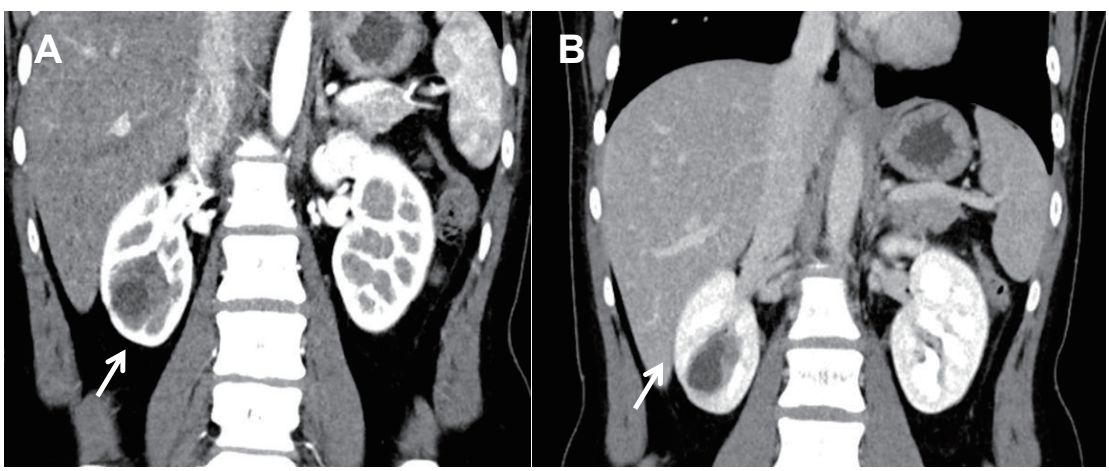

Fig. 2. Computed tomography angiography images obtained in the arterial phase (A) and magnetic resonance images obtained in the portal (delayed) phase (B) show a mass-like lesion (white arrows) with an internal cystic area and peripheral eccentric soft tissue.

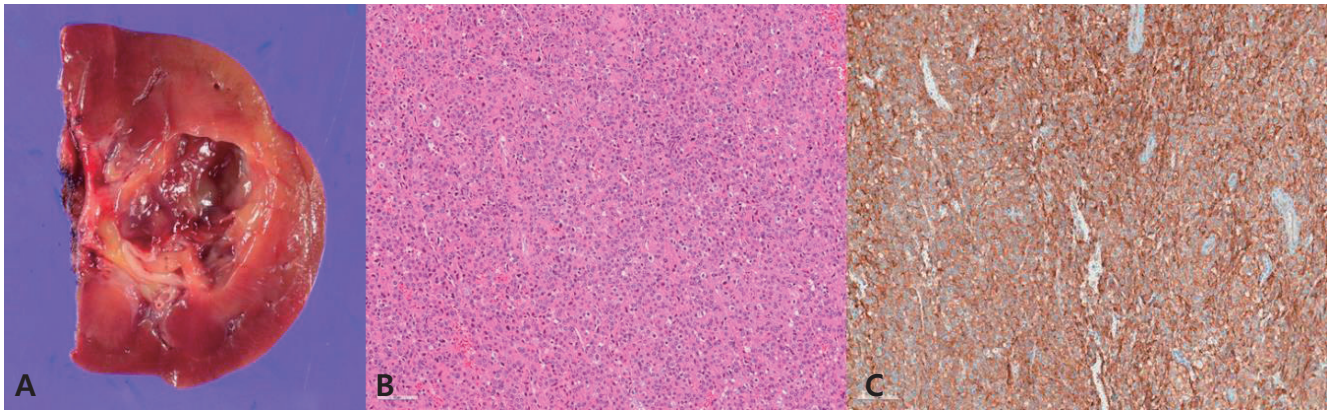

Fig. 3. Histopathological examination of the resected tumor shows: (A) the gross appearance of a cross-section of the partial nephrectomy specimen in which a well-circumscribed mass with a partially cystic cut surface can be observed, (B) the sheets of polygonal tumor cells (H&E, ×200), and (C) that the tissue stained positive for CD34 (×200).

tissue (Fig. 2A). During the delayed phase, its eccentric capsule showed enhancement, and an intact mass could be observed (Fig. 2B), consistent with CT findings of JGC tumors.

A right partial nephrectomy was performed, and a clear resection margin was identified. The well-encapsulated mass measured 2.5 cm ×2.2 cm×2.0 cm in size with a partially cystic-appearing cut surface. Microscopic examination revealed sheets of polygonal tumor cells with amphophilic cytoplasm. Immunohistochemical examination showed that the tumor cells stained positive for CD34 and focally positive for CD117 (C-Kit) and smooth muscle actin. (Fig. 3)

Postoperatively, her blood pressure returned to normal (105/63 mmHg) without using any antihypertensive medication. On the 3rd postoperative day, the plasma renin activity (0.52 ng/mL/hr), serum aldosterone (3.9 ng/dL), and serum potassium (3.6 mmol/L) levels returned to normal. Her blood pressure and laboratory findings remained within the reference range over the next 3 years postoperatively until her last follow-up.

Discussion

JCT is a rare cause of secondary hypertension. Excessive amounts of renin secreted by the JCT cause secondary hyperaldosteronism and hypertension with accompanying hypokalemia. Since the first case of JCT reported by Robertson et al.[2] in 1967, more than 100 cases have been reported to date.[3] JCT occurs more commonly in women with a sex ratio of 2:1 and is predominantly diagnosed in adolescents or young adults. The mean age of onset is 27 years with a median age of 22 years (range, 6–69 years).[4] To date, 8 cases have been reported in Korea, primarily among adolescents and young adults (17–33 years), except 1 case of a 47-year-old patient.

Our case was a 16-year-old girl presenting with hypertension. As previously described, our case was also diagnosed in adolescence. And ours is the youngest reported case in Korea.[5-12] Two previous reported Korean adolescent cases were as follows. Case 1: a 17-year-old adolescent male presented with hypertension, proteinuria, hypokalemia, metabolic alkalosis, high renin activity, and aldosterone levels similar to our patient. His blood pressure and laboratory test results improved after partial nephrectomy without using any antihypertensive medication. Unlike our patient, he showed proteinuria, which resolved postoperatively. Proteinuria, reported in 11% of patients with a reninoma, resolves in most patients after surgical resection.[12] Case 2: a 19-year-old woman was misdiagnosed with essential hypertension and received calcium channel and angiotensin II receptor blockers for 2 years. An abdominal CT performed to diagnose acute appendicitis incidentally detected the JCT, and the tumor was diagnosed based on biopsy and investigations revealing high renin activity and angiotensin levels. She was treated using CT-guided percutaneous radiofrequency ablation (RFA).[9]

The most common symptom of reninoma is headache (48%) in addition to nausea, polyuria, nocturia, excessive thirst, and fatigue, although 10% of patients are asymptomatic.[4] Our patient presented with severe hypertension, which was refractory to amlodipine (a calcium channel blocker). Patients with a reninoma show excessively high plasma renin levels (typically more than 10 times the upper limits of normal). Interestingly, plasma renin and aldosterone levels in our patient were not significantly elevated; therefore, the first impression in our patient was that of renovascular hypertension, which is a more common form of renin-dependent hypertension and needs to be differentiated from JCT. Imaging work-up performed to examine the renal vasculature incidentally revealed the renal tumor. CT angiography is a useful imaging modality for the evaluation of renin-mediated hypertension in children; however, imaging studies may miss a small-sized reninoma. Using dynamic CT, a reninoma can be identified as a low to iso-density lesion before contrast enhancement, which remains unenhanced during the early phase and shows moderate enhancement during the late phase. This feature distinguishes it from other renal lesions,[13] as was observed in

our patient. Fortunately, the size of the reninoma in our patient was large enough to be detected by CT.

Clinical features of our patient were not severe compared to typical reninoma cases. The lowest level of potassium before treatment was 3.2 mmol/dL and plasma renin and aldosterone levels were not significantly elevated. And there were no complications such as cardiomyopathy, proteinuria, or retinopathy observed.

Surgical resection is the major treatment modality for reninoma, because of its benign course; only 1 case was reported as recurred after initial mass resection.[3,4] JCT can be treated with a nephron-sparing partial nephrectomy (as was performed in our patient) because these tumors are usually superficially located. However, occasionally, radical nephrectomy may be required for deep-seated masses.[4] Additionally, percutaneous RFA can be a useful therapeutic option as described in the 19-year-old Korean woman's case.[9] However, although RFA may be less invasive compared with surgical resection, RFA should be considered cautiously because long-term follow-up over more than 2 years has not been reported with this procedure.[14] Previous reports have described a low surgical complication rate, and minimal renal damage associated with RFA treatment for other kidney tumors; however, no studies have compared RFA and surgical resection as treatments for a reninoma.

Histopathological examination is the gold standard to diagnose a reninoma because other renal malignancies including a renal cell carcinoma, hemangiopericytoma, or a Wilm's tumor can also secrete renin.[15] A reninoma is typically a solitary, well-circumscribed tumor partially surrounded by fibrous tissue with a yellow to gray-tan surface and hemorrhagic or cystic changes,[15] as was observed in our patient. The diagnosis of a reninoma was confirmed in our patient following histopathological examination, and additional treatments including chemotherapy and/or radiation therapy were not considered after surgical resection of the tumor.

In conclusion, we report a case of a 16-year-old female adolescent with a reninoma, who presented with severe renin-dependent hypertension and hypokalemia. Surgical resection of the tumor completely cured her hypertension. Although a reninoma is a rare cause of secondary hypertension, it should be considered among the differential diagnoses of renin-dependent hypertension because it is a curable condition.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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