Juxtaglomerular Cell Tumor: Reviewing a Cryptic Cause of Surgically Correctable Hypertension

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Key Words

Juxtaglomerular cell tumor • Reninoma • Renin • Secondary hypertension • Partial nephrectomy

Abstract

Juxtaglomerular cell tumor (JGCT), or reninoma, is a typically benign neoplasm generally affecting adolescents and young adults due to modified smooth muscle cells from the afferent arteriole of the juxtaglomerular apparatus. Patients experience symptoms related to hypertension and hypokalemia due to renin-secretion by the tumor. MRI, PET, CT, and renal vein catheterizations can be used to capture JGCTs, with laparoscopic ultrasonography being most cost-effective. Surgical removal is the best option for management; electrolyte imbalances are a potential complication which may be assuaged via pre-surgical administration of aliskiren, a renin inhibitor. Considering the vast etiology for hypertension and rarity of JGCT, the diagnosing physician must have a high index of suspicion for JGCT. Early recognition and management can help prevent cardiovascular or pregnancy complications and fatalities, vascular invasion and metastasis, improve quality of life, and limit socioeconomic liabilities. Herein we review the epidemiology, genetics, histopathology, clinical presentation, and management of this rare condition. The impact of genetics on prognosis warrant further research.

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Introduction

Juxtaglomerular cell tumor (JGCT), or reninoma, is a rare disease resulting from renin-induced hypertension. Dysfunction in juxtaglomerular cells lead to the over-expression of renin. Although presented with limited cases, diagnosis of JGCT occurs within young adults and adolescents with some occurrences within young children [1, 2]. JGCT-induced hypertension is the primary symptom with other rare occurrences such as myocardial infarction. JGCT can coexist with various forms of cancer, indirectly enhancing those various types of cancers. In most cases presented within literature, JGCTs are benign tumors in the kidney. Malignant tumors may be expressed in the kidney or liver, however only a handful of cases have shown this result. Herein we review the epidemiology, genetics, histopathology, clinical presentation, and management of this rare condition.

Anatomy and Physiology of Juxtaglomerular Apparatus

Under normal conditions, the production of the protease renin occurs within juxtaglomerular cells and the functions as the rate-limiting step within the renin-angiotensin system. Renin is converted to its active form

through proteolysis within juxtaglomerular cells and stored within granules. The number of juxtaglomerular cells varies based on age and intensity of stimulation [3]. Renin is rapidly released upon response to a stimulus. Beta-adrenergic receptors are crucial for the rate of renin generation, modulated through cyclic adenosine monophosphate, the primary catalyst for renin mRNA [4]. The angiotensin II pathway contributes as a negative feedback regulator indirectly through mediation of macula densa inputs and the baroreceptor [4]. COX-2 and nNOS pathways are other significant regulatory mechanisms of renin through fluctuation of PGE2, nitric oxide and PGI2 [4, 5]. As renin granules function deplete, surface area of the cell membrane increases, leading to oversaturation of renin at a quantal rate [3]. Imbalance of renin secretion hinders neurotransmitter pathways, endocrine and paracrine receptors, and disruptions of cells dependent on cyclic AMP pathway [6]. Other components indirectly impacted are cAMP response element-binding protein, a substrate essential for renin gene expression, and the respective activator p300 [7]. Overproduction of renin escalates aldosterone levels, leading to hypertension [2, 8]. Mechanical disruption has been associated with JGCT and connexin proteins within the cellular gap junction. Substantial depletion of connexin-40 have been associated with JGCT-induced hypertension within a mice model [6, 9, 10]. Connexin-45 demonstrates identical effects as connexin-40, to a lesser extent [11].

Epidemiology

There are approximately 100 reported cases of JGCT in the literature. Based on the current cases, diagnosis of JGCT is consistent between the ages of adolescent and young adults [2]. It is also twice as common in women as men. Suspicion of JGCT is viable within young hypertensive females [12]. A 60-year-old patient case study revealed the occurrence of a renal producing tumor shortly after a menopausal syndrome diagnosis. Hypertension was diagnosed 6 months prior to the procedure. Tumor was identified as benign and removed with a unilateral adrenalectomy. Diagnosis of hypertension may indicate the reoccurrence of adrenocortical carcinoma [13]. A similar case presented in a 12-year-old female patient experiencing elevated levels of blood renin concentration, aldosterone and high blood pressure. Blood potassium was slightly decreased from normal ranges, as the patient was experiencing extended salt hunger. CT scan revealed 6 cm tumor on her left kidney [14].

Table 1. Renin-producing tumors included in the differential diagnosis for JGCT

Renin-producing tumors
Adrenocortical carcinoma
Adrenal adenomas
B-cell leukemia
Breast carcinoma
Cystadenocarcinoma
Desmoplastic small round cell tumor
Endocrine hypertension
Hepatoblastoma
Juxtaglomerular cell tumor
Wilm's tumor
Uterine leiomyosarcoma

Genetics

Based on a dual case study with a 12-year-old patient and 41-year-old patient, genetic analysis revealed a loss in chromosome 9, 11 and X in both tumors. Although no pathology has been revealed, the specified chromosomal loss may be directly linked to JGCT, as both tumors expressed JGCT phenotypically [14]. The roles of alleles *p53* and *Rb* are significant for renin-gene expression. In an animal study, *p53* and *Rb* alleles were selectively deleted causing elevated levels in glucagon and presence of metastatic tumors [15].

Histopathology

There are several other renin-producing tumors that correlate with JGCT, as listed in table 1. Development of JGCT as a secondary cause of hypertension can remain undetected and lead to miscarriage if not treated immediately, as shown previously in a case study [16]. Symptoms of desmoplastic small round cell tumor are consistent with that of JGCT. A case study shows a 20-year-old patient experiencing elevated plasma renin levels, aldosterone, and severe hypertension and hypokalemia. Desmoplastic small round cell tumor is a malignant tumor and derives from the same mRNA precursor for renin and shares identical metabolic processes as JGCT [17]. A similar case is presented in a 4-year-old male patient diagnosed with Wilms' tumor. The symptoms of hypertension and increased renin expression are consistent in patients diagnosed with Wilms' tumor, a possible correlation with undetected JGCT [18, 19].

Deletion of *RBP-J*, a progenitor within bone marrow which expresses renin, is linked to inducing B-cell leukemia. Under conditions of JGCT, the expression of *RBP-J* is hindered, leading to the overexpression of renin, a possibility that JGCT and B-cell leukemia may be correlated [20]. Pro-renin receptors are higher in concentration when plasma renin levels are elevated, a symptom of JGCT. Pro-renin receptors have been associated in cell proliferation within breast cancer cells [21]. Pro-renin receptors were overexpressed in 4 types of breast cancers causing small RNA interference of healthy cells [21]. Cystadenocarcinoma (ovarian cancer) identified in a 46-year-old patient, included hypertension, hypokalemia and elevated plasma renin concentration and aldosterone (JGCT-identical symptoms). Lab analysis revealed overexpression of renin and abnormalities in juxtaglomerular cells [22]. Identical symptoms were expressed in renin-producing metastasized adrenocortical carcinoma, with serum staining revealing positively marked antibodies against renin and cytochrome P450 [23]. A few cases studies assessed the relevance of JGCT in uterine leiomyosarcoma. Symptoms in JGCT have been identical to case reports involving uterine leiomyosarcoma [24]. Angiotensin II receptors AT1 and AT2 (disrupted function expressed in JGCT) show dysfunction in human leiomyosarcoma cells to induce apoptosis [25].

Renin-producing hepatoblastoma is caused by severe hypertension and elevated plasma renin activity induced neurological dysfunction. Such a case is presented in a 22-month-old infant presented with right-side partial seizures. Due to the rarity of the secreting tumor, a clear pathology cannot be established because of insufficient laboratory assays. Assessment of this case was based on slightly elevated concentration of liver enzymes and CT scans revealing the metastasized tumors [26]. Positive results of JGCT was conducted through CD 34 staining with follow-ups on blood pressure and serum potassium levels [12].

Clinical Presentation

History and Physical Examination

Angiotensin receptor blocker medication may disguise the symptoms of JGCT based on a delayed diagnosis of a 33-year-old woman undergoing pregnancy. A tumor was located on the right kidney after the patient suspended the administration of the angiotensin receptor blocker due to pregnancy. The tumor identified as benign was removed by a right partial nephrectomy and invasive

procedure [27]. Another case study involving a 24-year-old male patient showed a polymorphism of the *ACE* gene. The patient underwent thyroidectomy with lymphadenectomy at the age of 20 according to previous medical record. Abnormal decrease of urinary catecholamines and metanephrines were reported with a MRI screening of a lesion on the right kidney confirming diagnosis of JGCT and pheochromocytoma.

Laboratory Studies

Severe hypokalemia and hyperaldosteronism have been reported before diagnosis of JGCT. Increased levels of kaliuresis, plasma renin, pro-renin, and aldosterone according to bioassays are indications for the possibility of JGCT, as shown within the case study of a 22-year-old male patient [28]. Urinalysis showed hypokalemia and hypochloremia in a case study with 4 patients. Twenty four hour monitoring revealed elevated potassium levels and no significant changes in urea and creatinine [29]. Common symptoms include headache, nocturia, myalgia, and polyuria with the average blood pressure of 201/130 mmHg over a mean duration of 47 months [29].

Genetic Studies

Genetic tests revealed a *RET* mutation of codon 918, however the epidemiology is yet to be determined [30]. Diagnosis of a 10-year-old boy with cerebral hemorrhages caused by hypertension and JGCT is a rare manifestation of JGCT within children. Hypertension led to reoccurring headaches and neurological deficient symptoms [31]. JGCT induced myocardial infarction in a 28-year-old female was presented as a rare case. Immune-histochemical signaling revealed positive results for CD34 but negative for HMB-45, cytokeratin, and actin [32].

Imaging

Laparoscopic ultrasonography is an effective method to locate renin tumors. Location, blood supply, size, and boundaries of the renal tumors are defined with accuracy, as presented within the diagnosis of 19 clinical cases [33]. MRI and ultrasound scanning assists in locating the size and setting of the tumor [32, 34, 35]. Bioassays of plasma renin activity, aldosterone, and hypertension assist in determining the severity or presence of tumor. Immunohistochemical markers do not follow a particular pattern unlike microscopic and contrast scanning [36]. Renal artery Doppler ultrasound and DTPA scan can be administered to rule out renal artery stenosis [12]. CT scans and renal vein renin ratios assist in locating the

tumor before performing nephrectomy [12]. Renal vein sampling and cross-sectional imaging are increasing in use to diagnose for JGCT within the last decade [37]. Precise location and dimensions of tumors are often located with CT scans of the abdomen [38, 39]. Florescent markers are implicated in order to track the progression of metastatic tumors [15]. Further identification of renal lesions can involve selective renal venous catheterization with an administration of ACE inhibitor prior to a nephrectomy [40].

Presentation of Malignant Reninoma

Most reported cases of JGCT are benign neoplasms, with very few reports of metastasized tumors. JGCTs located within a 46-year-old man were found identical in masses located in the lungs and kidneys. A 15-cm tumor from the right kidney was removed 6 years prior to the formations of the bilateral lung masses. After microscopic examination, masses from the kidney and lung had identical attributes such as abundant delicate vasculature intermingled with uniform solid sheets of polygonal cells [41]. Severe hypertension caused by JGCT in an 18-year-old lead to congestive heart failure. Presentation of cardiomyopathy was found significant due to the patients lack of hypertension in medical history, and elevated levels of plasma renin and high blood pressure were associated with the diagnosis of malignant hypertension from JGCT [42]. After an unsuccessful nephrectomy in a young female patient, an aggressive mass induced severe hypertension and ACE inhibitors masked hypokalemia pre-surgery [43].

Management

Surgical Resection

During the resection of a JGCT, general anesthesia is administered for percutaneous CT-guided radiofrequency. Patients may experience dizziness and nausea post-surgery and be diagnosed with hypotension. In a case, hypotension was experienced after the surgical procedure, but later corrected with a saline infusion of 30 minutes [44]. Blood sample is drawn to determine whether hypokalemia persists, along with elevated concentration of plasma renin and aldosterone. With a positive result, the diagnosis is carried further with contrast CT scan or MRI to locate the tumor [1, 45].

Partial nephrectomy through an incision is an effective and common approach for removing JGCT-associated tumors [34]. Few situations involved other procedures

such as laparoscopic nephron-sparing surgery, as shown within a case of JGCT in a 14-year-old patient with lesions to the right kidney [46]. Time periods ranging from 4–5 days to 1 month after the surgery require blood sample follow-ups to monitor for reoccurring symptoms [34, 46, 47]. Other post-surgery assessment includes CT scan and glomerular filtration rate in the affected kidney, ranging 6–20 month follow-ups [47].

Aliskiren

Oral treatment with aliskiren, a renin inhibitor, has shown promising effects to patients with JGCT, however prolonged use decreases efficacy and may induce reactive renin release [48]. Failure to lower plasma renin activity and blood pressure are associated with prolonged use of aliskiren [49]. However, during a 2-month treatment period pre-surgery described in a case report, blood pressure was normalized and serum potassium levels increased with a 300 mg aliskiren oral treatment. Aliskiren can be beneficial to ease symptoms before a surgical procedure [50].

Conclusion

Although presented with few cases pertaining to JGCT, hypertension remains a persistent condition in adolescents and young adults. Misdiagnosis can lead to undetected JGCT and indirectly impact other malfunctioned systems such as the renin-angiotensin system and juxtaglomerular cell apparatus. Although most cases are presented with benign tumors on the kidney and removed through a nephrectomy, coexistence is possible with other forms of cancers such as B-cell leukemia and breast cancer. Mediation in JGCT can provide mediation in these other forms of cancer, such as regulating the overexpression of renin. Research into the pathological systems involving JGCT should be further encouraged.

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