



Reninoma as a cause of severe hypertension and poor pregnancy outcome in young woman

Reninom kao uzrok teške hipertenzije i lošeg ishoda trudnoće mlade žene

Danica Stamenković-Pejković*, Mirjana Šumarac-Dumanović*[†],
Nebojša Bojanić[‡], Jasmina Marković-Lipkovski[§], Jelena Vještica[§],
Aleksandar Ivanović^{||}, Goran Cvijović*[†], Ana Gligić*, Uroš Bumbaširević[‡],
Svetlana Jelić[¶], Snežana Polovina*, Dragan Micić*[†]

Clinical Center of Serbia, *Clinic for Endocrinology, Diabetes and Diseases of Metabolism, [‡]Clinic for Urology, [§]Institute for Pathology, ^{||}Center for Radiology and Magnetic Resonance, Belgrade, Serbia; University of Belgrade, [†]Faculty of Medicine, Serbia; [¶]Clinical Hospital Center “Bežanijska kosa”, Belgrade, Serbia

Abstract

Introduction. Juxtaglomerular cell tumor (JGCT) or reninoma is a very rare cause of curable hypertension among young people. The early diagnosis is the most important based on the clinical presentation, hormonal and radiological findings observed on computed tomography (CT) and/or magnetic resonance imaging (MRI). The final confirmation of the JGCT is the lateralization of the plasma renin activity (PRA) during the selective renal venous sampling. **Case report.** This report presents a typical case of young women with JGCT which was manifested for the first time with severe hypertension during the pregnancy and was the reason of fetal death. After the miscarriage, the diagnosis of JGCT was made by the CT scanning and confirmed by the selective renal venous sampling. After the partial nephrectomy, the blood pressure and serum potassium normalized without the medications. **Conclusion.** Reninoma should be considered in the differential diagnosis as a cause of severe hypertension in pregnancy and also should be suspected in young hypertensives (especially females) with hypokalemia and secondary hyperaldosteronism after the exclusion of other causes particularly renal artery stenosis. A dynamic contrast-enhanced CT, MRI and selective renal venous sampling are the most important tools in the diagnosis of JGCT.

Key words:

juxtaglomerular apparatus; kidney neoplasms; hypertension; fetal death; diagnostic techniques and procedures; diagnosis, differential; urologic surgical procedures.

Apstrakt

Uvod. Jukstaglomerularni ćelijski tumor (JGĆT) ili reninom je veoma redak uzrok hipertenzije kod mladih ljudi. Najvažnija je rana dijagnoza koja se postavlja na osnovu kliničke prezentacije, hormonskih i radioloških nalaza, pre svega kompjuterizovane tomografije (KT) i magnetne rezonance (MR). Finalna potvrda dijagnoze JGĆT je prisustvo lateralizacije plazma reninske aktivnosti (PRA) tokom selektivnog uzorkovanja krvi iz renalne vene. **Prikaz slučaja.** Prikazan je tipičan slučaj mlade žene sa JGĆT koji se prvi put manifestovao ozbiljnom hipertenzijom tokom trudnoće i bio uzrok smrti ploda. Nakon pobačaja dijagnoza JGĆT postavljena je na osnovu CT pregleda i potvrđena je selektivnim uzorkovanjem krvi iz renalne vene. Nakon parcijalne nefrektomije došlo je do normalizacije vrednosti krvnog pritiska i vrednosti kalijuma u serumu. **Zaključak.** Na JGĆT treba misliti u diferencijalnoj dijagnozi ozbiljne hipertenzije tokom trudnoće kao i kod mladih ljudi (naročito žena) sa hipokalijemijom i sekundarnim hiperaldosteronizmom nakon isključenja drugih uzroka kao što je renalna arterijska stenozna. Dinamski kontrastni KT, MR i selektivno uzorkovanje krvi iz renalne vene najvažnije su procedure u postavljanju dijagnoze JGĆT.

Ključne reči:

jukstaglomerularni aparat; bubreg, neoplazme; hipertenzija; fetus, smrt; dijagnostičke tehnike i procedure; dijagnoza, diferencijalna; hirurgija, urološka, procedure.

Introduction

Juxtaglomerular cell tumor (JGCT) or reninoma is a very rare cause of curable hypertension among young people. It is typically presented with hypertension, hypokalemia, and hyperaldosteronism secondary to excessive renin secretion by tumor cells¹. Approximately 119 cases were published and the majority of the reported cases were benign tumors, except in four cases²⁻⁵. However, its clinical behavior can be malignant as a result of severe systemic complications of hypertension. The early diagnosis is the most important based on clinical presentation, hormonal and radiological findings observed on computed tomography (CT) and/or magnetic resonance imaging (MRI). The final confirmation of the JGCT is the lateralization of the plasma renin activity (PRA) during the selective renal venous sampling^{6, 7}. However, patients with JGCT can be misdiagnosed due to the small size of the tumor which can not be visualized and/or the lack of the lateralization of PRA during the selective renal venous sampling. The usual treatment consists of partial or complete nephrectomy which results in normalization of blood pressure.

This report presents a typical case of young women with JGCT WHO manifested for the first time severe hypertension during the pregnancy, which was the reason of fetal death. After the miscarriage, the diagnosis of JGCT was made by using CT scanning and confirmed by the selective renal venous sampling.

Case report

A 20-year old female patient was referred to our hospital for a further examination of persistent and severe hypertension and hypokalemia lasting for over one year. The diagnosis of severe hypertension was established at 20th gestational weeks at 19 years of age. Antihypertensive therapy was started with methyldopa (500 mg two times daily). Except for occasional headache, the patient denied any other symptoms. PRA and plasma aldosterone concentration (PAC) were elevated (PRA 23.6 ng/mL/h, normal range 0.2–2.8 ng/mL/h; PAC 949 ng/L, normal range 42–201.5 ng/L). The pregnancy was discontinued at 24th gestational week when fetal death was diagnosed. Pathoanatomical diagnosis of the fetus and pathohistological diagnosis of the placenta showed the fetal mass of 425 g which was adequate for the 22 weeks of gestation. In the placental bed and in the intervillous space recent hemorrhage and fibrin deposits were seen. Significant syncytial nodules and villous fibrosis were present. Thickened walls of fetal blood vessels were also present.

Few months after the miscarriage she was still hypertensive and because of the hypertensive crisis (blood pressure – BP 240/120 mmHg) she was hospitalized in the regional clinical center. The renal vascular stenosis and aortic coarctation were excluded using renal angiography and cardiac ultrasound, but severe hypokalemia (2.6 mmol/L) was noticed. The antihypertensive therapy was changed to captopril (50 mg three times a day), bisoprolol (5 mg twice a day), amlodipine (10 mg once a day) and potassium chloride

(1 g twice a day) in the local hospital. After that, she was referred to our hospital for further investigation of hypertension and hypokalemia. On admission, her blood pressure was normal (115/70 mmHg) and the physical examination showed no significant findings. The serum potassium level was normal on the substitution therapy and the results of other routine laboratory tests were within the normal ranges. The endocrine examination was performed after washout period of two weeks (taking amlodipine 10 mg only) and it revealed elevated PRA (27.6 ng/mL/h, normal range 0.2–2.8 ng/mL/h) and PAC levels (1,633.7 ng/L, normal range 42–201.5 ng/L) indicating secondary hyperaldosteronism. Adrenocorticotropin (ACTH), cortisol, dehydroepi-androsterone-sulfate (DHEA-S), thyroid-stimulating hormone (TSH), thyroxine (T4), catecholamines and chromogranin were normal. Fundoscopy demonstrated hypertensive retinopathy grade II.

A dynamic contrast-enhanced CT image revealed a small renal tumor (10 mm in diameter) (Figure 1, A and B). On the other hand, there was no evidence of renal artery stenosis and the adrenal glands were normal. However, considering the findings of dynamic contrast-enhanced CT we could not completely exclude the possibility that the renal tumor was not JGCT, but rather some other tumor of the kidney and the possibility that renin was being secreted by an ectopic extrarenal tumor. Therefore, we performed selective renal venous sampling to assess the level of PRA and direct renin secretion by the tumor of the left kidney described on CT scan. We did not perform a strict low-sodium diet four days before the test nor did apply the intravenous fast acting angiotensin converting enzyme (ACE) inhibitors during the venous sampling. The only preparation for the test was discontinuation of potentially interfering medications 4 weeks before the test (the patient was on amlodipine therapy 10 mg once daily). The renal venous sampling was done in the early morning after overnight recumbency. Consequently, the PRA level was 37.9 ng/mL/h in the left renal vein, 3.1 ng/mL/h in the right renal vein and 31.7 ng/mL/h in the low inferior vena cava. This indicated the clear lateralization of PRA on the left side as the lateralization rate was 12.2 (the accepted rate of lateralization is > 1.5). At the same time, the renin concentration was measured. At first, we got the same high values in both veins (> 500.0 μ IU/mL, normal range 2.8–39.9 μ IU/mL, CLIA). After dilution, the renin concentration in left vein was 2,796.0 μ IU/mL and in the right vein 520 μ IU/mL. Taken together, we strongly suspected that the tumor in the left kidney was JGCT and the patient was prepared for the operation with the spironolactone (50 mg twice a day) and fosiopril (20 mg once daily) having achieved excellent control of blood pressure and potassium level. The open partial nephrectomy with intraoperative ultrasound was done and no complications were observed (Figure 1, C and D). The histological examination and immunohistochemistry confirmed the diagnosis of JGCT (Figure 2). After the operation, the measured levels of PRA and PAC were in the normal ranges (PRA 0.74 ng/mL/h, PCA 74.2 ng/L). The blood pressure and serum potassium normalized without the medications.

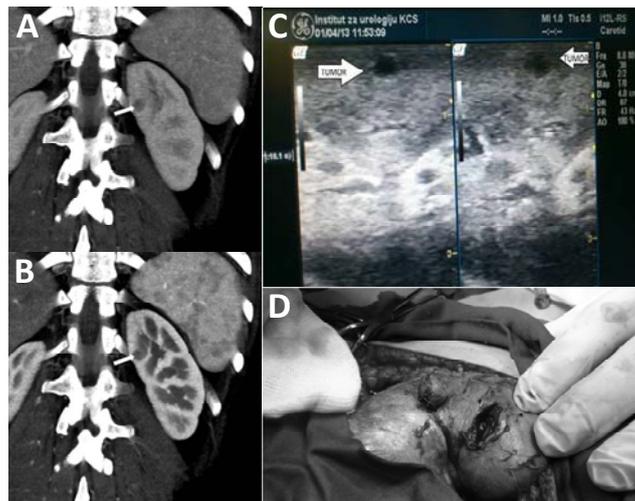


Fig. 1 – A) Contrast enhanced multidetector computed tomography (MDCT) of the left kidney, cortical phase. Frontal multiplanar reformation. Picture shows discrete rounded 10 mm lesion, that appears izodense with surrounded medulla of the upper third of the left kidney (arrow). Renal cortex is normal; **B)** Contrast enhanced MDCT of the left kidney, nephrographic phase. The lesion is well bordered with kidney during nephrographic phase, nonenhanced, low attenuated and hypovascular (hypodense), typical for reninoma (arrow). Contour of the kidney is not altered, no distortion of the renal hilum; **C)** Intraoperative ultrasound of small renal tumor – reninoma (arrow); **D)** Operative finding of small tumor immunohistochemically confirmed as reninoma.

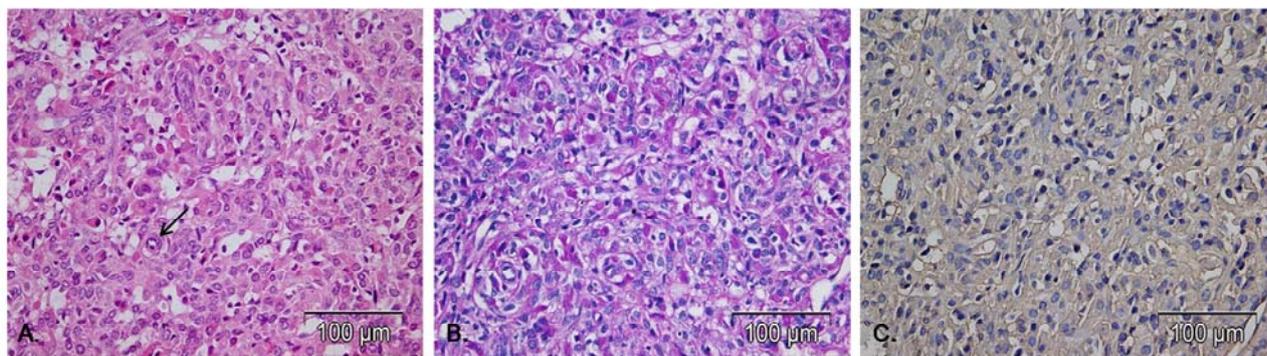


Fig. 2 – A) Reninoma: the tumor is highly cellular, composed of round, polygonal or spindle cells with granular eosinophilic cytoplasm and distinct cell borders, in the background of minimal mixomatous stroma, some of them forming the walls of small vessel (arrow) hematoxylin and eosin staining; **B)** the cytoplasmic granules react with periodic acid-schiff (PAS); **C)** Immunohistochemical positivity of the tumor to CD34. Original magnification $\times 400$. Scale bar = $100 \mu\text{m}$.

Discussion

Herein we presented the case of a typical JGCT in a young woman with severe hypertension in pregnancy, hypokalemia and secondary hyperaldosteronism diagnosed with JGCT after poor fetal outcome by using the CT and selective renal venous sampling.

Diagnosis of hypertension was made during the pregnancy which was terminated at 24th gestational week due to fetal death. To the best of our knowledge this is the fourth case of JGCT complicating pregnancy^{8–10}. Secondary aldosteronism in pregnancy is a normal physiologic response to estrogen-induced increases in circulating levels of renin substrate and PRA and to the anti-aldosterone actions of progestagens. The pregnancy might be the trigger for aggravation and manifestation of existing hypertension and secondary aldosteronism in JGCT. As it was mentioned above the pati-

ent has high PRA and aldosterone levels measured at 20th gestational weeks.

JGCT primarily affects adolescents and young adults, with peak prevalence in the second and third decades of life, and it is twice as common in women. Haab et al.¹¹ described eight JGCT among 30,000 hypertensive patients, the largest series in the literature. Average age at diagnosis was 22 years (range: 7 to 58 years). Our patient was 19 years old women when the diagnosis of hypertension was made, and she was in the typical age group for the diagnosis of JGCT. According to the clinical presentations, laboratory and imaging examinations and pathologic results the JGCT can be classified into 3 types: typical, atypical and non-functioning type¹². The typical JGCT is characterized by marked hypertension, severe hypokalemia and hyperaldosteronism secondary to tumor renin secretion. The typical variant is the most common type of JGCT. Our patient is the example of

the typical JGCT with all the mentioned features and with the excellent control of severe hypertension on the ACE inhibitor and spironolactone therapy using small doses. The clinical presentation of atypical JGCT includes marked hypertension with normal serum potassium and renin secretion. The clinical presentation of the non-functioning JGCT includes renal tumor with normal blood pressure and potassium^{12,13}. A non-functioning variant is the rarest and is thought to produce inactive renin¹³.

In our case, the suspicion of JGCT was made after the exclusion of the other causes of hypertension in young adults such as renal artery stenosis, aortic coarctation, pheochromocytoma and causes of primary aldosteronism. MRI and CT are generally able to identify renal tumors accurately and can be equally effective in the detection of JGCT with rates of detection approaching 100% in some series^{1,14}. However, JGCT tumors smaller than 5 mm can cause severe hypertension and can not be seen using standard imaging techniques¹⁵. JGCT usually appears isodense or hypodense to the renal medulla. If the tumor is small and isodense to the renal medulla on non-enhanced CT, it may not be detected. Taken together, the use of enhanced CT should be considered in all cases of suspected JGCT⁶. In our case, CT revealed small tumor and in combination with secondary aldosteronism, it was obvious that JGCT can be the cause of hypertension. However, considering the findings of CT we could not completely exclude the possibility that the renal tumor was not JGCT but rather another type of tumors such as angiomyolipoma or renal cell carcinoma and that renin was being secreted by an extrarenal tumor (lung carcinomas, pancreatic adenocarcinomas, fallopian tube adenocarcinomas, ovarian leiomyosarcoma)^{16,17}. Therefore, we performed selective renal venous sampling to evaluate direct PRA and renin secretion from the tumor and we got the clear lateralization rate of 12.2. A previous study of 50 cases of renal venous sampling reported that the sensitivity and specificity were 56% and 94%, respectively for the lateralization rate of 1.5¹. However, the variable success of this procedure in achieving accurate lateralisation of the JGCT has been published in the literature. Haab et al.¹¹ reported that 3 of 8 patients with JGCT were unable to be diagnosed by the selective renal venous sampling despite repeated attempts and its visualization on CT. Although the detailed reasons for the failure of previously reported cases of renal venous sampling are

unclear, one proposed that the tumors are primarily located on the surface of the kidneys and most of the venous supply of the tumors is collected into the perivascular veins instead of the main renal vein^{11,18}. Precise details for preparing patients for the selective renal venous sampling still do not exist but there are some recommendations as the administration of dietary salt restriction (40 mmol/day) for 4 days before the sampling. In addition, cessation of potentially interfering medications is recommended (diuretics, beta blockers, ACE inhibitors, angiotensin II receptor blockers, spironolactone) where it is possible for at least 4 weeks before the test. The overnight recumbency is also proposed⁷. The administration of a rapidly acting ACE inhibitors during the sampling can be beneficial improving the sensitivity of the test¹⁹. In our case, we did not perform dietary salt restriction before the sampling and we did not use ACE inhibitors during the procedure but we got the clear lateralization of the PRA and renin. As there are many cases of unsuccessful renal venous sampling we suggest careful patient preparation.

Clinical behavior of JGCT can be malignant due to severe systemic complications of hypertension, especially in cases with a delayed diagnosis of the tumor. Retinopathy, renal insufficiency and left ventricular hypertrophy have been reported in 24%, 3% and 7% of cases, respectively¹. Cerebrovascular accident and intestinal ischemia have been also reported^{20,21}. Our patient had hypertensive retinopathy grade II and it significantly resolved few months after the operation.

Because JGCT is mostly benign, partial nephrectomy is the proposed treatment with successful outcomes reported. Laparoscopic partial nephrectomy is particularly recommended as the tumor is usually small^{1,11}.

Conclusion

This case of JGCT was diagnosed during the pregnancy and was the reason of poor fetal outcome. This tumor should be considered in the differential diagnosis as a cause of severe hypertension in pregnancy. The tumor had the typical presentation and after the exclusion of the other causes of hypertension in young adults, particularly renal artery stenosis, the investigation was directed to the JGCT. A dynamic contrast-enhanced CT, MRI and selective renal venous sampling are the most important tools in the diagnosis of JGCT.

R E F E R E N C E S

1. *Wong L, Hsu TH, Perloth MG, Hofmann LV, Haynes CM, Katznelson L.* Reninoma: case report and literature review. *J Hypertens* 2008; 26(2): 368–73.
2. *Duan X, Bruneval P, Hammadeh R, Fresco R, Eble JN, Clark JI, et al.* Metastatic juxttaglomerular cell tumor in a 52-year old man. *Am J Surg Pathol* 2003; 28(2): 1098–102.
3. *Beaudoin J, Perigny M, Tetu B, Lebel M.* A patient with a juxttaglomerular cell tumor with histological vascular invasion. *Nat Clin Pract Nephrol* 2008; 4(8): 458–62.
4. *Shera AH, Baba AA, Baksbi IH, Lone LA.* Recurrent malignant juxttaglomerular cell tumor: A rare cause of malignant hypertension in a child. *J Indian Assoc Pediatr Surg* 2011; 16(4): 152–4.
5. *Cucchiari D, Bertuzzi A, Colombo P, De Sanctis R, Faucher E, Fusco N, et al.* Juxttaglomerular cell tumor: multicentric synchronous disease associated with paraneoplastic syndrome. *J Clin Oncol* 2013; 31(14): e240–2.
6. *Osawa S, Hosokawa Y, Soda T, Yasuda T, Kaneto H, Kitamura T, et al.* Juxttaglomerular cell tumor that was preoperatively diagnosed using selective renal venous sampling. *Intern Med* 2013; 52(17): 1937–42.
7. *Wolley M, Gordon RD, Stowasser M.* Reninoma: the importance of renal vein renin ratios for lateralisation and diagnosis. *Am J Nephrol* 2014; 39(1): 16–9.

8. Lachavac L, Svajdler M, Valansky L, Nagy V, Benicky M, Froblíčková L, et al. Juxtaglomerular cell tumor, causing fetal demise. *Int Urol Nephrol* 2011; 43: 365–70.
9. Henderson NL, Mason RC. Juxtaglomerular cell tumor in pregnancy. *Obstet Gynecol* 2001; 98(Pt 2): 943–5.
10. Shin YS, Cha JS, Kang MJ, Park JK, Kim HJ, Kim MK. Newly developed hypertension due to juxtaglomerular cell tumor in pregnancy. *Clin Nephrol* 2012; 78(4): 325–7.
11. Haab F, Duclos JM, Guyenne T, Plouin PF, Corvol P. Renin secreting tumors: diagnosis, conservative surgical approach and long-term results. *J Urol* 1995; 153(6): 1781–4.
12. Dong D, Li H, Yan W, Xu W. Juxtaglomerular cell tumor of the kidney – a new classification scheme. *Urol Oncol* 2010; 28(1): 34–8.
13. Endob Y, Motoyama T, Hayami S, Kihara I. Juxtaglomerular cell tumor of the kidney: report of a non-functioning variant. *Pathol Int* 1997; 47(6): 393–6.
14. Kang SK, Chandarana H. Contemporary imaging of the renal mass. *Urol Clin North Am* 2012; 39: 161–70, VI.
15. Robitaille P, Mongeau JG, Garel L, Dubois J, Russo P. A tiny renal renin-secreting tumor. *Scand J Urol Nephrol* 1994; 28(3): 297–9.
16. Anderson PW, Macaulay L, Do YS, Sherrod A, d Abblaing G, Koss M, et al. Extrarenal renin-secreting tumors: insights into hypertension and ovarian renin production. *Medicine (Baltimore)* 1989; 68(5): 257–68.
17. Taylor GM, Cook HT, Sheffield EA, Hanson C, Peart WS. Renin in blood vessels in human pulmonary tumors. An immunohistochemical and biochemical study. *Am J Pathol* 1988; 130(3): 543–51.
18. Corvol P, Pinet F, Plouin PF, Bruneval P, Menard J. Renin secreting-tumors. *Endocrinol Metab Clin North Am* 1994; 23(2): 255–70.
19. Tomoda F, Takata M, Ohashi S, Ueno H, Ikeda K, Yasumoto K et al. Captopril-stimulated renal vein renin in hypertensive patients with or without renal artery stenosis. *Am J Hypertens* 1990; 3(12 Pt 1) 918–26.
20. Broadis E, Ntoto C, Kamiza S, Borgstein E. Ward Round-A rare tumor of the kidney resulting in hypertension, renal failure and cerebrovascular accident in a young female. *Malawi Med J* 2011; 23(1):18–9.
21. Liborio AB, Marques Fde O, Testagrossa L, Leite CA, Leitao AA, Praxedes JN. Malignant hypertension with intestinal ischemia secondary to juxtaglomerular cell tumor. *Am J Kidney Dis* 2005; 46(5): 957–61.

Received on December 15, 2015.

Revised on February 1, 2016.

Accepted on March 3, 2016.

Online First October, 2016.