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

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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 localization 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.

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Apstrakt

Uvod. Jukstaglomerularni čelijski tumor (JGČT) 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 JGČT je prisustvo lateralizacije plazma reninske aktivnosti (PRA) tokom selektivnog uzorkovanja krvi iz renalne vene. Prikaz slučaja. Prikazan je tipičan slučaj mlade žene sa JGČT koji se prvi put manifestovao ozbiljnom hipertenzijom tokom trudnoće i bio uzrok smrti ploda. Nakon pobačaja dijagnoza JGČT postavljena je na osnovu CT pregleda i potvrđena je selektivnim uzorkovanjem krvi iz renalne vene. Nakon parcialne nefrectomije došlo je do normalizacije vrednosti krvnog pritiska i vrednosti kalijuma u serumu. Zaključak. Na JGČT treba misliti u diferencijalnoj dijagnozi ozbiljne hipertenzije tokom trudnoće kao i kod mladih ljudi (naročito žena) sa hipokalijemijom i sekundarnim hiperaldosteronom nakon isključenja drugih uzroka kao što je renalna arterijska stenoza. Dinamski kontrastni KT, MR i selektivno uzorkovanje krvi iz renalne vene najvažnije su procedure u postavljanju dijagnoze JGČT.
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 cells. Approximately 119 cases were published and the majority of the reported cases were benign tumors, except in four cases. 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. However, patients with JGCT can be misdiagnosed due to the small size of the tumor which cannot 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 syncytiotrophoblast 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, dehydroepiandrosterone-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 μIU/mL, normal range 2.8–39.9 μIU/mL, CLIA). After dilution, the renin concentration in left vein was 2,796.0 μIU/mL and in the right vein 520 μIU/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 fosinopril (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, PAC 74.2 ng/L). The blood pressure and serum potassium normalized without the medications.

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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 isodense 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 ×400. Scale bar = 100 µm.

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. 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 patient 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. 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 type. 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. A non-functioning variant is the rarest and is thought to produce inactive renin.

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. However, JGCT tumors smaller than 5 mm can cause severe hypertension and can not be seen using standard imaging techniques. 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 JGCT. 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 angiomylolipoma or renal cell carcinoma and that renin was being secreted by an extrarenal tumor (lung carcinomas, pancreatic adenocarcinomas, fallopian tube adenocarcinomas, ovarian leiomyosarcoma). Therefore, we performed selective renal venous sampling to evaluate direct PRA and renin secretion from the tumor and 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, respectively. There are some recommendations as the administration 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 proposed. The administration of a rapidly acting ACE inhibitors during the sampling can be beneficial improving the sensitivity of the test. 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.

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.

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.

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