

Dopamine-secreting adrenal ganglioneuroma presenting with paroxysmal hypertension attacks

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ABSTRACT

يعتبر ورم الأعصاب الحبيبية من الأورام النادرة وينشأ من نسيج الحرقفة العصبية للجهاز العصبي اللاعراضي. الحالة السريرية لمعظم المرضى غير عرضية ومعظم هذه الأورام هرمونات لا عرضية. يبحث هذا التقرير عن حالة تعاني من ورم الأعصاب الحبيبية في الغدة الكظرية المفرزة للدوبامين مع نوبات ارتفاع ضغط الدم الاشتدادية في مريض بالغ. أدخلت مريضة تبلغ من العمر ٤٦ عاماً للمستشفى وهي تعاني لمدة عامين من نوبات ارتفاع ضغط الدم الاشتدادية مصحوبة بصداق وخفقان وعصبية وتعرق. أظهر الفحص بالأشعة المقطعية للبطن وأشعة الرنين المغناطيسي وجود ورم صلب دائري يبلغ قطره حوالي ٤ سم في القطب العلوي للكليبة اليمنى. كانت مستويات البول وحمض هوموفانيلاك مرتفعة. على الرغم من دعم مستويات البول للميتانيفرين ونورميتافرين. كانت مستويات إينيفورين ونوبيبينيفرين للبول وحمض فيتيلماندسيلييك ضمن الحدود الطبيعية. أجريت عملية استئصال الغدة الكظرية اليمنى لأغراض علاجية. كان التشخيص المرضي للمرض بورم الأعصاب الحبيبية في الغدة الكظرية ينشأ من لب الكظر. في الختام، هذه الحالة هي أول تقرير عن حالة مصابة بورم الأعصاب الحبيبية في الغدة الكظرية المفرزة للدوبامين ومصحوبة بنوبات ارتفاع ضغط الدم الاشتدادية في مريض بالغ.

Adrenal ganglioneuromas are rare tumors originating from the neural crest tissue of the sympathetic nervous system. The clinical presentation for most patients is asymptomatic, and most of these tumors are hormone silent. We report a case of dopamine-secreting adrenal ganglioneuroma associated with paroxysmal hypertensive attacks in an adult patient. A 46-year-old woman was admitted to our hospital with a 2-month history of right flank pain, and a 2-year history of paroxysmal hypertensive attacks associated with headaches, palpitations, nervousness, and sweating. Abdominal CT and MRI revealed a solid round tumor approximately 4 cm in diameter on the upper pole of the right kidney. Urinary levels of dopamine and homovanillic acid were slightly elevated, although urinary levels of metanephrine and normetanephrine were suppressed. The urinary levels of epinephrine, norepinephrine, and vanillylmandelic acid were within normal limits. Right adrenalectomy

was performed for treatment purposes. Histological diagnosis of the tumor was a ganglioneuroma originating from the adrenal medulla. In conclusion, this is a case of dopamine-secreting adrenal ganglioneuroma associated with paroxysmal hypertensive attacks in an adult patient.

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Ganglioneuromas are rare benign, differentiated neoplasms of the neural crest, origin arising from the sympathetic ganglia or the adrenal medulla, and composed of mature ganglion cells and Schwann's cells in a fibrous stroma.¹ They are situated at one end of a spectrum that includes neuroblastoma and ganglioneuroblastoma.¹⁻³ The incidence of ganglioneuromas is unknown; however, they are frequently associated with von Recklinghausen's disease and occur most commonly in the posterior mediastinum and retroperitoneum. The occurrence of these tumors in the adrenal medulla is less common, but they may present diagnostic difficulty.⁴ Adrenal ganglioneuromas occur most commonly in children and young adults.⁵ Characteristically, ganglioneuromas do not secrete excess catecholamines or steroid hormones, so they are rarely associated with hypertension.⁶ Although ganglioneuromas are generally considered to be nonsecretory, some endocrinologically active ganglioneuromas have been reported.^{1,3,7} Such patients often present with paraneoplastic symptoms such as

diarrhea and hypertension.⁵ We report an adult case of endocrinologically active adrenal ganglioneuroma.

Case Report. A 46-year-old female was admitted to our hospital with a 2-month history of right flank pain and a 2-year history of paroxysmal hypertensive attacks (210/150 mm Hg) associated with headaches, palpitations, nervousness, and sweating. On admission, her blood pressure was 130/80 mm Hg and arterial pulse was 102/min, rhythmic. She had postural hypotension and minimal tenderness in the right adrenal area. Routine laboratory investigation failed to show any abnormality; however, ECG revealed sinus tachycardia. Tension Holter monitoring revealed paroxysmal hypertension attacks (190/110 mm Hg) alternating with periods of normotension and hypotension (the lowest value was 73/47 mm Hg). Urine norepinephrine (NE): 29 mcg./24 hours (N: 8-103), urine epinephrine (E): 12 mcg./24 hours (N: 0.5-20), urine normetanephrine: 34 mcg./24 hours (N: 88-444), urine metanephrine: 43.3 mcg./24 hours (52-341), urine vanillylmandelic acid (VMA): 7.1 mg/24 hours (N: 1.8-9.8), urine dopamine: 473 mcg/24 hours (65-400), homovanillic acid (HVA): 11.2 mg/24 hours (N: 1.4-8.8). The levels of serum calcitonin, intact parathyroid hormone, cortisol, aldosterone, plasma renin activity, and urine free cortisol were within normal range. Abdominal CT showed a well-demarcated solid mass (30 x 35 mm) with faint calcifications on the upper pole of the right kidney. Abdominal MRI revealed a well-demarcated hyperintense mass measuring 30 x 25 mm, located in the right adrenal gland (**Figure 1**). A ¹³¹Iodine-metaiodobenzylguanidine (¹³¹I-MIBG) scan could not be performed. From these findings, a pheochromocytoma

arising within the right adrenal gland was suspected. Following the administration of adequate alpha-receptor blocking agents with phenoxybenzamine 60 mg/day, a beta-adrenoceptor blocker (propranolol) was added to the therapy and normotension was reached. Right adrenalectomy was performed by the transabdominal route under general anesthesia. Gross pathological appearance of postoperative resected right adrenal tumor was encapsulated, well-circumscribed, measuring 40 x 40 x 25 mm in dimension. The tumor showed a whitish grey and gelatinous appearance in the cut surface without evidence of hemorrhage or necrosis. Microscopically, the sections showed irregular proliferation by spindle shaped cells with scattered mature ganglionic cells (**Figure 2a**). The spindle shaped cells stained strongly with monoclonal antibody to S-100 protein (**Figure 2b**) and the ganglionic cells stained with monoclonal antibody to neuron-specific enolase, synaptophysin, and chromogranin-A. The histologic diagnosis was adrenal ganglioneuroma. Six weeks after the surgery, the patient was well and had no recurrence

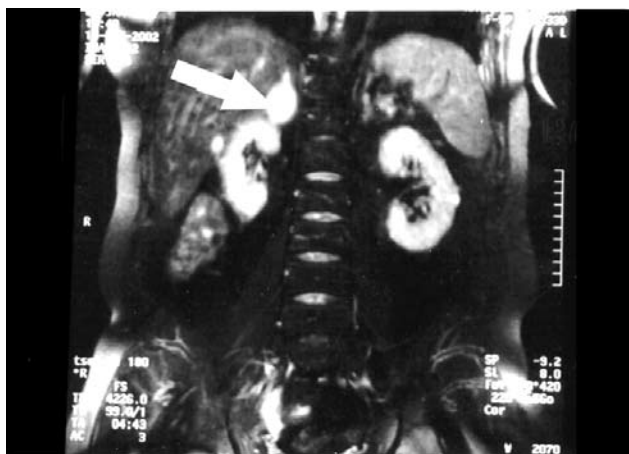


Figure 1 -T₂-weighted magnetic resonance image demonstrating round homogeneous tumor with hyperintensity signal on the pole of the right kidney (arrow).

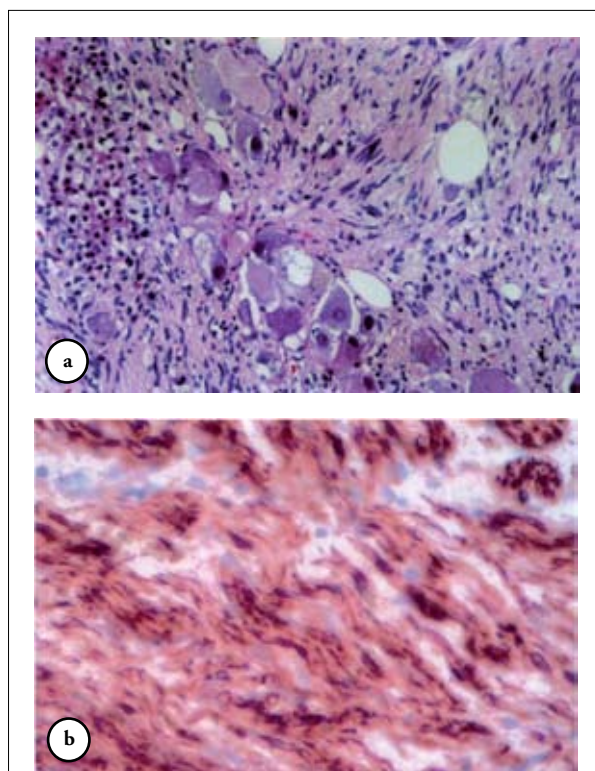


Figure 2 -Microscopic findings showing a) scattered mature ganglionic cells in background of spindle shaped cells, (hematoxylin and eosin staining, original magnification x 400), b) Spindle-shaped sustentacular cells (Schwann cells) stained brown for S-100 protein immunoperoxidase staining, x 100).

of symptoms. Levels of urinary catecholamines and their metabolites as well as blood pressure were within normal limits (urine normetanephrine: 226 mcg/24 hours [normal: 75 - 375 mcg/24 hours, urine metanephrine: 158 mcg/24 hours [normal: 140 - 785 mcg/24-hours], urine dopamine: 213 mcg/24 hours [65 - 400 mcg/24 hours], Homovanillic acid: 5.8 mg/24 hours [normal: 1.4-8.8 mg/24 hours]).

Discussion. Ganglioneuromas may arise anywhere along the paravertebral sympathetic plexus and occasionally are found within the adrenal medulla.⁸ They are generally considered to be nonsecretory; thus, systemic manifestation of disease would not be expected. On reviewing the literature, we found only 4 reports of secretory retroperitoneal ganglioneuroma occurring in adult patients.^{1,9-11} These tumors were reported to secrete NE. Our case describes dopamine-secreting adrenal ganglioneuroma associated with paroxysmal hypertension attacks. The circulating catecholamines are mainly metabolized by catechol-o-methyltransferase, which occurs in high concentrations in the liver and kidneys, while monoamine oxidase, which occurs in the mitochondria of sympathetic cells, is responsible for catecholamine metabolism within the biosynthetic tissue. The major urinary metabolites HVA and VMA are formed from dihydroxyphenylalanine (DOPA) plus dopamine and NE, respectively.² Being well established that neuroectodermal tumors produce one or more of the catecholamines and their metabolites in excessive amounts, their determination in urine has proved to be useful as a tumor marker and diagnostic tool for the detection of recurrences and assessment of treatment results. The urinary excretory pattern of DOPA metabolites in ganglioneuroma and neuroblastoma varies widely. There is the possibility of a normal excretion of NE and its metabolites, including VMA, with an elevated excretion of DOPA, dopamine, and their metabolites, including HVA. This can be explained by the high production of DOPA and dopamine from the tumor, with a relative insufficiency of dopamine-beta-hydroxylase, or by abnormal tumor enzymatic systems and altered regulatory mechanisms.¹² One can expect normotension or hypotension in dopamine-secreting tumors,^{1,3} however, in the present case, Tension Holter monitoring revealed paroxysmal hypertension attacks in the background of normotension and hypotension. We found no explanation for the paroxysmal hypertension attacks in our patient. No abdominal massage or palpation was applied, and the patient was not administered any medication causing hypertension. Yet after surgery, the

paroxysmal hypertension never reappeared. In our case, we observed a small increase in the urinary levels of both dopamine and HVA. This could be explained by the aforementioned mechanism, consisting of a relative insufficiency of dopamine-beta-oxidase, resulting in accumulation of dopamine and a small increase of its metabolites like HVA. Interestingly, the urinary levels of metanephrine and normetanephrine were suppressed. The urinary values obtained over a period of 6 months after surgery showed normal values for dopamine, HVA, metanephrine, and normetanephrine. Ganglioneuromas represent the most mature form of neuroblastoma-type tumors.¹ But malignant transformations into malignant peripheral nerve sheath tumors,¹³ or neuroblastomas,¹⁴ have been reported. Therefore, ganglioneuromas should be surgically excised completely and also be followed for long periods after the operation.

In conclusion, as with pheochromocytomas, dopamine-secreting ganglioneuroma may also be symptomatic, and in these patients the diagnosis is made on the surgically resected specimen. The present case is report of a dopamine-secreting adrenal ganglioneuroma associated with paroxysmal hypertension attacks in an adult patient.

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References

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