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Retroperitoneal Functioning Paraganglioma - A Rare Case of Secondary Diabetes

Radu Mihail Mirica[1,2], Octav Ginghina[1,2], Gabriela Zugravu[1], Razvan Iosifescu[1,2], Mihai Ionescu[1], Anca Ichiman[3], Adrian Rosca[2], Alexandra Mirica[2,4], Nicolae Iordache[1,2], Rubin Munteanu[3]

[1]Emergency Hospital "St. John", Bucharest
[2]University of Medicine and Pharmacy "Carol Davila", Bucharest
[3]Euroclinic Regina Maria Hospital
[4]National Institute of Endocrinology "C. I. Parhon", Bucharest

Rezumat

Paragangliom retroperitoneal - o cauză rară de diabet zaharat secundar

Introducere: Paraganglioamele sunt tumori neuroendocrine rare care se pot dezvolta pe structurile ganglionare autonome extra-adrenale și care poate deriva fie din paraganglioamele parasimpatice sau simpatice și sunt strâns legate de feocromocitoame.
Prezentare de caz: Prezentăm cazul unui pacient de sex masculin, de 37 de ani, internat pentru criză hipertensivă și palpitații. Istoricul medical include diabet zaharat tip 2, (diagnosticat acum 10 luni) controlat medical, hepatita A. Evaluarea hormonală dezvăluie metanefrine și normetanefrine urinare crescute, cu creșterea în principal a normetanefrinelor (2330 ug/24h). Metanefrinele plasmatice au fost în limite normale, dar concentrațiile de normetanefrine plasmatice au fost crescute (952pg/ml). Evaluarea axei hipofizare și a axei renină-aldosteron au fost în limite normale. Tomografia computerizată abdominală a arătat leziune nodulară suprarenală stângă, bilobulată, dimensiune de 32/33mm cu diametrul maxim cranio-caudal de cca. 45cm, sugestiv pentru o leziune benignă, păstrând planul de clivaj cu structurile de vecinătate. S-a practicat adrenalectomie stângă pe cale laparoscopică. De menționat este că imediat după inducerea anesteziei a fost înregistrată tensiune arterială de 298/143 mmHg. Histopatologic și imunohistochimic a fost diagnosticat paragangliomul, fără invazie a țesuturilor adiacente. Evoluția pacientului a fost favorabilă, cu remiterea simptomelor și normalizarea markerilor hormonale si valorile Hb glicate. Este imperativ să rețineți remiterea diabetului în perioada post-operatorie.
Discuții: Acesta este cazul unui pacient tânăr cu paragangliom retroperitoneal funcțional, care s-a prezentat cu simptome specifice feocromocitomului. Comparativ cu feocromocitomul, paragangliomul este rareori simptomatic și funcțional. Asocierea cu diabet zaharat este chiar mai rară. Investigațiile de specialitate au permis un diagnostic corect și abordarea terapeutică a fost rezultatul unei cooperări multidisciplinare.

Cuvinte cheie: paragangliom, feocromocitom, adrenalectomie, normetanefrine

Corresponding author: Octav Ginghina, MD
Emergency Hospital "St. John"
University of Medicine and Pharmacy
"Carol Davila", Bucharest
Vitan-Berzesti nr 13, Sector 4
Consulent at Hepatobiliary and
Transplantation Surgery, University Hospital
Antwerpen, Belgium
E-mail: octavginghina@gmail.com

Abstract

Introduction: Paragangliomas are rare neuroendocrine tumors that arise from the extra-adrenal autonomic paraganglia, which can derive from either parasympathetic or sympathetic paraganglia and are closely related to pheochromocytomas.

Case report: We present the case of a young male patient of 37 years old, who was admitted for hypertensive crisis and palpitations. His medical history included medically controlled type 2 diabetes mellitus, (diagnosed 10 months ago), Hepatitis A. Hormonal evaluation revealed elevated urinary metanephrines and normetanephrines, with mainly increased normetanephrines (2330 ug/24h). Plasmatic metanephrins were in normal range, but levels of plasmatic normetanephrins were elevated (952 pg/ml). The assessment of pituitary and aldosterone-renin axis values were within normal limits. Abdominal computed tomography showed left adrenal nodular lesion on the external arm, bilobulated, size 32/33 mm with maximum axial and cranio-caudal diameter of approx. 45cm, suggestive of a benign lesion, keeping the cleavage plane to vecinatate structures. Left adrenalectomy was performed by laparoscopic approach. We mention that immediately after induction of anesthesia were recorded blood pressures of 298/143 mmHg. Histopathologic and immunohistochemical examination diagnose paraganglioma, without invasion of adjacent tissues. The patient evolution was favorable, with the remission of the symptoms and normalization of hormonal markers. It is imperative to note the remission of diabetes in the postoperative period.
Discussion: This is the case of a young patient with functional retroperitoneal paraganglioma, who presented with symptoms of pheochromocytoma. Compared to pheochromocytomas, paragangliomas are rarely symptomatic and functional. Association with diabetes is even more rare. Specialized investigations allowed the proper diagnosis and the therapeutic approach above was the result of a multidisciplinary cooperation.

Key words: paraganglioma, pheochromocytoma, adrenalectomy, normetanephrines

Introduction

Paragangliomas are rare tumors arising from extra-adrenalchromaffin cells within the sympathetic nervous system (found in 0.05- 0.2% of hypertensives) (1–3). They appear in all races, but less frequently in black people, they can be develop at any age, with a higher incidence between the 3rd and 5th decades of life, and affect both sexes equally (4,5). They can be found anywhere from the neck to the pelvis inthe vicinity of sympathetic ganglions, and belong to the family of neuroendocrine tumors. An incidence rate of 2–8 cases per million is reported, and tumors can be either functional or non-functional. When functional they can secrete catecholamine, epinephrine, or norepinephrine.

Most paragangliomas are benign, the clinical symptoms they cause are resulting from excess production of catecholamines (normetanefrines and metanefrines); patients typically present with hypertension, tachycardia, headache and diaphoresis (4, 5, 6-8). They can be also completely asymptomatic, being only detected accidentally in imaging studies, and they are called "incidentalomas" (4, 5, 6-8). They are a potentially treatablecause of hypertension (4, 5).

There are two groups of paragangliomas derive from the ganglia along the sympathetic nervous chain. One group is parallel with the paravertebral sympathetic chain, placed retroperitoneal, along the aorta, including the most frequently encountered locations such as suprarenal, renal hilar and infrarenal. This group of paraganglioma can frequently have a norepinephrine secretory profile (9).

Positive diagnosis is based on measurement of serum and urine catecholamines and their metabolites and is confirmed by imaging studies, such as CT scan and MRI of the adrenal glands and abdomen, and functional exams such as scintigraphy and PET CT scan to exact locate the tumor (5, 10, 11). The high risk and low specificity of provocative tests such as clonidine suppression testing mean that they are not recommended (12). Although most paragangliomas are sporadic, an increasing number of hereditary cases are being reported (10-50%), many of which are associated with genetic syndromes (5-8,13). It may be worth performing genetic testing in patients diagnosed with paraganglioma, even if they have no known family history, but this ideea is still debating (5-8,13).

Treatment consists of surgical excision of the tumor, which usually resolves the hypertension. Preoperative administration of alphaand beta-blockers is also essential to control hypertension and to prevent intraoperative hypertensive crises (4-8,13). Benign and malignanttumors are not distinguished on the basis of clinical manifestations, imaging studies or histology, or even the extent of local invasion, they are distinguished by the presence or absence of distantmetastasis, which are most commonly in bone, liver or lymph nodes (4-7). Chemotherapyand radiotherapy brings some benefit to patients with metastatic tumors (about 10% of cases)(4,6), but long-term follow-up with monitoring of catecholamine levels is essential, giventhe potential for these tumors to recur (5-8).

Case report

A 37-year-old man, with a personal history of episodic headaches and diaphoresis, was diagnosed with hipertension two years ago. His blood pressure was controlled with Perindoprilum + Amlodipinum 5/5 mg, Indapamidum 1.5 mg, Pentaerithrityli Tetranitrans 20 mg, Trimetazidinum 35 mg, he had also diabetes, under treatment with oral antidiabetics (Siofor 1000 mg, Diaprel 30 mg) for over 10 months and a history of hepatitis A. On physical examination he was in good general health, with skin and mucous membranes normal colored and hydrated; currently bilateral vesicular murmur without rales, blood pressure (BP) was 170/110 mmHg and heart rate 88 bpm, with no signs of systemic or pulmonary congestion, pulsatile peripheral arteries bilaterally symmetrical, slim abdomen, painless on palpation or spontaneous, fundus examination: flat papillae with central excavation, stage II hypertensive angiopathy, and no other relevant findings.

Biochemical tests showed plasma normetanefrine 952 pg/ml, plasma metanefrine 28 pg/ml, urinary normetanefrine

2330.2 ug/24h, urinary metanefrine 243.09 ug/24h, ACTH 23,19 pg/ml, plasmatic cortisol 23,60 pg/ml,glicemia 203,2 mg/dl, glycosylated hemoglobin 8.3%A1c. Abdominal computed tomography revealed: left adrenal nodular lesion on the externally arm of the gland, size 32/33 mm maximum axial and cranio-caudal diameter of about 45mm, native densities of about 45 UH, iodofila with wash-out in late sequences (about 60%) suggestive of a benign lesion, keeping the cleavage plane to neighboring structures. Right adrenal gland in normal CT appearance. Normal sized liver without focal lesions detectable. Periceliac localized lymphadenopathy, lumbo-aortic middle (in adjacent renal hilum) and lower left common iliac and intra-mezenteric, with maximum dimensions of 17.9 mm, some with lipomatous center. Free lung bases (Fig. 1).

Given the biochemical status, urinary and plasmatic catecholamines and CT appearance was established diagnosis of paraganglioma.

After preoperative preparation with alpha-blockers for 2 weeks, laparoscopic left adrenalectomy was performed. We used the transperitoneal technique with 12 mmHg intra-peritoneal pressure with medial mobilization of the speno-pancreatic block. Intraoperative we identify: malrotated spleen with the convex face on the anterior. Was carried out the left coloparietal dissection, descending colono-splenic angle. Identification of the left adrenal gland was difficult because it was a malrotated gland with ¾ cm tumor located on the front of the kidney in the upper third, placed over the renal hilum (Fig. 2). It intercepts the lower diaphragmatic artery and it was ligated. The circumferential dissection was practice and identifyed the central vein that was triple ligated (Ø = 5-6 mm) (Fig. 3). The complete hemostasis was perform and a drainage tube in the adrenal lodge was placed.

Immediately after induction of anesthesia the patient had blood pressures of 298/125 mmHg(blood preasure was monitorized by central catheter). During manipulation of the gland maximum blood pressure was 250 mmHg and it was used Nicardipina for maintaing at normal values. After isolation (clamping the central vein) and excision of adrenal gland the patient requested Noradrenalin and blood pressure did not exceed 130/90 mmHg.

In postoperative follow-up, the patient was asymptomatic, with blood pressures<130/85 mmHg and normal urinary catecholamines and metabolites.

Microscopic examination revealed a pattern of alveolar fine granular eosinophilic cytoplasm cells, nuclei with minimal atypia, stroma with prominent vascularity, focal hyaline. The differential diagnosis between paraganglioma and pheochromocytoma on microscopic images is very difficult, the two pathologies having an extremely similar aspect. These appearances recommend immunohistochemistry analysis for differential diagnosis of pheochromocytoma versus paraganglioma. The imunohistochemistry confirmd the diagnosis of paraganglioma beeing positive for: neuron-specific enolase, chromogranin A andsynaptophysin and negative for: cytokeratin, insulin, and glucagon.

The patient was discharged with good general condition, good digestive tolerance, surgical wounds healed with diagnosis of adrenal paraganglioma, considering in particular the appearance of biochemical huge amount of norepinephrine



Figure 1. *CT image of tumor formation*

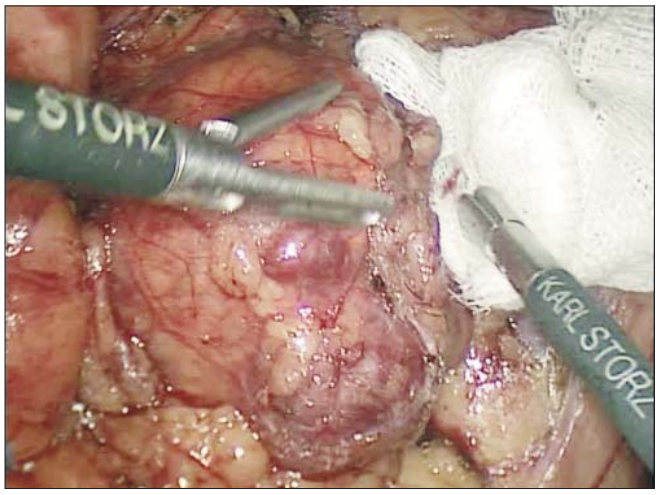


Figure 2. *Intraoperative image of the tumor*

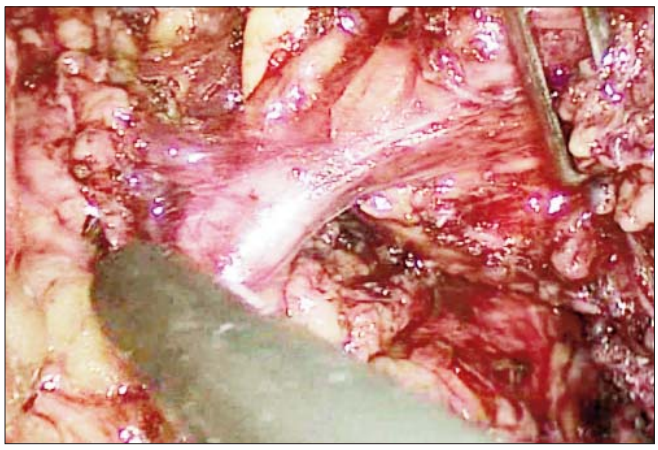


Figure 3. *Tumor vascular pedicle*

associated with epinephrine almost normal. The control at one month postoperatively showed general good condition, with no pain or other symptoms, with normal blood pressures. Ultrasound examination did not showed pathological changes. A very interesting aspect is that the patient has been free of diabetes after surgery, and never require treatment with oral agents, glycosylated hemoglobin reached within a few months at 5.2%.

Discussion

Paraganglioama may be hereditary or may be associated with neurofibromatosis type 1, von Hippel-Lindau, Carney triad disease, multiple endocrine neoplasia(MEN) type 2 and similar mutations of succinate dehydrogenase genes (SDHB, SDHC, SDHD) (14).

Increased secretion of catecholamines in functional tumors is responsible for the appearance of symptoms such as high blood pressure spikes, sweating, headache, anxiety, tachycardia, palpitations (14,15). Even if imaging studies are useful, accurate diagnosis is made by histopathology of the resected tumor formation, complete with immunohistochemical studies. Native CT examination with contrast is useful diagnosis, but there isn't a unique feature of paraganglioamas. (15).

Treatment of premium intent is surgery - radical excision, with no microscopic clear distinction criteria between benign and malignant forms. Chemotherapy and radiotherapy is unnecessary in cases of benign abdominal paragangliomas (15), in this cases long-term follow-up is required.

It is the first case , to our knowledge, that presents a paraganglioma that associate type 2 diabetes before surgery and after surgery, the excizion of the tumor formation determin the resolution of the diabetes. The diagnosis of paraganglioma is, in our case, in particular biochemical huge amount of norepinephrine associated with epinephrine almost normal. The patient had documented diabetes treated with oral agents, after surgery this has resolved and not required oral treatment. There is an explication of the phatophysiological mecanisms that can be consider as the cause of diabetes disapearence: the paraganglioma causes an hipersecretion of catecolamins and cortisol, and this hiperglicemic hormons can induce diabetes at patients with not very good pancreatic function. This situation is extremely rare and yet very little documented and researched in the literature.

In our opinion are very interesting to study, not only in surgical terms but olso from a phatophysiological point of view, there are not yet well documented the exact mecanism that induce diabetes in this cases and not induce in a case of phaeochromocytoma, paraganglioma is well known that have many similarities with much frequent pheocromocitomas.

Conclusions

In conclusion adrenal paraganglioma is highly rarely. Clinical and laboratory data of these patients are highly variable and nonspecific, while there are many asymptomatic, even in the case of large tumors. There are also associations with various other diseases, such as diabetes in our case, whose link is not yet well documented. Treatment of premium intent is surgery - radical excision, with no microscopic clear distinction criteria between benign and malignant forms. Chemotherapy and radiotherapy is unnecessary in cases of benign abdominal paragangliomas (14), in this cases long-term follow-up is required.

Author contributions

Concept - R.M.M., R.M.; Design – R.M.M.,R.M.; Supervision – R.M.,O.G.,N.I.; Resource – R.M.M., R.M.; Materials – G.Z., R.M.M.; Data Collection &/ or Processing – R.M.M; Analysis &/or Interpretation –R.M.M, R.M., O.G.; Literature Search – R.M.M, A.M.; Writing – R.M.M., R.M., O.G.; Critical Reviews –R.M., O.G., N.I., Suport and Advice – R.I., M.I., A.R., A.I.

Conflict of interest

No conflict of interest was declared by the authors.

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