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Review With Case Report

ORGAN OF ZUCKERKANDL AS A SOURCE OF PARAGANGLIOMA PHEOCHROMOCYTOMA

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Abstract

Pheochromocytoma and paraganglioma of the organ of Zuckerkandl are rare neuroendocrine tumors of neural crest cells with the classic symptomatic triad of tachycardia, headache, and profuse sweating. To confirm the diagnosis of pheochromocytoma and paraganglioma, increased plasma concentrations of metanephrines and increased fractionated metanephrines in 24-hour urine are determined. A computed tomography is the most reliable diagnostic test method, and magnetic resonance imaging may be done. The main treatment of pheochromocytoma and paraganglioma is divided into medicinal, surgical, and auxiliary tumor treatments.

The patient was admitted to the surgical department in 2017 with complications of abdominal and lumbar pain, general weakness. In the past 8 years, the patient has suffered from an aggressive form of arterial hypertension (systolic pressure ranges within 170220 mmHg). Since 2011, there has been an increase in blood glucose levels between 17 and 22 mmol/L, which is difficult to control with insulin injections only.

A clinical preoperative diagnosis was made: pheochromocytoma and paraganglioma of the organ of Zuckerkandl. The tumor was removed through the median laparotomy access. The course of postoperative period was uneventful. Starting from the second day after the surgery and in the following months, blood pressure did not rise above 120/80, and blood glucose levels returned to normal.

To avoid intra- and postoperative complications, 1-14 days prior to surgery, patients should be given appropriate α-blockers, calcium channel blockers, and β-blockers that are alternative or auxiliary treatment; which ensure increased circulating blood volume achieved by saline infusion; then after 6 months, after a year, annual tumor imaging is also required. Postoperative treatment of pheochromocytoma and paraganglioma of the organ of Zuckerkandl is the main most effective treatment, it is necessary to identify and take measures to combat metastases in time.

Keywords: *organ of Zuckerkandl, paraganglioma, pheochromocytoma, neuroendocrine tumors.*

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INTRODUCTION

Pheochromocytoma and extraadrenal paraganglioma are rare neuroendocrine tumors of neural crest cells that lead to catecholamine hyperproduction and are diagnosed by plasma and urinary concentrations of metanephrine and normetanephrine [*Pacak K, Wimalawansa SJ, 2015*]. According to "Endocrine Tumors," the World Health Organization classification updated in 2017, a new definition was introduced called paraganglioma (PGL), with the term of "pheochromocytoma" (PCC) currently referring to intraadrenal tumors, whereas similar tumors outside the adrenal medulla have been referred to as "extraadrenal paragangliomas" [*Lam AK, 2017*]. Sources of PCCs and extraadrenal PGLs are chromaffin adrenal cells or similar extraadrenal paraganglia [*Chen H et al, 2010*]. Depending on the location, these tumors are identified by different methods and may manifest variably from the absence of metastasis to aggressive growth with a high risk of metastasis [*Guilmette J, Sadow PM, 2019*]. Both tumor types are classically manifested by paroxysmal attacks of headaches, tachycardia, and profuse sweating. Most of these tumors are associated with certain genetic abnormalities, and genetic testing is therefore necessary for diagnosis [*Pacak K, Wimalawansa SJ, 2015; Favier J et al, 2015*]. Moreover, has been reported that operative mortality was as high as 50% in unprepared patients with phaeochromocytoma [*Prejbisz A et al, 2013*].

In 1901, the Austro-Hungarian anatomist and anthropologist Emil Zuckerkandl first described para-aortic paraganglia as a paired retroperitoneal organ located lateral to the abdominal aorta at the inferior mesenteric artery level [*Zuckerkandl E, 1901*]. Subsequently, this paraganglionic complex was referred to as "the organ of Zuckerkandl" (OZ), which also included small paraganglia located anterior to the aorta, in the region of its bifurcation [*Unsicker K et al, 2005*]. In 1903, the head of the Institute of Histology at the German University in Prague, Alfred Kohn found that OZ usually originates from chromaffin cells similar to those of the adrenal medulla [*Kohn A, 1903*]. Later, it was found to be the largest accumulation of extraadrenal chromaffin cells in mammals. In humans, OZ reaches its maximum size by 3 years of life and subsequently regresses after its peak in autophagia [*Schober A et al, 2013*]. Organ of Zuckerkandl plays an important physiological role during the early gestational period during which it secretes catecholamines into the fetal circulation, functioning as a homeostatic blood pressure regulator [*West GB et al, 1953*]. In adults, OZ may be a source of development of PGLs, which predominantly release noradrenaline and cause symptoms of catecholamine excess [*Martucci VL, Pacak K, 2014; Le HDT et al, 2021*].

CASE REPORT

Patient Information: The patient, M.N., man 65 years old, Armenian, was admitted to the surgical department of the "Astghik" Medical Center in March 2017. At the time of admission, the patient reported complaints of abdominal and lumbar pain, marked general weakness.

Clinical Data: In the past 8 years, the patient has suffered from an aggressive form of arterial hypertension and against the background of antihypertensive drugs, systolic pressure ranges within 170220 *mmHg*. Since 2011, there has been an increase in blood glucose levels between 17 and 22 *mmol/L*, which is difficult to control with insulin injections only.

Diagnostic Data: The performed hematology and chemistry blood tests did not detect other pathological shifts. Electrocardiography showed left ventricular hypertrophy and atrial fibrillation. Radiologic examination of the chest did not describe any pathological changes. The performed contrast-enhanced computed tomography of the abdominal cavity and retroperitoneal space (Fig. 1) identified a

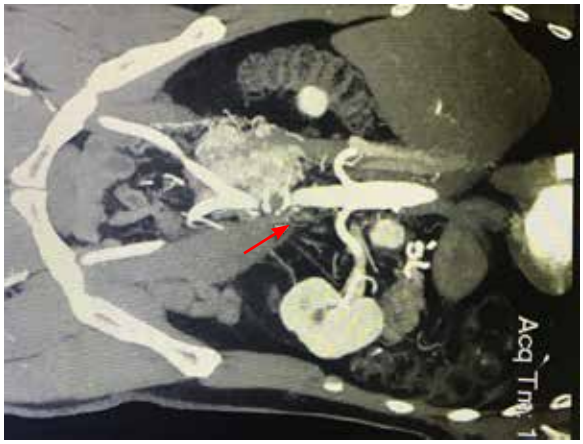

FIGURE 1 *Computed tomography of the abdominal cavity and retroperitoneal space with identification of pheochromocytoma, frontal section.*

highly vascularized tumor-like mass 14×6 *cm* in size, which was located paraaortically, at the level of origin of the inferior mesenteric artery, extending and compressing the aorta and inferior vena cava.

At the same time, the inferior mesenteric artery, starting from the point of origin from the aorta and for up to 5-6 *cm*, was within the complex of tumor mass and was difficult to differentiate. The mass intensively accumulated the contrast material, and even in the delayed phase of the examination, after 10 minutes, the contrast was not discarded. When additional specific tests were performed for the detection of catecholamine derivatives in 24-hour urine, an acute increase in the level of normetanephrine was determined – 19.230 *nmol*/24 *h* (upper reference limit): <1900 *nmol*/24 *h*) with normal levels of metanephrine. A clinical preoperative diagnosis was made: pheochromocytoma, paraganglioma of the organ of Zuckerkandl.

Drug Treatment (Preparation for Surgery): Doxazosin (2 *mg/day* - 7 days, 4 *mg/day* - 7 days) was prescribed in combination with amlodipine 5 *mg/day* as a preoperative preparation drug in our case according to international clinical guidelines [*Jacques W. M. Lenders et al, 2014*]. In parallel with the achievement of normalization of blood pressure, infusion therapy and general preoperative measures were prescribed to the patient.

Surgical Treatment: Two weeks after the patient was admitted, the tumor was removed through the median laparotomy access. Intraoperatively, a pronounced fusion of the tumor with the trunks of aorta and inferior vena cava was noted, which continued on the right common iliac artery. The inferior mesenteric artery was difficult to differentiate from the tumor process complex, starting from the site of its origin from the aorta and up to 5-6 *cm* (Fig. 2A, 2B). No intraoperative complications were noted. The maximum increase in systolic blood pressure prior to tumor removal reached 280 *mmHg* and the minimal fall after paraganglioma removal reached 60 *mmHg*, which was easily managed by IV infusions. Total intraoperative blood loss was 250 *mL*.

The diagnosis of paraganglioma was confirmed by pathomorphological examination (***Fig. 3A, 3B; Fig. 4A, 4B***). The course of postoperative period was uneventful, without complications. It is noteworthy that starting from the second day after the

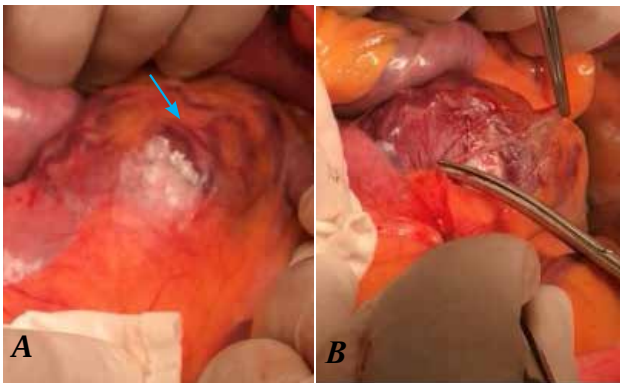

Figure 2 *Intraoperative view of tumor before and after dissection of the visceral peritoneum. A bulging formation with dense consistency and rough surface is determined (noted with arrow), after retracting the loops of the small intestine (**A**). After dissection of the layers of the visceral peritoneum, an expressive initiation of the vessels and hypervascularization of the formation are determined, which separates the abdominal aorta and the vena cava inferior to the sides. Located at the level of the inferior mesenteric artery, which comes from the aorta (**B**).*

Figure 3. *Removed tumor from different aspects. There are two rounded fragments of the neoformation, measuring 9x7.5x4.5cm (longitudinal aspect) (A), 3x2.5x1cm (transverse aspect) (B), with dense consistency and gray-yellow color on the cur. There are also areas of mucus*

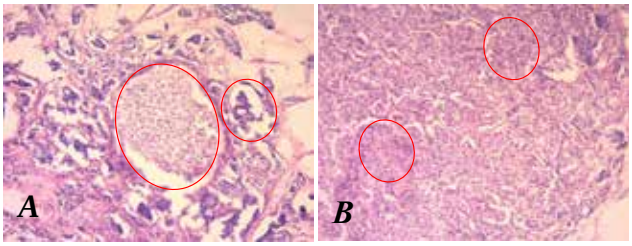

Figure 4. *Morphological structure of the tumor. The organoid structure of the neoformationis under the microscope, which reproduces the structure of the parasympathetic paraganglion. There are nests of cells similar to epithelioid ones, which are surrounded by thin stromal septums (noted with circles) (A) made of reticulin fibers and a large number of capillaries, in some places from papillary structures (mixed type of structure). The nuclei are polymorphic and atypical; in some places there are symplasts and giant cells. However, figures of miosis is very rare. In a smaller fragment, tumor growth is detected in one of the edges.(hematoxylin-eosin 20) (B)*

surgery and in the following months, blood pressure did not rise above 120/80, and blood glucose levels returned to normal on their own and did not exceed 5 *mmol/L*. At the same time, the patient did not receive any antihypertensive drugs, and the injections and oral administration of insulin drugs were discontinued.

DISCUSSION

In recent clinical studies, approximately 80-85% of chromaffin-cell tumors have been reported to be pheochromocytomas, of which 15-20% are paragangliomas [*Chen H et al, 2010*]. At the same time, the prevalence of pheochromocytomas and paragangliomas in the general population ranges from 0.005% to 0.1%, and the prevalence of pheochromocytomas and paragangliomas in adult patients with hypertension in outpatient clinics ranges from 0.1% to 0.2% [*Mittendorf EA et al, 2007; Holland J, Chandurkar V, 2014*]. Development of pheochromocytomas and paragangliomas is most commonly observed in individuals aged 40-50 years, with a slight predominance in females (55.2%) than in males (44.8%) [*Adas M et al, 2016*]. The diagnosis of PCC and PGL can be missed during life, and in 0.05–0.1% of patients, only autopsy studies show undiagnosed tumors [*Platts JK et al, 1995; Lo CY et al, 2000; McNeil AR et al, 2000*]. In almost 5% of patients with incidentally identified adrenal masses, anatomic images show a pheochromocytoma [*Mansmann G et al, 2004*].

In 2004, the World Health Organization determined that the primary source of pheochromocytomas and various paragangliomas is neuroectoderm, and they are found in patients with the same genetic predisposition [*Pacak K et al, 2001a*]. Up to 25% of pheochromocytomas and paragangliomas have been found to be hereditary [*Goldman L, Schafer AI, 2012*]. According to Bryant J. et al., various genetic syndromes transmitted in an autosomal dominant manner may be associated with an increased risk of developing pheochromocytomas and paragangliomas [*Bryant J et al, 2003*]. At the same time, up to 41% of patients with pheochromocytomas and paragangliomas have mutations in certain genes (Neurofibromatosis type 1, Von Hippel-Lindau, succinate dehydrogenase complex iron sulfur subunit B, succinate dehydrogenase complex subunit D, succinate dehydrogenase complex subunit C) [*Fishbein L et al, 2013; Rao D et al, 2017*].

It should be noted that pheochromocytomas and paragangliomas are malignant and metastasis may be observed even 20 years after removal of the primary tumor [*Ayala-Ramirez M et al, 2011; Fishbein L et al, 2013; Rao D et al, 2017*].

According to the data obtained in PCC, excessive production of adrenaline and noradrenaline is observed, while in PGL, noradrenaline is predominantly formed, and in very rare cases dopamine hyperproduction is also possible [*Tank AW, Lee WD, 2015*]. At the same time, catecholamines formed in excess are distributed throughout the body, affecting effector organs and tissues, leading to a variety of biological responses and clinical manifestations. Thus, activation of postsynaptic α_1-receptors and α_2-receptors leads to vasoconstriction and, as a result, to hypertension. When stimulating β_1-adrenoceptors predominantly localized in the heart, positive inotropic and chronotropic effects develop [*Fang F et al, 2020*].

Data have been obtained on impaired glucose tolerance, development of diabetic ketoacidosis and hyperglycemic crisis in patients with pheochromocytoma and paraganglioma [*Hope DC, Palan JM, 2016; Mirica RM et al, 2016*] the cause is stimulation of β_2-receptors with excessive uncontrolled amounts of catecholamines, resulting in activation of gluconeogenesis and glycogenolysis in the liver, and stimulation of α_2-receptors of pancreatic β-cells, leading to decreased insulin secretion [*Komanda H, 2017*]. At the same time, stimulation of β_2-receptors and $\alpha_1$receptors of pancreatic α-cells is observed, resulting in increased glucagon secretion [*Vieira E, 2004*]. In addition, there is evidence that catecholamines cause the development of insulin resistance due to desensitization of β adrenoreceptors [*Paolo S et al, 1989; La Batide-Alanore A et al, 2003*].

The main symptoms of pheochromocytomas and paragangliomas are related to excess production and secretion of catecholamines, with which such clinical symptoms (in 95% of patients) as paroxysmal hypertension are associated. The classical clinical triad of symptoms is headache, tachycardia, and profuse sweating, is observed in about 25% of patients, and less than half of patients have only one of these symptoms [*Calhoun DA et al, 2008; Guérin M et al, 2010; Pogorzelski R et al, 2014*]. Less commonly, orthostatic hypotension,

pale skin, tremor, weakness, nausea, weight loss, constipation, anxiety, up to the development of panic attacks are observed [*Chen H et al, 2010*]. In addition, as already noted, impaired glucose intolerance with the development of diabetic ketoacidosis and hyperglycemic crises in patients with PCC and PGL are also observed [*Hope DC, Palan JM, 2016; Mirica RM et al, 2016*].

Currently, the diagnosis is established based on the findings of ultrasonography, computed tomography, magnetic resonance imaging, and determination of increased plasma and 24-hour urine concentrations of fractionated metanephrines [*Leung K et al, 2013; Lenders JW et al, 2014; Megias MC et al, 2016*].

Pheochromocytoma and paraganglioma treatment is divided into medicinal, surgical, and auxiliary tumor treatments. Preoperative patient preparation is a prerequisite for PCC and PGL treatment because surgical intervention without preoperative preparation may lead to the development of hypertensive crises, arrhythmias, strokes, and death. Removal of pheochromocytomas and paragangliomas surgically is the main method for treatment of this disease. The most common and main clinical manifestation of pheochromocytoma and paraganglioma is the sudden onset of hypertensive crisis with tachycardia, blanching of skin and mucous membranes. One of the leading syndromes in PCC and PGL is a decrease in circulating blood volume with a high concentration of catecholamines in the blood plasma. Therefore, preoperative blood pressure correction and increased circulating blood volume are essential to prevent the development of complications during surgery [*Li J, Yang CH, 2014*]. Risks occurring during surgery should be minimized by preoperative patient preparation at least 10-14 days prior to surgery [*Pacak K, 2007*]. The primary goal of preoperative patient preparation should be to normalize blood pressure and heart rate, restore circulating blood volume, improve metabolic status, and prevent the patient from developing catecholamine storm and hemodynamic instability during surgery [*Pacak K et al, 2007*].

Preoperative blockade of α-receptors significantly reduces the risk of surgical complications and, therefore, α-blockers are drugs of the first choice. On the other hand, the use of α-blockers with calcium channel blockers during the preoperative period prevents hemodynamic instability during PCC and PGL removal surgery [*Brunaud L et al, 2014*]. The nonselective α-blocker, phenoxybenzamine, is most commonly used as a blood pressure α-blocker for preoperative control [*Liu C et al, 2017*]. As an alternative to phenoxybenzamine, selective competitive α_1-blockers such as terazosin, prazosin, and doxazosin, which have a shorter half-life and correspondingly lower risk of postoperative hypotension, may be used for preoperative blockade of catecholamine-induced vasoconstriction [*Chen H, 2010; Li J, Yang CH, 2014; Challis BG et al, 2017*].

β-blockers can be used to preoperatively control reflex tachycardia, various arrhythmias, and angina. However, the lack of vasodilatory activity of β-blockers against the background of catecholamine-induced vasoconstriction may lead to a dangerous increase in blood pressure [*Farrugia FA, 2019*]. Therefore, β-blockers are only used after prior use of α-blockers [*Farrugia FA et al, 2017*].

Calcium channel blockers are the most commonly used drugs combined with α-blockers in patients with pheochromocytoma and paraganglioma. Compared with α-blockers, calcium channel blockers do not cause orthostatic hypotension and reflex tachycardia [*Pacak K, 2007; Lenders JW et al, 2014*].

Decrease in circulating blood volume associated with vasoconstriction is a common symptom of PCC and thus an increase in circulating blood volume achieved by saline infusion is also recommended to reduce the risk of postoperative hypotension. Keeping a high-salt diet (for example 5000 *mg* daily) is also recommended [*Chen H et al, 2010; Lentschener C et al, 2011; Neumann H, Young WJ, 2019*].

Hypoglycemia after pheochromocytoma removal is a rare and poorly understood complication, it is possibly due to hyperinsulinemia and increased peripheral glucose uptake [*Chen Y et a, 2014*].

Metastases of these tumors have been observed in 15-17% of cases [*Ayala-Ramirez M et al, 2011*]. PGLs have a higher risk for malignancy than PCCs. Regular imaging, recurrence of symptoms, or positive biochemical results may detect the presence of metastases and confirm malignancy. Recurrence of PCC and PGL after removal is observed in 6.5-16.5% of patients and is more difficult to treat due to delayed diagnosis and metastasis [*Ellis RJ et al, 2013; Press D et al, 2014*]. That is why early diag-

nosis of relapse is very important. It was determined that if the tumor size is greater than > 5*cm*, regular monitoring of the patient's condition with neoplasm imaging and determination of 24-hour urinary plasma metanephrine and normetanephrine concentrations was recommended to avoid recurrence of the disease with fatal outcome [*Press D et al, 2014*]. Press et al. (2014) recommends postoperative followup of patients during the first month after surgery to remove PCC and PGL, then after 6 months, then after 1 year, and then annual tumor imaging is recommended. In addition, laboratory data should also be reviewed annually.

Many factors affect mortality rate, relapse development, and prognosis in patients diagnosed with pheochromocytoma and paraganglioma. Thus, the succinate dehydrogenase complex iron sulfur subunit B mutation, infiltrative tumor growth, incomplete removal, metastasis, etc. significantly increase the risk of relapse development and mortality of this disease [*Pacak K, 2007; Pacak K et al, 2007*]. Distant metastases are commonly observed, in about 5 to 13% of PCC cases and in 2 to 23% of PGL cases [*Pacak K, Wimalawansa SJ, 2015*]. Metastases typically involve local lymph nodes, bones (50%), liver (50%), and lungs (30%) [*Chrisoulidou A, 2007*].

Various methods are used to treat pheochromocytoma and paraganglioma complications, such as: radiofrequency ablation is an alternative, relatively safe, predictable and effective method for the treatment of pheochromocytoma and paraganglioma complications by local destruction of the tumor and its metastases [*Pacak K, 2001a*]; the use of radioactive agents – ^{131}I-metaiodobenzylguanidine is the most widely used and well-tolerated treatment for the metastasis of pheochromocytoma and paraganglioma at present, although at high doses may cause myelotoxic effects [*Pryma DA et al, 2019*]; chemotherapy with cyclophosphamide, vincristine and dacarbazine is used to control tumor growth in the metastatic pheochromocytoma and paraganglioma [*Niemeijer ND et al, 2014*].

Conclusions

Thus, pheochromocytomas and paragangliomas of the organ of Zuckerkandl are a rare pathology, with the classic symptomatic triad of tachycardia, headache, and profuse sweating, but many other symptoms may also be present.

To confirm the diagnosis of pheochromocytoma and paraganglioma, increased plasma concentrations of metanephrines and increased fractionated metanephrines in 24-hour urine are determined. A computed tomography is the most reliable diagnostic test method, and magnetic resonance imaging may be done.

To avoid intra- and postoperative complications, 1-14 days prior to surgery, patients should be given appropriate α-blockers, calcium channel blockers, and β-blockers that are alternative or auxiliary treatment; which ensure increased circulating blood volume achieved by saline infusion, which is recommended to reduce the follow-up should be performed with assessment of laboratory data during the first month after surgery, then after 6 months, after a year, annual tumor imaging is also required. Although surgical risk of postoperative hypotension.

Postoperative treatment is the main most effective treatment, it is necessary to identify and take measures to combat metastases in time.

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