MANAGEMENT AND TREATMENT OF A PATIENT WITH A HORMONALLY ACTIVE ADRENAL TUMOR

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In spite of all existing achievements, modern endocrinology comes across a rather complex issue such as treatment of patients with catecholamine secreting tumors. True prevalence of pheochromocytoma is not known, as data obtained during the research depend on criteria of patients' selection and can vary significantly. The tumors have numerous pathophysiological mechanisms of disease development due to a wide variability of symptoms and complex diagnostics. Meanwhile, timely diagnosis produces a direct effect on prognosis and quality of life. Catecholamine secreting tumors are commonly not detected. In such cases, there is a high risk of severe cardiovascular complications up to a lethal outcome. Complex diagnostics of this pathology also means that the tumors can have adrenal and extraadrenal localization and that the disease is hereditary. This makes diagnostics and treatment of pheochromocytoma even more complex. Timely detection of concomitant tumor and hormonal manifestations belongs to an important factor of management of patients with genetically determined pheochromocytomas. Thus, examination of pheochromocytoma is a pressing issue of modern endocrinology.

Keywords: pheochromocytoma, arterial hypertension, metanephrines and normetanephrines

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НАБЛЮДЕНИЕ И ЛЕЧЕНИЕ ПАЦИЕНТКИ С ГОРМОНАЛЬНО-АКТИВНОЙ ОПУХОЛЬЮ НАДПОЧЕЧНИКА

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Современная эндокринология, не смотря на все существующие достижения, сталкивается с довольно сложной проблемой — это лечение пациентов с опухолями, секретирующими катехоламины. Истинная распространенность феохромоцитомы неизвестна, так как данные, полученные в исследованиях, зависят от критериев подбора пациентов и могут значительно различаться. Данные опухоли характеризуются многообразием патофизиологических механизмов развития заболевания, что обусловливает широкую вариабельность симптоматики и сложности в диагностике. При этом своевременный диагноз непосредственно влияет на прогноз и качество жизни пациентов. Нередко опухоли, секретирующие катехоламины, остаются не выявленными, в таких случаях очень высок риск тяжелых сердечно-сосудистых осложнений вплоть до смертельного исхода. Сложность диагностики данного вида патологии заключается также и в том, что данные опухоли могут иметь надпочечниковую и вненадпочечниковую локализацию, а также наследственный характер заболевания, что еще больше добавляет сложностей в диагностике и лечении феохромоцитомы. Своевременное выявление сопутствующих опухолевых и гормональных проявлений является важным фактором в ведении пациентов с генетически-детерминированными феохромоцитомами. В связи со всем вышеперечисленным изучение феохромоцитомы является актуальной проблемой современной эндокринологии.

Ключевые слова: феохромоцитома, артериальная гипертензия, метанефрины и норметанефрины

Вклад авторов: А. Н. Жилина — ведение пациентки до оперативного лечения, написание данной статьи, суммирование всех данных лабораторной и инструментальной диагностики на дооперационном и послеоперационном этапах, Ю. Е. Мельникова — МРТ диагностика с контрастированием феохромоцитомы, Е. А. Воронина — расшифровка генетических исследований, А. В. Мартышова — литературный обзор современных сведений и рекомендаций по ведению пациентов с данной патологией.

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Pheochromocytoma is a tumor of the adrenal medulla composed of chromaffin cells that produce catecholamines (adrenalin, noradrenalin and dopamine). For the first time, it was mentioned in 1886 by Frankel, a German pathologist. He found it on autopsy in two adrenal glands of an 18-year-old woman who suddenly died from collapse. A variety of pathophysiological mechanisms of this disease caused by tumor produced hormones explains a wide variability of symptoms and difficulties in diagnostics.

Timely set diagnosis produces a direct effect on prognosis and quality of life [1]. Incidence of pheochromocytoma among patients with hypertension is 0.2–0.6%. Hereditary mutation is a reason for pheochromocytoma in at least one third of patients [2]. It is known that in the majority of cases pheochromocytoma produces large amounts of catecholamines, whereas a lack of therapy can result in cardiovascular diseases and cerebral catastrophes, even fatal [3]. An increasing tumor can lead to compression syndrome [4]. Detection of pheochromocytoma as part of hereditary syndromes can be the reason for timely diagnostics and treatment of other members of proband family. Incidence of malignant pheochromocytoma is 10–17%. Its malignancy can be determined not just using

standard morphological and immunohistochemical criteria, but also by presence of metastases in non-chromaffin tissue. Pheochromocytoma is malignant in over 40% of observations in case of mutations in a gene that encodes succinate dehydrogenase complex subunit B (SDH-B) [5].

CLINICAL CASE

Patient K, 38 y. o., went to see an endocrinologist at the Lokomotiv Center for Sports Medicine on December 15, 20. She complained of crisis increase of BP to 220 mm Hg (systolic) accompanied by a fear of death, tachycardia up to 120 beats per minute, tremor in the body, pulsating headache in the occipital area, tingling and burning sensation in the fingers, sudden reddening of the face prior to an increase in BP. The increase in BP was noted at least 4–5 times a day. Such an increase was stopped in approximately 30 minutes after taking 40 mg of propranolol. The decrease in BP was accompanied by involuntary release of a large amount of light urine, cold sticky sweat, and pressing sensation behind the sternum without irradiation.

Anamnesis morbi: first complaints of increased BP to 220 mm Hg occurred in January 2020. They were developed due to emotional overload, leaving a room and going to the cold air and physical loads (skiing). The patient referred to a cardiologist numerous times and was diagnosed with stage 3, grade 2, risk 3 hypertension, antihypertensive therapy with various combinations of medicinal agents (bisoprolol 10 mg + perindopril 10 mg + moxonidine 0.6 mg; bisoprolol 10 mg + azilsartan + chlorthalidone; amlodopine 10 mg + bisoprolol 10 mg + hypothiazid 25 mg) was provided. None of the provided antihypertensive treatment option failed to prevent hypertensive crisis. In April 2020, the patient was recommended to refer to an endocrinologist. Due to a complex epidemiological situation associated with COVID pandemics and unavailable planned aid of narrow specialists, the patient managed to consult an endocrinologist only in December 2020. Until that time, she used previously suggested antihypertensive agents without a positive effect trying to stop hypertensive crises with propranolol. However, the abovementioned attacks were observed even more frequently, and the patient's well-being worsened.

Anamnesis vitae: concomitant diseases: 1 grade obesity; 2B dyslipidemia, disturbed tolerance to carbohydrates, chronic calculous cholecystitis, non-acute, varicose disease, reticular form, chronic atrophic gastroduodenitis, non-acute. Infectious hepatitis, sexually transmitted diseases, tuberculosis, allergic reactions are denied. No hemotransfusions. Bad habits are absent. Positive family history as far as hypertension goes (mother and father), nodular goiter. 2 pregnancies, 2 labors. The menstrual cycle is not disturbed.

Status praesens: height = 165 cm, weight = 86 kg, BMI = 31.6 kg/m^2. Upon referral, the general condition is relatively satisfactory. Hyperemic and edematous face. Skin with increased moisture. No skin eruptions. The peripheral lymph nodes are not enlarged.

Respiratory system: free nasal breathing, respiratory rate 16 beats per minute. Vesicular respiration, no rales.

Cardiovascular system: the cardiac area is not changed. Limits of relative dullness of the heart are expanded to the left, +2.0 cm outwards from the left midclavicular line. Clear and regular heart tones, no cardiac sounds, heart rate is 110 beats per minute, BP at examination is 150/100 mm Hg for the left hand, and 145/100 mm Hg for the right hand. Preserved pulsation on the peripheral vessels.

Digestive system: moist and clean tongue. Treated teeth. The abdomen is soft and painless upon palpation, involved in respiration. The liver and spleen are not enlarged. Constipation.

Urinary system: the renal area is not visually changed. Negative bilateral Pasternatsky's symptom. Free and painless urination. Involuntary flow of a large amount of light urine following hypertensive crisis.

Additional testing methods were used:

ECG as of December 15, 20 — sinus rhythm with heart rate of 102 beats per minute, diffuse changes in the myocardium, signs of decreased coronary blood flow in inferior and lateral sections.

Endocrinologist recommended to test total metanephrines and normetanephrines in daily amount of urine. Total — free and associated metanephrines and normetanephrines — intermediate products of adrenaline and noradrenaline metabolism. The test is used to diagnose and monitor adrenal tumors (pheochomocytoma) and nervous tissue (neuroblastoma, ganglioneuroma).

Unlike other products of catecholamine metabolism, antihypertensive drugs produce no effect on normetanephrines. However, for a proper analysis it is necessary to exclude serotonin-containing products such as bananas, chocolate, cheese, strong tea, coffee, alcohol. Physical exertion, stress, smoking, painful impact should be avoided three days prior to the suggested collection of urine for analysis. Regular drinking regimen is recommended during urine collection. Metanephrines are continuously produced in tumor cells and are not associated with release of catecholamine active fractions. Thus, urine metanephrine test is done irrespective of episodes of increased blood pressure. Intra-tumor process of catecholamine methylation occurs on a constant basis and does not depend on time when active catecholamines were released into the bloodstream. Determination of metanephrine and normetanephrine is a golden standard in diagnostics of pheochromocytoma. The method sensitivity is 99%. Specificity is 85–89%. Negative testing result is enough to exclude pheochromocytoma [6].

Metanephrine = 890 mg/day (less than 320.0), **nor-metanephrine** = 560 (less than 390) as of December 25, 20.

Creatinine as of December 25, 20 is 89.0 mcmol/l, ion selective analysis of electrolytes (**potassium** = 4.29 mmol/l, **ionized calcium** = 1.21 mmol/l, **sodium** = 133.0 mmol/l, chlorides = 102.3 mmol/l). Clinical blood analysis as of December 25, 20, **Hb** = 117 g/l, **WBC** = 11.75 *10^9/l, **PLT** 341*10^9/l, **RBC** = 4.09*10^{12}/l. Acid-alkali balance as of December 25, 20 **ABE**, mmol/l = 0.6, **GGLU** = 5.1, **cHCO3(P)** = 23.5, **cLac** = 0.7, **ctHBg\l** = 122, **mOsm, mmol\kg** = 270.2, **pCO2, mmHg** = 37.1, **ph** = 7.412, **pO2, mmHg** = 40.8, **sO2%** = 74.9, **time** = 16:32, **HCT** = 37.4.

Blood glucose = 7.5 mmol/l, **glycohemoglobin** = 6.0% (increased blood glucose is associated with pathophysiological effect of 'secondary' diabetes or disturbed tolerance to glucose due to intense glycogenolysis in the liver, decreased production of insulin due to stimulation of alpha-adrenoreceptors in the pancreas) [3].

Computed tomography of the abdominal organs with i/v bolus contrast enhancement as of December 28, 20. Conclusion: the testing was done in the multispiral regimen in accordance with the standard program with i/v bolus image enhancement. On a series of multispiral computed sectional images, the liver is of a regular shape, size, position with no foci of abnormal density and abnormal accumulation of contrast. Intrahepatic bile ducts and bile ducts are not enlarged. The gall bladder is not enlarged in size and contains no radiopaque stones. The pancreas is not located normally, has a multilobular

structure, the Wirsung's duct is not visualized. No focal changes and abnormal lesions are found in the glandular tissues. Parapancreatic cellular tissue is not changed. The spleen is not enlarged in size; it has regular outlines, and homogenous density with no focal changes. Kidneys are located as usual. Parenchyma has no foci of abnormal density. Renal collecting system is not enlarged. Renal vascular pedicles are structural. Paranephral cellular tissue is not changed. Adrenal glands are located as usual. The right adrenal gland is not changed. A round lesion with distinct and regular outlines sized 4.0*3.9*4.5 cm with +30 HU density is visualized in the left adrenal gland, in the body and medial limb.

Following administration of contrast, regular accumulation occurs: +88 HU during phase I, + 65 HU during phase II and + 50 HU in 10 minutes. The left renal vein goes along the inferior pole of the lesion. No free fluid is found in the abdominal cavity. The lymph nodes in the abdominal cavity and retroperitoneal space are not enlarged. No destructive bone changes are found in the scanning area. Conclusion: CT signs of abnormal lesion in the left adrenal gland.

Chest X-ray as of December 25, 20: on a survey radiograph, the lungs are expanded and have no focal and infiltrative changes. Pulmonary roots are not enlarged. The dome of the diaphragm is located normally. The shadow of the heart and vessels is not enlarged. Free sinuses.

The clinical diagnosis was made.

Principal diagnosis: pheochromocytoma of the left adrenal gland, mixed type (ICD-10: E27.5. Hyperfunction of the adrenal medulla).

Complications: Grade III symptomatic arterial hypertension. Symptomatic hyperglycemia.

Treatment: doxazosin has been given since December 28, 20 to conduct stabilizing preoperative preparation. Doxazosin is a selective prolonged α1-adrenoblocker for peroral use that produces an effect on the entire specter of α1-adrenoreceptors of resistance vessels. Half-life is 22 h. The effective dose is achieved in 2–3 h. The patient is given 4 mg doxazosin BID with up-titration to 20 mg once every 3 days with blood pressure control. In case of tachycardia, the patient was recommended to take bisoprolol in the initial dose of 2.5 mg OD in the morning under control of pulse. It was recommended to take bisoprolol after achievement of a stable α-blocking effect. In failure to comply with this condition, paradoxical worsening of hypertensive crises due to leveling of β2 dilatating effect of adrenaline is not excluded. The same was observed in the patient as a decreased severity of condition, duration and frequency of hypertensive crisis while taking antihypertensive agents recommended by a cardiologist prior to diagnosis.

No postural hypertension is found following intake of doxazosin and bisoprolol. Postural hypotension can develop during postoperative preparation using the abovementioned agents. Postural hypotension is considered by some doctors as a signal to withdrawal or decrease of a dose of α-blockers which is a typical mistake. In fact, occurrence of postural hypotension is associated with initial and pathogenetically explained deficiency of circulating fluid but not with the direct effect of the agents. Thus, upon occurrence of postural hypertension, the dose of α-blockers should not be reduced and drugs belonging to this groups should not be withdrawn [6]. The most severe patients include those with stable hypotension or tendency hereto between the attacks. In them, α-adrenoblockers belong to a means of choice, that allows to avoid the 'uncontrolled hemodynamics' and catecholamine shock [7]. Complete disappearance of hypertensive crises, BP stabilization and lack of tachycardia occurred in the patient by January 20, 21.

Based on ECG as of January 19, 21, the rhythm was sinus, with heart rate of 80 beats per minute and diffuse changes in the myocardium.

Acid-base balance (ABB) as of January 19, 21 **ABE**, mmol/l = 0.5, **GGLU** = 2.0, **cHCO3(P)** = 24.7, **cLac** = 0.6, **ctHBg\l** = 122, **mOsm, mmol\kg** = 267.1, **pCO2, mmHg** = 46.7, **ph** = 7.36, **pO2, mmHg** = 52.6, **sO2%** = 86, **time** = 6:10, **HCT** = 37,6, **potassium** = 3.1 mmol/l, ionized **calcium** = 1.18 mmol/l, **sodium** = 134.3 mmol/l, chlorides = **99.7** mmol/l). Clinical blood analysis as of January 19, 21 **Hb** = 122 g/l, **WBC** = 8.3 $*10^9$/l, **PLT** = $300*10^9$/l, **RBC** = $4.05*10^{12}$/l. Blood sugar = 6.8 mmol/l.

Criteria for surgical intervention in pheochromocytoma:

- decrease (disappearance) of hypertensive crises;
- stopping the hypovolemic syndrome (clinically and based on the results of preoperative measurement of the central venous pressure);
- avoiding rhythm disturbances;
- correction of metabolic disturbances.

Typical mistakes in preoperative practice:

- withdrawal or decrease of the dose of α-adrenergic blocking agents in postural hypotension and tachycardia during the initial period of medicinal agent intake;
- presence of initial hypotension is estimated as a contraindication to administration of α-adrenergic blocking agents;
- attempt to compensate hypovolemia and hypotension with fluid infusion or administration of pressor agents with no use of α-adrenergic blocking agents;
- attempt to compensate tachycardia with administration of β-adrenergic blocking agents with no previous use of α -blocking agents.

On January 20, 21, the patient had retroperitoneoscopic adrenalectomy on the left under combined anesthesia with ALV. Dermabond cyanoacrylate cement was applied. Postoperative period without abnormalities. Postoperative wound healed by primary intention. Results of a histological study (autopsy study of surgical specimen with tumor): pheochromocytoma of the left adrenal gland (4.5 cm in diameter) with focal vascular invasion and without signs of capsular invasion. The patient was recommended to limit physical load during 6–8 weeks after the conducted surgery with subsequent administration of Cortef (2 tablets in the morning, 1.5 tablets in the afternoon, 1 tablet at 8 p. m.). In a month, the dose of Cortef was gradually reduced with subsequent complete withdrawal of the medicine three months after prescription. When the dose of Cortef was gradually decreased, the patient had episodes of BP drop twice accompanied by a sharp general weakness, nausea, which slowed down the rate of lowering the dose of Cortef.

Since complete withdrawal of Cortef, the patient had an examination: since April 25, 21, ACTH was 28 pg/ml (10–185), urine cortisol test was 8.3 mcg/day (4.3–176), blood cortisol was 5.9 (3.7–19.4) mcg/dl. The patient underwent genetic testing for RET, VHL, SDHB, SDHD mutations.

Result of molecular and genetic testing as of July 09, 21 Target sequence analysis (Hereditary tumor syndromes panel) was performed. Examined genes: APC, ATM, ATR, BAP1, BARD1, BLM, BLPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDKN2A, CHEK2, EPCAM, FANCM, FH, FLCN, GNAS, GREM1, MAX, MEN1, MLH1, MRE11, MSH2, MSH3, MSH6, MUTYH, NBN, NF1, NF2, NTHL1, PALB2, PMS1, PMS2, POLD1, POLE, PRKAR1A, PTCH1, PTEN, RADSD, RADS1, RADS1C, RADS1D, RB1, RET, SDHA, SDHAF2, SDHB, SDHC, SDHD, SLX4, SMAD4, SMARCA4, SMARCB1, STK11, SUFU, TMEM127, TPS3, TSC1, TSC2, VHL, WRN. Conclusion: pathogenic/probably pathogenic gene variants associated with hereditary tumor syndromes are not detected.

DISCUSSION

According to retrospective and prospective genetic research done on large samples of patients with chromaffin tumors, almost 30% of patients have autosomal dominant genetic defects. In 32–38% of observations, mutations of genes associated with synthesis of succinate dehydrogenase, D-or B-subunit (SDHD or SDHB) are developed [5]. The disease occurs due to numerous functioning paragangliomas that have highly malignant potential. In these patients, phenotypic penetrance of pheochromocytome is 15–40%. Bilateral damage of adrenal glands is observed in 40% of cases, whereas extra-adrenal lesion is found in 70% [3]. In presence of this genetic defect, paragangliomas have mainly noradrenal type of secretion. Genetic testing was recommended as based on numerous genetic research on large samples of patients with chromaffin tumors it has been found out that 25–35% of patients with pheochromocytoma have genetic defects transmitted in an autosomal dominant type and responsible for the disease [7].

Thus, in 32–38% of observations, pheochromocytoma can occur in SDH syndrome or syndrome of functioning paraganglioma (SDH-B (1p35–36) or SDH-D (11q23) mutations along with A and C subunits). Pheochromocytoma is a sign of Von Hippel-Lindau disease (VHL-gene 3 chromosome mutation) in 30–35% of cases, type 2A multiple endocrine neoplasia or Sipple syndrome (mutation of the RET proto-oncogene of 10 chromosome in exon 10–16), type 2B multiple endocrine neoplasia or Gorlin syndrome (mutation of the RET proto-oncogene of 10 chromosome in codon 883 or 918 of exon 11) in 4–6% of cases, and 1 type neurofibromatosis or von Recklinghausen disease (mutation of NF-1 gene (17q11)) in 8–14% of cases [5].

One year following the surgery, the patient underwent follow-up examination and investigation.

January 20, 22. No complaints. Height =165 cm, weight = 92 kg, BMI = 34.07 kg/m^2.

Respiratory system: free nasal breathing, heart rate = 15 minutes per minutes, vesicular respiration, no rales.

Cardiovascular system: the cardiac area is not changed. The boundaries of the relative dullness of the heart are expanded to the left, +2.0 cm outwards from the left midclavicular line. Clear and rhythmic heart tones, no cardiac murmur, heart rate 80 beats per minute, BP upon examination 120/80 mm Hg (left hand), and 115/70 mm Hg (right hand). Peripheral pulsation is preserved.

ECG as of January 20, 22 –sinus rhythm with heart rate of 76 beats per minute, diffuse changes in the myocardium.

Metanephrine = 210 mg/day (less than 320.0), **nor-metanephrine** = 300 (less than 390) as of January 24, 22.

ACTH as of January 21, 22 ACTH = 38 pg/ml (10–185), urine cortisol test in a 24-hour sample of urine was 9.6 mcg/day (4.3–176), blood cortisol = 5.4 (3.7–19.4) mcg/dl.

MRI of kidneys and adrenal glands with contrast enhancement as of January 23, 22. Right kidney 95*45*43 mm, left kidney 96*48*45 mm. Clear and distinct outlines. Well-differentiated cortical and medullary substance. No changes in the vascular pedicles. No changes in the paranephral cellular tissue. Distinct and regular outlines of the right adrenal gland, the adrenal gland is of a regular triangular shape, sized 3.49*2.8 cm. The pedicular depth is 3.3 mm, homogenous structure of the adrenal gland. Condition following removal of pheochromocytoma of the left adrenal gland. No additional mass lesions are found in the removed adrenal bed. The lymph nodes are not enlarged. Free fluid in the abdomen is not visualized. Conclusion: condition following removal of the left adrenal gland due to pheochromocytoma in 2021. No MRI data of the recurrence.

CONCLUSION

A specific feature of the presented clinical case is that pheochromocytoma has not been diagnosed long-term. The patient diagnosed with hypertension has been examined by a cardiologist for a long period of time. It should be noted that the patient had a very high initial level of metanephrine and normetaneprine with a large tumor sized 4.0*3.9*4.5 cm and relative effectiveness of used medicines. It was difficult to take a decision under conditions of comorbid pathology bearing both endocrinological and surgical issues. Modern surgical correction that produced an indirect effect on prognosis and quality of life of the patient is important in this clinical case.

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