DOI: 10.20514/2226-6704-2019-9-4-316-322 UDC 616.452-006.488-06:616.12-008.331.1

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CASE OF PHEOCHROMOCYTOMA WITH PERMANENT HYPERTENSION

Abstract

Pheochromocytoma is a tumor of chromaffin tissue that produces a large amount of biologically active substances (adrenaline, noradrenaline, dopamine), clinically manifested by hypertension and various metabolic disorders. Quite often the diagnosis is made only after autopsy. One of the reasons for late diagnosis is a great number of different clinical masks of the disease. Usually pheochromocytoma is suspected in patients with paroxysmal hypertension. We present a 37-year-old pregnant female (week 8 of pregnancy) with pheochromocytoma and permanent hypertension and sustained elevation of blood pressure up to 220/150 mm Hg. Her only complaint was vision disorder that started 3 months ago. Also, she noted a weight loss of 4 kg over the last 6 months. Retinopathy, left ventricle hypertrophy, tumor of right adrenal gland and glucose level disorders were revealed. Pregnancy was terminated for medical reasons. The patient took combination of doxazosin 0.4 mg, metoprolol 100 mg and moxonidin 0.4 mg per day and blood pressure was normalized to 130/90 mm Hg. Due to hypertension and tumor of right adrenal gland that are accompanied by retinopathy and metabolic disorders, pheochromocytoma was suspected. Contrast-enhanced computed tomography confirmed the tumor (60×73×70 mm) of right adrenal gland. Urinary normetanephrine level was 5.5 times higher than the norm. Magnetic resonance angiography of cerebral vessels was done because of malignant hypertension and family history (the patient's sister had died of cerebral hemorrhage). Fusiform aneurysm of right internal carotid artery was revealed. The patient underwent laparoscopic resection of right adrenal gland. Histologic examination: pronounced cellular and nuclear polymorphism, invasion of tumor cells into a fibrous capsule, which does not exclude the malignant nature of pheochromocytoma. Follow-up period lasted for 8 months and was characterized by normalization of blood pressure, glucose level and weight gain of 3.5 kg. Computed tomography of retroperitoneal space and normal urinary metanephrine tests revealed no recurrent pheochromocytoma.

Key words: *pheochromocytoma, hypertension*

Conflict of interests

The authors declare no conflict of interests

Source of financing

The authors states that no finding for the study has been received

Article received on 03.04.2019

Accepted for publication on 19.06.2019

For citation: Yakovleva E. V., Lobanova O. S., Zhukova E. V. et al. CASE OF PHEOCHROMOCYTOMA WITH PERMANENT HYPERTENSION. The Russian Archives of Internal Medicine. 2019; 9(4): 316-322. [In Russian]. DOI: 10.20514/2226-6704-2019-9-4-316-322

BP — blood pressure, DBP — diastolic blood pressure, SBP — systolic blood pressure, ECG — electrocardiogram

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Pheochromocytoma is a tumor of chromaffin tissue that produces a large amount of biologically active substances (adrenaline, noradrenaline, dopamine), clinically manifested by hypertension of varying severity and various metabolic disorders. The prevalence of pheochromocytoma among patients with hypertension does not exceed 1 %, the peak incidence is in the age of 30–50 years [1, 2]. In one third of patients with chromaffin tumors the cause of the disease is hereditary mutation [1, 5]. The diagnosis of pheochromocytoma is often established post mortem [1, 3]. At the same time, patients with pheochromocytoma belong to the rare category of patients with hypertension, in whom timely diagnosis and provision of effective medical care can contribute to recovery. One of the main reasons for the late diagnosis of chromaffin tumors is the variety of clinical masks of the disease [3]. The combination of symptoms and their severity even in one patient can vary significantly. We followed-up a female patient with pheochromocytoma, who may have had no symptoms of increased BP, but had only bradycardia with ventricular bigeminy or ventricular paroxysmal tachycardia with episodes of ventricular fibrillation or had a developing crisis with vivid manifestations in the form of muscle tremors, profuse sweat, fear of death, feelings of suffocation, nausea and vomiting at the same degree of BP increase [4]. Among the causes of underdiagnosis lack of awareness of doctors about the various manifestations of the disease should be noted. In clinical practice, a targeted search for pheochromocytoma is carried out mainly in the presence of paroxysmal hypertension. However, in chromaffin tumors, a course with permanent hypertension is possible [3]. The idea of the possibility of low-symptomatic adrenal tumors has expanded in recent decades, due to the active introduction of imaging techniques into practice. According to the latest data, in 4–5 % of patients exposed to radiological imaging adrenal incidentaloma (from the English word «incidental») — a mass formation larger than 1 cm in diameter detected by accident and requiring nosological specification — was revealed [5]. Approximately 5 % of patients with adrenal incidentaloma were diagnosed with pheochromocytoma [2]. With all the improvement and increase in the availability of instrumental methods of examination, the timeliness of the beginning of the diagnostic search for chromaffin tumors when patients turn to primary care doctors remains relevant. In this regard, the clinical case of a female patient with pheochromocytoma with permanent hypertension, identified when visiting a doctor for another reason, is of interest.

Patient K., 37 y.o., visited maternity welfare clinic at gestational age of 8 weeks. During the initial examination, an increase in BP to 220 and 150 mm Hg was reported, which was the reason for hospitalization in Cardiology Department of Saratov Regional Clinical Hospital. When collecting medical history, it was found that the main complaint of the patient was deterioration of vision during the last 3 months. Also, the patient noticed a decrease in body weight by 4 kg for six months, which she did not consider as important. This is the third pregnancy, during the previous two pregnancies at the age of 20 and 28 years BP did not increase. Delivery was performed by caesarean section according to obstetric indications (contracted pelvis). During the annual preventive medical examination (worked as a teacher in kindergarten), the BP level increase was not observed. The last measurement of BP was performed a year ago. Clarification of data on hereditary diseases was difficult, since there is no information about the parents; the patient grew up and was brought up in a foster home from the age of five. It is known that her sister died suddenly at the age of 37 years from a cerebral hemorrhage. She denies the use of alcohol, drugs. She smoked from 29 to 36 years. On examination, the condition was relatively satisfactory. Height 147 cm, weight 50 kg, body mass index 23.14 kg/m^2. The skin is clean, of normal color and moisture. Musculoskeletal system — without pathology. Apex beat is palpated in the 5th intercostal space along the left mid-clavicular line, coincides with the left border of relative cardiac dullness. Heart sounds are rhythmic and clear. Heart rate was 82 per minute. BP on the right hand was 220 and 130 mm Hg, BP on the left hand was 210 and 125 mm Hg. Examination of respiratory, gastrointestinal, urinary, nervous system revealed no pathology. The thyroid gland at palpation had soft and elastic consistency, and it was not increased, nodular formations are not

palpated. Upon admission, the patient was prescribed methyldopa 1,000 mg followed by an increase in the daily dose to 2,000 mg per day and metoprolol 50 mg per day. On the third day, BP decreased to 150 and 90 mm Hg.

In blood count hemoglobin was 134 g/l, red blood cells — 4.24×10^{12} g/l, white blood cells — 9.9×10^{9} g/l, platelets — 293×10^{9} g/l, increased erythrocyte sedimentation rate up to 30 mm per hour. Blood chemistry showed an increase in fasting blood glucose up to 6.4 mmol/l, glycated hemoglobin — up to 6.0 %, cholesterol — up to 6.0 mmol/l, C-reactive protein — up to 30 mg/l. The content of serum creatinine, urea, electrolytes, total protein, albumin, bilirubin, aspartate aminotransferase and alanine aminotransferase activity are within normal values. In urinalysis proteinuria of 0.15 g/l was revealed. Daily proteinuria was 1.57 g/l, and it was not revealed in re-examination. In ECG sinus rhythm was reported with heart rate of 67 bpm, and normal semihorizontal electrical axis. According to the echocardiographic dimensions of the heart chambers, the global contractility of the left ventricular myocardium is within normal limits, EF was 59.8 % by Simpson. Concentric left ventricular hypertrophy: myocardial mass of 142 g, the index of myocardial mass of left ventricle 142 g/m^2, the thickness of the left ventricle posterior wall of 1.23 cm, the interventricular septum of 1.14 cm. Diastolic function of the left ventricle impaired with relaxation type, there are false chords in the apical region of the left ventricle. The results of daily monitoring of blood pressure revealed a change in the daily BP profile of "non-dipper" type, increased variability of SBP. In the daytime, the average SBP was 221 mm Hg, average DBP — 132 mm Hg; at night the average SBP — 234 mm Hg, average DBP — 135 mm Hg. Ultrasound examination of the thyroid gland revealed no pathology. Data on abdominal and renal ultrasound: deformation of the gallbladder; position, size, echogenicity of the kidneys are within normal limits. In the projection of the right adrenal gland there was a formation of increased echogenicity measuring 63×52 mm. In the duplex study of renal arteries, hemodynamically significant blood flow disorders in the common renal arteries were not revealed, resistance indices were normal. Ophthalmologist diagnosed neuroretinopathy of both eyes, reduced visual acuity in both eyes to 0.8. Upon re-examination after 4 days, a negative change was noted: reduced visual acuity in the right eye — to 0.7, left eye — to 0.6; increase in the number of stroke-like hemorrhages, plasmorhagia, exudates in the macula, increase in the number of newly formed vessels in the optic disc.

Taking into account the 3rd stage of hypertension with the development of rapidly progressed retinopathy and left ventricular hypertrophy, and the formation of the right adrenal gland, the patient was offered an abortion for medical reasons by the decision of the multidisciplinary team meeting. Instrumental curettage of the uterine cavity was performed at 8 weeks of gestation. After the abortion, the patient assessed her state of health as satisfactory, the only complaint was a decrease in vision. The presence of malignant hypertension and adrenal gland formation, accompanied by metabolic disorders, determined the need for priority search for pheochromocytoma. With this in mind, antihypertensive therapy was changed: methyldopa (the drug is contraindicated in pheochromocytoma) was discontinued, doxazosin 0.4 mg, metoprolol 100 mg, moxonidin 0.4 mg per day were prescribed. Combined antihypertensive therapy allowed to maintain the SBP within 125–135 mm Hg, DBP — 90–95 mm Hg. The orthostatic test showed a positive result: in the transition from horizontal to vertical position SBP decreased by 20 mm Hg. On the first day after the abortion in the absence of coronary and heart failure symptoms on ECG in the leads from V_2 to V_6 the appearance of symmetrical negative T-waves was reported (Fig. 1).

Test for blood troponins did not reveal excess of normal values. According to repeatedly performed echocardiographic studies no negative change was observed.

After curettage of uterine cavity, there was a decrease in RBC to 3.74×10^{12} g/l, hemoglobin to 97 g/l, thrombocytosis 485×10^{9} g/l, ESR 40 mm/h. During the week after the abortion, the blood WBC remained within normal values, then a short-term leukocytosis of 18×10^{9} g/l appeared twice in the absence of signs of any infectious process. The data from blood chemistry: cholesterol of 6.0 mmol/l, low density lipoprotein cholesterol

of 4.2 mmol/l, blood glucose of 10.6 mmol/l, potassium of 4.19 mol/l, sodium of 142 mmol/l, creatinine of 74.3 mmol/l, C-reactive protein of 39.5 mg/l. Glycemic profile: 08.00 — 5.6 mmol/l, 13.00 — 14.9 mmol/l, 18.00 — 11.6 mmol/l, 22.00 — 11.2 mmol/l. In urine tests, transient glucosuria, microalbuminuria were noted.

Hormonal status study: cortisol at 08.00 — 556 nmol/l (norm of 138–690 nmol/l), at 18.00 — 150 nmol/l (norm of 69–345 nmol/l); thyroid stimulating hormone — 2.1 IU/ml, free triiodothyronine — 3.0 pmol/l, free thyroxine — 10 nmol/l, antibodies against thyroid peroxidase — 66 IU/ml. The study of urine metanephrine and normetanephrine was performed by high-performance liquid chromatography. Analysis results: total metanephrine 23 μg/day (norm of <320 μg/day), free metanephrine 90 μg/day (norm of 1.6–192 μg/day), total normetanephrine 2,148.0 μg/day (norm of <390 μg/day), free normetanephrine 111 μg/day (norm of 7–158 μg/day). Thus, the content of total normetanephrine exceeded normal values by 5.5 times, which confirmed the presence of chromaffin tumor.

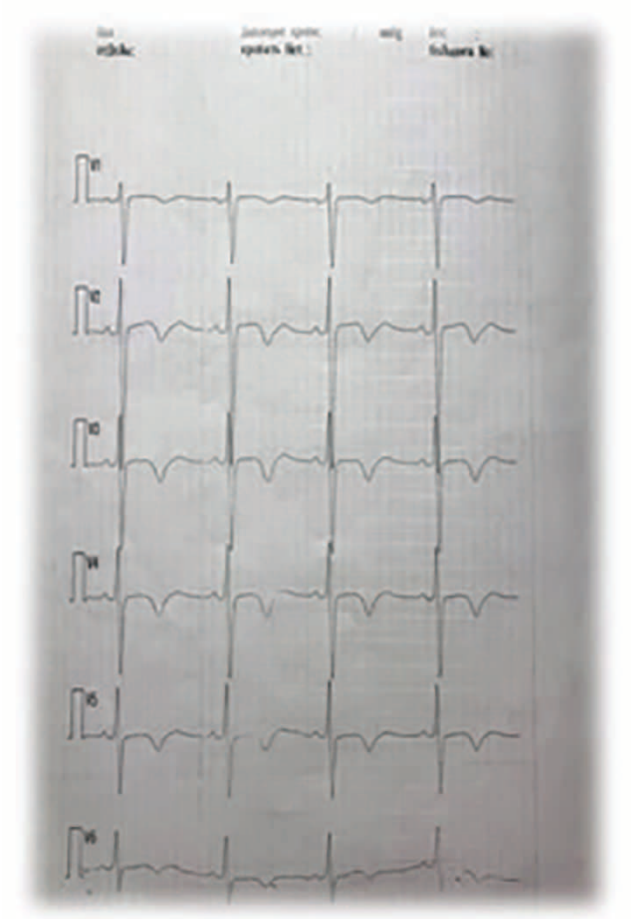

Figure 1. *Catecholamine-induced cardiomyopathy. ECG chest leads symmetric negative T-wave*

For the purpose of topical diagnosis of the proposed tumor, computed tomography of the abdominal cavity and retroperitoneal space was performed. In the right adrenal gland, a pathological soft tissue formation with dimensions of 57×72×74 mm with uneven contours, an inhomogeneous structure, without a clear border with the right lobe of the liver, the right kidney, the lower vena cava was found. The left adrenal gland is normal. To determine the surgical strategy of patient's treatment an additional study with contrast enhancement using Scanlux was performed. The following results are obtained: in the right adrenal gland, a formation measuring 60×73×70 mm with a round shape and clear smooth contours was revealed, its structure is heterogeneous due to the presence of a centrally located area of reduced density. With the administration of a contrast agent, the accumulation of contrast in the arterial phase along the periphery in the form of lumps was noted, in the central part contrast accumulation was not observed. The formation closely adheres to the liver, right kidney, inferior vena cava without growth into the adjacent organs. The renal hilum of the right kidney is pushed down by the formation. Lymph nodes of the abdominal cavity and retroperitoneal space, pelvic cavity are not enlarged. Taking into account the malignant course of hypertension and a positive family history, magnetic resonance angiography of brain vessels is included in the examination plan. On a series of angiograms performed in the ToF mode (time-of-flight magnetic resonance angiography), an uneven expansion of the lumen of the right internal carotid artery to 7.8 mm at the level of C3–C4 segments is determined, indicating the presence of a fusiform (spindle-shaped) aneurysm of the petrous segment of the right internal carotid artery.

<u>Preoperative clinical diagnosis:</u>

Primary disease: Pheochromocytoma (formation of the right adrenal gland). Secondary hypertension. Left ventricular hypertrophy. Catecholamine-induced cardiomyopathy. Hypertensive neuroretinopathy. Fusiform aneurysm of petrous segment

of the right internal carotid artery. Impaired fasting glucose. Dyslipidemia. Condition after instrumental curettage of the uterus at 8 weeks of gestation. Uterine scar.

Concomitant disease: Connective tissue dysplasia syndrome: false chords in the apical region of the left ventricle. Deformation of the gallbladder. Mild chronic normochromic anemia. Secondary thrombocytosis.

The patient underwent laparoscopic adrenalectomy on the right with technical difficulties in isolating the right adrenal vein. The removed right adrenal gland is 8×7×7 cm in size, and the section revealed a tumor of 7.0 cm in size, typical of a variegated pheochromocytoma with multiple foci of hemorrhage (Fig. 2).

Histologic examination: solid alveolar complexes consisting of large polygonal cells with pronounced cellular and nuclear polymorphism, surrounded by a fibrous capsule, with invasion of tumor cells into this capsule (Fig. 3, 4).

The early postoperative period was complicated by acute adrenal insufficiency, which required intravenous administration of prednisolone 180 mg, hydrocortisone 400 mg on the first day. In the next two days, hydrocortisone was intramuscularly administered at a dose of 175 mg per day. On the fourth day there was a normalization of BP and carbohydrate metabolism parameters. In the postoperative period ECG revealed no negative changes, blood troponins did not increase, electrolytes were within normal values. The patient was discharged in a satisfactory condition on the tenth day after surgery. After the rehabilitation period, the patient returned to work.

Eight months after the right-sided adrenalectomy, the patient was hospitalized in Endocrinology Department of Saratov Regional Clinical Hospital. She assessed her health as good, she had no complaints and noted a weight gain of 3.5 kg. Blood count and urinalysis was normal. Blood glucose — 5.4 mmol/l, glycated hemoglobin — 5.2 %, increased total cholesterol to 6.2 mmol/l; other blood chemistry parameters are normal. BP at home and office measurement did not exceed 120 and 80 mm Hg. According to the daily monitoring of blood pressure, there was a slight increase in the mean value of SBP at night (122 mm Hg), the daily profile of BP is changed by "non-dipper"

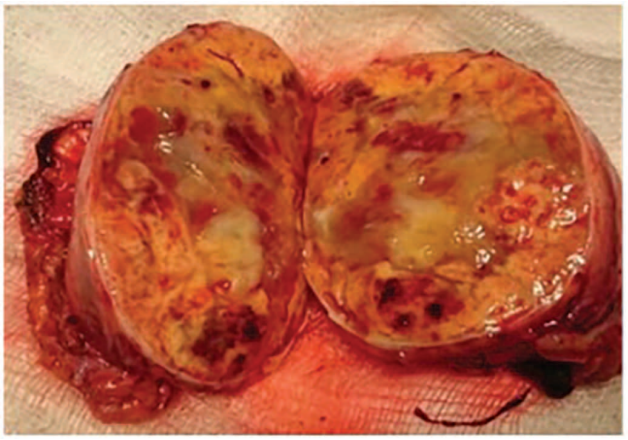

Figure 2. *Tumor 7 cm in diameter of specific for pheochromocytoma gray cherry color with multiple foci of hemorrhage in the section of the removed adrenal gland*

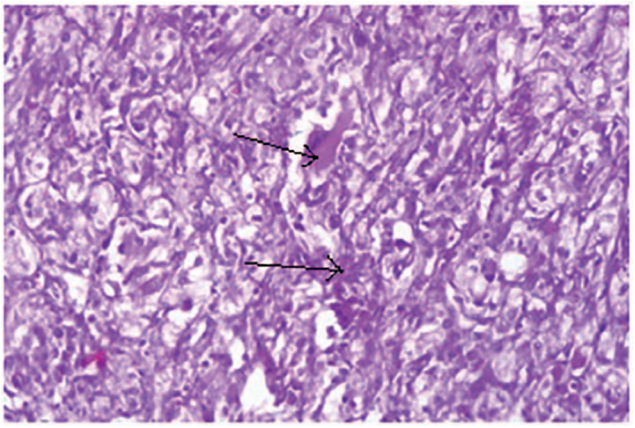

Figure 3. *Histological pattern of adrenal gland formation (hematoxylin and eosin). Large polygonal cells with pronounced cellular and nuclear polymorphism*

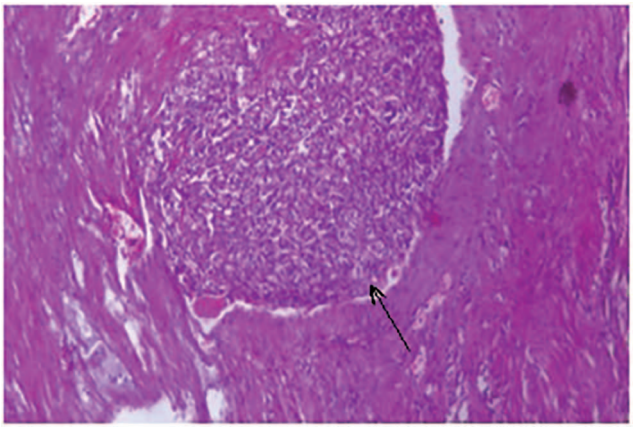

Figure 4. *Histological pattern of adrenal gland formation (hematoxylin and eosin). Invasion of tumor cells in the fibrous capsule*

type. Computed tomography of the retroperitoneal space was performed, evidence of recurrent pheochromocytoma was not found. Visual acuity of the right eye was 0.8, of the left eye — 0.9. The optic disc is pale pink with clear boundaries; the arteries are tortuous, narrowed; the veins are dilated, the macula has dystrophic foci. On ECG there was a positive change, but without full recovery of repolarization processes (Fig. 5).

Urine content of metanephrines was within normal values: total metanephrine of 48.00 μg/day, free metanephrine of 5.75 μg/day, total normetanephrine of 131.0 μg/day, free normetanephrine of 15.4 μg/day. Blood cortisol at 8.00 — 454 nmol/l, at 18.00 — 95 nmol/l.

Thus, in the presented clinical case of pheochromocytoma, hypertension was characterized by resistance and absence of crises. Weight loss should be noted as the earliest manifestation of the disease. Pregnancy in the patient occurred on the background of the existing tumor, since the first symptoms (decreased vision and weight loss) were already present in the early stages of the pregnancy. Of the organ lesions, the most severe was retinopathy, the rapid progression of which corresponded to the malignant course of hypertension. The formation of a fusiform aneurysm of the internal carotid artery is regarded as a consequence of persistent systolic-diastolic hypertension, possibly secondary to connective tissue dysplasia. Catecholamine-induced cardiomyopathy, diagnosed according to the appearance of myocardial focal changes on ECG in the anterior-septal-apical-lateral region of the left ventricle was not accompanied by clinical signs. Its development in pheochromocytoma is associated with catecholamine-induced non-coronary myocardial necrosis, leading to disruption of intercellular and intracellular ion exchange and oxidative intracellular cycle [3]. The metabolic disorders diagnosed in the patient are quite typical for chromaffin tumors. In 10–40 % of patients with chromaffin tumors there is impaired glucose tolerance and paroxysmal hyperglycemia during a hypertensive attack, in 10–29 % of patients — diabetes mellitus [3]. Leukocytosis and thrombocytosis in patients with chromaffin tumors are due to the shrinkage of the spleen under the influence of catecholamines. In the presented case, as in the previous one, leukocytosis reached a significant degree of severity — 18×10^9 g/l [4].

Histological features of the tumor, namely the presence of severe cellular and nuclear polymorphism, invasion of tumor cells in the fibrous capsule, do not exclude the malignant nature of pheochromocytoma. However, it should be noted that the question on the criteria for malignancy of pheochromocyte has not yet been resolved and is debatable. The discussion is based on the fact that in pheochromocytoma there is a discrepancy between the morphologically benign nature of the primary tumor and the subsequent metastatic lesion. On the other hand, when using the criteria of nuclear and cellular polymorphism, atypia and the presence of vascular and capsular invasion, the incidence of malignant lesions is 35–65 %, but clinically aggressive course is practically not found [1].

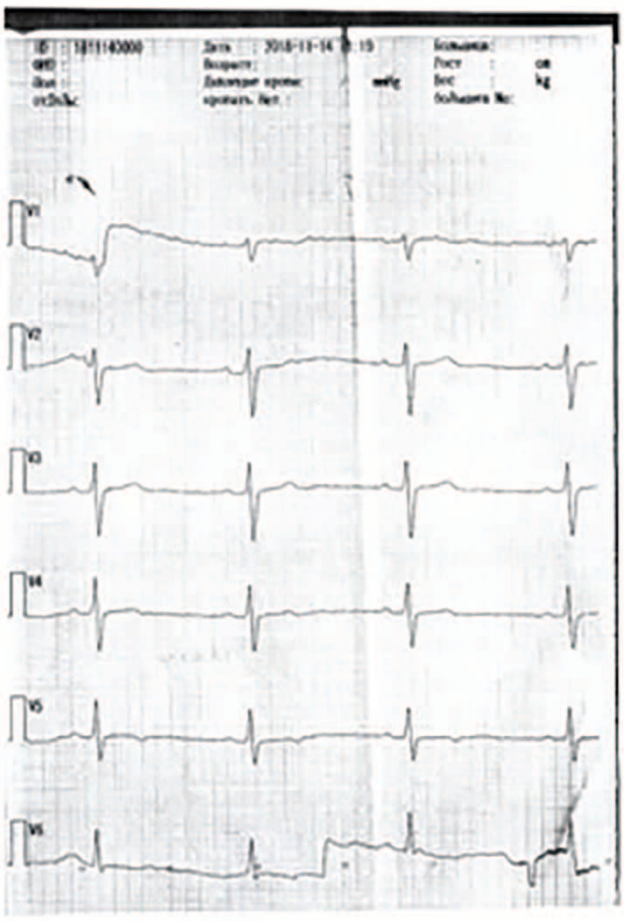

Figure 5. *ECG recorded 8 months later after adrenalectomy. Disorders in repolarization processes in the myocardium: the T-wave is low-amplitude in the thoracic leads and weakly negative in V5 lead*

It is possible that the sudden death of the sister at the age of 37 years from a cerebral hemorrhage was associated with pheochromocytoma and the disease has a family history. In this case, the probability of recurrent pheochromocytoma increases, which necessitates further careful monitoring of the patient. We believe that in this case the combination of circumstances allows us to hope for a favorable outcome. If there was no reason to see a doctor because of her pregnancy, the situation could have developed unfavorably, since in the presence of malignant hypertension and formed aneurysm of the internal carotid artery, the development of fatal cardiovascular events in the short-term was very likely.

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