

CASE REPORT

Myocardial infarction in a 30-year-old patient with pheochromocytoma and type 1 neurofibromatosis

Anna Babińska, Alicja Gnacińska, Renata Świątkowska-Stodulska, Krzysztof Sworczak

Clinic of Endocrinology and Internal Diseases, Medical Academy, Gdańsk, Poland

KEY WORDS

myocardial infarction,
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ABSTRACT

Chromaffinoma of the adrenal medulla (pheochromocytoma – PHEO) is a rare cause of arterial hypertension which is diagnosed incidentally or run in a family as a component of disease syndromes of the genetic origin. PHEO is diagnosed in about 5–10% of patients with type 1 neurofibromatosis (NF1). In a patient group with diagnosed arterial hypertension and NF1, PHEO is diagnosed with a much higher frequency, i.e. 20–56%.

Myocardial injury in a patient without coronary risk factors is very rare. Increased circulating levels of catecholamines in patients with chromaffinoma may cause damage to myocardium without any atherosclerotic lesions in the coronary arteries. A correct diagnosis of PHEO allows the right treatment to be administered. The present paper discusses the case of a patient with NF1 and periodic arterial hypertension in the course of unidentified chromaffinoma, which was complicated with myocardial infarction. The evaluation of the secondary arterial hypertension led to the detection of the adrenal tumor. Based on the clinical presentation and the tumor characteristics, on computed tomography, PHEO was suspected. The level of methoxycatecholamines in a 24-hour urine sample significantly exceeded the reference values. The patient underwent laparoscopic, right-sided adrenalectomy, and the histopathological examination definitely concurred with the diagnosis of PHEO. During the post-surgical period, the arterial hypertension normalized without the administration of hypotensive drugs. The patient is still cared for by the clinic.

The diagnosis toward PHEO is recommended if the patient with NF1 shows arterial hypertension. Proper diagnosis and treatment protects the patient against life-threatening cardiovascular complications.

INTRODUCTION Chromaffinoma of the adrenal medulla (pheochromocytoma – PHEO) is rarely a cause of arterial hypertension. Its prevalence is estimated at 0.1–0.6% in all patients with arterial hypertension.^{1–4} Pheochromocytoma can occur sporadically or be of a hereditary nature as a component of syndromes of genetically determined diseases such as multiple endocrine neoplasia type 2, von Hippel-Lindau disease, type 1 neurofibromatosis (NF1; Recklinghausen disease) and pheochromocytoma-paraganglioma syndrome.^{1–3}

The prevalence of PHEO in the NF1 patient group is estimated at 5–10%.^{1–3} In patients with

arterial hypertension and NF1, PHEO is diagnosed in 20–56% of all cases.⁴

A diagnostic evaluation to exclude or confirm PHEO is recommended in patients with NF1 and arterial hypertension^{2,4} before scheduling any surgery which can provoke hypertensive crisis, and in women planning pregnancy.^{4,5} A correct diagnosis and treatment protect a patient against life-threatening cardiovascular complications.^{4,5}

CASE REPORT The present article describes the case of a 30-year-old woman with NF1 diagnosed in 2001. Based on the medical history of the patient, the patient had periodic

Correspondence to:

Anna Babińska, MD, PhD,
Klinika Endokrynologii
i Chorób Wewnętrznych,
Akademia Medyczna, ul. Dębinki
7, 78-952 Gdańsk, Poland,
phone: +48-58-349-28-40,
fax: +48-58-349-28-41,
e-mail: a.mail@wp.pl

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FIGURE 1 Computed tomography of the abdomen. In the right adrenal gland a pathological mass present with dimensions of $57 \times 57 \times 42$ mm, of heterogeneous density, undergoing contrast enhancement

hypertension for 1.5 years with the systolic pressure increase to the value of >200 mmHg (regardless of physical exercise, meal or stressful situations) with accompanying headache, palpitations, pallor of the skin, vomiting, and tremors in the upper limbs. These symptoms usually occurred once a week. The patient self-reported taking neither amphetamines nor cocaine.

Because of arterial hypertension, the patient was treated with an angiotensin-converting enzyme inhibitor. For the past 5 months she was also treated for symptoms suggesting epilepsy (valproic acid preparations).

The patient was hospitalized in a non-academic cardiology department where she was admitted because of strong retrosternal pain radiating to the vicinity of the shoulder blades, accompanied by stiffening and tremors in the upper limbs, dyspnea, vomiting and an increase in blood pressure to $230/100$ mmHg. The physical examination revealed numerous *café au lait* spots all over the skin, and cutaneous and subcutaneous nodules of a neurofibroma structure, as concluded from the histopathological examination done a few years before. A family history of NF1 was negative.

The ECG examination showed sinus rhythm of 100/min disturbed by ventricular extrasystoles with QS syndrome in the V_1 and V_2 leads and with the ST segment elevation the V_2 and V_3 leads. The serum troponin I level was elevated (0.33 ng/ml, norm: ≤ 0.01 ng/ml). Based on the case history and laboratory tests, there were no risk factors for ischemic heart disease in this patient. Echocardiography showed hypo/akinesis of the anterior wall anterior part of the interventricular septum in the region of middle and apical segments with a significantly lower left ventricular ejection fraction (about 40%). Initially, the anterior wall myocardial infarction was diagnosed, and the patient was qualified for coronary angiography which no significant stenosis in the coronary vessels did not visualize. The patient was treated pharmacologically. She was

administered acetylsalicylic acid, β -adrenolytic, and statin. The administration of β -adrenolytic did not normalize blood pressure, and tachycardia persisted.

A secondary arterial hypertension was suspected and the ultrasound examination of the abdomen was performed revealing a hyperechogenic lesion at the upper pole of the right kidney with hypoechogenic area dimensions of $57 \times 48 \times 50$ mm. The imaging examination was supplemented with computed tomography (CT). In the right adrenal gland a pathological mass of non-homogenous density with dimensions of $57 \times 57 \times 42$ mm, undergoing contrast enhancement, was visualized (**FIGURE 1**).

Because of suspected PHEO the patient was referred to the Endocrinology and Internal Diseases Department of the Medical Academy in Gdańsk for further diagnostic evaluation and treatment.

The laboratory test results obtained till that time were supplemented with hormonal tests, including serum cortisol and adrenocorticotrophic hormone levels during a 24-hour period, and a suppression test with 1 mg of dexamethasone, androstendione and dehydroepiandrosterone sulfate serum levels, excreting free cortisol and its metabolites in a 24-hour urine collection sample. The above test results were normal. The aldosterone level in serum and urine, and plasma renin activity were not measured because this test was unavailable at that time. The diagnostic results were supplemented with the methoxycatecholamine level from the 5-hour urine sample during and after an episode of blood pressure elevation to a value of up to $230/120$ mmHg, and with the methoxycatecholamine level in random 24-hour urine samples. Both values significantly exceeded reference values and were respectively: 1550 $\mu\text{g}/5\text{h}$ and 8280 $\mu\text{g}/24$ h (norm: ≤ 1000 $\mu\text{g}/24$ h). Serum chromogranin A (CgA) levels also significantly exceeded normal values, i.e., 197.9 U/l (norm: $2\text{--}18$ U/l).

Despite the lack of specific recommendations of the Polish Society of Hypertension (PSH), magnetic resonance (MR) examination was performed. A large tumor mass was visualized, with dimensions at the coronal plane of 61×46 mm (**FIGURE 2A**), at a axial plane of 62×45 mm (**FIGURE 2B**), with high signal intensity in T_2 -weighted sequences, and also in the sequence with fat-suppression refinement. The mass was of low signal intensity in the T_1 -weighted sequences and was enhancing intensively after contrast injection. In the dorsal part of the tumor, a small focal lesion was observed that most probably corresponded to disintegration. In the anti-phase sequence the tumor signal did not decrease. The mass was attached to the kidney, it was slightly pressing down on the upper pole, went into the right liver lobe, and showed no unequivocal characteristics of infiltrating into the neighboring organs. The overall image suggested PHEO or another malignant tumor. Considering the relation

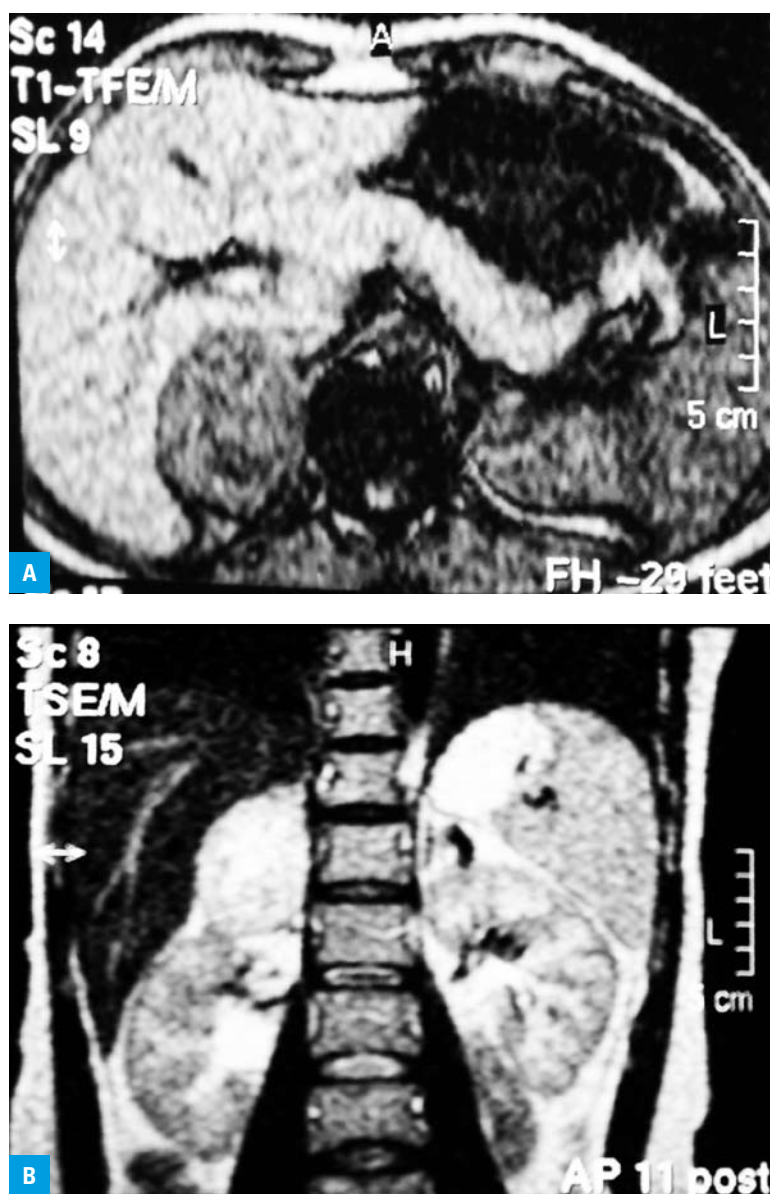


FIGURE 2 Magnetic resonance imaging of the adrenal glands with chemical shift. A large tumor mass with dimensions at the coronal plane of 61×46 mm (A), at the axial plane of 62×45 mm (B), with high signal in the T2-weighted images. At the antiphase sequence the tumor signal did not decrease.

of incidents stated in the patient's medical history that suggested epilepsy attacks with the diagnosis of NF1 in the patient, the MR examination of the brain was performed, which visualized a lesion in the lobe of the corpus callosum with dimensions of 11×6 mm, which could have suggested glioma or hamartoma from NF1, although the localization was not typical.

Taking the clinical picture under consideration, the nature of the tumor as seen in the imaging examinations and the high amine metabolite level in urine, PHEO of the right adrenal gland was diagnosed. During the preparation for surgical treatment, phenoxybenzamine, which blocks α_1 - and α_2 -adrenergic receptors, was considered for use; however, due to this drug's unavailability, α_1 -adrenolytic was finally administered. Pharmacotherapy was administered for 2 weeks before scheduled surgical treatment. During that time arterial hypertension normalized and the epilepsy symptoms subsided. The drug was well tolerated; no orthostatic hypotonia was observed. The patient underwent surgery at the General,

Endocrinology and Transplantation Surgery Clinic of the Gdańsk Medical Academy. A laparoscopic, right-sided adrenalectomy was performed and a histopathological examination confirmed the diagnosis of chromaffinoma. The tumor tissue reached the edge of the surgical incision. During the postoperative period the arterial hypertension normalized and there was no further need to administer anti-hypertensive drugs. The patient stayed under the supervision of the Departments of Endocrinology, Cardiology, and Neurology. During the echocardiography performed 5 months after the myocardial infarction, segmental disturbances of the myocardial contractility were not initially noticed, and the ejection fraction increased to 50–55%. The stress test was negative. In the ultrasound check-up examination of the abdomen, the bilateral adrenal gland areas showed no pathology. In the follow-up hormonal examination 6 months after the surgery, a concentration decrease in CgA serum levels was observed (36.6 U/l), and the catecholamine metabolite level in the urine normalized ($512 \mu\text{g}/24 \text{ h}$). The patient did not require gluco- and mineral-corticosteroid substitution.

During the subsequent cardiological examination, the stress test remained negative (the pulse limit was reached, a very high stress tolerance was obtained). However, in the course of the next echocardiography examination, a subtle hypokinesis at the $\frac{1}{2}$ apical septal segment with ejection fraction of 60%. Due to persisting contractility disturbances, the initial myocardial infarction diagnosis was maintained, and it was decided to continue treatment recommended for secondary prevention including β -adrenolytic, statins and acetylsalicylic acid preparation. Since adrenalectomy, no epilepsy incidences had been observed. However, the control EEG reading was abnormal. A brain MR examination was again performed, which revealed the above described lesion localized at the posterior of the callous corpus to be reduced (7×4 mm). The syncope (without consciousness loss) reported by the patient before adrenalectomy might have been actual epilepsy incidences of a partial type, provoked by increased catecholamine synthesis by the adrenal gland tumor. The pathologic EEG recording before and after adrenalectomy and lesions in the brain MR examination convinced the consulting neurologist to continue the patient's anti-epilepsy treatment.

DISCUSSION About 30% of PHEO cases are hereditary. One of the syndromes with a genetic background where PHEO is present is NF1.^{1,2,4} This disease occurs in 1/3000 newborns, with no race or sex discrimination. The fundamental cause of PHEO is a mutation of the gene encoding neurofibromin, which is located on the long arm of chromosome 17 (17q.11, 12) at the centromere region. The gene mutation leads to neurofibromin protein inactivation and an increase in the *Ras* oncogene activity that is the cause

of many tumors.^{4,6} NF1 is inherited in a dominant autosomal fashion, however, in half of those afflicted there was no family history, in which case the reason for its occurrence was a new mutation in germinal cells.^{4,6}

The basic symptoms of NF1 are numerous elastic nodules and cutaneous-subcutaneous nodules of various sizes with histological tissue of a neurofibroma type. These changes are derived from peripheral nerves and structures related to them, and are present in all parts of the body, but rarely on the hands and feet. Characteristic features also involve skin hyperpigmentation in the color of coffee with milk (*café au lait*); freckle-like pigmentation with a diameter of 2–3 mm in the vicinity of armpits, the groin and the neck (Crowe symptom); and hamartoma-type nodules of the iris – yellow-brownish spots called Lisch nodules.^{1,3,6} Abnormalities in the digestive tract are rarely observed in NF1 patients, which might be a consequence of mechanical obstruction or malabsorption syndrome.⁶ Frequently, specific neurological symptoms are present, i.e. peripheral nerve neuralgia, spastic paresis, eye disturbance and incidents of epilepsy.^{4,6} About 5.4% of NF1 patients have epilepsy.^{1,7} Based on the guidelines set by the Neurofibromatosis Study Group, the patient described in this article meets the criteria for the NF1 diagnosis.

Up to 20–56% of NF1 with arterial hypertension patients are diagnosed with PHEO.⁴ Based on some papers, patients with NF1 and PHEO have a higher risk for developing its more malignant form (3–15%).⁶ These results are in disagreement with the British multi-center experiments done on 448 patients with NF1. The authors showed that only connective tissue tumors and central nervous system are more frequent (2.7×) in patients with NF1. In a large patient test group, only 1 patient was diagnosed with paraganglioma during the follow-up, which did not allow for the verification of data given by other authors.⁷

Testing for NF1 is recommended if the patient with NF1 is diagnosed with arterial hypertension^{4,5}, before scheduled surgery, and in women with NF1 before a planned pregnancy⁴.

The clinical PHEO symptomatology is decided by the increase in catecholamine release by this tumor. The typical symptoms are paroxysmal and the releasing factors can be: physical stress, abdominal cavity pressure, a hearty meal, some drugs and stimulants (ephedrine, phenylephedrine, amphetamine), stressful situations and general anesthesia. The most frequent PHEO symptom is arterial hypertension (permanent or paroxysmal). An increase in arterial hypertension is usually accompanied by: headache, accelerated heart action, pale skin and excessive sweating.¹⁻⁴ In several cases, cardiomyopathy (dilated or hypertrophic) with different degrees of heart failure symptoms might be suspected based on the clinical picture. These changes are caused directly by the catecholamines and usually subside after

the tumor is surgically removed.^{1,4,8} Cardiovascular symptoms can also be exhibited in the form of arrhythmia (from supraventricular tachycardia up to ventricular fibrillation) and myocardial infarction. The ECG changes during the course of PHEO include: inverted or high, symmetric T wave, low voltage of waves, changes in the ST segment, elongation of the QT distance, and nonspecific changes.³ During echocardiography global or segmental contractility disturbances can be observed. Enzymatic markers of myocardial necrosis are not always elevated.^{3,8}

Noradrenaline is mostly responsible for the damage to the myocardium during the course of PHEO.³ It restricts the coronary flow causing, at the same time, a coronary vessel spasm, and an increased demand for oxygen by the heart muscle, resulting in a positive chrono- and inotropic effect and increasing the afterload. This causes myocardial ischemia. The direct, toxic effects of catecholamines on cardiomyocytes are also significant.³ They cause a long-chain fatty acid accumulation in cardiomyocytes, which favors free radical production.⁸ The oxidation of catecholamines also leads to the increase in their production.⁸ The toxic effect of elevated calcium levels in cardiomyocytes should be also considered.⁸ A long-lasting, powerful coronary vessel spasm can damage their endothelium, which can cause the aggregation of blood platelets, activation of the clotting system and thrombosis.³ These disturbances can lead to stunned myocardium and then to necrosis, if PHEO is undiagnosed and untreated.³

Differentiating between myocardial infarction and stress-induced cardiomyopathy (takotsubo syndrome) in PHEO patients is challenging. The clinical picture of takotsubo syndrome (cardiomyopathy caused by intense stress) resembles acute coronary syndrome and includes chest pain and heart failure symptoms until a sudden circulatory arrest in the ventricular fibrillation mechanism.^{9,10} The etiology is not clear. Intense stress can cause a sudden “stunning” of myocardium. The dysfunction is especially intense in the region of heart apex, which is most susceptible to adrenergic stimulation.¹⁰ Electrocardiography suggests a myocardial infarction; in the enzymatic tests slightly elevated necrosis marker levels are observed.^{9,10} The clinical course, electrocardiography and biochemical tests suggest, as in the case of the discussed patient, myocardial infarction, and that is why the patients, as the patient described here, qualify for coronary angiography. The examinations performed so far have not revealed stenosis of the coronary vessels, or the angiographical characteristics of plaque rupture. In takotsubo cardiomyopathy, discomfort, heart contractility disturbances and ECG abnormalities subside over a period of a few weeks or more.^{9,10} In the case of the patient discussed here, the maintained hypokinesis at the ½ apical septal segment definitely led to the final diagnosis of myocardial infarction and

the prolongation of administered treatment for secondary prevention.

An acute coronary syndrome, being a symptom of PHEO, requires special treatment. The administration of anticoagulant drugs like heparin, aspirin and clopidogrel is recommended, as in the case of infarction during the course of coronary atherosclerosis.³ Due to labile hypertension there is a heightened risk of hemorrhagic complications after thrombolytic therapy.³ A higher risk is also present with coronary angiography and coronary angioplasty. The contrast agent can cause a sudden catecholamine release, resulting in higher arterial hypertension and heart muscle damage.⁵ Additionally, in the case of PHEO, the administration of β -adrenolytics before the beginning of α -adrenolytic treatment can intensify the coronary artery spasm. An alternative to this is the administration of calcium channel blockers in addition to nitrates.³

A fundamental significance in PHEO patients with heart muscle damage symptoms is, thus, attributed to fast and safe diagnostics. In the opinion of some authors, the evaluation of serum metanephrine levels, which positively correlates with the catecholamine metabolism in the tumor tissue, is considered the best diagnostic test for PHEO.⁸ Currently, it is believed that the most reliable method in PHEO diagnostics is the measurement of metoxycatecholamines in plasma. However, this method is not widely available and in many institutions an equally reliable method involves the measurement of methoxycatecholamines in urine. Its sensitivity is 86% and its specificity 92%.^{11,12} In the case of the described patient, the methoxycatecholamine level in the 24-hour urine collection sample, taken both during resting and during "an attack", significantly exceeded the reference values. Additionally, the CgA level in PHEO patients can be raised because these tumors are considered neuroendocrine tumors. Both methoxycatecholamines in the 24-hour urine collection sample, and the CgA level can be considered PHEO markers. After adrenalectomy, the discussed patient exhibited the normalization of methoxycatecholamines in the 24-hour urine sample, and a significant decrease (after 6 months) in and normalization (after a year) of CgA levels.

The fundamental examination in PHEO imaging diagnostics is CT, and the highest sensitivity is assigned to MR.^{2,11} In the guidelines developed by the PSH Working Group, the authors suggest performing a monophasic CT examination without intravenous administration of the contrast medium, in addition to a tumor density test. An intravenous administration of the contrast material (biochemical tests in patients with confirmed PHEO) is unnecessary, as it can cause a sudden increase in the arterial blood pressure.¹¹ In the discussed case, the CT examination was performed in a non-academic institution, before an earlier evaluation of PHEO biochemical markers. The USG image was interpreted

as an incidentally discovered adrenal gland tumor, which is why further diagnostic tests were planned based on the contrast CT. The CT image unequivocally suggested PHEO diagnosis due to high tumor density and a lack of fat-suppression in T₂-weighted images. The MR picture confirmed the earlier suspicion of PHEO.

A different imaging method that found its use in PHEO diagnostics is scintigraphy, which uses meta-iodobenzylguanidine labeled with radioactive iodine (MIBG).^{2,11} This compound is concentrated selectively in the chromophil tissue, enabling the localization of tumors placed both in the adrenal gland areas and in their vicinity. In the described patient MIBG scintigraphy was not used.

The PHEO treatment by choice is a surgical procedure. During the pre-operative period, arterial blood pressure should be lowered, and its periodic increase should be prevented, which could be life-threatening.^{2,4} The drugs used are those which block α -adrenergic receptors in the cardiovascular system. Patients who during the pre-surgical period maintain significantly accelerated heart action and/or rhythm complications are also administered drugs blocking the β -receptors. They should only be administered in conjunction with drugs blocking α -receptors.^{1,8} Patients who are only administered β -receptor blockers could develop an increase in periodic complications in the relative predominance mechanism of the α -receptors-adrenergic. After about 2 weeks of preparation, the normalization of RR and the regression of periodic hypertension were observed in the discussed patient. The patient underwent a safe operation using the laparoscopic method. This method is recommended for adrenal gland tumors which are smaller than 6 cm. In comparison with classical adrenalectomy, it is considered to involve a smaller risk of post-surgical complications, smaller blood loss during the surgery, shorter hospitalization and convalescence time. The risk of surgical complications in the form of acute arterial pressure fluctuation and rhythm abnormalities is similar to that observed in classical adrenalectomy.¹³

All the patients after the PHEO removal should be under constant care, as the disease can reoccur (17–20% cases over a 10-year period) and there may be distal metastasis in the case of a malignant tumor.^{1,2,11} Permanent arterial pressure normalization after the procedure should be expected in about half of PHEO patients.^{8,11} The case of the discussed patient points to the necessity of an increased diagnostic alert for secondary arterial hypertension in patients with NF1. An early PHEO diagnosis is necessary for patients with acute myocardial ischemia symptoms. The established treatment with β -adrenolytics in this patient group could enhance ischemia. The modification of traditional treatment is necessary in patients with myocardial infarction and PHEO.

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