Cardiovascular complications induced by pheochromocytoma associated with neurofibromatosis type 1 (von Recklinghausen's disease) – case report and review of literature

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Abstract

Neurofibromatosis type 1 (also known as von Recklinghausen's disease) is a genetic disorder characterized by neurofibromas, skin pigmentation, eye and bone abnormalities. It is associated with pheochromocytoma in 1 to 5% of cases which determines symptoms related to catecholamine excessive secretion. We present the case of a 54-year-old man that was admitted to the cardiology clinic due to acute onset of tachyarrhythmia (atrial flutter) and high blood pressure. Neurofibromatosis type 1 was diagnosed by clinical examination while laboratory exams, 24-hour continuous blood pressure monitoring and imaging exams raised the probability of pheochromocytoma. After proper pharmacological stabilization, the patient underwent surgery and the 110/110 mm left adrenal mass was removed via abdominal laparotomy. The patient evolution was favorable and regular follow-up is scheduled. In conclusion, even though asymptomatic screening for pheochromocytoma is not recommended, this pathology should be suspected in all patients with neurofibromatosis especially if they present acute onset of cardiovascular signs.

Keywords: *neurofibromatosis type 1, von Recklinghausen's disease, pheochromocytoma, cardio-vascular, arterial hypertension*

Introduction

Pheochromocytoma (PHEO), although rare, is a tumor of the chromaffin tissue with 90% localization in the adrenal medulla. It causes an excessive secretion of catecholamines that leads to symptoms such as headaches, excessive sweating, flushing or anxiety as well as cardiovascular signs – palpitations, tachycardia or paroxysmal arterial hypertension [1].

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PHEO represents one the main causes of secondary arterial hypertension and may be so severe to induce hypertensive emergencies [2]. The diagnosis is important since, in most cases, hypertension is reversible after surgical excision. Most of PHEO are sporadic but in different genetic disorders, PHEO is associated mainly with multiple endocrine neoplasia type 2, von Hippel-Lindau disease or neurofibromatosis type 1 (NF-1) [3].

NF-1, also known as von Recklinghausen's disease, is an autosomal dominant genetic disease with an incidence of about 1 per 3500 births.

NF-1 is characterized by cutaneous and plexiform neurofibromas, skin pigmentation (axillary and inguinal freckling, café-au-lait

spots), Lisch nodules, optic glioma or skeletal dysplasias [4, 5].

Cardiovascular effects are relatively common in patients with NF-1 due to coartation of the aorta, renal artery stenosis or PHEO [6]. Even though PHEO has tenfold higher incidence in NF-1 patients, this association is identified in 1 up to 5 percent of individuals [7]. Thus, we present the case of a patient that was diagnosed with NF-1 and PHEO due to initial cardiovascular events and we make a brief review of the literature concerning this rare disease association.

Case report

We present the case of a 54-year-old man who was admitted in emergency to the Cardiology Clinic of "Sf. Spiridon" Clinical Emergency Hospital Iasi accusing palpitation, dizziness and high blood pressure (BP) values (maximum systolic BP 200 mmHg).

The patient had no personal history of cardiovascular diseases (CVD) and his symptoms presented an acute onset a couple of hours before presenting to the emergency unit. He was non-smoker, without family history of CVD and he was under chronic medication for an organic depressive disorder.

Clinical evaluation showed a normal weight patient (body mass index 21 kg/m^2), resting BP 120/80 mmHg and heart rate 150 bpm.

The skin examination revealed multiple papilloma lesions of 0.5 to 5 centimeters in diameter located on the anterior and posterior thorax, abdomen and upper limbs that were interpreted as neurofibromas, along with café-au-lait spots and axillary freckling (Figure 1).

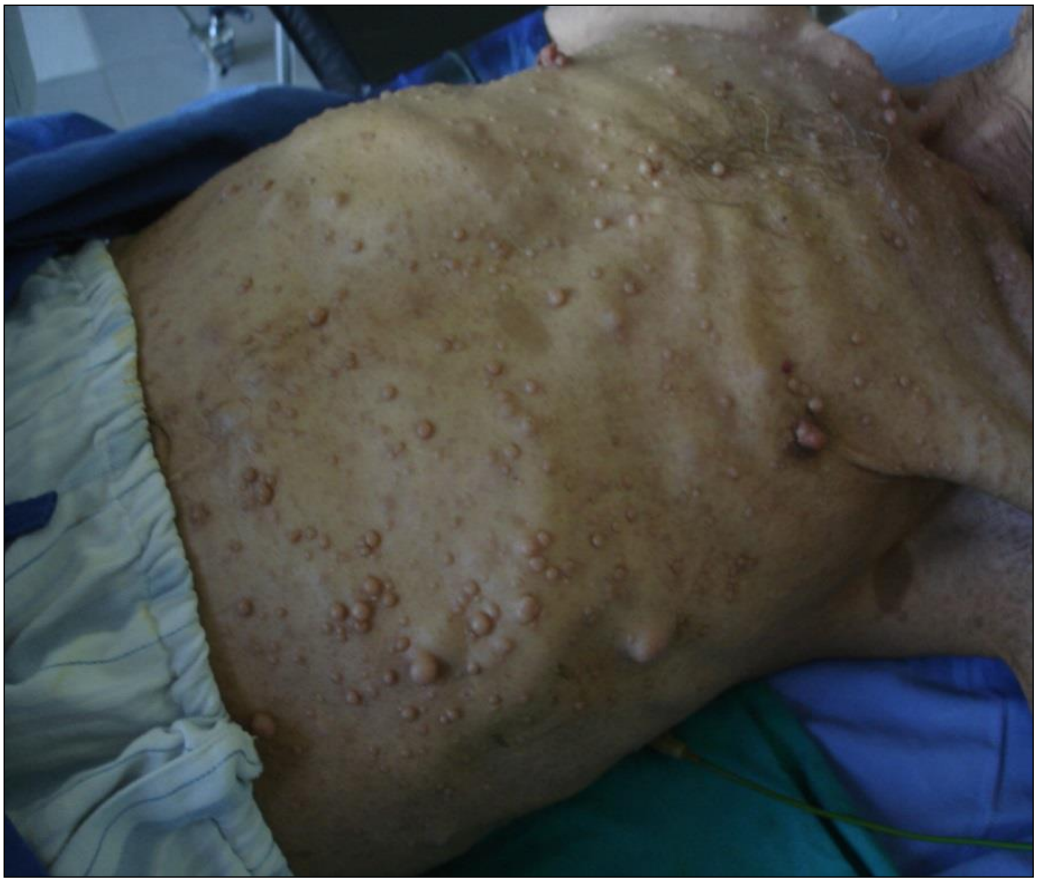

Fig. 1. Axillary freckling plus neurofibromas and café-au-lait spots located on anterior thorax and abdomen

Electrocardiogram at rest revealed atrial flutter with a fast ventricular rate 150 bpm (Figure 2). The 2D transthoracic Doppler echocardiography showed cavities and ventricular walls of normal kinetic and dimensions with an ejection fraction of 50%.

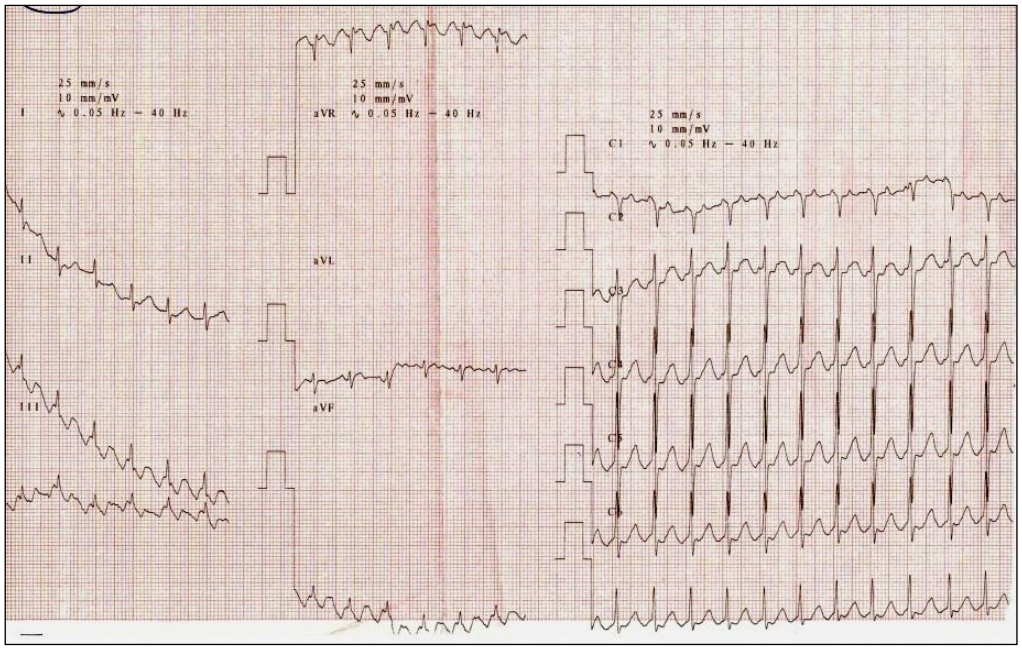

Fig. 2. Atrial flutter with fast ventricular rate 150 bpm

Laboratory exams showed multiple abnormal values: mild inflammatory syndrome (increased leukocytes number and fibrinogen) with normal red blood cell count, mild increase of serum creatin kinase (CK) (total CK 705 U/l and CK-MB 52 U/l) and hyperglycemia (175 mg/dl).

The hepatic and renal functions were impaired as well (AST 68 U/l, ALT 79 U/l, respectively serum creatinine 1.31 mg/dl), cholesterol parameters were increased (total cholesterol 242 mg/dl, LDL cholesterol 151 mg/dl) while sodium and potassium levels were in normal ranges.

The 24-hour continuous blood pressure monitoring revealed a disturbed BP profile with important differences between the lowest and highest values (Table 1).

Table 1. 24-hour continuous blood pressure monitoring results

	Systolic BP (mmHg)	**Diastolic BP** (mmHg)
Average	116	70
Maximum	195	113
Minimum	80	31

Taking into consideration the clinical presentation and examination, the abnormal laboratory results and the extreme oscillating values obtained by BP monitoring, we thought of a secondary neuro-endocrine cause for the patient cardiovascular manifestations. The abdominal echography revealed an extensive mass of 110/114 mm with a 70 mm inside necrosis area that was located in the left adrenal gland. The serum catecholamine levels were elevated (metanephrine 420 pg/ml and normetanephrine 1000 pg/ml). Thus, based on clinical symptoms, echography and biochemical markers the diagnosis of pheochromocytoma was likely probable. The abdominal computed tomography scan confirmed the mass located in the left adrenal area but pointed out multiple other lesions located in the digestive system: on the duodenal papilla (10 mm) and also colon lesions that could indicate an inflammatory bowel disease. However, the endoscopic biopsy results revealed no malign aspects, only chronic inflammatory infiltrate. In the cardiology clinic, the patient was stabilized by receiving anticoagulant (in prophylactic dose),

alpha and beta-blocker and antiarrhythmic (amiodarone) treatment, with spontaneous conversion to sinus rhythm (Figure 3).

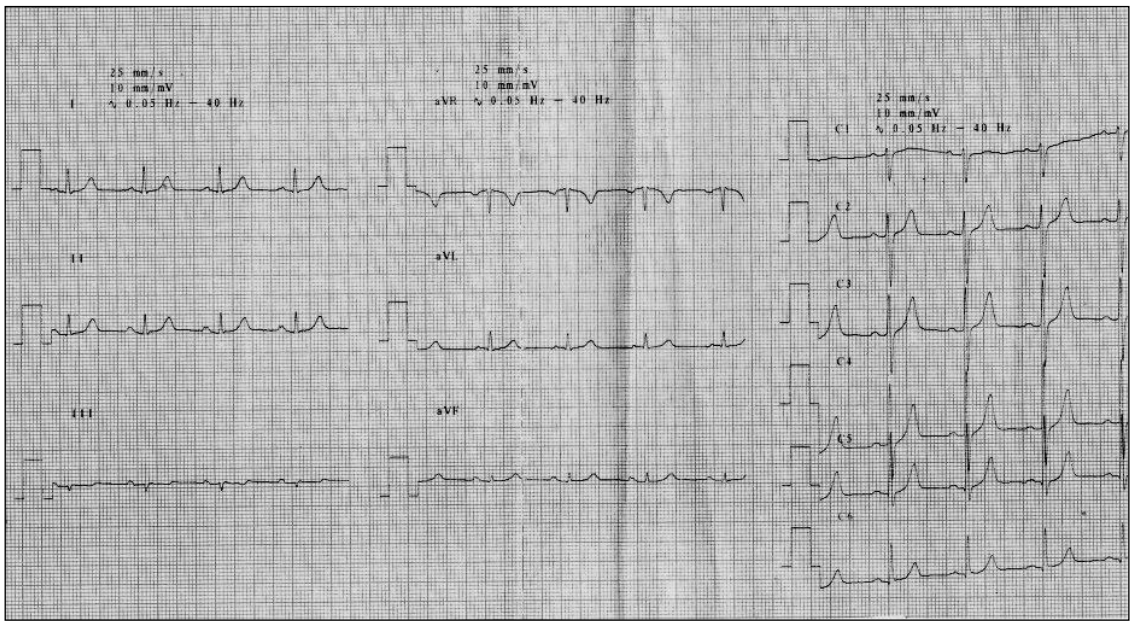

Fig. 3. Sinus rhythm, 75 bpm, intermediate axis, normal wave morphology.

The patient was transferred to the surgery department where the 110/110 mm tumoral mass was removed by abdominal laparotomy (Figure 4).

The histopathological diagnosis confirmed the initial supposition – pheochromocytoma with benign aspect.

In dynamic, the patient biochemical markers have normalized, the initial values being caused by the adrenergic cardiomyopathy and increased basal metabolism. After the surgery, the evolution was favorable, the patient being scheduled for regular follow-up visits in our department.

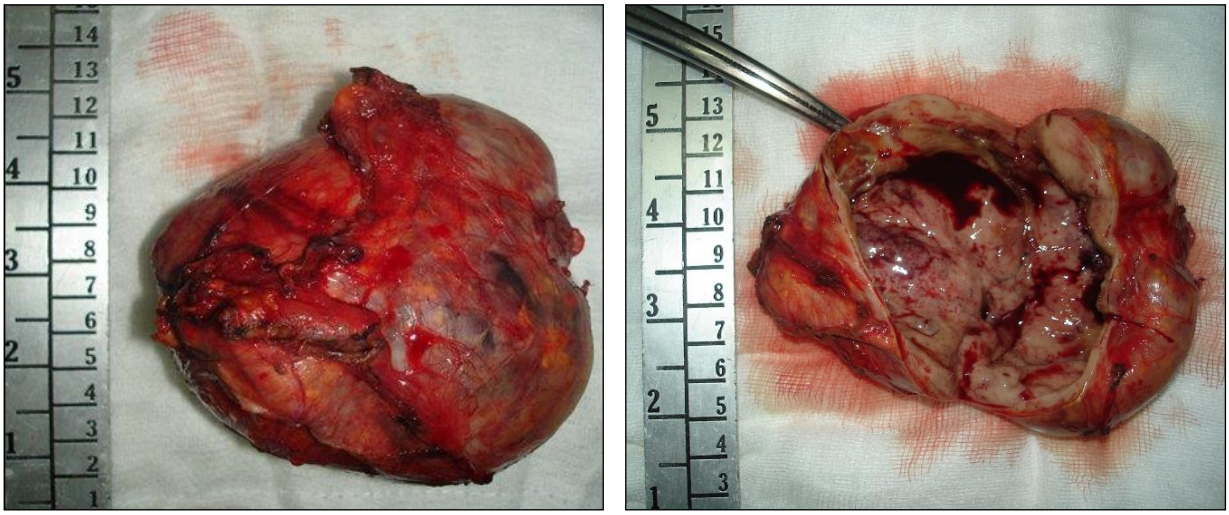

Fig. 4. After surgical excision: 110/110 mm left adrenal tumor – pheochromocytoma

Discussion

NF-1 represents a complex disease and the patients have an increased prevalence for both benign and malignant disorders involving neuroectodermal or mesenchymal origin tissues [7]. Despite modern approach and research, the diagnosis is still based on clinical criteria developed by National Institutes of Health Consensus Conference in 1987 [8]. Besides PHEO (which is up to 5% of cases), gastrointestinal tumors (neuroendocrine tumors of the duodenum, mesenchymal neoplasms or gastrointestinal stromal tumors) occur in up to 20% of patients [4]. However, very few cases associate at the same time NF-1, PHEO and gastrointestinal tumors. In our patient, even though he presented abnormalities at the digestive system, the histopathological exams did not confirm the neoplasia at this level.

Another particular aspect is that we present the case of a 54-year old man with NF-1 and PHEO while this association is predominantly in women around 40 years. Around 20% of patients are asymptomatic and only 10% of patients have bilateral adrenal tumors [9].

Neurofibromin (the protein encoded by NF-1 gene) is an important element in the heart development and is expressed in both endothelial and smooth muscle cells of blood vessels [10]. Brannan et al. proved that mice which were homozygous for the Nf1 mutation died prematurely from severe cardiac malformation [11]. About 2% of patients with NF-1 present cardiovascular malformations, especially pulmonary stenosis [10]. Regarding arterial hypertension, PHEO occurs in 20-50% of NF-1 hypertensive patients, compared to 0.1% of all hypertensive subjects [12]. Along with tachyarrhythmia disorder, arterial hypertension was the reason for admission of our patient confirming the acute cardiovascular manifestations that are observed in this category of patients.

A study conducted on 48 consecutive NF-1 patients revealed that patients with NF-1 and PHEO presented decreased obesity parameters as compared to NF-1 patients. Moreover, 71% of them presented higher BP values and a non-dipper profile assessed by ambulatory blood pressure measurement. Left ventricular mass index and intima media thickness were significantly pronounced as well, leading to the conclusion that NF-1 individuals with PHEO had an increased cardiovascular risk [7]. Walther et al. characterized patients with NF-1 and PHEO and showed that mean age of patients was 42 years, 84% had unilateral adrenal tumors and 11% presented malignant PHEO [12]. Our patient was evaluated and diagnosed at the age of 54, probably due to the absence or mild symptoms that did not determine the patient to address earlier to the hospital.

A recent retrospective analysis on PHEO resection concluded that NF-1 patients had significantly smaller adrenal tumors (median tumor dimension, 2.75 cm vs. 5.9 cm; $p = 0.014$) and less arterial hypertension compared to other subjects treated for PHEO [13]. The results are non-consistent with the literature data probably due to the retrospective character of the study and due to the small number of patients included in the analysis. In our case, the tumor size is not directly associated with the clinical presentation and patient past medical history. However, tumor size as well as open adrenalectomy are independent predictors for intraoperative hemodynamic instability [14].

No specific mutation has been found in patients with NF-1 and PHEO. In a genetic study conducted in 37 subjects, the authors discovered 36 different mutations with no correlation with a certain hot spot [6]. Biochemical and imaging diagnostic and screening tests are not different from those used in sporadic PHEO [15]. Routine screening for PHEO is not recommended in patients with NF-1 because of the low association. However, in hypertensive NF-1 patients, the presence of PHEO should be ruled out.

Children with NF-1 require yearly clinical evaluation and assessment of education and development while adults require lifelong management by a multidisciplinary team [8]. The elective treatment of PHEO is surgical, preferably by laparoscopy, after adequate preparation. The regular strategy includes initial alfa-adrenergic blocker. Beta-blockers should be added after a few days and in the

presence of an effective alpha-adrenergic blockade since they can worsen the BP profile by inhibiting vasodilatation mediated by beta-2 adrenergic receptors and thus increasing vasoconstriction [16]. Nowadays, the main choice is represented by cardioselective beta-blockers.

Conclusions

There are no general recommendations for the management of patients with NF-1 and PHEO especially when they associate other comorbidities such as arterial hypertension or rhythm disorders as was the case of our patient. We consider the cardiology medical treatment as a milestone for an adequate preparation in order to perform the elective treatment – PHEO resection.

Even though life expectancy is reduced in patients with such medical conditions, our patient presents a favorable evolution and a proper follow-up is needed.

We highlight the importance of detecting and evaluating cardiovascular signs in all patients with NF-1 since they could unmask a possible secondary cause and disease association.

Authors declare no conflicts of interest.

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