Neurofibromatosis type 1 and phaeochromocytoma – a clinical case report

Ana Norte, Patrícia Alves, Manuel Batista, Benilde Barbosa, Isabel Fonseca, M. H. Saldanha

Abstract

The authors present a case of a 49-year-old man, referred to the Emergency Department with headache, palpitations, abdominal pain and nausea. He had a past medical history of neurofibromatosis type 1 (NF1) and hypertension. On examination there was intense perspiration, blood pressure 240/173 mmHg and tachycardia. Laboratory findings revealed raised metanephrines in the 24-h urine specimen and imaging tests displayed a solid nodule in the left adrenal gland. Further evaluation led to the diagnosis of phaeochromocytoma. After appropriate pre-surgery therapy, a left adrenalectomy was performed. On follow up, 6 months after surgery, the patient was asymptomatic with good blood pressure control.

The reason for presenting this case is not only its rarity, since phaeochromocytoma occurs in only 1% of NF1 patients, but also to point out the need to look for specific causes of hypertension in young patients, mainly those with NF1.

Key words: neurofibromatosis type 1, phaeochromocytoma, arterial hypertension.

INTRODUCTION

Neurofibromatosis type 1 (NF1), or Von Recklinghausen's disease, is an autosomal dominant disease with an incidence rate of 1 in 3,500 live births. It has complete penetrance but variable symptoms.[1] It is the result of a deactivation (by mutation or deletion) of the NF1 gene located on chromosome 17 that encodes a protein called neurofibromin.[1] The neurofibromin acts as a tumor suppressor, and its loss of function leads to the development of a series of tumors.[1] Two or more of the following criteria are necessary to establish a diagnosis of NF1: 1) six or more *café au lait* spots over 5 mm in prepubertal individuals, or over 15 mm in postpubertal individuals, 2) two or more neurofibromas of any type or one plexiform neurofibroma; 3) freckling in the axillary or inguinal regions, 4) optic glioma, 5) two or more Lisch nodules (iris hamartomas) 6) distinctive bone lesions, such as sphenoid dysplasia or thinning of the long bone cortex with or without pseudarthrosis, and 7) a first-degree relative with NF1.[2]

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About 6% of patients with NF1 develop high blood pressure; secondary causes of high blood pressure (HBP), such as renovascular disease, aortic coarctation and phaeochromocytoma can be identified in up to one third of the patients.[1] Phaeochromocytoma occurs in 0.1% to 5.7% of these patients.[1,3] The average age of onset is 42 years.[1] The clinical symptoms are variable, but generally include high blood pressure, palpitations, paleness, headache, feeling of panic and anxiety.[4,5] Most patients have a single non-malignant tumor, but 22% have bilateral or multiple tumors, or both. Extra-adrenal phaeochromocytomas are rare.[1]

CASE REPORT

Male patient, aged 49, Caucasian, a bricklayer, born and resident in Mortágua, who visited the *Serviço de Atendimento Permanente* (SAP - Permanent Care Service) of Mortágua due to epigastralgia, nausea, palpitations, sweating and frontal headache since the day before. A hypertensive crisis was observed - blood pressure (BP): 180/125 mmHg – which was treated with captopril 25 mg sublingual (sl), furosemide 40 mg intravenous (iv), and isosorbide dinitrate 5 mg sl. In a second measurement of blood pressure, BP of 280/130 mmHg was observed, which was again treated with captopril 25 mg sl and furosemide 40 mg iv. The patient was taken to the Emergency Room (ER) of Coimbra University Hospitals, having been administered propranolol 0.5 mg iv and metoclopramide 10 mg iv.

Objective examination carried out in the ER showed the patient to be conscious, oriented in time and space, and collaborative, with skin and mucous membranes flushed and hydrated, afebrile, eupnoeic, capillary glucose of 162 mg/dl, BP of 240/173 mmHg (measured in both arms and legs) and arrhythmic radial pulse of 150 beats per minute. The neurological examination showed no abnormalities. The fundoscopy showed no changes. The cardiac auscultation revealed tachyarrhythmia with a heart rate of 150 bpm and no audible murmurs. The pulmonary auscultation was normal. The abdomen was painful on palpation of the epigastrium, but had no signs of peritoneal irritation. The patient had no peripheral edema. The pulses were palpable and symmetrical. On physical examination, the patient had multiple neurofibromas dispersed on the skin surface, especially on the trunk, and several café au lait spots.

The patient's personal history included hypertension since the age of 20, herniated lumbar disc, and neurofibromatosis type 1. The patient's family history included a brother with neurofibromatosis type 1. With regard to the patient's habits, he consumed approximately 50g of alcoholic drinks per day and used to be a heavy smoker (60 pack-years), but had been an ex-smoker for two years. The patient was treated with lisinopril-hydrochlorothiazide 20 mg + 12.5 mg id and glucosamine 1500 mg id.

The additional diagnostic methods initially performed were analytical blood test, chest X-ray, plain x-ray of the abdomen, electrocardiogram and abdominal ultrasound. In the analytical blood test, the presence was noted of erythrocytosis (hemoglobin of 18.6 g/dl), leukocytosis with neutrophilia (27.7 G/L with 89.2% neutrophils), renal insufficiency (blood urea nitrogen of 45 mg/dl and creatinine of 2.0 mg/dl) and a high myoglobin count (262 ng/mL) (Table I). Gasometry in room air showed no respiratory insufficiency. Neither chest x-ray nor plain abdominal x-ray showed any changes. The electrocardiogram confirmed tachyarrhythmia - supraventricular tachycardia. The patient was treated with enoxaparin 40 mg subcutaneously (sc) and amiodarone 300 mg in 100 ml of glucose solution 5% iv. As this therapy was not effective, adenosine 6 mg iv and propranolol 0.5mg iv were administered, which led to a reduction in blood pressure and heart rate. The abdominal ultrasound revealed hypoechogenic nodules of 8.4 x 6.4 cm, with no further increase, apparently following the inner contour of the top 1/3 of the left kidney.

TABLE I

Serum blood count and biochemistry on the day of admission

Description	Result	N Values
Hemograma		
Erythrocytes (T/1)	6,08	3,8 – 5,8
Hemoglobin (g/dL)	18,6	11,5 – 16,5
Hematocrit (%)	54,5	37 – 47
Mean globular volume (fl)	89,6	76 – 96
Leukocytes (G/l)	27,7	4,0 – 11,0
Neutrophils (%)	89,2	45 – 74
Eosinophils (%)	0,0	0 – 7
Basophils (%)	0,0	0 – 2
Lymphocytes (%)	5,8	16 – 45
Monocytes (%)	5,0	4 – 10
Platelets (G/l)	330	150 – 400
Biochemistry		
Blood urea nitrogen (mg/dL)	45	5 - 23
Creatinine (mg/dL)	2,0	< 1,3
Glycaemia (mg/dL)	160	60 – 120
Sodium (mmol/L)	143	135 – 145
Potassium (mmol/L)	4,7	3,5 – 5,3
Calcium (mg/dL)	10,6	8,4 – 10,4
Chlorine (mmol/L)	102	97 – 107
Osmolarity (mosm/kg)	299,9	260 – 302
Total protein (g/dL)	9,3	6,2 – 8,1
Albumin (g/dL)	5,9	3,5 – 5
CK (U/L)	91	23 – 203
Mass CK-MB (ng/mL)	3,5	< 3,6
Myoglobin (ng/mL)	262	9 – 82
Troponin I (ng/mL)	0,14	0,0 – 0,2
CRP (mg/dL)	0,7	< 1

The patient was then hospitalized at the Medicine Service I for further investigation of the nodule in the top 1/3 of the left kidney.

Bearing in mind that this is a patient with neurofibromatosis type 1, and symptoms of hypertensive cri-

TABLE II

24-hour urine metanephrine and vanillylmandelic acid levels

Description	Value (mg/L)	24-hour urine volume (mL)	Value/24 h (mg/time)	Value/24 h N (mg/time)
Metanephrine	6.000	1.900	11.400	0,020 – 0,350
Vanillylmandelic acid	24,30	1.900	46,2	0,0 – 15,0

sis associated with epigastralgia, nausea, palpitations, sweating, headache, and a nodule in the top 1/3 of the left kidney detected by abdominal ultrasound, three diagnostic hypotheses are possible: 1) phaeochromocytoma, 2) kidney tumor, and 3) neurofibromas causing compression of the kidney and/or renal artery.

The additional analytical study showed a significant increase in 24-hour metanephrine and vanillylmandelic acid counts in the 24H urine (11,400 mg/time, and 46.2 mg/time, respectively) (*Table II*). The urine ionogram showed no changes. The serum renin and aldosterone counts were initially high, but returned to normal in a subsequent analysis. Erythropoietin was normal.

CT of the kidneys and adrenal glands revealed a massive oval mass (8.2 x 6.3 cm axial axes) in the left adrenal gland, which was solid and heterogeneous both before and after intravenous contrast, with hypodense areas inside it, characterizing necrosis. There appeared to be no cleavage plane with the homolateral renal artery, but the latter was preserved for the other adjacent structures (*Figure 1*). MRI of the adrenal glands confirmed the existence of a massive solid nodule attached to the left adrenal gland, without apparent cleavage plane with the homolateral renal artery and vein, although the vessels were permeable (*Figure 2*). Doppler revealed that the left renal vein and artery were permeable; however, new vessels were observed, some heading towards injuries and others towards the psoas muscle, which made analysis of the renal vessels difficult. Renal scintigraphy with 99m Tc-DTPA showed a left kidney that was reduced in size and prolonged parenchymal transit, with an appearance suggestive of vascular impairment. Whole-body MIBG-I^{123}scintigraphy revealed a single focus of radiotracer uptake corresponding to the known lesion.

In view of these results, a definitive diagnosis of phaeochromocytoma of the left adrenal gland was reached.

With regard to the therapy, the patient was initially treated with enoxaparin 40 mg sc id, amiodarone 200 mg *per os* (po) id, amlodipine 10 mg po id and bisoprolol 5 mg po id, the latter two being suspended in order to perform the MIBG scintigraphy; phenoxybenzamine was later added to the treatment regimen. A clinical and analytical improvement was observed, with blood pressure and heart rate controlled. Seeking to exclude catecholamine cardiomyopathy, an echocardiography was performed, which showed a slight enlargement of the left atrium, mild mitral regurgitation and left ventricular hypertrophy of the interventricular septum with good global and segmental systolic function.

The patient underwent left adrenalectomy by median laparotomy. Histology revealed a phaeochromocytoma of 10.5 cm at its widest point, with large areas of necrosis, without capsular infiltration or vascular embolism. In relation to the immunohistochemistry, intense and diffuse positivity was found for NSE neuroendocrine markers, synaptophysin and chromogranin A, and immunonegativity for pankeratin MNF116 and vimentin.

Today, six months after surgery, the patient is in follow-up at the Outpatient department, and is clinically well without any analytical changes; his high blood pressure is controlled with the antihypertensive he was taking prior to hospitalization.

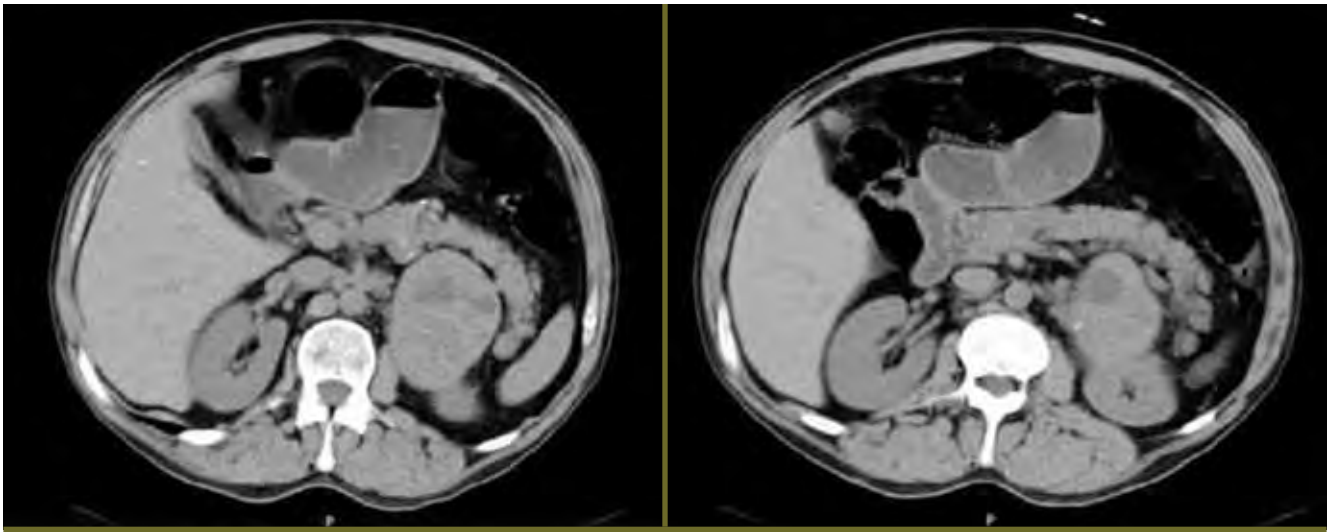
DISCUSSION

The patient had a history of neurofibromatosis type 1 and high blood pressure, with relatively nonspecific clinical symptoms (epigastralgia, nausea, palpitations, sweating and frontal headache); objective examination revealed tachycardia and systolic-diastolic hypertension. Laboratory tests revealed erythrocytosis, leukocytosis with neutrophilia, renal insufficiency and an increased myoglobin count. Abdominal ultrasound revealed a nodule at the top 1/3 of the left kidney.

Given these results, three diagnostic hypotheses are possible:

- Phaeochromocytoma,
- Kidney tumor, and
- Neurofibromas causing compression of the kidney and/or renal artery.

Phaeochromocytoma is a neuroendocrine tumor



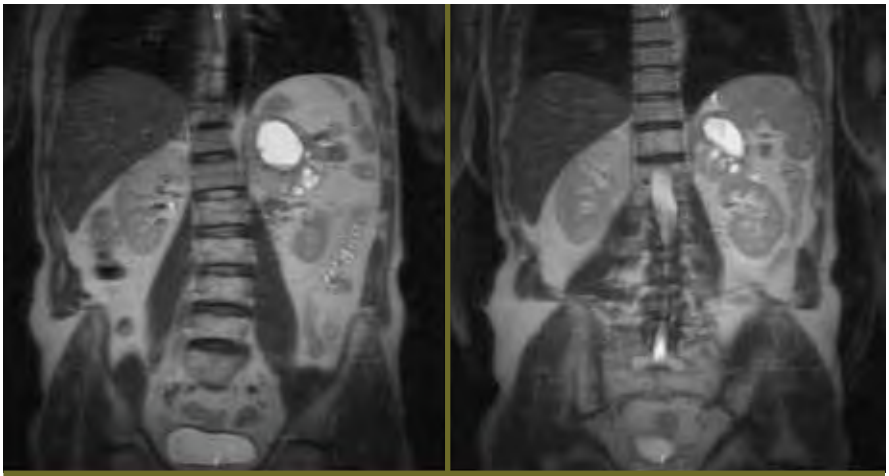
CT of the kidneys and adrenal glands – a large oval mass (8.2 x 6.3 cm axial axis) in the left adrenal gland, which was solid and heterogeneous before and after intravenous contrast, with hypodense areas inside it, characterizing necrosis.

FIG. 1

that originates in the adrenal medulla or extra-adrenal chromaffin tissue (paraganglioma or extra-adrenal phaeochromocytoma), a producer of catecholamines, the release of which may be due to changes in blood flow or the occurrence of necrosis in the tumor.[6,7] The prevalence of phaeochromocytoma in hypertensive patients is 0.1% to 0.6%, with an incidence of 1 in 200,000 individuals in the general population.[3] The "rule of 10" is used to characterize phaeochromocytomas – 10% are extra-adrenal and of these 10% are extra-abdominal, 10% are malignant, 10% occur in hypertensive patients, 10% are hereditary and 10% are bilateral. However, this "rule" was questioned in a recent publication.[8] Hereditary phaeochromocytomas occur in multiple endocrine neoplasm type 2A or type 2B, von Hippel-Lindau disease, neurofibromatosis type 1 and inherited paragangliomas. The remaining 90% of phaeochromocytomas are classified as sporadic.[3,7,9]

The clinical symptoms are variable, but generally include sustained or paroxysmal hypertension, headache, palpitations, sweating, feelings of panic or anxiety and pallor.[4,5] Nausea, vomiting, chest or abdominal pain, fever, weight loss, weakness, orthostatic hypotension, glucose intolerance, ventricular and supraventricular arrhythmias, ischemic cardiopathy, etc. may also occur.[9] The hematocrit can be high as a result of a reduction in plasma volume.[6] In rare cases, the tumor may secrete erythropoietin, creating a true erythrocytosis.[6] Phaeochromocytoma may be associated with direct compression of the renal artery and catecholamine-induced vasospasm, thus contributing to a situation of renal insufficiency.[6] On the other hand, any mass causing compression of the renal artery – renal tumor or neurofibroma – can lead to high blood pressure.[6] Renal artery stenosis (intrinsic or extrinsic) leads to decreased perfusion of the renal tissue.[10] This decreased perfusion of the renal tissue activates the renin-angiotensin system.[10] The circulating angiotensin II raises the blood pressure causing direct vasoconstriction, stimulating the secretion of aldosterone, which results in sodium retention and/or stimulating the adrenergic nervous system.[10] A renin-producing tumor would cause high blood pressure however, hypokalaemia and sodium retention should also be present, but they are not.[10] The sudden onset of severe hypertension, the associated symptoms and the analytical changes suggest secondary hypertension.[10] As mentioned previously, about 6% of the individuals with NF1 develop hypertension, and secondary causes of high blood pressure, such as renovascular disease (renal artery stenosis secondary to fibromuscular dysplasia), aortic coarctation and phaeochromocytoma can be identified in up to one third of patients.[1,11]

All the patients with suspected phaeochromocytoma should undergo biochemical analysis, as the diagnosis usually requires biological evidence of the excessive production of catecholamines by



MRI of the adrenal glands – a large solid nodule attached to the left adrenal gland, with no apparent cleavage plane with the homolateral renal artery and vein.

FIG. 2

the tumor.[8] The traditional biochemical analysis includes plasma and urine catecholamine levels, urine metanephrine (normetanephrine and metanephrine) levels and urine vanillylmandelic acid levels.[5] Determination of plasma free metanephrines is the most recently available test.[5] The determination of plasma chromogranin A, due to its low sensitivity and specificity, has no benefits over the above analysis in the initial diagnosis of pheochromocytoma.[5] There is increasing evidence to suggest that the fractionated urine metanephrine (normetanephrine and metanephrine separately) assays, and especially the plasma free metanephrine assays, are the most sensitive tests for diagnosis and the most appropriate ones for to excluding the presence of pheochromocytoma.[5] There are three advanced explanations for this: 1) unlike catecholamines, which are secreted sporadically, the plasma free metanephrines are continuously produced by the catecholamine metabolism in the tumor cells; 2) the sympathetic-adrenal stimulation causes a large increase in the release of catecholamines, while plasma free metanephrines are little affected; 3) the vanillylmandelic acid and total and fractionated urine metanephrines are different metabolites from plasma free metanephrines, and are produced in different parts of the body by metabolic processes that are not directly related to the tumor.[12] There are, however, three potential sources of false positive results in the biochemical phaeochromocytoma tests, including drugs, dietary factors and "stress" factors (with an increase in sympathetic-adrenal activity).[5,8,12] Many true positives can be distinguished from false positives by how far the results have increased compared with the reference ranges.[5] Clonidine, glucagon and tyramine levels are rarely used.[8]

Only after biochemical confirmation should the tumor site be identified, either by CT or by MRI (morphological criteria) or through whole-body MIBG-I^{123} scintigraphy (functional criteria).[8] Abdominal-pelvic CT is the most frequently used test for the initial identification of phaeochromocytoma sites. MRI is preferred over CT for the identification of extra-adrenal tumors in patients who are pregnant, in children, or in patients who are allergic to the contrast solution. Both have a similar sensitivity and specificity, of 90% to 100%, and 70% to 80%, respectively. Whole-body MIBG-I^{123} scintigraphy has sensitivity of 83% to 100% and specificity of 95% to 100%, and is indicated particularly for patients with extra-adrenal or adrenal tumors over 5 cm with increased risk of malignancy, or in patients with a high suspicion of multifocal disease. [5,6]

The additional investigation performed on admission led to a definitive diagnosis of phaeochromocytoma. The 24-hour urine metanephrine and vanillylmandelic acid levels were high, and a CT scan of the kidneys and adrenal glands revealed that the mass was located in the left adrenal gland. The normal urine ionogram results enabled a renin-producing tumor to be ruled out. In a first analysis, the serum renin and aldosterone levels were increased, which may be related to catecholamine-induced vasoconstriction. Whole body MIBG-I^{123} scintigraphy revealed a single focus of radiotracer hyper-uptake corresponding to the known lesion.

In the case of phaeochromocytoma, the medical therapy is essentially a preoperative therapy, which seeks to minimize surgical complications.[5] Phenoxybenzamine is the drug of choice.[5] It is an alpha-blocker, which should be administered at least 10 to 14 days before surgery.[5] A dose of 10 mg 2 id should initially be administered, and it should be increased

to 1 mg/kg/day.[5] Beta blockade is important in patients with tachyarrhythmia.[5] Beta blockade should not be initiated before the alpha blockade, because the loss of vasodilation mediated by the beta receptors leads to unopposed alpha-adrenergic stimulation, and can cause hypertensive crisis.[5] In this case, when no diagnosis is found, and a difficult-to-control tachyarrhythmia is observed, the use of a beta-blocker prior to the alpha-blocker should be chosen.

It is not possible to predict the development of malignant disease based on the histological findings of the resected tumor. The presence of metastatic disease is the only indicator of malignancy.[5] The main sites of metastasis are the bones, lungs, liver and lymph nodes.[5] The risk of malignancy is higher in tumors over 5 cm (as in this case) and tumor site is usually the extra-adrenal glands.[5] The prognosis of a separate sporadic phaeochromocytoma is excellent.[5] The recurrence rate is less than 10%.[5] In extra-adrenal disease and inherited cases, the recurrence rate is higher.[5] After surgery, high blood pressure may persist in 50% of patients.[5]

Careful postoperative monitoring is important, and should include clinical, analytical and imaging analysis. ■

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