Phaeochromocytoma associated to Von Recklinghausen Neurofibromatosis type I: a rare clinical case

Vanda Jorge, Inês Pires da Silva, Miguel Sousa, Carla Noronha, Manuel Vaz Riscado

Abstract

Phaeochromocytoma is a tumor derived from the chromaffin cells located mainly in the adrenal gland medulla neural crest and also in the sympathetic ganglia (paraganglioma).

90% of cases are sporadic. However, in about 10% of cases, phaeochromocytoma is a feature of neoplastic autosomal dominant syndromes, such as Von Hippel Lindau's disease, Multiple Endocrine Neoplasia type 2 (MEN 2) seldom associated to Von Recklinghausen Neurofibromatosis type I – NF1 (3-5%).

The authors present the case of a 54 year-old male with a personal and family background of Von Recklinghausen Neurofibromatosis type I in whom a right adrenal asymptomatic mass was detected ("incidentaloma"). Further investigation disclosed a phaeochromocytoma producing high levels of epinephrine and nor-epinephrine. Despite this secretory pattern, normotension was established by 24h ambulatory blood pressure measurement, as well as an absence of family history of hypertension, both fairly uncommon.

Some pathogenic mechanisms involved in such tumoral syndromes are debated along with their clinical manifestations, stressing the need for a systematic oncological screening in NF1 patients and family members, even if asymptomatic.

Key words: phaeochromocytoma, neurofibromatosis type 1, hypertension.

INTRODUCTION

Phaeochromocytomas are rare neoplasms (2 – 8 per million people/year) with higher incidence on the fourth and fifth decades of life, affecting equally both genders.[1] The diagnosis is based on high blood pressure, associated with headaches, palpitations and facial redness. The screening includes dosing plasmatic metanephrine and catecholamine or metanephrine in the 24 hours urine output, and image tests (CAT scan or NMR and scintigraphy with ^{123}I–MIBG).[2] Therapy is a surgical one (laparoscopy or open), preceded by pharmacotherapy (α adrenergic blockade with or without β adrenergic blockade and /or α methyl tyrosine).[3]

Medicine II Service, Curry Cabral Hospital, Lisbon
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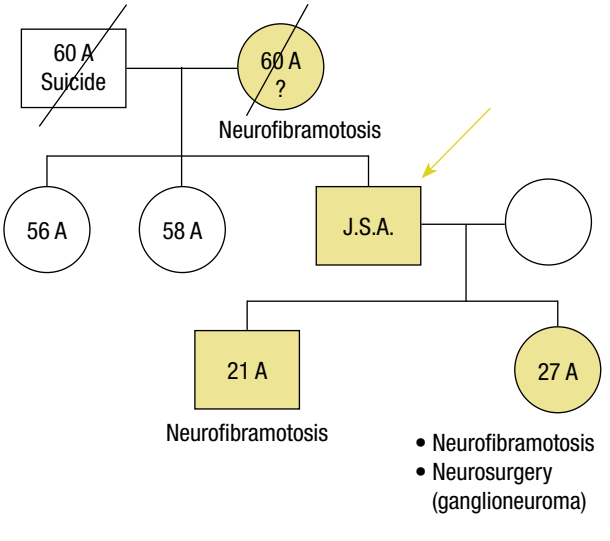
Phaeochromocytomas occur mainly in the sporadic form, however accounting for 10% of cases, after dominating autosomal syndromes being the most rare association with the Von Recklinghausen's Disease or type I neurofibromatosis (3 – 5%).[1,4]

Type I neurofibromatosis accounts for over 8% of all cases of neurofibromatosis, presenting an incidence of 1: 3500 people.[5] It is one of the most frequent neurocutaneous diseases. It has a dominating autosomal transmission, although 50% of cases are due to new mutations. Its clinical manifestations are extremely variable among individuals, even those who are related and also variable throughout the life of the same individual. Its diagnosis requires the presence of at least two major criteria:

- 6 *café-au-lait* spots with dimensions above 0.5 cm in pre-puberty children or above 1.5 cm after the puberty period;
- Axillary or inguinal ephelides;
- Two or more cutaneous neurofibromas;
- A plexiform neurofibroma;
- Two or more Lisch (Hamartoma affecting the iris);
- Optical glioma;
- Bone lesion: sphenoid dysplasia, long bones cortical layer lesion;
- NF1 family background (first-degree).[6]



Genogram.

FIG. 1

In the clinical case presented, it is highlighted the rare association between phaeochromocytomas and type I neurofibromatosis, as well as the absence of high blood pressure.

CLINICAL REPORT

A 54 year-old male patient, Caucasian, referred to the internal net in consultation due to the appearance of painful neurofibromas, with marked growth in number and size: predominantly in the abdomen.

This was a patient with a known history of type I neurofibromatosis or Von Recklinghausen's disease from birth. Inguinal herniorrhaphy (2002) and pulmonary tuberculosis (2003), subject to antibacillary therapy for six months.

In the family background to be highlighted type I neurofibromatosis affecting the mother and both sons (*Fig. 1*).

The patient denied complaints related with high blood pressure, diabetes mellitus, kidney or thyroid pathology.

The objective examination showed he was normotensive (BP: 120/70 mmHg), and normocardic (FC: 75 beats per minute). To highlight, multiple neurofibromas (*Fig. 2*) spread all over the skin, with higher expression on the dorsal, lumbar and abdominal region. The most painful were located in the lower quarters of the abdomen (in the belt area). *Café-au-lait* spots spread in the trunk (*Fig. 2*). With no other objective changes.

Analytically: complete hemogram, liver and kidney profile, total proteins and albumin and and a brief urine test within normal ranges with exception of the ionogram persistent hyperkalaemia ($K^+ = 5.3$ mEq/L).

ECG which sinusal rhythm (heart frequency: 80 bpm) and presence of peak T-waves.

The thorax X-ray has shown bilateral hilar reinforcement and right apical hypo-transparency.

According to the ionogram changes and the presence of painful abdominal neurofibromas, an abdominal and renal ultrasound was carried out revealing: solid hypo-echogenic node formation, about 4 cm in diameter, at the level of the right adrenal, being this an *incidentaloma*.

In this context it was carried out the screening of a possible adrenal tumor (causing Cushing's syndrome, primary hyperaldosteronism or phaeochromocytoma) or other endocrinal tumors (thyroid or parathyroid), normal 24-hour pressure metrics normal; cortisol, ACTH, renin, aldosterone, PTHi, calcitonin, total and ionized calcium, pentagastrin test, normal thyroid function and ultrasound. Homovanillic acid, 5-hydroxyindoelacetic acid and urinary metanephrines within normal ranges. However the urinary vanilmandelic acid (142 mg/24 hours) and serial catecholamine were high (*Table 1*).

Thoraco-abdominal CT scan has shown: homogenous node lesion on the right adrenal, with around 4 cm in diameter. (*Fig. 3*).

Scintigraphy with ^{123}I – MIBG, to confirm the activity of the tumoral mass was carried out revealing focal hyperfixation only on the right adrenal (Figure 4).

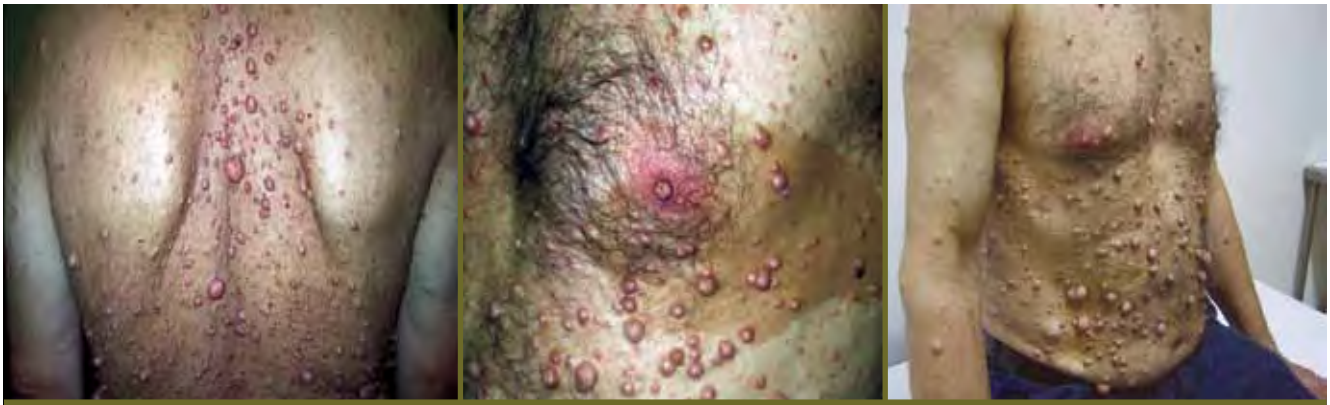
It was then established the phaeochromocytoma diagnosis in association with type I neurofibromatosis, and the patient was medicated previously to the surgical intervention with phenoxybenzamine (30 mg per day *per os*).

He was then subject to the right adrenalectomy via laparoscopic route (pathologic anatomy exam compatible with phaeochromocytoma) and excision of some painful neurofibromas.

Genetic studies confirmed the mutation to the type I neurofibromatosis gene, in the patient and his two sons.

The patient kept asymptomatic.

Subsequently was carried out the family oncological screening, mainly with endocrinological dosage



Café-au-lait spots and widespread neurofibromas on the cutaneous surface.

FIG. 2

and image methods (ultrasound, CAT scan and eventual scintigraphy with ^{123}I – MIBG).

His daughter was subject to the extraction of a cerebral ganglioneuroma without analytical endocrinological changes. There was no evidence of other cases of adrenal tumor in the family.

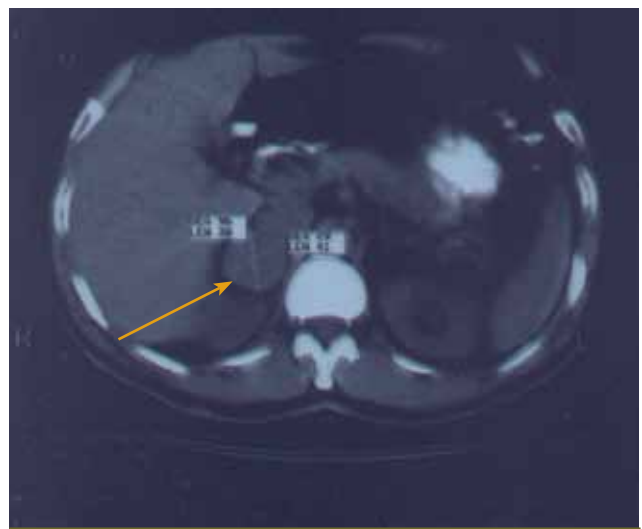
DISCUSSION

The clinical case refers to a 54 year-old man, with a personal and family history of type I Von Recklinghausen's neurofibromatosis, where it was detected a right adrenal tumor, asymptomatic ("incidentaloma"),[7] which subsequent investigation proved to be a phaeochromocytoma producing higher levels of epinephrine and norepinephrine.

TABLE I

Laboratorial values: urinary vanilmandelic acid and serial catecholamine increase

Substance	Value
Urinary homovallinic acid	5,7 (N: 1-12 mg/24 hours)
Urinary 5-Hydroxyindolaceatic acid	6,6 (N: 2-8 mg/24 hours)
Urinary vanilmandelic acid	142 (N: 2-8 mg/24 hours)
Urinary metanephrine	0,05 (N: < 5,5 µmol/24 hours)
Total catecholamine	195,8 (N: 10-100 pg/mL)
Epinephrine	202 (N:<70 pg/mL)
Norepinephrine	912 (N: 450 pg/mL)
Dopamine	10 (N: 130 pg/mL)



Thoraco-abdominal-pelvic CT scan: homogenous node lesion on the right adrenal, with about 4 cm in diameter.

FIG. 3

The biochemical study of phaeochromocytoma is recommended not only in symptomatic individuals, but also in those with identified adrenal or genetic predispositions (type I neurofibromatosis, Von Hippel-Lindau's Disease, multiple endocrine neoplasms and phaeochromocytoma – paraganglioma syndromes). Recent studies suggest that measuring urinary and plasmatic metanephrines is the most sensitive test for diagnosis.[8,11]

Scintigraphy with ^{123}I – MIBG main purpose is to confirm functionally the tumor which was lo-

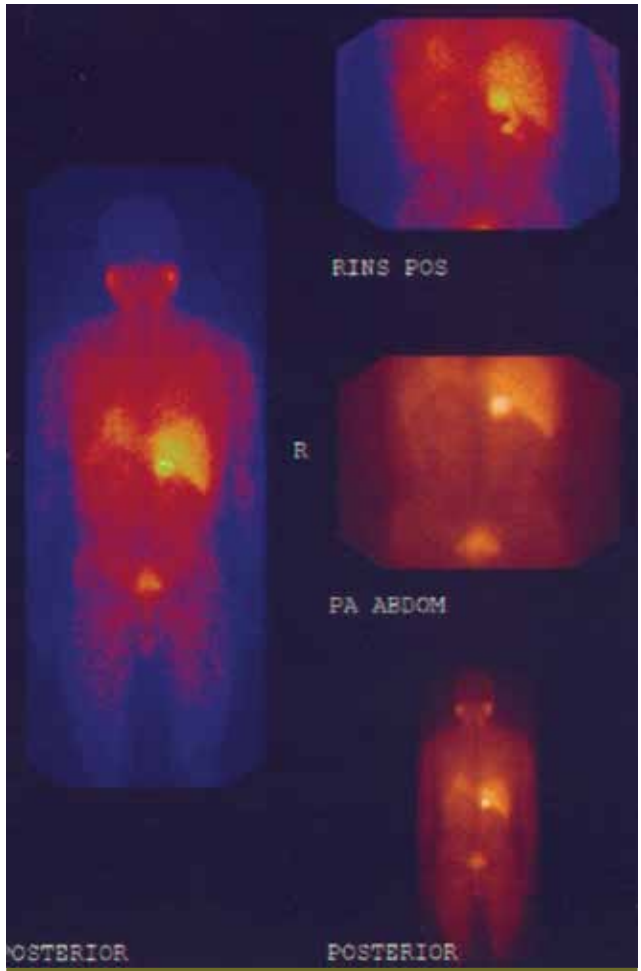
cated whether by CT scan or NMR. It also has an important role in the diagnosis of the extraglandular phaeochromocytoma and remaining tumoral tissue after surgery.[1] It has a high sensitivity (83 – 100%) with specificity above 95%. Octreotide scintigraphy, a somatostatin analog, has a rather lower sensitivity (25%).[11]

In spite of the catecholamine secretory pattern, it was confirmed by 24-hour pressure metrics, the existence of normal tension. It was also verified the absence of a high blood pressure family history, facts also uncommon (only in 10% of cases of phaeochromocytomas normotension is evident).[1]

In the phaeochromocytoma, catecholamine excessive secretion and high serial levels are responsible for typical symptoms: paroxysmal hypertensive crisis (expressed by headache, profuse sweating and palpitations) or persistent high BP, in most cases refractory to the conventional pharmacological treatment.[1] The predominantly secreted catecholamine is norepinephrine, originating the vasoconstriction mediated by α receivers, associated to the diastolic hypertension. Epinephrine is less frequently secreted, leading to a higher cardiac stimulation mediated by β receivers, with predominance of systolic hypertension and tachycardia. The reason for some patients with phaeochromocytoma being normotensive it is not known. A possible explanation could be however a hypersecretion of other vasodilating components, as adrenomeduline, natriuretic peptic, nitric oxide, dopa or dopamine.[9]

However, it was verified that the blood pressure can be persistently normal, mainly in patients with adrenal incidentaloma, with identifiable family syndromes or with a small dimensions. [8]

The definite treatment is the surgical removal of the tumor that should be preceded by α adrenergic blockade for 1 to 4 weeks, preferably with oral phenoxybenzamine.[10] An adequate hydration should be started and a diet free of salt, to enable the volume re-expansion. The tumor removal by laparoscopic surgery is the preferred surgical approach reducing the post surgical morbidity. The complications that might occur during surgery express themselves by haemodynamic instability with hypotensive periods, hypertensive peaks and tachydysrhythmia. The immediate postsurgical period should be made in an intensive care setting with special attention to hypotension situations (through abrupt drop in the



Scintygraphy with 123I-MIBG: focal hyperfixation on the right adrenal.

FIG. 4

circulating catecholamines after removing the tumor and the presence of phenoxybenzamine) solved with fluid reposition and occasionally endovenous ephedrine or vasopressin, and hypoglycaemia (by an hyperinsulinaemia rebound due to the recovery of insulin release after the tumor removal).[8]

To highlight still in this case the extremely rare association of phaeochromocytoma with type I neurofibromatosis (3 to 5%), (*Table 2*).[1] What regards the clinical presentation in 90% of cases the phaeochromocytoma is benign and in 84% this is a unique tumor.[11]

Genetic studies have confirmed the mutation for the gene of type I neurofibromatosis in the patient and his 2 children. Subsequently it was carried out the fa-

TABLE II

Feocromocitomas familiares

Syndrome	Gene	Locus
Type 2 multiple endocrine neoplasm 2 (MEN2), (30-60%) - Thyroid medullar carcinoma - Phaeochromocytoma A: Hyperparathyroidism B: Multiple neuroma	Ret-proto-oncogene	10q11.2
Von Hippel-Lindau's Disease (VHL), (15-20%) type 2 A: CNS and retine haemangioblastoma; phaeochromocytoma; Endolymphatic tumors; cystadenoma B: + Carcinoma and renal cysts + Carcinoma and pancreatic cysts C: Phaeochromocytoma (only)	Tumoral suppressor gene - VHL	3p25-26
Type 1 Neurofibromatosis (NF1), (3-5%) Multiple neurofibromas in the skin; "café-au-lait" spots; Lisch nodes in the iris	Gene NF-1	17q11.2
Phaeochromocytoma-paraganglioma (70-80%) Head and neck tumors (Extra-adrenal); phaeochromocytomas	Gene SDHB Gene SDHD	1p35-36 11q21-23

mily oncological screening, without evidence of other cases of adrenal tumor. His daughter was diagnosed with a cerebral ganglioneuroma, and it was considered to be associated with type I neurofibromatosis. Analytically without biochemistry or endocrinology changes, being subject to tumor excision.

In the phaeochromocytoma, the more recent literature recommendations point out to be crucial to excluding the hereditary syndromes, through a clinical, thorough and directed evaluation, through the screening of the most likely candidates to gene mutations (*Table 2*).[12] Genetic tests enable to identify mutation carriers in an early stage of the disease or before the symptoms to emerge. The chances of curing a phaeochromocytoma and also associated tumors (e.g., thyroid medullar tumor in MEN-2) increase significantly with an early diagnosis.[1,4]

Due to the possibility of recurrent phaeochromocytoma, the follow-up is for the whole life of the patient, particularly when it is a hereditary form or extra adrenal location. The follow-up is a clinical, biochemical and imaging should be quarterly in the first year and yearly in the following 5 to 10 years full. [11]

The prognosis, different from patients with metastases (high dimensions tumors, paragangliomas) is usually excellent.[11] ■

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