

## DIAGNOSIS OF NEUROFIBROMATOSIS TYPE 1 – RELATED PHEOCROMOCYTOMA AFTER STROKE AND MYOCARDIAL INFARCTION

Ana Valea<sup>1,2</sup>, Andra Morar<sup>3</sup>, Adina Ghemigian<sup>4,5</sup>, Eugenia Petrova<sup>4,5</sup>, Claudiu Tupea<sup>4</sup>,  
Mihaela Popescu<sup>6</sup>, Nicoleta Dumitru<sup>4</sup>, Mara Carsote<sup>4,5</sup>

<sup>1</sup> County Clinical Emergency Hospital, Cluj-Napoca, Romania

<sup>2</sup> "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania

<sup>3</sup> "Leon Daniello" Clinical Pneumophysiology Hospital, Cluj-Napoca, Romania

<sup>4</sup> "C.I. Parhon" National Institute of Endocrinology, Bucharest, Romania

<sup>5</sup> "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

<sup>6</sup> University of Medicine and Pharmacy, Craiova, Romania

### ABSTRACT

Hereditary syndromes underlying neuroendocrine tumours are extremely heterogeneous and, despite the genetic background, their recognition may actually be done later in life in many cases. Our purpose is to introduce a case of neurofibromatosis type 1 – related pheocromocytoma on a patient within his six decade of life after multiple cardiovascular complications. A 53-year old male is admitted for loss of appetite with weight loss, decreased exercise tolerance, transient occipital headache, night sweats. His medical history revealed arterial hypertension, right carotid artery ischemic stroke, and a recently non-STEMI myocardial infarction diagnosed two months ago. The pathological family history illustrated mother and a brother prematurely dying of myocardial infarction (no date of skin anomalies). Clinical examination reveals café-au-lait spots, axillary freckles, skin neurofibromas and a large plexiform neurofibroma in the right thigh. Evaluation of the adrenal gland revealed highly elevated values of urinary metanephrines and normetanephrines. Computed tomography showed a left adrenal gland tumour of 31/39 mm. Thus neurofibromatosis type 1 in addition to a left pheocromocytoma was confirmed. A cardiologic examination before surgery was re-done. Given previous pathological history (cardiovascular events like stroke and nonSTEMI infarction) adrenalectomy was delayed for the moment in addition to second antiplatelet agent and the alpha blocker medication in increasing doses. The adrenal tumour removal is planned to be done as soon as cardiovascular risk is acceptable. The importance of endocrine check is seen in young patients with severe cardiovascular and neurological acute conditions that are actually caused by a hormonal excess like found in pheocromocytoma. Nevertheless, the spectrum of tumours associated with neurofibromatosis type 1 is heterogeneous and screening protocols are still a matter of debate. Delayed diagnosis worsens the overall prognosis.

**Keywords:** arterial hypertension, neurofibromatosis, adrenal tumour, pheocromocytoma

### INTRODUCTION

Hereditary syndromes underlying neuroendocrine tumours are extremely heterogeneous and, despite the genetic background, their recognition may actually be done later in life (1,2). The endocrine/neuroendocrine tumours that are found in relationship to genetic conditions varies from pituitary tumours to thyroid cancer or adrenal tumours

or neuroendocrine neoplasia, frequently requiring a multi-disciplinary team (3,4). Some of these tumours have a late onset thus they are detected due to associated hormonal production or due to local compressive symptoms/distant metastasis or they are detected by accident during a screening imaging procedure (5,6,7). In this large field of hereditary syndromes, neurofibromatosis type 1 is an autosomal dominant condition caused by a muta-

tion at the level of NF1 tumour suppress gene (8). The skin hallmark is represented by café-au-lait spots, skinfold freckling as well as Lish nodules in addition to different forms of dermal neurofibromas (1,8,9). Bone anomalies like scoliosis are positive in various combinations (1,8,9). The associated tumour panel includes non-endocrine masses like optic gliomas, spinal neurofibromas, etc. and endocrine neoplasia like somatostatinoma or pheochromocytoma (10,11).

### AIM

Our purpose is to introduce a case of neurofibromatosis type 1 – related pheochromocytoma with late recognition during life after multiple cardiovascular complications are already diagnosed.

### METHOD

This is a case report. The patient agreed for anonymously description of his medical records.

### CASE PRESENTATION

A 53 - year old former smoker male was admitted for loss of appetite with weight loss (10 kg within last 2-3 months), decreased physical exercise tolerance, transient occipital headache, night sweats, insomnia, low back pain and productive cough. His medical history revealed arterial hypertension, right carotid artery ischemic stroke, chronic obstructive pulmonary disease and a recently non-STEMI myocardial infarction diagnosed two months ago. The pathological family history illustrated mother and a brother dying of myocardial infarction, two brothers with type 2 diabetes mellitus and father with Parkinson's disease. At admission, the patient was under treatment with ivabradine, conversion enzyme inhibitors, antiplatelet agents, lipid-lowering drugs, and bronchodilators.

The physical examination reveals: height of 165 cm, weight of 53 kg, BMI (Body Mass Index) of 19 kg/m<sup>2</sup>, dysarthria, slightly elevated blood pressure, areas of hyperpigmented skin, café-au-lait spots, axillary freckles, skin neurofibromas and a large plexiform neurofibroma in the right thigh (Figure 1,2).

Evaluation of the adrenal gland revealed elevated values of urinary metanephrines and normetanephrines, normal values of serum aldosterone and aldosterone-renin ratio, normal serum and urinary cortisol levels (Table 1).



**FIGURE 1.** Café-au-lait spots and cutaneous neurofibromatosis in a 53-year-old man diagnosed with neurofibromatosis type 1 and pheochromocytoma



**FIGURE 2.** Plexiform neurofibroma in the right thigh in a 53-year-old man diagnosed with neurofibromatosis type 1 and pheochromocytoma and multiple cardiovascular complications

**TABLE 1.** Biochemical and hormonal profile of a 53-year old male with pheochromocytoma

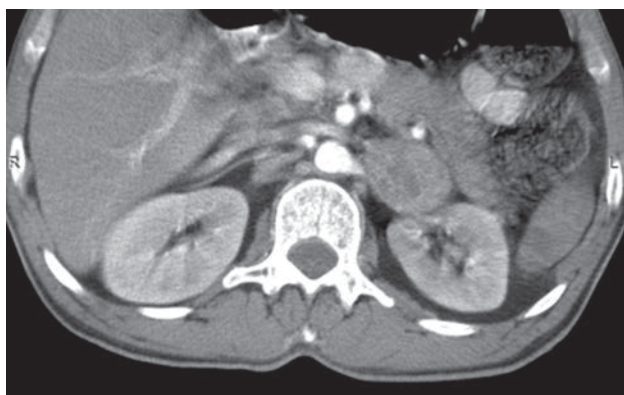
Parameter	Patient's value	Normal limits	Units
Haemoglobin	9.6	13-17	g/dl
Haematocrit	31.7	40-54	%
Platelets	882	150-400	10 <sup>9</sup> /l
Leukocytes	12.54	4-10	10 <sup>9</sup> /l
Iron content	9	70-180	µg/dl
Total cholesterol	193	< 200	mg/dl
Triglycerides	77	< 150	mg/dl
Total serum calcium	9.12	8.8-10.6	mg/dl
Ionic serum calcium	4.69	4.4-5.4	mg/dl

Parameter	Patient's value	Normal limits	Units
Urea	45	17-43	mg/dl
24-hour urinary metanephrines	1,165.8	59-394	µg/24 h
24-hour urinary normetanephrines	2,694.05	128-934	µg/24 h
Plasma aldosterone	2.75	1.17-23.6	ng/dl
Aldosterone-renin ratio	0.04	< 3.7	
Morning plasma cortisol	17.51	6.4-22.8	µg/dl
24-hour free urinary cortisol	3.96	1.5-63	µg/24 h
Parathormone	47.6	12-88	pg/ml
Calcitonin	8.4	0.5-18	pg/ml
TSH	0.97	0.4-4	µIU/ml
FT4	1.04	0.61-1.35	ng/dl

TSH = thyroid stimulating hormone; FT4 = free thyroxine; µg = microgram; fL = femtoliters

The hormonal profile also indicated normal values for TSH (thyroid stimulating hormone), FT4 (free thyroxine), PTH (parathormone) and calcitonin (Table 1). Moreover, the assessments pointed slightly elevated carcinoembryonic antigen of 5.42 ng/ml (normal levels < 3 ng/ml), iron deficiency related anaemia, leukocytosis and thrombocytosis (Table 1).

Thoracic-abdominal CT (computed tomography) angiography exam with contrast showed left lobe lung node of 16.8 mm, normal right adrenal gland and an expansive formation in the left adrenal gland, inhomogeneous, with a non-uniform contrast uptake of 31/39 mm (Figure 3).



**FIGURE 3.** CT angiography exam with contrast in a patient diagnosed with pheochromocytoma show a tumour mass of 31/39 mm located in the right adrenal gland

Thus neurofibromatosis type 1 in addition to a left pheochromocytoma was confirmed. A cardiovascular examination before surgery was re-done. Given previous pathological history (cardiovascular events like stroke and nonSTEMI infarction)

adrenalectomy was delayed for the moment in addition to second antiplatelet agent and the alpha blocker medication in increasing doses. The adrenal tumour removal is planned to be done as soon as cardiovascular risk is acceptable.

## DISCUSSIONS

This case illustrates several practical aspects that we consider useful to be mentioned.

### Late diagnosis of a conditions with a genetic background

The patient presents the association of some systemic diseases with potential for genetic transmission (like skin anomalies and pheochromocytoma) but with late diagnosis, at least in the case of type I neurofibromatosis, for which specific clinical hallmarks, such as café-au-lait spots and plexiform neurofibroma appeared before the age of 4 years (12,13). For this patient, the diagnosis of type I neurofibromatosis was established based on the presence of 3 of the specific clinical elements, namely café-au-laits pots, axillary freckles, skin neurofibromas and plexiform neurofibroma in the right thigh (14). We do not have information about the presence of the disease among first-degree relatives but the death due to cardiovascular complications of his mother and one of his brothers is highly suggestive to a pheochromocytoma most probably related to neurofibromatosis type 1 (15). Neurofibromatosis type 1 (von Recklinghausen's disease) is an autosomal dominant disorder thus the genetic consulting of the entire family is needed (1).

### Neurofibromatosis type 1 and a pulmonary nodule

The pulmonary nodule described on CT examination maybe an accidental association but also it be attributed to neurofibromatosis and related tumours, recognized for the 10% risk of mediastinal tumours (16,17). Routine screening of lung conditions in this genetic syndrome is not implemented yet (18). A second neuroendocrine tumour may be positive under these circumstances as seen in other locations (19,20). For instance, the NF1 gene mutations via signal transduction of p21, MAP or RAS pathways underlines a heterogeneous spectrum of abdominal tumours which is found in one out of four patients like gastrointestinal stromal tumours, neuroendocrine neoplasia, rhabdomyosarcoma (21). Nevertheless routine screening of

these anomalies is not introduced in protocols of neurofibromatosis type 1 but specialised multidisciplinary teams should follow the subjects in any medical and surgical area (22). In this particular case, serial imagery is needed for the follow-up of the nodule since biopsy or other potential traumatic interventions are less feasible due to active pheochromocytoma at this point.

### Pheochromocytoma and neurofibromatosis type 1

The association with pheochromocytoma is mentioned in 2% (varying from 1 to 5.7%) of cases as oppose to general population (of less than 1%) (23,24). As of this patient, the pheochromocytoma usually has a unilateral location (25). Delaying the recognition of catecholamines producing tumour is dramatic due to negative effects on cardiovascular and neurological status as seen here, even causing cardiac arrest, sudden death or premature death thus adrenalectomy is needed as soon as possible even in bilateral tumours (26). As seen in other tumours that were mentioned before, the screening of pheochromocytoma in families with the NF1 gene mutation is less established in guidelines even it seems extremely useful (25). In this case we have the first information about high blood pressure values from the age of 43 years. Screening for pheochromocytoma was performed in the context of the association of arterial hypertension in young age complicated with ischemic stroke that occurred 4 years after the onset of hypertension. The high cardiovascular risk for ischemic events is also supported by recent myocardial infarction and suggestive family medical background. Other adrenal tumours causing massive cardiovascular damage includes Cushing's syndrome and Conn's syndrome (27,28). Elevated blood pressure due to endocrine tumours in young patients is also caused by pituitary tumours like somatotropinoma or corticotropinoma (29,30). Moreover, thyrotoxicosis or even hypercalcemia (but parathyryn secreting tumours are more frequent in females) may be associated with arterial hypetension (31,32).

### Other aspects

The normal ultrasound appearance of the thyroid, normal values of calcitonin, PTH and calcaemia excluded other multiple neoplasia syndromes in this particular case but their routine endocrine evaluation is necessary (33). In order to have an adequate preoperative approach and to control blood pressure values, alpha blocker medication was included in the therapeutic scheme. Based on cardiologist evaluation, the surgery was delayed for the moment in addition to new medication but adrenalectomy is needed since excessive levels of metanephrines/normetanephrines worsen the cardiovascular status. Associated thrombocytosis is an additional risk factor for ischemic phenomena (34,35). Also, iron deficiency – related anaemia which seems of unknown cause, probably as a sign of chronic illness. Thrombocytosis is mostly caused by other amines that are produced by pheochromocytoma apart for catecholamines, knowing the complex cocktail of molecules produced by such tumours similar to neuroendocrine neoplasia (34,35). Surgical removal of adrenal tumour secreting catecholamines has a curative effect but complex cardiovascular medication is needed before, during, and after surgery (36,37). However, the risk of other cardiac and neurological emergencies is very high (38). Therefore close endocrine, cardiac, neurological, biochemical, and imagery check-up is recommended.

### CONCLUSIONS

The importance of endocrine check is related to young patients with severe cardiovascular and neurological acute conditions that are actually caused by a hormonal excess like seen in pheochromocytoma. Nevertheless, the spectrum of endocrine and non-endocrine tumours associated with neurofibromatosis type 1 is heterogeneous and screening protocols are still a matter of debate.

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