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Non-syndromic pheochromocytoma: From post-operatory scores to lifetime follow-up

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Abstract

We introduce a case report of an adult male diagnosed with non-syndromic pheochromocytoma with a first pathological post-operatory report of malignant type with further re-considerations during follow-up for a 6-year period of time. This is 46 - year old male admitted for: post-adrenalectomy status reassessment. In 2013 he was diagnosed with high blood pressure requiring a complex regime of anti-hypertensive drugs to control it. In 2015 he was referred for an endocrine check-up which revealed a pheochromocytoma (noradrenaline type). Computed tomography imaging of the abdomen showed a right adrenal tumour of 28/38 mm, a mass that was clearly contoured, with heterogeneous pattern, and with moderate caption of intravenous contrast. Laparoscopic right adrenalectomy is performed with normalization of high pre-operatory normetanephrines and a dose reduction of anti-hypertensive medication which was still necessary. Pathological report suggested a malignant pheochromocytoma; the initial PASS score of 8 was later re-calculated, and a GAPP score of 5 was achieved showing a moderately differentiated tumour. No genetic backup was identified. Within the first year after tumour removal, the patient suffered a stroke, proving the higher cardiovascular risk than general population even after hormonal imbalance is restored. Lifelong surveillance is the rule.

Keywords: pheochromocytoma, adrenalectomy, high blood pressure, PASS score, GAPP score, stroke

INTRODUCTION

There are multiple endocrine causes of high blood pressure like pituitary related causes (acromegaly, Cushing disease), adrenal-related causes (like pheochromocytoma, Conn's syndrome, adrenal Cushing syndrome, certain types of bilateral macronodular hyperplasia, adrenocortical carcinoma, etc.), some thyroid conditions, especially those with hyper-function or overtreatment with levothyroxine, and, also particular types of neuroendocrine neoplasia (1-5). Pheochromocytoma is a rare, yet potentially deadly condition, due to increased cardiovascular risk, as well as potential malignant status in some cases as shown by high GAPP/PASS scores (6,7). Malignant pheochromocytoma, however, is traditionally considered if the positive metastatic status is found (8,9). Despite progress in early

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approach and advanced imaging like 68Ga-DOTATATE and 64Cu-DOTATATE, pheochromocytoma has usually a strong genetic background, and the potential of aggressive profile remains an open issue, thus lifelong surveillance is indicated in majority of cases (10,11).

AIM

We introduce a case report of an adult male diagnosed with non-syndromic pheochromocytoma with a first pathological report of malignant type with further considerations during follow-up. The patient agreed to use the medical records, respecting the anonymous presentation.

CASE PRESENTATION

This is 46 - year old male admitted for: post-adrenalectomy status reassessment. His medical family history is negative.

The personal medical history includes:

- 2013: diagnostic of high blood pressure at Cardiology Department. Anamnesis showed that the patient had paroxysmal hypertension with the highest values of 220/120 mmHg, with palpitations, intensive sweating, muscle weakness, pallor, tachypnea. The patient started antihypertensive treatment with modest control of arterial pressure values: Metoprolol 50 mg/day; Pentaeritril Tetranitrate 2.6 mg (1-0-0); Trimetazidine 20 mg (0-1-0); Perindopril 10 mg (0-0-1); Indapamide 2.5 mg (0-0-1)
- 2013-2015: anamnesis revealed paroxysmal hypertension under antihypertensive treatment (different regimes were taken into consideration)
- June 2015: recommendation for an endocrine check-up since a secondary endocrine cause is suspected. On admission, the endocrine evaluation confirmed a pheochromocytoma apparently of sporadic type with predominant secretion of normetanephrines opposite to metanephrines (Table 1). Computed tomography imaging of the abdomen and pelvis showed a right adrenal tumour of 28/38 mm, a mass that is clearly contoured, with heterogeneous pattern, and with moderate caption of intravenous contrast.
- July 2015: laparoscopic right adrenalectomy (with typical pre-operatory preparation consisting in alpha and beta adrenergic blockage and calcium blockers) went without adverse events. Postoperatively, the patient had a satisfactory evolution, with fast resumption of intestinal transit and per primam healing of surgical wounds. Arterial hypertension was control after adrenalectomy allowing the reduction of antihypertensive mediation without actually stopping it. Three months after adrenalectomy, computed tomography showed a mild fibrous pericarditis and a right kidney stone. Periodical computed tomography scans were used for sequential follow-up (Figure 1).
- The patient was followed for another 6 years, without the confirmation of relapse or metastases. He remained hypertensive. No other endocrine condition was confirmed during surveillance (Tables 2 and 3).

TABLE 1. *Endocrine panel before and after adrenalectomy on an adult male with high blood pressure which was related to a non-syndromic pheochromocytoma*

Parameter	June 2015	July 2015- Unilateral Adrenal Surgery	2016	2017	2018	2019	2020	Value	Normal ranges	Units
Plasma metanephrines	11.9		10.8	15.4	22.5	13.6	17.5	21.5	10-90	pg/ml
Plasma normetanephrines	1945		23	42.3	52	51	46.7	56.5	15-180	pg/ml
24-hour urinary metanephrines	80.56		90.6	94	98.7	110	92	53.72	50-350	µg/24 h
24-hour urinary normetanephrines	2935		152	116	123.4	175	110	317.73	100-600	µg/24h
Plasma aldosterone	112		120	154.3	120.4	136	210	115	40-310	pg/ml
Plasma renin	43.8		25.4	23.3	18	20.3	17.6	2.78	2.64-27.66	ng/ml
Cromogranin A	717.7		63.2	50.4	53.2	70.5	68	78.2	20-100	ng/ml
Fasting glycaemia	82		94	98	102	87	88	9.3	8.5-10.2	mg/dl
HbA1C (glycated hemoglobin)	7.5		5.1	5.2	4.9	4.9	5	24.7	30-100	ng/ml

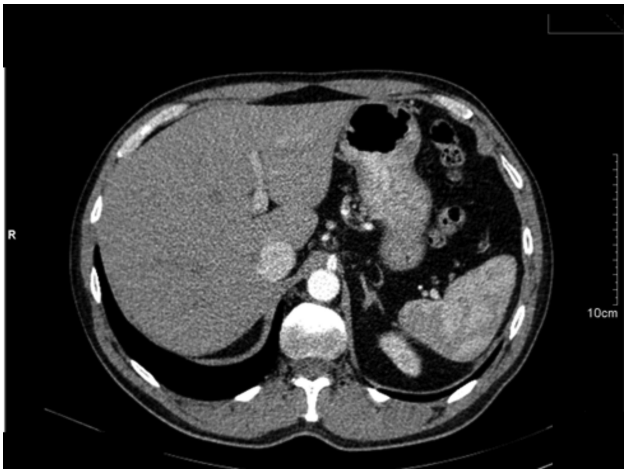

FIGURE 1. *Computed tomography of the abdomen on an adult male patient after a right adrenal pheochromocytoma was removed*

TABLE 2. *The biochemistry panel 6 year after adrenalectomy during follow-up of a male diagnosed with pheochromocytoma*

Parameter	Value	Normal ranges	Units
Uric acid	2.3	3.5-8.5	mg/dl
ALT	28	0-55	U/L
AST	17	5-34	U/L
Ionic calcium	4.23	3.9-4.9	mg/dl
Total serum calcium	9.3	8.5-10.2	mg/dl
cholesterol	193	0-200	mg/dl
Alkaline phosphatase	58	38-129	U/L
Serum phosphorus	3.5	2.3-4.7	mg/dl
Fasting glycaemia	82	70-105	mg/dl
HDL-cholesterol	61	40-60	mg/dl
LDL-cholesterol	122.4	60-160	mg/dl
Potassium	4.1	3.5-5.1	mmol/L
Magnesium	1.9	1.6-2.4	mg/dl
Sodium	143	136-145	mmol/L
Total proteins	6.8	6.5-8.7	g/dl
Triglycerides	48	50-200	mg/dl
Urea	39	15-50	mg/dl
Creatinine	0.75	0.6-1.3	mg/dl

TABLE 3. *Endocrine panel 6 year after pheochromocytoma removal on a 46-year old hypertensive man*

Parameter	Value	Normal ranges	Units
Plasma metanephrines	21.5	10-90	pg/ml
Plasma normetanephrines	56.5	15-180	pg/ml
24-hour urinary metanephrines	53.72	50-350	µg/24h
24-hour urinary normetanephrines	317.73	100-600	µg/24h
24-hour urinary 5-hydroxyindolacetic (5HIIA)	6.35	1-10	mg/24h
plasma aldosterone	115	40-310	pg/ml
plasma renin (clinostatism)	12.78	2.64-27.66	ng/ml
ACTH (adrenocorticotropic hormone)	60.9	3-66	pg/ml
Morning plasma cortisol	14.81	6.2-19.4	µg/dl
Morning plasma cortisol after 1 mg dexamethasone suppression test	1.15	<1.8	µg/dl
24-urinary free cortisol	201.85	58-403	µg/24 h
Cromogranin A	78.2	20-100	ng/ml
Serum serotonine	121.8	80-400	ng/ml
Neuron specific enolase	8.31	0-12	ng/ml
TSH (thyroid stimulating hormone)	2.43	0.5-4.5	µUI/ml
FT4 (free levothyroxine)	10.45	9-19	pmol/l
Plasma calcitonin	4.32	8.31-14.3	pg/ml
ATPO (anti-thyroid antibodies)	0.25	0-5.61	UI/ml
ATG (aAnti-thyroglobulin antibodies)	12.59	0-115	UI/ml
PTH (parathormone)	28.73	15-65	pg/ml
25OHD (25-hydroxyvitamin D)	24.7	30-100	ng/ml

DISCUSSION

The clue of the case is the fact that first pathological report suggested a malignant pheochromocytoma despite the fact that at that moment no metastasis was revealed at typical computed tomography evaluation with intravenous contrast. I (iodine)^{131} MIBG (meta-iodobenzylguanidine) scintigraphy was not available, neither during the 6-year period of follow-up. The first score applied to the tumour was PASS score of 8 based on capsular invasion, atypical mitotic count, tumour cell spindling in addition to >3 out of 10 mitotic account. In 2017, it became available GAPP score and we recalculated the tumour scoring. Based on moderate cellularity, the presence of capsular invasion in association with a Ki67 index of 10% at immunohistochemistry and hormonal balance showing a noradrenaline type, the grading was of 5, meaning a moderately differentiated type (between 3 and 6) (12). At immunohistochemistry report, we also mention negative reaction for Melan A, S100 and positive for SYNAPTO and CROMO.

Other elements that are potentially useful for a malignancy profile, a part of identification of a metastasis, like gene mutations associated with highly aggressive profiles (for instance, certain types of succinyl dehydrogenase enzyme mutations) or imaging with suspected features were not identified (13,14).

Other aspects of the case that worth to be mention include anomalies of glucose profile that were confirmed at diagnosis and normalized after surgery. It is well known that 50% of subjects with pheochromocytoma might associate this type of anomalies, which aggravate the overall picture of morbidity and mortality

(15). Interestingly, the patient also experienced within the first year after adrenalectomy, a stoke episode, associating neurological complications that were remitted. The risk of stroke is, of course, higher pre-operatory, but certain persistent endothelial effects and lack of adequate control regarding the blood pressure values may contribute to further cardiovascular events (16). This chapter of pheochromocytoma complications also include cardiac events like acute damage of myocardial tissue and arrhythmia (17). Exceptionally, Takabuso syndrome has been described (18). Moreover, immediately after tumour manipulation during surgical procedure, hypotension, and cardiac arrest are described unless the patient's pre-operative and intra-operative preparation is adequately done (19). Approximately 20% of subjects with pheochromocytoma do not have high blood pressure; the risk of cardiovascular damage is closely related to hormonal excess which is rather associated with certain gene mutations, and less with the aggressively of the tumour (20). A mild vitamin D deficiency was also confirmed in our patient that most probably it is not related to the adrenal condition itself. The abdominal scans also identified kidney stones but the patient did not experience hypercalcemia or high parathormone levels, neither calcitonin, so a type 2A multiple endocrine neoplasia syndrome was excluded.

CONCLUSIONS

Patients with a prior adrenalectomy for a pheochromocytoma need to be reconsidered in order to address the changes of scoring systems, thus to have a better prognostic score and an improvement of long term surveillance protocol. Reconsidering immunohistochemistry profile which was not a criterion of PASS score is essential in addition to re-asses the adrenaline versus noradrenaline secretor type that is regarded as a more severe prognostic. Overall, except for identifying the metastasis, no single criteria work as a definitive prognostic feature in this complex and challenging condition.

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