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-operative 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
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; Pentraeritil Tetranitrate 2.6 mg (1-0-0); Trimetazidine 20 mg (0-1-0); 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-operative 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 | 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       | µg/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/24 h |
| 24-hour urinary normetanephrines| 317.73 | 100-600      | µg/24 h |
| 24-hour urinary 5-hydroxyindolacetic (SHIIA) | 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 |

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...
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