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Particular aspects in pheochromocytoma

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Abstract

We aim to address incomplete procedures of adrenalectomy for pheochromocytoma (PHEO) on a bases of a mini-review. Dopamine, adrenaline and noradrenaline – secretor tumors are rare in general population, representing a neuroendocrine neoplasia with a strong genetic driving force and uncertain profile concerning a malignant behavior which may be less or more predicted based on initial post-operative report. There is no linear correlation with the post-operative recurrence in terms of clinical presentation, timing and prognostic. The first laparoscopic – based PHEO removal was done in 1992; and since then, the open procedure was replaced in majority of cases by the new gold standard – laparoscopic adrenalectomy; a current conversion rate is of 5%; alpha and beta - blockade is mandatory for preoperative management since an adrenergic crisis might be triggered by higher intraabdominal pressure during laparoscopy; bilateral PHEO may be addressed through one time procedure; minimally invasive technique is done trans-peritoneal or retroperitoneal; robotic – assisted laparoscopic procedure is the next logical step from traditional laparoscopy; in children, minimally invasive procedure is less likely to be used as in adults. Partial adrenalectomy (in terms of cortical - sparing technique) should be rarely performed for unilateral PHEO; its potential utility is for cases with non-feasible total removal due to tumor anatomy (like advanced local disease) or bilateral adrenal involvement in hereditary syndromes (like MEN 2A, VHL), especially in children and young adults to overcome the need of life long glucocorticoid replacement due to chronic adrenal insufficiency. A meta-analysis focusing on recurrence after total adrenalectomy revealed a 3% ratio after 2 years in PHEO. The percent for partial procedure is more than 10% depending on study.

In conclusion, a particular aspect in PHEO management is the recurrence after an adrenalectomy, typically after a partial procedure. Unless bilateral involvement or a clear diagnostic of a hereditary syndrome involving bilateral PHEO, partial adrenalectomy should be limited.

Keywords: pheochromocytoma, adrenal tumor, adrenalectomy, laparoscopic, partial adrenalectomy, cortical sparing adrenalectomy

INTRODUCTION

Dopamine, adrenaline and noradrenaline – secretor tumors, namely pheochromocytoma and paraganglioma, are rare in general population (1,2). The exclusive secretion of dopamine as a precursor of epinephrine and norepinephrine is exceptional, but usually adrenaline and noradrenaline excess is present (it might be dominant one of them, noradrenaline predominance

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associating a more severe prognostic) causing cardiovascular complications up to sudden death, but, notably, the clinical picture might also be pauci-symptomatic or lacking (3,4). Pheochromocytoma is part of the adrenal tumors that cause secondary hypertension in addition to Conn syndrome and adrenal Cushing syndrome (5,6,7). The catecholamine – producing tumor is a neuroendocrine neoplasia with a strong genetic driving force and uncertain profile concerning a malignant behavior which may be less or more predicted based on initial post-operative report (8-11). Hormonal assessment is essential to diagnostic and recurrence while the tumor may be imagistic explored through computed tomography, magnetic resonance imaging or specific investigations like ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy, etc.; the tumor (solid or mixt with cystic component) affects both children (for instance, pheochromocytoma and paraganglioma accounts for 1% of pediatric hypertensive population) and adults individuals (12,13,14) (Figure 1, Table 1).

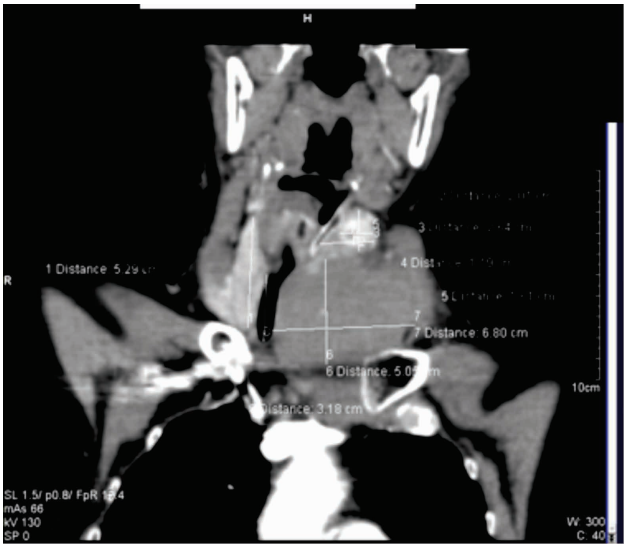

FIGURE 1. *Computed tomography of 66-year-old male adult who had a right adrenalectomy done 8 years prior: small tumor on right adrenal area (probably a post-operative recurrence) and another newly detected left adrenal tumor*

METHOD

We address incomplete procedures of adrenalectomy for pheochromocytoma. We made a brief review including papers published from 2011-2021 is based on the key words of search as following: "pheochromocytoma" or "adrenal tumor" and "adrenalectomy" or "surgery" or "recurrent pheochromocytoma". General data from literature are organized in distinct sub-sections. As sample value, we introduce a computed tomography and a panel of hormonal assays accompanying a non-syndromic pheochromocytoma with post-adrenalectomy recurrence. The case has not been previously published and the patient agreed for anonymously use of his medical records.

PHEOCHROMOCYTOMA: PRESENTATION ON FIRST ADMISSION VERSUS RECURRENCE

A heterogeneous profile is described in relationship with pheochromocytoma; it is not a linear correlation with the recurrence, meaning that the clinical picture from the start might not be reproduced (15,16,17). Following the clinical index of suspicion, the endocrine and imaging step is mandatory at first admission and during post-operative follow-up or during the surveillance of a patient identified with a mutation like RET gene in multiple endocrine neoplasia type 2A (prophylactic adrenalectomy is forbidden, opposite to prophylactic thyroidectomy for certain mutations associating a high risk of medullary thyroid cancer) (18,19,20).

ADRENALECTOMY FOR PHEOCHROMOCYTOMA

The first laparoscopic-based pheochromcytoma removal was done in 1992; and since then, the open procedure was replaced in majority of cases by the new gold standard – laparoscopic adrenalectomy; a current

TABLE 1. *Hormonal picture of a 66-year old patient who was diagnosed with right pheochromocytoma which was removed; 8 years later, normetanephrines excess is re-confirmed in addition to right adrenal recurrence and a newly detected tumor on the left adrenal (the patient is RET-negative)*

Hormone	At first diagnostic	After 8 years	Normal ranges	Units
ACTH (adrenocorticotropic hormone)	11.38	7.76	3-66	pg/ml
Morning plasma cortisol	9.96	12.02	4.82-19.5	µg/dl
24-urinary free cortisol	NA	NA	58-403	µg/24 h
Plasma metanephrines	33.6	54.2	10-90	pg/ml
Plasma normetanephrines	**233.6**	**596.2**	15-180	pg/ml
24-hour urinary metanephrines	NA	131.56	50-350	µg/24 h
24-hour urinary normetanephrines	NA	**1058.4**	100-600	µg/24 h
Chromogranin A	92.3	**1.881**	20-100	ng/ml
5-HIIA (5-hydroxyindolacetic)	NA	8.89	1-10	mg/24 h

NA = not available

conversion rate is of 5%; alpha and beta blockade is mandatory for preoperative management since an adrenergic crisis might be present due to higher intraabdominal pressure during laparoscopy; bilateral pheochromocytoma may be addressed through one time (preferably to two times) procedures; minimally invasive technique is done trans-peritoneal or retroperitoneal; robotic – assisted laparoscopic procedure is the next logical step to surpass the traditional to modern era of laparoscopy; in children, minimally invasive procedure is less likely to be used as in adults (21-30).

PARTIAL ADRENALECTOMY

In cases hormonally confirmed with a unilateral pheochromocytoma, partial adrenalectomy is rarely indicated; the potential utility is for cases with non-feasible total removal due to tumor anatomy (like advanced local disease) or bilateral adrenal involvement in hereditary syndromes (31,32,33).

It was proposed that partial adrenalectomy (in terms of cortical - sparing technique) should work for bilateral phechromocytoma in pediatric population with hereditary conditions to overcome the need of life long glucocorticoid replacement due to chronic adrenal insufficiency, but it mostly dependents on a multidisciplinary decision and on the surgical team experience in this particular matter (34,35,36). A study on children with von Hipple-Lindau syndrome and bilateral phechromocytoma included 10 patients (between 1994 and 2011) who underwent 18 partial adrenalectomies (median tumor diameter of 2.6 cm); they were followed for a median of 7.2 years; recurrence was detected in 20% (34). A single – centric, population – based study from 2021 included data from 1975 to 2016 concerning 286 individuals with partial over total adrenalectomy for pheochromocytoma (101 versus 185 patients); partial adrenalectomy was done less frequent than total procedure in tumors larger than 8 cm diameter and also it was more often done in subjects with local advanced disease; the authors found similar rated of mortality in both groups (35). A study on 42 children with pheochromocytoma (88% of them with hereditary syndromes) were operated based on minimally invasive surgery (between 2001 and 2016) identified 70 tumors of an average size 2.7 cm; 2 out of 42 individuals had a conversion; 1 patient died of cardiac arrest; average hospital stay was of 3 days; after 8.5 years, 2 patients out of 42 had a recurrence after partial adrenalectomy (36).

RECURRENCE AFTER ADRENALECTOMY

New evidence suggests that follow-up after adrenalectomy for a confirmed pheochromocytoma should be lifelong (37-41). In addition to a gene mutation that might not be evident on admission, the recurrence is related to an aggressive behavior that can only be predicted based on scores like PASS, GAPP but are not precise (42-46). A meta-analysis focusing on recurrence after adrenalectomy (which was performed with the intention with radical excision) revealed a 3% ratio on 430 individuals (from 13 studies) with a mean time of post-operative recurrence of 49.4 months (mean follow-up of 77 months) (47). Another meta-analysis on 60 studies found an 8% rate of recurrence after partial adrenalectomy for adrenal tumors (the highest rate is for pheochromocytoma of 10% and the lowest rate is for Conn syndrome of 2%) while 85% of patients did not glucocorticoid replacement (48). A study from 2005 to 2018 analyzed 140 individuals with a mean age of 43 years with a laparoscopic adrenalectomy for a functioning adrenal tumor; the clinical improvement concerning catecholamine-related signs were similar among patients with partial versus total adrenalectomy, but 2 out of 12 patients with partial procedure had a recurrence of the pheochromocytoma (49).

DISCUSSIONS

The importance of knowing the genetic background in addition to extensive genetic testing before adrenalectomy is obvious; however, real life medicine showed us that is less likely to be feasible on many cases, especially at the beginning; RET testing for multiple endocrine neoplasia type 2A seems the most accessible assay as oppose to SHD, VHL, MENIN (50-53). Genetic context, a part from already known family with a certain mutation, is suggested by young age, aggressive profile and recurrence after adrenalectomy (50-53).

CONCLUSIONS

A particular aspect in pheochromocytoma management is the recurrence after an adrenalectomy, typically after a partial procedure. Unless bilateral involvement or an adequate diagnostic of a hereditary syndrome involving a further bilateral pheochromocytoma, partial adrenalectomy should be limited in this particular type of tumor.

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