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PITFALLS OF ADRENAL TUMORS' MANAGEMENT IN REAL-LIFE MEDICINE: A CASES SERIES

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The genetic of adrenal tumors represents a complex, yet incompletely described field, involving either benign or malign neoplasia, secretor or not, uni- or bilateral, hereditary or non-hereditary, underlying germline or somatic mutations; isolated or in combination with a multitude of endocrine and non-endocrine conditions. Our purpose is to introduce clinical aspects based on real-life medicine experience concerning adrenal tumors with unexpected or partially explained aspects, as well as limits of daily practice, like the decision of bilateral adrenal removal in pheochromocytoma without clinical evidence of an underlying genetic condition; the association of pheochromocytoma with lichen planus lesions; the co-presence of adrenal tumors with thyroid cancer (an apparently non -MEN syndrome combination); the decision of adrenalectomy in primary hyperaldosteronism where the patient delays the intervention. This is a cases series of patients who were followed at different medical and surgical centers. Even though our females' cases phenotype does not entirely fit any of the classical genetic syndromes, genetic testing, for a wider range of genetic anomalies, might be useful in order to identify a possible genetic link. While multiple gene studies are related to adrenal tumors, real-life medicine data are no conclusive in many cases which are not the typical scenario of MEN syndrome. This is a topic of further advance for the purpose of clinical benefit in the multidisciplinary management of these cases.

Keywords: adrenal, management, case management, tumor, lichen planus, hyperaldosteronism, thyroid, pheochromocytoma

Abbreviations

ACTH = adrenocorticotropic hormone
CT = computed tomography
IGF1 = Insulin-like growth factor 1
25OHD = 25-hydroxyvitamin D
MTC = medullary thyroid carcinoma
MEN = multiple endocrine neoplasia
NA = not available
PTH = parathormone
TBS = trabecular bone score

INTRODUCTION

The genetic of adrenal tumors represents a complex, yet incompletely described field, involving either benign or malign neoplasia, secretor or not, uni- or bilateral, hereditary or non-hereditary, underlying germline or somatic mutations; isolated or in combination with a multitude of endocrine and non-endocrine conditions [1-10]. For instance, PKA signaling pathways are related to adrenal Cushing syndrome, Carney syndrome, and McCune-Albright syndrome; GNAS anomalies are related to cortisol producing tumors; KCNJ5, CACNA1D genes involve masses like aldosteronoma; germline mutations of ARC5 are linked to primary bilateral adrenal hyperplasia (macronodular or micronodular); TP53 is related to adrenocortical carcinoma, especially with pediatric onset, *etc*. [1-10]. Also, pheochromocytoma, as part of the large heterogeneous class of neuroendocrine tumors, is related to hereditary conditions as neurofibromatosis type 1, multiple endocrine neoplasia (MEN) type 2A, von Hipple-Lindau disease etc. [11-21].

AIM

Our purpose is to introduce clinical aspects based on real-life medicine experience concerning adrenal tumors with unexpected or partially explained aspects, as well as limits of daily practice, like the decision of bilateral adrenal removal in pheochromocytoma without clinical evidence of an underlying genetic condition; the association of pheochromocytoma with lichen planus lesions; the co-presence of adrenal tumors with thyroid cancer (an apparently non-MEN syndrome combination); the decision of adrenalectomy in primary hyperaldosteronism where the patient delays the intervention.

METHOD

This is a cases series of patients who were followed at different medical and surgical centers. The patients agreed for anonymous use of their medical records.

CASE 1

This is a 69-year-old female admitted for periodic checkup after bilateral adrenalectomy for pheochromocytoma that was done 2 decades prior. By the age of 50, she was first admitted for episodes of high blood pressure (highest value of 240/110 mm Hg) associated with headache and palpitation; the endocrine investigations confirmed a pheochromocytoma. She underwent simultaneous right total and left subtotal adrenalectomy; early after surgery, she experiences hypotension, but

Table 1. Post-adrenalectomy sequential assessment of catecholamine metabolites in a patient with prior surgery for pheochromocytoma

Parameter	Value 2012	Value 2013	Value 2014	Value 2015	Value 2016	Value 2017	Value 2018	Value 2019	Value 2020	Value 2021	Value 2022	Normal ranges	Units
Plasma metanephrines	19	30	10	27.01	22.8	22.9	25.2	11.3	NA	5	5	10-90	pg/ml
Plasma normetanephrines	50	30	34	47.2	134.8	97.02	161.5	122.4	NA	70.9	54.8	20-200	pg/ml
24-h urinary metanephrines	340	57	72	50	78.15	200	50	30.2	79.56	31.08	NA	50-350	µg/24 h
24-h urinary normetanephrines	610	252	156	461.56	422.38	464	418.3	374.85	259.02	360.6	NA	100-600	µg/24 h

Table 2. Serial check-up of phosphor-calcium metabolism

Parameter	Value 2016	Value 2017	Value 2018	Value 2019	Value 2020	Value 2021	Value 2022	Normal ranges	Units
Total serum calcium	9.9	10	9.6	9.86	10	9.1	9.58	8.4-10.2	mg/dL
Phosphorus	4.81	4.7	4.9	3.44	4.5	3.8	3.6	2.5-4.5	mg/dL
Parathormone (PTH)	44.47	35.25	37.15	47.57	50.06	33.73	49.78	15-65	pg/mL
25-hydroxyvitamin D (25OHD)	NA	27.71	17.6	NA	23.75	23.7	32.3	30-100	ng/mL

Figure 1. Lichen planus lesions on the posterior thoracic area

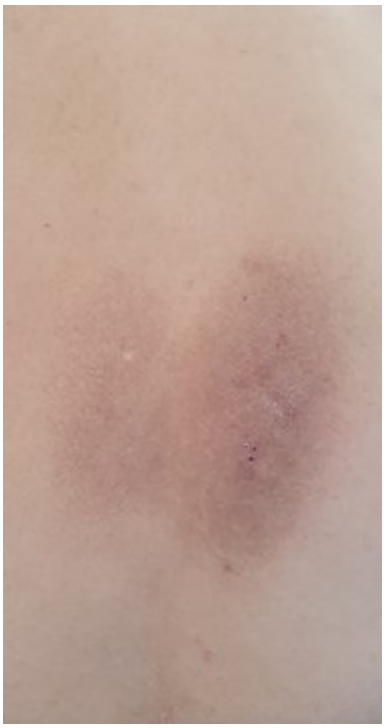

Table 3. DXA assessment on a menopausal female with a history of thyroid cancer, primary hyperparathyroidism and a current diagnostic of adrenal incidentaloma

Region	BMD(g/sqcm) Bone Mineral Density	T-score (SD)	Z-score (SD)	TBS Trabecular Bone Score
L1-4	0.820	-3	-2	1.210
Femoral neck	0.836	-1.5	-0.3	
Total hip	0.888	-0.9	-0.2	
1/3 distal radius	0.663	-0.7	-0.2	

chronic iatrogenic primary adrenal insufficiency was adequately replaced with glucocorticoids, then, during follow-up, she had fluctuating values of the blood pressure with no relapse of increased catecholamines profile (Table 1).

5 years later, the patient underwent thyroidectomy for benign multinodular goiter, with levothyroxine replacement that was necessary after procedure. No medullary thyroid carcinoma (MTC) was confirmed based on calcitonin assessments at diagnostic and during follow-up; neither at pathological report; neither she had criteria for primary hyperparathyroidism (Table 2).

After another 5 years, she had a routine head imaging done; computed tomography (CT) revealed a pituitarymicroadenoma of 6.5mm (transverse) and 4.5 mm (craniocaudal), that was considered anincidentaloma. On current admission, clinical examination was within normal limits, except for a brown lesion at the level of posterior thoracic area, consistent with a diagnostic of lichen planus that was initially detected a decade prior (Figure 1). The patient also presents palmar and plantar spotty hyperpigmentation. Endocrine assessments were within normal limits, while CT scan identified a right adrenal tissue of 14/6 mm (a potential remnant) with a small calcification and a left adrenal nodule of 15/12/18 mm with calcifications at the level of upper pole.

CASE 2

A 56-year-old female patient isadmitted for the assessment of a recently discovered adrenal tumor. Her medical history includes: papillary thyroid carcinoma (treated

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Table 4. Biochemistry panel on 56-year-old female with adrenal incidentaloma

Parameter	Value	Normal ranges	Units
Ionic serum calcium	4.4	3.9-4.9	mg/dL
Total serum calcium	9.83	8.4-10.2	mg/dL
Total cholesterol	212.6	0-200	mg/dL
Phosphorus	3.08	2.5-4.5	mg/dL
Fasting glycaemia	109.8	70-100	mg/dL
Glycosylated hemoglobin A1c	5.4	4.8-5.9	%
HDL-cholesterol	52	40-65	mg/dL
Potassium	5.4	3.5-5.1	mmol/L
Magnesium	1.93	1.6-2.55	mg/dL
Sodium	144	136-145	mmol/L
Total proteins	6.99	6.5-8.7	g/dL
Urea	35.9	15-50	mg/dL
Creatinine	0.83	0.5-1	mg/dL

with total thyroidectomy and radioiodine therapy 100 mCi), primary hyperparathyroidism complicated with kidney stones (a right inferior parathyroid adenoma was removed a few years after thyroidectomy in addition to a local lymph node that turned out to be a single ganglion metastasis from prior thyroid cancer), and treated high blood pressure. The family medical history includes father with malignant melanoma. 6 years after she had a physiological menopause, a diagnostic of osteoporosis was confirmed; she was offered alendronic acid/cholecalciferol 70 mg/5600 IU weekly during the last year, with a mild improvement of T-score at current DXA exam (Table 3).

On admission, physical examination revealed a body mass index of 21.4 kg/m^2, facial plethora, and mild onychomycosis. The biochemistry panel showed hypercholesterolemia, a fasting blood glucose level of 109.8 mg/dl (normal:70-100) with glycosylated hemoglobin 5.4% (normal: 4.8-5.9), and an increased potassium value of 5.41 mmol/l (normal: 3.5-5.1) (Table 4).

The thyroid endocrine panel showed a partial thyroid suppression - TSH of 0.43 µUI/ml (normal: 0.5-4.5), FT4 of 11.69 pmol/l (normal:9-19) on Levothyroxine 125 µg/day and negative thyroglobulin. The thyroid ultrasound showed total post-thyroidectomy status. Bone metabolism assays were within normal limits. Possible autonomous cortisol secretion is confirmed by low-normal baseline ACTH (adrenocorticotropic hormone) of 6.21 pg/ml (normal: 3-66) with a plasma morning cortisol level of 15.97µg/dl (normal: 4.82-19.5) and a morning plasma after dexamethasone inhibition test 2X2 mg of 2.21 µg/dl (normal <1.8). CT showed bilateral hyperplasia and a right nodule of 1.57 cm by 2.19 cm and a left nodule of 1.47 cm by 1.82 cm. The diagnostic of bilateral adrenal macronodular hyperplasia was established; for the moment, close surveillance was recommended, in addition to medication for high blood pressure, anti-osteoporotic medication zolendronic acid 15 mg/year, vitamin D3 1000 UI/day, and suppressive levothyroxine therapy.

CASE 3

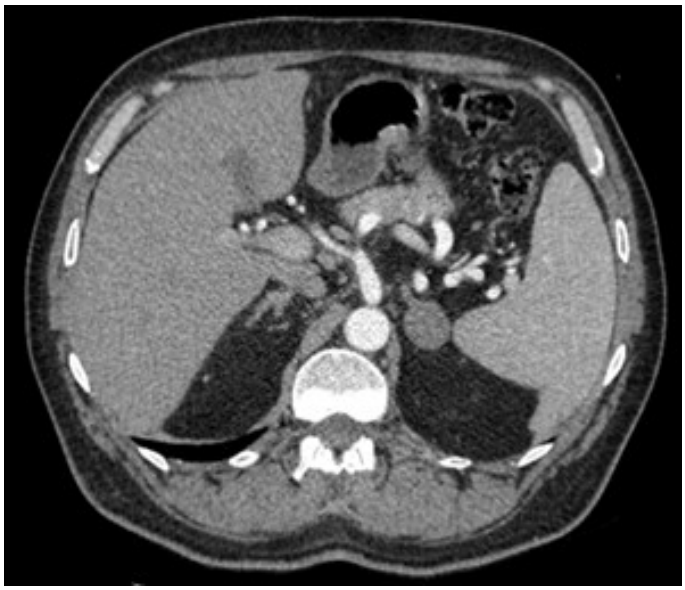
This is a 60-year-old, non-smoking male patient who is admitted for endocrine assessments of high blood pressure. He is known with arterial hypertension since last decade, with partial compliance to therapy and intermittent episodes of acute hypertension which were not suggestive for a pheochromocytoma crisis. Thyroid function was normal, the same was baseline ACTH and dexamethasone suppression test with adequate suppression of cortisol levels, thus excluding an adrenal Cushing syndrome. However, primary hyperaldosteronism was confirmed based on plasma aldosterone of 83.4 ng/dl, respective plasma renin of 3.55 µUI/ml (normal aldosterone values in orthostatic position between 2.21 and 35 ng/dl, respective renin ranges between 4.4 and 46.1 µUI/ml), with renin/aldosterone ration of 23.49 (normal ration below 3.7). Intravenous contrast CT scan confirmed bilateral hyperplasia with a left adrenal nodule of 2.5 by 2.2 cm and a density below 10 UH in native phase, suggestive for an adenoma of lipid rich type with an absolute wash out of 72% and a relative wash out of 65% (Figure 2).

The family history was irrelevant for any medical conditions, bilateral adrenal venous sampling was not available. The patient was further treated with anti-hypertensive drugs including spironolactone. Due to COVID-19 pandemic circumstances, he delayed the presentation to our department in order to decide the adrenalectomy.

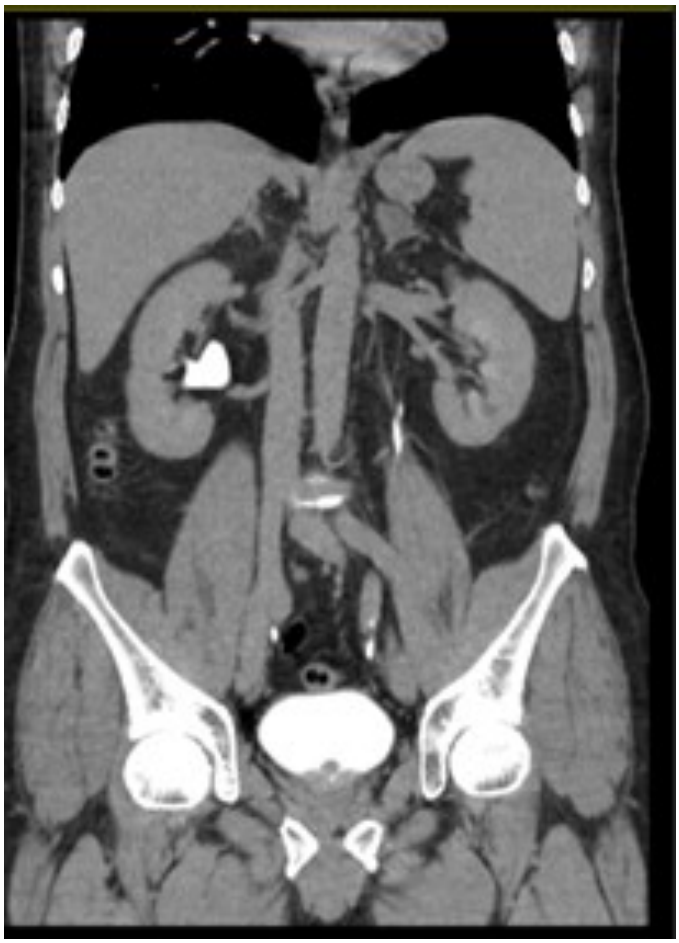
DISCUSSION

The first case introduces a bilateral procedure of adrenalectomy for bilateral pheochromocytoma, a diagnostic that was considered adequate at first diagnostic, meaning 20 years prior. However, currently, the patient still associates bilateral adrenal lesions at CT scan with negative hormonal profile, which are not consistent with initial diagnostic. In the absence of a clear genetic link, bilateral pheochromocytoma is suspected if large adrenal tumors with specific imaging aspects are identified at imaging techniques in addition to a positive hormonal panel; but, the most useful investigation remains radiolabeled MIBG scintigram which is not available in many centers, neither in ours; the investigation is particularly useful in genetic syndromes, bilateral tumors, extra-adrenal involvement, and metastatic disease [22-30]. Also, the subject had a pituitary microadenoma which was suggestive for an incidentaloma. The association of a hypophyseal tumor with an adrenal disease is mostly found in MEN 1 syndrome, which was not clinically sustained in this case; most frequent secretor tumors of pituitary gland that are involved in various endocrine syndromic combinations are prolactinoma, somatotropinoma and corticotropinoma [31-41]. In case 1, lichen planus lesions were confirmed by the dermatological team. Lichen planus is a chronic inflammation with potential malignant transformation; high levels of cortisol have been reported as part of pathogenic loop; an association with cardio-metabolic features was described, too [42-49]. The association of lichen planus with endocrine diseases has been revealed especially considering thyroid disorders with autoimmune background

Figure 2. CT scan of an adult male patient confirmed with primary hyperaldosteronism; bilateral adrenal hyperplasia with a right adrenal tumor
2.A. Axial section



2.B. coronal plan



[50-56]. When it comes to the association with pheochromocytoma, there are only a few reports in literature outside the association of MEN2A with cutaneous lichen amyloidosis; thus in our case this exceptional association seems accidental; but genetic tests were not available [57-63].

The second case introduces the situation of possible autonomous cortisol secretion due to bilateral adrenal lesions; the presence of high blood pressure, and even onychomycosis, and potentially osteoporosis might be related to that. However, due to similar gland involvement, the decision of adrenalectomy was postponed for the moment. Bone loss might be related to chronic suppressive therapy for thyroid carcinoma, a prior history of primary hyperparathyroidism, and menopausal status (64-70). Also, the subject had impaired glucose profile which is reflected at bone level by low trabecular bone score (TBS) as seen here, with an additional contribution due to cortisol excess (70-80). The association of endocrine tumors of different origin, and, potentially, family history of malignant melanoma indicates a possible underlying genetic cause. We identified two similar cases in literature with underlying genetic diagnostic remaining unknown. ACTH-independent Cushing's syndrome due to adrenal bilateral hyperplasia and papillary thyroid cancer on a 33-year-old female patient with a history of multifocal, thyroid papillary carcinoma and subsequent adrenal tumor treated by right laparoscopic adrenalectomy [81]. Another case report presented a 70-year-old male with total thyroidectomy for simultaneous papillary, medullary and follicular carcinoma; two months later, he was diagnosed with Cushing's syndrome due an adrenal tumor that was treated with laparoscopic left adrenalectomy [82]. A genetic link was not identified in neither of the cases [81,82]. A genetic mutation worth taking into account is BRAF 600E, a mutation associated with several neoplasms such as papillary thyroid carcinoma, colorectal cancer, melanoma, hairy cell leukemia and Langerhans histiocytosis [83]. BRAF V600 mutations are common in both melanoma and papillary thyroid carcinoma, indicating a potential more aggressive behavior in both cancers [84-86]. BRAF V600 mutations are associated with aggressive clinic-pathological factors such as extra thyroidal extension, higher TNM stage, lymph node metastasis, and recurrence [87]. The association of papillary thyroid cancer and nodular adrenocortical disease are identified in Carney syndrome [88]. As mentioned, synchronous and methacronous tumors of endocrine glands are a characteristic of the MEN syndromes [89-91]. Also, DICER syndrome might associate thyroid tumors etc. [92]. Our patient had primary hyperparathyroidism and adrenocortical bilateral hyperplasia, but mutation in menin or RET genes was not done. The association of tumors underlying endocrine origin with onset at a young age (differentiated thyroid carcinoma, primary hyperparathyroidism, and adrenal Cushing syndrome caused by macronodular bilateral adrenal hyperplasia) supports the possibility of a genetic cause.

The third case introduces two particular aspects: one is the issue of patients with bilateral adrenal involvement in a Conn's syndrome; the adrenalectomy of the gland with a macronodular lesion might not cure the disease if a genetic condition is associated [93]. 9 out of 10 subjects with aldosteronoma carry somatic mutations of potassium channels proteins, while bilateral adrenal disease might involve germline mutations of CYP11B1/2 gene [94]. In real-life medicine management, the access to genetic

assessments is less feasible. The second issue is postponing the presentation for check-up and next-step decision due to coronavirus pandemic. This is also a real-life medicine aspect that affected the medical practice concerning different endocrine tumors from pituitary gland, to thyroid, adrenals etc. [95-101].

CONCLUSIONS

Even though our females' cases phenotype does not entirely fit any of the classical genetic syndromes, genetic testing, for a wider range of genetic anomalies, might be useful in order to identify a possible genetic link. While multiple gene studies are related to adrenal tumors, real-life medicine data are no conclusive in many cases which are not the typical scenario of MEN syndrome. This is a topic of further advance for the purpose of clinical benefit in the multidisciplinary management of these cases.

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Conflict of interest: none

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