Ref: Ro J Med Pract. 2021;16(4)
DOI: 10.37897/RJMP.2021.3.20

Follow-up of second adrenal tumor after remission of Cushing syndrome

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Abstract

Bilateral adrenal tumors (BAT) represent a vast domain of endocrinology and connected medical and surgical fields. Our purpose is to introduce several key points in relationship with long time management on a 56-year old female case who is currently admitted for reassessment of a left adrenal tumor with potential autonomous cortisol secretion. She is also known with pituitary incidentaloma since 2014, cerebral meningioma which was partially removed in 2015, uncontrolled diabetes mellitus under metformin and insulin therapy since 2017, and high blood pressure since 2021. Her medical history includes right adrenalectomy for Cushing syndrome in 2014. At that moment, she was first admitted for BAT, a tumor of 2 centimeters (cm) on the left gland according to computed tomography, respective of 3.5 cm maximum diameter on the right adrenal. The hormonal panel confirmed adrenal Cushing syndrome. After 6 months of non-interventional follow-up, the right tumor increased to 4 cm, also associating small areas of necrosis, thus a decision of unilateral laparoscopic adrenalectomy was done with good clinical post-operatory outcome. She did not develop adrenal insufficiency at any point in time, moreover, a low-normal ACTH (Adrenocorticotrop Hormone) with intermittent elevation of morning plasma cortisol levels after Dexamethasone suppression test showed a possible autonomous cortisol secretion of the left adrenal tumor during a 7-year follow-up. In 2014, the female patient received the confirmation of an adrenocortical adenoma which was consistent with cortisol over-secretion. Particular gene contributions are attributed to protein kinase A (PKA) defects (or B) that usually induce bilateral adrenocortical hyperplasia; however, they are not routinely tested in daily endocrine practice, neither had we performed it. Interestingly, the patient was detected with a cerebral meningioma after years of intermittent, mild headache. The diagnostic was established during initial endocrine evaluations. The headache was not associated with uncontrolled high blood pressure, as first expected due to excessive cortisol amount. Recently, it was identified that mutations of ARMC5 (armadillo repeat containing 5) gene are responsible for macronodular adrenal hyperplasia, but also meningioma. They may be also responsible for severe diabetes mellitus as seen here. The key points of following a patient with bilateral adrenal tumors include the timing of uni/bilateral adrenalectomy, the multidisciplinary management of associated complications, as well as the need of understanding the genetic rational behind it.

Keywords: adrenal tumor, bilateral adrenal tumor, Cushing syndrome, adrenalectomy, cortisol, endocrine, adrenal incidentaloma, secondary diabetes mellitus, secondary osteoporosis

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Article History:
Received: 16 December 2021
Accepted: 21 December 2021

INTRODUCTION

Bilateral adrenal tumors represent a vast domain of endocrinology and connected medical and surgical fields (1,2,3). The condition might affect both adrenal cortex (of adrenal or pituitary origin as in Cushing disease) or adrenal medulla (4,5,6). The lesions may be congenital, spontaneous or accompanying syndromes like type 1 neurofibromatosis, multiple endocrine neoplasia type 2A, Von Hippel-Lindau disease, etc. (7,8,9) The pattern/structure/consistence might be solid, cystic or cystic-like including elements of necrosis, hemorrhage; either underling adenoma, carcinoma or adenomatous – like hyperplasia as seen in congenital adrenal hyperplasia (10,11,12). Tumors with non-adrenal origin might be mielolypomas or metastases arising from endocrine or non-endocrine cancers (like renal carcinoma or hematological malignancies etc.) (13-16). Depending of endocrine profile, co-morbidities and tumors' anatomy, surgical removal represents a major line of management in cases with bilateral adrenal tumors (17,18,19). The decision of adrenalectomy is essentially based on a multi-disciplinary approach (20,21,22). The adrenalectomy, either open or laparoscopic, usually addresses the entire tumor as well as ipsilateral gland; however, some adrenal – sparing techniques are used for selective conditions, especially in youth and accompanying genetic syndromes (23,24,25). In cases with adrenal incidentalomas (as reflected by the clinical, hormonal and radiological definition), surgery is mostly unnecessary (26,27,28).

AIM

Our purpose is to introduce the difficulties of management in female case with bilateral adrenal tumors.

METHOD

This is a case report. The patient agreed to anonymous presentation of her medical data. The subject was followed from 2014 to 2021 at different medical centers. As discussions, several aspects of the case are introduced like bone status, Cushing syndrome related diabetes mellitus, decision of adrenalectomy if bilateral adrenal masses are confirmed.

CASE PRESENTATION

Admission

This is a 56-year old smoking female who is currently admitted for reassessment of a left adrenal tumor with potential autonomous cortisol secretion. She is also known with pituitary incidentaloma since 2014, cerebral meningioma which was partially removed in 2015, diabetes mellitus under metformin and insulin therapy since 2017, and high blood pressure since 2021.

Medical history

Her medical history includes right adrenalectomy for Cushing Syndrome in 2014. At that moment, she was first admitted for two bilateral adrenal tumors, of 2 centimeters (cm) on the left gland according to computed tomography scan, respective of 3.5 cm maximum diameter on the right adrenal. The hormonal panel confirmed adrenal Cushing syndrome. After 6 months of non-interventional follow-up, the right tumor increased to a maximum diameter more than 4 cm, also associating small areas of necrosis thus a decision of unilateral adrenalectomy was done with good clinical post-operatory outcome. After unilateral laparoscopic adrenalectomy, she did not develop adrenal insufficiency at any point in time, thus glucocorticoid replacement was unnecessary.

Biochemistry panel

On current admission, the biochemistry panel showed a small increase of calcium levels which was undetected at prior assessments; also, hypercholesterolemia and uncontrolled diabetes mellitus, and mildly elevation of ALT (alanine aminotransferase) (Table 1). The glucose profile was under oral antidiabetics and insulin therapy. Negative viral markers for chronic hepatitis were conclusive (in addition to liver ultrasound) for chronic steatohepatitis.

TABLE 1. *The biochemistry panel of a 56-year-old female with unilateral adrenalectomy for Cushing syndrome and a current adrenal tumor on opposite gland*

Parameter	Value	Normal ranges	Units
Uric acidum	4.1	2.6-6	mg/dl
ALT (alanine aminotransferase)	**35**	**0-31**	**U/l**
AST (aspartate aminotransferase)	30	0-32	U/l
Conjugated bilirubin	0.18	0-0.5	mg/dl
Total bilirubin	0.38	0.2-1.2	mg/dl
Ionic serum calcium	**4.51**	**3.9-4.9**	**mg/dl**
Total serum calcium	**10.4**	**8.4-10.2**	**mg/dl**
Serum phosphorus	3.1	2.3-4.7	mg/dl
Fasting glycaemia	**140.2**	**70-105**	**mg/dl**
Glycated hemoglobin	**8.4**	**4.8-5.9**	**%**
HDL- cholesterol	65.3	40-60	mg/dl
Total cholesterol	**239**	**0-200**	**mg/dl**
LDL - cholesterol	147	60-160	mg/dl
Potassium	4.5	3.5-5.1	mmol/l
Triglycerides	132	0-149	mg/dl
Magnesium	1.85	1.6-2.55	mg/dl
Sodium	141	136-145	mmol/l

Parameter	Value	Normal ranges	Units
Total proteins	7.3	6.4-8.3	g/dl
Urea	24.7	15-50	mg/dl
Creatinine	0.77	0.5-1.2	mg/dl
Fibrinogen	442.182	200-500	mg/dl

Endocrine assessments

Hormone panel (as well as bone turnover markers) showed a mild reduction of serum 25-hidroxyvitamin D and a small increase of parathormone (PTH) levels. However, when repeated the total calcium and PTH assays, the anomalies were not consistent, thus the diagnostic of concurrent primary hyperparathyroidism was not sustained (Table 2).

TABLE 2. *Endocrine panel on a 56-year old female with unilateral adrenal tumor*

Parameter	Value	Normal ranges	Units
TSH (Thyroid stimulating hormone)	1.13	0.5-4.5	µUI/ml
FT4 (Free levothyroxine)	14.46	9-19	pmol/l
ATPO (Anti-thyroid antibodies)	1.01	0-5.61	UI/ml
Plasma calcitonin	1	5.17-9.82	pg/ml
25OHD (25-hydroxyvitamin D)	**26.9**	**30-100**	**ng/ml**
CrossLaps	0.43	0.162-0.436	ng/ml
Osteocalcin	21.44	11-43	ng/ml
P1NP	47.39	14.28-58.92	ng/ml
PTH (Parathormone)	**74.53**	**15-65**	**pg/ml**

The assays of adrenal function since unilateral adrenalectomy showed no adrenal insufficiency (Table 3). Moreover, a low-normal ACTH (Adrenocorticotrop Hormone) with intermittent elevation of morning plasma cortisol levels after Dexamethasone suppression test showed a possible autonomous cortisol secretion of the adrenal tumor.

Other evaluations

Central DXA (dual energy X-ray absorptiometry) scan was normal (Table 4). Thyroid ultrasound showed right thyroid lobe of 1.45 by 1.78 by 5 cm, isthmus of 0.4 cm, left thyroid lobe of 1.46 / 1.58 / 4.83 cm, discrete hypoechoic, and low Doppler signal. Pituitary computed tomography showed stationary micronodule of 0.5 cm; abdominal scan confirmed stationary aspects of the left adrenal tumor (2.22 by 2.81 cm) and right suprarenalectomy.

TABLE 4. *Central DXA (dual energy X-ray absorptiometry) on a post-menopausal female with prior diagnostic of Cushing syndrome and current adrenal tumor-related potential autonomous cortisol excess*

Regions	BMD (g/cm^2)	T score (SD)	Zscore (SD)
lumbar 1-4	1.151	-0.4	-0.6
left femoral neck	0.984	-0.4	0
left total hip	1.049	0.3	0.3

Management

A more intense regime for glucose profile control was recommended in addition to vitamin D supplements and cardiovascular medication to control arterial hypertension and statin for high cholesterol. The decision of second adrenalectomy was discussed with the patient (including the pros like improvement of glycaemia profile) and cons (like lifelong requirement of glucocorticoid substitution because of post-operatory adrenal insufficiency).

DISCUSSIONS

Bilateral adrenal tumors and cortisol over-secretion

As mentioned, various histological entities are associated with bilateral tumors of endocrine and neuroendocrine origin (29-32). In mentioned case, at first, the patient was admitted for Cushing syndrome with bilateral adrenal tumors. In this situation, the cause may be either: a Cushing disease, an adrenal Cushing syndrome due to bilateral and unilateral secretion of cortisol or even an ectopic production of ACTH with macronodular/adenoma-like presentation of both adrenals (33-36). The tumor-like masses that associate cortisol excess may be, from a histological point of view, an adrenocortical adenoma, an adrenocortical carcinoma

TABLE 3. *The values of cortisol – ACTH assays between 2014 and 2021 on a patient with right adrenalectomy for Cushing syndrome (in 2014, before current data), and a unilateral left adrenal tumor*

Parameter	Year of assessment									
	2014	2015	2016	2017	2018	2019	2020	2021	Normal ranges	Units
ACTH (Adenocorticotropic Hormone)	7	6.9	6.28	22	24	10	8.8	11.61	3-66	pg/ml
Morning plasma cortisol	11.9	16	**20.9**	11	10	**44**	**21**	15.65	4.82-19.5	µg/dl
Morning plasma cortisol after 1 mg dexamethasone suppression test			1.29	1.5		**2.8**		1.26	<1.8	µg/dl
Morning plasma cortisol after 2 days x 2 mg dexamethasone suppression test	1.15	1.1					1.7		<1.8	µg/dl

or bilateral macro-nodular hyperplasia (which is associated in majority of cases with genetic anomalies) (37,38,39). In 2014, the female patient received the confirmation of an adrenocortical adenoma which was consistent with cortisol over-secretion. Particular gene contributions are attributed to protein kinase A (PKA) defects (or B) that induce bilateral adrenocortical hyperplasia; however, they are not routinely tested in daily endocrine practice, neither had we performed it (40-43). By the presence of the second cortisol excess (after unilateral adrenalectomy), even intermittently and mild, we know that the left adrenal tumor is derivate from adrenal cortex. Second adrenal surgery might improve glucose profile, but it was ruled out by the patient at this stage.

Meningioma and bilateral adrenal tumors

Interestingly, the patient was detected with a cerebral meningioma after years of intermittent, mild headache. The diagnostic was established during initial endocrine evaluations. The headache was not associated with uncontrolled high blood pressure, as first expected due to excessive cortisol amount. The lady became hypertensive only during follow-up (7 years since initial detection of active Cushing syndrome). Recently, it was identified that mutations of ARMC5 (armadillo repeat containing 5) gene are responsible for macronodular adrenal hyperplasia, but also meningioma (44-47). Familial cluster is also described (48-51). According to anamnesis, the female patient has not significant conditions in her family. Also, ARMC5 mutations are described in association with PRKAR1A gene anomalies or in connection with the presence of multiple endocrine neoplasia type 1 syndrome (52,53). ARMC5 gene variants are linked not only to cortisol changes, but also to aldosterone and glucose profile anomalies (54).

Assessment of bilateral masses in daily practice

When a first diagnostic of bilateral adrenal masses is established, a part from radiological findings, the endocrine panel might be suggestive for a cortisol and/or aldosterone excess as indicators of adrenal cortex involvement (55,56). Whether the secretion is due to unilateral or bilateral endocrine production represents a milestone of practical approach (57). In order to establish the origin of hormonal excess, at first, imaging aspects as provided by computed tomography or even SPECT-CT are very useful (58,59). In our case, the largest tumor as provided by intravenous contrast computed tomography was considered as cause of Cushing syndrome and its removal was associated with clinical improvement for that moment (the diabetes mellitus was not difficult to be managed during the first 4 years after adrenalectomy). Steroidogenesis assessment based on mass spectrometry might add information related to uni/bilateral hormone over-production (60,61). Adrenal venous sampling represents an elegant option under these circumstances; yet, in many centers this is not routinely feasible (62-65). Adrenal scintigraphy (with ^{131}I-6beta-iodomethyl-19-norcholesterol) is selectively useful if available (66).

Increased dimensions of an adrenal tumor

An adrenal tumor might increase during follow-up, and this typically indicates surgery, as seen here, in addition to small cystic-like areas as due to mild necrosis (67,68). However, under more severe circumstances, a large necrosis and/or hemorrhage induces an enlargement of both adrenal glands and an associated decline of hormonal excess representing an emergency due to lifesaving need of glucocorticoid replacement (69-72).

Pitfalls of "adrenal incidentaloma"

This lady had first two adrenal tumors; the largest mass was associated with Cushing syndrome which was remitted after unilateral adrenalectomy suggesting a contralateral incidentaloma. However, during follow-up, an incomplete picture of potential autonomous cortisol secretion was identified (as previously called "subclinical Cushing syndrome") (73,74,75). We already know that one third of apparently non-functioning adrenal adenomas have a latent cortisol excess and this may be the case or, in fact, this is a bilateral adrenal hyperplasia with macronodular pattern (76,77,78).

Adrenal function after adrenalectomy in patients with bilateral tumors

In cases with bilateral adrenalectomy, adrenal insufficiency is the rule; generally, laparoscopic approach is recommended (uni or bilateral) whenever is feasible (79,80). In cases with unilateral adrenalectomy on subjects with bilateral masses, if the remnant tumor is a true incidentaloma, adrenal insufficiency should be expected, which was not our case (81,82,83). Further on, the patient may become a candidate to a second surgical approach; the timing and technique depends on a multidisciplinary decision in addition to patient' option (84,85,86).

Anomalies of glucose profile

Impaired glycaemia profile is expected in patients with active Cushing syndrome, but also in cases with subclinical type (87,88). In our case, diabetes mellitus was more severe when the subclinical cortisol excess was identified, rather than initial. The negative role of glucocorticoids on glucose metabolism is enhanced by other hormones like aldosterone or GIP (glucose-dependent insulinotropic polypeptide) (89). In a case with subclinical Cushing syndrome and severe diabetes (if

the patient is compliant to anti-diabetic regime), the indication of having an adrenalectomy done is highly suggested (79,80).

Phospho-calcium metabolism

Our patient experienced a mild reduction of vitamin D levels, which is common in menopausal population (90,91). Chronic excess of glucocorticoids might cause bone loss/increased fracture risk, as seen at DXA or TBS (Trabecular Bone Score) which was not our case (92,93). A primary hyperparathyroidism was suggested, but currently not confirmed in this case. A few series reported the co-presence of an active parathyroid adenoma and Cushing syndrome which is exceptional (94,95,96).

CONCLUSION

The key points of following a patient with bilateral adrenal tumors include the timing of uni/bilateral adrenalectomy, the multidisciplinary management of associated complications, as well as the need of understanding the genetic rational behind it.

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