

A New Insight into the Surgical Treatment of Primary Macronodular Adrenal Hyperplasia

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Purpose: This prospective study presents the results of a new approach in the treatment of primary macronodular adrenal hyperplasia (PMAH), with simultaneous total adrenalectomy of the larger adrenal gland and partial adrenalectomy of the contralateral adrenal gland (adrenal-sparing surgery).

Materials and Methods: We performed a prospective study including 17 patients with PMAH treated surgically with adrenal-sparing surgery in a tertiary referral hospital, with a median follow-up of 41 months. Clinical, hormonal, and genetic parameters were evaluated before surgery and during follow-up. All patients had at least 1 radiological examination before and after the procedure.

Results: Among the 17 patients, all but 1 patient had complete hypercortisolism control, and 12 recovered normal adrenal function after surgery. Significant improvement in clinical parameters was observed: weight loss ($P = .004$); reduction of both systolic ($P = .001$) and diastolic ($P = .001$) blood pressure; and reduction in the number of antihypertensive drugs ($P < .001$). Intra-, peri-, and postoperative complications were not observed.

Conclusion: Adrenal-sparing surgery is a safe and feasible procedure to treat patients with PMAH, providing a substantial chance of hypercortisolism control without the disadvantages of lifetime corticosteroid replacement.

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Key Words: PMAH, partial adrenalectomy, hypercortisolism, adrenal surgery, *ARMC5*

Primary macronodular adrenal hyperplasia (PMAH) is a rare cause of adrenal Cushing syndrome (CS). In general, PMAH presents bilateral adrenal nodules with variable cortisol production [1-3].

Abbreviations: ACTH, adrenocorticotropin; CCI, Charlson comorbidity index; CS, Cushing syndrome; CT, computed tomography; HPA, hypothalamic–adrenal–pituitary; PMAH, primary macronodular adrenal hyperplasia; SH, subclinical hypercortisolism

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The clinical spectrum of presentation ranges from mild hypercortisolism to overt CS. Recent studies demonstrated an association between germline/somatic mutations in the tumor suppressor gene *ARMC5* in approximately 50% of cases [4, 5]. The increased frequency of early-diagnosed familial PMAH rendered subclinical hypercortisolism (SH) a frequent manifestation of this disease, corresponding to a majority of cases in specific populations [6]. Because of uneven presentation and severity of this disease, its treatment is challenging.

Clinical treatments for PMAH have included different steroidogenesis inhibitors (ketoconazole; mitotano) and abnormally expressed antagonists of G protein receptors (β -adrenergic receptor antagonists; long-acting leuprolide acetate); however, these have low efficacy to control hypercortisolism [7-10]. Thus, surgical treatment has been widely used. Bilateral adrenalectomy was the standard option in the past for PMAH associated with CS and bilateral involvement [6]. However, this modality leads to permanent adrenal insufficiency and has the drawback of requiring lifetime hormonal replacement. In addition, patients with this condition have a significantly impaired quality of life and a high risk of adrenal crisis, and mortality ranges from 6% to 8% [11]. To avoid this, unilateral adrenalectomy was proposed as a treatment option for patients with mild CS [12-15]. A retrospective study involving 15 patients with a median follow-up of 60 months demonstrated good results with this procedure, reporting 60% of hypercortisolism remission. Nevertheless, in this same cohort, the authors observed 13% hypercortisolism relapse [16]. Therefore, the gold standard treatment for PMAH has not been set yet.

Partial adrenalectomy was described for treatment of diseases affecting both adrenal glands [17]. Current evidence regarding the use of partial adrenalectomy for PMAH is limited, with only a small number of PMAH cases [18-20]. To overcome hormonal replacement caveats while minimizing the risks of hypercortisolism relapse, we performed a series of simultaneous total adrenalectomy of the largest adrenal gland and partial adrenalectomy of the contralateral gland (adrenal-sparing surgery) to treat patients with PMAH. Interestingly, PMAH nodules may exhibit increased uptake of ^{18}F -fluorodeoxyglucose (^{18}F -FDG) (Fig. 1), although lesions are benign [21, 22].

A strong correlation between ^{18}F -FDG uptake and the largest adrenal diameter was observed in patients with PMAH [21, 22]. Thus, performing this functional examination is not essential for deciding which side to perform total adrenalectomy and a decision based on gland size is feasible.

In this prospective study, we evaluate the short-term outcomes of adrenal-sparing surgery for the PMAH treatment, assessing the impact on hypercortisolism control, the improvement of clinical and metabolic parameters, and the recovery of a normal cortisol secretion.

1. Materials and Methods

The ethics committee of the hospital approved the study and written informed consent was received. This study included 17 patients (12 females, age range from 18 to 70 years). All underwent adrenal-sparing surgery with a median follow-up of 41 months after surgery. The choice of which adrenal gland to be completely resected was based on the findings of computed tomography (CT) and ^{18}F -FDG positron emission tomography. PMAH diagnosis was suspected in patients with classical features of CS ($n = 7$) and in patients with SH associated with incidental bilateral nodular adrenal glands on CT scan ($n = 10$). Patients with CS were classified according to high clinical index of suspicion for hypercortisolism, such as facial plethora, easy bruising, large violaceous striae, and proximal myopathy. In addition, they presented with at least 2 abnormal results of the following examinations: 24 hour urinary cortisol, midnight salivary cortisol, and nonsuppression of serum cortisol after low-dose dexamethasone suppression test (DST) with 1 mg of dexamethasone overnight (F cut-off $>1.8 \mu\text{g/dL}$ or 50 nmol/L) and with low/suppressed plasmatic levels of adrenocorticotropin (ACTH) [23]. Patients with SH presented with metabolic syndrome (obesity; blood hypertension; glucose intolerance; or diabetes mellitus type 2 and dyslipidemia) and were lacking typical clinical signs of hypercortisolism (facial

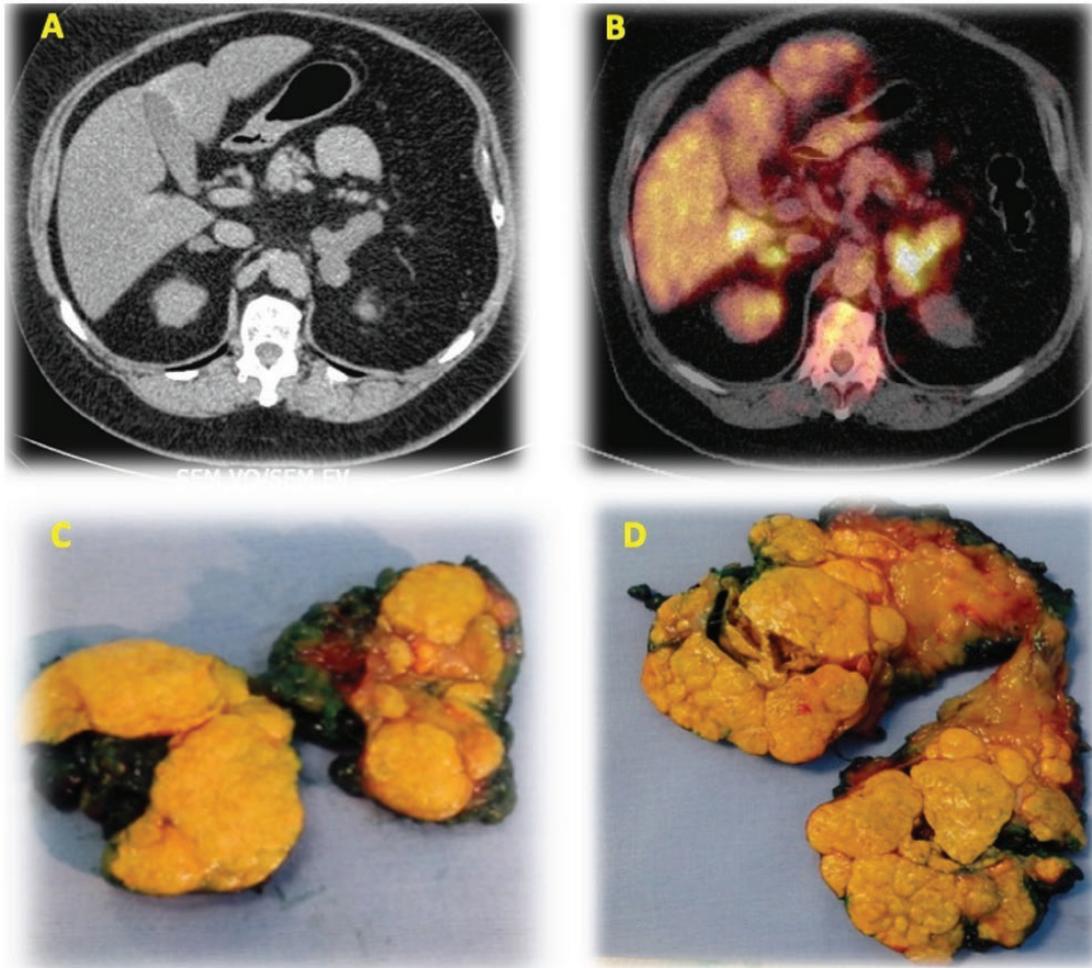


Figure 1. Enlarged adrenal glands in PMAH and surgical pieces after adrenal sparing surgery. (A) CT image. (B) image in ^{18}F -FDG-PET/CT. (C) opened surgical piece with nankin ink on surface – right partial adrenalectomy. (D) opened surgical piece with nankin ink on surface – left total adrenalectomy.

plethora; proximal muscle weakness; easy bruising; and violaceous striae wider than 1 cm). All patients presented normal values of midnight salivary cortisol and 24-hour urinary cortisol with abnormal serum cortisol levels after low-dose DST with 1 mg of dexamethasone overnight (F cut-off $>1.8 \mu\text{g/dL}$ or 50 nmol/L) [24]. We also evaluated aldosterone and renin or renin plasmatic activity and Na/K, and all were at normal levels without suspicion of primary aldosteronism.

For serum cortisol, we used an antibody from Beckman (RRID:AB_2802133 [25]) (during 2019, we used an antibody from Abbott, RRID:AB_2783639 [26]). For salivary cortisol, we used an antibody from Roche (RRID:AB_2802131 [27]). For ACTH we used RRID:AB_2783634 [28]. To measure the dexamethasone and the urinary cortisol dosage we used liquid chromatography mass spectrometry. The total urinary cortisol dosage, from 2009 to 2015, was measured using a chemiluminescent immunoassay.

Adrenal volume measurement was performed at preoperative CT and 3-month postoperative CT by 2 experienced radiologists. *ARMC5* was analyzed from all patients; germline and somatic mutations were evaluated (Table 1) and sited according to the National Institutes of Health recommendation [29]. Histological diagnosis of PMAH was confirmed by an expert pathologist (M.C.N.Z.).

Table 1. Summary of *ARMC5* allelic variants identified

Subject	<i>ARMC5</i> germline allelic variant	Location	State	Prediction	<i>ARMC5</i> Somatic Alteration	Location	State	Prediction
1	normal							
2	c.476-1G>C	Intron1	Heterozygous	Pathogenic ^a	NA	Exon 6	Heterozygous	Uncertain significance ^b
3	c.1181T>C (p.Leu394Pro)	Exon 3	Heterozygous	Uncertain Significance ^b	c.2053_2055delCTT (p.Leu685del)	Exon 4	Heterozygous	pathogenic ^b
4	c.170dupG (p.Ile58Asnfs*45)	Exon 1	Heterozygous	Pathogenic ^b	c.1559delG (p.Gly520Aspfs*24) LOH			
5	c.2423A>C (p.His808Pro)	Exon 6	Heterozygous	Likely pathogenic ^b	c.283_295delTCGGCCGGCTCGGG (p.Ser96Serfs*2)	Exon 1	Heterozygous	Likely pathogenic ^b
6	c.170dupG (p.Ile58Asnfs*45)	Exon 1	Heterozygous	Pathogenic ^b	c.2082_2088delCCCCGCTC (p.Pro695Serfs*20)	Exon 6	Heterozygous	Likely pathogenic ^b
7	c.280_281delT (p.Ser94Valfs*8)	Exon 1	Heterozygous	Likely pathogenic ^b	Absent			
8	Normal							
9	c.1960C>T (p.Arg654*)	Exon 5	Heterozygous	Likely pathogenic ^b	NA	Exon 4	Heterozygous	Likely pathogenic ^b
10	Normal				c.1575_1582delCCTGCTGC (p.Leu526Alafs*9)			
11	Normal				NA			
12	c.799C>T (p.Arg267*, rs369721476)	Exon 3	Heterozygous	Uncertain significance ^b	NA			
13	Normal				NA			
14	Normal				NA			
15	c.407T>C (p.Leu136Pro, rs771845578)	Exon 1	Heterozygous	Uncertain significance ^b	NA			
16	c.1094T>C (p.Leu365Pro, rs587777663)	Exon 3	Heterozygous	Uncertain Significance ^b	c.295G>T (p.Gly99*)	Exon 1	Heterozygous	Likely pathogenic ^b
17	c.1094T>C (p.Leu365Pro, rs587777663)	Exon 3	Heterozygous	Uncertain Significance ^b	LOH			

^aPrediction made using the Human splicing finder (<http://www.umd.be/HSF/>).^bPrediction made using the Varsome The Human Genomics Community (<https://varsome.com/>).

We used the Charlson comorbidity index (CCI) to evaluate the mortality risk for patients. The CCI is among the best-known and widely used indexes of comorbidity and was originally developed to predict 1-year mortality in a mixed population of internal medicine patients using comorbidity derived from a chart review. The CCI consists of 19 selected conditions that are weighted and summed to an index on a 0 to 33 scale [30, 31].

A. Surgical treatment

Surgical treatment was indicated in 3 circumstances: (1) presence of CS regardless of age; (2) SH in patients with aged <50 years; (3) SH associated with difficult to control blood hypertension, dyslipidemia, or diabetes mellitus in patients aged between 50 and 70 years.

In cases of symmetric adrenal gland size and uptake, the right side was elected for partial resection. Surgical treatment was performed in 2 sequential steps, as described by Srougi et al. [32]. (1) Partial adrenalectomy: the incision of the adrenal gland was done with the aim of resecting at least two-thirds of the gland parenchyma, removing all visible nodules and preserving the main adrenal vein whenever possible. For hemostasis, 10-mm Hem-o-lock® clips (Morrisville, NC, USA) and monopolar electrocautery were used. (2) Total adrenalectomy: after repositioning the patient, the entire contralateral gland was removed. Whenever possible, the midline laparoscopic port used in partial adrenalectomy was also used for contralateral total adrenalectomy. Intraoperative ultrasound imaging was not used. Resection of the nodules was performed based on CT scan reconstruction planning and intraoperative visual estimation. Specimens were weighted and sent for pathological evaluation. The diagnosis of PMAH was confirmed by pathological analysis performed by the same pathologist. The same experienced urologist proctoring a urology resident operated on all patients. Intra- and postoperative data were recorded, including medical and surgical complications.

B. Treatment outcomes

All patients received 100-mg of hydrocortisone dose in anesthetic induction and, thereafter, 50 mg every 8 hours. After the return of oral ingestion, all patients started oral hydrocortisone replacement (20 mg at 8 AM and 10 mg at 2 PM). During follow-up, medical visits were monthly in the first trimester, every 3 months until completion at 1, year, and every 6 months thereafter. Morning serum cortisol was measured before hydrocortisone intake every medical visit. Hydrocortisone dose was adjusted based on serum cortisol measurement and the presence of clinical symptoms. Fludrocortisone replacement (50 µg/day) was prescribed when the patient had either hypotension episodes or low aldosterone levels associated with high levels of plasmatic renin. Glucocorticoid replacement was interrupted when serum cortisol level was >8.8 µg/dL [33]. The cosyntropin test was performed in order to evaluate remnant adrenal response (250-µg bolus; cut-off for response was serum cortisol over 18 µg/dL at 60 minutes). This test was not performed in the whole cohort as it was not available in our institution during most of the study period (Table 2). The endpoint was control of hypercortisolism, defined when the patient presented physiologic levels of serum

Table 2. Results of cosyntropin test

Subject	Baseline serum cortisol (µg/dL)	Post cosyntropin cortisol (µg/dL)	
		30 minutes	60 minutes
9	5.9	18.8	19.9
12	11.9	N/A	21.3

HPA axis recovery: serum cortisol >18 µg/dL measured 60 minutes after endovenous administration of 250 µg of synthetic cosyntropin.

cortisol (5–25 µg/dL; 0.18–0.90 nmol/L) without needing hormonal replacement. When clinical signs of adrenal insufficiency were detected and/or serum cortisol levels were below 5 µg/dL (8:00 AM), additional oral hydrocortisone was replaced with a dose of >0.2 mg/kg/day. Blood pressure, serum glucose, serum triglycerides, serum cholesterol (high-density lipoprotein and low-density lipoprotein), and body mass index (BMI) were compared before surgery, 12 months after surgery, and at the last visit for each patient. The number of medications to control blood hypertension, diabetes mellitus, and dyslipidemia were recorded and compared.

Remission of hypercortisolism after surgery was assessed and correlated with age, gender, BMI, serum cortisol, plasmatic ACTH, serum cortisol after DST, presence of germline/somatic *ARMC5* mutation, and time between PMAH diagnosis and surgical treatment. Preoperative largest adrenal volume and postoperative adrenal volume were also correlated with time to hypothalamic–adrenal–pituitary (HPA) axis recovery.

C. Statistical analysis

Kaplan–Meier survival curves were used to estimate the time for the HPA axis to recover. Curves were compared using the log-rank test, and risk factors were evaluated using the Cox proportional hazards model. In comparisons of clinical and metabolic parameters, the nonparametric Friedman test was used. Whenever a significant difference was observed, the Bonferroni correction was applied. Statistical significance was considered when $P < .05$. Statistical tests were performed using IBM SPSS® version 24. (IBM, USA).

2. Results

Clinical characteristics at presentation are summarized on [Table 3](#). At the time of surgical treatment, the median age was 50 years (range 41–69 years), and median BMI was 29 (range 31–48 kg/m²). All surgeries were successfully performed via laparoscopy access. Seven patients presented classical CS, while 10 had SH. Two patients from the same family had the same germline *ARMC5* mutation.

Right partial adrenalectomy was performed in 11 patients, 3 of whom presented both adrenal glands with similar volume in CT scan and uptake in ¹⁸F-FDG PET/CT ([Table 4](#)).

Patients operated on showed significant improvement in clinical parameters after surgery: reductions in weight (88–82 kg; $P = .004$), in systolic (145–121 mmHg; $P = .001$) and diastolic blood pressure (91–78 mmHg; $P = 0.001$), in the number of hypertension medications (2.8–1.1; $P < .001$), and in the number of antidiabetic drugs (1–0; $P = .021$). These differences were noted between preoperative and both postoperative measures (12 months and last visit) ([Fig. 2](#)). Other metabolic parameters did not change significantly ([Table 3](#)).

In a median follow-up of 41 months, 12 patients achieved control of hypercortisolism, while the other 5 still had adrenal insufficiency ([Fig. 3](#)). The mean time to adrenal function recovery was 32.4 months (median 17 month; range 6–84). At postoperative CT, the mean adrenal volume was 4.07 cm³ (range 0.6–12.1). As expected, we observed that normal ACTH before surgery was a predictor for faster recovery of the physiological HPA axis. None of the studied variables was significant for determining the maintenance of postoperative adrenal insufficiency ([Tables 5 and 6](#)). One patient (subject 4) developed hypercortisolism recurrence, which was diagnosed because of abnormal elevation in serum cortisol after DST ([Fig. 2](#)). This patient underwent a second surgical procedure.

3. Discussion

Adrenal-sparing surgery exhibited good results, achieving satisfactory hypercortisolism remission and improvement of clinical parameters. In our cohort, 95% and 70.5% of the patients achieved normocortisolemia and recovery of the physiologic HPA axis, respectively.

Table 3. Patients characteristics at presentation

N	Age	Sex	BMI (kg/m ²)	Charlson score	Clinic presentation	ARMC5 mutation	MENI	Serum cortisol (µg/dL)	Salivary cortisol (µg/dL)	Urinary cortisol (µg/24 h)	ACTH (pg/mL)	Dexamethasone test (µg/dL)	Adrenal volume in CT scan (cm ³)		Adrenal uptake in PET/CT (SUV)	
													Left	Right	Left	Right
1	53	F	49	1	SH	-	-	8.9	0.21	172	<5	5.0	26.4	13.2	5.0	5.1
2	63	F	41	3	CS	+	+	25.9	0.48	450	<5	32.8	54.5	19.2	8.9	7.1
3	49	F	27	2	CS	+	-	27.8	0.32	364	<5	27.1	11.4	47.2	4.1	5.5
4	45	F	23	1	CS	+	-	18.5	0.65	389	<5	18.7	17.4	38.1	3.4	2.7
5	45	M	29	1	CS	+	-	26.6	0.75	1419	<5	3.9	220	67	4.9	3.3
6	45	F	31	1	CS	+	-	12.7	0.08	78	<5	7.2	10.1	9.3	3.6	3.8
7	52	M	35	4	CS	+	-	26.8	0.85	100	<5	25.1	48.6	41.2	5.6	5.0
8	50	F	28	1	CS	-	-	28.6	0.98	619	<5	29.6	2	-	4.2	-
9	41	M	27	0	SH + INC	+	-	13.7	0.19	28	<5	10.5	33.5	52.8	4.4	4.9
10	68	M	28	3	SH + INC	-	-	24.9	0.03	157	13.9	6.3	19.1	8.4	6.8	5.7
11	47	F	34	2	SH + INC	-	-	6	0.09	90	<5	12.4	33.1	15.3	3.0	2.6
12	47	F	41	1	SH + INC	+	-	17	0.13	213	<5	15.7	23	18.3	4.1	4.7
13	49	F	21	3	SH + INC	-	+	16	0.11	80	16.9	4.9	7.9	5	4.0	4.8
14	69	F	26	3	SH + INC	-	-	10.5	0.05	34	20	3.2	13.2	16.3	3.2	3.4
15	69	F	36	2	SH + INC	+	-	10.8	0.014	21	<5	13.9	50.5	9.8	4.7	4.3
16	61	M	35	3	SH + FAM	+	-	9.1	0.06	17	<5	3.7	9.5	12.6	2.3	4.1
17	41	F	48	0	SH + FAM	+	-	14.9	0.07	12	16.7	7.8	4.8	5.1	4.4	4.5

Reference ranges: serum cortisol = 5–25 µg/dL; midnight salivary cortisol = 0.274 µg/dL; urinary cortisol = 50–310 µg/24 hours (subjects 1–13 excluding 6); free urinary cortisol = 3.0 at 43 µg/24 hours (subjects 14–17 including 6); ACTH = 7.2–63.3 pg/mL; dexamethasone suppression test = cortisol <1.8 µg/dL. Abbreviations: CS, Cushing's syndrome; SH, subclinical hypercortisolism, INC, adrenal incidentaloma; MENI, meningioma; FAM, familial screening.

Table 4. Intraoperative characteristics and follow-up

N	Surgical time(min)	Anesthesia time (min)	Postoperative ICU	Hospital stay(days)	Partial adrenalectomy side	Surgical specimen weight (g)		Postoperative adrenal volume (cm ³)		Hormonal axis recovery	Hormonal reposition (months)	Follow-up(months)
						Left	Right	Left	Right			
1	180	280	-	4	R	40.2	9.4	0	0.6	+	40	54
2	200	270	+	23	R	158.9	15.9	0	6.2	+	32	52
3	170	285	-	9	L	50	(both)	6.9	0	-	88	88
4	195	300	-	3	R	65.8	11.8	0	8.5	+	17	40
5	240	390	+	3	R	57	22.9	0	12.1	-	52	52
6	160	390	+	7	R	32.3	23.1	0	2.1	+	18	47
7	190	510	+	5	R	65	33.2	0	3.6	-	42	42
8	125	210	-	11	R	-	18	0	0.4	-	42	42
9	240	320	-	8	L	45.9	74.2	5	0	+	15	41
10	190	370	+	10	R	46.6	13.9	0	3.3	+	6	38
11	210	330	-	8	R	55.5	22.3	0	0.5	-	28	28
12	180	330	-	8	L	46.7	39.6	6.7	0	+	10	26
13	190	280	+	5	L	21.3	29.0	3	0	+	14	23
14	205	250	-	10	L	17.3	31.5	3.6	0	+	4	17
15	300	385	+	5	R	90.3	20	0	2	+	12	15
16	240	360	-	4	L	30.8	22	3	0	+	8	14
17	180	225	+	3	R	36.7	22	0	1	+	6	13

Abbreviations: R, right; L, left; ICU, intensive care unit; min, minutes.



Figure 2. Patient with PMAH. Before (A,C) and after surgical treatment (B,D). Patient consented to the use of images.

Hormonal Function Evolution

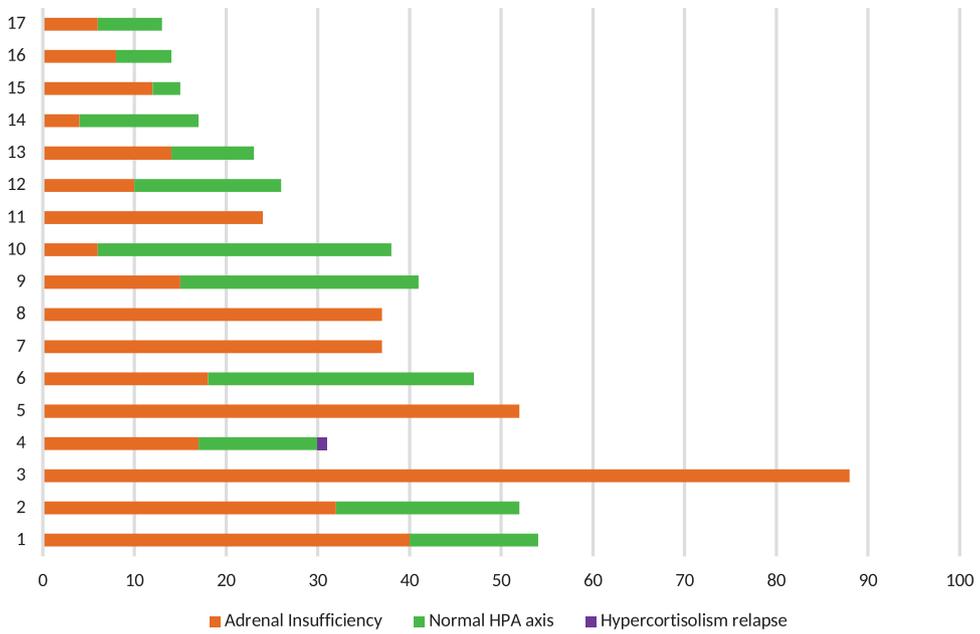


Figure 3. Hormonal function evolution. Patient × time (months).

Table 5. Pre- and postoperative clinical and metabolic parameters

Variable	Average	Median	Standard deviation	IQR	P*	Multiple Comparison	
						Moment	adjusted P**
Weight (kg)							
Initial	87.9	86	23.7	42.0	.004	1–2	.003
12 months	81.5	85	19.9	33.7		1–3	.31
Last visit	83.3	88	20.3	36.3		2–3	.31
Body mass index (kg/m²)							
Initial	32.8	30.5	8.2	11.4	.051		
12 months	30.5	29.0	6.3	9.5			
Last visit	29.9	30.0	5.6	9.5			
Systolic blood pressure (mmHg)							
Initial	145.2	140	23.9	30.0	.001	1–2	.002
12 months	121.6	120	17.9	20.0		1–3	.018
Last visit	125.9	130	9.5	10.0		2–3	1
Diastolic blood pressure (mmHg)							
Initial	91.1	90	10.9	20.00	.001	1–2	.024
12 months	79.4	80	11.9	20.00		1–3	.008
Last visit	78.8	80	6.0	5.00		2–3	1
Drugs: dyslipidemia (n)							
Initial	0.58	1	NA	1.00	.368		
12 months	0.41	0	NA	1.00			
Last visit	0.41	0	NA	1.00			
Drugs- diabetes (n)							
Initial	0.9	1	NA	2.00	.021	1–2	.368
12 months	0.5	0	NA	1.00		1–3	.595
Last visit	0.6	0	NA	1.00		2–3	1
Drugs: hypertension (n)							
Initial	2.8	3	NA	2.00	<.0001	1–2	.006
12 months	1.1	1	NA	2.00		1–3	.002
Last visit	1.0	1	NA	2.00		2–3	1
Glucose (mg/dL)							
Initial	116.4	108,0	38.4	40.50	.138		
12 months	99.5	98,0	20.9	21.50			
Last visit	97.6	90,0	21.3	24.00			
Glycated hemoglobin (%)							
Initial	6.6	6,2	1.2	1.44	.42		
12 months	6.2	5,9	0.9	1.00			
Last visit	6.0	5,9	0.6	0.95			
Cholesterol (mg/dL)							
Initial	207.0	199,0	38.8	69.00	.092		
12 months	185.1	179,0	38.7	54.00			
Last visit	184.8	181,0	32.9	56.00			
Low-density lipoprotein(mg/dL)							
Initial	117.4	110,0	30.7	47,50	.664		
12 months	105.8	112,0	34.2	53,50			
Last visit	111.5	113,0	39.8	68,00			
High-density lipoprotein (mg/dL)							
Initial	50.2	50,0	12.9	27.00	.884		
12 months	50.2	48,0	14.5	25.00			
Last visit	49.0	48,0	11.7	19.00			
Triglycerides (mg/dL)							
Initial	180.5	156,0	92.6	111.50	.356		
12 months	160.3	148,0	60.7	96.00			
Last visit	174.7	176,0	75.5	104.50			

IQR, interquartile ranges.

Table 6. Influence in time to recover HPA axis function

Variable	P	RR	CI (95%) for RR	
			Inferior	Superior
ACTH (measurable)	.003	12.15	2.366	62.38
Serum basal cortisol	.077	0.936	0.870	1.007
DST cortisol	.104	0.949	0.892	1.011
Bigger adrenal volume	.150	0.980	0.954	1.007
SUVMAX	.822	0.952	0.622	1.458
SUVMAX (>3,1)	NA			
<i>ARMC5</i> mutation	.972	0.979	0.294	3.256
Meningioma	.672	1.393	0.300	6.482
Gender	.799	1.186	0.320	4.398
Age	.063	1.069	0.996	1.146
BMI	.747	1.012	0.943	1.085
BMI (>30)	.655	1.302	0.409	4.152
Disease time	.103	1.011	0.998	1.025
Postoperative adrenal volume	.486	0.942	0.797	1.114

Abbreviations: ACTH, adrenocorticotropin; BMI, body mass index; DST, dexamethasone suppression test; RR, relative risk; CI, confidence interval.

Moreover, this surgical approach was safe, with an acceptable rate of complications in a cohort of patients with important clinical comorbidities associated with metabolic syndrome.

Lowery et al. assessed a cohort of 23 patients with CS or SH harboring bilateral adrenal disease caused by different pathologies, treated with simultaneous total adrenalectomy and contralateral partial adrenalectomy. Corticosteroid supplementation was needed in 78% of the patients and mean time of hormonal reposition was 32 months [20]. In the present study, all patients needed corticosteroid replacement after surgery, and median time of hormonal reposition was 17 months (range 4-84). In our analysis, patients with preoperative mild hypercortisolism presented a better recovery of the HPA axis. Recently, Di Dalmazi et al. published a systematic review involving 28 studies, with 248 patients operated on due to SH and 377 patients operated on due to overt CS [34]. The prevalence of adrenal insufficiency immediately after surgery was 65.3% in the SH group and 99.7% in the CS group, while the time to HPA axis recovery was 6.5 and 11.2 months, respectively [34].

In our analysis, patients with mild hypercortisolism more commonly presented HPA axis recovery; this is in agreement with an important previous study published in 2014. Prete et al., in a recent retrospective analysis, observed that patients with primary adrenal overt CS treated with unilateral adrenalectomy had a median period of adrenal insufficiency of 18.5 months, compared with 6 months in patients with primary adrenal SH treated the same way [35].

The volume of remnant adrenal gland seems to have a pivotal role in the outcome of adrenal-sparing surgery for PMAH. One may infer that patients treated with this approach will wait longer for recurrence due to the smaller volume of remnant adrenal gland compared with patients treated with unilateral adrenalectomy. It has been suggested that 15% to 30% of remnant adrenal gland would be sufficient to maintain physiologic adrenal hormonal production when performing partial adrenalectomy for most adrenal diseases [36]. However, this proportion might be different when dealing with PMAH, which affects the entire gland. In addition, PMAH is frequently associated with germline mutations, considerably increasing the risk of recurrence. It should be emphasized that adrenal glands afflicted by PMAH have inefficient steroidogenesis. Thus, theoretically more remnant adrenal tissue should be kept compared with other adrenal pathologies, with the aim of recovery of the HPA axis.

Debillon et al. [16] described the treatment of PMAH with unilateral adrenalectomy in 15 patients, reporting 60% of hypercortisolism remission. However, in the same cohort the rate of disease recurrence was 13% after 7 years of follow-up [16]. More recently, Osswald et al. [37] reported that up to 68% of patients with PMAH treated with unilateral adrenalectomy sustain or present hypercortisolism recurrence. In our series, we observed 1 case of hypercortisolism recurrence, within 41 months of follow-up [37]. Considering the heterogeneous presentation of PMAH, there are probably patients in which unilateral adrenalectomy is more suitable, while in others the same approach may lead to early hypercortisolism recurrence. We hypothesize that the ideal surgical treatment for PMAH should be chosen according to each specific PMAH presentation.

This study has inherent limitations, namely the small number of patients and absence of a control group. However, this is the first prospective series addressing PMAH treatment with adrenal-sparing surgery. In addition, we are the first to evaluate the use of pre- and postoperative adrenal volume measurement in PMAH. Another important issue is that as family cases of patients with germline mutations in *ARMC5* are screened more cases of PMAH will be diagnosed at an early stage, and the precise indication of each surgical procedure will be challenging.

To the best of our knowledge, surgical treatment should be indicated in strictly selected patients and the choice between unilateral, bilateral, and adrenal-sparing surgery tailored for each case.

In conclusion, adrenal-sparing surgery is a safe and feasible procedure for PMAH, providing hypercortisolism remission while potentially avoiding the drawbacks of corticosteroid replacement. Additionally, patients undergoing this treatment exhibited substantial improvement of clinical parameters. Within a short follow-up, adrenal-sparing surgery proved to be an effective alternative. Further studies with a higher level of evidence and comprising larger cohorts are necessary to validate the role of this therapeutic modality.

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