Brief Communication

Prolonged adrenal insufficiency after unilateral adrenalectomy for Cushing's Syndrome

Bindu Kulshreshtha, Arpita Arora, Anshita Aggarwal, Minakshi Bhardwaj[1]

Departments of Endocrinology and [1]Pathology, PGIMER, Dr. RML Hospital, New Delhi, India

ABSTRACT

The contralateral healthy adrenal in patients undergoing unilateral adrenalectomy for Cushing's is known to be suppressed temporarily and forms the basis of peri and postoperative steroids. We present four cases of Cushing's who had prolonged adrenal insufficiency with continued requirement for steroids for periods ranging 1–4 years after unilateral adrenalectomy for Cushing's. We further review literature regarding the recovery of the hypothalamo pituitary adrenal axis postsurgery in patients with Cushing's syndrome.

Key words: Adrenal insufficiency, Cushing's syndrome, unilateral adrenalectomy

Introduction

The suppression of the hypothalamo pituitary adrenal (HPA) axis by cortisol producing adrenocortical tumors is well-recognized. This forms the basis of peri- and post-operative cortisol replacement in patients with cortisol producing adrenal tumors. However, the duration for which the cortisol replacement needs to be given in these patients could be highly variable. Recently, a review published by Di Dalmazi *et al.* indicated that the average time to recovery of adrenal function post unilateral adrenalectomy for cortisol producing tumors was around 11 months.[1] We discuss here four of our patients with adrenocortical tumors who required steroids for a prolonged period ranging from 1-year to 4 years.

Patient Profile

Patients who underwent unilateral adrenalectomy for Cushing's syndrome from 2010 to 2014 were identified from the pituitary clinic of our department. Four females, ages ranging from 16 to 60 years, diagnosed to have Cushing's syndrome were analyzed. The clinical details of these patients are given in Table 1. All underwent unilateral adrenal gland removal for Cushing's syndrome. All four patients had the nonsuppressible cortisol post high dose dexamethasone suppression test (HDST). Three had adrenocortical tumors while one had adrenocorticotropic hormone (ACTH) dependent adrenal hyperplasia. Though bilateral adrenalectomy was planned for this patient, only unilateral adrenalectomy was performed by the surgeon because of long operating time required for removal of first adherent adrenal gland and pending OT list. Patient one had adrenocortical adenoma on histopathology, but investigations also revealed high basal testosterone around 4.4 nmol/L that was not suppressed by HDST. All except one patient went into adrenal crises postsurgery. Patient three required hospitalization twice when steroid dose was not increased adequately during infection. Clinical details of these patients post adrenalectomy are provided in Table 2. All four patients had adrenal insufficiency for periods ranging from 1 to 4 years with continued requirement for steroids at the time of writing this article. Though there was a reduction in the steroid dose requirement during follow up, basal cortisol levels in the range of 0.1–3.5 mcg/dl (after 1-day of steroid withdrawal) indicated a continuing phase of adrenal insufficiency in them.

Access this article online	
Quick Response Code:	Website: www.ijem.in
	DOI: 10.4103/2230-8210.152794

Corresponding Author: Dr. Bindu Kulshreshtha, Department of Endocrinology, PGIMER, Dr. RML Hospital, New Delhi, India. E-mail: drbindu25@yahoo.co.uk

Table 1: Clinical details of patients at initial presentation

	Case 1	Case 2	Case 3	Case 4
Initials	S	P	MJ	F
Age	16 years	35 years	60 years	39 years
Duration of disease	1-year	2 years	8 years	10 years
HDDST	Not suppressible (24.4 mcg/dl)	Not suppressible (30.9 mcg/dl)	Not suppressible (21.0 mcg/dl)	Not suppressible (8.9 mcg/dl)
Adrenal imaging	Right adrenal mass (4.8 cm×7 cm) (Figure 1)	Right adrenal mass (4.4 cm×4.9 cm)	Left adrenal mass (1.9 cm×1.7 cm)	Bilateral adrenal hyperplasia
Histopathology	Adrenocortical adenoma (Figure 1)	Adrenocortical carcinoma (Figure 2)	Adrenocortical adenoma	Not available
Diagnosis	Cortisol producing adrenocortical adenoma	Cortisol and testosterone producing adrenocortical carcinoma	Cortisol producing adrenocortical adenoma	ACTH dependant Cushing's (primary not known)

HDDST: High dose dexamethasone suppression test, ACTH: Adrenocorticotropic hormone

Table 2: Follow-up information after unilateral adrenalectomy

Clinical features	Case 1	Case 2	Case 3	Case 4
Diagnosis	Cortisol and testosterone producing adrenocortical adenoma	Cortisol and testosterone producing adrenocortical carcinoma	Cortisol producing adrenocortical adenoma	ACTH dependant Cushing's
Postoperative follow-up	2 years	1-year	4 years	3 years
Adrenal crisis	+ (5 months postoperative)	-	+ thrice (5 months, 1-year and 2 years after surgery)	+ (2 months and 2 years 8 months postoperatively)
Steroid dose used initially	Prednisolone 7.5 mg	Hydrocortisone 25 mg	Prednisolone 15 mg	Prednisolone 10 mg
Present steroid dose (daily)	Hydrocortisone 10 mg	Hydrocortisone 15 mg	Hydrocortisone 40 mg	Prednisolone 2.5 mg
Withdrawal attempted	No	No	No	Yes, patient stopped herself for 2 months (had vomiting) restarted again
Average cortisol during follow-up	0.1-0.2 mcg/dl	1.1–3.2 mcg/dl	Basal cortisol-0.1–2 mcg/dl ACTH stimulated cortisol-0.16 mcg/dl	1.4–3.5 mcg/dl

ACTH: Adrenocorticotropic hormone

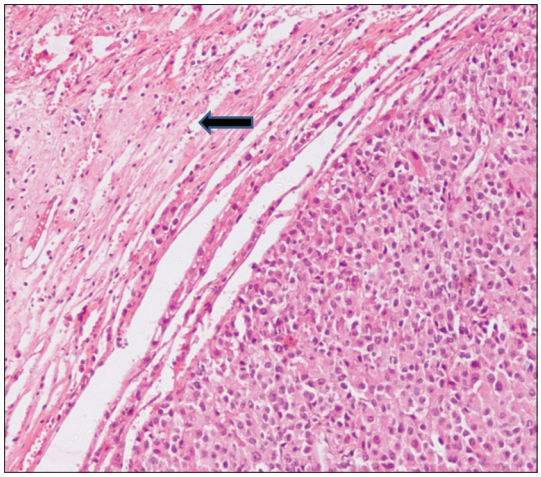

Figure 1: Adrenal adenoma: Pushing border with pseudocapsule (arrow) (×10)

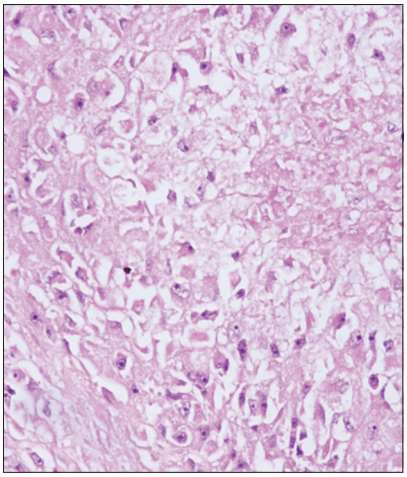

Figure 2: Adrenocortical carcinoma. Pleomorphic tumor cells with prominent nucleoli (H and E, ×40)

Discussion

Cortisol producing tumors are known to suppress the HPA axis, which forms the basis of cortisol replacement postoperatively. However, the extent and the duration for which this axis remains suppressed could be highly variable depending on duration and severity of cortisol excess, tumor size, and other unknown factors. Di Dalmazi *et al*. in a metaanalysis observed that postoperative adrenal insufficiency was found in 65% of 248 patients with subclinical hypercortisolism, whereas 99.7% of those with overt Cushing's had postoperative adrenal insufficiency.[1] Most of them had adrenal recovery within 20 months except two studies involving 11 and 4 patients who had

mean adrenal recovery of around 25–30 months.[2,3] The authors suggested that the degree of hypercortisolism could affect the recovery of adrenal axis since those with subclinical Cushing's had adrenal recovery within 6 months compared with those with overt Cushing's who required 11 months for adrenal recovery.

The concept that HPA axis could be differently affected has also been shown in some previous studies. Eller-Vainicher *et al*. showed that the risk to develop adrenal insufficiency rose when more than one diagnostic test to define subclinical hypercortisolism was pathological.[4] After adjustment for age, body mass index, adrenal size, duration of hypercortisolemia, patients with association of at least two criteria including post dexamethasone suppression test cortisol >5 mcg/dl, midnight serum cortisol >5.5 ncg/dl and ACTH lower than 10 pg/ml showed the highest risk of developing postsurgical adrenal insufficiency. Alesina *et al*. reported a mean time of 12 months of steroid replacement post adrenalectomy in 136 patients with Cushing's syndrome: Maximum time of steroid withdrawal was 60 months, however details of this individual patient were not given.[5]

All our patients had adrenal insufficiency requiring steroids for a prolonged duration ranging from 1 to 4 years postsurgery. Three went into delayed adrenal crises postsurgery. Basal cortisol levels during follow up were very low (<3 mcg/dl) precluding the need for stimulation tests. All our patients had overt Cushing's of prolonged duration (1–10 years) with a nonsuppressible HDST. This could be the reason for the delayed adrenal function recovery. The other reason for prolonged steroid requirement in our patients could be use of potent steroids like prednisolone instead of hydrocortisone in the postoperative period. Three patients were later switched to hydrocortisone, one is on small doses of 2.5 mg prednisone after she developed anorexia and vomiting after stopping steroids.

Patients with cortisol producing adrenal adenoma are known to have suppressed testosterone levels due to suppression of hypothalamoadrenal axis by cortisol.[6,7] However, patient one with adrenocortical adenoma on histopathology had high testosterone and cortisol levels, (not suppressed with dexamethasone), thereby indicating a possible co-secretion of testosterone and cortisol from the tumor. Few previous studies have also documented dual hormone production either by adrenocortical venous sampling from benign adrenocortical tumors or by immonohistochemistry of the tissue.[8,9] The adrenal crises and requirement for steroids after single adrenal gland removal in patient 4 (ACTH dependent Cushing's) is surprising. Lamas *et al*. also reported four patients with macronodular adrenal hyperplasia, of which two developed adrenal insufficiency for 14 and 60 months respectively after unilateral adrenalectomy.[10]

In conclusion, all our subjects had prolonged periods of adrenal insufficiency after unilateral adrenalectomy. A longer follow up for these patients is required to look for recovery of the contralateral adrenal gland.

References

1. Di Dalmazi G, Berr CM, Fassnacht M, Beuschlein F, Reincke M. Adrenal function after adrenalectomy for subclinical hypercortisolism and Cushing's syndrome: A systematic review of the literature. J Clin Endocrinol Metab 2014;99:2637-45.
2. Skalkeas G, Gogas JG, Sechas MN, Kostakis A, Pavlatos F. Cushing's syndrome. Analysis of 18 cases. Am J Surg 1982;143:363-6.
3. Klose M, Jørgensen K, Kristensen LØ. Characteristics of recovery of adrenocortical function after treatment for Cushing's syndrome due to pituitary or adrenal adenomas. Clin Endocrinol (Oxf) 2004;61:394-9.
4. Eller-Vainicher C, Morelli V, Salcuni AS, Torlontano M, Coletti F, Iorio L, *et al*. Post-surgical hypocortisolism after removal of an adrenal incidentaloma: Is it predictable by an accurate endocrinological work-up before surgery? Eur J Endocrinol 2010;162:91-9.
5. Alesina PF, Hommeltenberg S, Meier B, Petersenn S, Lahner H, Schmid KW, *et al*. Posterior retroperitoneoscopic adrenalectomy for clinical and subclinical Cushing's syndrome. World J Surg 2010;34:1391-7.
6. Horio S, Funahashi H, Mizuno S. Plasma steroid hormones in Cushing's syndrome: Their relation to cause and clinical manifestations (author's transl). Nihon Naibunpi Gakkai Zasshi 1981;57:807-25.
7. Smals AG, Kloppenborg PW, Benraad TJ. Plasma testosterone profiles in Cushing's syndrome. J Clin Endocrinol Metab 1977;45:240-5.
8. Ghazi AA, Mofid D, Salehian MT, Amirbaigloo A, Zare K, Jafari B, *et al*. Functioning adrenocortical tumors in children-secretory behavior. J Clin Res Pediatr Endocrinol 2013;5:27-32.
9. Murakami Y, Sasaki M, Sasano H, Suzuki T, Kitamura N, Tomoi M, *et al*. Young female patient with testosterone-producing adrenocortical adenoma also showing signs of subclinical Cushing's syndrome. Endocr J 1995;42:283-8.
10. Lamas C, Alfaro JJ, Lucas T, Lecumberri B, Barceló B, Estrada J. Is unilateral adrenalectomy an alternative treatment for ACTH-independent macronodular adrenal hyperplasia? Long-term follow-up of four cases. Eur J Endocrinol 2002;146:237-40.

Cite this article as: Kulshreshtha B, Arora A, Aggarwal A, Bhardwaj M. Prolonged adrenal insufficiency after unilateral adrenalectomy for Cushing's Syndrome. Indian J Endocr Metab 2015;19:430-2.
Source of Support: Nil, **Conflict of Interest:** None declared.