

Role of bilateral adrenalectomy in adrenocorticotrophic hormone-dependent Cushing's syndrome

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Cushing's syndrome (CS) is associated with significant morbidity and mortality as a consequence of catabolic effects of hypercortisolemia. Indications for bilateral adrenalectomy (BA) in adrenocorticotrophic hormone (ACTH) dependent Cushing's, include occult/unresectable source of ACTH secretion (pituitary or ectopic), hypercortisolemia, which does not improve after definitive surgery or for rapid correction of hypercortisolemia as a life-saving procedure in very sick patients before a definitive tumor removal is performed.

A recent study from our center,^[1] includes 293 ACTH-dependent and 71 ACTH independent CS. Among them, 215 were due to Cushing's disease and 22 due to ectopic ACTH syndrome (EAS). In 19%, the ACTH source could not be identified. Source of EAS was bronchial carcinoid (7), thymic carcinoid (6), pancreatic neuroendocrine tumor (NET) (4), MEN 2 (1) and metastatic carcinoma (4).

In a previous study from our center,^[2] 16 patients with severe hypercortisolism underwent BA as a life-saving measure, which was followed by definitive surgery later in cases where pituitary or ectopic source was identified. BA reduced catabolic features of severe hypercortisolism rendering the patient fit for definitive surgery later. Benefits and risks of pituitary exploration, BA and medical therapy

were discussed with the patient and their families and treatment provided as per their choice.

In a study from KEM, Mumbai,^[3] out of 100 consecutive patients of CS who underwent transsphenoidal surgery, the cure rate for microadenoma was 77% and for macroadenoma was 36%. A second trans-sphenoidal surgery, radiotherapy, and BA were additional modalities used (in that order), in patients who were not cured or who had recurrence.^[3] In a study from PGI, Chandigarh, among 12 patients of EAS, five patients had thymic carcinoid, 3 bronchial carcinoid and one each had islet, hepatic, gut carcinoid and medullary thyroid carcinoma (MTC). During mean duration of follow-up of 43 months, only two could sustain cure while remaining had either residual tumor or recurrence.^[4]

In a study from SGPGI, Lucknow, that assessed the long-term outcome of adrenalectomy in patients with CS, it was observed that BA provides early control of hypercortisolism in cases of unlocalized/EAS or failed transsphenoidal surgery. Even though, after adrenalectomy patient requires lifelong steroid replacement, quality of life and productivity improves considerably.^[5]

As illustrative cases, let us go through why BA was chosen for few patients of ACTH-dependent Cushing's in the last 1-year at our center.

A 43-year-old gentleman presented with complaints of progressively increasing proximal muscle weakness, low back pain, breathlessness, weight gain, stria and generalized edema for 6 weeks.

Serum total protein and albumin was 4.8 g/dl and 2.6 g/dl respectively. Morning and evening serum cortisol were 63.44 and 51.76 µg/dl respectively and morning plasma ACTH was 61.58 pg/ml. He had tachycardia, tachypnea,

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dysglycemia, resistant hypertension, metabolic alkalosis, and developed respiratory distress. There was a rapid progression of generalized edema, persistent hypokalemia in spite of potassium supplementation, fall in serum albumin, in spite of multiple medications including somatostatin analog.

Magnetic resonance imaging (MRI) of pituitary revealed partial empty sella. Computed tomography (CT) abdomen showed bilateral adrenal hyperplasia, mass in pancreaticoduodenal groove measuring 3.3 cm × 2.6 cm with adjacent nodal involvement. MRI confirmed this finding. A diagnosis of EAS was made. Patient's condition worsened. Although the primary lesion had been identified, we proceeded for B/L adrenalectomy for rapid resolution of hypercortisolism.

The major challenge for the anesthetic team was persistent hypokalemia, a known risk factor for cardiac arrhythmia, hypoalbuminemia associated with bilateral pleural effusion with poor respiratory reserve. The patient required intensive care postsurgery.

There was prompt symptomatic relief following surgery. Patient was started on mineralocorticoid and glucocorticoid replacement.

Three months later, he was readmitted for definitive surgery. After surgical removal of NET, serum ACTH was <1 pg/ml, serum cortisol 1.07 µg/dl. Histopathology revealed metastatic differentiated NETs, WHO grade 1.

The patient is doing well on follow-up for last 1-year.

This case was an example of a patient who presented with worsening features of hypercortisolemia, which progressed despite medical therapy. Even though the ectopic source was identified, emergency laparoscopic BA was performed as a life-saving measure to control morbidity of hypercortisolemia to salvage the patient for future definitive surgery.

Ectopics co-secreting ACTH and corticotropin-releasing hormone (CRH) are known.^[6] NET of the gastro-entero-pancreatic system and pancreatic neuroendocrine tumors (p-NETs) are rare, and those that are responsible for ectopic adrenocorticotrophic hormone secretion are even more uncommon.^[7] ACTH-producing p-NETs can metastasize to the mediastinal and paraaortic lymph nodes, pelvis, hilus, hepatic portal region, and lungs.^[8] Sometimes an ectopic tumor that is degranulating fast, might not stain positive for ACTH on histopathology even if it is being secreted.^[7] Immunohistochemically, the primary

tumor may stain negative for ACTH and cortisol, whereas hepatic metastases stain strongly positive for ACTH. There are reports of negative expression for ACTH in primary tumors and positive expression in metastasis.^[8] An active tumor that releases hormones rapidly might stain negatively.^[8]

A 15-year-old boy presented with newly detected uncontrolled diabetes along with frank Cushing habitus and hypertension for past 1-year. He had profound weakness and left lung consolidation. There was a history of total thyroidectomy with radical neck dissection 6 years back. Histopathology was suggestive of MTC along with cervical lymphnode metastasis. For MTC, no follow-up or treatment was taken. Though he developed a gradually progressive left neck swelling postoperatively, he remained otherwise absolutely asymptomatic till last year.

On examination, he had left cervical hard irregular swelling and left lower chest breath sound were diminished. Severe proximal myopathy was present.

Serum cortisol was >63.66 µg/dl ACTH - 156 pg/ml, TSH - 24 uIU/ml and HbA1c 13.6%.

Computed tomography neck, chest and abdomen suggested B/l adrenal hyperplasia with 2 para-aortic lesions and left lung lower lobe consolidation.

His metaiodobenzylguanidine scan showed increased uptake in left mediastinal, both adrenals and left the cervical region. His positron emission tomography scan was also positive for above lesions.

He developed severe respiratory distress due to consolidation and could not maintain saturation even on oxygen. MRI sella could not be done due to respiratory distress and inability to hold the breath.

Possible differential diagnosis were-metastatic MTC with ectopic Cushing or metastatic MTC with co-existing Cushing disease. Urgent BA was planned so as to salvage the sick patient. MTC even with metastasis has a good prognosis with 10 years survival up to 30%.

Bilateral adrenalectomy went well, but extubation was challenging. Later he was put on BiPAP. His metabolic parameters such as hypertension, blood glucose levels, and serum albumin improved. A tracheotomy was done 4 days later, and he maintained good saturation on T-piece with oxygen.

He developed sudden onset respiratory discomfort probably secondary to some large mucus plug which

occluded his large airway or tracheostomy tube. He could not be saved.

This case represents a patient with the severe catabolic state of Cushing's due to ectopic who succumbed in the postoperative period. Patients with severe Cushing's disease undergoing BA are prone to complications and require intensive monitoring postoperatively.^[9]

A 46-year-old lady presented in an emergency with rapidly developing proximal muscle weakness, dyspnea on less than ordinary activity and swelling all over the body since 20 days. Since 2 years, she was experiencing episodes of anxiety associated with headache and sweating, during which she was found to have high blood glucose values and hypertension two 2 months back. The evaluation was suggestive of severe hypercortisolemia with ACTH excess. Hypokalemia, metabolic alkalosis, severe proximal muscle weakness, nonsuppressible high-dose dexamethasone suppression test (HDDST) and rapid course of disease all pointed an ectopic CS. Adrenal imaging revealed two nodules of 3 cm and 1.5 cm each raising the possibility of adrenal NET producing excess ACTH. MRI pituitary revealed partial empty sella. She also had central hypothyroidism. DOTANOC imaging revealed uptake and presence of somatostatin receptor expressing tumor in left adrenal gland. Urinary metanephrines were significantly elevated. Thus, in view of fulminant disease course, severe hypercortisolemia, nonsuppressible HDDST and somatostatin receptor expressing nodules in left adrenal with elevated urinary metanephrine, provisional diagnosis of pheochromocytoma with ectopic ACTH production was made and a decision of BA was taken. The patient underwent BA following which she was kept in Intensive Care Unit for a week. She was then shifted to ward on oral glucocorticoid and mineralocorticoid replacement. The ACTH levels fell to < 1 pg/ml after surgery proving that the left adrenal pheochromocytoma was possibly the source of excess ACTH. Ectopic CRH/ACTH secretion by adrenal pheochromocytoma though reported, is rare.^[10,11]

This case of ectopic ACTH/CRH secretion from pheochromocytoma, had BA in view of fulminant disease course.

A 28-year-old girl presented with headache and ptosis for 1-year. MRI revealed a parasellar mass, which on MRI was opined to be meningioma. She underwent a transcranial surgery for meningioma removal, but there was no relief of headache and histopathology showed normal brain tissue. Over next 3 years, she developed

weight gain, stria, and amenorrhea. She underwent a gamma knife for meningioma without relief. Her biochemical investigations were suggestive of ACTH-dependent Cushing's. HDDST was suppressed. MRI revealed a pituitary tumor. Trans-sphenoidal surgery was done. Histopathology showed ACTH staining pituitary adenoma. Post operatively she had no symptomatic improvement. Features of Cushing's worsened. Biochemical reinvestigation confirmed Cushing's. SGOP/PT were raised more than thrice the upper limit of normal, ruling out the use of ketoconazole or paserotide. MRI sella did not show any residual tumor. CT abdomen showed bilateral adrenal enlargement.

Meningiomas are known to produce CRH/ACTH leading to Cushing's.^[12] In this case since the primary, possibly parasellar meningioma is unresectable, we are planning BA.

CONCLUSION

Indications for BA for ACTH-dependent Cushing's, includes occult or unresectable source of ACTH secretion (pituitary or ectopic), hypercortisolemia which does not improve after definitive surgery or in very sick patients, for rapid correction of hypercortisolemia as a life-saving procedure before a definitive tumor removal can be performed.

A team of endocrinologist, anesthesiologist and surgeons willing to do high-risk life-saving intervention is required for managing these morbid patients. Postoperative intensive care is important as morbidity/mortality is high. Patient and their family needs to be communicated about the nature of the disease, treatment options, risks involved with/without surgery and need for steroid replacement and follow-up.

REFERENCES

1. Ammini AC, Tandon N, Gupta N, Bhalla AS, Devasenaspathy K, Kumar G, *et al.* Etiology and clinical profile of patients with Cushing's syndrome: A single center experience. *Indian J Endocrinol Metab* 2014;18:99-105.
2. Ammini AC, Bhattacharya S, Sahoo JP, Philip J, Tandon N, Goswami R, *et al.* Cushing's disease: Results of treatment and factors affecting outcome. *Hormones (Athens)* 2011;10:222-9.
3. Shah NS, Goel AH, Nagpal RD, Menon PS. Cushing's disease: Management outcome in a tertiary care centre. *J Assoc Physicians India* 2006;54:919-22.
4. Bhansali A, Walia R, Rana SS, Dutta P, Radotra BD, Khandelwal N, *et al.* Ectopic Cushing's syndrome: Experience from a tertiary care centre. *Indian J Med Res* 2009;129:33-41.
5. Mishra AK, Agarwal A, Gupta S, Agarwal G, Verma AK, Mishra SK. Outcome of adrenalectomy for Cushing's syndrome: Experience from a tertiary care center. *World J Surg* 2007;31:1425-32.
6. Karageorgiadis AS, Papadakis GZ, Biro J, Keil MF, Lyssikatos C, Quezado MM, *et al.* Ectopic adrenocorticotrophic hormone and corticotropin-releasing hormone co-secreting tumors in children and

- adolescents causing cushing syndrome: A diagnostic dilemma and how to solve it. *J Clin Endocrinol Metab* 2015;100:141-8.
7. Patel FB, Khagi S, Daly KP, Lechan RM, Ummaritchot V, Saif MW. Pancreatic neuroendocrine tumor with ectopic adrenocorticotropin production: A case report and review of literature. *Anticancer Res* 2013;33:4001-5.
 8. Miehle K, Tannapfel A, Lamesch P, Borte G, Schenker E, Kluge R, *et al.* Pancreatic neuroendocrine tumor with ectopic adrenocorticotropin production upon second recurrence. *J Clin Endocrinol Metab* 2004;89:3731-6.
 9. Sommerey S, Foroghi Y, Chiapponi C, Baumbach SF, Hallfeldt KK, Ladurner R, *et al.* Laparoscopic adrenalectomy-10-year experience at a teaching hospital. *Langenbecks Arch Surg* 2015;400:341-7.
 10. Bayraktar F, Kebapcilar L, Kocdor MA, Asa SL, Yesil S, Canda S, *et al.* Cushing's syndrome due to ectopic CRH secretion by adrenal pheochromocytoma accompanied by renal infarction. *Exp Clin Endocrinol Diabetes* 2006;114:444-7.
 11. Willenberg HS, Haase M, Papewalis C, Schott M, Scherbaum WA, Bornstein SR. Corticotropin-releasing hormone receptor expression on normal and tumorous human adrenocortical cells. *Neuroendocrinology* 2005;82:274-81.
 12. Pecori Giraldi F, Terreni MR, Andreotti C, Losa M, Lanzi R, Pontiroli AE, *et al.* Meningioma presenting with Cushing's syndrome: An unusual clinical presentation. *Ann Neurol* 2003;53:138-42.

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