Case Report

# Unilateral nodular adrenocortical hyperplasia presenting as Cushing's syndrome: a case report

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## ABSTRACT

*Cushing syndrome results from chronic exposure to excess cortisol. Nodular adrenal hyperplasia is usually bilateral and has only a few case reports of unilateral presentation. Biochemically it is presented as hyperaldosteronism or as Cushing's syndrome. Here, we are reporting a 17-year-old female presenting with weight gain over 5 months and uncontrolled hypertension. Biochemically she was found to have diabetes mellitus, secondary hypothyroidism and hypogonadotrophic hypogonadism due to Cushing's syndrome of adrenal origin. Unilateral adrenal adenoma/hyperplasia in right adrenal gland was evident by radiology. Histopathological examination was done after laparoscopic adrenalectomy showed nodular adrenocortical hyperplasia in right adrenal mass. Following surgery, clinical features of the patient improved notably. Cushing syndrome due to unilateral nodular adrenocortical hyperplasia is a rare entity. Biochemical evaluation of hypothalamo-pituitary-adrenal axis, radiological evidence and histopathology are the important armaments can guide to final diagnosis.*


***Key words:*** *Cushing syndrome, Hyperaldosteronism, Nodular adrenocortical hyperplasia.*

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## INTRODUCTION

Endogenous Cushing's syndrome is relatively rare with incidence reported by a US-based study is only 8 per million people.[1] Pituitary Cushing's disease, accounts for approximately 70% of cases, while ectopic adrenocorticotropic hormone (ACTH)-secreting tumors for about 10% cases.[2] ACTH-independent Cushing's syndrome due to adrenal disorder accounts for 20%–30% of total cases. Among which, adrenocortical adenoma (ACA) contributes to 10–15% cases; adrenocortical carcinomas (ACC) for less than 5% cases and bilateral adrenal hyperplasia (BAH) for approximately 10% cases.[3] The commonest bilateral adrenal hyperplasias are macronodular adrenal hyperplasia (AIMAH), primary pigmented nodular adrenocortical disease (PPNAD) and isolated micronodular adrenocortical disease (iMAD).[3]

Unilateral adrenal hyperplasia is very rare and is notified by few case reports only. Here, we are reporting a teen age girl presenting with ACTH-independent Cushing syndrome due to rare unilateral nodular adrenocortical hyperplasia.

## CASE REPORT

A 17-year-old female presented with the history of weight gain from 45 Kg to 70 Kg, facial plethora, roundening of face and central obesity over 5 months. She had irregular menstruation with less menstrual bleeding for the same duration. Subsequently she developed hypertension for about 4 months. Despite of taking anti-hypertensive medications her blood pressure was not under control. Subsequently on her follow up, she was found diabetic and hypothyroid. She had no history of taking steroids or renal disease and other family members were in good health. On examination, she was found obese with height 5 ft. weight 70 Kg and body mass index 30.1 Kg/m². Her body hair distribution was normal with no hirsutism. She had central obesity, dorsocervical pad of fat and pink striae over lower abdomen. She was found to have proximal muscle weakness and easy bruisability. Her BP was 160/95 mm Hg.

Her plasma glucose at fasting, 2 hours after breakfast and HbA1c were 7.5mmol/L, 11.9 mmol/L and 6.8% respectively. Complete blood count, electrolytes, lipid profile, liver function test and renal function tests were normal.

Hypercortisolism of this case was evident by high midnight salivary cortisol; 24 hours urinary free cortisol (UFC) by more than three folds and non-suppression with 1 mg overnight dexamethasone (1mg-ONDST) (Table I). High morning serum cortisol with low plasma ACTH was favoring adrenal pathology for the apparent hypercortisolism (Table II). Normal Aldosterone-Direct Renin Concentration Ratio (ARR) excluded Conn's syndrome (Table III). Serum androgen levels (DHEA-S and Testosterone) were in the normal range. Biochemically pheochromocytoma was excluded by normal levels of serum or urinary catecholamines and their metabolites.

Thyroid function tests showing low TSH and low thyroid hormones i.e. T3, T4, FT3, FT4 were suggested for secondary hypothyroidism (Table IV). Low-normal serum FSH, low LH and estradiol were suggestive of hypogonadotropic hypogonadism (Table V). Serum prolactin was normal, 26.5 ng/mL (2.8-29.2 ng/mL).

**Table I** Tests for evidence of hypercortisolism

| Investigation | Result | Reference value |
|---|---|---|
| Midnight salivary cortisol | 50.6 nmol/L | <7.56 nmol/L |
| 24 hrs Urinary Free CortisolUrine Volume | 7460nmol/L/24 hrs2000 mL/24 hrs | 57 – 807 nmol/24 hrs |
| **1 mg-ONDST:** | | <50nmol/L: Cushing Syndrome is excluded |
| Serum Cortisol | 504.4 nmol/L | 50-275nmol/L: Further evaluation is required |
| | | >275 nmol/L: Cushing syndrome likely |

**Table II** Plasma ACTH and serum cortisol

| Investigation | Result | Reference value |
|---|---|---|
| Plasma ACTH | 12.3 pg/mL | 10-80 pg/mL |
| Serum Cortisol (0830-0930 hrs) | 618.4 nmol/L | 138-690 nmol/L |

**Table III** Status of adrenal mineralocorticoids

| Investigation | Result | Reference value |
|---|---|---|
| Serum Aldosterone (Supine) | 84.4 pmol/L | 69.8-1085.0 pmol/L |
| Plasma Direct Renin Concentration (Supine) | 3.12 µIU/mL | 2.8 – 39.9 µIU/mL |
| Aldosterone - Direct Renin Ratio | 27.05 pmol/L/µIU/mL | >91 pmol/l/µIU/mL: Suggests Primary Aldosteronism |

**Table IV** Thyroid function tests

| Investigation | Result | Reference value |
|---|---|---|
| Serum TSH | 0.16 µIU/ml | 0.27-4.20 µIU/ml |
| Serum FT3 | 2.2 pmol/l | 2.8-7.1 pmol/l |
| Serum FT4 | 9.2 pmol/l | 11.5-22.7 pmol/l |
| Serum T3 | 0.8 nmol/l | 1.3-3.1 nmol/l |
| Serum T4 | 56.7nmol/l | 66-181 nmol/l |

**Table V** Gonadal function tests

| Investigation | Result | Reference value |
|---|---|---|
| Serum FSH | 5.1 mIU/mL | 2.5 – 10.2 mIU/mL (follicular phase) |
| Serum LH | 1.8 mIU/mL | 1.9 – 12.5 mIU/mL (follicular phase) |
| Serum Estradiol | 15.8 pg/ml | 24-195 pg/ml (follicular phase) |

Endoscopy of upper gastrointestinal tract revealed esophageal moniliasis. Her X-ray Chest PA View was normal. Normal MRI of brain excluded hypothalamo-pituitary disorder. CT Scan of Abdomen showed right sided adrenal mass and mentioned adrenal hyperplasia as a possibility. CT Angiogram of adrenal gland noted soft tissue mass (CC 3.1cm X TD 2.3cm X AP 2.5 cm) in right adrenal gland could be due to adenoma/adrenal hyperplasia. The lesion and right adrenal gland had normal circulation as that of suprarenal gland. MRI of adrenal gland revealed soft tissue intensity area (AP 2.7 cm X TD 2.5 cm X CC 3.0 cm), homogenously iso-intense on T1W and mildly hyper intense on T2W and SPAIR images in the right adrenal gland were suggestive of soft tissue mass in right adrenal gland– likely adenoma.

Laparoscopic right adrenalectomy was done under general anesthesia. Histopathological specimen revealed right adrenal mass as single grayish brown nodule (3.0X2.5X1.5 $cm^3$) and weigh 0.5 gram. Microscopic examination revealed a circumscribed nodular mass surrounded by fibrous capsule composed of nests of cells from all three layers of adrenal cortex. Some of the cells had eosinophilic cytoplasm and some of the cells had lipofuscin pigments within cytoplasm with no evidence of malignancy. Findings were compatible with nodular adrenocortical hyperplasia in right adrenal mass (Figure 1).

So, this is a case of Cushing syndrome due to right sided nodular adrenocortical hyperplasia with diabetes mellitus and secondary hypothyroidism.

The patient improved following right sided adrenalectomy, her blood pressure and diabetes mellitus became under control. During follow up 2 weeks after operation, her BP was 110/80 mm of Hg. Her fasting plasma glucose was 4.9 mmol/L. Her post-operative pituitary-adrenal axis evaluated by Plasma ACTH, morning and evening cortisol revealed suppression of endogenous cortisol secretion (Table VI). This adrenal suppression was further reconfirmed by synacthen (250 µg) stimulation test (Table VI).

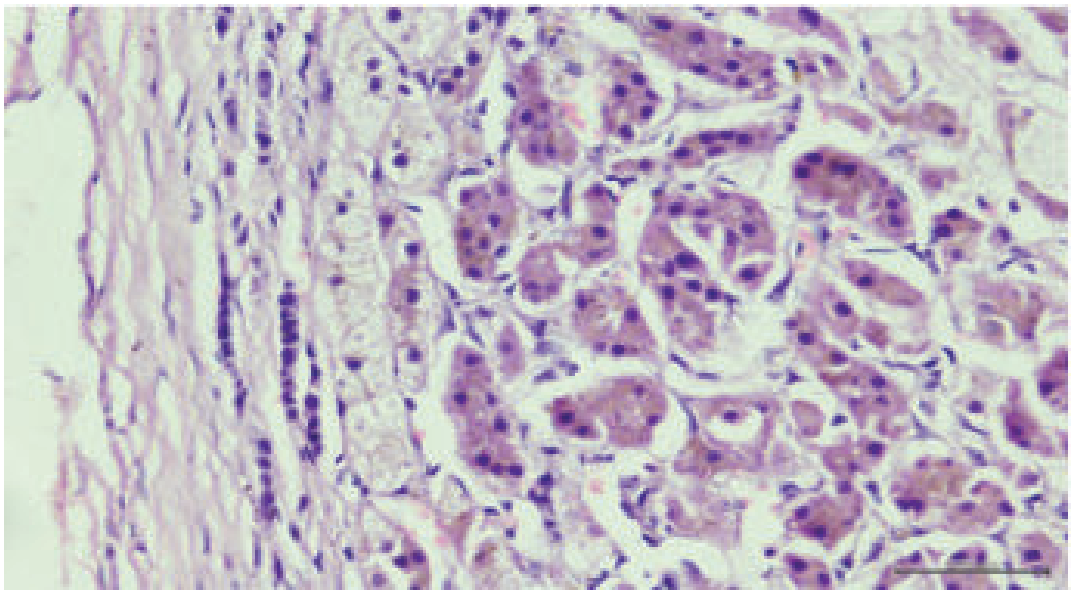

**Figure 1** Histopathology of adrenal tissue (HE 40X) - nodular adrenocortical hyperplasia

**Table VI** Post-operative follow up of plasma ACTH and serum cortisol

| Investigation | Result | Reference value |
|---|---|---|
| Plasma ACTH | 15.9 pg/ml | 10-80 pg/ml |
| Serum Cortisol (at 0830-0930 hrs) | 71.92 nmol/l | 138-690 nmol/l |
| Serum Cortisol (at 1630-1730 hrs) | 14.38 nmol/l | 69-345 nmol/l |
| Synacthen (250 µg) stimulation test | | |
| Serum cortisol after 30 min of inj. Synacthen | 78.26 nmol/l | |
| Serum cortisol after 60 min of inj. Synacthen | 66.07 nmol/l | |

## DISCUSSION

Here, we are presenting a case of 17-year-old female, who gained 25 Kg weight over 5 months and had central obesity, oligomenorrohea, uncontrolled hypertension, diabetes mellitus, secondary hypothyroidism and hypogonadotrophic hypogonadism due to ACTH-independent Cushing syndrome of adrenal pathology. Radiological and histopathological findings finally revealed the case as right sided nodular adrenocortical hyperplasia.

Nodular adrenal hyperplasia is rare and usually bilateral in presentation.[4] Only few publications mention about unilateral nodular adrenal hyperplasia, most of which are associated with hyperaldosteronism or less commonly with Cushing syndrome. Three cases of histopathologically proven unilateral nodular adrenal hyperplasia, two with primary hyperaldosteronism and one with Cushing syndrome were reported by Kotb et al.[4] A series of 4 cases, all with unilateral micronodular adrenal hyperplasia by histopathology and biochemically presented with primary aldosteronism were stated by Omura et al. in 2002.[5] A 49-year-old woman was described by F Otsuka et al, who had obesity with loss of normal circadian rhythm of serum cortisol despite of normal plasma ACTH & serum cortisol levels along with hypothyroidism due to unilateral left adrenocortical nodular hyperplasia.[6]

Diabetes mellitus presented in our case is a common complication of Cushing's syndrome results from both direct and indirect effects of excess glucocorticoid due to stimulation of liver gluconeogenesis & inhibition of insulin sensitivity both in the liver and in the skeletal muscles. The prevalence of diabetes mellitus in patients with Cushing's syndrome ranges from 20 to 50%.[7]

Central hypothyroidism of this case results from the inhibitory effect of endogenous hypercortisolemia on the hypothalamic-pituitary-thyroid axis that reduces the release of TRH & TSH from hypothalamus and anterior pituitary respectively. In addition, glucocorticoids increase type 2 deiodinase activity that converts T4 to T3 in the central nervous system that eventually suppress the secretion of TSH and also the thyroid hormones e.g. T3, T4, FT3, FT4.[8]

Besides, Cushing syndrome reduces GnRH drive results in reduced secretion of gonadotrophs from anterior pituitary causes hypogonadotrophic hypogonadism.[9]

Our patient had esophageal moniliasis might be due to hypercortisolemia impairs neutrophil adherence to the endothelium, decreases degranulation capacity and phagocytic action, diminishes maturation of macrophages and down-regulates multiple pro-inflammatory cytokines are responsible for different invasive fungal infections.[10]

## Conclusion

Cushing syndrome due to unilateral nodular adrenocortical hyperplasia is a rare entity. Such a case may present with hyperaldosteronism or with ACTH-independent Cushing syndrome. Our patient had Cushing syndrome of adrenal origin with diabetes mellitus, secondary hypothyroidism and hypogonadotrophic hypogonadism. Such diversified clinical presentations would divert clinical approach and may make the diagnosis a challenging one. Judgmental use of salivary cortisol, 24 hours urinary free cortisol and LDDST are very helpful screening tests for approaching the diagnosis of Cushing syndrome. Plasma ACTH, serum cortisol and radiological findings could be important clue to find the source of excess cortisol and post-operative histopathology can settle the final diagnosis in such cases.

**Authors' contribution:** LN was involved in diagnosing the case and preparation of the case report. SG was the overall supervisor and guide. SMJI and SY were involved in histopathology diagnosis of the case. KRA and MRI were involved in preparation of the case report. All authors read and approved the final manuscript for submission.

**Conflicts of interest:** Nothing to declare.

**Consent:** Informed written consent was taken from the patient.

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