

Lean Cushing's

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ABSTRACT

This is a case report of 59 years old male with adrenocorticotrophic hormone ACTH-independent macronodular adrenal hyperplasia (AIMAH), which is a rare cause of Cushing's syndrome. He was detected to have adrenal lesions incidentally on imaging. The biochemical evaluation was suggestive of endogenous ACTH-independent Cushing's syndrome. Contrast Enhanced CT of the abdomen done to characterize the lesion was suggestive of bilateral macro-nodular adrenal hyperplasia. There was no evidence of cushingoid features except for type 2 diabetes mellitus suggestive of subclinical Cushing's. He was not planned for any immediate medical/surgical management since metabolic control was achieved with oral anti-diabetics (OADs) and anti-hypertensive medications. He is on regular follow up with well-controlled sugars and blood pressure.

Keywords: ACTH, adrenal hyperplasia, AIMAH, cortisol, DST, subclinical Cushing's, UFC

Introduction

Adrenocorticotropin-independent macronodular adrenal hyperplasia (AIMAH) is a rare cause of endogenous Cushing's syndrome.^[1] Most of the patients have only mild cortisol production and usually present as bilateral incidentalomas.^[2] Multiple bilateral non pigmented enlarged macro nodules (greater than 1 cm) are seen in adrenal glands (each adrenal weighing from 25 to 500 mg) that produce excess cortisol independent of adrenocorticotrophic hormone (ACTH) that leads to the development of Cushing's syndrome.^[2] In routine practice, diagnosis is based on the clinical presentation, biochemical evaluation and imaging. However, it is confirmed by histopathology of the adrenal tissue.^[3] Depending on the amount of cortisol excess management can vary from regular monitoring to surgical resection of the adrenal gland. Recently,

it has been attributed secondary to aberrant hormone receptor thereby providing the potential for pharmacological therapies.

Case Report

59 year old male presented with complaints of nocturia from the past 3 months. There was no history of fever with chills, dysuria, dribbling after micturition, increased urgency or hematuria. He was known to have type 2 diabetes mellitus and hypertension that was well controlled on oral anti-diabetics (OADs) and anti-hypertensive agents. He had a history of diabetic ischemic mononeuropathy of the left lateral rectus which was managed conservatively. There was no history of allergy and substance abuse. Historically there was no complaint of osteoporotic fracture, depression, weight gain, irritability, or fatigue.

On physical examination, patient's weight was 66 kg, BMI 25.14 kg/m², pulse rate of 80 beats per minute, blood pressure of 140/90 mmHg. Systemic examination was inconclusive.

On evaluation, his blood reports showed HbA1C of 5.7%, Na-134 meq/L, K- 4.83 meq/L, Complete blood count,

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fasting lipid profile, and urine analysis were otherwise normal. Ultrasonography of the abdomen revealed bilateral grade-I renal parenchymal changes, prostatomegaly (45 g, postvoid residual volume 15 mL), fatty liver, and enlarged right adrenal gland (3 cm × 2.2 cm). In view of adrenal incidentaloma, the patient was further subjected to contrast-enhanced computed tomography (CECT) of the abdomen. As described in the image below CECT of the abdomen showed bilaterally enlarged adrenals with multiple nodules—likely macronodular adrenal hyperplasia possibility of AIMAH [Figures 1 and 2].

Further biochemical evaluation was done to confirm the diagnosis of AIMAH. Morning serum cortisol was elevated, which ruled out exogenous consumption of glucocorticoids [Table 1].^[4]

After exogenous glucocorticoid consumption was ruled out, diagnostic tests were done to confirm hypercortisolism. The following three tests are commonly used.^[4-6] The patient had elevated midnight cortisol, 24-h urine free cortisol (UFC) and lack of cortisol suppression after 1 mg dexamethasone suppression test (DST) [Table 2].

Once endogenous Cushing's was confirmed, morning and midnight ACTH levels were done to look for ACTH-independent Cushing's syndrome.^[6] As both the values were low, a diagnosis of ACTH-independent Cushing's was made [Table 3].

Plasma metanephrines level was normal, which ruled out pheochromocytoma/paragangliomas.

Discussion

Endogenous Cushing's syndrome secondary to AIMAH is extremely rare, comprising less than 1% of all the cases.^[2] This clinical entity has a bimodal age distribution. Few patients present during the 1st decade of life, associated with McCune-Albright syndrome but most of the cases present during the 5th and 6th decade.^[2] It is more prevalent in middle-aged women. Usually, patients present with Cushingoid features like obesity, facial plethora, moon face, purple striae, proximal muscle atrophy and skin pigmentation. But our patient is a rare case of subclinical Cushing's syndrome in which there was endogenous hypercortisolism independent of ACTH levels without any overt signs or symptoms of hypercortisolism. Hypertension and diabetes can be attributed secondary to hypercortisolism. The diagnosis is made using biochemical tests and imaging; which is confirmed by biopsy.^[7]

The treatment of AIMAH depends on the severity of hypercortisolism. In patients with mild cortisol excess, yearly biochemical assessment and CT scans are sufficient, in the case of disease progression steroid synthesis inhibitors like ketoconazole or even adrenalectomy can be considered. For patients with moderate to severe life-threatening hypercortisolism surgical resection of one or both the adrenals with postoperative hormonal supplementation is the treatment of choice.^[1,2,8,9] Recently, it has been revealed that most of the patients with

Table 1: Baseline Evaluation for Cushing's

Test	Results	Principle
8 AM cortisol	18.63 mcg/dL	Rules out exogenous Cushing's

Table 2: Screening for Cushing's Syndrome

Test	Results	Principle
Midnight cortisol	12.62 mcg/dL	>1.8 mcg /dL awake >7.5 mcg/dL sleeping Shows loss of normal diurnal rhythm
24-h urine-free cortisol	347.2 mcg/day	> 300 confirms cortisol secretion is elevated
Overnight DST (1 mg)	15.55 mcg/dL	> 1.8 mcg /dL shows loss of normal sensitivity to negative feedback

Table 3: Evaluation for ACTH dependent vs ACTH independent Cushing's syndrome

Test	Results	Comments
8 AM ACTH	3 pg/L	In favor of ACTH-independent Cushing's syndrome
Midnight ACTH	4 pg/L	< 7.5 pg/L suggestive of ACTH independent cause

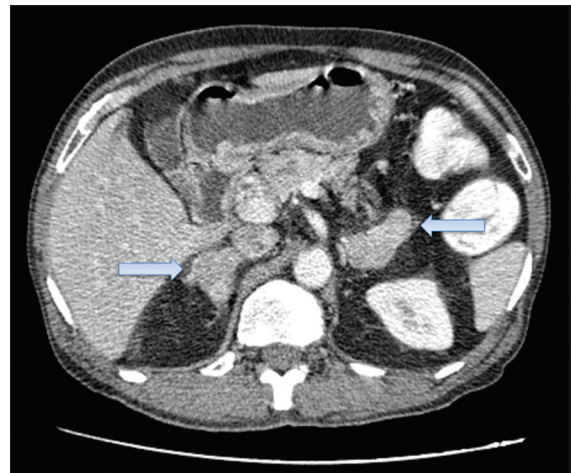


Figure 1: Axial Post contrast : Bilateral grossly enlarged adrenal glands (Arrows)

AIMAH and Cushing's syndrome have aberrant cortisol response to various endogenous hormones like vasopressin, gastric inhibitory polypeptide, serotonin, luteinizing hormone/beta-HCG, etc., suggesting the presence of aberrant ectopic receptors. These patients can be treated with a pharmacological antagonist with regular monitoring of UFC levels.^[2,10-13] Our patient with subclinical Cushing's syndrome is on regular follow up and biochemical monitoring.

Conclusion

Patients presenting with common illness may have underlying rare disorders, which can be diagnosed if evaluated carefully.

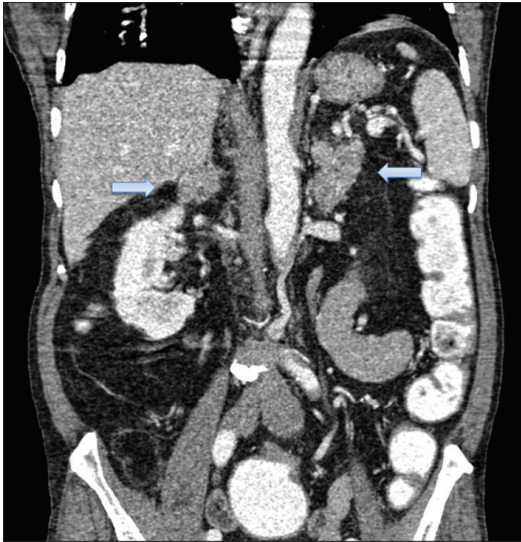


Figure 2: Coronal Post contrast: Grossly enlarged bilateral adrenal glands (Arrows) with multiple hypodense nodules and predominant peripheral enhancement

A systematic approach as discussed in our case report helped us recognize a rare cause of Cushing's syndrome. Treatment of patients with subclinical Cushing's is based on the degree of hypercortisolism. Imaging and biochemical assessment should guide the further course of management.

Adrenal incidentalomas are not routinely evaluated, but in a patient with multiple comorbidities like diabetes, hypertension, obesity, and osteoporosis, a thorough workup can help us to diagnose rare treatable conditions like AIMAH.

As primary care providers, we come across patients with hyperglycemia who are treated as insulin resistant Diabetes. But as we all know, most of the clinical features like obesity, dyslipidemia, osteoporosis, and hypertension overlap between Type 2 diabetes mellitus and Cushing's syndrome; it is desirable to do at least one cortisol value and rule out a treatable condition like Cushing's syndrome.

Acknowledgment

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Ethics approval

Ethical clearance was obtained from the institutional ethical committee, Kasturba Medical College, Mangaluru (Reg no ECR/541/inst/KA/2014/RR-17).

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his clinical information to be reported in the journal. The patient understand that their names and initials will not be published and due efforts will be made to conceal his identity.

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Conflicts of interest

There are no conflicts of interest.

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