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Case Report

Prolonged Hypothalamo - Pituitary - Adrenal Axis Suppression Following Unilateral Adrenalectomy for a Cortisol Secreting Adrenal Adenoma : A Case Report

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Abstract

This article presents a comprehensive exploration of a complex case of Cushing's syndrome in a 29-year-old woman, characterized by significant weight gain, diabetes, and hypertension. The diagnostic journey involves meticulous examination, radiological imaging revealing an adrenal adenoma, and an unexpected twist in the immunohistochemical analysis - diffuse ACTH positivity despite suppressed plasma ACTH levels. This finding challenges conventional understanding and raises questions about paracrine influences. The patient's postoperative course is marked by undetectable serum cortisol levels, indicating successful surgical intervention, yet an unforeseen challenge emerges—prolonged suppression of the hypothalamo-pituitary-adrenal axis. This persistent adrenal axis suppression, even at two years postoperatively, presents a noteworthy and intricate aspect of the case. Through this case study, we aim to contribute valuable insights into the complexities of Cushing's syndrome, emphasizing the importance of recognizing atypical presentations, understanding histological nuances, and addressing the prolonged consequences of adrenal axis suppression.

Keywords: Adrenal, Cushings, Hypothalamo-pituitary-adrenal, axis, recovery

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Introduction

Cushing's syndrome, a rare endocrine disorder, manifests as excessive cortisol production, leading to a myriad of clinical manifestations. Distinguishing between ACTH-dependent and ACTH-independent causes is pivotal for effective diagnosis and management. This article delves into a compelling case study of a 29-year-old woman presenting with significant weight gain, diabetes, and hypertension, ultimately diagnosed with an adrenal adenoma causing Cushing's syndrome. Through detailed examination, radiological imaging, and immunohistochemical analysis of the resected adrenal adenoma, we unravel the complexities surrounding ACTH secretion and paracrine influences. Additionally, we explore the protracted suppression of the hypothalamo-pituitary-adrenal axis at 2 years post-surgery, emphasizing the importance of long-term follow-up in mitigating potential complications. This comprehensive exploration aims to contribute valuable insights into the intricate facets of Cushing's syndrome, enriching the existing literature and informing future clinical practices.

Case Presentation

A 29-year-old woman presented with a one-year history of significant weight gain, accompanied by the onset of diabetes and hypertension. Notably, she did not report any symptoms of virilization or hirsutism and maintained regular menstrual cycles. Physical examination revealed a BMI of 29, with central obesity predominance. Additionally, thin skin, purpura, a dorsocervical fat pad, and an interscapular fat pad were observed. However, there were no striae, acne, or signs of virilization.

Upon evaluation, Cushing's syndrome was confirmed through a non-suppressed Overnight Dexamethasone Suppression Test (ODST) and a Low-Dose Dexamethasone Suppression Test (LDDST), which showed suppressed plasma ACTH concentration. Adrenal imaging revealed a 2.3x2.5x2.7 cm mass in the right adrenal gland with a high precontrast density of 37Hu with homogenous avid contrast enhancement to a density of 177 Hu in arterial phase and a delayed washout density in 15 minutes of 55HU.

Absolute washout and relative washout was 76.6% and 51.8% respectively. There were also two small discrete focal lesions in the segment VI of liver that were isodense to the liver showing avid enhancement in arterial phase and subsequent gradual washout suggesting a flash filling hepatic haemangioma or hepatic metastasis. (Figure 1 - 4). Pheochromocytoma was considered as other possible differential diagnosis but her 24 hour urinary metanephrine levels remained negative in repeated assays. Serum metanephrine/ normetanephrine assays were not freely available.

Table 1: A summary of the investigations

Investigation	Patient's Result	Normal Range
1. Overnight Dexamethasone Suppression Test (ODST)- nmol/L	590	<50
2. Low-Dose Dexamethasone Suppression Test (LDDST)-nmol/L	610	<50
3. Plasma ACTH Concentration- pg/L	<1.6	4.7-48.8
4. 24-Hour Urinary Metanephrines - mcg	31 and 30	24-96 / 24 hours
5. DHEAS (Dehydroepiandrosterone Sulfate)-micromol/L	1.05	1.75-10.2
6. Plasma Aldosterone Concentration (PAC)-ng/dl	5.70	6
7. Plasma Renin Activity (PRA) - ng/ml/hr	<0.5	<0.5

She underwent laparoscopic right adrenalectomy as part of her treatment for Cushing's syndrome with preoperative optimization of blood pressure for pheochromocytoma due to uncertain radiological features. Post-operative recovery was uneventful. Her measured postoperative morning serum cortisol level was undetectable, indicating a successful surgery. She was commenced on oral hydrocortisone with a plan to continue until full recovery of her (Hypothalamic Pituitary Adrenal) HPA axis. Following the recovery, her blood sugar levels and blood pressure normalized without medication.

Histological analysis of the excised tissue revealed an adrenocortical adenoma with nests of polygonal cells with abundant eosinophilic cytoplasm separated by sinusoidal vasculature with Weiss criteria for malignancy 1/9. The tumor showed granular cytoplasmic positivity for Synaptophysin and Melan A, and negative immunohistochemical staining for chromogranin and S100. Notably, despite low serum ACTH levels, the biopsy sample showed diffuse ACTH positivity in immunohistochemical staining, suggesting paracrine secretion and action of ACTH.

Attempts to taper off hydrocortisone were unsuccessful, and short synacthen test performed at 6, 12 and 24 months post-surgery failed to show an adequate cortisol response, indicating prolonged suppression of the hypothalamo-pituitary-adrenal axis. Her serum ACTH level still remained suppressed at 24 months with post synacthen cortisol levels of 180nmol/l. However her recent Synacthen test at 36 months showed partial response. Table 2

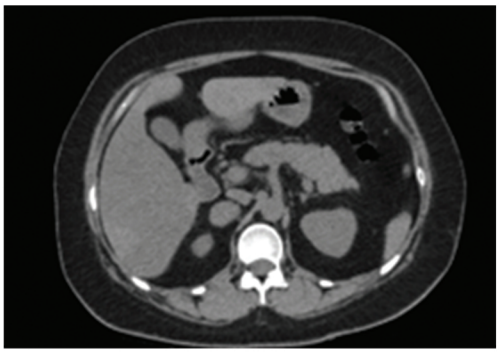

Figure 1: Right adrenal lesion - Non contrast

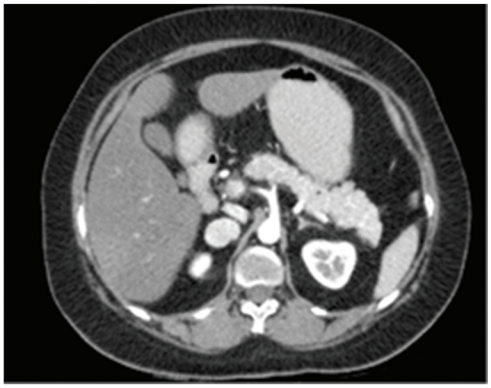

Figure 2: Adrenal lesion – Contrast – Arterial phase

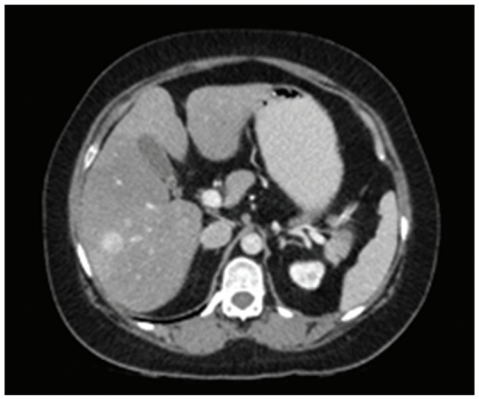

Figure 3: Liver and Adrenal lesions - Venous phase

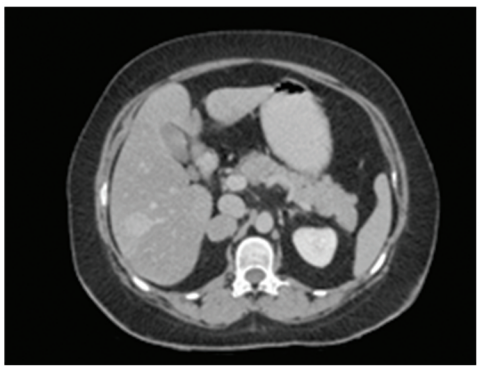

Figure 4: Delayed phase image

Table 2: Summary of short synacthen tests

	Basal cortisol (nmol/l)	60 minutes post synacthen (nmol/l)	Dose of Hydrocortisone given prior to the synacthen test
At 6 months	4.29	102	10mg mane and 5mg vesper
At 12 months	5.8		7.5mg mane and 5mg vesper
At 24 months	67	180	5mg twice daily
At 36 months	161	328	5mg twice daily

Discussion

Cushing syndrome is considered ACTH dependent when serum ACTH levels are high despite a high cortisol level, caused mainly due to an ACTH-secreting pituitary adenoma and less commonly due to extra-pituitary neoplasm with ACTH secretion. ACTH-independent Cushing syndrome occur due to an adrenal cortical adenoma with autonomous cortisol production with appropriate suppression of pituitary ACTH production. Our patient had Cushing syndrome with suppressed plasma ACTH and an adrenal adenoma on imaging. However immunohistochemical staining of the resected adenoma revealed diffuse ACTH positivity. The literature extensively documents paracrine secretion of ACTH from pheochromocytoma causing Cushing syndrome. [1] In fact, imaging features in our patient with high precontrast density of 37Hu with homogenous avid contrast enhancement to a density of 177 Hu in arterial phase and delayed washout density of 55HU although the absolute washout in 15 minutes was 76.6% raised the possibility of a pheochromocytoma.[2] However she did not have suggestive spells in the history, her urine metanephrine levels were repeatedly negative and biopsy revealed polygonal cells with eosinophilic cytoplasm with negative chromogranin A, S100 staining and positive Melan A staining making pheochromocytoma unlikely based on biopsy findings.[3]

Suppression of hypothalamo pituitary adrenal axis due to excess cortisol production in Cushing syndrome leads to functional adrenal insufficiency following resection of the culprit pituitary corticotroph adenoma or adrenal adenoma. The undetectable serum cortisol level on post-op morning serum sample indicates the cure of the disease and is associated with a lower risk of long-term recurrence[4]. Median duration to recovery of the axis was reported as 4months to 2 years in different studies.[5–7] The recovery of the axis occurs in a stepwise pattern with recovery of the Corticotropin releasing hormone(CRH) followed by recovery of the ACTH secretion and subsequent recovery of the cortisol secretion.[8] Our patient had suppressed ACTH even at 2 years post operatively and had severe glucocorticoid withdrawal symptoms and inadequate response to ACTH stimulation test at 2 years. Even at 3 years she showed only a partial response to ACTH stimulation. High ODST cortisol level, younger age, presence of symptoms for more than 1 year prior to surgical resection of the tumor are risk factors identified in the literature that were present in our patient. Despite a normal replacement dose of hydrocortisone of 12-15 mg/m^2/d, cortisol axis recovery has occurred in most patients.[6]

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