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Case Report

ACTH Independent Cushing's Syndrome Secondary to a Right Adrenal Adenoma Masked by Pregnancy

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ABSTRACT

Cushing's syndrome can occur as a consequence of prolonged exposure to excessive amounts of circulating free cortisol and the various causes can be broken down into exogenous causes, such as from steroid treatment for chronic illnesses, or endogenous as in this case. Cushing's syndrome can be further classified into ACTH-dependent and ACTH-independent, for which the latter accounts for 15-20% of all cases. This report highlights the case of a 35 year old female patient who presented with Cushing's syndrome, the symptoms of which were concomitant with pregnancy, unmasked following delivery. She was found to have an ACTH-independent adrenal adenoma found incidentally during the workup for a pulmonary embolism following delivery via Caesarean section. Biochemical testing indicated cortisol excess and CT-adrenal scanning confirmed the presence of a tumour that kept in with an adrenal adenoma. Her case was discussed in our local MDT meeting and she was subsequently referred for laparoscopic adrenalectomy following which she had complete resolution of her symptoms.

Keywords: Adrenal adenoma; Incidentaloma; Cushing's syndrome; ACTH independent; Pregnancy; Cortisol

INTRODUCTION

Adrenal adenomas are rare benign tumours found incidentally in 0.08% to 0.25% of subjects on autopsy series [1,2] and are single, unilateral lesions however they can be bilateral in rare cases [3,4]. The rise in the use of cross-sectional imaging has led to the incidental discovery of adrenal adenomas in up to 4% of the middle-aged population and in 10% of the elderly population [5]. Arnold first reported myeloid tissue in the adrenal gland [6], and Gierk described it as a tumour which has both adipose and haematopoietic tissue which Oberling first named myelolipoma [7]. The pathogenesis of adrenal myelolipoma is highly controversial. In literature review, most case reports and series support the hypothesis that hyper stimulation caused by increased ACTH, owing to continuous stress, may be related to myelolipoma [8,9]. However, Plaut et al. reported that Cushing's syndrome was related to adrenal myelolipoma while Bennett et al. performed bilateral adrenalectomy on a patient who had adrenal cortical hyperplasia with success [10].

The two most common aetiologies of ACTH-independent Cushing's syndrome are adrenal adenoma and adrenal carcinoma. Other differentials include primary bilateral macro nodular adrenal hyperplasia, primary pigmented nodular adrenal hyperplasia and McCune–Albright syndrome. Adrenal adenomas are responsible for approximately 10-15% of cases of Cushing syndrome while adrenal carcinomas are responsible for <5% of cases of Cushing's syndrome [11] with the onset of clinical features being gradual in patients with adenomas but often rapid in those with adrenal carcinoma.

CASE STUDY

We explore the case of a 35 year old female with a background of type II diabetes mellitus and hypertension that had an emergency Caesarean section for breech presentation. Post-procedure, she developed right sided chest pain with her ECG demonstrating sinus tachycardia. She was investigated with a CTPA to rule out a pulmonary embolism, and while the scan was negative for a PE, it showed an incidental finding of a 2.5 x 4 cm fat containing right adrenal nodule keeping in with an adrenal adenoma. Subsequently, she was seen in the endocrine outpatient department where she mentioned a history of weight gain over the last 4 years with facial acne and increased hair

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growth over the chin, upper lip and sideburns upon enquiry. She demonstrated clinical findings of cortisol excess notably, Cushingoid features with facial plethora, acne, supraclavicular fat pad, dorsocervical fat pad, acanthosis nigricans and violaceous wide purple striae over the abdomen with no evidence of skin bruises or proximal myopathy. Her glycaemic control and hypertension was sub-optimal throughout pregnancy and she required insulin along with metformin with the addition of two antihypertensive agents.

Blood tests were done to check for cortisol excess after changing her antihypertensive agent from ramipril to amlodipine. Her blood tests showed a random cortisol level elevated at 734 nmol/L (normal range 172-497 nmol/L) and an overnight dexamethasone suppression test demonstrated cortisol not suppressed at 664 nmol/L (normal range 172-497 nmol/L). A 48 hour dexamethasone suppression test revealed a cortisol level not suppressed at 681 nmol/L (normal range 172-497 nmol/L), two 24-hour urinary catecholamine secretion tests were normal, testosterone and dehydroepiandrosterone were normal, adrenocorticotropic hormone was suppressed at <5.0ng/l (normal range 7.2-63.3 ng/l), renin was suppressed at <8.0mU/l (normal range 13-34 mU/l) and aldosterone was normal at 422 pmol/l (normal range 28-860 pmol/l).

A non-contrast CT adrenal showed a 4.5 cm by 3.09 cm hypo-attenuating right adrenal mass with a CT density of -5.7 Hounsfield units in keeping with a benign adenoma (Figures 1 and 2).

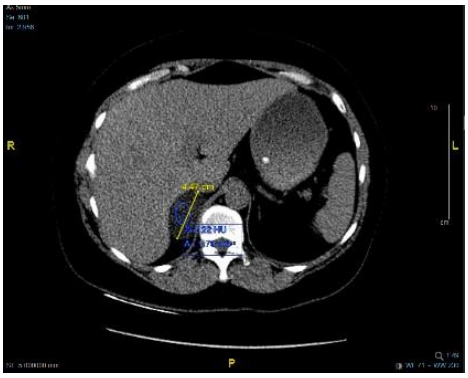

Figure 1: Non-contrast CT adrenals (axial view) demonstrating a 4.47 cm by 3.09 cm hypo-attenuating right adrenal mass with a CT density of -5.7 HU.

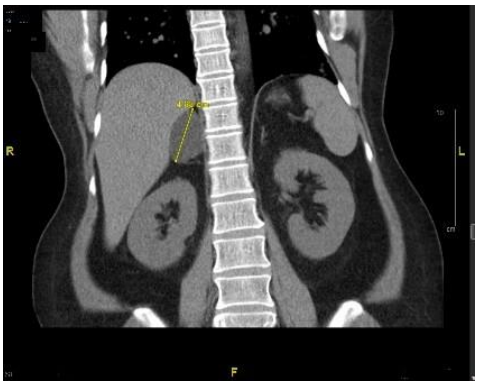

Figure 2: Non-contrast CT adrenals (sagittal view).

Because of the patient's age and the fact that she had a more than 4 cm right adrenal incidentaloma with investigations pointing towards cortisol excess, she was referred to the endocrine/adrenal multidisciplinary clinic at a local tertiary care centre where a decision was made to offer her a laparoscopic adrenalectomy on the right side. Following the laparoscopic adrenalectomy, the histological findings were consistent with an adrenal adenoma and she demonstrated marked improvement with complete resolution of her symptoms. She is now on single anti-hypertensive medication, ramipril 2.5 mg and her blood pressure readings are well controlled. Insulin was stopped and glycaemic control is optimal on metformin.

DISCUSSION

This report describes a patient with Cushing's syndrome secondary to an ACTH-independent cause, an adrenal adenoma, which has an incidence rate of around 10-15% on autopsy series [11]. The incidence of Cushing's syndrome is in the region of 10 to 15 people per million, with a higher incidence in people with diabetes, obesity, hypertension or osteoporosis, with the prevalence in obese patients with type II diabetes and hypertension in the range of 2-5% [12]. Cushing's syndrome due to an adrenal or pituitary tumour is more common in females (ratio 5:1) with the peak incidence of Cushing's syndrome caused by an adrenal or pituitary adenoma being between the ages of 25 and 40 [13,14]. The clinical features of CS during pregnancy may overlap with normal pregnancy in terms of many symptoms and signs such as weight gain, malaise and oedema therefore in the majority of cases Cushing's syndrome in pregnancy is often not discovered until mid-pregnancy [15-17]. Furthermore, some of the symptoms of Cushing's syndrome may also be attributed to pregnancy complications such as gestational diabetes or eclamptic syndromes thus leading to a delay in the diagnosis of Cushing's syndrome with pregnancy [18-20].The incidence of ACTH-independent CS is rising in pregnant women in comparison to the non-pregnant CS populations whereas in non-pregnant women with CS, the incidence of adrenal adenomas is only approximately 15%. Wy La et al. [21-23] has reported that the mechanism of increased incidence of adrenal adenoma in pregnancy with Cushing's syndrome may be linked to a variety of hormone receptors, especially ectopic expression of luteinizing hormone and chorionic gonadotropin receptor in the adrenal cortex and estrogen-dependent nodular adrenal hyperplasia. Ballian et al. did not find any ACC in lesion sizes less than 4 cm and suggest that a 4 cm threshold for resection would identify primary malignant lesions and decrease the surgery for benign lesions with a high sensitivity of 93%, albeit a low specificity of 42%, in predicting malignant lesions [24-26]. One of the limitations is the presence of malignant lesions identified measuring <2.5 cm at the time of diagnosis, found in a few case reports. The European Society of Endocrinology recommends the criteria of surgical intervention should be guided by the likelihood of malignancy, the presence and degree of hormone excess, age, general health and patient preference. Cushing's syndrome caused by an adrenal adenoma is rare during pregnancy. In adrenal Cushing's syndrome diagnosed during pregnancy, medical treatment with metyrapone can be

started after the diagnosis and laparoscopic surgery can be performed in the second trimester. Early intervention is useful in preventing complications secondary to hypercortisolism and is safe both for the mother and infant. Adrenalectomy is the preferred mode of treatment for all adrenocortical causes of Cushing's syndrome with laparoscopic procedures minimising morbidity and leading to rapid recovery after resection in patients who are hypertensive preoperatively or have other complications [27].

CONCLUSION

In conclusion, our case report represents the unusual circumstance in which the sequential development and overlapping of Cushingoid symptoms with pregnancy have been documented and complete resolution of endogenous glucocorticoid excess with unilateral adrenalectomy, as observed in our case, is rarely achieved. Another important message is that Cushing's syndrome must be excluded as a secondary cause of hypertension especially in the workup of young patients presenting with hypertension. A last thought is that adrenal masses are usually considered atypical if they are larger than 4 cm in size however histopathological findings in this case confirmed an adrenal adenoma.

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