CASE REPORT

Adrenal myelolipoma(s) as presenting manifestation of subclinical Cushing's disease (eutopic ACTH-dependent Cushing's syndrome)

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SUMMARY

Primary adrenal myelolipomas, relatively rare benign tumours of the adrenal cortex are typically unilateral, hormonally inactive and asymptomatic, hence often diagnosed as 'adrenal incidentaloma'. Bilateral adrenal myelolipomas, in particular, may be associated with underlying endocrinopathies associated with elevated circulating adrenocorticotrophic hormone (ACTH) concentration. Subclinical cortisol hypersecretion, irrespective of its ACTH dependency, does not manifest typical clinical phenotype of hypercortisolemia, and thus termed subclinical Cushing's syndrome. In this article, hormonal evaluation in a middle-aged woman with diabetes, hypertension and incidentally discovered unilateral adrenal myelolipoma revealed underlying subclinical Cushing's disease. Abdominal CT revealed another tiny focus in the contralateral adrenal gland, probably representing incipient myelolipoma.

and development of necrosis within the enlarged adrenals.^{1,2} One of such postulations is that haematopoietic and fat elements of the tumour could derive from common progenitor cells under the influence of some stimulatory factors.³ The trophic role of adrenocorticotrophic hormone (ACTH) and/or cortisol in tumour formation has been identified as many patients of adrenal myelolipoma have underlying ACTH excess with/without hypercortisolism.⁴ Prolonged and excessive stimulation of the adrenals by ACTH has been proposed as the main hypothesis to explain the higher frequency of bilateral giant myelolipomas in inadequately treated or non-compliant patients with congenital adrenal hyperplasia (CAH). Findings of adrenal myelolipoma in individuals suffering from chronic systemic ailments, malignancies and formation of such tumour following administration of crude anterior pituitary extracts in rodents underline the putative role of ACTH in tumour development.

BACKGROUND

Adrenal myelolipoma, a benign tumour consisting of admixtures of fat cells and haematopoietic tissue, is essentially non-functional and usually discovered as 'adrenal incidentaloma'. The underlying pathophysiology of tumourigenesis is yet to be crystallised and a number of hypotheses have been put forward. Some of those proposed theories include the presence of bone marrow rest within the developing adrenals during embryonic life and subsequent establishment of viable areas of bone marrow, adrenal embolization of bone marrow cells, metaplasia of the adrenal tissue

CASE PRESENTATION

A 53-year-old woman with a year-long history of diabetes and hypertension was referred for right adrenal mass, detected on ultrasonography (40 mm × 36 mm × 32 mm hyperechoic lesion) (figure 1) during evaluation of right hypochondriac pain. Clinical examination was unremarkable except for central obesity (body mass index: 28.9 kg/m²; waist circumference: 102 cm) (figure 2). She did not demonstrate moon face, proximal myopathy, ecchymosis, thin skin or wide purple striae. Her blood pressure was 138/82 mm Hg. Contrast enhanced CT of the abdomen revealed a heterogeneous hypoechoic space-occupying lesion (43 mm × 38 mm × 29 mm) arising from lateral limb of right adrenal gland having fat density within. The medial limb of the right adrenal appeared thick compared with right crus of the diaphragm. A small hypoechoic area with fat density was also noted within the left adrenal gland with thickening of the medial limb of the left adrenal (figure 3). This may represent an incipient myelolipoma arising from the left adrenal gland.

INVESTIGATIONS

Fasting plasma glucose: 116 mg/dL; Postmeal plasma glucose: 162 mg/dL; haemoglobin A1c: 7.1%.

Serum potassium: 3.9 mmol/L

Figure 1 Well defined hyperechoic mass near upper pole of right kidney in abdominal ultrasonography.

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Figure 2 Clinical photographs without signs, suggestive of cortisol excess (no moon face, no wide purple striae).

Basal cortisol: 13.9 µg/dL (384 nmol/L); urinary free cortisol: 192 µg/day (530 nmol/day) (reference: 4–50 µg/day (11–138 nmol/day)).

Overnight 1 mg dexamethasone suppression test (ONDST) cortisol : 4.5 µg/dL (124 nmol/L); 48 hours low-dose dexamethasone suppression test (2 mg/day)(LDDST)cortisol : 4.2 µg/dL (116 nmol/L) (in normal individuals, serum cortisol is usually suppressed to <1.8 µg/dL (49.7 nmol/L) following ONDST and LDDST).

Midnight sleeping cortisol: 6.2 µg/dL (172 nmol/L) (a value of more than 1.8 µg/dL (50 nmol/L) has 100% sensitivity for endogenous Cushing's syndrome (CS)).

Morning plasma ACTH: 30.7 pg/mL (6.8 pmol/L) (plasma ACTH of more than 10 pg/mL (2.2 pmol/L) suggests adrenal-independent/ACTH-dependent CS).

Dehydroxyepiandrosterone sulfate: 172 µg/dL (4.7 mmol/L) (reference: 25–131 µg/dL (0.68–3.6 mmol/L)).

Forty-eight hours high-dose dexamethasone suppression test (8 mg/day): more than 50% suppression of serum cortisol at 48 hours from baseline (about 90% of patients with Cushing's disease have more than 50% suppression of cortisol value at 48 hours from baseline values compared with 10%–50% of those with the ectopic ACTH syndrome).

Dynamic MRI of hypothalamopituitary area: asymmetry of the pituitary gland (right half was bigger than left half) with deviation of stalk towards left. No definite adenoma could be identified.

Dual-energy X-ray absorptiometry: T score: –2.3 (Z score: –1.5) at lumbar spine.

Figure 3 Axial CT scan sections at different levels: heterogeneous hypoechoic space-occupying lesion arising from lateral limb of right adrenal gland having fat density within. The medial limb of the right adrenal appeared thick compared with right crus of the diaphragm. A small hypoechoic area with fat density was also noted within the left adrenal gland (arrow head in left panel and arrow in right panel) with thickening of the medial limb of the left adrenal (right panel).

TREATMENT

The woman was counselled about bilateral inferior petrosal sinus sampling (BIPSS) and subsequent trans-sphenoidal surgery with an attempt to peroperative localization of pituitary tumour if an increased central to peripheral gradient of ACTH could be obtained in BIPSS. However, she declined both the procedures and chose to remain in follow-up with oral antidiabetic agents, antihypertensive, calcium and vitamin D supplementation.

DISCUSSION

Adrenal myelolipomas, bilateral disease in particular, have been well described in CAH and Nelson syndrome, where ACTH levels are significantly elevated. Myelolipoma, both unilateral and bilateral, has also been associated with CS, both ACTH dependent (eutopic and ectopic) and ACTH independent.^{4,5} In these conditions, circulating ACTH is normal, minimally elevated or suppressed but still demonstrates significant driving force for tumour formation. Increased tissue expression of ACTH (melanocortin 2 receptor) receptors within the tumour perhaps perpetuates the effect of ACTH in these conditions.⁶ Excess circulatory androgen is a 'sine qua non' in individuals with inadequately treated CAH. Adrenal androgens, synthesised in zona reticularis of adrenal cortex are ACTH dependent and ACTH dependent CS syndrome patients often have hyperandrogenemia. Over expression of androgen receptors (AR) has also been observed in such tumours and thus may play a stimulatory role in these patients.⁶ However, earlier study looking at increased tissue expression of these receptors in giant adrenal myelolipoma by a semiquantitative approach to analyse mRNA expression did not demonstrate similar findings and this particular mechanism of tumour formation is not sacrosanct.⁷

Adrenocortical cells, particularly those within the hyperplastic tissue synthesise ACTH locally by tissue expression of the gene encoding the ACTH precursor pro-opiomelanocortin. They also express prohormone convertase type 1, suggesting generation of bioactive corticotrophin. This intra-adrenal ACTH can potentially drive tumorigenesis in conditions when plasma ACTH is normal, minimally elevated or suppressed.^{8–10}

Subclinical CS previously termed as 'pre-Cushing's syndrome' and 'preclinical Cushing's syndrome' is a milder form of the disease in which circulatory cortisol level is minimally elevated. This has most often been described in patients with adrenal incidentalomas. Existing data on increased frequency of subclinical CS in patients with bilateral adrenal incidentalomas is conflicting.¹¹ Patients with subclinical CS do not demonstrate the typical signs/symptoms of cortisol excess, hence difficult to pick up in clinical practice and the diagnosis is based on biochemical evaluation in appropriate settings. Management of such individuals is also controversial but successful surgery in appropriately selected individuals harbouring functionally active adrenal mass can reverse the systemic detrimental effects of hypercortisolemia and result in long-term cure from the disease. Deciding on treatment modalities in subclinical CS secondary to Cushing's disease is even more difficult as pituitary surgery is always challenging particularly in not so experienced hands. Functionally active unilateral adrenal myelolipoma has been found to be associated with subclinical CS,¹² but adrenal myelolipomas secondary to subclinical Cushing's disease (eutopic ACTH dependent) has not been described yet.

To conclude, patients with diabetes, hypertension and adrenal myelolipomas, bilateral in particular irrespective of their size should be evaluated thoroughly to unveil underlying endocrinopathies as early intervention and successful

elimination of the driving force can potentially prevent progressive enlargement of these tumours.

Learning points

- Adrenal myelolipoma, a relatively rare primary benign tumour of the adrenal cortex, composed of mature adipose tissue and bone marrow elements in variable amount is usually unilateral, non-functional and does not require hormonal evaluation. However, bilateral adrenal myelolipomas should be investigated thoroughly for underlying endocrinopathies.
- Although the underlying pathogenesis of tumour formation is still unclear, chronic adrenocorticotrophic hormone (ACTH) hyperstimulation is assumed to be the most important factor irrespective of circulating ACTH concentration.
- Subclinical Cushing's syndrome (CS) is essentially a biochemical diagnosis as the patients do not manifest overt signs of cortisol excess. Patients with ACTH-dependent CS, even if subclinical, may develop adrenal myelolipoma; otherwise asymptomatic individuals with bilateral adrenal myelolipoma should be evaluated for underlying ACTH-dependent hypercortisolemia.

Contributors PPC, SP and SNB were involved in diagnosis, management of the patient, literature search and writing the manuscript. RB contributed in work-up of the patient and provided intellectual inputs.

Competing interests None declared.

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REFERENCES

- 1 Plaut A. Myelolipoma in the adrenal cortex; myelolipoid structures. *Am J Pathol* 1958;34:487–515.
- 2 Dean G. Myelolipoma of the adrenal gland. *Scott Med J* 1971;16:513–8.
- 3 Selye H, Stone H. Hormonally induced transformation of adrenal into myeloid tissue. *Am J Pathol* 1950;26:211–33.
- 4 Yoshioka M, Fujimori K, Wakasugi M, et al. Cushing's disease associated with adrenal myelolipoma, adrenal calcification and thyroid cancer. *Endocr J* 1994;41:461–6.
- 5 Sieber SC, Gelfman NA, Dandurand R, et al. Ectopic ACTH and adrenal myelolipoma. *Conn Med* 1989;53:7–10.
- 6 Almeida MQ, Kaupert LC, Brito LP, et al. Increased expression of ACTH (MC2R) and androgen (AR) receptors in giant bilateral myelolipomas from patients with congenital adrenal hyperplasia. *BMC Endocr Disord* 2014;14:42.
- 7 Hagiwara H, Usui T, Kimura T, et al. Lack of ACTH and androgen receptor expression in a giant adrenal myelolipoma associated with 21-hydroxylase deficiency. *Endocr Pathol* 2008;19:122–7.
- 8 Lefebvre H, Duparc C, Chartrel N, et al. Intraadrenal adrenocorticotropin production in a case of bilateral macronodular adrenal hyperplasia causing Cushing's syndrome. *J Clin Endocrinol Metab* 2003;88:3035–42.
- 9 Iwata M, Oki Y, Okazawa T, et al. A rare case of adrenocorticotrophic hormone (ACTH)-independent macroadrenal hyperplasia showing ectopic production of ACTH. *Intern Med* 2012;51:2181–7.
- 10 Louisset E, Duparc C, Young J, et al. Intraadrenal corticotropin in bilateral macronodular adrenal hyperplasia. *N Engl J Med* 2013;369:2115–25.
- 11 Zografos GN, Perysinakis I, Vassilatou E. Subclinical Cushing's syndrome: current concepts and trends. *Hormones* 2014;13:323–37.
- 12 Boronat M, Moreno A, Ramón y Cajal S, et al. Subclinical Cushing's syndrome due to adrenal myelolipoma. *Arch Pathol Lab Med* 1997;121:735–7.

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