CASE REPORT

Bilateral adrenal myelolipoma in Cushing's disease: a relook into the role of corticotropin in adrenal tumourigenesis

Partha Pratim Chakraborty,¹ Rana Bhattacharjee,² Pradip Mukhopadhyay,² Subhankar Chowdhury²

¹Department of Medicine, Midnapore Medical College & Hospital, Midnapore, West Bengal, India

²Department of Endocrinology & Metabolism, IPGME&R/SSKM Hospital, Kolkata, West Bengal, India

Correspondence to

Dr Partha Pratim Chakraborty, docparthapc@yahoo.co.in

Accepted 2 June 2016

SUMMARY

Adrenal myelolipomas are infrequently encountered benign tumours of unknown aetiology. In the majority of cases they are unilateral, and clinically and hormonally silent, only requiring periodic follow-up. However, bilateral adrenal myelolipomas are sometimes associated with endocrine disorders and warrant appropriate evaluation. Though the understanding of the pathophysiology of adrenal myelolipomas has long been elusive, adrenocorticotrophic hormone (ACTH) has been proposed as the main tropic factor in a number of studies. Cushing's disease is rarely associated with bilateral and sometimes giant myelolipomas. In this article, the association of bilateral adrenal myelolipomas with Cushing's disease has been discussed and the role of ACTH in the tumourigenesis has been reviewed.

BACKGROUND

Adrenal myelolipomas are benign neoplasms of the adrenal glands, consisting of adipose and mature haematopoietic tissue with a reported overall incidence of <0.5% in the population (15% of all adrenal incidental masses). In the past, these tumours were detected at autopsy; but with the widespread use of abdominal imaging in recent times, they are commonly being discovered as 'adrenal incidentalomas'. Owing to their high macroscopic fat content, they appear hyperechoic on ultrasound and have low attenuation on CT scans. They are virtually silent both clinically and biochemically. Symptoms such as pain and renovascular hypertension due to compression of surrounding structures by a giant myelolipoma are rare; even rarer is the presence of a hormonally active tumour or hypofunction of the involved adrenal gland. These tumours are usually unilateral but, in rare instances, they can arise from both the adrenal glands simultaneously. Bilateral adrenal myelolipomas warrant a detailed work up for underlying endocrinological disorders. Though congenital adrenal hyperplasia (CAH) is the most common underlying disorder in adult patients with bilateral adrenal myelolipomas, at times, Cushing's disease may also present with these benign adrenal tumours.¹

CASE PRESENTATION

A 64-year-old normotensive man with a 3-year history of non-insulin treated diabetes and dyslipidaemia had been evaluated by his general

practitioner for an ill-defined abdominal pain, and found to have a hyperechoic space-occupying-lesion over the left supra-renal area on abdominal ultrasound (figure 1). CT scan of the abdomen was suggestive of bilateral adrenal myelolipoma and the patient was referred for endocrine opinion. On thorough clinical examination, the patient was found to have central obesity and thin skin without other stigmata of hypercortisolism. Complete blood count revealed polymorphonuclear leucocytosis with eosinopenia indicative of excess circulating glucocorticoid. Screening tests were suggestive of endogenous hypercortisolism. Morning plasma adrenocorticotrophic hormone (ACTH)/corticotropin value indicated ACTH dependent hypercortisolism. Dynamic MRI of the hypothalamopituitary area revealed a microadenoma over the right half of anterior pituitary and bilateral inferior petrosal sinus sampling (BIPSS) confirmed Cushing's disease.

INVESTIGATIONS

Complete blood count: total leucocyte count: $14\,500/\mu\text{L}$ ($14.5 \times 10^9/\text{L}$) ($P_{86}L14E_0M_0B_0$).

Glycated haemoglobin: 7.7% (61 mmol/mol).

Creatine: 1 mg/dL (88.4 $\mu\text{mol/L}$); sodium: 142 mmol/L; potassium: 4.3 mmol/L; bicarbonate: 26.1 mmol/L.

CT of the abdomen: 14.4 cm $\times$ 11.4 cm heterogeneous space-occupying lesion with fat attenuation in the left adrenal; 1.3 $\times$ 1.1 cm right adrenal with fat attenuation in medial limb (figure 2).

Basal cortisol: 24.2 $\mu\text{g/dL}$ (668 nmol/L); urinary free cortisol: 831 $\mu\text{g/day}$ (2294 nmol/day) (reference: 4–50 $\mu\text{g/day}$ (11–138 nmol/day)).

Overnight 1 mg dexamethasone suppression test (ONDST): 29.4 $\mu\text{g/dL}$ (811 nmol/L); 48-hour low-dose dexamethasone suppression test (2 mg/day) (LDDST): cortisol: 32.2 $\mu\text{g/dL}$ (889 nmol/L) (in normal individuals, serum cortisol is usually suppressed to <1.8 $\mu\text{g/dL}$ (49.7 nmol/L) following ONDST and LDDST).

Midnight sleeping cortisol: 9.9 $\mu\text{g/dL}$ (274 nmol/L) (a value of more than 1.8 $\mu\text{g/dL}$ (50 nmol/L) has 100% sensitivity and a value of more than 7.5 $\mu\text{g/dL}$ (207 nmol/L) has 87% specificity for Cushing's syndrome).

Morning plasma ACTH: 55.8 pg/mL (12.3 pmol/L) (plasma ACTH of more than 10 pg/mL (2.2 pmol/L) suggests adrenal independent/ACTH dependent Cushing's syndrome).

CrossMark

To cite: Chakraborty PP, Bhattacharjee R, Mukhopadhyay P, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2016-214965

Figure 1 Hyperechoic space-occupying lesion over the left supra-renal area (marked 's') on abdominal ultrasound.

Dehydroxyepiandrosterone sulfate: 181 µg/dl (4.9 µmol/L) (reference: 25–131 µg/dL (0.68–3.6 µmol/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 to 10–50% of those with the ectopic ACTH syndrome).

Twenty-four hours urinary metanephrine: 158 µg (801 nmol) (reference: <400 µg/day (<2028 nmol/day)).

Twenty-four hours urinary normetanephrine: 432 µg (2358.7 nmol) (reference: <900 µg/day (<4914 nmol/day)).

Dynamic MRI of hypothalamopituitary area: a microadenoma (7 mm) over the right side of the anterior pituitary (figure 3).

BIPSS with intravenous vasopressin: Central: peripheral ACTH gradient of more than 7 (a ratio of central to peripheral ACTH of more than 3 is consistent with Cushing's disease).

TREATMENT, OUTCOME AND FOLLOW-UP

The patient underwent trans-sphenoidal surgery along with removal of the pituitary microadenoma. Post-operative day 5 morning cortisol was undetectable suggesting early remission. The rest of the post-operative anterior pituitary hormones were normal. He was put on supplemental hydrocortisone and

Figure 2 CT scan of the abdomen showing a massive left adrenal myelolipoma (arrow heads) and enlarged right adrenal gland with myelolipoma (arrow).

Figure 3 Microadenoma over the right side of the pituitary on dynamic MRI (white arrow).

3 months post operatively his morning serum cortisol remained suppressed. We noticed a significant decrement in his requirement for antidiabetic agents. His blood sugars remained controlled with metformin alone. In view of the large size of the left-sided adrenal myelolipoma, surgical removal of the mass was discussed, but the patient decided against it and at post-operative 3 months we noticed no change in the size of the tumour.

DISCUSSION

The underlying mechanisms of tumourigenesis in adrenal myelolipomas are largely undefined and several hypotheses have been postulated. These include origin of the tumour from primitive embryonic mesenchymal cells, lodging of bone marrow emboli in the adrenal glands, and subsequent proliferation of those cells and metaplastic transformation of undifferentiated stromal cells. The occurrences of bilateral adrenal myelolipomas in conditions with excessive secretion of ACTH such as CAH, ectopic ACTH producing oat cell lung carcinoma, Nelson's syndrome and Addison's disease, perhaps suggest a role of ACTH in the pathogenesis.

The probable role of ACTH in the pathogenesis of myelolipomas originated in an experimental study way back in 1950, when injection of crude anterior pituitary extracts into the adrenal cortex of rats gave the tissue a myelolipomatous appearance.² Adrenal myelolipomas are also found to be associated with severe or chronically stressful conditions such as extensive burns, uncontrolled diabetes mellitus, obesity, chronic inflammatory diseases and malignancy in which endogenous ACTH is expected to be elevated. Prolonged stimulation of the adrenals by high levels of ACTH may cause metaplasia of adrenocortical cells. However, in Cushing's disease, plasma ACTH levels are usually not very high and about half of the patients have values within the normal reference range. In Cushing's disease, the hyperplastic adrenals secrete proportionately more cortisol in response to a given increment in plasma ACTH.³ Moreover, normalisation of cortisol has been found to be more difficult in Cushing's disease compared with ectopic ACTH production, emphasising significant stimulation of the adrenal glands in Cushing's disease despite normal or mildly elevated corticotropin.⁴ Interestingly, such prolonged stimulation of the adrenals by normal levels of ACTH may also give rise to myelolipoma formation, as evidenced by association of myelolipomas with Cushing's disease. On the contrary, there is evidence to show that myelolipomas do not overexpress ACTH receptors; and

myelolipomas have also been found in several patients with suppressed levels of corticotrophin.^{5 6} Consequently, hypercortisolaemia itself was thought to be the driving force. Reports of coexistent myelolipomas in ipsilateral adrenal glands in patients of ACTH independent unilateral macronodular adrenal hyperplasia suggested the role of locally produced adrenal growth factors acting in paracrine fashion.⁷

In a recently published study involving patients with so called ACTH-independent bilateral macronodular adrenal hyperplasia, hypercortisolism was found to be regulated by corticotrophin produced by a subpopulation of steroidogenic cells in the hyperplastic adrenals. Cortisol production was thought to be controlled both by aberrant membrane receptors and by locally produced corticotrophin acting as a local amplifier on these receptors. This finding perhaps strengthens the role of ACTH in myelolipoma formation and explains normal or low ACTH in a particular subgroup of patients.⁸ There is no definite consensus or guideline on surgical removal of adrenal myelolipoma. Considering minimal risk of bleeding or spontaneous rupture in small sized myelolipomas, a close follow-up with annual CT scan is recommended when the tumour diameter is <4 cm. Surgery is preferred if the tumour exceeds 7 cm, to avoid complications such as spontaneous rupture, retroperitoneal haemor-

rhage, haematuria and renovascular hypertension.⁹ Though the association of adrenal myelolipoma with Cushing's disease was described a long time ago,¹⁰ there are only a handful of such cases documented in the world literature. Despite the fact that the understanding of the pathophysiology of myelolipomas has long been elusive, recent identification of the novel intra-adrenal pathways might lead to a better understanding of adrenal tumourigenesis.

Contributors PPC, RB, PM and SC were involved in diagnosis and management of the patient. PPC, RB and PM were involved in the literature search and preparation of the manuscript. SC was involved in providing intellectual inputs and finalising the draft.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Al-Bahri S, Tariq A, Lowentritt B, *et al.* Giant bilateral adrenal myelolipoma with congenital adrenal hyperplasia. *Case Rep Surg* 2014;2014:728198.
- 2 Selye H, Stone H. Hormonally induced transformation of adrenal into myeloid tissue. *Am J Pathol* 1950;26:211–33.
- 3 Orth DN, Kovacs WJ. The adrenal cortex. In: Wilson JD, Foster DS, Kronenberg HM, *et al.*, eds. *Williams text book of endocrinology*. 9th edn. W.B Saunders Company, 1998:569.
- 4 Juszczak A, Morris DG, Grossman AB, Cushing's syndrome. In: Jameson JL, De Groot LJ, de Kretser DM, *et al.*, eds. *Endocrinology: adult and pediatric*. 7th edn. Philadelphia: Elsevier Saunders, 2016:302.
- 5 Rockall AG, Babar SA, Sohaib SA, *et al.* CT and MR imaging of the adrenal glands in ACTH-independent cushing syndrome. *Radiographics* 2004;24:435–52.
- 6 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.
- 7 Jenkins PJ, Chew SL, Lowe DG, *et al.* Adrenocorticotrophin-independent unilateral macronodular adrenal hyperplasia occurring with myelolipoma. An unusual cause of Cushing's syndrome. *Clin Endocrinol* 1994;41:827–30.
- 8 Louiset E, Duparc C, Young J, *et al.* Intraadrenal corticotrophin in bilateral macronodular adrenal hyperplasia. *N Engl J Med* 2013;369:2115–25.
- 9 Daneshmand S, Quek ML. Adrenal myelolipoma: diagnosis and management. *Urol J* 2006;3:71–4.
- 10 Bennett BD, McKenna TJ, Hough AJ, *et al.* Adrenal myelolipoma associated with Cushing's disease. *Am J Clin Pathol* 1980;73:443–7.

Learning points

- ▶ Though adrenal myelolipomas are functionally inactive, bilateral tumours warrant detailed work up for underlying endocrinological diseases.
- ▶ Cushing's disease is an uncommon cause of bilateral adrenal myelolipomas.
- ▶ Corticotropin (both circulating and locally produced) is perhaps the main tropic factor behind myelolipoma formation in the adrenals.

Copyright 2016 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.

BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow