CASE REPORT

Primary hypercortisolism and phaeochromocytoma next to, but not related to, each other

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Accepted 29 March 2016

SUMMARY

This is the first report of unilateral hypercortisolism and phaeochromocytoma that cannot be explained by medullary tumourigenic adrenocorticotrophic hormone (ACTH) excretion. The patient was referred for an adrenal incidentaloma with hypertension but no Cushingoid features, disturbed glucose tolerance and osteopaenia. Additional testing revealed hypercortisolism with suppressed ACTH, and a right-sided phaeochromocytoma with typical radiographic appearance. Resection of the right adrenal completely normalised the clinical symptoms and biochemistry, and increased ACTH concentrations, implicating initial suppression. Histology revealed a tumour consisting of chromaffin cells, with only pre-existing cortical tissue containing groups of ACTH-positive cells. Recent human studies in primary Cushing's syndrome demonstrated that a paracrine effect of these aberrant cells, assumed to be Leydig cells in origin, results in hypercortisolism by stimulation of surrounding steroidogenic cells, leading to systemic ACTH suppression. We propose that 2 diagnoses within 1 adrenal, being phaeochromocytoma and autonomous cortisol overproduction due to adjoining aberrant ACTH-producing cells, explain the clinical picture.

BACKGROUND

Two rare hormone overproduction diseases, hypercortisolism and catecholamine excess, can be present concomitantly in the case of an ACTH-producing phaeochromocytoma.^{1 2} Cushing is reported with an estimated incidence of two or three per million,³ mainly due to pituitary ACTH overproduction (70%), but in 10% it is caused by ectopic ACTH production, among which is ACTH-producing phaeochromocytoma.¹ Phaeochromocytoma itself is a very rare disease, with an incidence of 1:100 000.⁴ We, however, present a case with circumstantial evidence for suppressed pituitary ACTH secretion secondary to paracrine-acting ACTH-expressing cells within the adrenal cortex,⁵ next to a phaeochromocytoma in the same adrenal.

CASE PRESENTATION

A 58-year-old woman was referred with an incidentally discovered adrenal mass on CT scan performed for analysis of diarrhoea with weight loss, with weight having stabilised, however, at the time of referral. She had no symptoms of catecholamine excess, such as flushes or panic attacks. Medical history revealed mild asthma, impaired glucose tolerance and osteopaenia with a peripheral fracture. The patient felt perfectly well. Medication consisted of calcium/vitamin D supplementation,

multivitamin tablets and inhalational medication if necessary (salbutamol if necessary and salmeterol/fluticasone 50/100 µg/dosage, one dosage twice a day). With a body mass index of 23.3 kg/m², and absence of any Cushing's signs such as buffalo hump, moon face, striae or skin abnormalities, physical examination was unremarkable besides showing hypertension (170/100 mm Hg).

INVESTIGATIONS

According to Dutch guidelines for adrenal incidentaloma, biochemical evaluation for catecholamine, cortisol and renin/aldosterone production was performed. This was carried out under strict dietary regulations (patient abstained from bananas, nuts, alcohol, coffee, tea and other caffeine-containing beverages for 2 days preceding and during urine collection) and after adequate discontinuation of inhalational medication for 2 weeks. This revealed (table 1) evident catecholamine excess (24 h urine measurement: metanephrine 3805 and 3693 µmol/mkreat, reference <99; normetanephrine 2661 and 3676 µmol/mkreat, reference <260) as well as hypercortisolism (24 h urinary-free cortisol 210 and 267 nmol, reference <150; 1 mg dexamethasone suppression test: cortisol 184 nmol/L, reference <50; midnight salivary cortisol: 10.4 and 7.6 nmol/L, reference <5).⁶ Electrolytes and kidney function were normal (potassium 3.7 mmol/L, sodium 143 mmol/L, blood urea nitrogen 5.4 mmol/L, creatinine 51 µmol/L). Basal ACTH amounted to 14 and 10 ng/L (reference 0–75). Renin and aldosterone values were normal (renin 2.4 µg/L/h (reference 0–2.5) and aldosterone 0.16 nmol/L (reference 0–0.35), respectively), with a normal ratio (66, reference <750). CT scan had demonstrated a right adrenal mass with heterogeneous aspect, no calcifications and clear margins, although some fatty infiltration was described, measuring 7×7×7 cm. The contralateral adrenal was slightly enlarged, being 2×2×3 cm. Subsequent MIBG scanning was compatible with a phaeochromocytoma in the right adrenal and no other positive lesions.

DIFFERENTIAL DIAGNOSIS

The combination of phaeochromocytoma and hypercortisolism is extremely rare, but known in ACTH-producing phaeochromocytoma.^{1 2} In most cases, ACTH values are far above reference values, but a few cases report normal values, although still in the upper reference ranges (with the lowest reported value being 59 ng/L).^{1 7} Moreover, almost all cases reported hypokalaemia, reflecting severe

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To cite: Winter EM, Pereira AM, Corssmit EP. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2015-213359

Table 1 Table showing laboratory values at presentation and after surgery

Chemistry	At presentation	After surgery	Unit	Reference
Metanephrine (urine)	3805 3693	41 46	μmol/mcreat	<99
Normetanephrine (urine)	2661 3676	273 281	μmol/mcreat	<260
Cortisol (urine)	210 267	114 137	nmol/24h	<150
Midnight salivary cortisol	10.4 7.6	1.9 <1.5	nmol/L	<5
Cortisol after 1 mg dexamethasone	184	19	nmol/L	<50
ACTH	14 10	56	ng/L	0–75
Potassium	3.7	3.7	mmol/L	3.6–4.8
Sodium	143	140	mmol/L	136–144
Creatinine	47	41	μmol/L	49–90
BUN	5.4	2.7	mol/L	2.5–7.5

BUN, blood urea nitrogen.

hypercortisolism as a result of excessive mineralocorticoid receptor stimulation by cortisol. Under physiological circumstances, the mineralocorticoid receptor is protected by 11B OH steroid dehydrogenase type 2 (which converts cortisol to the inactive cortisone) from inappropriate activation by cortisol. In case of severe hypercortisolism, however, such as in ACTH-producing pheochromocytoma, this enzyme is saturated resulting in inappropriate and excessive receptor activation, and, finally, in hypertension and hypokalaemia. Besides ACTH-producing pheochromocytomas, one case reported pheochromocytoma with contralateral non-ACTH-dependent hypercortisolism.⁸ Since our patient had a low serum ACTH and normal serum potassium, in the presence of a slight enlargement of the contralateral adrenal, we considered a right-sided pheochromocytoma with contralateral non-ACTH-dependent hypercortisolism due to an adenoma most likely.⁸ Our differential diagnosis included an ACTH-producing pheochromocytoma, simply because of the increased a priori chance.

TREATMENT

With the differential diagnosis of an ACTH-producing pheochromocytoma on the one hand, and a right-sided pheochromocytoma with contralateral autonomous cortisol production on the other hand, the right adrenal was to be resected first, in a step-wise approach. In case of persistent hypercortisolism, the left adrenal could be resected at a later stage. This was not

considered a priori due to the increased morbidity of life-long mineralocorticoid and glucocorticoid replacement. The right-sided adrenalectomy was performed according to the national protocol, with extensive preoperative α_1 receptor blockade (using doxazosine 32 mg twice a day) to reach orthostatic hypotension. Finally, metoprolol 50 mg twice daily was added because of tachycardia. Prophylactic hydrocortisone replacement was given during surgery, since the residual adrenocortical function of the left adrenal gland might have been impaired.

OUTCOME AND FOLLOW-UP

Immediately after surgery, catecholamine and cortisol secretion, blood pressure, and glucose tolerance completely normalised (table 1; 24 h urine measurement: metanephrine 46 and 41 μmol/mkreat, reference <113; normetanephrine 281 and 273 μmol/mkreat, reference <342; free cortisol 114 and 137 nmol, reference <150; 1 mg dexamethasone suppression test revealed cortisol level of 19 nmol/L, reference <50). Moreover, ACTH increased from 14 and 10 to 54 ng/L. Histological investigation of the tumour revealed a pheochromocytoma of 7 cm maximum diameter, with clear margins. Immunohistochemical staining for ACTH revealed no positive cells in the medullary tumour. Surprisingly, some groups of positive cells were detected in the pre-existing adrenal tissue (figure 1). Immunohistochemical analysis for succinate dehydrogenase subunit b (SDHB) revealed decreased staining with normal amounts of the A subunit SDHA. Genetic analysis did not reveal any mutation in the well-known pheochromocytoma-associated genes SDHA, SDHB, SDHC, SDHD, SDHAF2, VHL, RET, MAX and TMEM127.

DISCUSSION

From the fact that surgical resection of the pheochromocytoma and right adrenal normalised cortisol, blood pressure and glucose, we conclude that all symptoms had been caused by this adrenal. Remarkably, ACTH values were initially low, but increased after adrenalectomy. Together with the fact that the tumour consisted of pheochromocytoma only, without ACTH-positive cells within the chromaffin cells, the well-known though rare ACTH-producing pheochromocytoma could not explain the concomitant hypersecretion of catecholamine and cortisol. Cortical steroidogenic tissue might, however, have been stimulated in a paracrine manner by yet unknown peptides produced by chromaffin cells, as recently suggested,^{9 10} or by aberrant receptor expression.⁵ However, if that were true, the combination of hypercortisolism and catecholamine excess would have been observed and reported more often.¹¹ The inhalational corticosteroids were considered unlikely to affect pituitary ACTH secretion and systemic hypercortisolism because

Figure 1 Photomicrograph showing pre-existing adrenal tissue (A; H&E, ×20 magnification) with groups of ACTH-positive cells (B; ×20 magnification).

this has only been reported from daily dosages of 500 µg or higher, while our patient used at most 200 µg per day.¹² This is further accentuated by the postsurgical rise in ACTH and normalisation of cortisol levels while continuing the same medication after resection. Moreover, prior to each reported test, the patient had adequately discontinued the inhalational corticosteroids. Interestingly, some ACTH-positive cells were present in the normal pre-existing cortex. Intra-adrenal ACTH production has been described in a case of Cushing's syndrome in the presence of bilateral macronodular hyperplasia,¹³ with recent confirmation in specimens of 30 patients, both on mRNA and protein level.⁵ The intra-adrenal production of ACTH results in hyperstimulation of neighbouring steroidogenic cells leading to systemic hypercortisolism with suppression of pituitary ACTH.^{5 13} Primary hypercortisolism might be explained by this mechanism more often than currently known. With proven expression of specific Leydig cell markers, it was proposed that the ACTH-producing steroidogenic cells are Leydig cells in origin, with disturbed migration to the gonads during embryogenesis,^{5 13} as counterpart to the presence of remnants of adrenal tissue in the gonads.^{14 15} Our findings are in line with this concept, which has hardly been recognised in the literature to date. In case of medullary ACTH overproduction, the reported systemic ACTH values were increased in virtually all cases due to secretion of this hormone by the neuroendocrine tumour. In this case, however, ACTH production appears to act in a paracrine manner within the cortex,⁵ resulting in local hyperstimulation of neighbouring cortisol secreting cells. As a result of the hypercortisolism, the pituitary ACTH secretion was

suppressed. We therefore conclude that our case can be explained by the coexistence of a pheochromocytoma next to, but not related to, cortical cortisol overproduction, most likely due to paracrine functioning aberrant ACTH production.

Contributors Both EPMC and AP contributed to the manuscript by supervision during treatment of the patient and by editing the manuscript.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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Learning points

- Hypertension and glucose intolerance in non-obese patients with adrenal incidentaloma merit thorough endocrine evaluation to exclude rare causes such as hypercortisolism and pheochromocytoma; these severe illnesses may appear asymptomatic.
- The combination of pheochromocytoma and hypercortisolism is not always due to ACTH-producing pheochromocytoma.
- Paracrine functioning cortical ACTH-producing cells can cause adrenal hypercortisolism, with or without Cushing's syndrome, resulting in suppression of systemic ACTH.

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