Endocrine (2012) 42:69–73
DOI 10.1007/s12020-012-9646-7

MINI REVIEW

Mini-review: pheochromocytomas causing the ectopic ACTH syndrome

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Received: 13 January 2012 / Accepted: 24 February 2012 / Published online: 7 March 2012

Abstract Cushing's syndrome (CS) is a condition associated with high cortisol levels and affects around 0.7–2.4 cases per million population per year [1–3]. Approximately 80 % of cases of CS are secondary to excess adrenocorticotrophin (ACTH) secretion, while in around 20 % the primary abnormality lies in the adrenal, most often an adrenal adenoma or carcinoma. Of the ACTH-dependent causes, some 80–90 % are due to a pituitary adenoma—Cushing's disease—but in a significant proportion the cause is ectopic secretion from a non-pituitary source, the ectopic ACTH syndrome (EAS) [4]. The commonest source of ACTH secretion in these patients is a bronchial carcinoid. However, many other tumors are capable of secreting ACTH, and in most series a small but significant number are secondary to an ACTH-secreting pheochromocytoma. Amalgamating the data from 6 large series of patients with ectopic ACTH, pheochromocytoma was the source of ACTH secretion in 19 out of 363 patients (5.2 %) [5–11]. In this mini-review, we present a patient presenting to our department with a pheochromocytoma as well as Cushing's syndrome due to ectopic ACTH secretion by the pheochromocytoma, and we discuss published cases in the world literature to assess its significance. We emphasize the problems in the simultaneous management of these two serious endocrine conditions.

Keywords Pheochromocytoma · Cushing's syndrome · ACTH · Review

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Case report

A 49-year-old lady presented with a 2 month history of headache, generalized swelling, and palpitations. She had typical Cushingoid features, with facial erythema, supraclavicular fat deposits, bruises, purple striae, and proximal myopathy, but no hyperpigmentation. She was also noted to be hypertensive (BP 200/98 mmHg) with a regular pulse of 70 bpm. Routine biochemistry was normal apart from hypokalemia (serum potassium 2.8 mEq/l, reference range: 3.5–5.0 mEq/l).

She was investigated for Cushing's syndrome and endocrine hypertension. Urine and plasma metanephrine were found to be significantly elevated, suggesting the presence of a pheochromocytoma (urinary normetanephrine 4185 μg/24 h, reference range: 0–632; urinary metanephrine 2714 μg/24 h, reference range: 0–276; plasma metanephrine 380 pg/ml, reference range: 16–101, plasma normetanephrine 848 pg/ml, reference range: 24–216). Serum cortisol remained grossly elevated (>63 μg/dl, normal <1.8) after overnight 1 mg dexamethasone suppression. Furthermore, her 24-h urinary-free cortisol was very high (>875 μg/24 h, reference range: 10–110). The plasma ACTH was high (550 ng/l at 09.00 h, reference range: 9–52) suggesting ACTH-dependent CS. All other anterior pituitary hormone levels were within the normal range. She thus had evidence of catecholamine-secreting tumor as well as ACTH-dependent Cushing's syndrome.

CT scanning of the abdomen revealed bilateral adrenocortical hyperplasia (Fig. 1, upper panel) plus a left adrenal mass lesion measuring 4.1 × 3.8 cm, with a central area of necrosis (Fig. 1, lower panel). The mass showed ring enhancement with ^{123}I-MIBG scintigraphy. CT scanning of the neck, thorax, and pelvis was normal.

The relatively short onset, severe CS associated with hypokalemia, and very high ACTH level supported an ectopic source of ACTH. With biochemical investigation suggesting ACTH-driven hypercortisolemia as well as elevated catecholamine metabolites, the left adrenal mass was hypothesized to be an ACTH-secreting pheochromocytoma. As early as 1979, Forman et al. [12] had proposed criteria for the diagnosis of ACTH-secreting pheochromocytomas. Following publication of a series of such cases, Chen et al. [13] reported 4 further patients and updated the criteria proposed by Forman in 1995 to include (1) clinical and laboratory evidence of hypercortisolism, (2) elevated plasma ACTH levels, (3) biochemical evidence of a pheochromocytoma (elevated urinary catecholamines, metanephrines or vanillylmandelic acid excretion) and MRI evidence of an adrenal mass with a bright T2 signal, (4) resolution of symptoms and signs of adrenocorticoid and catecholamine excess after unilateral adrenalectomy, and (5) rapid normalization of plasma ACTH levels after adrenalectomy. Our case satisfied the first three of these criteria. The remaining criteria could only be fulfilled after surgical removal of the adrenal mass. In most cases of ACTH-dependent CS, we would be inclined to perform bilateral inferior petrosal sinus sampling to exclude a pituitary source, but in this case the patient was sufficiently unwell to mandate immediate therapy, and in addition as her pheochromocytoma was to be removed in any case we thought it more prudent, and safe, to proceed to operative removal of the tumor first.

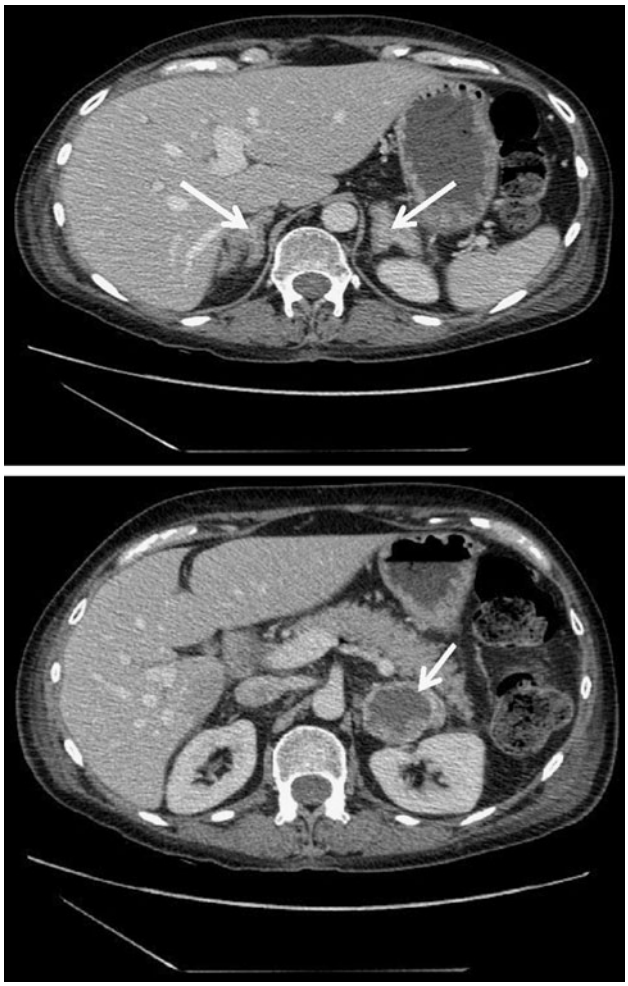

Fig. 1 CT scan of adrenals showing bilateral adrenal hypertrophy (*top panel*) and 4.1 × 3.8 cm left adrenal nodule with central necrosis (*bottom panel*)

A left adrenalectomy was planned, and she was initiated on α- and β-adrenoceptor blockade treatment (phenoxybenzamine titrated up to a dose of 8 mg tds, followed by propranolol 40 mg qds). At the same time the hypercortisolemia was treated with the 11β-hydroxylase inhibitor metyrapone 1 gm qds. However, while awaiting surgery she acutely developed respiratory distress and the oxygen saturation of her blood fell dramatically. Plain chest radiography showed ground glass opacification, while CT scanning revealed multiple small pulmonary emboli and evidence of consolidation. She was transferred to intensive care, and treated with heparin anti-coagulation and broad-spectrum antibiotics for a presumptive infection, although microbiology of her blood and bronchial fluid was negative. The metyrapone alone failed to control the hypercortisolemia, the mean serum cortisol remaining at 48 μg/dl on the metyrapone alone, and after 14 days ketoconazole 400 mg tds was added. Over the next 3 days her mean serum cortisol fell to 7 μg/dl (normal range: 5.4–10.8).

She eventually recovered from this acute respiratory decompensation and proceeded to left laparoscopic adrenalectomy. A necrotic mass was found arising from her left adrenal, and histopathology confirmed an adrenomedullary chromaffin tumor: on immunostaining 40 % of the tumor stained positively for ACTH (Fig. 2). Post-operatively, her metanephrine excretion normalized. There was no residual ^{123}I-MIBG avid disease on follow-up scanning.

Following surgery she had transient adrenal insufficiency, requiring treatment with oral hydrocortisone. At re-investigation 4 weeks post-operatively, after discontinuing hydrocortisone, her serum cortisol level suppressed on a low-dose dexamethasone suppression test (dexamethasone 0.5 mg 6-hourly for 48 h, serum 09.00 h at completion 0.3 μg/dl, normal <1.8) and ACTH levels had normalized. Her Cushingoid features, hypokalemia and hypertension all resolved dramatically following the adrenal surgery. She is currently under regular follow-up and

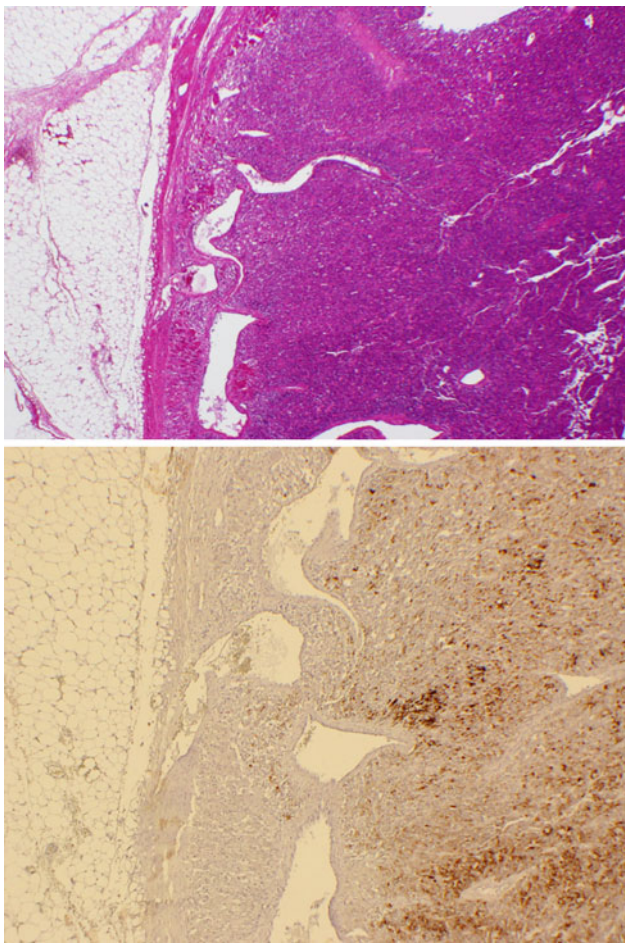

Fig. 2 Histopathology of the adrenal tumor. Adrenomedullary tumor with hematoxylin and eosin staining (*top panel*); approximately 40 % of cells stained immunopositive for ACTH (*bottom panel*)

remains well 12 months after her original presentation. The histology, the clinical and biochemical resolution of hypercortisolemia and catecholamine excess finally fulfilled all of the criteria devised by Forman et al. confirming the diagnosis of an ACTH-secreting pheochromocytoma.

Discussion

ACTH-secreting pheochromocytoma was described as early as 1964 by Bourgoignie et al. [14]. They reported 11 previous patients where a chromaffin tumor co-existed with adrenocortical hyperplasia or adenomata. In 1979, Forman et al. devised the criteria described in our case report for diagnosing such patients. Including our case, there are now 25 reported cases of ACTH-secreting pheochromocytomas since 1977 [15]. ACTH-secreting pheochromocytomas form a distinctive subset of patients with CS: the mean age of presentation was 46.8 (range 25–74) years. It is also of interest that 22 of these 25 patients, some 88 %, were female.

The presentation here is typical of CS. Hypertension was more common and present in 19 out of 25 (76 %) of these patients compared to 57 % in a large series of patients with CS from an ectopic source of ACTH [2]. Hypertension was severe in 9 of these 25 patients (36 %). In the two cases reported in pregnancy, it resulted in a severe pre-eclampsia-like syndrome; in one case there was fetal death, while in the other patient there was cerebral embolism leading to maternal death [16, 17].

High cortisol levels in CS may act as mineralocorticoids after saturating 11β-hydroxysteroid dehydrogenase type 2, the enzyme responsible for its metabolism, leading to hypokalemia [18]. In CS from ectopic ACTH, a higher rate of cortisol production makes hypokalemia more likely [15]. Hypokalemia affects around 10 % of patients with CS, but may be present in 74–95 % of ectopic ACTH patients [6, 10, 11]. Hypokalemia, as in our patient, was present in 19 of the 25 (76 %) patients with ACTH-secreting pheochromocytomas.

Hypercortisolemia leads to hyperglycemia by increasing insulin resistance, and preventing the usual compensatory increase in insulin secretion from β cells. The incidence of diabetes is 36 % and impaired glucose tolerance another 17 % in overt CS [19, 20]. In a series of 25 patients with EAS, 14 patients (56 %) had steroid-induced diabetes [11], and remarkably 21 of the 25 (84 %) patients with ACTH-secreting pheochromocytomas had diabetes. Our patient was an exception as her glucose levels remained normal.

The diagnosis of CS requires biochemical confirmation of endogenous hypercortisolism, which may be demonstrated by one of the following methods: (1) measuring urinary free cortisol levels (at least 2 measurements), (2) late-night elevated salivary cortisol levels (at least 2 measurements), or (3) elevated either cortisol levels after either 1 mg overnight dexamethasone or in the 48 h low-dose dexamethasone (2 mg/day) test [21]. Raised urinary free cortisol levels were reported in 19 of the 25 patients while raised urinary ketogenic steroids were used for diagnosis in 4 patients prior to 1986. In one case the CS was noted to display a cyclical pattern [22]. In another patient there was spontaneous clinical and biochemical resolution of ACTH secretion from the pheochromocytoma for 18 months before adrenalectomy [17]. Plasma ACTH levels are higher in EAS than in CS from a pituitary adenoma tumor, although there remains considerable overlap [23]. In patients with ectopic ACTH, mean plasma ACTH levels were 358 ng/l in the series by Isidori et al. [5], and 204 ng/l in the series by Ilias et al. [6]. Consistent with this, the 25 patients with ACTH-secreting pheochromocytomas had a mean ACTH of 344 ng/l. In the series reported by Salgado et al. [11], interestingly all 4 of their patients had ACTH

levels within the normal range, demonstrating the diagnostic challenge that some of these patients may pose.

An extrapituitary source for ACTH is more likely in a patient of CS when the ACTH level is very high and in the presence of hypokalemia: the tests which may help in biochemically confirming this are failure of suppression of cortisol levels with 48 h high-dose dexamethasone (8 mg/day), or a poor or absent cortisol and/or ACTH response to intravenous corticotrophin releasing hormone (CRH). However, there are many exceptions, and the highest diagnostic accuracy is provided by bilateral inferior petrosal sinus sampling, where a ratio of ACTH levels in central: peripheral venous circulation is used to identify a pituitary source for the ACTH [24]. However, a suggestive clinical presentation and biochemistry, with clear imaging suggestive of an ectopic source, may obviate the need for this relatively invasive investigation. Venous sampling was utilized in 10 of the 25 (40 %) reported patients of ACTH-producing pheochromocytoma. In most patients, as in our case, invasive venous sampling may be avoided by applying the criteria of Forman et al. [12] for diagnosis. In addition, we decided that our patient was too unwell for this investigation, and we would reassess the situation after removal of the pheochromocytoma.

Most of the 25 ACTH-producing pheochromocytomas were unilateral (18 in the left adrenal): there is a single report of ACTH secretion from bilateral pheochromocytomas in a patient with MEN 2A [25]. In case of bilateral adrenal masses, adrenal venous sampling should be used in addition to imaging to confirm secreting tumor mass preoperatively [26]. ACTH-producing pheochromocytoma was benign in the vast majority of the patients, with only one report of a malignant ACTH-producing pheochromocytoma with metastases in the liver, lung and ovary [27]. Clinical markers which would help predicting malignant potential in pheochromocytomas would include tumor size, presence of extra-adrenal disease, post-operative hypertension and biochemical markers such as high dopamine, and high norepinephrine and epinephrine to total catecholamine ratio [28]. High cortisol levels predisposed patients to venous thrombosis and infections which were reported in the preoperative clinical course in 4 (16 %) and 7 (28 %) of the 25 patients, respectively. Our patient had an acute episode of pulmonary embolism and consolidation for which she had to be intubated and ventilated before her surgery, and required intensive therapy before she became clinically stable and suitable for surgery. Most of the previous patients had a complete resolution of symptoms following adrenalectomy, as in our case, but death within 1 year of diagnosis was reported in 2 patients, from myocardial infarction [29] and septic cerebral embolism [17].

In conclusion, patients with ACTH-secreting pheochromocytoma are seen in $\sim$5 % of patients with the ectopic ACTH syndrome, and pose distinctive diagnostic and management challenges, but if diagnosed early and managed intensively they should be curable by surgery.

Acknowledgments We are grateful to Dr J Foote and Dr T Dugal, Royal Cornwall Hospital, Truro, UK, for referring this patient.

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