Pheochromocytoma with ectopic ACTH

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ACTH-secreting pheochromocytomas was described as early as 1964 by Bourgoignie et al [1]. They reported 11 previous patients where a chromaffin tumor co-existed with adrenocortical hyperplasia or adenoma.

In 1995, Forman et al [2] devised the criteria for diagnosing 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
5. rapid normalization of plasma ACTH levels after adrenalectomy

There are now 26 reported cases (include our case) of ACTH-secreting pheochromocytomas since 1977. ACTH-secreting pheochromocytomas form a distinctive subset of patients with CS: the mean age of presentation was 44.61 (range 25–74) years. It is also of interest that 23 of these 26 patients, some 88 %, were female.

Hypertension was more common and present in 20 out of 26 (76 %) of these patients compared to 57 % in a large series of patients with CS from an ectopic source of ACTH [3]. Hypertension was severe in 9 of these 26 patients (34 %). In the two cases reported in pregnancy, it resulted in a severe preeclampsia-like syndrome; in one case there was fetal death, while in the other patient there was cerebral embolism leading to maternal death [4, 5].

High cortisol levels in CS may act as mineralocorticoids after saturating 11b-hydroxysteroid dehydrogenase type 2, the enzyme responsible for its metabolism, leading to hypokalemia [6]. In CS from ectopic ACTH, a higher rate of cortisol production makes hypokalemia more likely [2]. Hypokalemia affects around 10 % of patients with CS, but may

be present in 74–95 % of ectopic ACTH patients [7, 8, 9]. Hypokalemia was present in 19 of the 26 (73 %) patients with ACTH-secreting pheochromocytomas. Our patient was an exception as her potassium levels remained normal.

Hypercortisolemia leads to hyperglycemia by increasing insulin resistance, and preventing the usual compensatory increase in insulin secretion from B-cells. The incidence of diabetes is 36 % and impaired glucose tolerance another 17 % in overt CS [10, 11]. In a series of 26 patients, 22 patients (84 %) with ACTH- secreting pheochromocytomas had diabetes.

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)
3. elevated either cortisol levels after either 1 mg overnight dexamethasone or in the 48 h low-dose dexamethasone (2 mg/day) test [12]

Raised urinary free cortisol levels were reported in 18 of the 26 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 [13]. In another patient there was spontaneous clinical and biochemical resolution of ACTH secretion from the pheochromocytomas for 18 months before adrenalectomy [5]. Plasma ACTH levels are higher in EAS than in CS from a pituitary adenoma tumor, although there remains considerable overlap [14]. In patients with ectopic ACTH, mean plasma ACTH levels were 35.8 pg/ml in the series by Isidori et al. [15], and 20.4 pg/ml in the series by Ilias et al. [7]. Consistent with this, the 26 patients with ACTH-secreting pheochromocytomas had a mean ACTH of 34.4 pg/ml. In the series reported by Salgado et al. [9], 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 [16]. 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 26 (38 %) reported patients of ACTH- producing pheochromocytomas. In addition, we decided not done for this investigation. Most of the 26 ACTH-producing pheochromocytomas were unilateral (18 in the left adrenal): there is two cases report of ACTH secretion from bilateral pheochromocytomas. In one case is a patient with MEN 2A [17] and the other patient is our case that waiting for genetic testing. In case of bilateral adrenal masses, adrenal venous sampling should be used in addition to imaging to confirm secreting tumor mass pre- operatively [18]. ACTH-producing pheochromocytomas was benign in the vast majority of the patients, with only one report of a malignant ACTH-producing pheochromocytomas with metastases in the liver, lung and ovary [19]. 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, high norepinephrine and epinephrine to total catecholamine ratio [20]. High cortisol levels predisposed patients to venous thrombosis, infections and psychiatric problems which were reported in the preoperative clinical course in 4 (15 %), 7 (26 %) and 7 (26 %) of the 26 patients, respectively. 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 [21] and septic cerebral embolism [5].

In conclusion, patients with ACTH-secreting pheochromocytomas are seen in ~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

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