CASE REPORT

Cushing´s syndrome due to ACTH-secreting pheochromocytoma

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BRENNER N, KOPETSCHKE R, VENTZ M, STRASBURGER CJ, QUINKLER M, GERL H. Cushing´s syndrome due to ACTH-secreting pheochromocytoma. The Canadian Journal of Urology. 2008;15(1):3924-3927.

Ectopic secretion of adrenocorticotropic hormone (ACTH) is an infrequent cause of Cushing´s syndrome. We report a case of ectopic ACTH syndrome caused by a pheochromocytoma. A 53-year-old female with clinical features of Cushing´s syndrome presented with serious recurrent hypertensive crisis. Endocrinological investigation confirmed the diagnosis of ectopic ACTH production and revealed markedly elevated urinary catecholamines leading to the diagnosis of pheochromocytoma. Abdominal computerized tomography (CT) scan showed a 3.5 cm left adrenal mass and a nodular hypertrophic right adrenal gland. Bilateral selective adrenal vein catheterization suggested bilateral pheochromocytoma. After treatment with phenoxybenzamine, bilateral adrenalectomy was performed and resulted in remission of Cushing´s syndrome and hypertensive crisis. In addition, this article provides a short guideline for endocrine testing if Cushing´s disease or pheochromocytoma is suspected. However, the most important message of this article is to think of them.

Key Words: pheochromocytoma, ectopic ACTH secretion, Cushing´s´s syndrome, hypertension, adrenal tumor

Case report

A 53-year-old woman presented with a 12-month history of malaise, fatigue, emotional lability, muscle weakness, rigors, edema, excessive sweating, polyuria and polydipsia. She had complained of intermittent headaches and palpitations. Examination revealed an anxious woman with Cushingoid features like truncal obesity with "moon face", facial plethora, "buffalo hump", proximal muscle atrophy and excessive sweating. Despite central obesity her body mass index was 22.8 kg/m^2. Blood pressure was markedly elevated (systolic: 190-220 mmHg; diastolic: 90-110 mmHg) and showed recurrent fluctuations. Laboratory investigations demonstrated fasting blood glucose of 220 mg/dl, glycosylated haemoglobin (HbA1c) of 11.8% (normal range 4.3%-6.1%), severe hypokalemia (2.3 mmol/l; normal range 3.4 mmol/l-5.2 mmol/l) and alkalosis, and leucocytosis (19.5/nl; normal range

Accepted for publication December 2007

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4.5/nl-11/nl), and she was referred to our hospital for further evaluation.

Endocrine assessment revealed absent circadian rhythm of cortisol [8:00 AM cortisol 1391 nmol/l (normal range 171 nmol/l-800 nmol/l); 11:00 PM cortisol 741 nmol/l (normal range < 50 nmol/l)]. Twenty-four hour urinary cortisol was elevated (7358 nmol/d; normal range 55 nmol/d-248 nmol/d). A 2 mg and 8 mg dexamethasone overnight suppression test failed to suppress morning cortisol below 50 nmol/l (1535 nmol/l and 1841 nmol/l, respectively) and showed elevated ACTH (62.8 pmol/l and 72 pmol/l, respectively) suggesting pituitary or ectopic ACTH production. MRI of the pituitary region showed no pathological findings. Corticotropine releasing hormone (CRH) test did not show an ACTH and cortisol stimulation thus favoring an ectopic ACTH source. Due to the findings of the pituitary MRI scan and the CRH test we did not perform a venous petrosal sampling. Computerized tomography (CT) of the chest and abdomen, after use of oral and intravenous contrast enhancement, demonstrated no pulmonary or mediastinal mass, but a well-defined 3 cm to 3.5 cm left adrenal mass and a hypertrophic right adrenal gland, Figure 1. Positron emission tomography (PET) did not detect any significant increased metabolism.

Further evaluation revealed normal renin concentration and aldosterone levels. Due to recurrent hypertensive crisis, which were life-threatening, palpitations and excessive sweating, 24h urinary collection of catecholamines was performed three

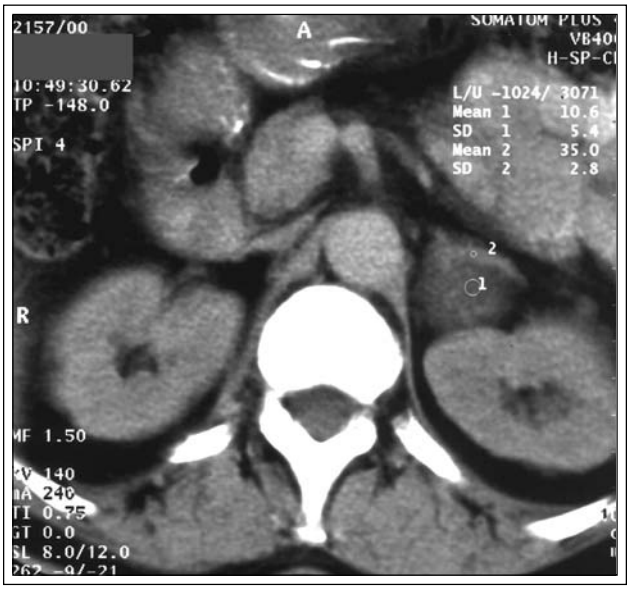

Figure 1. The CT scan showed a heterogeneous left adrenal mass and a hypertrophic right adrenal gland.

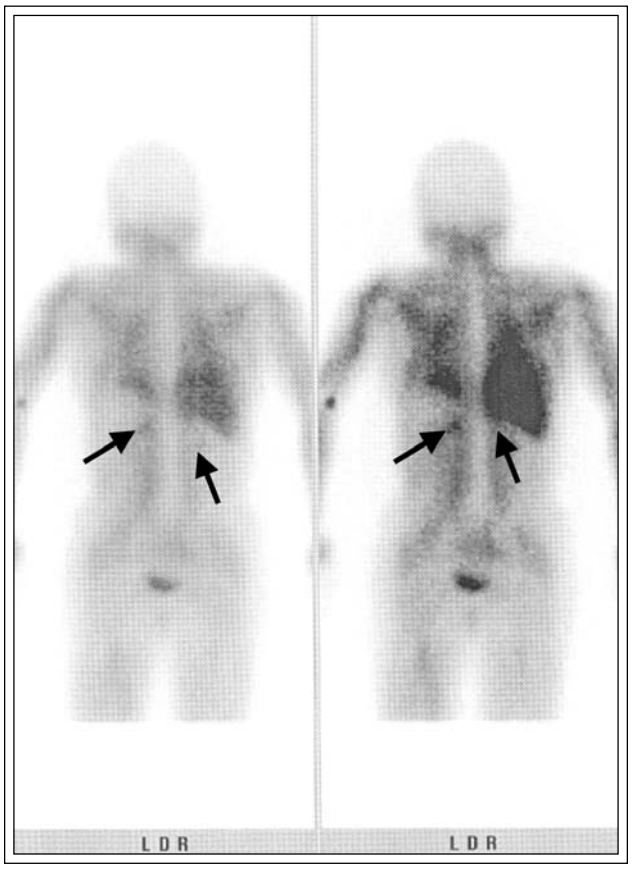

Figure 2. MIBG-scan detected relevant uptake in projection to both adrenals, although more in the left adrenal.

times and revealed markedly elevated adrenaline (up to 325 nmol/d; normal range 22 nmol/d-110 nmol/d) and noradrenalin (up to 3704 nmol/d; normal range 136 nmol/d-620 nmol/d) levels. For further evaluation a total body I^{131} metaiodobenzylguanidine (MIBG) scan was performed, which detected uptake in projection to both adrenals, Figure 2, although more in the left adrenal. Due to uptake in both adrenals, it was suggested to perform selective adrenal vein catheterization. The measurements for adrenaline, noradrenaline, cortisol and ACTH indicated a possible bilateral pheochromocytoma with pronounced ectopic ACTH secretion of the left adrenal.

During the stay on the intensive care unit, the patient received an α-adrenergic blockade with phenoxybenzamine (25 mg/day) for 10 days and subsequent β-adrenergic blockade (bisoprolol 10 mg/day) before operation. Hypercortisolism was treated with ketoconazol (600 mg/day) and total 24h urinary cortisol secretion dropped to 220 nmol/d-540 nmol/d (normal range 55 nmol/d-248 nmol/d). The patient underwent open bilateral adrenalectomy due to the

suspected bilateral pheochromocytomas. Pathological examination revealed pheochromocytoma of the left adrenal with immunostaining for ACTH. The right adrenal gland showed nodular cortical hyperplasia with no clear signs of pheochromocytoma. Genetic testing was performed and excluded mutations in the RET-protooncogene (multiple endocrine neoplasia type 2A), in the genes for succinat dehydrogenase B (SDH-B), SDH-C and SDH-D. After bilateral adrenalectomy ACTH was undetectable (< 1 pmol/l), serum cortisol was low (13 nmol/l), and catecholamine levels were significantly decreased (adrenaline < 5 nmol/d, noradrenalin 192 nmol/d). Blood pressure was within the normal range. After 6 years of follow-up, the patient is on glucocorticoid (prednisolone 5mg/d) and mineralocorticoid (fludrocortisone 0.05 mg/d) replacement therapy, and 24h urinary analysis shows no elevated catecholamines.

Discussion

Over 25% of ectopic Cushing´s syndromes are caused by small cell lung carcinomas, with other sources being islet cell tumors of the pancreas (16%), bronchial adenomas or carcinoids (11%), medullary carcinoma of the thyroid (8%), and thymic carcinoids (5%).[1,2] However, there are some reports of pheochromocytomas[3-13] and paragangliomas[14-16] causing ectopic ACTH syndrome. The diagnosis of Cushing´s syndrome from ectopic hormone production by a pheochromocytoma requires a high index of suspicion, repeated biochemical testing, imaging and often adrenal vein blood sampling. In our patient with a severe Cushing´s syndrome, the history of recurrent hypertensive crisis, extensive sweating and palpitations finally led the way to the diagnosis of ectopic ACTH-secreting pheochromocytoma. The performed hormone analysis and the MIBG-imaging confirmed the suspected diagnosis. The combination of the severe Cushing´s syndrome and hormone-producing pheochromocytoma was life-threatening for our patient, and required treatment on the intensive care unit. The MIBG scan suggested tracer uptake in both adrenals. For further clarification we performed a selective adrenal venous sampling. In general, it is quite controversial to perform adrenal vein sampling in pheochromocytoma, because of inducing hypertensive crisis during this manipulation. However, due to the inability of imaging and testing results to further clarify the origin of the elevated hormone production, we performed adrenal venous sampling. The results suggested bilateral

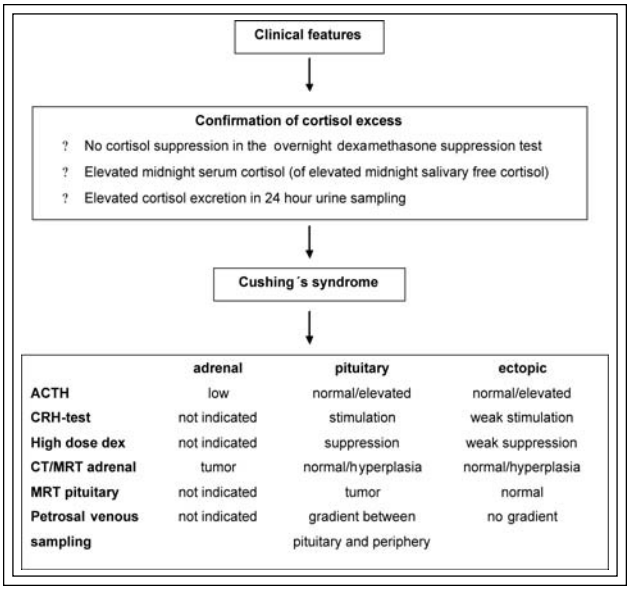

Figure 3. Flow-chart for the diagnosis of Cushing´s syndrome. Cushing´s syndrome is excluded if the morning cortisol after low dose dexamethasone test is below 50 nmol/l, or if midnight cortisol is below 50 nmol/l. Twenty-four hour urine sampling for free cortisol should be performed at least twice.

pheochromocytoma. During operation the surgeons investigated the right adrenal and confirmed suspicious nodular appearance of the gland and bilateral adrenalectomy was performed. However, histological diagnosis revealed pheochromocytoma only in the left adrenal indicating a discrepancy to endocrine testing and imaging. This case shows that the hormonal workup and imaging of an ectopic ACTH syndrome by pheochromocytoma is a challenge.

Repeat biochemical testing is often required because of atypical responses to testing in cases of Cushing´s syndrome from ectopic hormone production. In the case of Cushing´s syndrome a biochemical confirmation[17,18] should be performed followed by the determination of the cause of Cushing´s syndrome, Figure 3. A diagnostic challenge is to differentiate an occult ectopic ACTH-producing tumor from an ACTH-producing pituitary adenoma.

Investigations for pheochromocytoma should be started with at least two 24h-urine collections for urinary catecholamines (adrenaline, noradrenalin and dopamine) or for metanephrines (normetanephrine and metanephrine), Figure 4. Recent studies suggest that measurement of serum normetanephrine and metanephrine might have a high sensitivity and specificity.[19-21] Localizing the biochemical confirmed tumor is an important preoperative exercise, and often

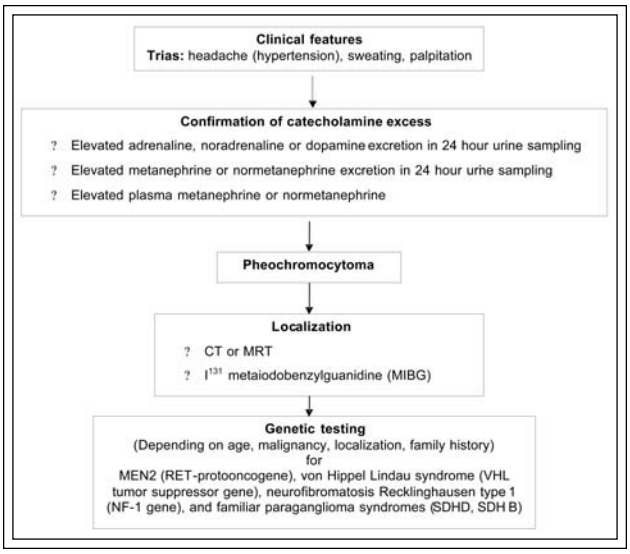

Figure 4. Flow-chart for the diagnosis of pheochromocytoma. Twenty-four hour urine sampling for catecholamines should be performed at least twice. MEN2 = multiple endocrine neoplasia type 2; SDHD = succinat dehydrogenases D.

difficult as indicated in the presented case. The preoperative treatment is essential: α-blockers, preferably phenoxybenzamine (dibenzyrane), should be given in increasing doses (up to 20 mg-80 mg per day) for at least 7-14 days. β-blockers should not used in first place, but as second-line treatment to ameliorate phenoxybenzamine induced tachycardia.[22] It is generally considered desirable to ensure that hypovolaemia has been reversed by α-blockade to significantly reduce the likelihood of hypotension after removal of the tumor. Occasionally, pheochromocytomas are malignant and even multiple and, therefore, follow-up is recommended for 10 years. Genetic testing depending on clinic, age and tumor localization is essential to identify mutation carriers of hereditary pheochromocytoma (up to 25% of sporadic cases) at an early stage of disease, Figure 4. □

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