Incidentally discovered pheochromocytoma and aldosterone-producing adenoma in the same adrenal gland

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ABSTRACT

Simultaneous occurrence of pheochromocytoma and aldosterone-producing adrenocortical tumor has been rarely reported in patients with symptoms or findings suggestive for both neoplasms. Herein, we report and discuss on a challenging case of synchronous pheochromocytoma and aldosterone-producing adenoma incidentally detected in the same adrenal gland and documented by biochemical studies and pathological examination.

Introduction

The simultaneous occurrence of pheochromocytoma and aldosterone-producing adrenal cortical adenoma is extremely rare.1-4 In such cases, the diagnostic pathway is often very challenging requiring a strict multidisciplinary cooperation and advanced lab and radiological tests and techniques. We present a case of pheochromocytoma and aldosterone-producing adenoma in the same adrenal gland, which were found incidentally and were documented by biochemical studies and pathological examination.

Case Report

A 65-year-old female was referred for the evaluation of bilateral adrenal masses, which had been found incidentally at abdominal ultrasonography performed for a clinical suspicion of gallbladder stones, and subsequently studied with magnetic resonance imaging at another institution (imaging unavailable).

She had been diagnosed with grade 2 hypertension at age 40, and her blood pressure values had become progressively resistant to antihypertensive therapy (ramipril 10 mg/day, amlodipine 10 mg/day and doxazosin 8 mg/day) in the last four years. During this period, routine blood chemistries revealed sporadically only mild hypokalemia (3 to 3.5 mEq/L) with normal renal function and blood glucose values. Therefore, spironolactone 50 mg/day was added to her drug therapy by general practitioner, with improvement in the control of her blood pressure values. She had family history of hypertension and coronary artery disease (both parents); neoplasms were not reported in any family members. Her past medical history included intolerance to statins prescribed for familial hypercholesterolemia. In the last five months, the patient had been complaining of epigastric and right flank pain besides mild anxiety and weakness; she denied palpitations, pallor, headache, sweating, tremor, leg cramps or polyuria. At physical examination, blood pressure was 162/94 mmHg and the heart rate was 78 bpm and no orthostatic pressure gradient was detected. She was still on treatment with ramipril, amlodipine, doxazosin and spironolactone. Blood cell count was within normal limits. Serum sodium was 143 mEq/L, potassium 3.7 mEq/L, chloride 101 mEq/L and bicarbonate 27.3
mEq/L, glucose 106 mg/dL, creatinine 0.6 mg/dL; urinalysis was unremarkable. Plasma renin activity (PRA) and serum aldosterone were 0.2 ng/mL/h and 19 ng/dL [normal range (n.r.) 0.7-15 ng/dL], respectively, with clearly elevated aldosterone/PRA ratio (95 ng/dL/ng/mL/h). Only moderately increased metanephrine and normetanephrine values were detected in 24-h urinary sample [521.5 mg/24 h (n.r. 74-297 mg/24 h) and 788.5 mg/24 h (n.r. 105-354 mg/24 h)], respectively. Morning (8 a.m.) plasma cortisol and adrenocorticotropic hormone concentrations were 102 ng/mL (n.r. 45-250 ng/mL) and 5 pg/mL (n.r. 5-50 pg/mL), respectively; while they were 45 ng/mL (n.r. 15-70 ng/mL) and <5 pg/mL (n.r. 5-50 pg/mL) at 8 p.m., indicating a preserved circadian rhythm of cortisol secretion. Chromogranin A was slightly increased at 210 ng/mL (n.r. 20-100 ng/mL). An abdominal computed tomography (CT) scan was performed for a clinical suspicion of primary aldosteronism, and revealed a 49x36 mm well-defined mass in the right adrenal gland, with low density (8 HU) and no contrast enhancement, suggestive for adenoma; another 20x18 mm well-defined mass with moderately higher density (19 HU) and contrast enhancement was present in the left adrenal gland (Figure 1A-C). A fluoro-deoxyglucose-positron emission tomography showed an area of very high uptake in the left adrenal gland [standardized uptake value (SUV) 38], whilst SUV was 2 in the right adrenal gland (Figure 1D). Therefore, after changing drug treatment to a combination of a calcium antagonist and an α-receptor blocker, bilateral adrenal vein sampling (AVS) was performed for selective aldosterone and cathecolamines determinations. Intraprocedural plasma cortisol measurement was performed to ascertain bilateral selectivity of AVS. The results revealed that the left adrenal gland was clearly the source of aldosterone and cathecolamines overproduction (Table 1). Consequently, a left sided adrenalectomy was performed under treatment with doxazosin (18 mg) and atenolol (50 mg).

At macroscopic examination, the surgical specimen showed a 2.5x2 cm reddish-brown tumor adjacent to a 1 cm yellowish, well defined nodule (Figure 2A). At histology, the reddish-brown tumor was composed by large sheets of highly pleomorphic cells, with bizarre hyperchromatic nuclei and abundant granular and basophilic cytoplasm. Occasional mitotic figures were present but no necrotic areas were seen.

Figure 1. Panels A-C show a large right adrenal mass, with low density, and a smaller left adrenal nodule with higher density and contrast enhancement. Panel D shows very high uptake in the left adrenal gland and fluoro-deoxyglucose-positron emission tomography.
The tumor was surrounded by a thin capsule that was focally infiltrated with invasion of the surrounding adipose tissue. At immunohistochemistry, the neoplastic cells were immunoreactive with chromogranin and synaptophysin (Figure 2B-E). Based on morphological and immunophenotypic data, a diagnosis of pheochromocytoma (the pheochromocytoma of the adrenal gland scaled score was 9), was made. The yellowish nodule was made up by monomorphous, bland cell with abundant microvescicular cytoplasm, arranged in

### Table 1. Biochemical results of adrenal venous sampling.

<table>
<thead>
<tr>
<th></th>
<th>Cortisol (ng/mL)</th>
<th>Aldosterone (pg/mL)</th>
<th>Adrenaline (pg/mL)</th>
<th>Noradrenaline (pg/mL)</th>
<th>SI*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left adrenal vein</td>
<td>3300</td>
<td>6000</td>
<td>4270</td>
<td>7938</td>
<td>5.70</td>
</tr>
<tr>
<td>Right adrenal vein</td>
<td>16,000</td>
<td>3000</td>
<td>714</td>
<td>1884</td>
<td>27.5</td>
</tr>
<tr>
<td>IVC</td>
<td>580</td>
<td>250</td>
<td>217</td>
<td>598</td>
<td>-</td>
</tr>
</tbody>
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SI, selectivity index; IVC, inferior vena cava. *SI = adrenal vein-to-IVC cortisol ratio. Lateralization index (for aldosterone secretion only) = 10.05 (cortisol-corrected aldosterone between dominant and nondominant side).

Figure 2. A) Gross section of the surgical sample showing a well-defined yellowish nodule (black arrow) close to a brownish tumor (*). The residual adrenal tissue is evident on the right (red arrow). B) At low power view, the distinction between pheochromocytoma on the left and cortical adenoma on the right is evident, with relatively well-defined margins. C) A high power view of the pheochromocytoma composed by pleomorphic elements, with bizarre nuclei. A mitotic figure is present in the center of the field (red arrow). D) A high power view of the cortical adenoma, made up by bland polygonal cells, with abundant clear cytoplasm (black arrow). E) The immunohistochemical stain with chromogranin is positive in pheochromocytoma and negative in cortical adenoma.
discrete nests mimicking the adrenal zona fasciculata. Non mitoses were noted. The lesion was then interpreted as a benign adrenal cortical adenoma adjacent to a pheochromocytoma (Figure 2C).

After surgery, the patient’s blood pressure was well controlled (136/82 mmHg) under pharmacological treatment with amlodipine 5 mg/day and ramipril 5 mg/day. At two months follow-up, PRA and aldosterone values were 1.15 ng/mL/h and 9.6 ng/dL, respectively. Complete normalization of 24-h urinary excretion of metanephrine (112.8 mg/24 h) and normetanephrine (279 mg/24 h) was also observed.

Discussion and Conclusions

The simultaneous occurrence of pheochromocytoma and aldosterone-producing adrenal cortical adenoma is extremely rare.1-4 Our case differs substantially from others reported in the literature, in as much as bilateral adrenal mass were detected incidentally on imaging studies, in a patient with very few symptoms or findings typical of secreting pheochromocytoma or hyperaldosteronism. In fact, only transient hypokalemia and gradual development of resistant hypertension oriented us towards an endocrine hypertensive disorder. In this setting, the very low PRA levels strongly pointed to primary aldosteronism; indeed, pheochromocytoma is more frequently regarded as the most potent stimulus for aldosterone secretion. Therefore, these Authors hypothesized that UII produced in larger extent in pheochromocytoma cells may stimulate aldosterone secretion modulating the expression of the CYP11B2 gene in the zona glomerulosa of the adrenal cortex.

We cannot establish whether the simultaneous finding of hyperaldosteronism and adrenocortical adenoma in our patient could be attributed to a prolonged stimulation by UII or other substances produced by the pheochromocytoma. Indeed, hyper-reninism may have resulted from circulating catecholamines stimulating β-adrenergic receptors in the JC cells, thus increasing serum levels of angiotensin II and finally of aldosterone. However, in our patient secondary aldosteronism was ruled out based on suppressed PRA levels together with an elevated level of plasma aldosterone. We can also speculate that the large mass with low density and no contrast enhancement, detected by the CT scan in the right adrenal gland, may have been expression of the continuum across hyperplasia to neoplasia, possibly induced by prolonged stimulation by a substance produced by the contralateral pheochromocytoma. Moreover, the right adrenal large mass will require a strict follow-up by functional and imaging tests.

In conclusion, during the work-up examination of a patient with suspected pheochromocytoma and history or concomitant hypokalemia a concomitant hyperaldosteronism should be included by the physicians in the differential diagnosis.

References