Primary Aldosteronism due to Adrenal Carcinomas

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Summary. In the present study two patients with aldosterone-producing adrenal carcinomas are reported. The clinical features were characterized by hypertension and severe hypokalemia with muscular weakness, flaccid paralysis of arms and legs, diarrhea and polyuria. In both cases excessively high plasma aldosterone levels and suppressed plasma renin activity were found. In contrast to most other cases with aldosterone-secreting tumours plasma cortisol, urinary free cortisol excretion, 17-hydroxy- and 17-ketosteroids were in the normal range. There was no clinical evidence of oversecretion of sex hormones. After adrenalectomy blood pressure and serum potassium normalized and the clinical symptoms disappeared. Plasma aldosterone and urinary aldosterone secretion returned to normal, while plasma renin activity remained low. Three and a half and 6 months later primary aldosteronism and the associated clinical symptoms reappeared due to hormonally active metastases. After introducing the antitumour drug o,p'-DDD in patient 1 aldosterone secretion normalized and the clinical status of the patient markedly improved. However, 10 months after diagnosis the patient died due to a haemorrhage from a liver metastasis. In patient 2 tumour-invaded regional lymph nodes were surgically removed with only minor changes in the hormone pattern.

Key words: Adrenal carcinomas – Aldosterone secretion – Hypokalemic alkalosis – Operation – Chemotherapy with o,p'-DDD

Introduction

Primary aldosteronism is usually caused by a unilateral adenoma or bilateral hyperplasia of the adrenal cortex [4, 9, 10, 15, 49]. Malignant aldosterone secreting tumours have rarely been reported [1, 12, 16, 17, 41]. In most patients concomitant oversecretion of other adrenal hormones such as cortisol, desoxycorticosterone, corticosterone androgens or oestrogens was present [2, 5, 8, 12, 42]. This paper reports the clinical course, diagnostic procedures and therapy of two cases with a malignant tumour of the adrenal cortex and hyperaldosteronism without concomitant hypersecretion of cortisol, 17-hydroxysteroids and 17-ketosteroids.

Methods

In the two patients plasma aldosterone, cortisol and urinary excretion rates of aldosterone, free cortisol, 17-hydroxysteroids and 17-ketosteroids were determined mostly by different biochemical methods, because they were seen in two different clinics.

Plasma renin activity was determined by radioimmunoassay [19, 39]. Normal values were 0.2-3.0 ng/ml·3 h in supine and < 10 ng/ml·3 h (case 1) and < 1.6 ng/ml·1 h (case 2) after stimulation by orthostasis.

Plasma aldosterone and urinary excretion rates of aldosterone were measured by radioimmunoassay [38, 47, 48]. Normal values of plasma aldosterone were 20–120 pg/ml in supine position and after 2 h standing ≤ 500 pg/ml (case 1) and ≤ 30 ng/dl (case 2). The normal ranges of urinary aldosterone excretion rates were 2–13 ug/24 h (case 1) and ≤ 30 ug/24 h (case 2).

Measurement of plasma cortisol (normal values 2–25 μg/100 ml) and 24 h urinary excretion rate of free cortisol (normal values 20–120 μg/24 h) were performed using the protein binding method [31] and a commercially available kit ("gamma coat" chemical assays) in case 2. 17-Hydroxysteroids were measured according to Peterson et al. [33] (normal values 3–13 mg/24 h). 17-Ketosteroids were measured according to Peterson and Pierce [34] (normal values 5–15 mg/24 h) in case 1. In the second patient a chromatographic photometric test (ketochrome TM Bio-Rad laboratories) was used (normal range: < 30 mg/24 h).

Results in Two Patients

Clinical Feature

The two patients described here were a 58-year-old woman (case 1) and a 43-year-old man (case 2), both presenting hyper-
Table 1. Clinical and routine laboratory data in two patients with aldosterone-producing adrenal carcinoma at admission to the hospital

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>58 years</td>
</tr>
<tr>
<td>Sex</td>
<td>female</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>180–200/100–80 mmHg</td>
</tr>
<tr>
<td>Clinical symptoms</td>
<td>muscular weakness, chronic diarrhoea, forearm oedema, polydipsia, nycturia, weight loss (2 kg)</td>
</tr>
<tr>
<td>Plasma potassium</td>
<td>1.4–3.4 mEq/l</td>
</tr>
<tr>
<td>Plasma sodium</td>
<td>150 mEq/l</td>
</tr>
</tbody>
</table>

Laboratory Data

Chest X-rays were normal, whereas the ECG showed typical features of hypokalemia in both cases. Renal function was normal. In both patients hypokalemia was severe. The values ranged between 1.4 and 3.4 mEq/l, and 1.7 and 2.5 mEq/l, respectively. In spite of severe hypokalemia urinary potassium excretion was 113 mEq/24 h and > 50 mEq/24 h. Urinary analysis revealed a pH value of 5 and > 7, respectively. In case 2 inconstant proteinuria was found. Red blood cells sedimentation rate was 40 mm/h in case 1, whereas the second case showed normal values. In case 1 the enzyme lactate dehydrogenase was constantly elevated between 371 and 465 U/l (normal range: ≤195 U/l).

Hormone Analyses

Plasma Renin Activity Values and Plasma Aldosterone. Hormone analyses revealed the typical feature of primary aldosteronism with excessive plasma aldosterone and very low plasma renin activity (PRA) values. Plasma aldosterone and urinary aldosterone excretion during an observation period of 15 and 11 months are shown in Fig. 1. In case 1 plasma aldosterone was 680 and 840 pg/ml (normal range: 20–120 pg/ml) supine and 960–1,480 pg/ml in the upright position, while PRA was undetectably low (≤0.2 ng/ml·3 h) and not responsive to orthostatic stimulation. The second case showed plasma aldosterone values of 124 ng/dl–246 ng/dl (normal value: ≤30 ng/dl) and PRA of 0.04–0.15 ng/ml·h⁻¹. The orthostatic test led to a small increment of plasma aldosterone from 136 ng/dl to 166 ng/dl after 2 h and 165 ng/dl after 4 h of standing. Urinary aldosterone excretion was markedly elevated to 163–346 μg/24 h in this patient (normal value: ≤30 μg/24 h).

Glucocorticoid Hormones. Plasma cortisol concentrations were 14 and 18 μg/dl at 8.00 a.m. and 7.8 and 13.2 μg/dl at 1.00 p.m. (normal range: 2–25 μg/dl) in cases 1 and 2, respectively. Urinary free cortisol excretion rates were 82±14 μg/24 h and 53 μg/24 h (normal range: 20–120 μg/24 h). 17-Ketosteroids and 17-hydroxycorticoids were in the normal range in both patients.

Radiological Investigations

131-I-Cholesterol scintigraphy showed no uptake of radioactivity in adrenal glands in both cases. In the first patient intravenous urography indicated an abnormal position of the left kidney apparently due to a suprarenal mass. Renal artery angiography suggested a large adrenal tumour (Fig. 2a). Arteriography of the left adrenal artery revealed an adrenal tumour of considerable size with signs of malignancy (Fig. 2b). In case 2 the presence of a well delimited mass in the upper pole of the left kidney was diagnosed by computerized tomography.

Therapy

Both cases were treated first with spironolactone and potassium substitution or ß-methyldopa before surgery. Clinical symptoms improved and blood pressure and serum potassium levels could be normalized. After diagnosis surgical exploration of the left adrenal gland was performed in both cases. In case 1 a fist-sized tumour was found, closely connected with the posterior part of the diaphragm and the upper third of the left kidney. Although the macroscopic aspect of the tumour indicated malignancy there was no evidence of regional metastases. In case 2 surgical exploration revealed the presence of a well encapsulated tumour the size of an orange without any evidence of local metastases. In both patients left adrenalectomy was performed.

Microscopic Examination

Microscopic examination presented adrenal carcinomas. The microscopic aspects are shown in Fig. 3. The tumour cells were arranged in an irregular trabecular fashion, resembling zona glomerulosa cells of a normal adrenal cortex (Fig. 3a). In the high power view nuclear polymorphism and mitoses were seen (Fig. 3b). The fibrous capsule and capsular veins were invaded by neoplastic cell lines (Fig. 3c). A regional lymph node, removed during the second operation of case 2, showed marked tumour cell invasion. The morphological aspect was similar to the original adrenal tumour (Fig. 3d).

Follow-Up

Clinical symptoms such as muscular weakness, flaccid paralysis and polyuria disappeared postoperatively; blood pressure, plasma potassium and plasma aldosterone levels became normal, whereas PRA remained very low. The follow-up of plasma aldosterone and urinary aldosterone secretion is shown in Fig. 1. Plasma aldosterone in case 1 was 20 and 80 pg/ml (Fig. 1a). PRA was again undetectably low (≤0.2 ng/ml·3 h). Plasma cortisol was 5.7 and 11.0 μg/100 ml, 17-hydroxycorticoids 10.5 μg/24 h, 17-ketosteroids 8.0 μg/24 h and free cortisol 73.8 μg/24 h. In the second patient plasma aldosterone was 25.3 and 21.1 ng/dl, 1 and 3 months, respectively, after surgery. Urinary aldosterone secretion normalized to 26.0 and 15.5 μg/24 h. PRA remained very low (0.08 and 0.67 μg/ml·1 h, respectively). In both patients the typical features of primary aldosteronism reappeared 3½ and 6 months after adrenalectomy (Fig. 1).