Case Report

Despite low plasma renin ACE inhibitor treatment causes recovery from acute renal failure in a patient with malignant hypertension

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Introduction

The pathogenesis of acute renal failure in malignant hypertension is incompletely understood. However, the activated renin–angiotensin system appears to be an important factor [7]. Since angiotensin II has potent vasoconstrictive properties, pharmacological inhibition of angiotensin II production appears rational for the treatment of acute renal failure in patients with malignant hypertension. In fact, a few case reports document reversal of acute deterioration of renal function in malignant hypertension following the treatment with angiotensin converting enzyme inhibitors [2–5]. Peripheral blood renin levels in most of these cases were markedly elevated.

We present herein a case of acute renal failure secondary to malignant hypertension. Treatment with angiotensin converting enzyme inhibitors reversed acute renal failure despite low plasma renin concentration.

Case report

A 47-year-old woman with at least a 5 year history of hypertension was referred for the treatment of severe hypertension on December 28, 1995. She had taken no regular medication for hypertension, and urinalysis had not been performed until admission. She had been well until 2 days earlier, when she experienced blurred vision, severe headache and nausea.

On admission, the blood pressure was 234/176 mmHg, and the pulse rate 59/min and regular. Funduscopic findings disclosed exudate retinopathy with papilledema, suggestive of malignant hypertension. A grade 3/6 systolic ejection murmur and coarse crackles were heard on auscultation of the chest. No bruit was audible in the abdomen.

The patient was anuric. The urine tested ++ for protein, and the sediment contained 15 red cells per high-power field. The urea nitrogen was 63 mg/dl and creatinine 5.8 mg/dl. The sodium was 136 mEq/l, potassium 3.2 mEq/l, chloride 95 mEq/l. A specimen of arterial blood, drawn while the patient was breathing room air, revealed a partial arterial pressure of oxygen (PaO₂) of 62 mmHg, pH 7.43, partial arterial pressure of carbon dioxide (PaCO₂) 41.6 mmHg, and bicarbonate 27.5 mmol/l. The haematocrit was 35.5%, and the white blood cell count was 6200 with a normal differential. The platelet count was 149 000. Fragmented red cells were slightly increased to 9% of red blood cells on the blood smear. Coagulation tests revealed increased fibrinogen/fibrin degradation product (FDP) ß-dimer (9.8 µg/l) with normal prothrombin time (PT) and activated partial thromboplastin time (aPTT). The blood chemistries were within normal range, except that lactate dehydrogenase (LDH) was 533 U (normal range 100–190 U) and serum haptoglobin was undetectable. The urinary osmolality was 343 mOsm/l, and the fractional excretion of sodium was 0.8%. Anti-nuclear antibody was not detectable, and measurement of anti-neutrophil cytoplasmic antibody was not performed.

Endocrinological tests were performed on admission just after one dose of treatment with antihypertensive agents. Plasma renin and aldosterone concentrations were 8 pg/ml (normal range 10–22 pg/ml) and 12.9 ng/dl (normal range 4.7–13.1 ng/dl), respectively. Plasma endothelin-1 concentration was high (3.9 pg/ml; normal range 1.0–2.0 pg/ml), as measured by radioimmunoassay using endothelin-1-specific antibody. Both plasma catecholamines and serum cortisol concentrations were within normal range.

Both kidneys were not atrophic on ultrasonographic examination. X-ray of the chest disclosed severe cardiomegaly with a cardiothoracic ratio of 71% and bilat-
Fig. 1. Serial changes of serum creatinine concentrations, plasma renin concentrations, blood pressure, and urine volume during hospitalization. The shaded area shows normal range of plasma renin concentration.
eral pulmonary congestion without pleural effusion. The central venous pressure was elevated.

The clinical course and the results of the serial measurements of plasma renin and aldosterone concentration in the present case are shown in Figure 1 and Table 1, respectively. One dose of the treatment with nifedipine (20 mg), atenolol (25 mg), and doxazosin mesilate (1 mg) reduced her blood pressure to 124/96 mmHg resulting in transient loss of her consciousness, and all antihypertensive agents were discontinued. These antihypertensive agents were used only once (data not shown). Hypoxia secondary to pulmonary congestion was improved by haemodialysis therapy, which was started on December 29. On January 4, the administration of 12.5 mg of captopril daily was started, and the dose was gradually increased to a maximum of 37.5 mg daily. The blood pressure was maintained ~130/80 mmHg. Since eosinophilia (15% of white blood cell count) developed, 1 mg daily of cilazapril was substituted for captopril on January 18 (Figure 1). Since the administration of cilazapril did not increase plasma renin concentration (6 pg/ml) despite suppressed plasma aldosterone concentration (4.2 ng/dl) as shown in Table 1 (indicating insufficient suppression of angiotensin converting enzyme activity) 2 mg daily of temocapril was started on February 6. The urine volume was gradually increased, and renal dysfunction also gradually recovered, leading to the discontinuation of haemodialysis therapy. Although plasma renin concentration was not elevated during the treatment with captopril, cilazapril alone or cilazapril combined with 2 mg of temocapril, the treatment with 4 mg of temocapril increased plasma renin concentration to 58 pg/ml on March 14 (Figure 1, Table 1).

Open renal biopsy samples disclosed global sclerosis in eight of 80 glomeruli. The remaining glomeruli revealed ischaemic changes and capillary wall wrinkling with mild mesangial expansion. Severe narrowing of the lumina of arterioles was observed. Most small and interlobular arteries exhibited considerable medial hypertrophy without leukocytic infiltration, in addition to markedly layered internal elastic lamina. Immunofluorescence study revealed negative staining for immunoglobulins and complements. On electronmicroscopic study, slight subendothelial widening with amorphous materials as well as partial foot process retraction was observed in some glomeruli. These pathological findings were compatible with malignant hypertension [12].

The patient was discharged on April 1. At that time, serum creatinine was 2.4 mg/dl, and LDH and haptoglobin in serum were normalized. Plasma renin and aldosterone concentrations were 29 pg/ml and 21.3 ng/dl, respectively. Neither cardiomegaly nor pulmonary congestion was observed on X-ray of the chest.

**Table 1. Results of serial measurements of plasma renin concentration and plasma aldosterone concentration**

<table>
<thead>
<tr>
<th>Date</th>
<th>29 December</th>
<th>18 January</th>
<th>5 February</th>
<th>19 February</th>
<th>14 March</th>
<th>1 April</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma renin concentration (normal range: 10–22 pg/ml)</td>
<td>8</td>
<td>13</td>
<td>6</td>
<td>18</td>
<td>58</td>
<td>29</td>
</tr>
<tr>
<td>Plasma aldosterone concentration (normal range: 4.7–13.1 ng/dl)</td>
<td>12.9</td>
<td>8.1</td>
<td>4.2</td>
<td>7.4</td>
<td>14.5</td>
<td>21.3</td>
</tr>
</tbody>
</table>

**Discussion**

The low plasma renin concentration in this case is not inconsistent with the diagnosis of malignant hypertension. Malignant hypertension with very low plasma renin has been previously reported [6,7]. In addition, Case et al. [8] have also shown that plasma renin activity was suppressed in two of 10 patients with malignant hypertension. In this case, plasma renin concentration measured on admission just after one dose of treatment with nifedipine, atenolol, and doxazosin mesilate was low, and remained low thereafter. Hypervolaemic state on admission judged by increased central venous pressure and severe cardiomegaly on X-ray of the chest might cause suppressed plasma renin concentration.

It is very interesting that the treatment with cilazapril and temocapril also induced the recovery from acute renal failure in this case with low-renin malignant hypertension. To our knowledge, there is no such a previous report. The reason why these angiotensin converting enzyme inhibitors were effective under the conditions of low plasma renin concentration is unclear. However, the activated intrarenal angiotensin II might play an important role in the development of acute renal failure secondary to malignant hypertension, and the angiotensin converting enzyme inhibitors might induce the recovery from acute renal failure through the suppression of intrarenal angiotensin II production. Circulating renin levels may not necessarily reflect local renin–angiotensin system activity [9]. In fact, the findings in this case that hypokalaemia, metabolic alkalosis, and elevated plasma aldosterone concentration relative to overhydration was observed on admission might be suggestive of the activation of angiotensin and aldosterone system.

Endothelin may also play an important role in the pathogenesis of acute renal failure secondary to malignant hypertension. In this case, plasma endothelin level was markedly elevated. Yoshida et al. [1] have demonstrated extremely high plasma endothelin-1 concentrations at the time of admission in three cases of malignant hypertension, and that the plasma level of...
endothelin-1 decreased in parallel with the decrease in serum creatinine concentration in all of these cases. It has been demonstrated in humans [10] and in experimental studies [11,12] that angiotensin converting enzyme inhibitors suppress both the vasoconstrictive effect of endothelin on the peripheral and renal vascular systems and the secretion of endothelin from vascular endothelial cells. Thus, it is also possible that the recovery from acute renal failure secondary to malignant hypertension by angiotensin converting enzyme inhibitors in this case might result from the suppression of the enhanced secretion or action of endothelin.

These findings in the present case suggest that the treatment with angiotensin converting enzyme inhibitors may be effective in inducing the recovery from acute renal failure in a patient with malignant hypertension, even though plasma renin level was very low.

References


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