Pheochromocytoma in a Long-Term Hemodialysis Patient, Discovered as an Adrenal Incidentaloma

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A case of pheochromocytoma was discovered incidentally during long-term hemodialysis for chronic renal failure due to acquired cystic kidney disease. A 52-year-old male patient was examined for weight loss of 3 kg during over a period of 3 months. Abdominal computed tomography (CT) revealed a left adrenal mass (3.0 cm in size). Plasma adrenaline and noradrenaline were increased to 521 pg/ml and 1,341 pg/ml, respectively, and the metoclopramide provocative test was positive. Further, in the scintiscan using 123I-metaiodobenzylguanidine (MIBG), an accumulation of the radionuclide in the left adrenal tumor region was confirmed. The patient is currently under observation and conservative treatment due to the possible occurrence of arterial hypotension after resection of the tumor, and to lesser possibility of the malignancy.

(Key words: metoclopramide test, 123I-metaiodobenzylguanidine (MIBG))

Introduction

Pheochromocytoma is one of the three major endocrine causes of hypertension, together with primary aldosteronism and Cushing’s syndrome. With the rapid advances in imaging techniques such as computed tomography (CT) scanning, magnetic resonance imaging (MRI), radionuclide scanning and arteriography, and their wide use for the detection of the endocrine tumors, the number of case reports of pheochromocytoma in Japan (1, 2) has increased in recent years to 80 to 90 cases per year, compared with an average of 40 cases per year in the 2 decades before the early 1980s.

Moreover, it is noteworthy that from 4 to 27% of the operated cases among the adrenal masses incidentally discovered (adrenal incidentaloma), are pheochromocytomas (3). Therefore, the measurement of catecholamine and its metabolites is indispensable to determine whether the incidentalomas are hormonally functional or not, even when the patient has no symptoms or signs characteristic of pheochromocytoma.

Recently we encountered a patient on long-term hemodialysis due to acquired cystic kidney disease in whom a pheochromocytoma was discovered incidentally. Because this is an extremely rare case, we wish to present our case and emphasize the importance of screening of endocrinopathy by means of hormone assays combined with imaging techniques in patients on long-term hemodialysis.

Case Report

A 52-year-old male patient with acquired polycystic kidney disease which developed secondary to glomerulonephritis, on long-term hemodialysis (3 times a week) for the past 20 years, was examined for weight loss of 3 kg during the 3 previous months. During the years of hemodialysis his systolic and diastolic blood pressure ranged from 160–170/70–90 mmHg and 120–130/60–80 mmHg before and after dialysis, respectively, without use of any antihypertensive drug. No other relevant symptoms or signs suggestive of pheochromocytoma were observed. The routine laboratory tests are listed in Table 1. No evidence of overt diabetes was noted. Fasting blood sugar level was 102 mg/dl and hemoglobin A1c was 5.6%. The examinations of gastrointestinal tract revealed no abnormal findings to explain the cause of the recent weight loss.

CT scan of the abdomen which was done to exclude occult malignant neoplasm, revealed a left adrenal mass (size, 3.0 cm) with homogenous radiodensity (Fig. 1). Plasma adrenaline (AD), noradrenaline (NA) and dopamine (DA) were found to be increased to 521 pg/ml (normal: <100 pg/ml), 1,341 pg/ml (normal: 100–450 pg/ml) and 58 pg/ml (normal: <20 pg/ml), respectively. Further the metoclopramide provocative test in-
Table 1. Laboratory Data

<table>
<thead>
<tr>
<th>Blood</th>
<th>Lipids</th>
<th>Serological</th>
<th>Electrolytes</th>
<th>Catecholamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC</td>
<td>Total cholesterol</td>
<td>C-reactive protein</td>
<td>Na</td>
<td>Cubital vein plasma</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Triglyceride</td>
<td>HBs-antigen (+)</td>
<td>K</td>
<td>3,506(^*1) 4,662(^*2)</td>
</tr>
<tr>
<td>Hematocrit</td>
<td></td>
<td>HCV-antibody (-)</td>
<td>Cl</td>
<td>Adrenaline 521</td>
</tr>
<tr>
<td>WBC</td>
<td></td>
<td>TPHA (-)</td>
<td>Ca</td>
<td>Noradrenaline 1,341</td>
</tr>
<tr>
<td>Platelets</td>
<td></td>
<td></td>
<td>P</td>
<td>Dopamine 58</td>
</tr>
</tbody>
</table>

Liver Function:
- Total protein: 7.1 g/dl
- Total bilirubin: 0.2 mg/dl
- AST/ALT: 34/26 IU/
- LDH: 331 U (Wroblewski)
- ALP: 3.6 U (Bessey-Lowry)
- Cholinesterase: 320 IU/
- γ-GTP: 26 μmol/L

Endocrinological:
- Plasma ACTH: 29 pg/ml
- Plasma Cortisol: 9.4 μg/dl
- Plasma Renin Activity: 0.3 ng/ml/h
- Plasma Aldosterone: 640 pg/ml
- Plasma ANP: 51 pg/ml (before HD)
- Plasma ANP: 27 pg/ml (after HD)

Electrolytes:
- Na: 134 mEq/l
- K: 6.3 mEq/l
- Cl: 102 mEq/l
- Ca: 10.2 mg/dl
- P: 5.4 mg/dl
- Cr: 12.6 mg/dl
- BUN: 81 mg/dl
- Uric acid: 8.3 mg/dl

Catecholamine:
- Adrenaline plasma: 3,506\(^*1\) 4,662\(^*2\)
- Noradrenaline plasma: 2,708 4,088
- Dopamine plasma: 58 54 50
- Plasma ANP: 51 pg/ml (before HD)
- Plasma ANP: 27 pg/ml (after HD)

#1 distal
#2 proximal


Figure 1. Abdominal computed tomographic scan. The arrow shows a pheochromocytoma located in the suprarenal region and the right kidney is delineated as a polycystic mass (acquired cystic kidney disease).

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Produced an elevation of blood pressure from 120/60 mmHg in the basal to 180/82 mmHg 6 minutes after intravenous injection of 5 mg of metoclopramide with an increase of plasma catecholamines, that is, from the basal value of 521 pg/ml to 959 pg/ml for AD and 790 pg/ml to 5,691 pg/ml for NA at the maximum values respectively. According to Yamaya et al., the metoclopramide test is judged as positive in a case when the value of increment (maximum value after injection of metoclopramide minus basal value) exceeds the mean value plus 4-fold the standard deviation (SD) of the non-pheochromocytoma group (4). In the non-pheochromocytoma group, the mean value plus 4 SD is 37 mmHg for systolic blood pressure, 181 pg/ml for AD and 226 pg/ml for NA. However, they said that 25 mmHg (mean plus 3 SD) for systolic blood pressure is a high enough value for diagnosis. In the present case, in scintiscan using \(^{123}\)I-MIBG, an accumulation of the radionuclide in the left adrenal tumor region was confirmed (Fig. 2). The plasma catecholamine concentration in the left adrenal venous plasma was remarkably high (Table 1). Analyses of the RET proto-oncogene revealed no mutation in exons 10, 11 and 16.
Discussion

The occurrence of pheochromocytoma in patients on long-term hemodialysis has been considered to be extremely rare (5–16) (Table 2). In general, patients with end-stage renal failure (ESRF) are often complicated with hypertension which may sometimes fluctuate and transiently rise after hemodialysis. Therefore, it is important to be cautious in the evaluation of the signs and symptoms suggestive of pheochromocytoma and to analyze for an excessive secretion of catecholamine. Recently, Bravo (17) emphasized that the determination of the combination of resting plasma catecholamines (adrenaline plus noradrenaline) and total urinary metanephrines is recommendable as an appropriate biochemical test for the diagnosis of pheochromocytoma. Regarding the demonstration of excessive secretion of catecholamines, one problem is that patients with ESRF are anuric and therefore we can only rely upon the assays of plasma adrenaline and noradrenaline. In patients on long-term hemodialysis, plasma noradrenaline has been reported to be almost consistently elevated. Stumvoll et al (15) described that in a patient on long-term hemodialysis a plasma noradrenaline concentration of greater than a 3-fold elevation compared with normal controls, should raise the suspicion of pheochromocytoma. In the present case, the plasma noradrenaline concentration was approximately 3-fold the upper value of normal controls. Moreover, the provocation test by metoclopramide gave a positive result.

The diagnostic problem in a case in which the determination of plasma catecholamine concentration gives an equivocal rise, not exceeding a 3-fold value, however, can be solved by localizing techniques for pheochromocytoma, in particular, \(^{131}\)I-metaiodobenzylguanidine (MIBG) scanning which has a specificity of 100% (17). In the present case, an adrenal mass was incidentally discovered by CT which was carried out as a series of examinations to explore the possible causes for weight loss. Then the tumor was found to be functional by the marked elevation of plasma catecholamine and also by \(^{123}\)I-MIBG scanning. Most cases of pheochromocytoma complicated with chronic renal failure on long-term hemodialysis have more or less episodic symptoms of headache, tachycardia, sweating, or transition of hypertension into a malignant phase. The chief complaint in the present case was weight loss which accounted for 36% of clinical manifestations in the previous analysis of 176 cases of pheochromocytoma in Japan from 1983 through 1986 (1). Priority of evaluation, therefore, should be given to the biochemical testing of catecholamines and image techniques by CT or MRI, and then \(^{123}\)I-MIBG scintigraphy should be employed to explore the suprarenal or abdominal masses even in patients with no cardinal manifestations of pheochromocytoma.

Regarding the treatment, resection of the tumor by operation is usually considered the first choice if possible. In fact, numerous previously reported cases of pheochromocytoma with ESRF on hemodialysis therapy were operated successfully (5–10, 12–16). However, the present case had little complaint except for weight loss. The systolic blood pressure usually decreased to 120–130 mmHg, sometimes below 100 mmHg, at the end of hemodialysis therapy, so that the extra-renal organ damage was not so severe (ocular fundus: Scheie H\(^+\), cardiothoracic ratio: 50–52%). Therefore we were rather concerned about the possible occurrence of arterial hypotension after resection of the tumor.

It is well known that many patients on long-term hemodialysis treatment suffer from hypotension. Daul et al (18) reported that increased plasma noradrenaline levels with longer duration of hemodialysis may induce \(\alpha\)-adrenoceptor down-regulation and the resulting reduction in \(\alpha\)-adrenoceptor responsiveness to \(\alpha\)-adrenergic stimuli might be an important cause of arterial hypotension in patients on long-term hemodialysis treatment. Because of the lengthy hemodialysis treatment reaching 20 years in the present case, it is more likely that the patient may suffer from difficult-to-control hypotension during hemodialysis therapy if the tumor is resected. Also, for low possibility of a malignant tumor, at present we are following-up the patient conservatively. Six months after the diagnosis, his body weight did not change at all and abdominal CT revealed no enlargement of the tumor size. However, if the tumor size increases and the blood pressure becomes higher, surgical operation should be considered.

References

Table 2. Review of Reported Cases of Pheochromocytoma Associated with Chronic Renal Failure on Long-Term Hemodialysis

<table>
<thead>
<tr>
<th>Ref. no.</th>
<th>Age</th>
<th>Sex</th>
<th>Symptoms</th>
<th>Imaging technique</th>
<th>NA (pg/ml)</th>
<th>A (pg/ml)</th>
<th>Operation</th>
<th>Localization of the tumor, size</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>54</td>
<td>F</td>
<td>Marked changes in blood pressure during HD</td>
<td>CT</td>
<td>5,760</td>
<td>376</td>
<td>yes</td>
<td>L</td>
</tr>
<tr>
<td>6</td>
<td>41</td>
<td>F</td>
<td>Palpitation, rush</td>
<td>CT</td>
<td>1,420</td>
<td>132</td>
<td>yes</td>
<td>R 5.0x4.0 cm</td>
</tr>
<tr>
<td>7</td>
<td>25</td>
<td>M</td>
<td>Headache, diaphoresis</td>
<td>CT</td>
<td>1,985</td>
<td>158</td>
<td>yes</td>
<td>R 4.0 cm</td>
</tr>
<tr>
<td>8</td>
<td>41</td>
<td>M</td>
<td>Palpitation, headache, blood pressure 146/92 mmHg</td>
<td>CT</td>
<td>1,100</td>
<td>2,910</td>
<td>yes</td>
<td>R 5.0x5.0x3.5 cm</td>
</tr>
<tr>
<td>9</td>
<td>45</td>
<td>F</td>
<td>Headache, nausea, episodic hypertension after HD</td>
<td>CT</td>
<td>420</td>
<td>800</td>
<td>yes</td>
<td>L 4.0 cm</td>
</tr>
<tr>
<td>10</td>
<td>33</td>
<td>F</td>
<td>Postmicturition hypertension</td>
<td>CT</td>
<td>520</td>
<td>40</td>
<td>yes</td>
<td>Bladder 4.5x4.2 cm (52g)</td>
</tr>
<tr>
<td>11</td>
<td>50</td>
<td>F</td>
<td>Episodic hypertension after HD (210/? mmHg)</td>
<td>CT</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>L 1.5 cm</td>
</tr>
<tr>
<td>12</td>
<td>46</td>
<td>F</td>
<td>Persistent hypertension on HD -&gt; malignant hypertension, blood pressure instability 120/80-230/120 mmHg</td>
<td>CT</td>
<td>WNL</td>
<td>WNL</td>
<td>yes</td>
<td>L (80g)</td>
</tr>
<tr>
<td>13</td>
<td>25</td>
<td>F</td>
<td>Epileptic seizure, high blood pressure (190/130 mmHg)</td>
<td>CT</td>
<td>8,002</td>
<td>304</td>
<td>yes</td>
<td>R 3.0 cm</td>
</tr>
<tr>
<td>14</td>
<td>50</td>
<td>F</td>
<td>Labile hypertension, sweating</td>
<td>CT</td>
<td>?</td>
<td>?</td>
<td>yes</td>
<td>R 6.0x4.0x3.0 cm (58g)</td>
</tr>
<tr>
<td>15</td>
<td>37</td>
<td>M</td>
<td>Paroxysmal hypertension with headache – polycystic kidney –</td>
<td>131I-MIBG</td>
<td>9,400</td>
<td>1,525</td>
<td>yes</td>
<td>L 3.0 cm (on CT)</td>
</tr>
<tr>
<td>16</td>
<td>53</td>
<td>M</td>
<td>Palpitation, hypertension on HD</td>
<td>131I-MIBG</td>
<td>?</td>
<td>?</td>
<td>yes</td>
<td>L 2.0 cm</td>
</tr>
<tr>
<td>present</td>
<td>52</td>
<td>M</td>
<td>Weight loss, episodic hypertension after HD</td>
<td>123I-MIBG</td>
<td>1,341</td>
<td>521</td>
<td>no</td>
<td>L 3.0 cm</td>
</tr>
</tbody>
</table>

CT: computed tomography, HD: hemodialysis, US: ultra sound, MRI: magnetic resonance imaging, WNL: within normal limit, MIBG: metaiodobenzylguanidine

1986.
Pheochromocytoma on Hemodialysis Therapy