Case Report

The Treatment of Pheochromocytoma Associated with Pseudo-obstruction and Perforation of the Colon, Hepatic Failure, and DIC

Yasuyoshi HASHIMOTO, Sadatoshi MOTOYOSHI, Hideki MARUYAMA, Michiharu SAKAKIDA, Tomohiko YANO, Kohei YAMAGUCHI, Kazuo GOTO*, Shigenori SUGIHARA**, Sadamu TAKANO***, Takeshi KAMBARA** and Motoaki SHICHIRI

The case of a 59-year-old man with paralytic ileus (pseudo-obstruction) associated with pheochromocytoma is reviewed. Paralytic ileus is believed to have been the result of overstimulation of $\alpha$ and $\beta$ receptors on the intestine by catecholamines. Phentolamine, bunazocin, propranolol, bethanechol and midaglizole in single administrations or in combination were administered. Phentolamine infusion clearly relieved the symptom, but ileus recurred, and the patient died of respiratory failure, liver dysfunction and disseminated intravascular coagulation syndrome. The significant role of catecholamines in causing these symptoms is discussed, and the management of this relatively rare complication is reviewed.

Key words: Phentolamine, Bunazocin, Midaglizole, Propranolol, Bethanechol, Platelet hyperaggregability

Management of malignant pheochromocytoma complicated by multiple metastases can be a difficult clinical problem, because it is usually impossible to cure through surgery (1).

Recently we treated a case of severe intestinal distension in a pheochromocytoma patient with multiple metastases. There is, as yet, no definite treatment regimen for paralytic ileus, thus the clinical course and autopsy findings of this case are presented.

CASE REPORT

A 59-year-old man, brought by ambulance, was admitted to our department because of severe constipation, abdominal distension and one week of jaundice. A diagnosis of malignant pheochromocytoma with multiple metastases had been made previously. The clinical history of the patient from the age of 38 is shown in Table 1. He was immediately transferred to the Intensive Care Unit of our hospital.

The patient was drowsy, blood pressure was 130/90 mmHg, and pulse rate was 120/min. Skin and conjunctiva bulbi were icteric. No rale was audible and heart sounds were clear. The abdomen was quite distended, and tympanic. Livedo racemosa was present bilaterally in the upper and lower extremities. Chest X-rays revealed bilateral pleural effusion, enlargement of the heart shadow, and a mass in the right upper field which was thought to be a metastatic lesion of the third rib. Plain films of the abdomen (Fig. 1) demonstrated a distended intestine, but no mechanical obstruction of the colon was found in the endoscopic examination. Echo-
Table 1. Clinical history.

<table>
<thead>
<tr>
<th>Age</th>
<th>Information</th>
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<tbody>
<tr>
<td>38</td>
<td>Diagnosis of diabetes mellitus.</td>
</tr>
<tr>
<td>49</td>
<td>Cerebral hemorrhage, left hemisphere.</td>
</tr>
<tr>
<td>51</td>
<td>Paralysis of both lower extremities due to a metastatic tumor on T1-T2. Clinical diagnosis of pheochromocytoma.</td>
</tr>
<tr>
<td>52</td>
<td>Right adrenal pheochromocytoma was removed. Radiation to T1-T2.</td>
</tr>
<tr>
<td>53</td>
<td>Myocardial infarction.</td>
</tr>
<tr>
<td>54</td>
<td>Bone pain due to metastases to the right third rib and the left scapula.</td>
</tr>
<tr>
<td>55</td>
<td>Attack of cardiac insufficiency. Improvement of general condition with Dacarbazine chemotherapy: 6 courses over 1 year (1 course: 200 mg/day, 5 days).</td>
</tr>
</tbody>
</table>

Fig. 1. Plain film of the abdomen. Taken at admission, plain film of the abdomen records the markedly distended intestine.

graphic examination detected no abnormality of liver or biliary systems. A $^{131}$I-MIBG (meta-iodo-benzylguanide) scintigraphy revealed uptake in the lesions of the right third rib and left scapula. Serum total bilirubin level was 23.7 mg (0.3–1.2 normal), serum GOT 1785 U/l (8–32), alkaline phosphatase 144 U/l (42–123), LDH 638 U/l (236–427) and blood ammonia 99 μmol/l (15–62). The plasma level of norepinephrine was 44.5–75.5 ng/ml (0.05–0.4), with a urinary output of 2430–10800 μg/day (10–90).

The patient was tentatively diagnosed as hepatic failure due to dacarbazine chemotherapy treatment. Plasmapheresis, performed on the second hospital day, lowered the level of serum bilirubin to 3.9 mg/dl; serum GOT and GPT levels also fell (Fig. 2). Although the intestinal distension was suspected to be due to the high catecholamine level, an α-blocker was not used because of the relatively low blood pressure (120/80 mmHg on the first hospital day). Various laxatives were administered with no evidence of improvement of the intestinal motility. Finally on the tenth hospital day, panperitonitis with free air occurred. A perforated lesion of the transverse colon was revealed in an emergent operation, and was exteriorized.

To prevent a recurrence of ileus, continuous infusion of phentolamine (8 mg/h) was started on the first post-operative day. Good passage of flatus was obtained within a day, and intestinal motility was maintained for 3 weeks following surgery.

To maintain intestinal motility with peroral drugs, phentolamine was decreased and a combination therapy of midaglizole (600 mg/day), bunazocin (9 mg/day), bethanechol (30 mg/day) and propranolol (30 mg/day) was started. However, this combination was not effective, and ileus symptoms recurred, which were again relieved by phentolamine infusion. In this combination therapy with midaglizole, informed consent of the patient and his family was obtained, and the study was approved by the Ethical Committee of Kumamoto University.

On the 116th hospital day, radiation with $^{60}$Co was begun on the metastatic lesion of the right third rib. A total dose of 35 Gy was administered for 29 days. However the patient's general condition gradually deteriorated with associated symptoms of nausea and general fatigue. Interstitial shadows of the lung were revealed on the chest X-rays on the 145th hospital day, the temperature rose to 39°C, and jaundice recurred with a bilirubin level of 14.9 mg/dl. The patient died of respiratory failure, hepatic failure and disseminated intravascular coagulation syndrome (DIC) on the 153rd hospital...
Various Symptoms Caused by Catecholamine

Fig. 2. Clinical course. Distension of the abdomen and jaundice occurred at the time of admission, and the time of death. This figure indicates the clinical effectiveness of the phentolamine infusion.

day.

Upon autopsy, brown colored metastatic tumors were found on the right third rib, the left scapula, and the seventh cervical vertebra with obvious bone structure destruction, and on the subclavicular lymph node. In addition, microscopic metastases on the third lumbar vertebra, the sternum and the right lung were observed. These tumors were composed of pleomorphic cells with basophilic cytoplasm and ovoid nuclei, arranged in small nests separated by delicate fibrous septa, with abundant sinusoidal capillaries (Fig. 3). These histological features are typical of pheochromocytoma. The catecholamine concentration in each metastatic tumor is shown in Table 2.

Atherosclerotic changes were observed in the aorta, coronary arteries, celiac and mesenteric arteries, and basilar artery of the brain, etc. There was, however, no obvious occlusion in the mesenteric arteries. Cardiac hypertrophy and previous ischemic changes were seen in the left ventricle, probably due to atherosclerosis and hypertension. The submucosa of the small intestine was slightly congestive, but no ischemic change was observed in the small or large intestines. Auerbach’s nerve plexuses were histologically normal. The

Fig. 3. Histological figure of the tumor on the third rib. The tumor was composed of pleomorphic cells with a faint basophilic cytoplasm and nuclei arranged in small nests with abundant capillaries (× 250).
Table 2. Catecholamine concentrations of each metastatic lesion.

<table>
<thead>
<tr>
<th>Location of metastatic tumors</th>
<th>Size (cm)</th>
<th>Concentration(μg/g) N</th>
<th>E</th>
<th>N</th>
<th>D</th>
<th>O</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subclavicle lymph node</td>
<td>1.90</td>
<td>2.23</td>
<td>0.33</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7th cervical vertebra</td>
<td>2x2x1</td>
<td>2.97</td>
<td>2.08</td>
<td>0.53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right third rib</td>
<td>5x4x2</td>
<td>92.61*</td>
<td>1.55</td>
<td>6.75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left scapula</td>
<td>*</td>
<td>60.24*</td>
<td>0.24</td>
<td>2.64</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Detected by 131I-MIBG scintigram. ( #: no data); NE, norepinephrine; E, epinephrine; DO, dopamine

spleen, which weighed only 13.3 g, showed severe fibrosis and the lymphatic follicle was lost. Remarkable fibrin thrombi and focal hemorrhage were found in many glomeruli of the kidneys and hyaline droplets and necrotic changes were observed in the tubules. Mild fibrosis with infiltration of lymphocytes was seen in Glisson’s sheath. Hepatic cells showed almost normal features despite mild biliary stasis in the bile canaliculi.

**DISCUSSION**

The intestinal distention in this patient was believed to be due to catecholamines, because there was no mechanical obstruction and adreno-receptor blockade relieved the symptoms. It is suspected that catecholamines caused the pseudo-obstruction and perforation of the intestine in the following way:

First, catecholamine stimulate α2- and β2-receptors in the smooth muscle cells of the intestine, decreasing intestinal motility and tone and contracting intestinal sphincters. Second, they also contract the smooth muscles of mesenteric arteries causing intestinal ischemia (2). There has already been a report of a case suggesting intestinal perforation due to catecholamines (3).

The actual catecholamine levels in the reported cases of intestinal pseudo-obstruction in pheochromocytoma vary. Brown and Borowsky reported urinary output of catecholamine and its metabolites of greater than 4500 μg/day (4), while in another report by Bernstein et al an output of 1000 μg/day was reported (5). Our case showed a urinary output of norepinephrine at a level of 13 mg/day for the previous 3 years. This level is thought to be relatively high among cases of gastro-intestinal pseudo-obstruction. However, there was no evidence of catecholamine secretion increase prior to the occurrence of the symptoms, as shown in Table 3. Therefore, the other factor, namely the duration of the high catecholamine levels, may also account for the occurrence of the intestinal distension. On this point, reported cases vary (4–7), therefore it is difficult to draw a conclusion concerning the specific hormonal features commonly seen in cases of intestinal pseudo-obstruction in pheochromocytoma.

The inadequate use of laxatives may be a direct cause of the perforation of the colon in our case. Since the mucosa of the colon in this patient was probably ischemic due to the high catecholamine levels, the hyperkinetic action of laxatives may have increased the damage. Furthermore, metoclopramide has the effect of enhancing catecholamine secretions (8). These factors, taken together, may have led to the perforation of the colon. This emphasizes the necessity of careful treatment of intestinal dysfunction in pheochromocytoma.

Among several medicament treatments, the efficacy of phentolamine infusion has been reported (9, 10). Phentolamine not only has a non-selective α-blocking effect but also has important action on the smooth muscles including the stimulation of the gastro-intestinal tract that is blocked by atropine (11). A combination therapy of adrenergic blockers and a cholinergic drug was tried, but was not effective. That may be due to the small dosage of...
the cholinergic drug bethanechol, because a successful case using maximum dosage of cholinergic drug has been reported (9). In the present case, it was not feasible to administer a higher dose of bethanechol because of severe nausea. In consideration of the important role of the $\alpha_2$-receptor in the intestine, midaglizole — a specific $\alpha_2$-blocker — in combination with the $\beta$-blocker propranolol, was administered. Unfortunately, this combination was also disappointing. These facts may suggest the important role of the cholinergic effect of phentolamine in the treatment for ileus. But there is the possibility of other unknown effects of phentolamine. Added to medicament treatment, resection of the tumor producing catecholamine has been shown to be occasionally effective (12). Brennann and Keiser reported that the aggressive use of surgery, even in the presence of pulmonary metastasis, should be encouraged (13). In our case, however, the resection of metastatic tumors might have shortened the patient’s life.

The cause of liver damage in our case was suspected to be due to the dacarbazine chemotherapy. The histological findings upon autopsy and the marked effectiveness of plasmapheresis were compatible with this supposition, but the exacerbation of jaundice just before death cannot be completely explained to be due to the adverse effects of the dacarbazine treatment. The possibility exists that enormous amounts of catecholamines have some harmful effects on the bile tract, due to the strange coincidence of liver dysfunction and abdominal distension.

A close relationship between DIC and catecholamine is also suspected. Oka et al reported that DIC in a patient with pheochromocytoma may be referable to the platelet hyperaggregability by catecholamine (14). The platelet aggregability in this patient did increase somewhat but is not reported.

Among the many metastases, the tumors on the right third rib and the left scapula were detected by $^{131}$I-MIBG imaging, but others were not detected. The $^{131}$I-MIBG-positive-tumors in this patient were of a larger size and had a higher concentration of norepinephrine than the negative ones as shown in Table 2. The tumor on the seventh cervical vertebra was negatively reported in the $^{131}$I-MIBG scintigram, but was thought to be large enough to be detected by $^{131}$I-MIBG. Moreover, the histological pattern was the same as those reported as positive seen though the catecholamine concentration was low. These facts suggest that active synthesis of catecholamine in the tumor may play an important role in the uptake of $^{131}$I-MIBG. In addition, there is a possibility that radiation applied to the 7th vertebra before admission may have affected the ability of the uptake of $^{131}$I-MIBG.

Thus, various symptoms may occur in patients with malignant pheochromocytoma because of stimulation by catecholamines to adrenergic receptors throughout the entire body. Unknown effects of catecholamines on the intestine, platelets, the liver, and biliary tracts are suspected in this case. The mechanisms of such a disorder have not yet been clarified.

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