Malignant Pheochromocytoma with Liver Metastasis Treated by Transcatheter Arterial Chemo-Embolization (TACE)

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Abstract

Multiple liver metastatic lesions were shown by computed tomography and scintigraphy with 123I-metaiodobenzylguanidine (MIBG) in a 76-year-old woman 2 years after resection of a pheochromocytoma of the right adrenal gland. Transcatheter arterial chemo-embolization (TACE) was performed for the liver metastasis, with blood pressure strictly controlled by administration of doxazosin and phentolamine for the prevention of hypertensive crisis after TACE. There were no severe adverse events associated with the treatment, and the number and size of the lesions were decreased. TACE with strict blood pressure control was an effective and safe therapy for multiple liver metastatic lesions related to malignant pheochromocytoma.

Key words: TACE, malignant pheochromocytoma, liver metastasis, doxazosin, phentolamine

Introduction

Previous reports have described patients with a malignant pheochromocytoma who developed distant metastasis several years after resection (1, 2). A malignant pheochromocytoma is rare, and an effective therapy for metastasis and/or recurrence has not been established. We successfully treated a case of liver metastasis using transcatheter arterial chemo-embolization (TACE) in a patient who previously underwent resection for pheochromocytoma and was diagnosed as benign.

Case Report

A 76-year-old woman had been treated for hypertension with anti-hypertensive agents for 10 years. An examination found an abdominal mass and she was admitted to our hospital, where computed tomography (CT) revealed a right adrenal gland tumor (13 cm). Following additional examinations, the tumor was resected and diagnosed as a benign pheochromocytoma, as there were no malignant findings in a histopathological examination. Thereafter, abdominal CT follow-up examinations were performed every 6 months. Two years after resection of the right adrenal gland tumor, multiple liver tumors were detected by CT and she was admitted for further examinations.

The patient was 148 cm tall and weighed 54.6 kg. Blood pressure was 126/74 mmHg under administrations of calcium (Ca) antagonist and angiotensin-II receptor blocker (ARB), and pulse rate was 70/min. There were no abnormal findings in the physical examination.

Laboratory data on admission are shown in Table 1, with endocrinologic data presented in Table 2. The levels of plasma dopamine and urinary excretion of noradrenaline were elevated.

Abdominal ultrasonography (US) and contrast enhanced US (CEUS) with Perflubutane Microbubble (Sonazoid®),...
Figure 1. Contrast-enhanced ultrasonography using Sonazoid. A hypoechoic tumor (arrow) was visualized in segment 7 with B-mode echography (a). The tumor accumulated Sonazoid and was hypervascular in the early phase (b), and was revealed as a defect in the delayed phase (c).

Daiichi Sankyo Co., Ltd., Tokyo) were also performed (Fig. 1). Multiple liver tumors were revealed as hypoechoic areas in conventional US findings, with the maximum diameter 27 mm (in segment 7). In the early phase of CEUS, the tumor of segment 7 was shown as a hypervascular tumor and all hepatic tumors were revealed as defects in the delayed phase. In the early phase of gadolinium ethoxybenzyl diethyleneetriaminepentaacetic acid (Gd-EOB-DTPA, EOB) enhanced liver dynamic magnetic resonance imaging (MRI), all tumors were shown to be hypervascular, similar to CEUS findings, and all were seen as defects in the hepatobiliary phase (Fig. 2). Scintigraphy with $^{123}$I-metaiodobenzylguanidine (MIBG) demonstrated multiple accumulations in the liver. Fluorodeoxyglucose (FDG)-positron emission tomography/CT (PET/CT) also demonstrated multiple accumulations in the liver and showed no other malignant tumors in the body (Fig. 3). There were 5 tumors in the liver: the diameters and location were 14 mm in segment 4, 27 mm in segment 7, 6 mm in segment 6, 8 mm in segment 6, and 7 mm in segment 6. Based on these findings, the hepatic tumors were diagnosed as multiple liver metastatic lesions from malignant pheochromocytoma.

We selected TACE for treatment in this case. CT arterial portography (CTAP) showed the multiple hepatic tumors as defects (Fig. 4a), which were clearly enhanced in CT angiography (CTA) findings (Fig. 4b). We preceded with the catheter and selected 6th, 7th, 8th, and middle hepatic artery, and TACE was done. All tumors were embolized using with Epirubicin-Lipiodol emulsion and multiparous gelatin particles (Gelpart®, Nippon Kayaku, Tokyo). Following TACE, dense accumulation of Lipiodol in the tumors was confirmed with plain CT (Fig. 4c).

To prevent hypertensive crisis following angiography, we changed the hypertensive agents from candesartan (ARB) and bendipine hydrochloride (Ca antagonist) to doxazosin ($\alpha$ blocker) after admission, with the dose of doxazosin...
Figure 2. Gadoxetate disodium enhanced liver dynamic magnetic resonance imaging. The tumor in segment 7 was enhanced in the early phase (a) and revealed as a defect in the hepatobiliary phase (b). A cyst was detected in segment 2.

Figure 3. Fluorodeoxyglucose (FDG)-positron emission tomography/computed tomography (PET/CT) revealed multiple accumulations in the hepatic tumors, with no other malignant tumors shown in other parts of the body.

Gradually increased (8 mg/day) until the angiography examination. During angiography, we started a bolus administration of phentolamine (α blocker) at 1 mg/hour to control blood pressure, with the dose increased to 10 mg/hour, while monitoring blood pressure. Following the TACE procedure, the general condition of the patients was carefully observed in the intensive care unit (ICU). The dose of phentolamine was gradually decreased with normalizing blood pressure and administration was stopped the day after TACE. The changes of blood pressure during admission are shown in Fig. 5. Adverse events after TACE were anorexia, fever, abdominal pain, and liver dysfunction, which all disappeared within 1 week. There were no severe adverse events, including hypertensive crisis.

Changes in the plasma levels of catecholamines during the TACE procedure are shown in Table 3. The plasma levels of noradrenaline were elevated the day after the procedure, and then returned to a normal range 3 days after TACE. The plasma levels of dopamine were decreased, but remained within a normal range the day after TACE. Two months after TACE, dynamic contrast enhanced CT showed a round tumor of which the diameter was increased to 15 mm and there was peripheral enhancement in segment 4 of the liver.

Other liver metastases previously treated by TACE were accumulated by Lipiodol, and there was no evidence of recurrence. Dense accumulation of Lipiodol was observed in the tumors of segment 7 (19 mm), segment 6 (3 mm), segment 6 (6 mm), and segment 6 (4 mm), respectively.

Recurrence of pheochromocytoma in segment 4 of the
Figure 4. Multiple hepatic tumors were shown as defects (arrows) in computed tomography (CT) arterial portography (CA-AP) (a) and all were enhanced clearly in CT angiography (CTA) (b). Following TACE, dense accumulations of lipiodol in the tumors were confirmed with plain CT (c).

Figure 5. Changes of blood pressure and using of anti-hypertensive drug were shown. Hypertensive crisis was not observed. ICU: intensive care unit.

Liver was suspected and TACE using Epirubicin-Lipiodol emulsion and multiparous gelatin particles from the middle hepatic artery was performed again without severe adverse events. Dynamic contrast-enhanced CT performed 2 months
Table 3. Changes of the Levels of Plasma Catecholamines among TACE

<table>
<thead>
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<th></th>
<th>Before TACE</th>
<th>1 day after TACE</th>
<th>3 days after TACE</th>
<th>5 days after TACE</th>
<th>7 days after TACE</th>
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<td>adrenaline (ng/mL)</td>
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<td>0.89</td>
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<td>0.11</td>
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<tr>
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<td>0.02</td>
<td>&lt;0.01</td>
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Figure 6. Dynamic contrast-enhanced computed tomography performed 2 months after the second transcatheter arterial chemo-embolization procedure. Dense accumulation of Lipiodol in the lesion of liver metastases was shown. There were multiple known cysts in the liver.

Discussion

A pheochromocytoma has characteristic features that differ from other malignant tumors. Even if a pheochromocytoma is initially diagnosed as benign by histopathological findings and resected, it is possible for metastasis to occur in other organs several years after resection, with the case then diagnosed as malignant pheochromocytoma. In the present patient, liver metastasis appeared 2 years after resection. The recurrence free period is variable. Mornex et al found that the mean period to first recurrence was 7.8 years in a series of cases, while the locations of metastasis varied [e.g., liver, lung, bone, lymph node, and brain (3)]. The overall survival rate for patients that show metastatic tumors from pheochromocytomas is 50% after 5 years (4).

No established therapeutic strategy for metastatic malignant pheochromocytoma has been presented, though surgical resection, chemotherapy, $^{131}$I-MIBG therapy, and TACE (1, 2, 5-12) have been reported. Some studies have shown that surgical resection was effective and achieved long-term survival, when the metastatic lesions could be

after the second TACE procedure showed dense accumulation of Lipiodol in the lesion of liver metastases and did not reveal recurrence (Fig. 6). Dense accumulation of Lipiodol was observed in the tumors of segment 4 (7 mm), segment 7 (16 mm), segment 6 (6 mm), and segment 6 (3 mm), and all of the tumors were smaller than pre-treatment. At the time of this writing (4 months after second TACE), the patient is alive without recurrence.
completely resected (13, 14). TACE is widely used for patients with unresectable hepatocellular carcinoma (HCC) and it is reported to improve the survival rate of affected patients (15, 16). In the present case, resection was not indicated due to multiple liver lesions, and we selected TACE, because metastasis was limited to the organ. Embolization with Epirubicin-Lipiodol emulsion and multiparous gelatin particles is used against HCC in our institute. Because TACE for liver metastasis from malignant pheochromocytoma has been reported in 10 known cases, of which 8 were recurrent cases with liver metastasis after surgical resection and 2 naïve cases with liver metastasis (Table 4) (1, 2, 5-12). Of the 8 recurrent cases, 2 were detected by follow-up CT and 6 were suspected by subjective symptoms, with metastasis found in multiple organs in 6 cases and recurrence observed only in the liver in 2. In 8 cases, α-blocker was added before and after TACE for preventing hypertensive crisis. In the present case, doxazosin administration was started after admission and at the start of TACE, administration of phenolamine was added for more strict control of blood pressure.

Hypertensive crisis has been reported as a common complication of angiography against pheochromocytoma (17, 18). Some reports have noted that blood pressure fell transiently 1-3 days after TACE (1, 2, 11), because catecholamines were released and their level in plasma was elevated just after TACE due to tumor necrosis, then returned to a normal range 2 weeks after TACE. In this case, the plasma level of noradrenaline was elevated the day after TACE, and the level was decreased within normal range 3 days after TACE. On the other hand, the plasma levels of adrenaline and dopamine were not elevated (Table 3). In 9 of the 10 previously reported cases, the plasma levels of catecholamines were elevated before TACE and decreased after TACE, and the procedure was considered to be effective. All malignant pheochromocytoma do not have the same potential of secreting noradrenaline, adrenaline, and dopamine. Fortunately, the present case showed elevation of only noradrenaline. TACE was considered and performed under strict control of blood pressure against all hepatic metastasis of malignant pheochromocytoma. In the present case, there was no severe adverse event related to TACE, and the patient is currently alive without any symptoms or recurrence.

Careful follow-up examinations are necessary after surgical resection, even if the histological findings show a benign pheochromocytoma. In the present case, we performed TACE without serious adverse events, and the procedure was safe and effective for liver metastasis from a pheochromocytoma (17, 18). Some reports have noted that blood pressure fell transiently 1-3 days after TACE (1, 2, 11), because catecholamines were released and their level in plasma was elevated just after TACE due to tumor necrosis, then returned to a normal range 2 weeks after TACE. In this case, the plasma level of noradrenaline was elevated the day after TACE, and the level was decreased within normal range 3 days after TACE. On the other hand, the plasma levels of adrenaline and dopamine were not elevated (Table 3). In 9 of the 10 previously reported cases, the plasma levels of catecholamines were elevated before TACE and decreased after TACE, and the procedure was considered to be effective. All malignant pheochromocytoma do not have the same potential of secreting noradrenaline, adrenaline, and dopamine. Fortunately, the present case showed elevation of only noradrenaline. TACE was considered and performed under strict control of blood pressure against all hepatic metastasis of malignant pheochromocytoma. In the present case, there was no severe adverse event related to TACE, and the patient is currently alive without any symptoms or recurrence.

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References


