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Transcatheter Arterial Embolization for the Treatment of Liver Metastases in a Patient with Malignant Pheochromocytoma

DAISUKE WATANABE, AKIYO TANABE, MITSUHIDE NARUSE**, MIKA TSUIKI, NOBUYUKI TORII*, TAKAO NOSHIRO*** AND KAZUE TAKANO

Department of Medicine, Institute of Clinical Endocrinology, Tokyo Women's Medical University, 8-1, Kawadacho, Shinjuku-ku, Tokyo 162-8666, Japan

**Department of Medicine, Institute of Clinical Gastroenterology, Tokyo Women's Medical University, 8-1, Kawadacho, Shinjuku-ku, Tokyo 162-8666, Japan*

***Division of Endocrinology, Clinical Research Institute of Endocrine and Metabolic Diseases, Kyoto Medical Center, 1-1, Mukaihatamachi, Fukakusa, Fushimi-ku, Kyoto 612-8555, Japan*

****Noshiro Clinic, 2398, Ishizukacho, Sano-shi, Tochigi 327-0103, Japan*

Abstract. A 63-year-old male patient was admitted for the treatment of malignant pheochromocytoma with multiple liver metastases. Plasma and urinary levels of catecholamines were elevated. Transcatheter arterial embolization (TAE) with concomitant administration of mitomycin C and gelatin sponge was performed for the treatment of liver metastases. Dose of alpha-1 blocker before TAE was increased to prevent hypertensive crisis during and after TAE. The hepatic metastatic lesion of CT findings was decreased after TAE. Although blood pressure showed a transient hypertension (180/100 mmHg) after every TAE, it returned rapidly to normal. The patient experienced transient abdominal pain, nausea, and loss of appetite after every TAE; however, those symptoms were readily controlled by conventional medications. Slight elevation of liver transaminases was recognized but returned to normal range within 3 weeks. No other major side effects were seen with TAE. While plasma and urinary level of catecholamines were unchanged, plasma chromogranin A (CgA) level was significantly decreased. These results suggest that TAE is a useful treatment for hepatic metastases. Plasma CgA level is a useful marker in the treatment of malignant pheochromocytoma.

Key words: Malignant pheochromocytoma, Multiple hepatic tumors, Transcatheter arterial embolization (TAE), Chromogranin A

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ALTHOUGH pheochromocytoma and paraganglioma are two representative causes of endocrine hypertension, approximately 10% of pheochromocytoma and 15–35% of paraganglioma are malignant. The prognosis has been reported to be poor with 5 year survival rate of 20–45% [1]. Metastatic lesions are frequently seen in the bone, liver, retroperitoneum with lymph nodes, brain, pleura, and kidney. Although surgical removal of the metastatic lesions, combined chemotherapy [2], ^{131}I-MIBG treatment and external radiotherapy have been demonstrated to be effective [3], no definitely effective treatments have been established for the management of metastatic lesions in the liver, the second most frequent site of metastases from malignant pheochromocytoma [4]. Although surgical removal remains the best treatment [5], it could be indicated for the solitary lesion but not for multiple lesions. More recently, transcatheter arterial embolization (TAE) has been successfully performed for the treatment of hepatocellular carcinoma (HCC). Only very limited cases of TAE for the metastatic lesions of malignant pheochromocytoma, however, have been reported in the literature [6–13].

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Correspondence to: Akiyo TANABE, M.D., Department of Medicine, Institute of Clinical Endocrinology, Tokyo Women's Medical University, 8-1, Kawadacho, Shinjuku-ku, Tokyo 162-8666, Japan

We report a 63-year-old male patient with malignant pheochromocytoma, in which a series of TAE was effective in reducing the mass size of the metastatic lesions in the liver. The changes in the plasma chromogranin A (CgA) were also in parallel to the tumor size in the liver, indicating its usefulness as a biochemical marker in this particular case for the treatment of malignant pheochromocytoma.

Case Report

A 63-year-old male patient was pointed out to be hypertensive at the age of 47 and treated by antihypertensive agents. At the age of 60, he experienced constipation for long periods. Abdominal computed tomography (CT) scan showed a left adrenal tumor of 8 cm in diameter. The tumor showed a low intensity signal in the T1-weighted image and a high intensity signal in the T2-weighted image of magnetic response imaging (MRI). Scintigraphy with ^{131}I-MIBG demonstrated an accumulation of isotope in the left adrenal tumor. Plasma levels of catecholamines (norepinephrine, 3510 pg/ml; epinephrine, 171 pg/ml) and urinary vanillylmandelic acid (55.6 mg/day) were elevated. Left adrenal tumor was surgically removed and was diagnosed as pheochromocytoma. Tumor cells were immunohistochemically positive for CgA, synaptophysin A, and neuron specific enolase. Since MIB-1 staining as a marker of cell proliferation [14] was 6%, the malignant nature of the pheochromocytoma was suggested. After surgery, blood pressure and plasma levels of catecholamines were normalized and remained low for 2 years. At the age of 63, his blood pressure elevated gradually and plasma levels of catecholamines were markedly elevated (norepinephrine, 862 pg/ml; epinephrine, 26 pg/ml). Abdominal CT scan performed as a systemic survey detected multiple high-density areas in the liver. The patient was admitted to our hospital for further investigation and treatment.

The patient was 160.8 cm tall and weighed 62.4 kg. His blood pressure was 110/70 mmHg under administration of alpha-1 blocker and pulse rate was 78 beats/min. There were no particular findings in the physical examination.

Laboratory data on admission is shown in Table 1. While data indicated normal liver and renal function, fasting blood sugar and HbA1c were elevated. The endocrinological findings are shown in Table 2. Plasma level of norepinephrine, urinary excretion of catecholamines and metabolites, and plasma CgA (714 ng/ml) were all elevated (normal range: CgA, 19.4–98.1 ng/ml).

Table 1. General urine and blood findings on admission

Urinalysis: occult blood (–), protein (–), sugar (–)			
Complete blood cell count			
WBC	5560/mcl	RBC	4.33×10^6/mcl
Hb	13.0 g/dl		
Plt	18.0×10^4/mcl		
Blood chemistry			
AST	18 IU/l	Na	141 mEq/l
ALT	16 IU/l	K	4.3 mEq/l
LDH	202 IU/l	Cl	105 mEq/l
γ-GTP	23 IU/l	T-cho	164 mg/dl
ALP	237 IU/l	HbA1c	7.3%
ChE	318 IU/l	FBS	126 mg/dl
BUN	25.2 mg/dl		
Cre	0.90 mg/dl		

ALP, Alkaline phosphatase; ALT, alanine aminotransferase; AST, asparate aminotranferase; BUN, blood urea nitrogen; ChE, cholinesterase; Cl, chloride; Cre, creatinine; γ-GTP, γ-glutamyl transpeptidase; FBS, fasting blood sugar; Hb, hemoglobin; HbA1c, glyco hemoglobin A1c; K, potassium; LDH, lactate dehydrogenase; Na, sodium; Plt, platelet; RBC, red blood cells; T-cho, total cholesterol; WBC, white blood cells

Table 2. Endocrinological findings on admission

		normal range
Plasma epinephrine	57.0 pg/ml	(<100)
Plasma norepinephrine	1260.0 pg/ml	(100–450)
Urinary epinephrine	52.6 mcg/day	(3.0–15.0)
Urinary norepinephrine	585.4 mcg/day	(26.0–121.0)
Urinary metanephrine	0.84 mg/day	(0.05–0.23)
Urinary normetanephrine	2.08 mg/day	(0.07–0.26)
Urinary VMA	25.8 mg/day	(1.3–5.1)
Plasma ACTH	28.8 pg/ml	(7.4–55.7)
Plasma cortisol	16.7 mcg/dl	(4.0–18.3)
Plasma renin activity	0.7 ng/ml/h	(0.3–2.9)
Plasma aldosterone concentration	82 pg/ml	(35.7–240)

VMA, vanillylmandelic acid

Ultrasound examination of the abdomen showed multiple metastatic tumors with homogenous internal echo level in the liver. CT scan with contrast medium enhancement of the abdomen showed multiple enhanced areas in the liver (Fig. 1a). MRI of the spine demonstrated multiple lesions with low intensity signal in the T1-weighed image and a high intensity area in the T2-weighed image and the short TI inversion recovery image in the 6th and 12th thoracic and 1st

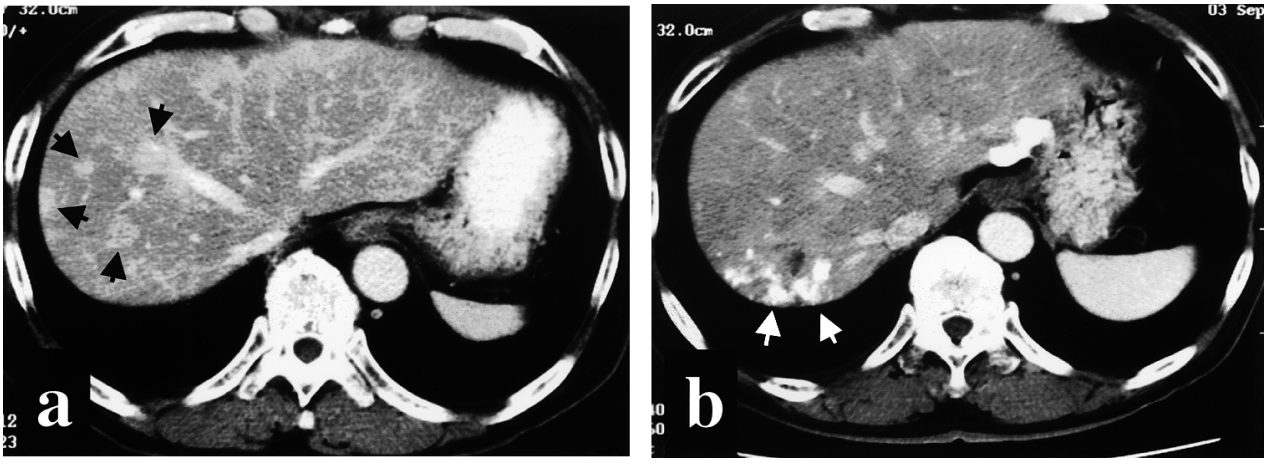

Fig. 1. CT scan with contrast medium before (a) and after TAE (b). The metastatic liver tumor was enhanced with contrast medium on CT scan before TAE (black arrows), while Lipiodol but not metastatic tumor tissue was visualized as a high density area after TAE (white arrows).

lumbar spine. These results suggested multiple bone metastases. Scintigraphy with ^{131}I-MIBG demonstrated a distinct accumulation in the liver and metastatic lesion in the thoracic and lumbar spine. Metastatic lesions in the bone were also documented by ^{99m}Tc-MDP scintigraphy.

The hypertension of the patient was treated by a combination of alpha-1 blocker (doxazosin, 8 mg/day) and beta blocker (carvedilol, 20 mg/day) and blood pressure was maintained in the normal range. Since the metastatic lesions of the liver were multiple, surgical removal was not indicated. TAE through the hepatic arteries was performed to the respective liver segment (Fig. 2a, b, c). In this case, the target liver area was divided into three segments according to their hepatic arterial branch. TAE was sequentially performed in each liver segment with an interval of 2 to 3 weeks to prevent hypertensive crisis associated with massive tumor necrosis.

Briefly, mitomycin C suspended in poppyseed oil (Lipiodol, 3 ml) was injected into the tumors through the hepatic artery of left lateral branch, followed by an injection of small pieces of gelatin sponge (Spongel) into the artery. Twenty-five days after the first TAE, the second TAE with mitomycin C (10 mg) and Lipiodol (4 ml) was performed through the hepatic artery of right anterior segmental branch. Fourteen days after the second TAE, the third TAE with mitomycin C (7 mg) and Lipiodol (3 ml) was performed through the middle hepatic artery and the hepatic artery of right anterior segmental branch. Angiography performed after each TAE showed effective embolization of the feeding artery of tumors (Fig. 3a, b, c).

Dose of alpha-1 blocker doxazosin before TAE was chosen to prevent possible hypertensive crisis after TAE. Although blood pressure showed a transient hypertension (180/100 mmHg) after every TAE, it returned to the normal range within 2 days and dose of doxazosin was reduced from 8 mg/day to 2 mg/day after the third TAE. In addition, plasma and urinary catecholamines showed a significant increase after each TAE and decreased gradually to the levels similar to those before TAE (Fig. 4). Plasma CgA level was decreased to 662 ng/ml after the first TAE and finally to 410 ng/ml (Fig. 4).

CT scan performed after 4 months of TAE showed a marked accumulation of Lipiodol in the metastatic tumors in the liver and the tumor volume was significantly decreased. The total hepatic tumor volume on CT scan, analyzed using NIH Imaging by personal computer, showed a tumor reduction by 98.5% after TAE from that before TAE (Fig. 1b).

Although the patient experienced abdominal pain, nausea, and loss of appetite after every TAE, those symptoms were readily controlled by conventional medications and disappeared within several days. Liver transaminases, AST and ALT, showed a slight elevation but returned to the normal range within 21 days. No other major side effects were seen with TAE. The patient has been treated with 6 series of combination chemotherapy [2] after TAE, and remains clinically stable during the one-year follow-up period.

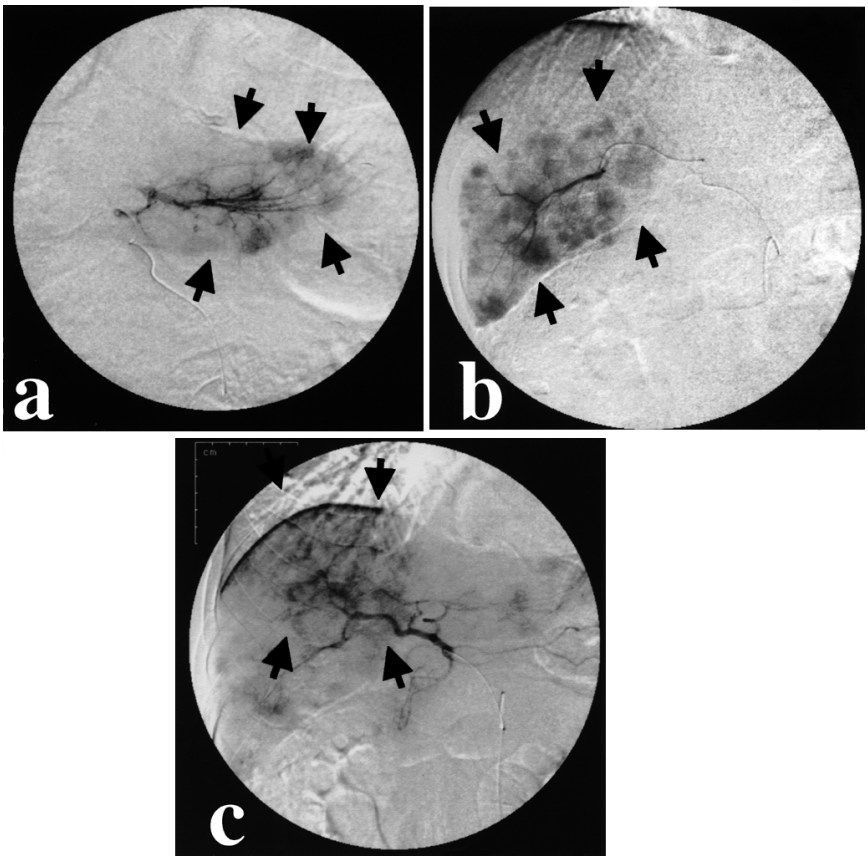

Fig. 2. The angiography before each of the three times of TAE (a, b, c). Multiple minute to small stains were visualized in each angiography.

Discussion

TAE has been accepted as one of the most effective treatments for patients with unresectable HCC [15]. While the blood supply of normal hepatocytes are mainly from the portal vein, that of HCC is almost exclusively from the hepatic arteries. This anatomical difference between the normal hepatocytes and hepatoma cells is the theoretical background for TAE leading to ischemic necrosis of HCC [15]. Since pheochromocytoma and its metastatic lesions are hypervascular, TAE has been successfully performed in the treatment of malignant pheochromocytoma with liver metastases (Table 3). The therapeutic effects of TAE have been demonstrated to be enhanced by the combination therapy with anticancer chemotherapy [15]. Lipiodol works as a carrier to deliver and slowly release anti-cancer agents in the tumor. The effectiveness of coadministration of mitomycin C has been established in TAE for HCC [15]. In addition, it has been successfully used in TAE for liver metastasis in 2 cases of malignant pheochromocytoma [7, 8]. We therefore used the mitomycin C as the anti-cancer agent for the treatment of metastatic lesions in the present case. Although mitomycin C may produce its anti-cancer effects through direct cytotoxic action on the tumor and/or indirect ischemic action, details of the mechanisms responsible for its effects remain to be elucidated.

CgA is an acidic glycoprotein with 439 amino acids and a molecular mass of 48 kDa, occurring in the secretory granules of most neuroendocrine cell types. Plasma CgA has been shown to correlate with tumor mass and to be an excellent marker for neuroendocrine tumors [16–18]. In the present case, plasma CgA level showed a significant decrease in parallel to the reduction of the tumor mass in the liver. There was no other factors possibly affecting plasma CgA level such as decreased renal function, type A gastritis, and treatment with proton pump inhibitors [16]. Plasma CgA could therefore be a useful marker in this particular case for

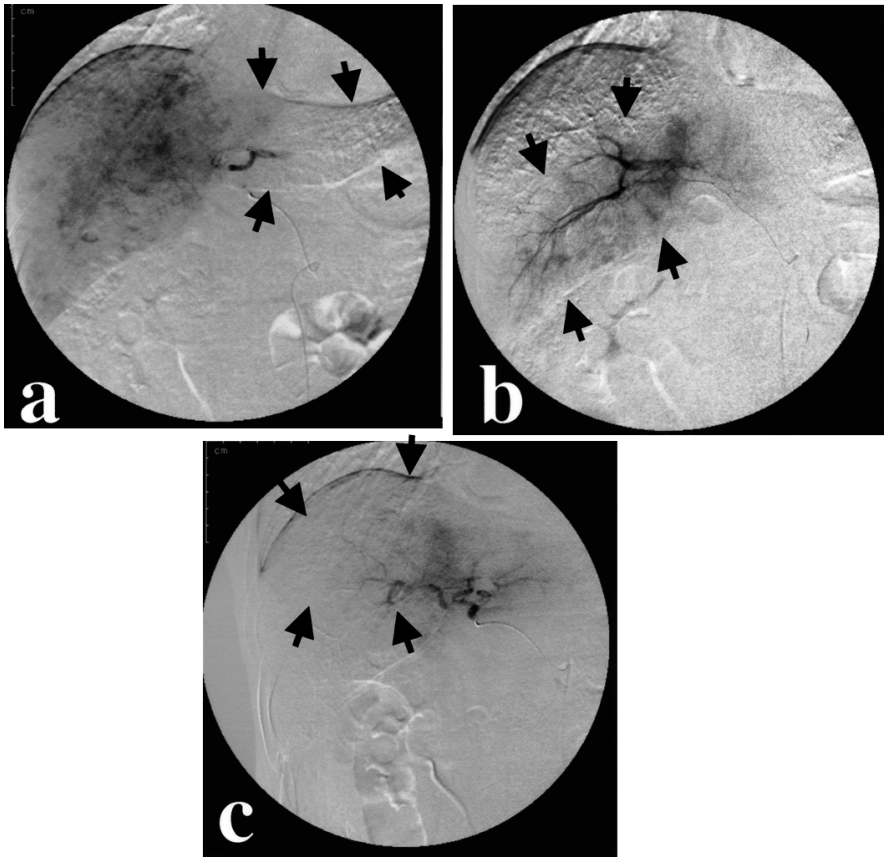

Fig. 3. The angiography after each of the three times of TAE (a, b, c). Tumor traces disappeared in the target lesions after each TAE.

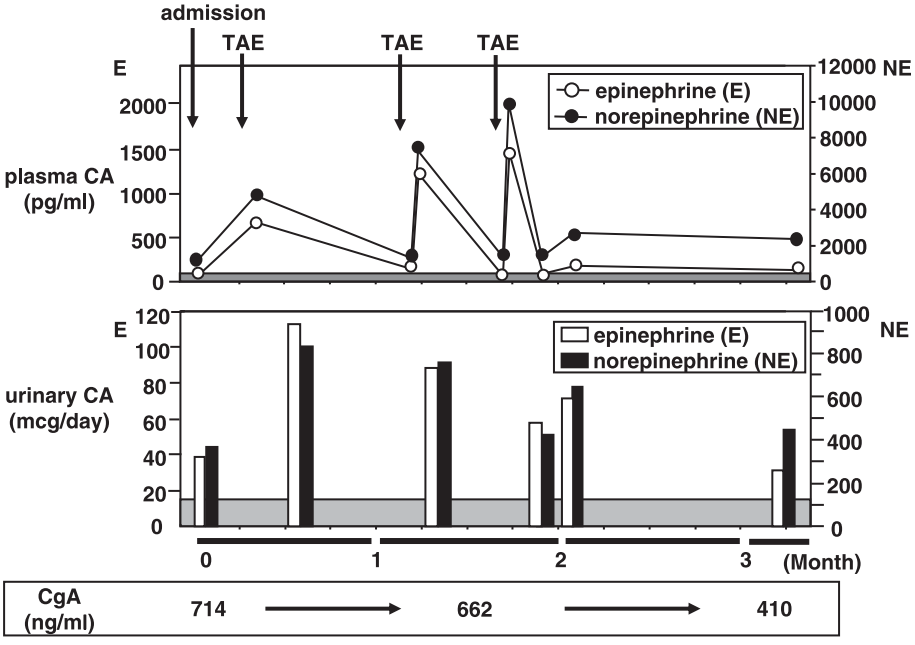

Fig. 4. Changes in plasma catecholamines (CA) and plasma chromogranin A (CgA) during TAE.

Table 3. Literature review of TAE for pheochromocytoma with liver metastases

Reference No.	Age/Sex	Localization and size of metastatic liver lesion (main tumor)	Number of TAE	Hormonal response/ Tumor response	Follow-up status	Side effects during TAE
6	56/F	Multiple (Right lobe)	1	Normalized/Reduced	Alive (4 months after TAE)	Temporary hypertension Tachycardia Hyperglycemia
7	62/M	Multiple (S4, 7 × 6 cm; S5, 5 × 4 cm)	1	Unknown/Disappeared	Successful, alive	NA
8	59/F	S2, 4 cm	1	Almost normalized/ Reduced	Successful, alive	Transient hypertension Transient tachycardia
9	59/F	S6, 2 cm	1	Normalized/Reduced	Alive (6 yr after TAE)	NA
10	62/M	Multiple (S4, 3.5 cm)	1	NA/NA	Successful, alive	Temporary hypertension Tachycardia Frequent PVC
11	48/F	Multiple	2	NA / NA	Successful, alive	Temporary hypertension Necrotizing-cholecystitis Liver abscess
12	54/M	Multiple	1	NA	Dead	Hypertension
13	30/M	Multiple (Right lobe, 5 × 4 cm)	3	Reduced/Disappeared	Successful, alive	Headache Tachycardia Temporary hypertension Nausea
Present case	63/M	Multiple	3	No change/Reduced	Successful, alive	Temporary hypertension

S, segment; NA, not available

the treatment of malignant pheochromocytoma with multiple metastases.

By contrast to CgA level, there was no significant change in the plasma and urinary catecholamines after TAE. The results agree with previous reports that changes in catecholamine levels do not necessarily correlate to the CgA levels [19] or the tumor mass reduction [20]. There was an exceptional case in which CgA was extremely high, but the CA level was normal [21]. The mechanism for the dissociation remains to be elucidated, but it is suggested that the metastatic tumor of the liver may not have been the major site of catecholamine secretion in this patient. Another possibility is that TAE itself and related tumor tissue necrosis could result in a secondary stimulation of catecholamine secretion from the residual tumor tissues. Further studies are needed, however, to elucidate the details of the mechanism for the dissociation.

Although blood pressure showed a significant elevation after TAE, the extent was modest and returned to the pre-TAE level within 2 days. Intravenous administration of phentolamine (20 mcg/kg/day) was used for the prevention of TAE-induced hypertensive crisis in a previous report [7]. However, we used high dose of alpha-1 blocker, doxazosin (8 mg/day), before TAE. Although plasma catecholamines showed a significant increase, no hypertensive crisis was experienced. Administration of a relatively high dose of alpha-1 blocker prior to the TAE could be of help for preventing hypertensive crisis. Although the patient suffered from abdominal pain and gastrointestinal symptom, they were controlled readily by standard medication. In addition, elevation of liver transaminases, AST and ALT, was minimal and returned to normal range within 3 weeks. Taken into account the positive effects and adverse effects, TAE with mitomycin C was ascertained to be effective in the treatment of metastatic lesion in the liver. Previous reports have described that when the metastatic liver lesions disappeared due to successful TAE, the patient's condition remained stable for several months [6–9]. Our patient also remains clinically stable during the one-year follow-up period.

It is well known that only 10% of the cases of pheochromocytoma are hereditary; however, it is now considered that 15–20% of the cases result from germ-line and/or de novo gene mutations, such as VHL, RET, SDHB, SDHC, SDHD, and NF1 [22, 23]. A recent retrospective study of 84 apparently sporadic pheochromocytoma showed that 12% of the patients had germ-line mutations of the VHL and succinate de-

hydrogenase subunit B (SDHB) genes. Moreover, the identification of a mutation in SDHB gene was indicated as a high risk factor for extra-adrenal location of paraganglioma and for malignant disease [24]. The present patient was not definitely diagnosed as malignant pheochromocytoma at time of first surgery. Analysis of germ-line mutations including SDH isozymes could have been meritorious in making the diagnosis and predicting the prognosis. Further studies are required to improve the clinical outcome of sporadic cases of pheochromocytoma [23].

In summary, TAE was indicated for the treatment of metastatic liver lesions in a patient with malignant pheochromocytoma. Increase in blood pressure after TAE could be controlled by preadministration of sufficient dose of alpha blocker. TAE resulted in a significant reduction in the tumor mass of the liver without any major adverse effects. TAE could be one of the therapies of choice for metastatic liver lesions in patients with malignant pheochromocytoma.

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