Spontaneous rupture of pheochromocytoma and its clinical features: a case report

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Rupture of adrenal pheochromocytoma is extremely rare and can be lethal because of dramatic changes in the circulation. We describe a 58-year-old Japanese man who suffered rupture of a pheochromocytoma. The patient was referred to our hospital because of severe hypertension (256/127 mmHg) and a left adrenal tumor. T2-weighted magnetic resonance imaging showed high signal intensity in the 50-mm left adrenal tumor. Endocrinological examinations showed elevated plasma and urinary catecholamine levels. These findings suggested that the left adrenal tumor was a pheochromocytoma. Phentolamine mesilate was administered intravenously. This resulted in a decrease of the systolic blood pressure to 100 mmHg. On the third hospital day, the patient complained of left back pain, and abdominal computed tomography showed rupture of the pheochromocytoma. Pulmonary congestion and effusion, and paralytic small-intestinal ileus occurred. Blood pressure was controlled, small-intestinal decompression was done with a Miller-Abbot tube, and body water was controlled by fluid replacement. After the general condition of the patient had became stable, laparoscopic adrenalectomy was performed. Phentolamine mesilate is a useful α-adrenergic blocker. However, care is needed with its administration, because rupture of pheochromocytoma may be related to a decrease in blood pressure induced by phentolamine mesilate.

Key words: Ruptured pheochromocytoma, Hypertensive emergency

INTRODUCTION

Pheochromocytoma is a catecholamine-secreting neoplasm of adrenal or extra-adrenal chromaffin tissue. In general outpatient clinics, the prevalence of pheochromocytoma in patients with hypertension is 0.1–0.6% [1–3]. Most but not all the clinical signs and symptoms of pheochromocytoma are due to the direct actions of secreted catecholamines. Hypertension, tachycardia, pallor, headache, and feelings of panic or anxiety usually dominate the clinical presentation. Metabolic effects include hyperglycemia, lactic acidosis, and weight loss. Less common signs and symptoms are nausea, fever, and flushing.

Rupture of adrenal pheochromocytoma is extremely rare and can be lethal because of dramatic changes in the circulation [4]. In this report, we describe a patient with a left adrenal pheochromocytoma presenting as hypertension, headache, nausea, vomiting, and renal failure. After admission, this pheochromocytoma ruptured. Pulmonary congestion and effusion, and small-intestinal ileus were observed. The characteristic signs, symptoms, clinical course and its management are discussed.

CASE REPORT

A 58-year-old Japanese man was admitted to our hospital because of hypertension and a left adrenal tumor. During the previous five years, the patient had had a history of hypertension and palpitation, and had been receiving anti-hypertensive medication comprising perindopril erbumine 4 mg/day, valsartan 40 mg/day, and betaxolol hydrochloride 5 mg/day, prescribed at another hospital. He had sometimes experienced headache, paroxysmal tachycardia, and sweating over the previous two years, and had visited the other hospital because of severe headache, nausea, and vomiting. On that occasion, severe hypertension was observed, and abdominal computed tomography (CT) demonstrated a left adrenal tumor. He was therefore referred to our hospital.

Upon presentation, the patient was 166 cm in height and weighed 70 kg. His blood pressure was 256/127 mmHg, and heart rate 82 beats/min and regular. Body temperature was 36.7°C. Ophthalmoscopic examination showed no hypertensive retinopathy. His father had died of old age, and his mother had died of subarachnoid hemorrhage. He had five sisters, and one sister had died of subarachnoid hemorrhage. However, there was no family history of pheochromocytoma. A complete blood cell count revealed elevated counts of white blood cells (10900/μl), red blood cells (523×10^4/μl), hemoglobin (16.2 g/dl), hematocrit (47.7%) and platelets (41.3×10^4/μl). Blood chemistry examination showed some abnormal values as follows: total protein 9.4 g/dl, serum albumin 5.4 g/dl, aspartate aminotransferase 34 IU/l, alanine aminotransaminase 59 IU/l, serum creatinine 2.1 mg/dl, plasma glucose 149

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Table 1

Complete blood cell counts	value	normal range
WBC	10900	4000-8000 (/μl)
RBC	523	380-480 ($\times 10^4$/μl)
Hemoglobin	16.2	11.5-15.5 (g/dl)
Hematocrit	47.7	34.0-42.0 (%)
MCV	91.2	84.0-99.0 (fl)
MCH	31.0	27.0-32.0 (pg)
MCHC	34.0	32.0-36.0 (%)
Platelets	41.3	14.0-40.0 ($\times 10^4$/μl)

Blood chemistry	value	normal range
Total protein	9.4	6.5-8.0 (g/dl)
Albumin	5.4	3.9-4.8 (g/dl)
Creatinine kinase	82	30-140 (IU/l)
Aspartate aminotransferase	34	<30 (IU/l)
Alanine aminotransferase	59	<35 (IU/l)
Creatinine	2.1	0.5-0.8 (mg/dl)
Urea nitrogen	20	8-20 (mg/dl)
Plasma glucose	149	70-109 (mg/dl)
Total cholesterol	416	140-220 (mg/dl)
Triglyceride	598	50-150 (mg/dl)
Sodium	142	136-145 (mEq/l)
Potassium	5.3	3.5-4.8 (mEq/l)
Chloride	98	98-108 (mEq/l)

Urinalysis	value	normal range
Urinary protein	3+	(-)
Urinary glucose	-	(-)
Urinary occult blood	3+	(-)

WBC, white blood cells; RBC, red blood cells; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration

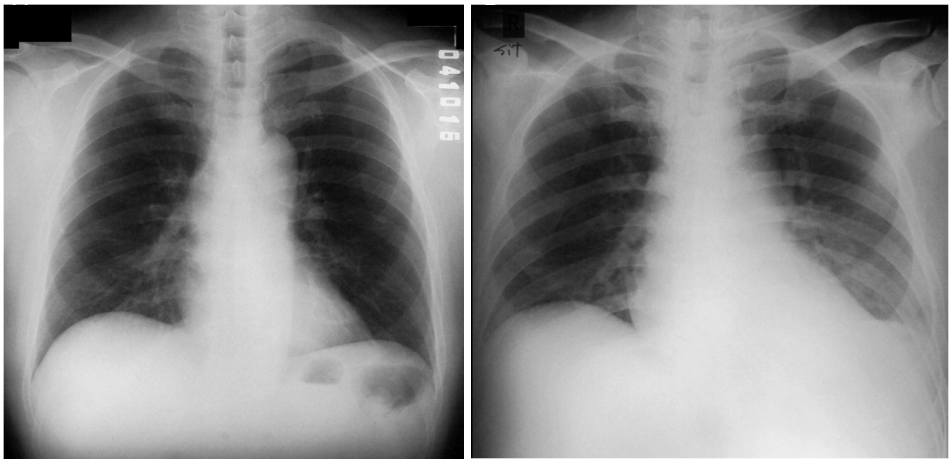

Fig. 1. A, Chest X-ray findings were within normal limits with a cardiothoracic ratio of 50%; B, Chest X-ray after rupture of the pheochromocytoma showed pulmonary congestion and effusion, and an increase in the cardiothoracic ratio to 56%.

mg/dl, total cholesterol 416 mg/dl, triglyceride 598 mg/dl, and serum potassium 5.3 mEq/l. Urinalysis showed urinary protein 3+ and urinary occult blood 3+ (Table 1). Electrocardiography showed sinus tachycardia. Chest X-ray findings were within normal limits, with a cardiothoracic ratio of 50% and no lung abnormalities (Fig. 1-A).

Abdominal CT detected a left adrenal tumor 50 mm in diameter (Fig. 2-A), and T2-weighted magnetic resonance imaging (MRI) showed high signal intensity in the tumor (Fig. 2-B). These findings suggested that the left adrenal tumor was a pheochromocytoma. An ultrasonographic study of the thyroid showed bilateral adenomatous nodules (2 mm and 5 mm in the right

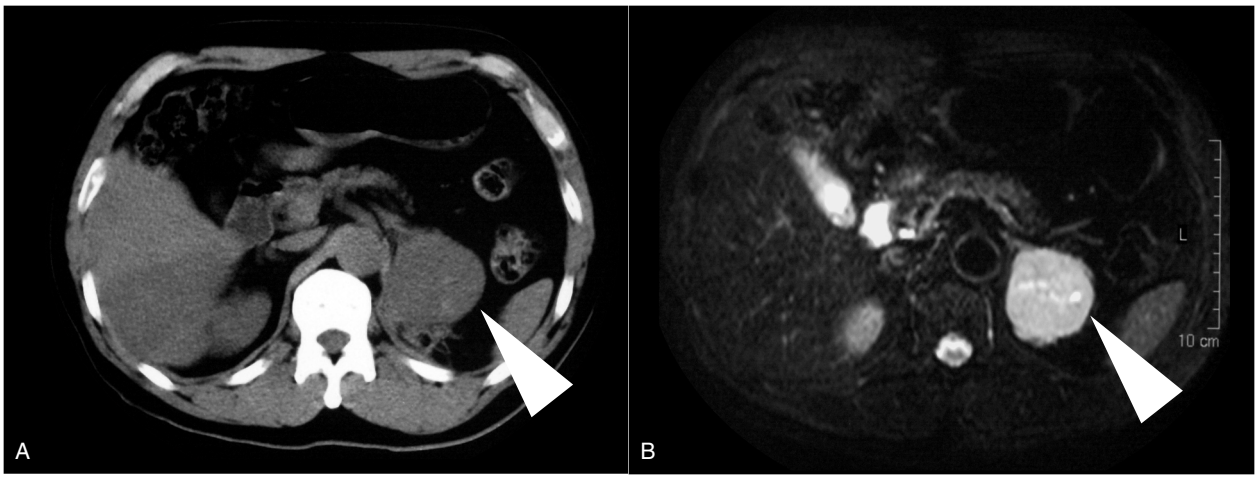

Fig. 2. A, Abdominal CT showed a 50-mm left adrenal tumor; B, MRI T2-weighted image showed high signal intensity in the left adrenal tumor. The findings suggested that the tumor was a pheochromocytoma. White arrowheads indicate the left adrenal pheochromocytoma.

Table 2

Endocrinological Tests	A/D	20th hospital day	normal range
Plasma epinephrine	3217	61	<100 (pg/ml)
Plasma norepinephrine	2208	462	100–450 (pg/ml)
Plasma dopamine	33	15	<20 (pg/ml)
Urinary epinephrine	1660	29.5	3.4–26.9 (μg/day)
Urinary norepinephrine	1250	246	48.6–168.0 (μg/day)
Urinary dopamine	460	652	365–961.5 (μg/day)
Urinary metanephrine	9.78	0.44	0.04–0.19 (mg/day)
Urinary normetanephrine	4.04	0.63	0.09–0.33 (mg/day)
Urinary vanillylmandelic acid	20.3	ND	1.5–4.3 (mg/day)

A/D, admission; ND, not determined

and left, respectively), but no findings of medullary thyroid carcinoma or parathyroid adenoma (data not shown).

Hypertensive emergency due to pheochromocytoma was suspected because of the patient's marked hypertension, severe headache, nausea, vomiting, and elevated serum creatinine level. Doxazosin mesilate, an α1-adrenergic blocker, and nifedipine, a calcium channel blocker, were given orally, but the patient vomited the medicines because of nausea. Therefore, 5 mg of phentolamine mesilate was administrated intravenously. However, this did not improve the hypertension, and another 5 mg of phentolamine mesilate was therefore added. This resulted in a decrease of the systolic blood pressure to 100 mmHg. However, the systolic blood pressure again increased to around 200 mmHg, and so intravenous administration of nicardipine hydrochloride was started. This had no effect, and therefore intravenous administration of diltiazem hydrochloride and nitroglycerin was added to suppress the hypertension.

The results of endocrinological examination included plasma epinephrine 3217pg/ml, plasma norepinephrine 2208 pg/ml, plasma dopamine 33 pg/ml, urinary epinephrine 1660 μg/day, urinary norepinephrine 1250 μg/day, urinary dopamine 460 μg/day, urinary metanephrine 9.78 mg/day, urinary normetanephrine 4.04 mg/day, and urinary vanillylmandelic acid 20.3 mg/day (Table 2). These findings were compatible with pheochromocytoma.

On the third hospital day, the patient suddenly complained of the left back pain. Physical examination revealed a distended abdomen without tenderness, and a decrease of bowel sounds. He complained of tenderness in the left lower back. Chest X-ray showed pulmonary congestion and effusion, and an increase of the cardiothoracic ratio to 56% (Fig. 1–B). Plain abdominal X-ray examination revealed multiple dilated small-intestinal loops (Fig. 3). Abdominal CT showed enlargement of the left adrenal tumor to 90 mm in diameter, and retroperitoneal hematoma (Fig. 4–A). Thus, rupture of pheochromocytoma was suspected.

Paralytic small-intestinal ileus was treated by decompression with a Miller-Abbot (M–A) tube, fluid replacement including intravenous hyperalimentation, and administration of meropenem trihydrate 1 g/day. Because systolic blood pressure stabilized at around 130 mmHg on the fifth hospital day, venous adminis-

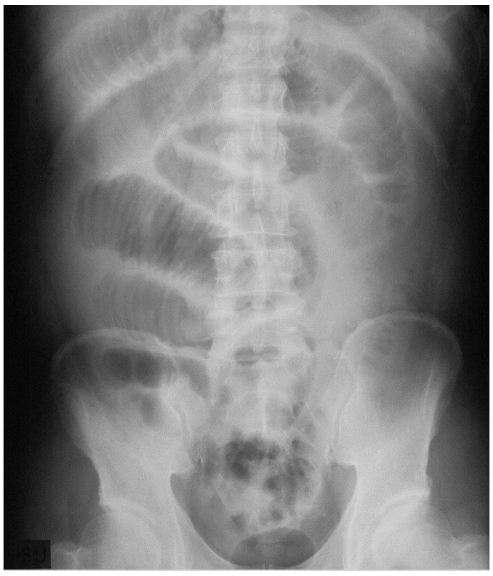

Fig. 3. Abdominal X-ray film showed multiple dilated small-intestinal loops.

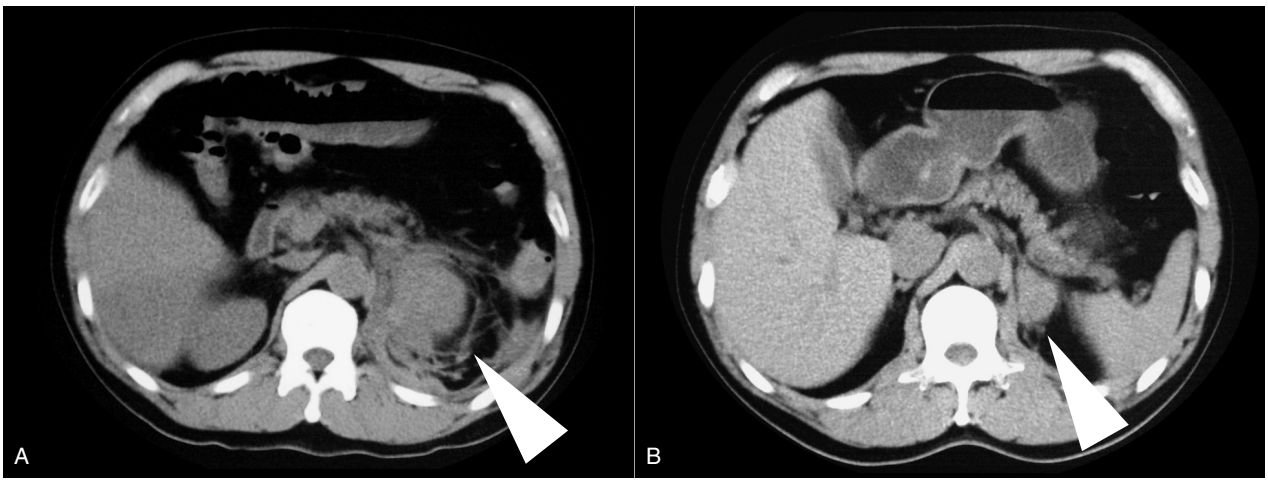

Fig. 4. A, Abdominal CT on the third hospital day showed rupture of the pheochromocytoma; The pheochromocytoma was enlarged to 90 mm in diameter, and surrounded by a retroperitoneal hematoma. White arrowhead indicates rupture of the pheochromocytoma; B, Abdominal CT on the 23rd hospital day showed shrinkage of the ruptured pheocromocytoma to 30 mm in diameter, and absorption of the retroperitoneal hematoma. White arrowhead indicates shrinkage of the ruptured pheochromocytoma.

tration of nicardipine hydrochloride and nitroglycerin was withdrawn.

On the 10th hospital day, small-intestinal ileus was improved, and the M-A tube was extracted. On the 14th day, oral administration of doxazosin mesilate 2 mg/day was started, and venous administration of diltiazem hydrochloride was stopped. The results of endocrinological examinations on the 20th hospital day included plasma epinephrine 61 pg/ml, plasma norepinephrine 462 pg/ml, plasma dopamine 15 pg/ml, urinary epinephrine 29.5 μg/l, urinary norepinephrine 246 μg/l, urinary dopamine 652 μg/l, urinary metanephrine 0.44 mg/l, and urinary normetanephrine 0.63 mg/l (Table 2). The patient's blood pressure remained stable at around 110/70 mmHg. Abdominal CT on the 23rd hospital day showed shrinkage of the ruptured pheochromocytoma to 30 mm in diameter, and absorption of the retroperitoneal hematoma (Fig. 4B). The patient was discharged on the 28th hospital day.

The patient did well on an outpatient basis, and blood pressure was maintained at around 110/60 mmHg on medication with doxazosin mesilate 2 mg/day. The patient was never aware of headache, palpitation, sweating, paroxysmal hypertension, or orthostatic hypotension. Twenty days after discharge, iodine 131-labeled metaiodobenzylguanidine (MIBG) scintigraphy confirmed involvement of the left adrenal gland, but there was no evidence of involvement of other organs (Fig. 5).

The patient was admitted to the hospital again 57 days after initial discharge, and underwent laparoscopic left adrenalectomy, necessitating nine days of hospitalization. Pathological examination showed that

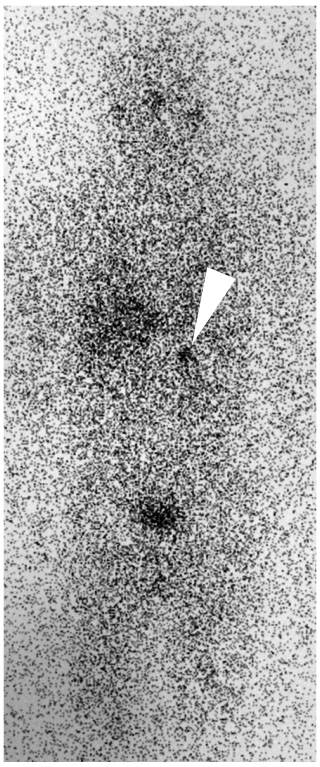

Fig. 5. Iodine 131-labeled metaiodobenzylguanidine scintigraphy confirmed involvement of the left adrenal gland. White arrowhead indicates the left adrenal pheochromocytoma.

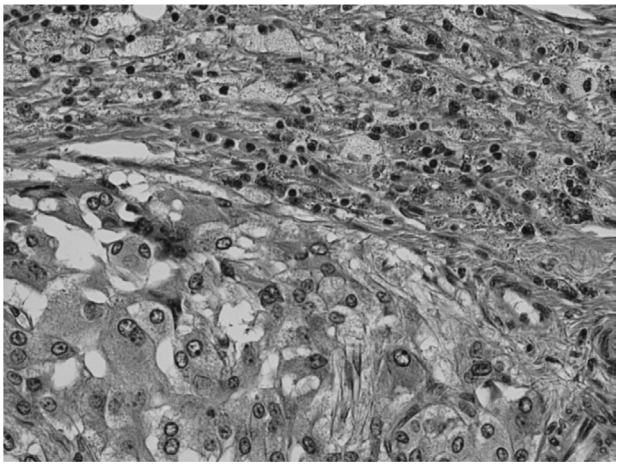

Fig. 6. Adrenalectomy specimen (H&E: original magnification × 50). The left adrenal gland tumor was composed of cells possessing round nuclei and abundant eosinophilic cytoplasm, arranged in a Zellballen pattern. Hemosiderin pigmentation and coagulation necrosis were frequently seen.

the left adrenal gland tumor was composed of cells possessing round nuclei and abundant eosinophilic cytoplasm, arranged in a Zellballen pattern. Hemosiderin pigmentation and coagulation necrosis were frequently seen (Fig. 6).

At the time of writing, four years after discharge, the patient has been doing well. Endocrinological examination showed a normal range of plasma catecholamine levels, and abdominal CT confirmed no recurrence of the pheochromocytoma (data not shown).

DISCUSSION

We have described a 58-year-old Japanese man with ruptured pheochromocytoma. Rupture of an adrenal pheochromocytoma is extremely rare, but some previous reports are available [5–7]. The exact mechanism of pheochromocytoma rupture is unknown, but a high intracapsular pressure may tear the capsule and also cause necrosis of the tumor. The high pressure may be caused by rapid tumor growth or intratumoral hemorrhage. Elevation of blood pressure is probably associated with vasoconstriction in the tumor and subsequent necrosis, causing massive release of catecholamine into the circulation. Our pathological findings of hemosiderin deposition and coagulation necrosis supported this assumption.

α1-Adrenergic blockers are the mainstay of treatment for hypertension due to pheochromocytoma [8]. However, it has been suggested that α1-adrenergic blocker may cause massive intratumoral hemorrhage [9] and or avascular necrosis of the tumor [10]. The proposed effects of α1-adrenergic blocker are suggested to be lowered systemic blood pressure, causing the already precarious blood supply within the tumor to become adequate. α1-Adrenergic blocker may result in vasodilatation within the tumor, flooding an already necrotic area with blood and initiating progressive interstitial hemorrhage within the tumor [9].

Phentolamine mesilate, a parenteral α1-adrenergic blocker, is used to treat hypertensive emergency caused by pheochromocytoma [11, 12]. Intravenous administration of phentolamine mesilate was needed in the present patient with hypertensive emergency, because he was unable to take oral medicine due to nausea and vomiting. There are a few reports suggesting that rupture of pheochromocytoma may be related to a decrease in blood pressure induced by phentolamine mesilate [9, 10]. It is unclear whether phentolamine mesilate was associated with rupture of the pheochromocytoma in the present case. However, it was indicated that careful use of phentolamine mesilate is necessary.

After recovery from rupture of the pheochromocytoma, the levels of plasma catecholamines, urinary catecholamines, urinary metanephrine, and urinary normetanephrine decreased. In particular, the values of plasma epinephrine and plasma dopamine decreased to the normal ranges, and it became easy to maintain the blood pressure at 110/60 mmHg with doxazosin mesilate at 2 mg/day in comparison with the first admission episode. Although MIBG scintigraphy confirmed involvement of the left adrenal gland, it was possible that progressive pheochromocytoma destruction caused by the rupture led to a pronounced decrease in catecholamine production, as described previously [10, 13].

Pulmonary congestion and effusion, an increased cardiothoracic ratio, and paralytic small-intestinal ileus were observed after rupture of the pheochromocytoma. Pulmonary edema is one manifestation of pheochromocytoma. In most patients with pheochromocytoma, pulmonary edema is cardiogenic in origin, because

marked catecholamine release from the tumor may cause cardiovascular emergencies, such as hypertensive emergency, myocarditis, cardiomyopathy, and myocardial ischemia [14, 15]. In addition, noncardiogenic pulmonary edema may also occur [16]. As an increased cardiothoracic ratio with pulmonary congestion was observed in this patient, it was thought that the pulmonary congestion was cardiogenic in origin. Stimulation of α receptors causes hyperpolarization and relaxation of intestinal smooth muscle, constriction of intestinal vascular smooth muscle, and contraction of ileocolic sphincters. Stimulation of β2 receptors causes arteriolar dilatation and intestinal smooth muscle relaxation. Therefore, high levels of circulating catecholamines will result in a decrease of intestinal peristalsis, motility, and tone. It has been reported that patients with pheochromocytoma develop ileus [17]. In the present patient, high levels of circulating catecholamines secreted by the ruptured pheochromocytoma caused paralytic small-intestinal obstruction.

Once a pheochromocytoma has been diagnosed, surgical treatment should be considered. Surgical approaches for ruptured pheochromocytoma involve either emergency or elective surgery. It is reported that emergency surgery is associated with a high mortality rate, whereas no mortality has been reported in patients undergoing elective surgery with good control of total body water using α-adrenergic blocker and fluid infusion therapy [4, 8]. After rupture of the pheochromocytoma in the present patient, blood pressure, total body water, and nutrition were maintained with α-adrenergic blocker, fluid replacement, and intravenous hyperalimentation. The patient was subsequently readmitted and underwent elective laparoscopic adrenalectomy. Thus an elective surgical approach was able to save the patient.

In conclusion, we have described a patient with ruptured pheochromocytoma. Phentolamine mesilate is a useful α-adrenergic blocker, especially in patients with nausea and vomiting due to pheochromocytoma. However, careful administration of this agent is needed, because rupture of pheochromocytoma may be related to a decrease in blood pressure induced by phentolamine mesilate.

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