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A Case of Pheochromocytoma Combined with Catecholamine Cardiomyopathy*)

Hideo MATSUURA[1], Masaharu YAMAMOTO[1], Shigeko KUBO[1], Hamed OEMAR[1], Ikuo KANAZAWA[1], Satoko MASAOKA[1], Akira YUASA[1], Yukiko TSUCHIOKA[1], Goro KAJIYAMA[1], Hiroki MITSUDA[2], Hikaru SATO[3] and Hiroyuki KUROGANE[4]

1) *The First Department of Internal Medicine, Hiroshima University School of Medicine, 1-2-3, Kasumi, Minami-ku, Hiroshima 734, Japan.*
2) *Hiroshima City Asa General Hospital, Hiroshima.*
3) *Hiroshima City Hospital, Hiroshima* 730.
4) *The Division of Cardiology, Himeji Brain and Heart Center, Hyogo.*

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ABSTRACT

A 40-year-old female with the left adrenal pheochoromocytoma showed ECG abnormalities and the clinical features similar to acute myocardial infarction. Enzymological studies and UCG findings in the acute phase revealed the same pattern as those in acute myocardial infarction. After finding the existence of the left adrenal pheochromocytoma, the differential diagnosis between myocardial infarction and catecholamine cardiomyopathy as the cause of ECG, UCG and enzymological changes was tried to make. However, the differential diagnosis was not established during the preoperative period.

The continued ECG abnormilities until the surgical removal of the tumor disappeared one week after the operation. Norepinephrine infusion test performed one and two weeks and 21 months after the operation could evoke the T wave change which disappeared soonly after norepinephrine infusion was stopped. Coronary angiography and ^{201}Tl myocardial scintigraphy revealed the normal findings. These findings suggested that catecholamines released from pheochromocytoma was the cause of the myocardial damages and ECG abnormalities.

The patient with catecholamine cardiomyopathy due to the adrenal pheochromocytoma whose ECG abnormalities continued until surgical treatment was reported.

INTRODUCTION

Catecholamines secreted from the sympathetic nerve ending and the adrenal medulla play the important roles to modulate the cardiac function and hemodynamics. These catecholamines have been widely used in the clinical and the experimental fields, but many harmful effects of catecholamines in excessive does upon the myocardium had been reported in the decade of this century by Pearce (1906)[10], Freisher et al. (1909, 1910)[3,4], and Christian et al. (1911)[1]. They reported such harmful effects as the expermental myocarditis in the rabbit hearts using epinephrine. Since 1940s, the electrocardiographic (ECG) abnormalities associated with pheochromocytoma have been reported (Espersen, 1947; Northfield, 1968, Pelkone, 1963 and Sayer, 1953)[2,9,11,14]. Lepeschkin et al.[7] reported the effects of catecholamines upon ECG of 100 normal subjects. Catecholamines induced myocardial damages and ECG abnormalities have been called as experimental myocarditis, catecholamine myocarditis or catecholamine cardio-

*) 松浦秀夫, 山本正治, 久保慈子, ハメッド・オエマル, 金沢郁夫, 正岡智子, 湯浅 明, 土岡由紀子, 梶山梧朗, 満田広樹, 佐藤 光, 鋏 寛之：カテコールアミン心筋症を合併した褐色細胞腫の1症例

myopathy.

From the clinical aspects, the important problem is how to make the differential diagnosis between acute myocardial infarction and catecholamine cardiomyopathy in the acute phase when the patient with pheochromocytoma shows ECG abnormalities, like as prolongation of QT interval, ST-T changes and/or abnormal Q wave, combined with the clinical features, such as chest pain, short of breath and cold sweat. The present case with the left adrenal pheochromocytoma was characaterized by hypertensive crisis associated with the clinical features similar to acute myocardial infarction. ECG abnormalities continued during the pre-operative period in spite of using adrenoceptor blocking agents, but they were disappeared at 9 days after operation. Coronary angiography and ^{201}Tl myocardial scintigraphy performed after operation failed to demonstrate the myocardial infarction and exogenous norepinephrine infusion test could evoke the same ECG abnormalities as that in the pre-operative period.

From these findings, the authors reported this case as catecholamine cardiomyopathy due to pheochromocytoma.

CASE REPORT

The patient was a 40-year-old female who had three normal deliveries and had appendectomy 6 years previously. She had no complaint until January, 1981, when she complained of palpitation. At June 2, 1981, she was initially pointed out hypertension, 180/110 mmHg. On the day of the admission, June 4, 1981, she suddenly had the feeling of the chest opression, headache and nausea. She consulted to a physician and was send to an emergency hospital and lost her consciousness. Since her ECG showed the similar pattern to acute myocardial infarction, she was referred to our hospital.

On admission, blood pressure (BP) was 150/120 and heart rate was 130/min. She was pale and had cold sweat. Her consciousness was drawsy. Systolic murmur was audible on the apex and moist rales were audible on both lung fields. No mass was palpable in the abdomen. Neurological findings were normal. Acute myocardial infarction was suspected because of ECG abnormalities as shown in Fig. 1. Enzymological examinations (Fig. 2) showed the increase in serum CPK, GOT and LDH,

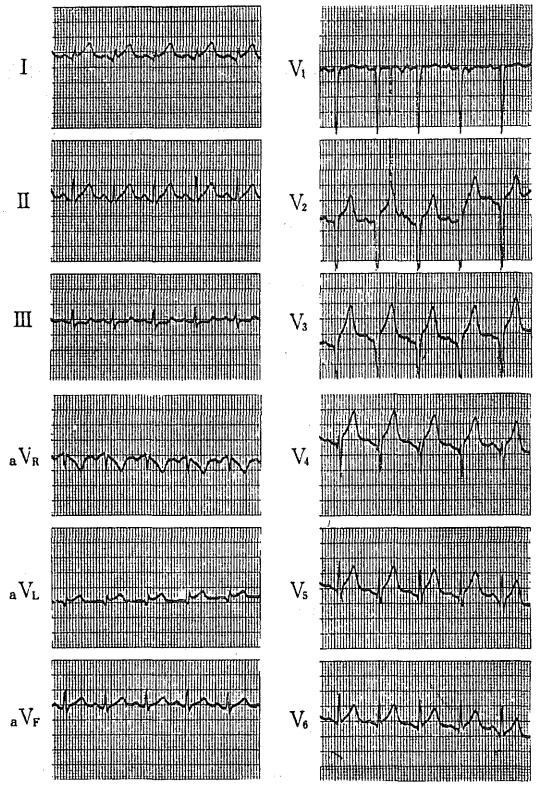


Fig. 1. ECG recorded on admission showed ST elevation in leads I, aV$_L$, V$_{2-6}$ and QS pattern in V$_2$, V$_3$.

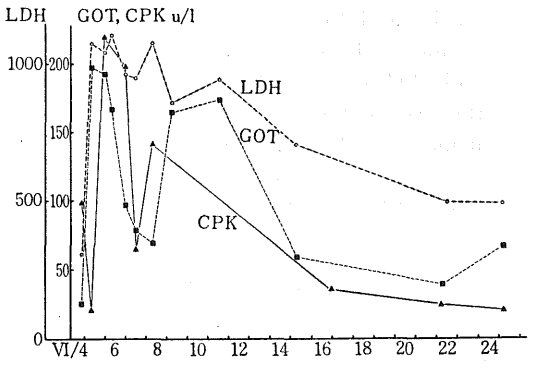


Fig. 2. The time course of the serum enzymes. Elevated CPK, GOT and LDH showed the same pattern as in acute myocardial infarction.

seemed to support this diagnosis. Re-elevation in CPK and GOT were observed at June 8. Other laboratory findings were indicated in Table 1. Inflammatory findings except blood sedimentation rate were observed. The chest X-ray film showed 50% in CTR.

Since hypertension and tachycardia had con-

Table 1. Laboratory findings on admission

Urine: protein (−), sugar (−), urobilinogen (N), sediments; RBC 1-2/F, WBC 5-6/F, epithelium 1/F

Stool: occult blood (−), warm egg (−)

Blood Analysis: RBC 582×10^4, Hb 15.7 g/dl, Ht 45.2%, WBC 18500 (non-seg. 26%, II35%, III 13%, IV II%, Baso. 1%, Eosino. 0%, Lymph. 13%, Mono. 1%) Platelets 28.9×10^4, Blood Type A, Bleeding Time 2.5 min, Coagguration Time 6 min, P. T. 10 sec (190%), P. T. T. 44.1 sec, Fibrinogen 448 mg/dl, FDP 10 μg/dl, BSR 1° 6 mm, 2° 18 mm

Serological Examinations: Wa-R (−), HBs Ag (−), HBs Ab (−), CEA (−), ASLO (−), CRP (++), RA (−)

Liver Function Tests: T. P. 8.0 g/dl (Alb 62.5%, α_1 4.0%, α_2 12.9%, β 10.4%, γ 10.2%), A/G 1.50, IgG 1050 mg/dl, IgA 280 mg/dl, IgM 230 mg/dl, TTT 1 u., ZTT 2 u., t-Bili. 0.8 mg/dl, d-Bili. 0.2 mg/dl, GOT 197 u/l, GPT 92 u/l, LDH 1075 u/l (I 29%, II 31%, III 21%, LV 10%, V 9%), Ch. E. 5790 u/l, Al. P. 730 u/l, LAP 67 u/l, γ-GTP 96 u/l, CPK 219 u/l (MM 92%, BB 0%, MB 8%), ICG R=3.1%, t-Chol. 209 mg/dl, HDL-C 46 mg/dl, LCAT 35.8 u/l, TG 88 mg/dl, Amylase 211 u., FBS 132 mg/dl

Renal Function Tests: BUN 35 mg/dl, Creatinine 1.9 mg/dl, Ccr. 95 ml/min, PSP 15 min 38%

Serum Electrolytes: Na 140 mEq/l, K 4.1 mEq/l, Cl 99 mEq/l, Ca 4.5 mEq/l, P 5.4 mg/l, Fe 86 μg/dl

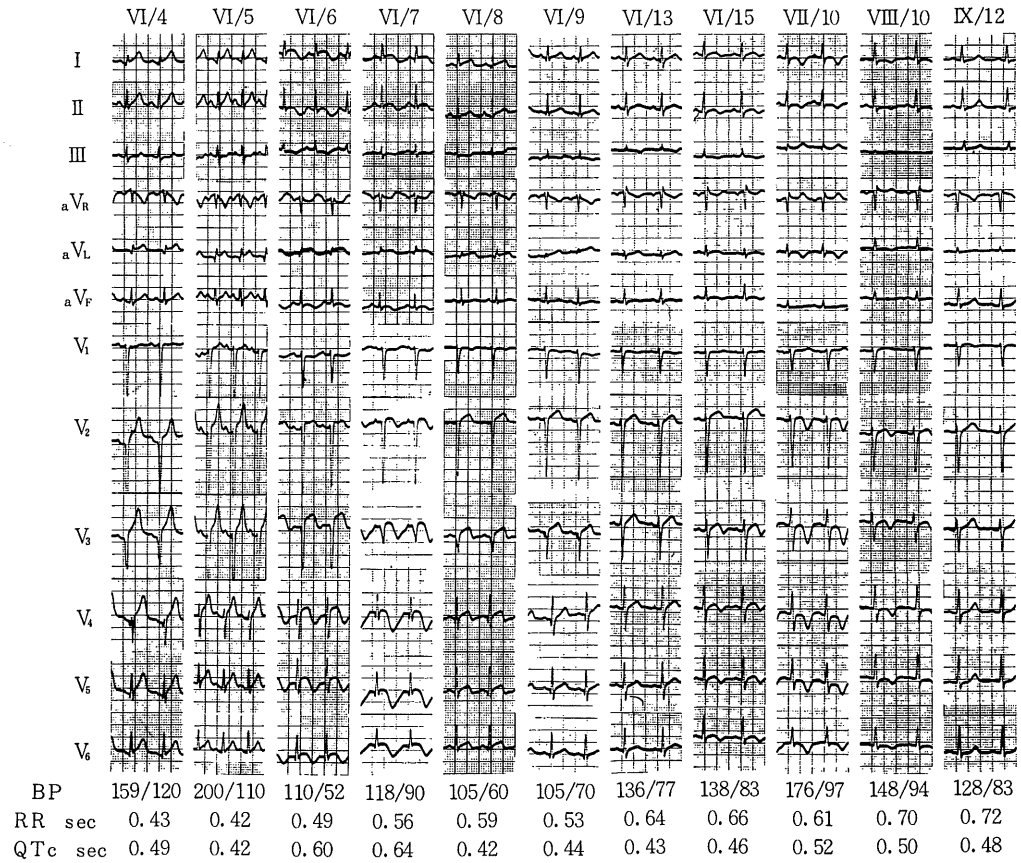


Fig. 3. The time course of ECG during admission. ST-T changes disappeared transiently at June 13, but it reappeared and continued until surgical operation. ECG recorded at September 12, 9 day after operation, showed the normal pattern.

tinued, pheochromocytoma was to be ruled out as the cause of ECG abnormalities and myocardial damages. The dramatic reduction in BP with phentolamine, from 193/91 to 89/53, indicated the existence of pheochromocytoma. However, ECG abnormalities did not disappear after phentolamine administration.

The time course of ECG changes was shown in Fig. 3. On the day of admission, June 4, 1981, ST elevation was observed in leads I, aV_L, V_{5-6}, and R wave was disappeared in leads V_{1-3}. These changes became apparent at June 5. At June 6, giant negative T wave was observed in leads I, II, aV_L, V_{2-6}, and QS in lead V_{2-3}. These abnormalities completely disappeared at June 15 transiently, but they continued until the surgical removal of the tumor in spite of using adrenoceptor blocking agents.

Table 2. Endocrinological examinations before and after surgical removal of the tumor

	Before Operation	After Operation
Urine		
Epinephrine (μg/day)	100	15.4
Norepinephrine (μg/day)	677-1000	122.6
Metanephrine (ng/day)	27.2-49.1	—
Normetanephrine (ng/day)	9.74-19.6	—
VMA (mg/day)	39.5-86.9	3.4
17-OHCS (ng/day)	4.8	6.0
17-KS (ng/day)	5.4	4.5
Blood		
Epinephrine (ng/ml)	0.64-10.0	0.02
Norepinephrine (ng/ml)	0.79-41.66	0.23
T_3 (μg/ml)	1.10	1.12
T_4 (μg/ml)	5.00	6.75
TSH (μg/ml)	1.25	1.66
Calcitonine (pg/ml)	62	100
PTH (ng/ml)	0.2	0.3
Cortisol (ng/ml)	153	144
PRA (ng/ml/hr)	9.20	0.70
PAC (pg/ml)	290	24

50 g OGTT

	Glucose (mg/dl)	IRI (ng/ml)	Glucose (mg/dl)	IRI (ng/ml)
Before	98	19.1	77	4.8
30 min	175	36.7	153	52.0
60 min	168	92.0	133	33.5
90 min	110	38.2	143	46.0
120 min	96	28.5	127	13.0
180 min	83	11.0	67	13.5

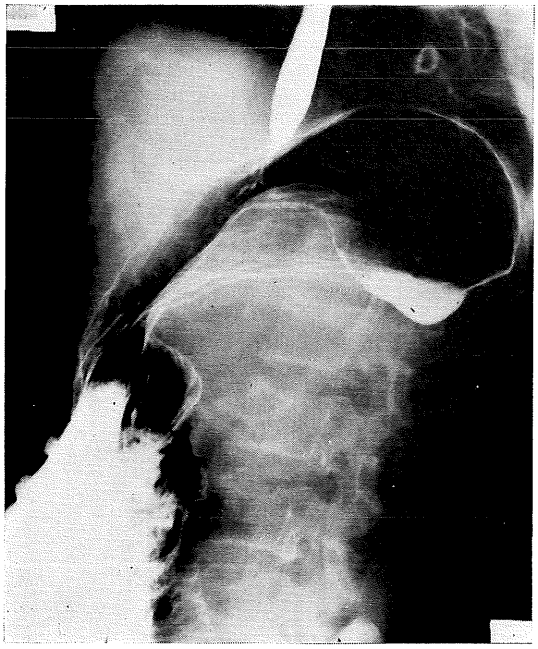


Fig. 4. Gastric fluoroscopy showed the compression of the grate curvature with a large mass

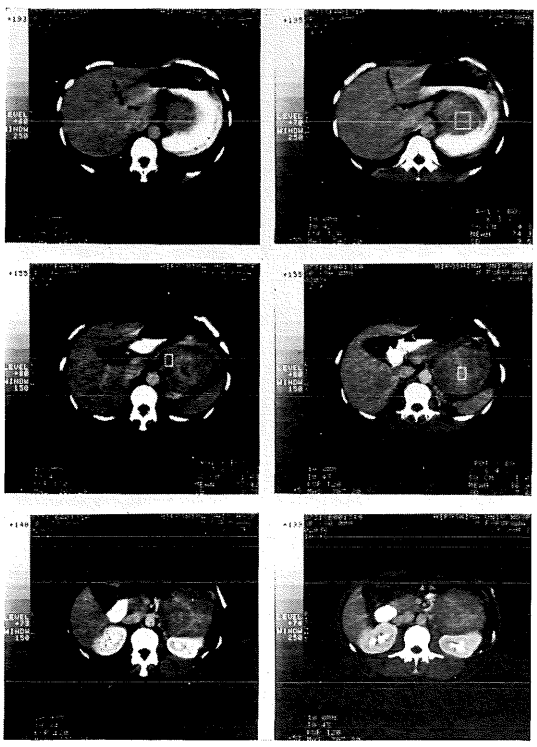
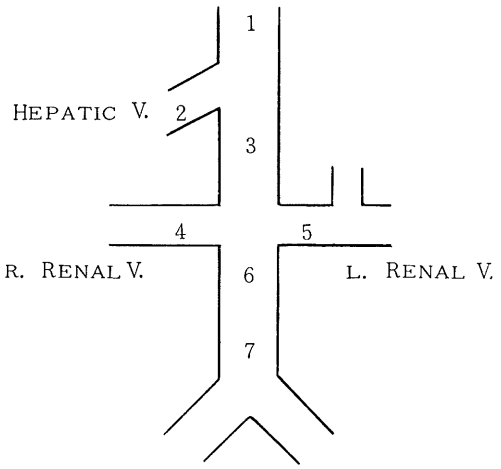


Fig. 5. Abdominal CT scan revealed a large mass between the stomach and the left kidney

QTc was prolonged, 0.49 sec to 0.64 sec, during pre-operative period. 9 days after operation (September 12), ECG returned to the normal pattern.

After the acute phase, variable examinations were performed to determine the diagnosis of pheochromocytoma. Plasma catecholamine concentration and urine excretion of catecholamines and their metabolites were very high as indicated in Table 2. Plasma renin activity (PRA) and plasma aldosterone concentration (PAC) were increased by β-adrenoceptor stimulation. Other endocrinological findings showed no abnormality. Glucose tolerance test revealed slight abnormality (Table 2).

Since the patient complained of palpitation and coldness of the extremities after meal, fluoroscopy of the stomach was performed. X-ray findings of the stomach showed the compression of the grate curvature with the tumor (Fig. 4).



	EPINEPHRINE	NOREPINEPHRINE
1.	3.97 ng/ml	4.70 ng/ml
2.	0.24 ng/ml	0.56 ng/ml
3.	5.17 ng/ml	5.76 ng/ml
4.	1.22 ng/ml	2.22 ng/ml
5.	7.42 ng/ml	6.73 ng/ml
6.	1.31 ng/ml	2.21 ng/ml
7.	1.13 ng/ml	2.05 ng/ml

Fig. 6. The plasma catecholamine concentration selectively sampled from each position as indicated in the figure, showed the remarkable elevation in the proximal portion of the inferior vena cava and in the left renal vein.

Abdominal CT scan showed the large tumor between the stomach and the left kidney (Fig. 5).

By selective venous catheterization, high concentration of catecholamines was observed in the blood from the left renal vein (Fig. 6). Abdominal aortography was performed to determine the position and the vascularization of the tumor. The tumor was recieved the nutrient vessels from the left renal artery and the ab-

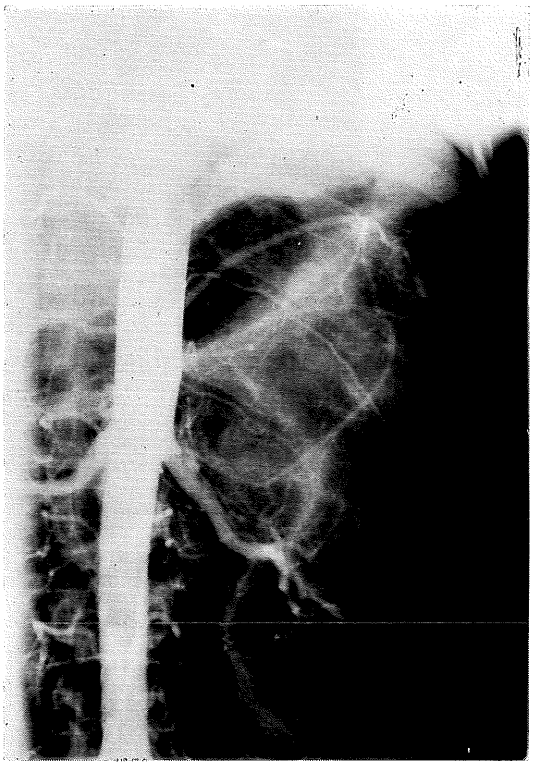


Fig. 7. Abdominal aortography showed the nutrient vessels from the abdominal aorta and the left renal artery

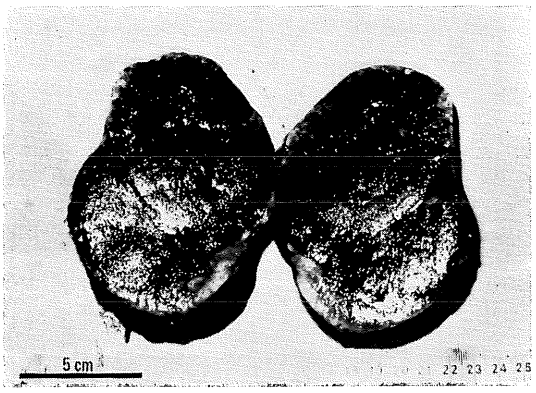


Fig. 8. Macroscopic finding of the excised tumor

dominal aorta (Fig. 7).

After the diagnosis of pheochromacytoma from the left adrenal medulla, α-β adrenoceptor blocking agents were administered to control BP and heart rate before the operation. BP and heart rate were controlled with these agents, but ECG abnormalities remained until the surgical removal of the tumor.

The tumor was removed at September 3, 1981. It was 479 g in weight (Fig. 8) and contained 4.80 mg/g wet weight of epinephrine and 3.58 of norepinephrine. The microscopic findings of the tumor revealed the typical pattern of pheochromocytoma (Fig. 9). After the operation, BP, heart rate, plasma catecholamine concentration, PRA and PAC returned to the normal range and glucose tolerance test showed the normal pattern (Table 2).

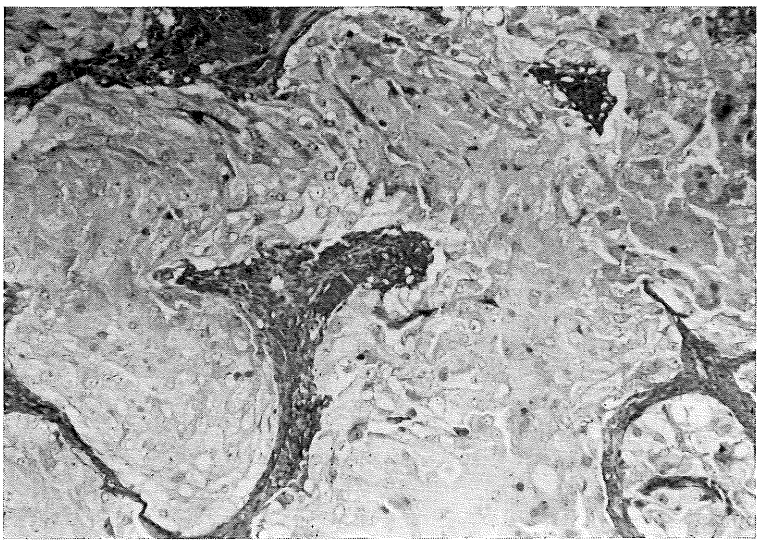


Fig. 9. Microscopic findings of the tumor showed the typical pattern of pheochromocytoma (Grimelius' staining, ×400).

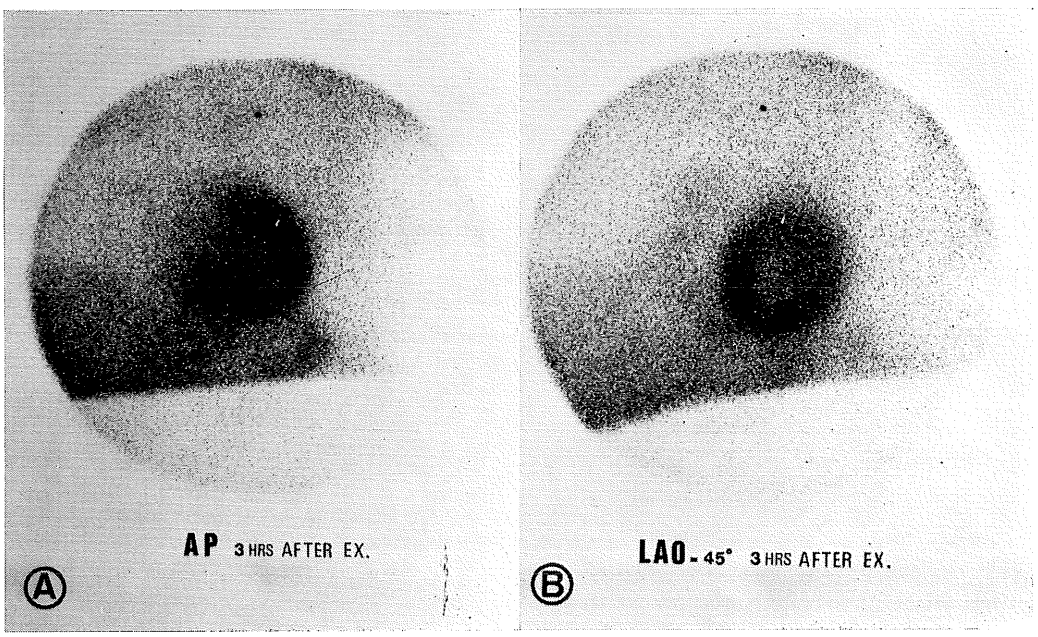


Fig. 10. ^{201}Tl myocardial stress scintigraphy performed after the surgical operation, (A) AP view and (B) LAO-45° view at three hours after exercise, revealed the normal pattern.

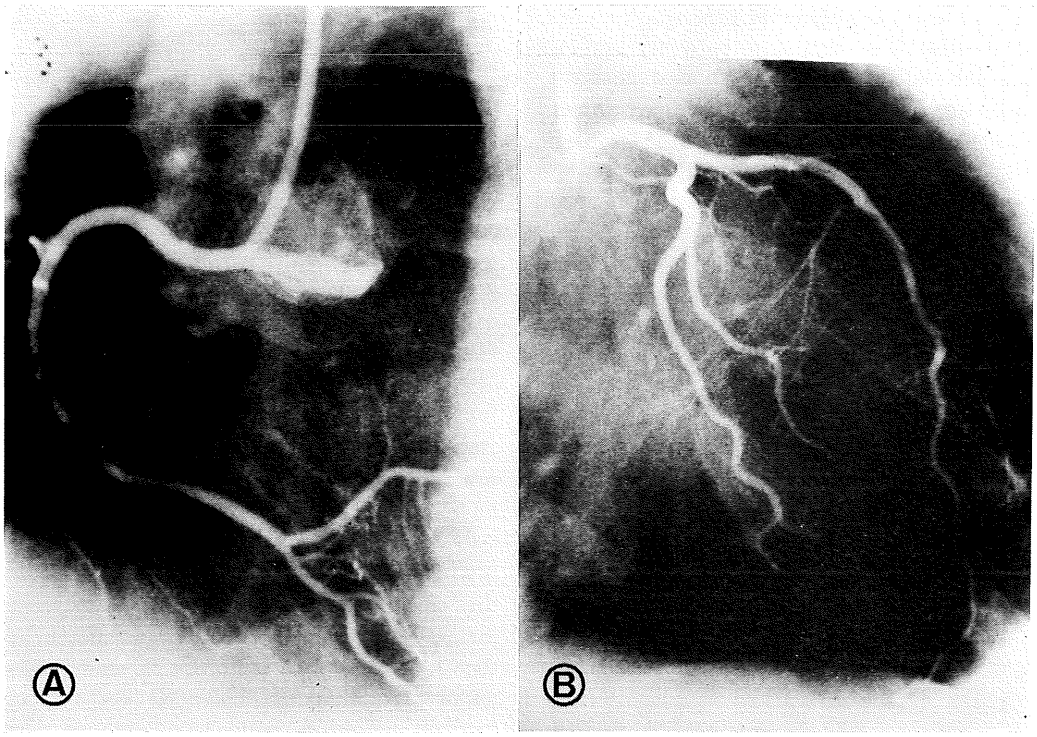


Fig. 11. Coronary angiography, (A) the right and (B) the left coronary artery, revealed no stenosis, but in generally, they seemed to be slightly spastic.

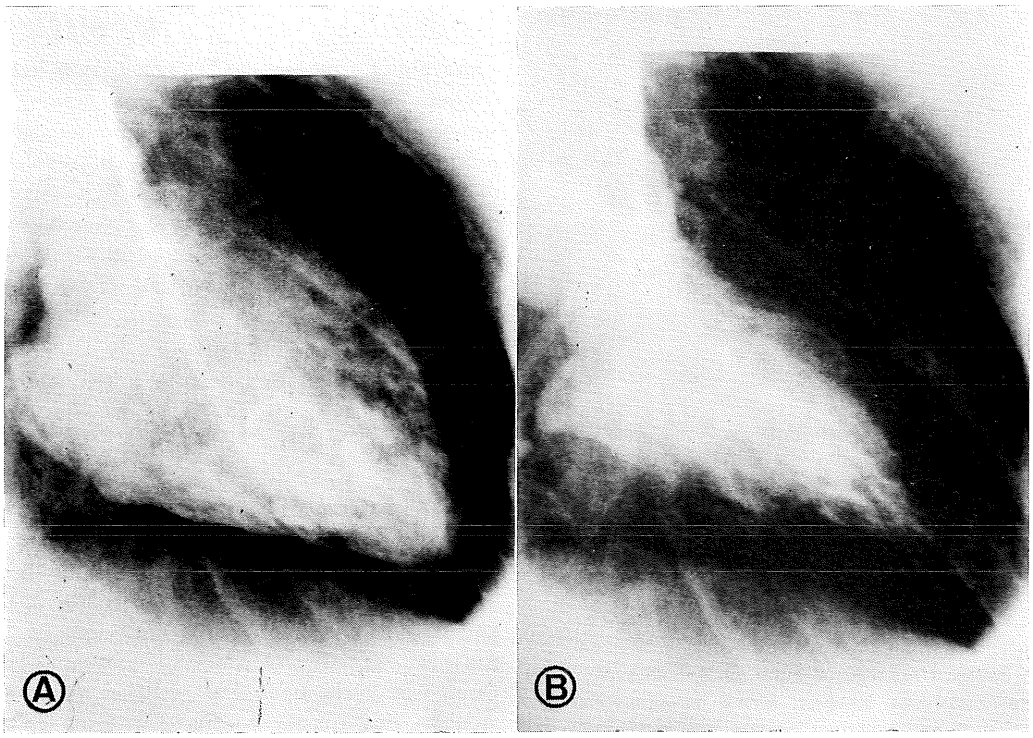


Fig. 12. Left ventriculography showed the normal contraction pattern in (A) diastolic and (B) systolic phases.

^{201}Tl myocardial scintigraphy revealed no ischemic lesion (Fig. 10) and coronary angiography showed no obstruction nor stenosis of coronary arteries, but in generally, the coronary arteries were slightly spastic (Fig. 11). Left ventriculography showed the normal contraction (Fig. 12). These examinations were performed only after the surgical removal of the tumor.

The exogenous norepinephrine infusion test at one and two weeks and 21 months after the operation evoked ECG changes, inversion of T wave, similar to the pre-operative ECG, but ECG changes disappeared soonly after the infusion test (Fig. 13). The depth of negative T wave seemed to depend on BP or elevation of plasma norepinephrine concentration after norepinephrine infusion. These findings suggested that ECG abnormalities in this patient was due to catecholamine cardiomyopathy.

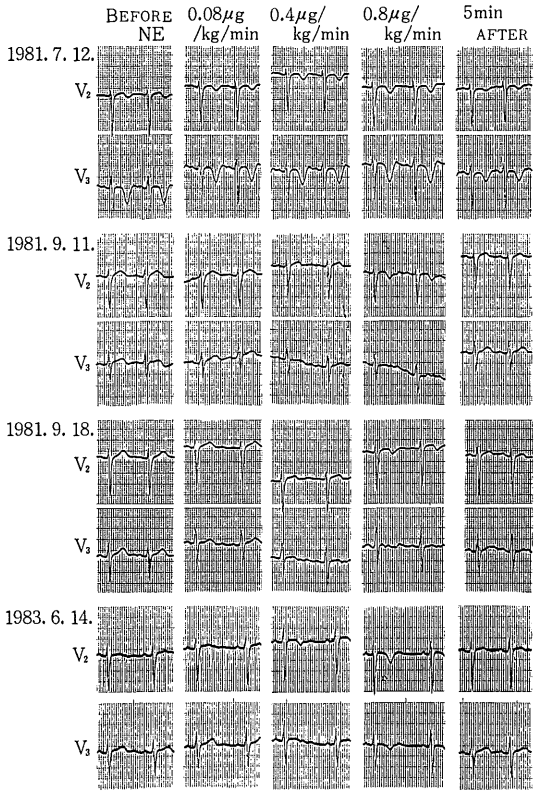


Fig. 13. Changes in ECG during and after norepinephrine infusion test performed before and after surgical removal of the tumor. The same T wave change was observed during norepinephrine infusion at one and two weeks and 21 months after operation, but it was disappeared 5 minutes after infusion.

DISCUSSION

The myocardial damages and ECG abnormalities due to catecholamines have been called as experimental myocarditis[3,4,10], catecholamine myocardities[5]. catecholamine induced myocarities[6], catecholamine cardiomyopathy or catecholamine cardiopathy[5], These variable nomenclatures of this pathological state reflect that the pathogenesis of myocardial damages with catecholamines have not been established. However, the histological findings of the myocardium have been similar in each literature[5,15,16]; 1) endocardial proliferation, thickening and edema, 2) myocardial edema, degenerating myofibrile, contraction band and picnosis of nucleus, 3) cellular infiltration by mononuclear cells, macrophages and polymorphonuclear leukocytes and 4) without significant stenosis of the coronary arteries. It has been reported that these findings are apparently different from that of myocardial infarction[16], and they can make the differential diagnosis between myocardial infarction and catecholamine cardiomoyopathy. Clinically, however, the differential diagnosis must be made without histological findings, only by the clinical features, the laboratory findings, ECG and UCG in the the acute phase. In our case, since enzymological studies showed the same course and UCG showed the same pattern as in acute myocardial infarction, the differential diagnosis was failed to establish. It was reported that ECG changes due to pheochromocytoma were reversible with pharmcological blockers[5] or surgical removal of the tumor[2,6,13]. In this case, phentolamine administered in the acute phase reduced BP remarkably, but failed to normalize ECG changes, and α-β adrenoceptor blockades administered in the chronic phase also failed to normalize ST-T changes. Coronary angiography for ruling out the organic stenosis of the coronary arteries did not performed before operation. Even if it was performed before operation and the organic stenosis was found in this patient, the possibility of the catecholamine cardiomyopathy should not be completely denied without histological support. Coronary angiography performed after the operation revealed no organic stenosis but spastic coronary arteries. These findings does not actively support the diagnosis of catecholamine cardiomyopathy without other

findings, because there is the possibility of myocardial infarction due to coronary spasm without organic stenosis. ^{201}Tl myocardial scintigraphy, left ventriculography and UCG recorded after operation, revealed the normal pattern respectively, indicated that the myocardial damage observed before operation might be the reversible change. NE infusion test performed one and two weeks and 21 months after operation could evoke the same T wave change as could be seen during pre-operative period. This T wave change was reversible after ending of NE infusion. From these findings mentioned above, the authors could diagnose this case as catecholamine cardiomyopathy. However, it was thought impossible to make the differential diagnosis between acute myocardial infarction and catecholamine cardiomyopathy in this case before operation. Furthermore, ECG changes, persisted until surgical removal of the tumor, made difficult to diagnose the pathological state. The clinical concept of catecholamine cardiomyopathy must be established to confirm a diagnosis without pathohistological finding.

From the clinical aspect, differential diagnosis between these pathological states becomes more difficult, when myocardial infarction is actually evoked by catecholamines released from pheochromocytoma. Priest[12] reported the young case of fatal myocardial infarction with pheochromocytoma, whose coronary artery revealed the organic change. On the other hand, Pelkonen et al.[11] reported 40-year-old female with fatal myocardial infarction. However, from the autopsy findings, myocardial damage was thought to be intoxication of noradrenaline. The diagnosis of these cases were decided by autopsy. As mention above, the precise mechanisms of myocardial damages with exessive catecholamines have not been established. However, many hypotheses which are thought to be the causes of catecholamine cardiomyopathy have been reported as follows; 1) relative hypoxia of myocardium produced by the positive inotropic effect and vasoconstrictive effect[5], 2) myocardial toxicity of catecholamine[11], 3) metabolic disturbance in the mitochondria[5] and 4) mechanical damage due to exessive positive inotropic effect[5]. These hypotheses are not useful for making the differential diagnosis between catecholamine cardiomyopathy and myocardial infarction, because they do not seem to produce the specific clinical features in catecholamine cardiomyopathy. Fujino et al.[5] reported that the existence of high catecholamine concentration of plasma was the important state to produce the pathologcal state or to make the differential diagnosis of catecholamine cardiomyopathy. The large part of the patients with catecholamine cardiomyopathy were able to diagnose rather easily by this concept. Since some case of acute myocardial infarction showed the high plasma concentration of catecholamines than pheochromocytoma and revealed hypertensive crisis in our hospital, the state of high concentration of plasma catecholamines and hypertensive crisis are not thought to be the sufficient condition for the diagnosis of catecholamine cardiomyopathy. Clinically, however, the high plasma concentration of catecholamines and reversible ECG abnormalities should be helpful to make the diagnosis of catecholamine cardiomyopathy.

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