Takotsubo Cardiomyopathy during Acute Adrenal Crisis due to Isolated Adrenocorticotropin Deficiency

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Abstract

We report a 69-year-old woman who had isolated adrenocorticotrophic hormone (ACTH) deficiency. Subsequently, she had Takotsubo cardiomyopathy during acute adrenal crisis. Replacement therapy with hydrocortisone sufficiently improved her cardiomyopathy. We conclude that her myocardial dysfunction was closely related to adrenal insufficiency and suggest that in certain circumstances, adrenal crisis may cause Takotsubo cardiomyopathy.

Key words: Takotsubo cardiomyopathy, adrenal crisis, isolated adrenocorticotropin deficiency

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Introduction

Takotsubo cardiomyopathy is characterized by transient left ventricular apical wall motion abnormality with electrocardiographic changes and minimal myocardial enzymatic release mimicking acute myocardial infarction, but without significant coronary artery disease (1-6). The causes of Takotsubo cardiomyopathy remain unclarified (7, 8).

Adrenal crisis is rapid and overwhelming intensification of chronic adrenal insufficiency. In the presence of severe stress, such as infection, trauma (including surgery), gastrointestinal upsets, or other stress, which requires an immediate increase in glucocorticoid, the blood pressure and the pulse fail as hypovolemic vascular shock ensues (9, 10). This state is usually termed adrenal crisis. However, cardiomyopathy induced by adrenal crisis is very uncommon (11-18).

Here, we report a case of Takotsubo cardiomyopathy during acute adrenal crisis due to isolated adrenocorticotrophic hormone (ACTH) deficiency. The possible relation of this disease combination will be discussed.

Case Report

A 69-year-old woman patient was admitted to Kyoto First

Red Cross Hospital in December 2002, complaining of general fatigue and loss of appetite for about six months. She had been in good health until that time. She lost 3 kg in 6 months. Family and past histories were noncontributory. When she delivered two healthy babies, there were no complications including massive bleeding or shock.

On admission, she was thin, 151 cm tall and weighed 40 kg. Her body temperature was 36.0°C, blood pressure; 106/60 mmHg, and pulse rate; 90/min. Physical examination showed no abnormalities except that she was apathic. Her skin and mucosa was free of unusual pigmentation. Laboratory findings revealed normochromic and normocytic anemia. Low serum levels of sodium (125 mEq/L), chloride, albumin and cholinesterase were evident (Table 1). On electrocardiogram (ECG), T waves were inverted in leads V1 and 2, and diphasic in leads V3, and 4, but these were minor abnormalities (Fig. 1). Since basal serum concentration of cortisol was undetectable (<0.1 µg/dL), further studies were designed for adrenocortical insufficiency.

However, on the following day, she was found to have impaired consciousness, and was pale and sweating. Her blood pressure was 80/58 mmHg, body temperature 40.2°C. The blood glucose was 0.88 mmol/L, and the diagnosis of acute adrenal crisis was made. She responded to intravenous glucose, sodium chloride and hydrocortisone. Initially, intravenous administration of 100 mg of hydrocortisone four

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Table 1. Laboratory Findings on Admission

Peripheral blood	
White blood cells	6,440 / μ L (3,000-8,600)
Neutrophils	53.2 % (40-76)
Lymphocytes	34.9 % (17-49)
Monocytes	5.9 % (2-11)
Basophils	0.5 % (0-2.5)
Eosinophils	3.2 % (0-8)
Red blood cells	346×10^4 / μ L (370-520)
Hemoglobin	10.7 g/dL (11.0-15.8)
Hematocrit	31.6 % (33-48)
Platelet	22.1×10^4 / μ L (15-40)
Serum chemistry	
Sodium	125 mEq/L (137-147)
Potassium	4.5 mEq/L (3.5-4.8)
Chloride	91 mEq/L (95-110)
Glucose	75 mg/dL (70-110)
Urea nitrogen	11 mg/dL (8-20)
Creatinine	0.43 mg/dL (0.4-1.1)
Uric acid	2.9 mg/dL (2.5-6.0)
Creatine kinase	140 IU/L (43-165)
Total protein	6.4 g/dL (6.0-8.0)
Albumin	3.7 g/dL (3.8-5.3)
AST *1	37 IU/L (7-40)
ALT *2	20 IU/L (7-40)
Lactate dehydrogenase	192 IU/L (106-211)
Choline-esterase	122 IU/L (190-420)
Total bilirubin	0.4 mg/dL (0.1-1.0)
Total cholesterol	168 mg/dL (150-220)
Triglyceride	76 mg/dL (50-150)
C reactive protein	0.6 mg/dL (<0.3)

Figures in parentheses indicate the normal ranges. *1: aspartate aminotransferase, *2: alanine aminotransferase.

times daily was started, and then 100 mg of hydrocortisone three times daily was given intravenously. Urine culture specimen obtained before antibiotic therapy demonstrated *E. coli* proliferation. On the third hospital day, she developed a sudden chest pain. From the ECG monitoring, ventricular tachycardia (VT) was detected. After intravenous administration of 50 mg of lidocaine, cardioversion with 200J was effective to terminate VT. Deep negative T waves in leads I, II, III, aVf and V1-6 were revealed on ECG (Fig. 1). Serum levels of creatinine kinase (CK)(6,732 IU/L), CK-MB (162 IU/L) and GOT (154 IU/L) elevated. Plasma levels of noradrenaline (1,038 pg/mL) and dopamine (507 pg/mL) also elevated. Echocardiography showed left ventricular systolic dysfunction [ejection fraction (EF) 33%]. On emergent cardiac catheterization, coronary arteriography showed no significant stenosis and the ergonovine provocation test was

negative. Left ventriculography revealed akinesis in antero-lateral, apical and diaphragmatic segments (Fig. 2). These findings were consistent with Takotsubo cardiomyopathy.

On the fifth hospital day, her chest pain disappeared. Steroid administration was changed to hydrocortisone 20 mg/day per os, and her clinical condition such as general fatigue and loss of appetite markedly improved in a few days. On the eighth hospital day, left ventricular wall motion abnormalities recovered except for apical segment, and systolic function improved (EF 74%) on the echocardiogram. Blood tests revealed CK of 168 IU/L, GOT of 29 IU/L. Three weeks later, left ventricular wall motion returned to normal. ECG showed improving T-wave inversion during the course, but was still apparent in leads V3-6 (Fig. 1). Abdominal computed tomography revealed no evidence of pheochromocytoma.

Figure 1. Time course of electrocardiogram. On admission (A), T wave changes were slight. At 2 days later (B), negative T waves were seen in leads I, II, III, aVf and V1-6. At 3 weeks later (C), improved T wave inversion was shown, but it was still slightly seen in leads V3-6.

Figure 2. Left ventriculography showed apical akinesis and basal hyperkinesis in the acute phase.

Endocrine studies showed decreased serum cortisol (<1.0 $\mu\text{g/dL}$) and a decreased urinary excretion of 17-hydroxy corticosteroids (17OHCS) (2.3 mg/day) with a decreased serum ACTH level (<5.0 pg/mL). Plasma cortisol responded slightly after a bolus injection of 0.25 mg ACTH, however, ACTH-Z (0.5 mg daily injection for 3 days) increased urinary 17OHCS excretion to 10 mg/day. ACTH-releasing hormone did not increase the plasma ACTH concentration (<5.0 pg/mL). Thyroid stimulating hormone (TSH) (basal value: 8.17- peak value: 36.0 $\mu\text{U/mL}$), prolactin (58-89 ng/mL), luteinizing hormone (LH) (0.9-12 mIU/mL), follicle stimulating hormone (19-43 mIU/mL) and growth hormone (GH) (3.31-30.6 ng/mL) were all increased by infusing TSH-releasing hormone, LH-releasing hormone and GH-releasing hormone. Plasma renin activity (0.8 ng/mL/h) and plasma aldosterone concentration (25 pg/mL) were normal. Therefore, the diagnosis of isolated ACTH deficiency was made. Magnetic resonance imaging (MRI) revealed no pituitary lesions nor adjacent lesions.

Discussion

Adrenal insufficiency may be secondary due to a primary failure in the elaboration of ACTH. The clinical signs of isolated ACTH deficiency are characterized by deficiencies of glucocorticoids and adrenal androgen, which is under the control of ACTH (9, 10, 19). The present case complained of fatigability and anorexia for 6 months, which agree with the clinical findings of deficiency of glucocorticoid. The cause of isolated ACTH deficiency is unclear, but it was considered that she had suffered from secondary insufficiency for at least 6 months (i.e., chronic adrenocortical insufficiency) and that pyelonephritis induced adrenal crisis.

Several reports from Japan have described patients with transient left ventricular apical ballooning without significant coronary artery disease. This asynergy is called Takotsubo cardiomyopathy (1-6), and the syndrome is now established worldwide (7, 8, 20, 21). However, universally accepted di-

Table 2. Reported Cases with Isolated ACTH Deficiency Complicated with Reversible Cardiomyopathy

Case	Age/ Sex	Underlying disorder	Trigger event	Symptoms	Coronary angiogram	Normalization of left ventricular contraction	Normalization of deep negative T waves	Biopsy pathology	Duration of hydrocortisone therapy	Reference
1	74/F	Degenerative joint disease	Knee joint surgery	-	No abnormalities	5 days	4 weeks	-	Details unclear	16
2	64/F	-	infection	unconsciousness	normal	2 weeks	5 weeks	-	Details unclear	16
3	62/F	-	-	fatigue	No significant stenosis	2 months	2 weeks	-	20 mg/d PO	17
4	53/F	Chronic thyroiditis	-	unconsciousness	No significant stenosis	2 weeks	-	Focal myocyte injury	200 mg/d IV for 1 week 15 mg/d PO for a further week	18
5	69/F	-	pyelonephritis	Chest pain	No significant stenosis	5 days	3 weeks	-	400 mg/d IV for 2 days 300 mg/d IV for 1 day 20 mg/d PO	Present case

PO: per os, IV: intravenously, d: day.

agnostic criteria for this syndrome are not yet available. Major clinical characteristics are that 1) the symptoms are similar to those of acute myocardial infarction; 2) most patients are elderly women; 3) takotsubo-like left ventricular dysfunction, which extends over more than one coronary artery region, is transient and dramatically resolves within several weeks. These findings are consistent with those of this patient. Myocardial damage is usually excluded when the CK-MB is <5 or 6% of the total CK activity (22). In the present case, the CK-MB was 2.4% of the total CK activity. The extent of CK elevation may result from not myocardial damage but skeletal muscle damage secondary to electrical cardioversion.

The present patient was shown to have isolated ACTH deficiency, and replacement therapy with hydrocortisone sufficiently improved her cardiomyopathy. Thus, we conclude that her myocardial dysfunction was closely related to adrenal insufficiency. Studies in adrenalectomized animals have suggested that cardiac function may be markedly impaired when stress is superimposed; increased catecholamine (cardioaccelerator) is toxic to a myocardium that is unprotected by glucocorticoids (23). Narayanan (24) showed that glucocorticoids are important for the maintenance of membrane calcium transport function in the cardiac sarcoplasmic reticulum from the rat, and may therefore affect myocardial contractility. He also demonstrated that microsomal phosphorylase activity in rat heart muscle is depleted by adrenalectomy. The decreased phosphorylase activity may impair glycogenolysis and thus induce the derangement of excitation-contraction coupling of the heart (25).

Cardiovascular complications have been associated with adrenal insufficiency (11-18, 26, 27). Four cases of reversible left ventricular dysfunction or cardiomyopathy associated with isolated ACTH deficiency have been reported (Table 2) (16-18). As far as we know, this is the first patient

who complained of chest pain and in whom isolated ACTH deficiency associated with acute adrenal crisis caused Takotsubo cardiomyopathy. A case similar to the present one has been reported (18); a partial empty sella was noted in that case (18), but MRI was normal in the present case. Therefore, the morphologically normal pituitary may induce isolated ACTH deficiency complicated with Takotsubo cardiomyopathy. Furthermore, in the past case (18), it took more days to normalize the left ventricular contraction than in our case. It took a few days to make the diagnosis and start hydrocortisone therapy. In the present case, acute adrenal crisis was diagnosed promptly and treatment with supplemental hydrocortisone began very early in the clinical course. It is possible that early supplemental hydrocortisone lead myocardial injury to recover soon in Takotsubo cardiomyopathy. In the past cases (16), there were no symptoms suggestive of heart disease and left ventricular wall motion abnormalities present mainly around the left ventricular apex, returned to normal in 5 days. Deep negative T waves normalized 4 weeks after corticosteroid administration.

The cause of left ventricular dysfunction in Takotsubo cardiomyopathy is still unknown (1-8). It may represent a catecholamine-mediated myocardial stunning that results from a combination of myocardial ischemia related to diffuse microvascular dysfunction and, in some cases, multivessel epicardial spasm and metabolic injury (7). In view of the absence of any apparent coronary vasospasm during coronary angiography, we determined that coronary artery vasospasm might not occur in the present case. However, we could not confirm the absence of coronary microvascular vasospasm.

It is possible that the cardiac injury observed in this patient was mediated by the sympathetic nervous system. Catecholamines can directly injure the myocardium (28, 29). In Takotsubo cardiomyopathy, physical stress is recognized

as an important predisposing factor (7). She was critically ill and undoubtedly had intense activation of the sympathetic nervous system. Experimentally, brain-mediated cardiac injury can be prevented by total cardiac sympathectomy (30). Pharmacologic sympathetic blockade with propranolol and phentolamine also prevents myocardial necrosis after subarachnoid hemorrhage (31). Although the evidence is strong that catecholamines can cause an acute reversible cardiac injury, it is unclear why the apex of the heart is affected and

the basal segments are spared. This may be partly explained by increased adrenergic receptor density in cardiac apical segments or increased apical myocardial responsiveness to adrenergic stimulation (32). Measurements of circulating catecholamine levels in patients presenting with the syndrome have shown inconsistent results (5). We suggest that in certain circumstances, adrenal crisis may cause Takotsubo cardiomyopathy.

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