Ampulla (Takotsubo) Cardiomyopathy Caused by Secondary Adrenal Insufficiency in ACTH Isolated Deficiency

SATORU SAKIHARA, KAZUNORI KAGEYAMA, TAKESHI NIGAWARA, YUKIE KIDANI AND TOSHIHIRO SUDA

Department of Endocrinology and Metabolism, Hirosaki University School of Medicine, 5 Zaifu-cho, Hirosaki, Aomori 036-8562, Japan

Abstract. We describe here a case of reversible ampulla (takotsubo) cardiomyopathy caused by secondary adrenal insufficiency in ACTH isolated deficiency. A 53-year-old woman was referred to our department for evaluation and treatment of unconsciousness. On admission, her plasma glucose level was 34 mg/dL, suggesting loss of consciousness due to hypoglycemia. Basal levels of ACTH, cortisol, and dehydroepiandrosterone sulfate in blood, and urinary free cortisol levels were all decreased. ACTH and cortisol levels were not adequately increased in response to CRH administration and the insulin tolerance test. Electrocardiography showed ST segment elevation and T wave inversion in leads V1–6. The coronary arteries were free of organic stenosis, and a left ventriculogram revealed severe hypokinesis, particularly in the anterior and posterior walls. Based on a diagnosis of adrenocortical insufficiency caused by ACTH isolated deficiency, hydrocortisone was administered. Two weeks after treatment, ultrasound studies of the heart showed recovery of left ventricular wall motion. Activation of the sympathetic nervous system, adrenocortical failure, and hypoglycemic attack were considered to be triggering factors for the takotsubo cardiomyopathy. Careful monitoring of cardiac function and appropriate treatments for both cardiomyopathy and adrenocortical failure are required to recover cardiac dysfunction.

Key words: Cortisol, Glucocorticoid, Catecholamine, ACTH, Cardiomyopathy

Received: January 22, 2007
Accepted: May 1, 2007
Correspondence to: Kazunori KAGEYAMA, M.D., Department of Endocrinology and Metabolism, Hirosaki University School of Medicine, 5 Zaifu-cho, Hirosaki, Aomori 036-8562, Japan

AMPULLA or “takotsubo” cardiomyopathy is a cardiac syndrome characterized by transient left ventricular dysfunction with chest pain, electrocardiographic changes and minimal release of myocardial enzymes [1]. Left ventriculograms show ballooning of the apex with systole, the shape of which resembles a type of bottle used in Japan for trapping octopus, the “takotsubo” [1]. Patients with this reversible cardiomyopathy typically suffer from preceding excess physical or emotional stress [1, 2], and pheochromocytoma, thyroid dysfunction, and anorexia nervosa are associated disorders [3, 4]. To date, only a small number of possible cases of adrenal insufficiency in adult patients have been reported in the literature [5–7]. In two such cases, the reversible cardiomyopathy was considered to be induced by secondary adrenal insufficiency [6, 7], although hormonal data were not reported in detail. We report here a case of reversible ampulla (takotsubo) cardiomyopathy caused by secondary adrenal insufficiency in ACTH isolated deficiency, providing hormonal data and describing the pathological findings.

Case Report

Clinical summary

In February 2006, a 53-year-old woman was referred to our department for evaluation and treatment of unconsciousness. At the age of 49 she had been diagnosed as having chronic thyroiditis. On admission to our hospital, her plasma glucose level was 34 mg/dL, suggesting loss of consciousness due to hypoglycemia. Conscious was recovered a few hours after treatment.
with glucose and hydrocortisone. The patient was not taking any hypoglycemic or anti-hypertensive drugs and was hypotensive with a blood pressure of 92/60 mmHg. Her thyroid was diffusely enlarged, and she had no pubic or axillary hair.

Peripheral blood tests on admission showed mild low levels of red blood cells \((367 \times 10^4/\mu L)\). Biochemical analyses revealed low levels of albumin \((2.9 \text{ g/dL})\), sodium \((133 \text{ mmol/L})\), and chloride \((97 \text{ mmol/L})\), and high levels of creatine kinase \((290 \text{ U/L})\), creatinine \((1.3 \text{ mg/dL})\), myoglobin \((5764 \text{ ng/mL})\), aspartate aminotransferase \((198 \text{ U/L})\), alanine aminotransferase \((66 \text{ U/L})\), and C-reactive protein \((4.8 \text{ mg/dL})\) in blood.

A few days after admission, electrocardiography showed ST segment elevation and T wave inversion in leads \(V_1-V_6\) (Fig. 1). Chest X-ray showed no cardiomegaly or congestion. The coronary arteries were free of organic stenosis, and left ventriculograms showed left ventricular (LV) apical ballooning and severe hypokinesis, particularly in the anterior and posterior walls (Fig. 2).

During a hypoglycemic attack (plasma glucose, 34 mg/dL), noradrenaline levels \((4.6 \text{ ng/mL})\) were remarkably elevated in blood, while adrenaline levels \(<0.01 \text{ ng/mL}\) were undetectable. Other hormonal data on admission showed decreased blood concentrations of ACTH, cortisol, and dehydroepiandrosterone sulfate (DHEA-S), decreased urinary free cortisol (UFC) levels, and mildly elevated serum LH, FSH, and TSH levels (Table 1). Neither ACTH nor cortisol levels were adequately increased in response to a mixed intravenous administration of CRH, GHRH, TRH, and LHRH, although other pituitary hormones were (Table 2a). The insulin tolerance test also showed loss of ACTH and cortisol responses to hypoglycemic stress (Table 2b). Magnetic resonance imaging of the head revealed a partial empty sella in the pituitary (not shown).

Based on a diagnosis of secondary adrenal insufficiency caused by ACTH isolated deficiency, hydrocortisone was started at 200 mg/day intravenously for one week and 15 mg/day per os for a further week. Two weeks after hydrocortisone treatment, ultrasound studies of the heart showed recovery of LV wall motion, and improvement of LV ejection fraction to 70%.

Light microscopic findings

Myocyte samples were obtained by biopsy during the ventriculography, and fixed in 10% formalin for
Serial sections were then prepared and stained with hematoxylin-eosin (HE). The stained sections revealed focal atrophy of myocytes and fatty infiltration of the myocardium (Fig. 3). There was no evidence of myocarditis or myocyte disarray.

**Discussion**

Patients with takotsubo cardiomyopathy typically suffer from various stressors or diseases [1–4]. We attributed the cause in our patient to secondary adrenal failure in ACTH deficiency, as evidenced by decreased
UFC levels and decreased ACTH, cortisol, and DHEA-S levels in blood, and the lack of adequate response of both ACTH and cortisol levels to CRH administration and the insulin tolerance test. Further, serum basal levels of LH, FSH, and TSH were mildly elevated, and all pituitary hormones except ACTH were increased in response to provocative tests. While there is still the possibility that the cardiomyopathy was caused by other factors, such as CRF deficiency, this would be very rare and we therefore made a diagnosis of takotsubo cardiomyopathy due to secondary adrenal failure in ACTH deficiency.

Addison’s disease, an autoimmune destruction of the adrenal glands, is the most common cause of primary adrenal insufficiency. The majority of cases of adrenal insufficiency accompanied by cardiomyopathy are reported to be caused by primary adrenal insufficiency in the pediatric age group [8–10]. Only three cases of reversible cardiomyopathy associated with adrenal insufficiency have been reported in adult patients [5–7]. Two of these cases were attributed to secondary adrenal insufficiency [6, 7], although hormonal data were not clearly shown. In all three cases, myocardial function improved after steroid therapy for adrenal insufficiency.

In our case, electrocardiography showed ST segment elevation and T wave inversion in leads V1–6, although the coronary arteries were free of organic stenosis. These changes are typical of takotsubo cardiomyopathy [11]. Our patient showed recovery of LV wall motion, but no remarkable changes in T wave inversion of the electrocardiography even after treatment with glucocorticoids, although reversible changes have been reported in some other cases [4, 6].

The mechanism underlying reversible cardiomyopathy is unclear. In our case, the biopsy specimen showed no contraction band necrosis, myocarditis, or myocyte disarray, but did show focal myocyte injury, suggesting that focal and disseminated myocardial damage had occurred. This finding is consistent with that of a previous case of takotsubo cardiomyopathy [12], indicating that focal atrophy of myocytes may be a typical feature of this disease. Plasma catecholamine levels are known to be elevated in some patients with stress-induced cardiomyopathy [13], suggesting a pathogenetic role for the increase in catecholamines. Previously, a case of pheochromocytoma accompanied by takotsubo cardiomyopathy was reported [14], and increased levels of catecholamines may therefore be related to the cardiomyopathy. In our case, noradrenaline levels were remarkably elevated, while adrenaline levels were undetectable during a hypoglycemic attack. Activation of a medullary enzyme, phenylethanolamine-N-methyltransferase, which synthesizes adrenaline from noradrenaline, requires high levels of glucocorticoids [15]. Therefore, adrenaline production is decreased without glucocorticoids, as in our case. We consider that increased noradrenaline levels or activation of the sympathetic nervous system contributed to the damage of cardiac myocytes causing cardiomyopathy in our case, because stimulation of the sympathetic nervous system would induce apoptosis or damage to the cardiac myocytes [16, 17].

Severe hyponatremia also leads to intracellular accumulation of calcium due to functional disturbance of membrane sodium/calcium ion pumps, because, in addition to L-type calcium ion channels, the sodium/calcium ion exchanger may play an important role in catecholamine-induced increases in intracellular calcium in cardiomyocytes [18]. Thus, cardiac sodium/calcium ion exchange is critical in the regulation of cardiac myocyte calcium, and its altered function contributes to systolic dysfunction in heart failure and arrhythmogenesis [19]. Hypoglycemic attack could also be a triggering factor for takotsubo cardiomyopathy [20], although onset of the syndrome was associated with a hypoglycemic episode in only one of 88 cases in the largest study conducted in Japan to date [11]. In addition, Ohwada et al. reported cases of ampulla cardiomyopathy occurring as a complication of hypoglycemic coma in anorexia nervosa [4]. Although the
mechanism has not been determined, hypoglycemia could have a direct or indirect effect on myocytes or ventricle contraction, because glucose is known to protect myocytes from injury [21]. Otherwise, stress-induced ampulla cardiomyopathy could be caused by hypoglycemia-induced stimulation of the sympathetic nervous system.

On the other hand, glucocorticoids play an important role in protecting myocytes as well as maintaining myocardial contraction [22]. For example, myocytes in culture maintain their structural integrity in the presence of dexamethasone [23]. Glucocorticoids reduce ischemia-reperfusion-induced myocardial apoptosis [24], and prevent progressive contractile dysfunction when given after microembolization [25] as well as contribute to maintaining a function of membrane calcium transport in the cardiac sarcoplasmic reticulum of the rat [26]. Furthermore, intracellular calcium concentration is affected by glucocorticoids [27, 28]. Taken together, these findings indicate that glucocorticoids have the ability to rescue myocyte apoptosis and improve cardiac function.

In summary, we reported a case of reversible ampulla (takotsubo) cardiomyopathy caused by secondary adrenal insufficiency in ACTH isolated deficiency. Careful monitoring of cardiac function and appropriate treatments for both cardiomyopathy and adrenocortical failure are required to recover cardiac dysfunction.

Acknowledgments

We thank the staff at Dr. Wakabayashi’s laboratory at the Institute of Brain Science and at Dr. Itoh’s laboratory at the Center for Advanced Medical Research for technical assistance.

Kazunori Kageyama is recipient of a grant from the Funds for the Promotion of Aomori Medical Research. This work was also supported in part by Health and Labour Science Research Grants (Research on Measures for Intractable Diseases) from the Ministry of Health, Labour, and Welfare of Japan, and by a grant to Toshihiro Suda from the Ministry of Education, Science and Culture of Japan (No. 18591014).

References


