An Atypical Case of “Takotsubo cardiomyopathy” during Alcohol Withdrawal: Abnormality in the Transient Left Ventricular Wall Motion and a Remarkable Elevation in the ST Segment

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Abstract

A 64-year-old man was admitted due to hypokalemia-related myopathy. He was heavy drinker. He felt the stress of alcohol withdrawal during his hospitalization. The patient suffered a cardiopulmonary arrest lasting approximately 5 minutes on the fifth hospital day. One day later, ST-segment elevation was observed in leads I, _aV_L, and V₂₋₆. Emergent cardiac catheterization was performed for suspicion of acute myocardial infarction. Normal coronary arteries with anterior akinesis of the left ventricle were revealed during the procedure. The present case may be an atypical form of “Takotsubo cardiomyopathy” in which the left ventricular contraction is due to focal anterior wall motion abnormalities. (Internal Medicine 43: 300–305, 2004)

Key words: hypokalemia-related myopathy, takotsubo cardiomyopathy, alcohol withdrawal

Introduction

“Takotsubo cardiomyopathy” is a newly identified heart disease characterized by reversible abnormal wall motion of the left ventricle with a systolic shape on left ventriculography similar to the shape of a Japanese octopus fishing pot, electrocardiographic changes reminiscent of acute myocardial infarction, and an absence of organic stenotic lesions in the coronary artery. The wall motion abnormalities in this disease exhibit both apical akinesis and basal hyperkinesis in the acute phase, neither of which is related to the coronary

blood distribution. The left ventricular dysfunction in Takotsubo cardiomyopathy has been reported to normalize within a few weeks to a month, and to differ markedly from the wall motion abnormalities seen in acute myocardial infarction and acute myocarditis.

On the other hand, chronic and acute alcohol intake are associated with a variety of cardiovascular effects, the best known being alcohol-induced cardiomyopathy, cardiac rhythm disorders, and sudden death (1, 2). We report a patient who exhibited a focal anterior wall motion abnormality more characteristic of acute anterior myocardial infarction than the typical wall motion abnormality seen in Takotsubo cardiomyopathy and remarkable ST segment elevation during a period of alcohol withdrawal.

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Case Report

A 64-year-old man was admitted to our hospital due to an inability to quickly rise to a standing position. For the previous five years he had consumed 1,000 ml of Japanese sake daily and had skipped most of his meals. Early in the morning on May 14, 2002, he found himself unable to quickly rise to a standing position. He promptly visited our institution for an examination. We recognized muscle weakness of both distal and proximal muscle, hypokalemia, and elevation of creatine kinase (CK) originating from the skeletal muscle (CK-MM 100%). He was diagnosed with hypokalemia-related myopathy by a neurologist in our institute and admitted for treatment.

On physical examination, the patient had a pulse of 90

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Table 1. Blood Examination on Admission

WBC	10.4×10 ³ /μl	γGTP	381 IU/l	BNP*	203 pg/ml
RBC	2.69×10 ⁶ /μl	CK	2,752 IU/l	Ad*	0.03 ng/ml
Hemoglobin	11.1 g/dl	CK-MB	3 ng/ml	Nad*	1.0 ng/ml
Hct	32.2%	Creatinine	0.67 mg/dl	DA*	0.02 ng/ml
Platelet	200×10 ³ /μl	BUN	3.5 mg/dl	TSH*	1.76 μIu/m
T. Protein	7.0 g/dl	Uremic acid	4.5 mg/dl	Free T3*	2.2 pg/ml
Albumin	3.4 g/dl	NA	139 mEq/l	Free T4*	1.5 ng/dl
T. bilirubin	2.2 mg/dl	K	2.3 mEq/l	GH*	4.35 ng/ml
AST	144 IU/l	T. Cholesterol	109 mg/dl	ACTH*	15 ng/ml
ALT	28 IU/l	Triglyceride	143 mg/dl	Vit B12*	1,170 pg/ml
LDH	544 IU/l	CRP	4.9 mg/dl		
ALP	186 IU/l	Glucose	112 mg/dl		

WBC: white blood cell, RBC: red blood cell, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, γGTP: γ-glutamyl transpeptidase, ALP: alkaline phosphatase, CK: creatine kinase, BUN: blood urea nitrogen, CRP: C-reactive protein, BNP: brain natriuretic peptide, Ad: adrenaline, Nad: noradrenaline, DA: dopamine, TSH: thyrotropin, T3: triiodothyronine, T4: thyroxine, GH: growth hormone, ACTH: adrenocorticotropin, Vit B12: vitamin cyanocobalamin, *: blood examination on the 6 th hospital day.

beats/min, blood pressure of 152/100 mmHg, and temperature of 37.5°C. Consciousness level was E4V5M6 on the Glasgow coma scale. His height and body weight were measured at 158 cm and 42 kg, and his gross appearance was severely cachectic.

The palpebral conjunctiva was not anemic and the bulbar conjunctiva was not icteric. No abnormalities were observed in the thorax or abdomen. There was no extra sound or significant heart murmur. His abdomen was soft and flat, and his liver and spleen were impalpable. Superficial lymph nodes were also impalpable. Muscle strength was diminished in all extremities (manual muscle testing from 0 to 3), especially the legs. Moreover, a tremor was recognized in both upper extremities.

The blood tests revealed a white blood cell count of 10,400/μl, C-reactive protein of 4.9 mg/dl, AST of 144 IU/l, ALT of 144 IU/l, LDH of 144 IU/l, γGTP of 381 IU/l, CK of 2,752 IU/l, and kalemia of 2.3 mEq/l (Table 1).

Figure 1 shows a chest X-rays taken on admission. The cardiothoracic ratio was 48% and no other remarkable findings were seen in the X-ray films. An electrocardiogram (ECG) showed sinus rhythm (a pulse of 96 beats/min) with QT prolongation (QTc=0.50 sec) (Fig. 3A).

Once the patient was hospitalized, his treatment focused chiefly on correction of kalemia and supplementation with various vitamins for prevention of Wernicke's encephalopathy. He responded favorably and showed a gradual improvement in general condition.

On the fifth hospital day, he suffered a decline in consciousness and cardiopulmonary arrest due to sustained ventricular tachycardia and ventricular fibrillation. Fortunately, his heart resumed beating after 5 minutes of cardiopulmonary resuscitation (Fig. 2). One day later, remarkable ST-segment elevation was observed in leads I, a_V_L, and V₂ through 6 (Fig. 3B). Echocardiography at that time exhibited

Figure 1. Chest X-ray film on admission. The cardiothoracic ratio and lung field are normal.

a focal anterior and septal akinesis of the left ventricle that closely resembled typical acute myocardial infarction. Emergent cardiac catheterization was performed for suspicion of myocardial infarction. Normal coronary arteries (Fig. 4A, B) with anterior akinesis of the left ventricle (Fig. 4C, D) were revealed. ST-segment elevation in leads I, a_V_L, and V₂ through 6 continued during cardiac catheterization (Fig. 3C). Deep inverted T waves were observed on the

Figure 2. Monitor electrocardiogram on the fifth hospital day. Monitor electrocardiogram shows an increase in premature ventricular contractions, ventricular tachycardia, and migration to ventricular fibrillation.

Figure 3. Electrocardiographic change. A: electrocardiogram on admission. B: electrocardiogram during an ST elevation attack on May 19. C: electrocardiogram during cardiac catheterization. ST elevation continued while the coronary arteries remained normal. D: convalescent electrocardiogram on May 20.

A. Right coronary artery

C. Diastole

B. Left coronary artery

D. Systole

Figure 4. Coronary angiograms (left) and left ventriculograms (right) in the left anterior oblique view. A, B) Coronary angiograms show normal coronary arteries. C, D) Left ventriculograms show anterior wall akinesis. No Takotsubo-like apical akinesis or basal hyperkinesis is observed.

morning after the catheterization of the seventh hospital day, after 12 hours of continued ST-segment elevation in leads I, V_L , and V_2 through 6 (Fig. 3D).

Thallium-201 (^{201}Tl) myocardial scintigraphy was performed on the tenth hospital day and I-123- β -methyl-iodophenyl pentadecanoic acid (^{123}I -BMIPP) myocardial scintigraphy was performed on the fourteenth hospital day.

No ^{201}Tl defect was shown, but ^{123}I -BMIPP uptake was decreased in the anterior and septal regions of the left ventricle (Fig. 5). By the tenth hospital day the left ventricular asynergy and elevated CK showed complete improvement without any specific treatment. A pilsicainide test was performed on the 28th day to rule out Brugada syndrome as a differential diagnosis for the ventricular fibrillation and ST

Figure 5. Thallium-201 (left) and Iodine-123 BMIPP (right) myocardial scintigraphy. Accumulated degradation of Iodine-123 BMIPP on the fourteenth hospital day was in agreement with anteroseptal area of left ventricular wall motion abnormality. However, the accumulated degradation of Thallium-201 on the tenth hospital day did not show any agreement with the wall motion abnormality.

elevation. The test was negative, confirming the absence of Brugada syndrome.

Discussion

In Japan there have been a number of reports of reversible left ventricular dysfunction with symptoms similar to those of acute myocardial infarction but without coronary artery stenosis/occlusion even during the acute phase with ST segment elevation. This transient left ventricular apical wall motion abnormality, so-called “Takotsubo cardiomyopathy”, was first described by Satoh (3) in 1990. In case studies reported since, this cardiac syndrome was shown to have the following characteristics: 1) emotional and somatic background (4), 2) onset symptoms resembling those of acute myocardial infarction, 3) apical akinesis and basal hyperkinesis, 4) T wave inversion (giant negative T wave) and QT prolongation following myocardial infarction-like ST elevation, 5) minimal myocardial enzyme release, 6) no angiographical stenosis in the epicardial coronary artery, 7) dissociation of findings between ^{201}Tl myocardial scintigram and ^{123}I -BMIPP myocardial scintigram, and 8) reversible left ventricular dysfunction (5). As of this writing 250 cases have been reported in Japan, rather many compared to the numbers reported in Europe and the United States (5). Mental and/or physical stress are suspected as causal factors leading to the appearance of this cardiac syndrome (6).

The following features of our patient are consistent with typical “Takotsubo cardiomyopathy”: 1) the presence of a trigger such as rapid alcohol withdrawal, ventricular fibrillation, and/or cardiopulmonary resuscitation; 2) ECG changes resembling acute myocardial infarction; 3) minimal myocardial enzyme release; 4) an absence of organic coronary artery lesions, including coronary spasms; 5) reversible ECG changes, left ventricular dysfunction, and myocardial enzyme release; and 6) dissociation of findings between ^{201}Tl

myocardial scintigram and ^{123}I -BMIPP myocardial scintigram. However, the degree of eminent ST elevation and the focal anterior wall motion abnormalities were not typical of “Takotsubo cardiomyopathy”.

A balloon-like asynergy in the apical regions and excessive contraction in the basal regions of the left ventricle have been demonstrated in “Takotsubo cardiomyopathy”. However, it remains unknown why the left ventricle assumes this specific shape. The numbers of sympathetic nerve endings and their receptors on the myocardium differ in the left ventricle of the dog (7). The number of sympathetic nervous endings in the apical region of the left ventricle is decreased, whereas the number of receptors is increased. The opposite is true in the basal region of the left ventricle. These disturbances might be related to the balloon-like asynergy in the apical regions and the hyperkinesis in the basal regions of the bilateral ventricles. However, the distribution of the sympathetic nerve endings and their receptors remains to be clarified in humans.

Akashi et al from our institute previously hypothesized that excessive activation of cardiac catecholamine receptors may have either the result or the origin of this cardiomyopathy (8). The excessive activation of cardiac catecholamine receptors in the left ventricle and the discrepancy in the distribution of sympathetic nerve endings and their receptors could explain the strong appearance of wall motion abnormalities in the anterior wall.

The precise pathophysiological basis is still not fully clarified. The mechanism of left ventricular dysfunction in “Takotsubo cardiomyopathy” has generally been reported as coronary vasospasm (9), microvascular disturbance in the myocardium (10), or acute myocarditis (11).

We diagnosed this case as “Takotsubo cardiomyopathy” with ischemic event-like ST elevation and no significant coronary lesion. In view of the sustained ST segment elevation during coronary angiogram in the absence of any appar-

ent coronary vasospasm, we determined that coronary artery vasospasm, one of the etiologies in "Takotsubo cardiomyopathy", did not occur in our case.

The latter, microvascular disturbance in the myocardium, is speculated to result from myocardial ischemia due to coronary microvascular spasm, which results in the focal stunned myocardium. In the present case, we could confirm the absence of epicardial coronary spasm in the left anterior descending artery. Regarding the presence of acute myocarditis, there was no evidence of early infection or any significant elevation of viral antibody titer.

Our institute previously reported high levels of circulating catecholamine in patients with this type of "Takotsubo cardiomyopathy" (12). We did not recognize any elevation of circulating catecholamine level in the present case, but the blood samples were taken at 24 hours after the onset of the ventricular fibrillation. Thus, it remains unclear whether there was any elevation in catecholamine at onset in our case.

Other diseases that have been reported to show ST segment elevation include Brugada syndrome (13) (idiopathic ventricular fibrillation), subarachnoidal hemorrhage (14), tension pneumothorax (15), commotio cordis (16) after strong chest compression, and others.

We could not completely exclude idiopathic ventricular fibrillation from the history of sudden onset of ventricular fibrillation and ST segment elevation in our patient. On the other hand, we consider Brugada syndrome fairly unlikely, as there was no evidence of typical right bundle branch block or pilsicainide-induced ST elevation when we tested the patient 28 days after the onset of the ventricular fibrillation. Further, subarachnoidal hemorrhage was excluded by computed tomography at the onset of the ventricular fibrillation. Commotio cordis following the strong chest compression was also not completely ruled out. Although commotio cordis is thought to be related to chest wall compliance and shock impact to the heart, the condition has never been reported to result directly from cardiopulmonary resuscitation. All of the above mentioned diseases were unlikely in this case.

Prior to the patient's cardiopulmonary arrest, the ECG showed only a mild QT prolongation. Moreover, there is no evidence that alcohol withdrawal triggered the disease onset. However, we cannot rule out the acute stress induced by the alcohol withdrawal during the hospitalization as a causal factor.

Conclusion

The present case may be an atypical form of "Takotsubo

cardiomyopathy" in which the left ventricular contraction is due to focal anterior wall motion abnormalities.

References

- 1) Takehana H, Izumi T. Alcoholic heart disease. *Nippon Rinsho* **58**: 151–156, 2000 (in Japanese).
- 2) Braunwald E. *Heart Disease: A Textbook of cardiovascular Medicine*, 5th ed (ed by Braunwald E), W.B. Saunders Company, Philadelphia, 1997: 1412–1414.
- 3) Sato H, Tateishi H, Uchida T, Dote K, Ishihara M. Stunned myocardium with specific (tsubo-type) left ventriculographic configuration due to multivessel spasm. in: *Clinical aspects of myocardial injury: From ischemia to heart failure*, Kodama K, Haze K, Hori M, Eds. Kagakuhyouronsya Co; Tokyo, 1990: 56–64 (in Japanese).
- 4) Moriya M, Mori H, Suzuki N, Hazama M, Yano K. Six-month follow-up of takotsubo cardiomyopathy with I-123- β -methyl-iodophenyl pentadecanoic acid and I-123-meta-iodobenzyl-guanidine myocardial scintigraphy. *Intern Med* **41**: 829–833, 2002.
- 5) Ishihara M, Sato H, Tateishi H, et al. "Takotsubo"-like Cardiomyopathy. *Kokyu To Junkan* **45**: 879–885, 1997 (in Japanese).
- 6) Kawai S. Ampulla-shaped ventricular dysfunction or amulla cardiomyopathy? *Kokyu To Junkan* **48**: 1237–1248, 2000 (in Japanese).
- 7) Murphree SS, Saffitz JE. Quantitative autoradiographic delineation of the distribution of beta-adrenergic receptors in canine and feline left ventricular myocardium. *Circ Res* **60**: 568–579, 1987.
- 8) Akashi YJ, Nakazawa K, Sakakibara M, Miyake F, Koike H, Sasaka K. The clinical features of takotsubo cardiomyopathy. *Q J M* **96**: 563–573, 2003.
- 9) Dote K, Sato H, Tateishi H, Uchida T, Ishihara M. Myocardial stunning due to simultaneous multivessel coronary spasms: A review of 5 cases. *J Cardiol* **21**: 203–214, 1991 (in Japanese).
- 10) Kurisu S, Inoue I, Kawagoe T, et al. Myocardial perfusion and fatty acid metabolism in patients with tako-tsubo-like left ventricular dysfunction. *J Am Coll Cardiol* **41**: 743–748, 2003.
- 11) Mitsuya N, Akashi Y, Ozawa Y, et al. A case of transient left ventricular dysfunction so called takotsubo-like wall motion abnormality that appeared to be caused by acute myocarditis. *Ther Res* **20**: 80–85, 1999 (in Japanese).
- 12) Akashi YJ, Nakazawa K, Sakakibara M, Miyake F, Sasaka K. Reversible left ventricular dysfunction Takotsubo cardiomyopathy related to catecholamine cardiotoxicity. *J Electrocardiol* **35**: 351–356, 2002.
- 13) Chinushi Y, Chinushi M, Toida T, Aizawa Y. Class I antiarrhythmic drug and coronary vasospasm-induced T wave alternans and ventricular tachyarrhythmia in a patient with Brugada syndrome and vasospastic angina. *J Cardiovasc Electrophysiol* **13**: 191–194, 2002.
- 14) Yasu T, Owa M, Omura N, Katsuki T, Saito M. Transient ST elevation and left ventricular asynergy associated with normal coronary artery in aneurismal subarachnoid hemorrhage. *Chest* **103**: 1274–1275, 1993.
- 15) Akashi YJ, Sakakibara M, Miyake F. Reversible left ventricular dysfunction "takotsubo" cardiomyopathy associated with pneumothorax. *Heart* **87**: E1, 2002.
- 16) Kohl P, Nesbitt AD, Cooper PJ, Lei M. Sudden cardiac death by Commotio cordis: role of mechano-electric feedback. *Cardiovasc Res* **50**: 280–289, 2001.