Reversible left ventricular apical ballooning associated with jet lag in a Taiwanese woman: A case report

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N-C Chang, M-S Lin, C-Y Huang, C-M Shih, W-F Bi. Reversible left ventricular apical ballooning associated with jet lag in a Taiwanese woman: A case report. *Int J Angiol* 2007;16(2):62-65.

Reversible left ventricular apical ballooning, without coronary artery stenosis, is a novel heart syndrome mimicking acute myocardial infarction, and is very rare in Taiwan. A 74-year-old Taiwanese woman returned from travelling abroad for one week and suffered from persistent, severe jet lag with sleep disturbance. She had a cold exacerbated by bronchial asthma for three days. She presented with sudden onset of chest pain after drinking three cups of coffee and taking a sauna for more than 1 h. On admission, an electrocardiogram showed ST segment elevation in leads II, III, aVF and V_{3,6}, and cardiac enzyme tests

revealed minimal elevation. An echocardiogram showed apical ballooning and basal hyperkinesias of the left ventricle (LV) in systole. A coronary angiogram on the second day was normal, while the ST segment was still elevated, and the patient continued to experience chest pain. A negative T wave developed three days later. The electrocardiogram abnormality and LV dysfunction resolved completely six months later. A takotsubo (ampulla) cardiomyopathy was diagnosed. The activated myocardial adrenergic nervous system, stimulated by acute and marked stress in this patient, with more adrenergic innervations distributed in the apex of the LV, may be the trigger for this novel cardiac syndrome.

Key Words: *Apical ballooning; Noradrenaline; Reversible; Stress; Taiwan; Takotsubo cardiomyopathy*

A number of reports in Japan (1-6) during the past decade, and in the past three years in Europe (7) and the United States (8), described a unique syndrome characterized by symptoms mimicking acute myocardial infarction (AMI). The features include ST segment elevation on electrocardiogram (ECG), extensive but reversible apical ballooning with hypercontractile basal segments during systole on echocardiogram (echo) and left ventricular (LV) angiogram, and minimal elevation of cardiac enzymes. Doctors usually diagnosed these patients as having AMI. The patients underwent emergent coronary angiograms (CAG), but no significant coronary artery stenosis was found in the acute phase, although the ST segment was elevated and the patient experienced ongoing chest discomfort. LV morphology and the ECG normalized within several weeks. The peculiarly shaped LV was originally named 'takotsubo' (ampulla) cardiomyopathy (CM) by Sato et al (3) in 1990 (1,3). Many cases are preceded by excessive emotional and/or physical stresses; however, the exact etiology has not yet been elucidated (2,5,6). We present a case of takotsubo CM in a Taiwanese woman associated with jet lag.

CASE PRESENTATION

A 74-year-old Taiwanese woman, who was travelling abroad, returned to Taiwan one week before admission. She had been suffering from severe, persistent jet lag, and on presentation had a cold exacerbated by bronchial asthma for the previous three days. She presented with sudden onset of chest tightness, radiating bilaterally to her shoulders, after drinking three

cups of coffee and taking a sauna for more than 1 h. She asked for help after experiencing persistent discomfort lasting 5 h. Her consciousness level was E₄M₆V₅, as measured by the Glasgow coma scale. Her blood pressure was 114/70 mmHg, her temperature was 36.2°C, and her pulse was regular, at 88 beats/min, and was essentially equal in all four extremities. There was no cardiac murmur or extra sound on heart auscultation, and no rales on lung auscultation. There was no jugular venous engorgement or leg edema. Her neurological examination and chest x-ray were normal. An ECG showed ST segment elevation in leads II, III, aVF and V_{3,6} (Figure 1A) not detected on a previous ECG. Cardiac enzymes revealed a creatine kinase (CK) level of 125 IU/L (normal range 15 IU/L to 100 IU/L), a CK muscle and brain (CK-MB) isoenzyme level of 4.0 IU/L (normal range 0 IU/L to 17 IU/L), and a cardiac troponin T level of 0.345 ng/mL (normal range <0.1 ng/mL). The patient was given morphine 3 mg by injection, and intravenous nitroglycerine; however, her chest pain did not disappear. The patient's symptoms gave the impression of AMI, so anticoagulant (heparin) was initiated. ECG showed persistent ST segment elevation with no dynamic change 8 h later and CK, CK-MB isoenzyme and troponin T levels were 112 IU/L, 3.0 IU/L and 0.265 ng/mL 12 h later, respectively. On hospital day 2, echo showed akinesis in the wide LV apical region and hyperkinesia over the basal portion (Figure 2A). The LV angiogram revealed apical ballooning and a hyperkinetic basal portion during systole (Figure 3A). The CAG on hospital day 2 was normal, with no spasm, thrombus or delay of antegrade

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Figure 1 12-lead electrocardiogram on presentation (A), on hospital day 3 (B) and six months later (C)

coronary flow, while the ST segment was still elevated, with ongoing chest tightness (Figure 3B). On hospital day 3, ECG showed a negative T wave in leads II, III, aVF and V_{3-6} (Figure 1B). On hospital day 4, ECG showed the same negative T wave in leads II, III, aVF and V_{3-6} , with no change. Mild chest pain persisted for one week. There was no fever or leukocytosis throughout the hospital course. Re-evaluation of the ECG (Figure 1C) and echo (Figure 2B) six months later showed complete resolution.

DISCUSSION

Takotsubo CM is a novel heart syndrome, characterized by transient and severe LV apical ballooning, and basal hyperkinesias in the acute stage (4,7,8). Because the shape of the LV resembles a round-bottomed, narrow-necked bottle used in Japan for trapping octopus, the disease is called takotsubo CM, derived from the Japanese words *tako*, meaning octopus, and *tsubo*, meaning bottle (1,3). Doctors also named this disease ampulla, or amphora, CM (1).

Despite the striking initial manifestations that closely resemble AMI, the minimal to modest changes of the cardiac enzymes are not consistent with the extent of the change in LV morphology in the acute stage and the complete normalization of the unusual LV morphology seen within several weeks in typical cases (4,7,8). Furthermore, the changes on the ECG are different from those that occur in anterior AMI. In typical cases of takotsubo CM, the ECG in the acute stage shows ST segment elevation, usually in leads V_{3-6} , and is often concave in shape, with little dynamic change for days. This is followed

Figure 3 A left ventricle angiogram showing apical ballooning during systole (A), and a coronary angiogram showing no significant stenosis (B). ED End diastole; ES End systole; LCA Left coronary artery; RCA Right coronary artery

Figure 2 Echocardiogram on hospital day 2 (A) and six months later (B). ED End diastole; ES End systole

by T wave inversion that resolves in approximately two to three weeks (4,9), and is associated with corrected QT interval prolongation (9). Abnormal Q wave and reciprocal changes are rarely seen (9). Ogura et al (9) found the ratio of ST segment elevation in leads V_{4-6} to V_{1-3} was significantly higher in patients with takotsubo CM than in those with anterior AMI. Using the combination of the absence of reciprocal change, and $\sum ST V_{4-6}/V_{1-3} \geq 1$ to diagnose takotsubo CM produced 100% specificity and 91% overall accuracy (9). The ECG on presentation in the present case showed a concave-shaped ST segment elevation in leads II, III, aVF and V_{3-6} , with no reciprocal change.

The etiology of takotsubo CM is still not clear, although Japanese doctors have reported more than 250 cases (10). Stunned myocardium has long been known as a prolonged postischemic LV dysfunction after brief myocardial ischemia, and presents as a reversible LV dysfunction (11). Normal or nonsignificant stenosis shows no spasm, thrombus or delay of antegrade coronary flow on CAG, with only mild elevation of cardiac enzymes. It is accompanied by a broad area of LV

dysfunction beyond the territory of one vessel on an LV angiogram in the acute phase, when chest discomfort is ongoing and the ST segment is elevated. Thus, thrombotic occlusion, followed by spontaneous recanalization or spasm in a single epicardial coronary artery, is not a possible etiology. Recently, a large observational study in the United States by Sharkey et al (8) included 22 elderly women with this disease from a community-based practice, and used cardiac magnetic resonance imaging for evaluation. The results showed myocardial viability without necrosis, loss of cellular integrity or scar formation in patients with takotsubo CM. Cardiac magnetic resonance imaging also detected diffusely allocated wall motion abnormalities that covered the LV myocardium beyond any single vascular territory in 95% of cases, and the vascular distribution of all three coronary arteries in 90% of cases. The authors confirmed the disease was not AMI, and excluded single epicardial vessel involvement. Moreover, many clinical and histological findings excluded the possibility of myocarditis (4,8,12). Thus, the potential causes are epicardial multivessel coronary spasm (13), microvascular multivessel coronary spasm (13) and catecholamine-induced cardiotoxicity (6). Epicardial multivessel coronary spasm is very rare (14). Moreover, absence of spasm during CAG in the acute phase indicated that spasm is not likely the cause (4,8,10). Indeed, the ergonovine provocation test proved positive in only one-fifth of cases in the Japan multicentre registry by Tsuchihashi et al (4), although only 55% of the patients were tested, and they were not in the acute phase (88 cases were enrolled, 48 cases had provocation and 10 cases were positive) (4). Moreover, in a prospective study by Abe et al (12), which investigated 17 patients, provocation was performed in seven of nine patients during CAG. Five of seven patients had positive results. However, the authors found dissociations between the hypokinetic area and the provocation-induced coronary artery territories. Epicardial multivessel coronary spasm is not likely the cause based on the above findings. Microvascular spasm-induced stunned myocardium is a possible etiology. Kurisu et al (15) performed emergent CAG in 14 patients with takotsubo CM. They found nonsignificant coronary stenosis, but they discovered that coronary blood flow was severely impaired in all the coronary arteries by measuring the Thrombolysis in Myocardial Infarction (TIMI) frame count. The authors (15) concluded that takotsubo CM may be stunned myocardium due to impaired multivessel coronary microcirculation. However, intracoronary Doppler flow wire, a new tool for confirming the patency of coronary microcirculation, produced controversial results. Ako et al (16) found impaired coronary microcirculation, but Abe et al (12) did not. Moreover, Tsuchihashi et al (4) stated that some autopsy cases by Kawai et al (1) did not show ischemic findings. Catecholaminergic, or adrenoceptor-hyperactive, myocardial toxicity, in cases of neurogenic stunned myocardium, has been presented as another possible mechanism (4,12,17,18). It is believed that, in some cases, excessive catecholamine release from undergoing severe psychological and/or bodily stresses resulted in cardiac dysfunction, although catecholamine levels are not inevitably elevated (2,10). Plasma noradrenaline levels may increase immediately and only transiently after the attack (17). Adrenergic nerve endings can take up radiolabelled ^{123}I -meta-iodobenzylguanidine (MIBG) (19). Owa et al (2) showed prolonged absence of MIBG accumulation in the apex of LV, which indicated a cardiac adrenergic denervation in

takotsubo CM. Reversible LV dysfunction is a short burst of powerful sympathetic discharge, such as in cases of heatstroke (20), head injury (21) and subarachnoid hemorrhage (22). Adachi et al (23) reported a patient who had crush syndrome with reversible LV dysfunction, who was buried for 24 h during the Kansai earthquake. The MIBG images showed continual defects, and thallium-201 images showed a notable recovery one month later. The authors suggested the stress-induced catecholamine release resulted in transient LV dysfunction. An animal study by Ueyama (5) showed immobilizing stress-induced ECG and LV changes in rats normalized by a combined blockade of alpha- and beta-adrenoceptors. The features resembled takotsubo CM in humans. Moreover, a molecular study revealed blocking alpha- and beta-adrenoceptors would remove the upregulation of immediate early genes induced by stress; conversely, alpha- and beta-agonists upregulated immediate early genes in the perfused heart. The sequential gene expression may be a stress-adaptive reaction. The author (5) concluded that emotional stress triggered activation of alpha- and beta-adrenoceptors, and yielded cardiac damage. However, the etiological explanation is still deficient because investigators studied each of these potentially causative mechanisms in a very limited number of patients. We did not consider an ischemic event in the present case because the CK-MB isoenzyme level did not increase, while the AMI-like elevated ST segment continued for more than 24 h, with a wide LV involvement. We suspect the activity of the cardiac adrenergic nerve might incongruously increase in the patient who was under acute and vigorous stress.

The key question is why takotsubo CM involves only the apex. The washout rate of MIBG in myocardial scintigraphy reflects cardiac adrenergic activation (24). Moriya et al (18) followed up with patients diagnosed with takotsubo CM, and found persistent differences between apical and total washout rates for six months in MIBG imaging. The researchers inferred that not all people showed apical ballooning after acute catecholamine overload, and suggested those who had uneven distribution of adrenergic innervations in the apical and basal regions may incur this particular pattern of LV change during the acute phase.

Takotsubo CM must be considered in the differential diagnosis of patients with prolonged chest pain, although the mortality rate in takotsubo CM (approximately 1%) is far less than that of AMI. Long-term prognosis does not change with drug therapy, and the rate of recurrence is 2% to 5% (4). Several clinical implications are noted: differential diagnosis between takotsubo CM and stenotic AMI is important when considering the use of intravenous thrombolytic therapy. In fact, clinicians diagnosed many cases retrospectively and it is often difficult to differentiate from stenotic AMI in daily practice. Takotsubo CM is likely when a minimally or modestly elevated, or even a normal CK-MB level, is associated with an AMI-like extensive elevated ST segment for more than 24 h, and when there is widespread LV apical involvement on echo. Identification of transient LV outflow obstruction may be important, because this finding may predispose a patient to apical ischemia, eventually forming an apical infarct, although Tsuchihashi et al (4) and Abe et al (12) reported 18% and 0% of patients had this phenomenon, respectively. The traditional strategies for treating ischemia, including nitrate and afterload vasodilators, may exacerbate the outflow tract obstruction and deteriorate the patient's condition. Beta-blocking agents and

intravenous fluid may be helpful and life saving (25). There are two quite important unanswered clinical problems: should acetylsalicylic acid be administered indefinitely, and can minor tranquilizers prevent attacks and recurrence (4)? Again, we do not know how many cases are typical takotsubo CM. However, in the face of establishing a completely novel disease or syndrome, the diagnostic criteria should be strict, and the definition should be narrow and confirmed with genetic studies.

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