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Transient Left Ventricular Apical Ballooning Mimicking Acute Coronary Syndrome in Four Patients from Central Europe

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Abstract The syndrome of "apical ballooning" consists of an acute onset of transient extensive akinesia of the apical portion of the left ventricle, without significant stenosis on the coronary angiogram. The syndrome is accompanied by chest symptoms, electocardiographic changes, and limited release of cardiac markers disproportionate to the extent of akinesia. So far, the vast majority of cases with this syndrome have been reported among Japanese population and only a few cases among Caucasian population. We describe "apical ballooning" in four Caucasian patients, three women and one man, who presented at a tertiary referral center over a period of eight months. Their age ranged between 64 and 84 years. Three of them presented with chest symptoms. All four patients had electrocardiographic changes and increased concentration of troponin T. One patient developed hemodynamic instability, but none died or showed recurrence of symptoms during the follow-up of 1-8 months. In all patients, a preceding triggering factor was identified, such as emotional or physical stress. In all patients left ventriculography showed extensive akinesia of the apex of the left ventricle ("apical ballooning") in the absence of a significant coronary artery stenosis. Left ventricular systolic function recovered completely within three days to three weeks. Emotional or physical stress or other preceding triggering factors might play a key role in this cardiomyopathy, but the precise etiology remains unknown. Despite severe initial presentation, conservative medical management leads to good long term outcome.

Previous studies reported several pathological entities associated with reversible left ventricular (LV) wall motion abnormalities, including ischemic myocardial stunning, pheochromocytoma crisis, multivessel vasospasm and subarachnoid hemorrhage, gastrointestinal bleeding, acute myocarditis, and tachycardia-induced cardiomyopathy (1-7). Satoh and Dote (8,9) were the first to describe a novel cardiac syndrome consisting of chest symptoms with acute onset, transient and reversible abnormalities of the left ventricular apical wall motion, electrocardiographic (ECG) changes, and minimal myocardial enzymatic release mimicking acute myocardial infarction in patients without stenosis on coronary angiogram. The disease was named "Takotsubo"-shaped cardiomyopathy, because of its unique "short neck round-flask"-like LV apical ballooning resembling the Japanese *tako-tsubo* (Japanese for octopus pot or trap). Subsequently, several cases and even larger series of Japanese patients were reported (10-15). Desmet et al (16) described the syndrome of "apical ballooning" in 3 Caucasian patients. Abe et al (17) suggested that neither abnormalities in the coronary circulation nor acute myocarditis was related to the etiology. Emotional or physical stress and other preceding triggering factors, such as cerebrovascular accidents, epileptic attacks, non-cardiac surgery, and emotional problems, including sudden accidents, death, or funeral of a family

member, might play a key role in this cardiomyopathy, but the precise etiology remains unknown.

We describe a case series of four patients who fulfilled the criteria for Takotsubo cardiomyopathy (17).

Case Series

All four patients presenting at our institution (a tertiary referral center, where approximately 4,000 cardiac catheterizations are performed per year) over a period of eight months, who fulfilled currently accepted criteria of the syndrome of "apical ballooning," including transient and reversible LV apical ballooning, ECG changes defined as ST-T segment elevation or depression in several leads, and no history of either previous myocardial infarction, valvular heart disease, subarachnoid hemorrhage, or pheochromocytoma. We evaluated clinical characteristics including sex, age, preceding triggering factors, duration of symptoms before admission, laboratory values (cardiac enzymes), ECG changes, cardiac images, and clinical outcome of all patients. Additionally, we reviewed and discussed the current literature on the syndrome.

Case 1

A previously fit 84-year-old Caucasian woman with a history of hypertension presented to the emergency department of a small district hospital with a two-hour history of chest pain and dyspnea. She had a three day history of severe lumboischialgia that was treated by intramuscular injections of diclofenac. The ECG on admission showed ST-elevation and normal R progression in the precordial leads. Thrombolysis for acute ST-elevation myocardial infarction was considered, but eventually given up because of increased risk of bleeding after several intramuscular injections. Over the following hours she developed hemodynamic instability with evolution to cardiogenic shock. Intravenous inotropic drugs were administered. Additionally, the patient was treated with aspirin, enoxaparin, and opiates for acute coronary syndrome. Subsequently, the patient was referred for coronary angiography to our institution. On admission, the serum troponin T concentration was 0.69 ng/mL (normal <0.03 ng/mL), creatine kinase (CK) was 570 U/L (normal <145 U/L), and CK myocardial band (CK-MB) was 34 U/L. An emergency echocardiography revealed anteroapi-

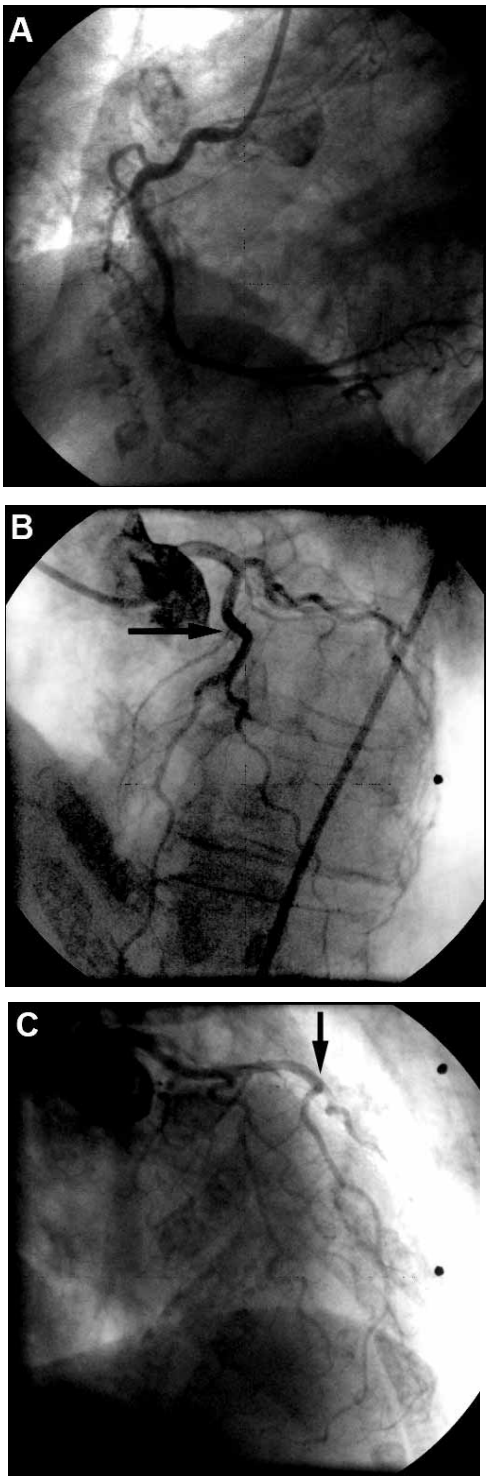

Figure 1. Coronary angiography of the patient from Case 1 showing no coronary artery stenoses, representative of all patients in the series. **A.** Right coronary artery, left anterior oblique (LAO) view; **B.** Left coronary artery, LAO view; **C.** left coronary artery, right anterior oblique view. Arrows indicate left anterior descending artery.

cal akinesia and global left ventricular ejection fraction was severely reduced. Coronary angiography showed normal coronary arteries (Fig. 1). Left ventriculography (Fig. 2) confirmed the presence of a large anteroapical akinesia with a severe decrease of global left ventricular ejection fraction (22%; normal value ≥60%). No intraventricular pressure gradient was observed. Serial ECG recordings showed the development of negative T waves in the anterolateral leads. The patient's clinical condition stabilized over the next 24 hours and after 4 days, the patient made a complete functional recovery with remarkable improvement of the wall motion and global left ventricular systolic function on echocardiographic evaluation. Subsequently, complete normalization of both global and segmental left ventricular systolic function could be documented by echocardiography three weeks later.

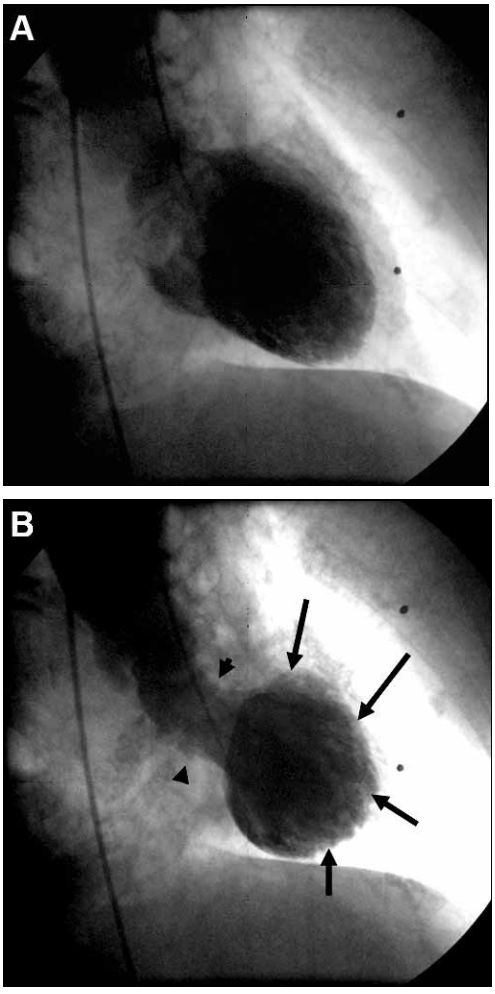

Figure 2. End diastolic (**A**) and end systolic (**B**) left ventriculograms of the patient from Case 1 showing extensive akinesia of the apical and mid portions (arrows) of the left ventricle, with hypercontractility confined to the basal parts of the heart (arrowheads), representative of all patients in the present series.

Case 2

A 64-year-old man with alcohol-related liver disease was admitted three hours after a fall, with severe hypothermia and a body temperature of 29°C, measured rectally. He was transferred to the intensive care unit and normal body temperature was restored by physical measures. Shortly after admission, ECG showed ST-depression and giant negative T waves in leads V2 to V5 and in leads I and aVL. The patient had no chest discomfort and complained of moderate dyspnea. He was treated by diuretics and oxygen. Biochemically, the serum troponin T concentration was 0.42 ng/mL (peak concentration), CK was 275 U/L (peak concentration, 945 U/L), and CK MB was 61 U/L. Echocardiography revealed severely depressed left ventricular systolic function and a large apical akinesia with hypercontractility confined to the basal parts of the heart. Subsequently, coronary angiography showed normal coronary arteries. Left ventriculography confirmed the presence of a large anteroapical akinesia with a markedly depressed global left ventricular ejection fraction (37%). Left ventricular end-diastolic pressure was 26 mm Hg. Treatment with a β-blocker and an angiotensin converting enzyme inhibitor was initiated. Additionally, amoxicillin was prescribed for bronchopulmonary infection. The patient made a slow but gradual functional recovery over the following seven days. On day 15, a control transthoracic echocardiography showed a significant improvement of the regional and global contractility.

Case 3

A 64-year-old woman with a fairly unremarkable medical history presented to the emergency department of a small district hospital with a ten-hour history of chest discomfort. Chest pain developed immediately after the patient became witness of her sisters' stroke that was complicated by several seizures.

On admission, the ECG showed normal R progression and slightly elevated ST-segments in the precordial leads. The serum troponin T concentration was 0.08 ng/mL (normal < 0.03 ng/mL), and CK was within the normal range (52 U/L).

Blood pressure was 125/75 mm Hg and the heart rate was 69 beats/min. Echocardiography showed a region of akinesia confined to the apex of the left ventricle. The patient was treated with aspirin, clopidogrel, enoxaparin, metoprolol, nitrates, and opiates for acute coronary syndrome and was subsequently referred for urgent coronary angiography. Surprisingly, this showed normal coronary arteries but large apical akinesia and a moderately decreased global left ventricular function (ejection fraction (EF) 45%).

Treatment with an angiotensin-converting enzyme inhibitor was initiated. After three days, the patient made a complete functional recovery, with an almost complete normalization of the wall motion and global left ventricular systolic function.

Case 4

A 82-year-old woman with a history of hypertension was admitted after an accident in which she suffered multiple contusions to the left knee, right arm, and right chest wall. X-ray revealed no rib fractures. Three days after the accident, the patient was admitted to the emergency department with a six-hour history of chest discomfort and progressive dyspnea.

On examination, her supine heart rate was 133 beat/min and she had absolute arrhythmia. Blood pressure was 170/121 mm Hg. Pulmonary examination revealed rales at both lung bases as a sign of congestive heart failure. ECG showed atrial fibrillation and ST-depression and negative T waves in leads V2 to V5 and in leads I and aVL. Biochemically, the serum troponin T concentration was slightly elevated (0.17 ng/mL) and CK was within the normal range (78 U/L). Echocardiography revealed moderately depressed left ventricular systolic function and a large apical akinesia. The patient was treated with digoxin, nitrates, diuretics, and oxygen. Additional treatment with aspirin, clopidogrel, enoxaparin, metoprolol, and opiates for acute coronary syndrome was initiated.

Subsequently, left ventriculography showed extensive akinesia of the apical and mid portions of the left ventricle (EF 39%) in the absence of significant coronary artery stenosis that might have corresponded with the segmental contraction abnormality.

After 12 hours, atrial fibrillation spontaneously converted to regular sinus rhythmus. After five days, the patient made a complete functional recovery, with normalization of the apical wall motion and global left ventricular systolic function on echocardiography.

Summary of Clinical Findings and Diagnostic Results

Three of the four patients were women. Patients' age ranged between 64 and 84 years. None of the patients had a history of angina-like complaints and all but one presented with chest symptoms. In all patients, a preceding triggering factor was identified – emotional stress, trauma, severe lumboischialgia, or severe hypothermia. The clinical presentation varied from chest pain, dyspnea, and hemodynamic instability to mere ECG abnormalities (Table 1).

The ECG on admission was abnormal in all patients (ST elevation in two patients, and T-wave inversion in two patients). In the patients with ST-segment elevation, negative T waves in the anterior leads developed over the following days. All patients had increased concentration of troponin T.

In all patients, echocardiography exhibited akinesia of the apical and mid portions of the left ventricle. Because acute coronary syndrome was suspected in all patients, coronary angiography was performed in all patients between 6 and 48 hours after the onset of symptoms. Left ventriculography showed extensive akinesia of the apical and mid portions of the left ventricle ("apical ballooning"), whereas basal contractility was normal or even supernormal, and coronary angiography revealed no significant "culprit" coronary artery stenosis responsible for the wall motion abnormality. Additionally, the region of akinesia did not correspond with the perfusion territory of a single epicardial coronary artery.

No patient died or showed recurrence during follow-up, which ranged 1-8 months. All patients had class I New York Heart Association function on discharge. In all patients, left ventricular systolic function recovered almost completely within three days to three weeks.

Discussion

Our case series of four patients with "apical ballooning" in four Caucasian patients showed the importance of emotional or physical stress or other preceding triggering factors in this

Table 1. Characteristics of four patients with "apical ballooning" syndrome (Takotsubo-shaped cardiomyopathy) who were admitted to the Department of Cardiology and Intensive Care, General Hospital Wels, Austria, within 8 months*

Characteristics	Case No.			
	1	2	3	4
Age (years)	84	64	64	82
Sex	female	male	female	female
Trigger event	lumboischialgia/ intramuscular injection	hypothermia	witnessing sister's stroke and seizures	accident with multiple contusions
External trigger duration (h)	72	5	10	78
Circumstances during 24 hours before external trigger	none	none	none	none
External trigger intensity (onset anger scale, ref. 18)	2	2	2	5
Symptoms	acute chest pain	chest discomfort	chest pain	chest pain
Coronary angiogram	normal	normal	normal	normal
Ventriculography (LVEF, %)	anteroapical akinesia (22%)	anteroapical akinesia (37%)	apical akinesia (45%)	apical akinesia (39%)
ECG	anterior wall ST-elevation	ST-depression and giant negative T waves V2-V5	ST-elevation V2-V5	ST-depression and negative T waves V2-V5 and I + avL
CK (initial/peak, U/L)	570/645	275/945	52/184	78/234
CK-MB (initial/peak, U/L)	34/39	34/61	-/24	-/36
Troponin T (initial/peak, ng/mL)	0.69/1.14	<0.03/0.42	<0.08/0.08	<0.17/0.18
Echocardiogram:				
at follow up	normal	slightly depressed	normal	normal
time after event	3 weeks	day 15	day 3	day 5
LVEF (%)	68	49	72	65

*Abbreviations: LVEF – left ventricular ejection fraction; ECG – electrocardiogram; CK – creatine kinase; CK-MB – creatine kinase myocardial band.

cardiomyopathy, such as acute onset and aggravation of various disorders, including lumboischialgia, hypothermia, cerebrovascular accidents, exacerbation of bronchial asthma, acute abdomen, and emotional stress, including death or funeral of a family member, inexperienced exercise, quarreling or excessive alcohol consumption, or vigorous excitation. Also, chest pain or discomfort as an initial symptom was present in three cases, and there was a transient extensive akinesia of the apical and mid portions of the left ventricle, without significant stenosis on the coronary angiogram, accompanied by ECG changes mimicking acute coronary syndrome.

Pathophysiology of Transient LV Apical Ballooning

"Classic" myocardial ischemia (and necrosis) as a result of obstruction of a large epicardial vessel seems to be unlikely pathophysiological mechanism as the results of coronary angiography performed immediately after the onset showed no definite evidence of myocardial ischemia originating from epicardial obstruction in any of the subjects (19). In contrast, Ibanez et al (20) found by ultrasound a ruptured atherosclerotic plaque in the middle portion of the left anterior descending artery in 5 patients with Takotsubo cardiomyopathy, without any other atherosclerotic disease. They speculated that the underlying cause of this enigmatic syndrome might be an acute coronary syndrome with early reperfusion and wide LV stunned myocardium. These findings are intriguing but seem an unlikely pathophysiologic explanation because angiographically detectable intracoronary thrombosis in the left anterior descending coronary artery would be expected more frequently if plaque rupture were the primary and major mechanism of the syndrome. Additionally, patients presenting with transient left ventricular apical ballooning commonly do not have long recurrent distal left anterior descending coronary arteries and indeed manifest wall-motion abnormalities beyond that of a single epicardial coronary artery distribution. Finally, acute transient right ventricular systolic dysfunction has been observed in many patients presenting with transient left ventricular apical ballooning, which could not be explained by isolated transient occlusion of the left anterior descending coronary artery (21).

The akinetic zone at the left ventricular apex usually does not correspond to the perfusion territory of a single epicardial coronary artery (22). In particular, the akinesia of the distal portion of the posterior and inferior wall extends well beyond what would be expected in the case of ischemia in the territory of the left anterior descending coronary artery (LAD). The perfusion territory usually corresponding to the LAD is con-

fined to the anterior and anteroapical region of the left ventricle without involving the apical posterior and inferior left ventricular wall (22,23). Moreover, the limited release of cardiac markers disproportionate to the extent of akinesia argues against the hypothesis of necrosis based on ischemia. ECG changes consist of ST-T segment elevation or depression in several leads. Some patients with "apical ballooning" present without ST segment changes that are typical for acute ST-elevation myocardial infarction. The dramatic improvement of systolic left ventricular function over a few days or weeks argues for a "functional" cause rather than necrosis caused by a "classic" acute myocardial infarction. Transient wall motion abnormality after vasospastic angina has been discussed to cause myocardial stunning (24,25). ECG abnormalities including symmetric diffuse T wave inversion and QT prolongation (a pattern that has been associated with left ventricular stunning (26) in unstable ischemic syndromes) were observed in our patients. However, in none of them or the patients described in other reports (16,19) was there definite evidence for a flow limiting lesion on coronary angiographic assessment. Mohri et al (19) reported recently that microvascular spasm is a type of myocardial ischemia without significant stenosis in an epicardial artery. We cannot definitely exclude the possibility of microvascular spasm because we did not examine microvascular function.

We agree that triggering factors are very important clinical information in the syndrome of "apical ballooning" (27). Most patients have undergone a recent emotional stress, but identical clinical presentation have been observed in patients after a wide variety of neurologic injuries and other types of stress, such as hypothermia or trauma, or catecholamine cardiomyopathy during the endocrine crisis of pheochromocytoma (2,27). The overlapping clinical features in all these presentations suggest that myocardial stunning resulting from emotional stress may share a common mechanism with neurogenic stunning of the myocardium described after subarachnoid hemorrhage and stroke, which is believed to be mediated by catecholamines (3,4,27,28). However, there was no case of acute cerebrovascular accident in our series.

Wittstein et al (27) reported that patients with "stress cardiomyopathy" had supraphysiologic concentration of plasma catecholamines and stress-related neuropeptides. Initial plasma concentrations were several times those of patients with myocardial infarction and remained markedly increased even a week after the onset of symptoms. Enhanced sympathoneural activity was also suggested by the increased plasma concentrations of dihydroxyphenylalanine, dihydroxyphenylglycol, norepinephrine, and normetanephrine, reflecting increased synthesis of norepinephrine, neuronal reuptake and metabolism, spillover, and extraneuronal metabolism, respectively (27). However, we did not measure endogenous norepinephrine concentration in our patients.

A possible mechanism underlying the association between mental stress, sympathetic stimulation, and myocardial stunning is ischemia resulting from epicardial coronary arterial spasm (27). Increased sympathetic tone from mental stress can cause vasoconstriction in patients without coronary disease. The patients reported in the present case series did initially have contractile abnormalities in multiple vascular territories, but multivessel epicardial spasm as an explanation for this finding seems unlikely, given the relative absence of ST-segment elevation and minimal enzymatic evidence of myocardial necrosis.

Catecholamine-mediated myocardial stunning may be a direct myocyte injury. Elevated catecholamine levels decrease the viability of myocytes through cyclic adenosine monophosphate (AMP)-mediated calcium overload and are also a potential source of oxygen-derived free radicals that may cause myocyte injury (29). Free radicals can interfere with sodium and calcium transporters, possibly resulting in myocyte dysfunction through increased transsarcolemmal calcium influx and cellular calcium overload. Kawai et al (13) recently reported histologic findings in patients with "apical ballooning" that are similar to those described in catecholamine-induced cardiomyopathy. Thus, this novel cardiac syndrome might be a clinical model of stress-related cardiomyopathy and subsequent sudden death (18,30,31).

There is a preponderance of women among patients with apical ballooning, which may suggest a biologic susceptibility of women to stress-related myocardial dysfunction. Sex hormones may influence both sympathetic activity and coronary vasoreactivity (32). Men produce higher concentrations of plasma catecholamines in response to emotional stress and are more sensi-

tive to catecholamine-mediated vasoconstriction (33). However, women seem to be more vulnerable to sympathetically mediated myocardial stunning and transient left ventricular dysfunction (34). Reduction of estrogen levels may underlie the high incidence of apical ballooning in postmenopausal women. Ueyama et al (35) subjected ovariectomized and estradiol-supplemented ovariectomized female rats to immobilization stress, an animal model of stress cardiomyopathy. They found that an increase in the serum estradiol concentration in this preclinical model can diminish the pathological changes in the heart induced by emotional stress.

Despite initially severe presentation of "apical ballooning," its medical management is safe and compatible with good long-term outcome in patients surviving the initial episode. Left ventricular function usually recovers completely within several weeks.

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