Takotsubo Cardiomyopathy

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5.1 Case Report

A 65-year-old woman presented to the emergency room for chest pain developed after a car accident, where she was involved, persistent for at least 30 min. The pain did not decrease by changing position. It consisted of a retrosternal pressure or heaviness ("angina") radiating to the neck, accompanied by dyspnea and palpitations.

Medical History and Cardiovascular Risk Factors

- Familiar history of ischaemic cardiovascular disease
- Current smoker (about ten cigarettes per day)
- Arterial hypertension
- Dyslipidemia
- Anxious depressive syndrome
- She doesn't refer any other previous cardiovascular disease

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Allergies

No allergy was referred by the patient.

Social History

- She has two sons in good health. At present, she is menopausal and retired.
- She drinks a glass of wine once in a while.
- She walks for about 3 km three times a week.

Medications

- Sertraline 50 mg/day at 8:00 am
- Valsartan 160 mg/day at 8:00 am

Vital Signs

- Temperature: 36 °C
- Heart rate: 110 bpm
- Blood pressure: 160/100 mmHg
- Respiratory rate: 18 breaths per minute
- Oxygen saturation while breathing ambient air: 98 %

Physical Examination

- *General*: agitated, alerted, awake, and oriented
- *Head*, *eyes*, *ears*, *nose*, and *throat*: normocephalic, atraumatic, mucous membranes moist, extraocular muscles intact, pupils equally round and reactive to light and

A. Capucci (ed.), *Clinical Cases in Cardiology: A Guide to Learning and Practice*,
DOI 10.1007/978-3-319-19926-9_5

accommodation bilaterally, bilateral tympanic membrane intact, bilateral sclera anicteric, and no conjunctival injection.
- *Neck*: supple, no jugular venous distension, no lymphadenopathy, and no carotid bruit.
- *Cardiovascular*: regular heart rate, protodiastolic gallop with S3 added, apical holosystolic murmur 2/6, no rubs, no hepatojugular reflux, and capillary refill less than 2 s.
- *Lungs*: no rales on auscultation, no rhonchi or wheezes, no egophony, no alterations in tactile fremitus, and normal upon percussion.
- *Abdomen*: plan, no pulsatile masses, normal bowel sounds in all four quadrants, no high-pitched or tinkling sounds, resonant on percussion, soft, nondistended/nontender, no rebound or guarding, no costovertebral angle tenderness, and no hepatosplenomegaly.
- *Extremities*: no cyanosis or clubbing. No peripheral edema.
- *Neurological*: no focal deficit.
- *Psychiatric*: normal affect, no hallucinations, normal speech, and no dysarthria.
- *Skin*: intact, no rashes, no lesions, and no erythema.

Routine EKG at Rest

Sinus tachycardia at 120 bpm, normal atrioventricular conduction (PR 120 ms), complete right bundle branch block (QRS 140 ms), ST segment depression from V1 to V6 with inverted T waves, and QTc interval of 460 ms (Fig. 5.1).

Routine Laboratory Tests

- Complete blood count: normal
- Renal function: creatinine 0.8 mg/dl (normal)
- Hepatic function (GOT, GPT, y-GT, ALP, total bilirubin, direct and indirect): normal
- Electrolytes: Na 137 mEq/L and K 4.1 mEq/L (normal)
- Fasting blood glucose: 156 mg/dl
- Troponin I: 0.13 ng/ml (n.v. <0.08 ng/ml)
- CK-MB: 1.7 ng/ml (n.v. <5 ng/ml)
- BNP 92 pg/ml (n.v. <100 pg/ml)
- Inflammation index: VES 25 mm/h (n.v. <27 mm/h;) and CRP 0.5 mg/dl (n.v. <0.6 ng/ml)
- D-dimers: 180 ng/ml (n.v. <230 ng/ml)

Chest X-Ray

Normal heart size and volumes. No bone fractures and no signs of trauma or dissection of the major mediastinal vessels. Absence of pulmonary congestion, pleural effusion, or signs of pneumothorax (not shown).

What Are the Possible Causes of Chest Pain in This Patient?

- *Myocardial disease*
  - Acute coronary syndromes without persistent ST elevation (NSTE-ACS) or unstable angina (UA)
  - Myocardial infarction secondary to an ischemic imbalance for rise of blood pressure or tachycardia
  - Coronary spasm
  - Cardiac contusion
  - Stress cardiomyopathy (Takotsubo syndrome)
  - Myocarditis, pericarditis, and myopericarditis
- *Valvular heart disease*
  - Severe aortic stenosis
  - Severe aortic regurgitation
- *Aortic disease*
  - Traumatic aortic injury
- *Thoracic trauma and/or fractures*
- *Pulmonary disease*
  - Pneumothorax
  - Pulmonary embolism

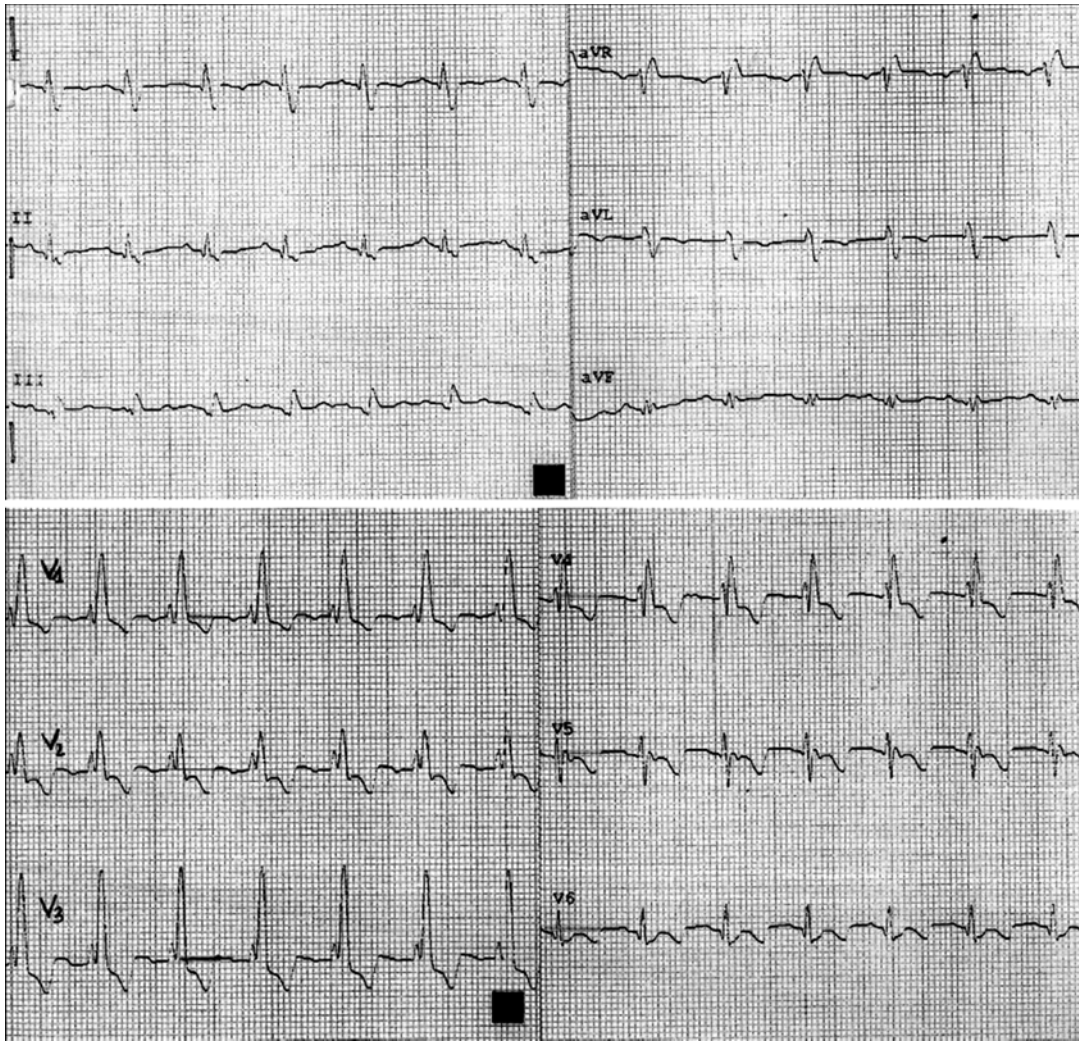

Fig. 5.1 EKG at rest while the patient was symptomatic

A pulmonary embolism is unlikely for the low pretest probability (the patient has never suffered previous pulmonary embolism or deep vein thrombosis; she didn't have previous surgery, trauma, long immobilization, or cancer; and she never used hormone replacement therapy). Furthermore, the normal D-dimer level excludes this affection with high sensitivity.

Pneumothorax and thoracic fractures can be excluded because physical examination and chest x-ray were normal.

The EKG shows ST segment depression in anterior leads which ruled out coronary spasm, usually characterized by ST elevation (Prinzmetal angina) although it may consider a possible posterior ST elevation with anterior ST depression as a mirror image.

A phlogistic damage (myocarditis, myopericarditis) is unlikely because the EKG modifications are not typical and not widely represented in all the EKG leads; moreover, the patient didn't report flu or gastrointestinal disease, and the laboratory tests did not show clear signs of a phlogistic state.

The chest pain referred by the patient was quite typical for "angina" or also could suggest an aortic damage caused by car accident. An echocardiography was done to evaluate those possible diagnostic alternatives.

Echocardiography

The aortic valve is trileaflet. Slight enlargement of the left atrium (LA diameter M-mode = 4.2 cm; area 4 c = 22 cm^2). Mild functional mitral regurgitation caused by displacement of the papillary muscles. Normal right atrium (area 4 c = 12 cm^2). Right ventricle also normal in size and function. Normal tricuspid valve. Mild tricuspid regurgitation centrally directed (PASP = 35 mmHg). Normal pulmonic valve. The interatrial septum is normal. The left ventricle is slightly hypertrophic (LV mass index 97 g/m^2) with apical and mid-left ventricular dilatation; moderate reduction of systolic global function for complete akinesis of the apical and mid-segments and compensatory basal hyperkinesis. The ejection fraction measured with Simpson's biplane method was 40 %. Normal pericardium and aorta (aortic root dimension = 3.0 cm; ascending aorta = 3.2 cm; aortic arch = 3.3 cm; thoracic aorta = 2.9 cm; abdominal aorta = 2.0 cm). The inferior vena cava was not dilated. Pseudonormal diastolic pattern with increased filling pressure (E/A 1.1, E/E' 16, E dec time 170 m/s) (Fig. 5.2).

Conclusion

- Severe valvular disease, hypertrophic cardiomyopathy, pericardial effusion, and rupture of the wall or septum were ruled out.
- Aortic root and aortic isthmus diameters were normal without any intimal flap or thrombus along the aortic wall. A traumatic aortic injury (TAI) was also unlikely because of features of the car accident suffered by the patient.
- The echocardiography findings showed moderate reduction of systolic function for apical and mid-left ventricular dilatation and akinesia with compensatory basal hyperkinesis compatible with ischemic injury. This pattern of wall motion abnormality ("apical ballooning") is quite typical for stress cardiomyopathy (Takotsubo-like), but also an AMI cannot be excluded without a coronary angiography.

While the patient has been prepared for coronary angiography, he has been treated with:

- Initial loading dose of aspirin (300 mg)
- Initial loading dose of ticagrelor (180 mg)
- Fondaparinux 2.5 mg/day
- Perindopril 2 mg/day
- Atorvastatin 80 mg/day
- Bisoprolol 2.5 mg/day

Coronary Angiography and Left Ventriculography

A coronary angiography was performed within 24 h from admission showing right coronary dominance and absence of significant coronary artery stenosis (Fig. 5.3).

The left ventriculography showed complete apical and mid-ventricular akinesis with systolic

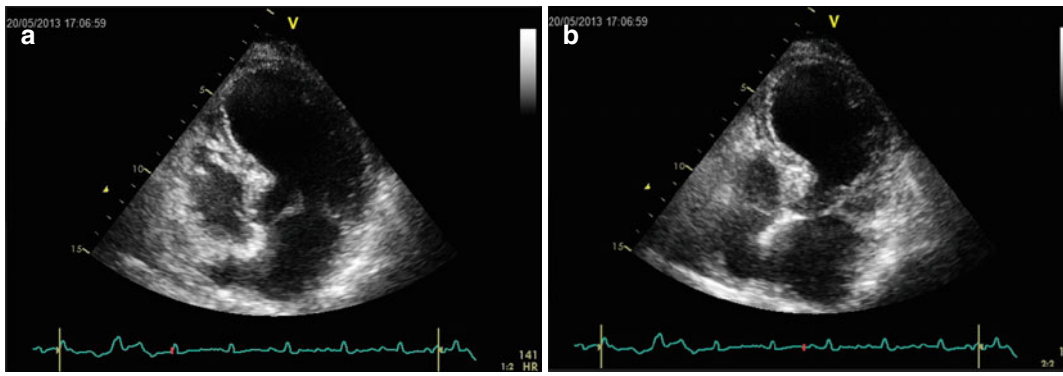

Fig. 5.2 Echocardiographic picture recorded at rest during systole (**a**) and during diastole (**b**); typical LV ballooning during systole is visible, characterized by complete akinesis in the apical to mid-segments circumferentially of the left ventricle with relative compensatory hypercontractility in the basal segments

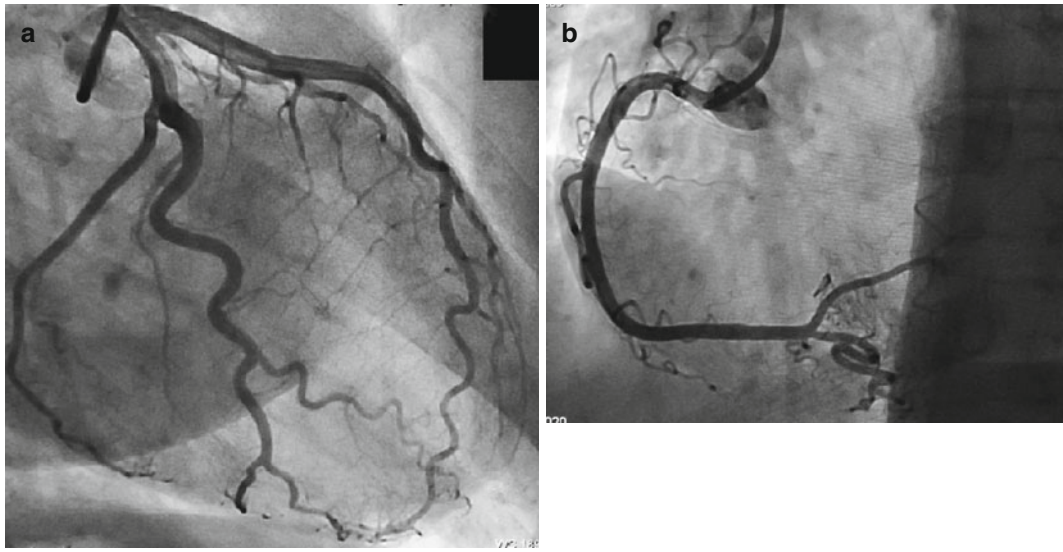

Fig. 5.3 Coronary angiography of left coronary artery (**a**) and right coronary artery (**b**); right coronary dominance and absence of significant coronary artery stenosis are shown

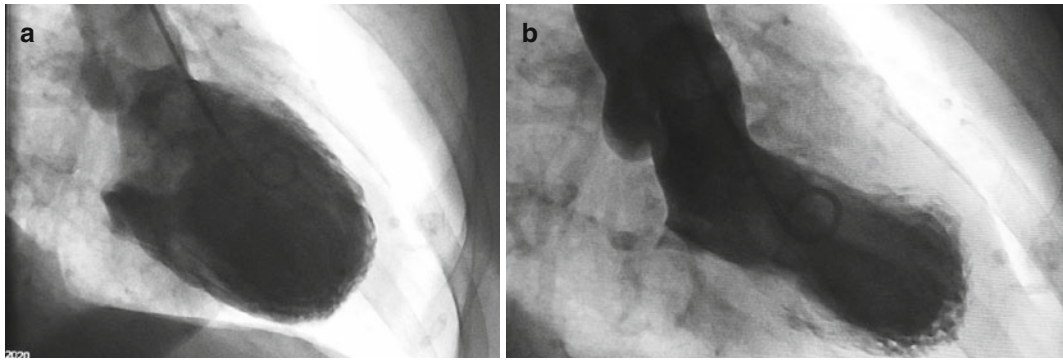

Fig. 5.4 Left ventriculography recorded during diastole (**a**) and systole (**b**); complete apical akinesis and mid-ventricular akinesis are shown, with systolic "apical ballooning" and moderate systolic dysfunction

"apical ballooning" and moderate systolic dysfunction. No spasm was recorded (Fig. 5.4).

Conclusion

- Absence of significant culprit coronary artery stenosis or intracoronary thrombosis
- "Apical ballooning" pattern

Final Diagnosis

The clinical presentation that mimics an acute myocardial infarction triggered by emotional stress (car accident) with modest EKG changes at presentation and with low plasma levels of cardiac biomarkers, disproportionate with the severity of ventricular dysfunction, could suggest the diagnosis of Takotsubo cardiomyopathy. This diagnosis is confirmed by findings on imaging (echocardiography and ventriculography) of transient apical- to mid-ventricular ballooning with compensatory basal hyperkinesis, without coronary stenosis.

Subsequent blood tests have shown normalization of cardiac biomarkers (max values: troponin I 2.45 ng/mL, CK MB 6.7 ng/mL), and echocardiography has displayed progressive recovery of contractile function until complete normalization.

Subsequent EKGs performed during hospitalization showed the typical evolution described in TC with new onset of negative and deep T waves and marked QTc interval prolongation and then slow and complete regression of these abnormalities after about 15 days.

EKG Performed at Day 3

Sinus rhythm at 65 bpm, normal atrioventricular conduction (PR 120 ms), complete right bundle branch block (QTS 140 ms), and normal ST segment with deep inverted T waves from V1 to V6 and DI, DII, AVL, and AVF (QTc interval of 624 ms) (Fig. 5.5).

The patient was discharged with the following therapy:

- Aspirin 100 mg/day
- Perindopril 2 mg/day
- Atorvastatin 40 mg/day
- Bisoprolol 5 mg/day

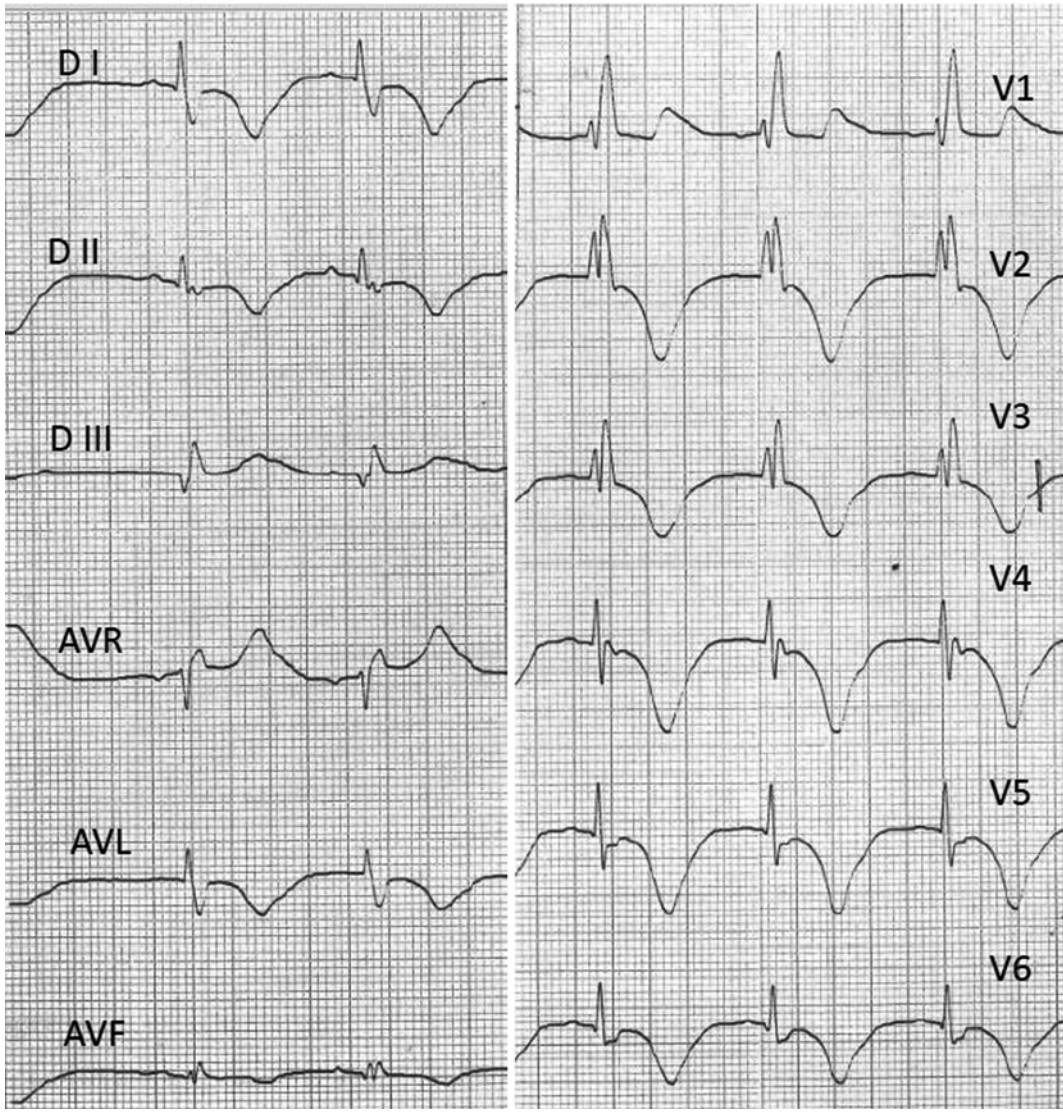

Fig. 5.5 EKG at rest during the third day of hospitalization while the patient was asymptomatic

5.2 Takotsubo Syndrome

Definition

Takotsubo syndrome (TS) is a reversible cardiomyopathy, first described in 1990 by Sato et al. in Japan [1], also known as "apical ballooning syndrome" or "stress cardiomyopathy," since it has become increasingly recognized worldwide.

It is characterized by signs and symptoms of acute myocardial infarction (AMI) but without demonstrable coronary artery stenosis.

Epidemiology

TS accounts for about 1–2 % of all cases of suspected AMI [2, 3].

It typically occurs in postmenopausal elderly women (average age 68 years); men account for a minority of cases (4–13 %), and rarely also children or young adults may be affected [4].

Pathogenesis

The exact pathogenesis of Takotsubo cardiomyopathy (TC) is still unknown, but various hypotheses have been suggested and discussed over the years.

- *Coronary artery spasm or transient acute artery thrombosis* [3, 5]: These hypotheses have been actually withdrawn because the typical "apical ballooning" is incongruent to a singular coronary artery supply region. The hypothesis of a multivessel coronary spasm would not explain the discrepancy between severe ventricular dysfunction and the only slightly increased levels of cardiac enzymes and why the recurrence could present different myocardial localization in the same patient or why some patients show the "apical sparing" variant [3].
- The long-lasting ST segment elevation in Takotsubo patients challenges strongly the hypothesis of a transient thrombosis which usually presents rapid resolution of ST segment elevation [6].
- Finally, the histological changes usually observed in TC (coagulative myocytolysis and myofibrillar degeneration) are different from those observed in ischemic disease (coagulative necrosis) [6].
- *Coronary microvascular dysfunction*: This hypothesis has been initially proposed based on findings of a diminished coronary flow reserve [7] and on a significant improvement of myocardial perfusion during adenosine infusion in patients with TC but not with STEMI [8]. However, other trials didn't confirm the "slow flow" phenomenon in many Takotsubo patients, so they supposed that this impairment of microcirculation could be a possible consequence of the myocardial dysfunction caused by TC itself [9].
- *Catecholamine toxicity*: Some authors found markedly elevated catecholamine levels in patients with TC, suggesting that these might be the main pathogenic factor [10]; however, many subsequent studies have not uniformly shown elevated plasma catecholamine levels in TC patients [11]. So it is likely that circulating catecholamines are somehow involved in the pathogenic process but not the only ones responsible.
- *Cardiac sympathetic disruption*: Recently a new hypothesis has been proposed regarding the disruption of local cardiac sympathetic nerve endings with local release of norepinephrine into the myocardial tissue, which could damage it and lead to the systolic dysfunction; moreover, it seems that the characteristic circular pattern of ventricular wall motion abnormality follows the cardiac sympathetic supply system [12].

Clinical Features

The clinical features of TS are usually completely superimposable with those of an acute myocardial infarction (AMI).

- *Symptoms*: acute and prolonged anginal chest pain, described like retrosternal pressure or heaviness, sometimes radiating to the left arm or

neck. When present, a typical aspect useful for diagnosis is that the chest pain usually occurs after mental or physical stress, such as the unexpected death of a relative or friend or receiving news of serious diagnosis or having a great fright [13]. However, recently an international meta-analysis (COUNTS study) has shown that these stressors have a limited impact occurring in about only 36 % of patients [14]. In men, physical stress rather than emotional stress is much more associated with the occurrence [4].

- Dyspnea, nausea, and diaphoresis can accompany chest pain.
- *Comorbidities*: A high number of patients affected by TS present cardiovascular risk factors like hypertension (54 %), dyslipidemia (32 %), diabetes mellitus, obesity, and history of smoking, similar to that seen in patients with AMI [14]. Moreover, it has been noted that sometimes TS can occur in patients affected by comorbidities that are usually associated with an excess of catecholamine systemic production like obstructive pulmonary disease, sepsis, thyroid (thyrotoxicosis), or neurological disease (cerebrovascular accidents, subarachnoid haemorrhage, etc.) [3], malignancy, or psychological disorders (22 %) [14].
- *12-Lead EKG*: During the acute phase, it usually shows ST segment depression or transient/persistent ST segment elevation in anterior leads, perfectly mimic king acute myocardial infarction [15–18]. Sometimes it can show also T-wave inversion or Q waves. In subsequent days, the EKG abnormalities follow a distinctive time sequence [19].
- *Cardiac biomarkers*: Troponin, creatinine kinase, and BNP are usually increased.
- *Echocardiography*: It plays a central role during diagnostic process because it shows a typical pattern of wall motion abnormality: complete akinesis or hypokinesis in the apical to mid-segments circumferentially of the left ventricle with relative compensatory hypercontractility in the basal segments (LV ballooning during systole). During left ventriculography, this particular systolic left ventricular shape is more evident and explains the reason why this syndrome has this particular name: it resembles a typical pot (called exactly "Takotsubo") used for a long time in Japan to capture octopuses, which has a round bottom and a narrow neck.
- Other patterns of wall motion abnormality have been reported less frequently, involving the basal-mid segment (apical sparing variant or "inverted Takotsubo") or the right ventricle. Typically, the wall motion abnormality involves regions which are incongruent to a particular coronary artery supply; instead during an AMI, it is more common to find these hypokinetic/akinetic areas supplied by a particular coronary artery.

Clinical Course and Complications

Clinical course of TC is usually characterized by the progressive lowering of chest pain and gradually complete resolution of the wall motion abnormality after some days; less frequently it needs some weeks or months, but differently from AMI, there aren't permanent areas of hypokinesis/akinesis of the left ventricle motion.

- *EKG evolution*: The EKG abnormalities show a slower progression than during AMI, with a specific evolution: gradually during the first hours from symptom onset, there is the complete resolution of ST segment elevation/depression. Negative T waves usually occur after 24–72 h and then gradually deepen progressively during the days/weeks following [20]. Abnormal Q waves could be seen in precordial leads, but these are transient in most patients and generally resolve within a few days to several weeks.
- QTc interval becomes prolonged (>500 ms) progressively as the negative T wave deepens, and this could favor life-threatening ventricular arrhythmias such as torsades de pointes and ventricular fibrillation [18].
- After some weeks, there is usually the complete restoration of the ECG pattern prior to the acute event [15].
- *Recurrences*: These may occur with a rate range from 0 to 15 % after the first episode

and may show the typical apical ballooning or even different patterns of wall motion abnormalities [21].

- *Acute complication*: Despite the most common general favorable course, the in-hospital death ranges from 0 to 8 % because of possible acute complications [22]. Congestive heart failure is one of the most common acute complications (approximately 3–46 %) occurring more frequently in patients with right ventricular involvement [22].
- As already mentioned, during the acute and subacute phases, corrected QT (QTc) interval is markedly prolonged (usually >500 ms), and this is a potential risk factor for life-threatening arrhythmias such as torsades de pointes and ventricular fibrillation that could require external defibrillation [23]. Bradycardia, hypokalemia, hypomagnesemia, and the use of antiarrhythmic drugs may favor arrhythmias when there is QTc prolongation, so they have to be quickly corrected. The reversible nature of the cardiomyopathy suggests that the use of systematic device implantation after a ventricular arrhythmias isn't recommended at the moment.
- Apical thrombosis may occur during the acute phase when the wall motion abnormalities are more evident, due to low blood flow within the apical segment. This could become a potential source of emboli especially when the resolution of the apical akinesis/dyskinesis occurs [24]. Prophylactic anticoagulation therapy should be considered to prevent apical thrombosis and embolic events until the resolution of the "apical ballooning."
- Hypotension occurs frequently and can result from LVOT obstruction associated with basal hypercontractility, complicated by systolic anterior movement of the mitral valve anterior leaflet and mitral regurgitation.
- Cardiogenic shock and ventricular rupture are rare complications described in literature.

Diagnosis

There is yet no consensus on the diagnostic criteria for TC: researchers at the Mayo Clinic proposed first diagnostic criteria in 2004, which have been modified recently (2008) and included [25, 26]:

1. Transient hypokinesis, dyskinesis, or akinesis of the left ventricular midsegments, with or without apical involvement; the regional wall motion abnormalities extend beyond a single epicardial vascular distribution, and a stressful trigger is often, but not always, present.
2. Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture.
3. New ECG abnormalities (either ST segment elevation or T-wave inversion) or modest elevation in cardiac troponin.
4. Absence of pheochromocytoma or myocarditis.

Patients were assigned this diagnosis when they satisfied all these criteria.

Japanese investigators have recently presented diagnostic guidelines [27].

There is not a single shared diagnostic test so TC is currently a diagnosis of exclusion.

Furthermore in addition to clinical features, EKG, and echocardiography abnormalities, coronary angiography is mandatory to exclude coronary plaque rupture (culprit lesion) which would need angioplasty and stent implantation or multivessel epicardial coronary spasm. Most patients have angiographically normal coronary arteries or mild atherosclerosis (considering advanced age and several coronary risk factors). In fact, many authors have attempted to find unique ECG criteria capable of distinguishing between Takotsubo and STEMI patients during the acute phase, but actually no criteria have been found, and ECG keeps a limited diagnostic role [18, 20].

Cardiac magnetic resonance is a suitable method to establish TC diagnosis. It allows to evaluate the global systolic function and the area of wall motion abnormalities; moreover, it shows the area of myocardial edema, which is a typical finding in TC, inflammation, and fibrosis. Contrary to myocardial infarction or myocarditis, there aren't areas of delayed enhancement because in TC there isn't an irreversible damage [28, 29].

Treatment

Medical treatment remains empirical.

During the acute phase, therapy must be individualized depending on the hemodynamic situation.

In stable conditions, patients are often treated with diuretics, angiotensin-converting enzyme (ACE) inhibitors, and β-blockers to prevent excessive sympathetic activation [13]. To reduce the risk of thromboembolism, patients with marked apical ballooning should be treated with anticoagulant therapy until the contractility of the apex is improved, unless there is a definite contraindication [24].

In hemodynamically unstable patients, early administration of intra-aortic balloon pump counterpulsation should be considered in addition to cardiopulmonary circulatory support and continuous venovenous hemofiltration. There is controversy on the use of cardiac stimulants because of increasing circulating catecholamines. For patients with severe LV outflow tract obstruction, treatment with β-blocker and volume expansion should be considered to reduce the obstruction and increase the cardiac filling.

There is no consensus regarding long-term management of TC [30], although it could be reasonable to treat patients with β-blockers and ACE inhibitors during the ventricular recovery period; however, no data support the continuous use of these drugs for the prevention of recurrence and improvement of survival rate [21]. Physicians may consider stopping those drugs after normalization of left ventricular function normalization.

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