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A left humerus fracture-induced Takotsubo syndrome

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**Patient consent for publication:** the patient gave his written consent to use his personal data for the publication of this case report and any accompanying images.

**Availability of data and materials:** all data underlying the findings are fully available.

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**Abstract**

Takotsubo Syndrome (TS) is a transient cardiac condition characterized by regional systolic dysfunction, often precipitated by emotional or physical stressors. The pathophysiology of TS is not fully understood, but evidence suggests that it may be influenced by multiple factors. We present a case of TS following a traumatic left humerus fracture in an 82-year-old male patient with hypertension. Diagnosis was confirmed through comprehensive clinical evaluation, identification of ECG abnormalities, echocardiographic findings, and exclusion of other diseases. The patient’s management consisted of β-blockers, aspirin, and supportive care. Despite initial concerns, the patient's clinical course was uneventful, illustrating the various presentations of TS. This case emphasizes that TS can occur as a result of a traumatic event, particularly among older individuals with comorbidities. Early recognition and appropriate management are essential for optimizing outcomes.
Introduction

Transient Left Ventricle (LV) apical ballooning, also referred to as Takotsubo Syndrome (TS), is characterized by short-lived (usually lasting 24 to 48 hours) regional systolic dysfunction, dilatation, and oedema involving the LV apex and/or midventricular region in the absence of coronary artery disease.\textsuperscript{1,2} The pathophysiology of TS is not fully understood, but evidence suggests that it may be influenced by various factors (i.e., acute multivessel coronary spasm, aborted myocardial infarction with spontaneous recanalization, and direct catecholamine-mediated myocardial stunning).\textsuperscript{3} A preceding emotional or physical stressor is a typical feature of TS; indeed, physical, emotional, or mixed stressful events have been identified in two-thirds of takotsubo cardiomyopathy cases (such as acute critical illness, trauma, respiratory failure, central nervous system disorders, and iatrogenic factors including surgery or dobutamine stress echocardiography).\textsuperscript{1} The incidence of TS has been reported to be between 5.7\% and 28.0\% in intensive care units.\textsuperscript{4} Post-traumatic TS has been reported mainly in brain injury, chest, and lower limbs. Accidental falls and road accidents are the main causes of injuries [4]. Herein, we describe the case of a patient admitted to the Emergency Department for a left humerus fracture who developed trauma-related TS.

Case Report

An 82-year-old male patient was admitted to the Emergency Department because of an accidental fall from a height of 1.5 meters, resulting in trauma to the left shoulder. The patient reported no loss of consciousness, chest pain, or dyspnea, and denied any head trauma or other injuries. His medical history disclosed arterial hypertension, for which he was treated with an Angiotensin Receptor Blocker (ARB). Physical examination revealed moderate left shoulder pain (NRS=6) with overt dislocation localized deformity, while neurological and thoraco-abdominal examinations were unremarkable. Vital signs were within normal limits. Computed Tomography (CT) of the head showed no abnormalities, while X-ray of the left shoulder revealed a displaced multi-fragmentary fracture of the humerus. The Electrocardiogram (ECG) showed slight T-wave inversion in V4-V5 (Figure 1, panel A), with no previous ECGs available for comparison. After three hours, the ECG showed deepening of T waves (Figure 1, panel B). A contrast-enhanced CT of the chest and abdomen ruled out post-traumatic effusions. Blood tests revealed elevated troponin levels, hypokalemia, and
hypocalcemia (Table 1). Transthoracic echocardiography (Figure 2A, B and C) showed no pericardial effusion, good contractility of the basal portions of the heart, slightly hypomobile apex, and an inferior vena cava of approximately 2 cm in caliber with poor respiratory excursions, a finding indicative of central venous pressure >8 mmHg. Coronary angiography was performed to exclude mechanical obstruction (Figure 2D). The patient met the Mayo Clinic diagnostic criteria with positive troponin delta, ECG abnormalities, apical ballooning on echocardiography, negative coronary angiography, and exclusion of other diseases. Because of this clinical picture, the patient was prescribed β-blockers, aspirin, and low molecular weight heparin, in addition to a combination of paracetamol and codeine for pain control. During hospitalization, ECG showed QT prolongation, which progressively normalized at discharge, along with troponin levels. Based on orthopedic consultation, the upper limb was immobilized with a collar and cuff sling, and non-operative management of the fracture was deemed the right therapeutic option based on the patient’s age and co-morbidities. The patient was discharged after 11 days in good conditions with a diagnosis of "Takotsubo syndrome associated to a fracture of the left humerus".

Three months later, a follow-up echocardiography showed no cardiac kinetic abnormalities, hence β-blockers were discontinued, while aspirin was maintained.

Discussion

Originally reported in Japan in 1990, TS and its variants is defined as an acute and reversible cardiac failure. The Mayo Clinic criteria are widely used for diagnosis and include: i) the presence of transient hypokinesis, akinesia / dyskinesia of the left ventricular mid-segments with or without apical involvement; regional wall motion abnormalities that extend beyond a single epicardial vascular distribution; and (frequently) a stressful trigger; ii) the absence of obstructive coronary disease or angiographic evidence of acute plaque rupture; iii) new ECG abnormalities and/or modest elevation in cardiac troponin; and iv) the absence of pheochromocytoma and myocarditis.

TS can be classified as primary or secondary. In primary forms, acute cardiac symptoms are the main reason for seeking medical attention. Conversely, secondary TS is recognized in patients who are already hospitalized for a medical or surgical condition (e.g., acute
respiratory failure, traumatic injury, sepsis), as in the present case. Furthermore, primary and secondary TS include different anatomical variants. A typical variant, found in about 50-70% of patients, including our patient, is characterized by left ventricular regional wall motion abnormality with apical and circumferential mid-ventricular hypokinesia. At end-systole, the left ventricle resembles the ‘Takotsubo’ (the Japanese fishing pot used for trapping octopus) with a narrow neck and globular lower portion. The other two common phenotypes include the basal or inverted variant with circumferential basal hypokinesia and the mid-left-ventricular variant, with circumferential mid-ventricular hypokinesia and both basal and apical hypercontractility. Rare variants encompass biventricular apical dysfunction and isolated right ventricular TS.

The exact pathophysiological mechanism of TS remains unclear, but it might include coronary vasospasm, microcirculatory dysfunction, catecholamine surge, and sympathetic overdrive. Excessive levels of catecholamines released by the sympathetic nervous system could result in intracellular calcium overload and cardiac dysfunction through the β1-adrenoreceptor signal transduction pathway. Moreover, patients with TS also consistently demonstrate microvascular dysfunction features, i.e., impairment of endothelium-dependent vasodilation, excessive vasoconstriction, and abnormalities of myocardial perfusion.

The incidence of TS is estimated to be around 2% of all acute coronary syndromes. In most cases, TS occurs in female and post-menopausal patients due to emotional stressful triggers, while it is rarely observed in male patients and is generally induced by physical stress (i.e., activity/trauma, infections, hypoxia, neurological disorders, surgery, pain). To our knowledge, male patients who develop TS are usually younger (69±13 vs. 71±11 years) and with higher prevalence of comorbidities (i.e., hypertension, diabetes, pulmonary disease, malignancies, and smoking habit) than females. In male patients TS manifests with chest pain, dyspnoea and palpitations with sinus tachycardia; in severe cases, pre-syncope and syncope due to ventricular tachycardia and Major Adverse Cardiovascular Events (MACEs) may occur. However, chest pain is not a frequent initial complaint in males; indeed, in a few cases, the main concern was the ECG findings, as in our case. Although no pathognomonic ECG findings have been described, reversible abnormalities like ST-segment elevation in the anterior leads (56%) and T-wave inversion (39%) are common. Less frequently, QT prolongation and malignant arrhythmias (i.e., ventricular tachycardia, ventricular fibrillation, and torsade de pointes) might occur. As shown in the present case, the ECG might change...
during the patient’s evaluation: in the first phase, which occurs within the initial 6 hours, changes in ST may be detected;\(^2,14\) the second phase involves T-wave inversion, predominant from V1 to V6 plus AVL with progressive deepening and QT prolongation;\(^2\) the third phase, occurring in weeks or months, shows a gradual resolution of T-wave and QT changes.\(^2,14,13\)

There are no sex differences regarding ECG findings and ballooning pattern, whereas initially a lower left ventricular ejection fraction has been reported in males.\(^12\) Furthermore, male patients develop MACEs (\(i.e.,\) cardiogenic shock, arrhythmias) more frequently and have a higher in-hospital mortality rate. This increased morbidity and mortality in the male population could be explained by the stronger adrenergic drive required to initiate TS in men. However, long-term mortality seems to be the same in both sexes.\(^12\) A poor prognosis is usually associated with male sex, advanced age, reduced left ventricular ejection fraction (below 35% at presentation), prolonged QT interval, atrial fibrillation, and the development of acute complications (malignant arrhythmias, syncope, and MACEs).\(^7\)

The management of TS includes oxygen inhalation, intravenous heparin, aspirin, and \(\beta\)-blockers. Targeted therapies are not available for TS. The use of \(\beta\)-blockers is reasonable due to the frequent occurrence of high catecholamine levels. Many studies reported that Angiotensin-Converting Enzyme Inhibitors (ACE-IIs) and ARBs can be used as part of regional wall motion abnormality management. Anticoagulation therapy should be continued even after TC diagnosis confirmation, as it is useful in preventing possible embolic events.\(^6,15\)

As observed, emotional factors play a significant role in the etiology of TS. However, also traumatic events seem to have a great impact on the onset of TS, as reported in the present case. Ghadri et al. suggested a new classification in order to predict short- and long-term outcomes. Class I includes TS related to emotional stress; class II encompasses cases secondary to physical activities / medical procedures and neurological disorders; and, finally, class III includes those patients without an identifiable triggering factor.\(^16\) It has been found that the degree of catecholamine surge is more severe in patients with physical or neurological triggers than in those with emotional triggers. The highest mortality was registered in TS patients secondary to neurological issues.\(^3,4,16\) In the literature, TS related to traumatic events is mostly linked to traumas (road accidents and falls) involving the head, chest, and lower limbs.\(^4,16\) There is no clear linear correlation between the type or severity of trauma and TS. However, Fernandez et al. found that TS was reported in all Glasgow Coma Scale (GCS) levels but more commonly in those with GCS > 13 or < 8. There are two subsets
of patients with trauma at risk to develop TS, namely those with GCS > 13 related to lower limb or chest injuries, and those with GCS < 8 and head injury. The indicative average age seemed to be 48 (age ranged from 1 to 83 years old) with a female prevalence. According to our knowledge, the majority of ECG and echocardiographic findings were consistent with the classical pattern, while four cases related a reverse echocardiographic pattern. By screening the literature, no previous cases associated a humerus fracture with TS, whereas the general involvement of the upper limbs has been reported in this condition.

Conclusions

TS can present in various clinical scenarios. In line with the literature, in our case physical stressors are one of the main predisposing factors for TS occurrence. MACEs and poor short-term prognosis usually affect more men than women with TS; however, in the herein reported patient, the outcome was uneventful. Since presenting symptoms may be not clear, any patient with trauma should be monitored via ECG to allow for an early detection of TS. A 24-hour observation is recommended in patients with TS-related predisposing factors (i.e., age over 45 and comorbidities such as hypertension, diabetes, pulmonary disease, malignancies, and smoking habit) even if they present to the Emergency Department with mild to moderate trauma.

References


Figure 1: Patient’s electrocardiogram (ECG) on admission to (Panel A) and after 3 hours in (Panel B) the Emergency Department.
Figure 2: Echocardiographic (A, B and C) and coronographic images (D) of the present case showing the typical left ventricular apical ballooning.

Table 1: Synopsis of the main laboratory features and troponin profile over time of the reported patient.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Values on admission to the emergency department</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>Result</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>--------</td>
</tr>
<tr>
<td>WBCs (x10^3/μl)</td>
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</tr>
<tr>
<td>RBCs (x10^6/μl)</td>
<td>4.31</td>
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<tr>
<td>HGB (g/dl) (13.0&lt;n.v.&lt;18.0)</td>
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</tr>
<tr>
<td>Plts (x10^3/μl)</td>
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<tr>
<td>INR (0.80&lt;n.v.&lt;1.20)</td>
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<tr>
<td>Creatinine (mg/dl)</td>
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<td>Sodium (mmol/L)</td>
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<tr>
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<td>Calcium (mg/dl)</td>
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<tr>
<td>Troponine (ng/L)</td>
<td>71</td>
</tr>
</tbody>
</table>

Notes: HGB: Haemoglobin; INR: International Normalized Ratio; Plts: Platelets; RBC: Red blood cell; WBC: White blood cell.