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Case Report

Takotsubo cardiomyopathy associated with Kounis syndrome: A clinical case of the "ATAK complex"

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ABSTRACT

A 60-year-old female developed cardiac arrest after experiencing an anaphylactic shock during administration of plasma-expanders. An electrocardiogram registered after restoration of sinus rhythm showed mild ST-elevation in the anterior precordial leads and T waves changes followed by appearance of echocardiographic alterations of left ventricular apex kinesis. Coronary angiography revealed normal coronary arteries, and cardiovascular magnetic resonance confirmed apical ballooning with late gadolinium enhancement in the segments with abnormal contractility. This uncommon clinical case confirms how takotsubo and Kounis syndrome may converge in a single nosological entity, the so-called "ATAK complex" (Adrenaline, Tako-Tsubo, Anaphylaxis, and Kounis), with a specific management and prognostic implications.

<**Learning objective:** The Kounis syndrome has a clinical presentation that poses a difficult differential diagnosis with takotsubo cardiomyopathy. Despite recent significant improvements in the understanding of these two clinical conditions, the pathogenesis of these two entities and, in particular, how they may converge into the clinical scenario of the "ATAK complex" remain to be clarified. We believe that this rare clinical case may help physicians in the correct identification and management of this frequently misdiagnosed clinical disease.>

Introduction

Takotsubo cardiomyopathy (TT) is a disease characterized by clinical, biomarker, electrocardiographic (ECG), and echocardiographic patterns that suggest an acute coronary syndrome [1]. TT usually affects elderly women, and is preceded by an emotional or physical trigger. Left ventricular (LV) systolic and diastolic dysfunction are transient and extend beyond the vascular territory subtended by a single coronary artery. The pathogenesis of this disease remains unknown, but many research data support the possible role of the brain-heart axis, endothelial dysfunction, epicardial, and microvascular damage [2]. Kounis syndrome (KS) is defined as an acute coronary syndrome which arises after an allergic or anaphylactic trigger. This syndrome mainly affects males between the age of 40 and 70 years, and includes as risk factors history of previous allergy, smoking, hyperlipidemia, and systemic arterial hypertension. Various agents have been found to trigger KS, the most common being antibiotics and insect bites [3].

We report an unusual clinical case with several elements common to both TT and KS. This case underlines how these disorders may overlap in the pathophysiology and in the clinical presentation and how they may converge in the scenario of

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"ATAK complex" (Adrenaline, Takotsubo, Anaphylaxis, and Kounis).

Case report

A 60-year-old female with a history of smoking, depression, allergy to aspirin, hypothyroidism, and systemic arterial hypertension was admitted to our Emergency Department for a serious post-abdominoplasty hemorrhage. On admission, the patient had a body temperature of 38.5 °C, blood pressure (BP) of 130/80 mmHg, and oxygen saturation of 97% on room air. Baseline ECG showed sinus rhythm without ST-T abnormalities (Fig. 1A). Blood analyses showed elevated C-reactive protein (CRP,196.9 mg/l, n.v. < 8 mg/l), normal leukocyte count (10.800/ul, n.v. 4.800–10.800/ul) with relative neutrophilia (79%, n.v. 40–70%). The day after admission, fever increased despite antibiotic therapy. An abdominal computed tomography (CT) was performed showing multiple abscesses with peritoneal effusion in the abdomen lower quadrants. At this stage, an echo-guided drainage was performed by the surgeon. Soon after the procedure hypotension (systolic BP of 80/50 mmHg) occurred and plasma expander (Gelofusine 500 ml i.v, B.Braun Milano Spa, Italy) was initially administered. A few minutes later, the patient developed dyspnea, diaphoresis and, despite administration of methylprednisolone and chlorphenamine, went into cardiac arrest with pulseless electrical activity. She was immediately treated with cardiopulmonary resuscitation and adrenaline 0.5 mg i.v, developed ventricular tachycardia, and after multiple direct current shocks returned to spontaneous circulation (ROSC). Immediately after ROSC, an ECG was performed showing mild ST elevation in the anterior precordial leads (Fig. 1B); BP was 130/70 mmHg, pH 7.05, and K + 2.8 mEq/L. The patient's hemodynamic condition was subsequently stabilized with amiodarone 300 mg i.v., furosemide 40 mg i.v., sodium bicarbonate 8,4% i.v., magnesium sulfate 2 g i.v., and 40 mEq of KCL i.v. The patient was then admitted to the cardiology department, hemodynamic profile remained stable, and she was weaned from noradrenaline on day 3. Nonetheless, blood examination showed an increase in troponin T levels (peak 18 ng/ml on day 1 after cardiac arrest, n.v. < 0.05 ng/ml), and ECG monitoring revealed progression toward the development of negative T waves in D1-aVL and V2-V6, and a slightly prolonged QT interval corrected for heart rate (481 ms) (Fig. 1C and D). Transthoracic echocardiography showed apical and middle-septal akinesia with a moderately reduced global ejection fraction (EF, 47%), suggesting the development of TT (Fig. 2). To rule out abnormalities of the coronary arteries, a coronary CT angiography was performed on day 6 and showed normal coronary arteries. During hospitalization the patient remained in a stable clinical condition, troponin levels decreased progressively and were within normal values on day 8. On day 12, cardiac magnetic resonance (CMR) continued to show apical ballooning with mildly impaired EF (46%) and minimal pericardial effusion. Late gadolinium images showed mild signal enhancement in the hypokinetic LV segments. The patient was discharged on day 16 on beta-blockers and angiotensin-converting enzyme inhibitors. After two months, a second CMR showed normal LV morphology and function, without evidence of edema on T2 weighted images, hyper-enhancement on LG analysis, or pericardial effusion (Fig. 3).

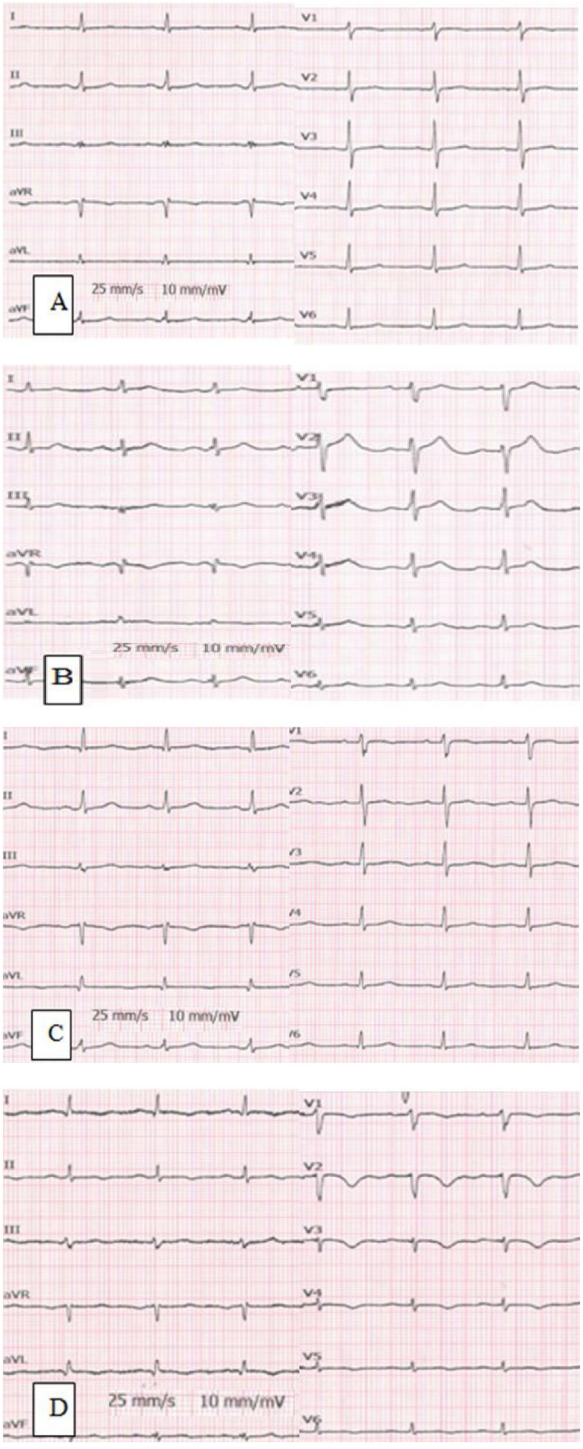

Fig. 1. Electrocardiography (ECG) images at admission (A), immediately after CPR (Cardio-Pulmonary Resuscitation) (B), on day 2 (C) and on day 3 (D) from admission. Panel A shows an otherwise normal ECG. Panel B shows mild ST-segment elevation in the anterior precordial leads. Panel C shows resolution of ST-segment elevation. Panel D shows sinus rhythm with negative T waves in the antero-lateral leads and a slightly prolonged QTc (481 ms).

Discussion

In the clinical case presented here, a clear differential diagnosis between TT and KS is challenging, since both conditions could be taken into consideration. Indeed, our patient presented with cardiac arrest and coronary spasm triggered by anaphylactic reaction to plasma expander infusion as in the Kounis syndrome, followed by signs of TT syndrome

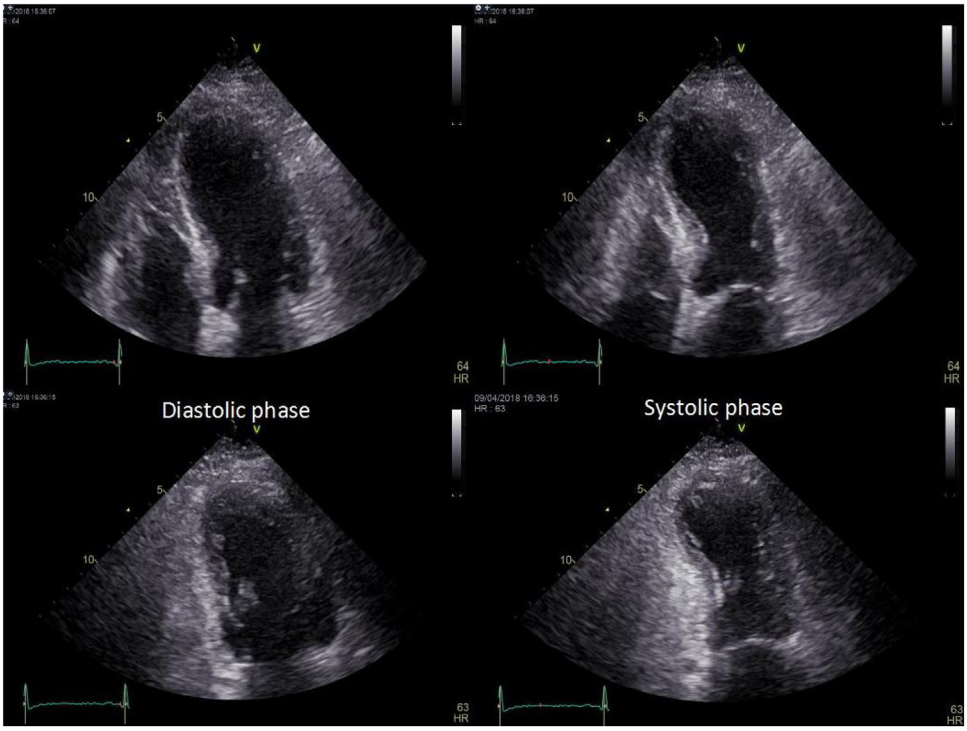

Fig. 2. Echocardiographic images. Four chambers (upper) and two chambers (lower) images showing diastolic and systolic phase with apical ballooning.

which include: acute coronary syndrome with transient LV dysfunction, typical kinetic segmental alterations with normal coronary arteries, T-wave inversion in the anterior leads, and a prolonged QT-c [2,4]. What is extremely uncommon in this clinical case is the onset of cardiac arrest after Gelofusine infusion and the development of a Kounis/TT-like pattern after successful resuscitation from cardiac arrest.

Gelofusine is known to have a possible role in the pathogenesis of KS [3]. Three different types of KS have been described: in the type I variant, the most common, release of inflammatory mediators induces coronary artery spasm with or without increase of cardiac enzymes and troponin; in the type II, acute coronary spasm is associated with plaque erosion or rupture resulting in acute MI; in the type III variant coronary artery stent thrombosis develops in patients with coronary artery disease and an acute allergic reaction [5]. Many features strongly suggest type 1 KS in our patient: history of previous allergy, ECG changes suggesting coronary spasm in the setting of an anaphylactic shock treated with adrenaline, increase of troponin levels with normal coronary artery. KS, through activation of macrophages and mast cells along with compensatory catecholamine release by the renin–angiotensin–aldosterone system during anaphylaxis, can induce also TT [6,7] with the typical transient changes of LV kinetics. It may be speculated that measurement of anaphylactic inflammatory mediators such as histamine, leukotrienes, and platelet activating factor or the use of corticosteroids or mast cell stabilizers may prevent TT occurrence and facilitate its treatment. Taking all of these concepts into account, our clinical case seems to support the hypothesis that a new nosological entity recently proposed (ATAK complex) [8] may link TT and KS by adrenergic exogenous and endogenous release.

Regarding the significant CMR findings, to the best of our knowledge this is one of the very few cases reported in literature of reversible late gadolinium enhancement in a patient with TT and the only one in a patient with KS type I. One possible interpretation of the presence of a mild late gadolinium enhancement in the acute phase, is that severe stress-induced stunning of the apical segments may have led to a patchy pattern of myocardial necrosis accompanied by a certain amount of myocardial edema. Both focal necrosis and tissue edema may contribute to an expansion of interstitial space causing an increase in the volume of distribution for gadolinium contrast. However, when the healing process takes place, edema reabsorbs completely, possibly leaving micro scars below voxel resolution: this explains why late gadolinium enhancement disappears at the follow up.

In conclusion, our case report indicates that acute coronary syndrome may follow an anaphylactic episode complicated by cardiac arrest as reported in the KS, then triggering the onset of TT and of the transient changes of ventricular dysfunction. KS may be a potential trigger for TT and it is mandatory to consider this syndrome whenever a patient is admitted with an acute coronary syndrome after an acute allergic episode. These considerations support the concept that the two syndromes may be considered in the scenario of the ATAK complex.

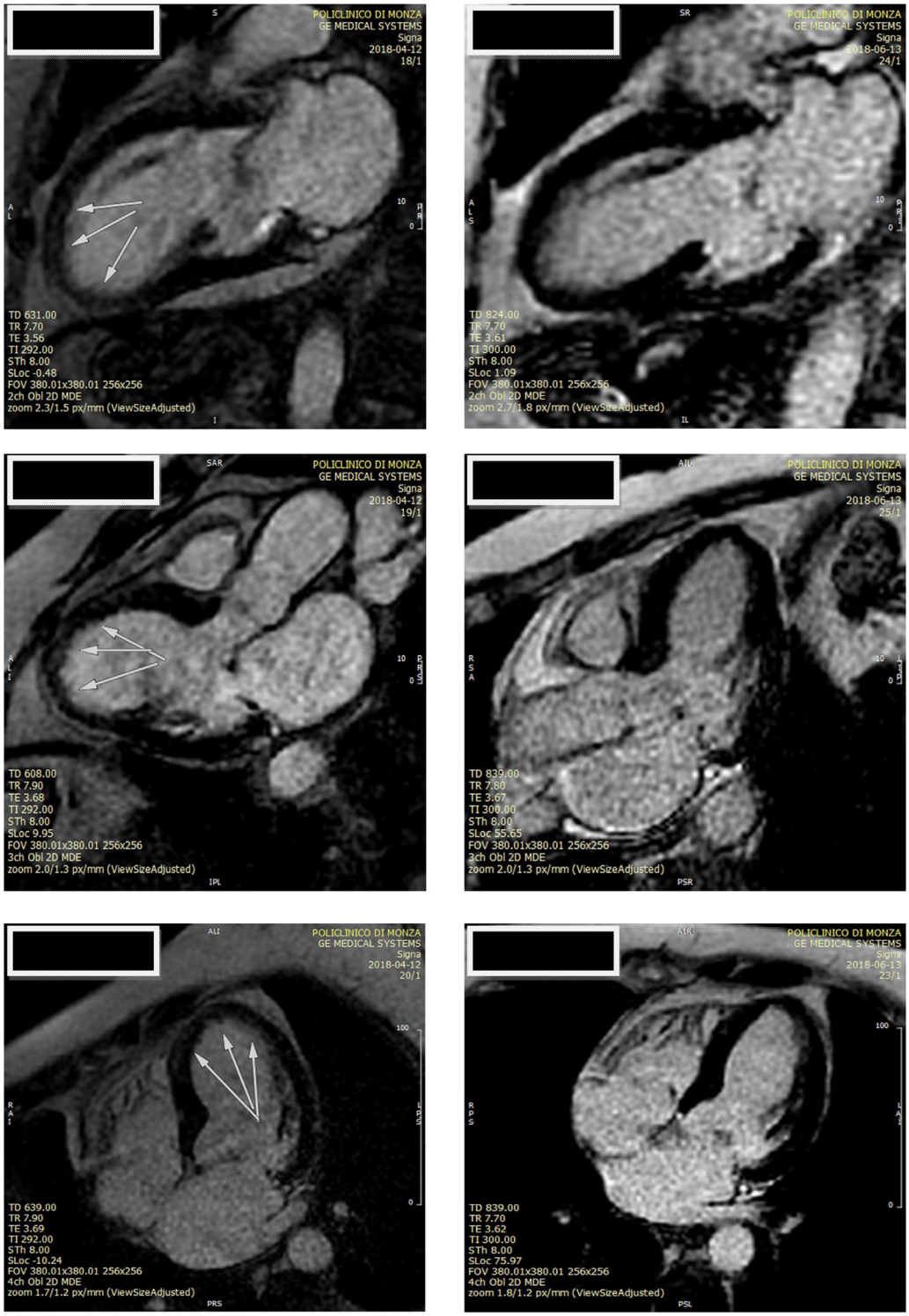

Fig. 3. Cardiac magnetic resonance late gadolinium enhancement images: mild signal enhancement in the apical segments (see arrows) at the baseline (left side); follow-up images (right side) showing no more evidence of late enhancement.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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