ATAK complex due to amoxicillin. A case report

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Takotsubo cardiomyopathy (TTC), also known as broken heart syndrome, transient left ventricular dysfunction syndrome or stress cardiomyopathy, is described by a temporary and reversible systolic abnormality of the left ventricle's (LV) apical area approaching myocardial infarction in the absence of coronary artery disease [1]. It was named after a round-bottomed and narrow-necked fishing pot (takotsubo in Japanese) for trapping octopus due to its resemblance to left ventriculogram. TTC usually occurs in post-menopausal women and is preceded by an emotional or physical trigger.

Kounis syndrome (KS), has been defined as the co-incidental occurrence of an acute coronary syndrome (ACS) in the setting of hypersensitivity reactions following an allergic event [2]. It was first described by Kounis in 1991 [3], and more than 300 cases have been published since, increasing in recent years, including children [4]. Nevertheless, it is easily overlooked and underdiagnosed. Various causes have been found to trigger KS, including so far drugs, insect stings, foods or medical conditions [2].

Recently the term ATAK complex (association of adrenaline, takotsubo, anaphylaxis, and Kounis syndrome) has been coined and few cases reported [5-7], being probably a new challenging complex to take into consideration. We here report an additional case.

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Case. A 77-year-old woman, with obesity (body mass index 31) and diabetes as remarkable backgrounds, presented to the emergency service with pruritus, generalized erythema, lingual edema and discomfort after being at the dentist. A few minutes after arrival, she lost consciousness. After recovering she referred chest and back pain. Intravenous adrenaline (0.5 mg), hydrocortisone 150 mg and dexclorfeniramine 5 mg, were administered. An electrocardiogram was performed revealing diffuse ST segment elevation of 3 mm in D-I, D-II, D-III, aVF, and V3 to V6 (Figure 1). Laboratory tests showed positive cardiac enzymes with troponin T elevation (Figure 1). Serum tryptase determination was not performed. The patient was transferred to the referral hospital with a suspected diagnosis of anaphylactic shock and secondary acute coronary syndrome. Upon her arrival clopidogrel 300 mg and acetylsalicylic acid 300 mg were administered and she was admitted to the Cardiology unit. The following day, coronary angiography was performed, revealing angiographically normal epicardial coronary arteries. The first echocardiogram performed revealed a moderately hypertrophic LV with depressed ejection fraction (EF 0.45); akinesis of the apical segments, hypokinesis of the middle segments, and hypercontractility of the basal segments. LV systolic function was mildly to moderately reduced, and moderate LV hypertrophy was observed (online repository material). The echocardiogram performed prior to discharge instead, showed normalized LVEF and regional abnormalities, suggesting resolved stress cardiomyopathy. During admission, the Allergy unit was consulted. The patient reported an amoxicillin 1g tablet in-take 30 minutes before the dental procedure. Therefore, beta-lactam antibiotics were preventively prohibited. The patient was discharged a few days later with a diagnosis of Kounis Syndrome with Stress Cardiomyopathy.

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Six weeks later the patient was visited at the Allergology Unit. She reported a previous history of allergy to penicillin with a pruritic erythematous generalized reaction approximately 45 years earlier, avoiding penicillin since then.

Allergy skin tests to penicilloyl-poly-L-lysine (PPL), minor determinant mixture (MDM), benzylpenicillin, amoxicillin, cefazolin, cefuroxime, ceftriaxone, cefepime, imipenem and meropenem, according to the European Network and European Academy of Allergy and Clinical Immunology Drug Allergy (ENDA/EAACI) Interest Group protocol [8], were positive for amoxicillin (2 mg/mL intradermal test (ID), benzylpenicillin (10000 UI/mL ID) and imipenem (0.05 mg/mL ID). Laboratory tests showed a basal tryptase 9.3 µg/L and 12.2 µg/L in two separate occasions, IgE 123 U/mL, and specific IgE to cefaclor and penicillin were negative (< 0.1 kU/L). Unfortunately, specific IgE to ampicillin and amoxicillin were not available at that moment. Oral challenge test with cefuroxime was performed with good tolerance.

Discussion

The KS is caused by mast-cell and platelet activation, involving interrelated and interacting inflammatory cells and mediators capable to induce coronary events. Previous history of allergies, hypertension, diabetes, and hyperlipidemia, among others, are predisposing factors [9]. Antibiotics are the most common cause and 70% of cases occur within 30 min after administration [9]. On a recent review regarding KS due to amoxicillin, the main clinical manifestations included chest pain, rash, pruritus, and erythema, and less frequently alteration of consciousness [9]; according to the review, echocardiography at the onset showed hypokinesis in 45% of patients, reduced EF only in 15%; and normal coronary angiography in 50% [9]. Our patient met all of the symptoms and cardiological alterations named above.

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This condition requires rapid treatment aimed not only to provide myocardium revascularization but also to treat the concomitant allergic reaction. Epinephrine is the main life-saving drug to treat an anaphylaxis [10], but as side effect can prolong the QTc interval, induce myocardial damage and/or coronary vasospasm and arrhythmias, especially when administered intravenously, as happened in our case, being likely the induced myocardial stunning of the TTC.

TTC usually occurs linked to over-stimulation of the sympathetic system, microvascular and myocardial tissue metabolism abnormality, and coronary artery vasospasm [1]. Both, the KS itself and the administration of epinephrine therefore favor this situation. Bearing in mind the severe cardiac side effects, intramuscular administration of adrenaline should be preferred.

In addition, serum tryptase should be measured when an anaphylaxis is suspected [10], but probably troponin measurement should be taken into consideration as well, and performed in order to detect and treat immediately potential myocardial damage.

Here we described another ATAK complex case, in which the acute coronary syndrome followed an anaphylactic reaction requiring epinephrine treatment that triggered the onset of TTC and of the transient changes of ventricular dysfunction. The slightly increase tryptase levels may suggest an underlying hereditary alpha-tryptasemia (HaT) or other mast cell disease to be considered.

Probably the ATAK complex is not such a rare situation, being underdiagnosed. Considering that both KS and TTC are themselves frequently misdiagnosed, as mentioned above, the suspicious diagnosis of the ATAK complex might be even more challenging but physicians should be aware of it for a correct identification and management.

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Conflicts of interest

None to be declared. The authors confirm that the study was approved by the ethics committee and that the patients gave their informed consent.

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FIGURE LEGENDS

1. Laboratory test: Biochemical markers of myocardial damage.					
		Troponin T [0 - 14]	CK [24 - 170]	Myoglobin [<70]	proBNP [0 – 300]
Day 1	(1st determination) 12:38 pm.	142 ng/L	35 U/L	-	-
	(2nd determination) 4:17 p.m.	660.6 ng/L	CK 73 U/L	-	-
Day 2	(3rd determination) 01:47 a.m.	519.3 ng/L	73 U/L	44 ng/mL	1724 pg/mL
	(4th determination) 07:45 a.m.	365.4 ng/L	64 U/L	40 ng/mL	2353 pg/mL

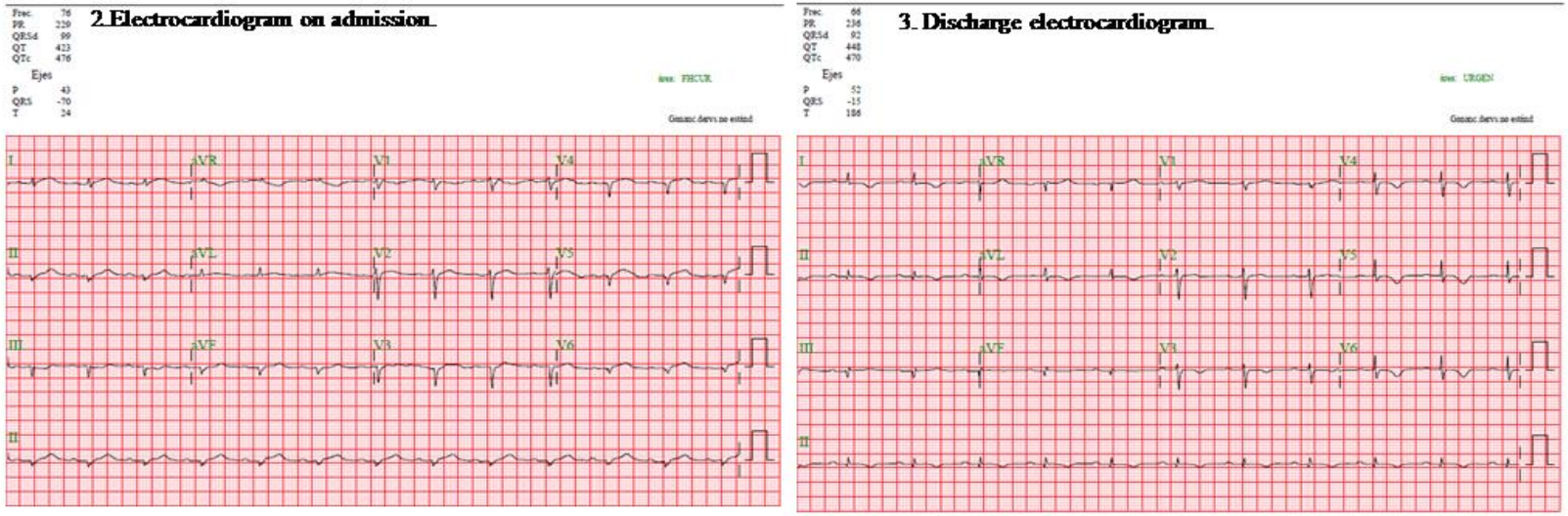

Figure 1. 1. Laboratory test. 2. Electrocardiogram on admission. 3. Discharge electrocardiogram.

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