ATAK Complex Induced by Ranitidine: A Comprehensive Concept for Cardiac Involvement in Allergic Reactions

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During a hypersensitivity reaction (HSR), cardiovascular symptoms are usually associated with other clinical manifestations within the context of systemic anaphylaxis. Less frequently, they present as the primary symptoms or even as the only manifestation of an HSR. In these cases, 2 main syndromes related to vasoactive molecules have been described. The first is Kounis syndrome (KS). KS is characterized by acute coronary events following the release of mast cell and basophil mediators during an HSR [1], which in many cases is due to drug sensitization [2,3]. The second is Takotsubo syndrome (TKS), which is a type of stress cardiomyopathy induced by endogenous or exogenous amines. In TKS, these amines can lead to hyperactivation of cardiac α- and β-adrenoceptors, coronary microvascular dysfunction, and intracellular calcium overload [4]. All these disorders contribute to myocardial dysfunction and typically result in associated acute cardiac ischemia.

An HSR with cardiovascular involvement, arterial obstruction, or plaque rupture observed in coronary angiography suggests KS type II-III. However, the differential diagnosis between KS and TKS can be challenging, especially in the case of KS type I, as both conditions have similar triggers, symptoms, and biomarkers [5]. This challenge could lead to treatment delays while attempting to make an accurate diagnosis, although management may be similar in such cases. In this context, the term *ATAK complex* (adrenaline + takotsubo + anaphylaxis + Kounis) was proposed in 2007 to encompass both overlap syndromes with predominant cardiac involvement [6]. Since then, the concept of ATAK complex has been widely accepted, likely improving both the diagnosis and the treatment of these disorders [7].

We present the case of a 32-year-old woman with a previous history of sulfonamide allergy and gastroesophageal reflux disease. In August 2020, she presented with abdominal pain and pyrosis, which were treated with intravenous ranitidine. A few minutes later, she developed generalized urticaria, vomiting, dyspnea, and precordial pain. She had previously tolerated oral ranitidine. Assessment in the emergency department revealed low blood pressure (69/44 mm Hg) and reduced oxygen saturation (87%). An electrocardiogram was consistent with myocardial ischemia in the inferior and lateral regions of the heart (Supplementary Figure 1) and elevated troponin T levels (27.1 ng/L, positive >14 ng/L).

Intramuscular adrenaline 1/1000 (1 mL), oxygen therapy, IV 0.9% saline solution 1500 mL, methylprednisolone, and acetaminophen were administered, resulting in improvements in both blood pressure and oxygen saturation. However, chest pain persisted, accompanied by bloody sputum and bilateral crackles on lung auscultation. A thoracoabdominal computed tomography scan showed extensive bilateral ground glass infiltrates, suggesting diffuse alveolar edema of a cardiologic origin. Additional laboratory tests revealed increased cardiac enzymes: troponin T (340 ng/L) as a marker of myocardial ischemia and B-type natriuretic peptide (974 pg/mL [positive >120 pg/mL]) as a marker of heart failure. Tryptase was not measured during the acute phase.

Transthoracic echocardiography (TTE) revealed marked akinesis in the anterolateral area of the midbasal segment. This was associated with apical hypercontractility and was suggestive of reverse TKS. Coronary angiography showed no vascular injuries. Myocardial ischemia and heart failure improved within 24 hours using diuretic treatment, with complete resolution in 2 days. Cardiac magnetic resonance imaging performed on day 3 and repeated 2 months later revealed no abnormalities in heart contractility.

Four weeks later, the patient was evaluated in the allergy department, where a skin prick test with ranitidine (at 10 mg/mL) was negative and an intradermal test was positive at 1 mg/mL (8-mm wheal with surrounding erythema) after 20 minutes. Skin tests with ranitidine were negative in 5 healthy individuals.

An in vitro study revealed a basal tryptase level of 4.1 µg/L (normal, 3.8-11.4 µg/L). A basophil activation test (BAT) with increasing concentrations of ranitidine up to 300 µg/mL revealed nonsignificant degranulation.

The patient gave her informed consent for the publication of this case report, along with all accompanying visual elements.

We present the case of a patient who developed ATAK complex due to allergy to ranitidine, with a predominance of reverse TSK. Interestingly, during an HSR with cardiovascular involvement, when a coronary lesion is absent, differentiating between KS type I and TKS is challenging, as both can induce symptoms of myocardial ischemia and heart failure without coronary artery lesions (Table). This overlap syndrome has been described previously, with patients exhibiting features corresponding to both entities [8,9]. More specifically, in the present case, the patient met the criteria for type I KS, namely, increased troponin T, electrocardiogram findings of myocardial ischemia, and an HSR (anaphylaxis) triggering endogenous amine release. Simultaneously, she presented criteria for TKS, with hypokinetic and hyperkinetic zones on the myocardium on TTE, as well as elevated levels of vasoactive amines, in this case, induced by the severe allergic reaction and by the administration of adrenaline. This type of overlap syndrome

Table 1. Comparison Between Characteristics of Kounis Syndrome Type I and Takotsubo Syndrome.

Clinical features	Kounis syndrome type I	Takotsubo syndrome
Type of syndrome	Ischemic heart disease	Stress cardiomyopathy (ischemia may be associated)
Sex	Male predominance	Female predominance
Age	40-70 y	Over 50 y (postmenopausal)
Trigger	Allergic reaction	Allergic reaction/physical trigger/emotional stress
Chemical mediator	Endogenous amines	Endogenous/Exogenous amines
Underlying effect	Vasospasm	Diffuse coronary microvascular disturb and intracellular calcium overload
Myocardial ischemia	Subendocardial ischemia	Subepicardial ischemia
Clinical presentation	Acute myocardial disease	Acute myocardial disease
Biomarkers	Increased tryptase Increased troponin T (+++)	Normal or increased tryptase Increased troponin T (+)
Coronary angiogram	Normal	Normal (with decreased distal flow sometimes)
Electrocardiogram	Myocardial involvement adjusted to a coronary artery	Myocardial involvement does not correspond to the perfusion territory of a specific coronary artery
Cardiac MRI	Normal	Image resembling an octopus trap, with sequences detecting edema and late gadolinium enhancement
Treatment	Allergic symptoms Ischemic symptoms	Heart failure Allergic and ischemic symptoms (if present)
Prognosis	Immediate: Good to severe (death) Delayed: Good	Immediate: Good to severe (death) Delayed: Good

Abbreviations: MRI, magnetic resonance imaging.

may result from mediator release during an allergic reaction or after administration of adrenaline to treat KS, leading to further TKS.

The trigger for ATAK complex in the present case seems to be IgE-mediated allergy to ranitidine, although HSRs to histamine type 2 receptor antagonists are rare. Involvement of an IgE-mediated mechanism is supported by the temporal relationship between administration of ranitidine and onset of symptoms, together with the positive intradermal skin test results at nonirritating concentrations. Moreover, the negative result of the BAT was expected, given the reported low sensitivity of ranitidine for in vitro allergy studies [10]. This may be because ranitidine could function as either an incomplete allergen or a precursor of an allergenic metabolite.

In conclusion, cardiac involvement in HSR is a diagnostic challenge, necessitating exclusion of coronary obstruction. In our opinion, the term ATAK complex is an appropriate designation that encompasses the various possible clinical presentations. Following this concept, the differential diagnosis between KS and TKS can be avoided in emergencies, thus facilitating prompt administration of appropriate treatment.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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References

1. Kounis NG. Kounis syndrome: an update on epidemiology, pathogenesis, diagnosis and therapeutic management. Clin Chem Lab Med. 2016;54(10):1545-59.
2. Giangrande N, Carral Maseda A, Lopez Arias JA, Perez Casares L, Martin Lazaro J, Nuñez, et al. Kounis Syndrome During an Oxaliplatin Desensitization Protocol. J Investig Allergol Clin Immunol. 2024;34(4):268-70.
3. Gogos C, Sachpekidis V, Moschovidis V, Styliadis I, Kounis NG. Kounis Syndrome in a Covid-19 Patient Following Intravenous Administration of Azithromycin. J Investig Allergol Clin Immunol. 2021;32(1):75-6.

4. Matta AG, Carrié D. Epidemiology, Pathophysiology, Diagnosis, and Principles of Management of Takotsubo Cardiomyopathy: A Review. Med Sci Monit. 2023;29:e939020.
5. Kounis NG, Filippatos GS. Takotsubo and Kounis syndrome: is there any association? Circ J. 2007;71(1):170, author reply 171.
6. Soufras GD, Kounis NG. Adrenaline administration for anaphylaxis and the risk of Takotsubo and Kounis syndrome. Int J Cardiol. 2013;166(2):281-2.
7. Kounis NG, Mplani V, de Gregorio C, Koniari I. Attack the ATAK; A Challenging Contemporary Complex: Pathophysiologic, Therapeutic, and Preventive Considerations. Balkan Med J. 2023;40(5):308-31
8. Alarcon Gallardo E, Escudero Apesteguía R, Sanz Bescos C. ATAK Complex due to Amoxicillin: A Case Report. J Investig Allergol Clin Immunol. 2024;34(1):62-4.
9. Puri P, Kachhadia MP, Sardana P, Bhagat R, Dekowski SS, Fohle E. Adrenaline, Takotsubo, Anaphylaxis, and Kounis Syndrome (ATAK) Complex unveiled: integrating Takotsubo and Kounis Syndromes in the context of chemotherapy-related anaphylaxis. Cureus. 2024;16(1):e53145.
10. Kim SY, Kim JH, Jang YS, Choi JH, Park S, Hwang YI, et al. The Basophil Activation Test Is Safe and Useful for Confirming Drug-Induced Anaphylaxis. Allergy Asthma Immunol Res. 2016;8(6):541-4.

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