Kounis Syndrome: Is it Really a Takotsubo-Like Syndrome?

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To the Editor:

We read with great interest the very well-presented article entitled "Kounis Syndrome After Levofloxacin Intake: A Clinical Report and Cross-reactivity Study" by García Nuñez et al [1]. The authors reported a case of a patient with Kounis syndrome who presented with acute coronary disease and generalized angioedema with urticaria after levofloxacin intake. However, it is noteworthy that anaphylactic mediators may also initiate Takotsubo syndrome [2-4]. Takotsubo cardiomyopathy has recently been reported to follow several predisposing factors (eg, anaphylaxis, mastocytosis, Kounis syndrome, hymenoptera stings, and status asthmaticus) and thus constitutes a known foe of asthma, as we recently reported [3], and even of treatment of anaphylaxis (ie, adrenaline) [2-4] in the form of a recently described disease complex known as ATAK (adrenaline, takotsubo, anaphylaxis, Kounis syndrome) complex [5]. Therefore, stress-induced cardiomyopathy is another entity that should be carefully investigated and excluded in allergic angina. As García Núñez et al [1] mentioned, there are no established clinical protocols for confirming a diagnosis of Kounis syndrome, and the presence of the disease must be confirmed by diagnosis of exclusion. Furthermore, few studies investigate a direct consequential link or distinct differences between Takotsubo cardiomyopathy and Kounis syndrome [5,6]. Both cardiac entities were born together in 1991, in different parts of the world, from different scientific minds. Shall they be together forevermore? Since the heart and, especially, the coronary arteries are the primary target of the released mediators in anaphylactic reactions, it is of paramount importance to discriminate between both entities.

Kounis syndrome, which was first described by Kounis and Zavras [7], is a coronary hypersensitivity disorder known also as syndrome of allergic angina or allergic myocardial infarction. It presents with clinical and electrocardiographic features suggestive of acute myocardial ischemia in the course of an allergic, hypersensitivity, anaphylactic, and anaphylactoid reaction [1,4-7] and affects patients of any age or gender [7]. The true estimation of its incidence is unknown. The diagnosis of Kounis syndrome requires a high index of suspicion based on clinical, laboratory, electrocardiographic, echocardiographic, and angiographic evidence. The main presentation is always as subclinical, clinical, acute, or chronic allergic reactions accompanied by cardiac symptoms and signs [7]. A variety of electrocardiographic changes ranging from ST segment elevation or depression to heart block (any degree) and cardiac arrhythmias indicating digoxin toxicity are always associated with the cardiac symptoms [7]. The mediators released induce myocardial injury, resulting in increased troponin levels [7-9]. Echocardiography and coronary angiography show absolutely normal coronary arteries with no luminal irregularities, thus excluding myocardial infraction [7]. Kounis syndrome is associated with mast cell and platelet activation with numerous inflammatory mediators such as histamine, platelet-activating factor, arachidonic acid products, neutral proteases, and a variety of cytokines and chemokines leading to significant coronary vasoconstriction [7]. Therefore, determining serum tryptase and histamine levels is particularly helpful [7]. However, these hormones are not easily measured in practice. Based on the suspected pathophysiology of the disease, antiallergic therapy with mast cell–stabilizing agents such as corticosteroids and antihistamines should always be initiated [7]. Vasodilators such as nitrates and calcium blockers are given when necessary [7].

Takotsubo cardiomyopathy is a syndrome characterized by transient regional systolic and diastolic dysfunction of the left ventricle leading to a variety of wall motion abnormalities [2,3]. It is often preceded by extreme physical or emotional triggers, as well as by acute allergic reactions and anaphylaxis [2,3]. Takotsubo cardiomyopathy can coexist with or follow Kounis syndrome [3,5,10]. It mimics myocardial infarction in terms of clinical presentation, electrocardiographic findings, and biomarker profile, although without angiographic evidence of obstructive coronary artery disease or acute plaque rupture [3,11]. It mainly affects postmenopausal women [12], and its incidence is unknown. The most common typical imaging finding is a systolic apical ballooning appearance of the left ventricle as a consequence of ventricular systolic dysfunction of the apical and mid segments and hyperkinesis of the basal walls [3,11-13]. The most recently proposed criteria for the diagnosis of stress-induced cardiomyopathy are the rapidly

reversible distinctive characteristics of echocardiography, electrocardiographic abnormalities (ST segment elevation, T-wave inversion), and modest elevation of levels of serum cardiac biomarkers, in combination with the presence of a stress trigger and the absence of pheochromocytoma or myocarditis [11]. The pathophysiological pathways involved in the onset of Takotsubo cardiomyopathy have not been well elucidated. The most accepted hypothesis for pathogenesis is rapid elevation of circulating catecholamine triggered by a stressful event [3,14]. Hypercatecholaminemia has a global effect on the myocardium, acting via stimulation of α- or β-adrenoceptors by two mechanisms [3,14-16]. First, it leads to diffuse microvascular spasm or dysfunction resulting in acute myocardial stunning [3,14]. Second, direct exposure of the myocardium to catecholamine is considered to be extremely toxic [3,15-17]. The occurrence of wall motion abnormalities could be explained by interindividual anatomical differences in the distribution of β-adrenergic receptors [16]. Furthermore, an inflammatory process characterized by macrophage and mast cell activation and further release of inflammatory mediators and cytokine production is observed [5,10,18-20]. Consequently, based on the pathophysiology of the disease, adrenergic blockade using β-blocker therapy should be used [3,20].

Given that allergic manifestations are associated with cardiac events, a potential cardiac injury manifesting as Kounis syndrome or as Takotsubo cardiomyopathy should be diagnosed early in the emergency department. Cardiac entities share the same clinical presentation, a cardiac enzyme profile that mimics heart attack, and common pathophysiologic pathways. Kounis syndrome basically affects the coronary arteries, while Takotsubo cardiomyopathy also affects the myocardium, leading predominantly to characteristic wall abnormalities. Echocardiography and coronary angiography discriminate efficiently between the syndromes and are necessary for diagnosis of the cardiac wall abnormalities that characterize Takotsubo cardiomyopathy and delineation of coronary anatomy in cases of Kounis syndrome [6]. Cardiac changes resolve completely over a few weeks in both entities. Hence, it is very important to consider that the possible acute cardiologic complications of an allergic reaction or anaphylaxis can take the form of Kounis syndrome and Takotsubo cardiomyopathy.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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