Kounis syndrome: first series in Turkish patients

Kounis sendromu: Türk hastalardaki ilk olgu serisi

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After the first report of acute myocardial infarction during a prolonged allergic reaction to penicillin was published in 1950 (1), the concurrence of allergic reactions and acute coronary syndromes called Kounis syndrome (KS) has gained acceptance as a new cause of coronary artery spasm (1-3). Kounis Syndrome was firstly described in 1991 as "the allergic angina syndrome" which could progress to acute myocardial infarction, which was named "allergic myocardial infarction" (2-4). There are several causes that have been reported as capable of inducing KS (5). These include a number of drugs (antibiotics, analgesics, antineoplastics, contrast media, corticosteroids, intravenous anesthetics, nonsteroidal anti-inflammatory drugs, skin disinfectants, thrombolytics, anticoagulants, proton pump inhibitors), various conditions (angio-edema, bronchial asthma, urticaria, food allergy, exercise induced allergy, mastocytosis, serum sickness), and environmental exposures (stings of ants, bees, wasps, jellyfish, grass cutting, millet allergy, poison ivy, latex contact, shellfish eating, viper venom poisoning).

In this report, we describe 6 patients (5 male, average age 27.7 years) with KS who were admitted or referred to our hospital in the last two years with acute-onset chest pain, accompanied by allergic symptoms, electrocardiographic changes and elevated cardiac enzymes. The characteristics of the patients who developed KS are given in Table 1.

Our patients consisted of 4 children and 2 adults, presented with acute-onset chest pain, accompanied by allergic symptoms, electrocardiographic changes and elevated cardiac enzymes. The reasons of KS were drugs in four, bee sting in one and wasp sting in the other patient. They did not have previous history of allergy, bronchial asthma, dermatitis, eczema, diabetes or coronary artery disease. Complete blood count, D-dimer, antithrombin III, lipoprotein (a), brain natriuretic peptide, serum cholesterol levels, antistreptolysin-O (ASO) titer, C3 and C4 levels and antinuclear antibody, anti-DNA tests were within normal limits. The serologic tests for viral etiology were also negative. Echocardiographic examination and coronary angiography was performed in all patients. While echocardiography showed segmental wall motion abnormality, coronary angiography revealed normal coronary arteries in first five patients and non-critical plaques in the left anterior descending and circumflex arteries in the sixth patient.

Kounis syndrome is characterized by the concurrence of acute coronary syndrome with mast cell activation induced by inflammatory mediators released during allergic reaction (5). Mast cell degranulation follows after antibody antigen reaction or sometimes direct action against the mast cell can happen (6, 7). Following mast cell degranulation several vasoconstricting and collagen degrading compounds are released locally and in the peripheral circulation. These compounds include preformed mediators such as, histamine, neutral proteases (tryptase, chymase), platelet activating factor and newly synthesized mediators such as an array of cytokines and chemokines and others by the metabolism of arachidonic acid through activation of a phospholipase (6, 7). Tryptase level, which has a half-life of 90 minutes, was elevated in all patients. However, subsequent daily estimations of serum tryptase were within normal limits. The increased levels of tryptase suggest an acute allergic reaction, where tryptase has been incriminated to induce coronary artery spasm and/or plaque erosion or rupture (5, 7). Total immunoglobulin (Ig) E levels were also elevated in four patients. Amoxicillin spesific IgE antibodies were negative in the second patient, but it does not exclude mast cell degranulation because as above-mentioned, sometimes direct action against the mast cell can happen (7). This applies especially for drugs.

Hymenoptera venoms mainly contain peptides, proteins, and vasoactive amines including histamine, acetylcholine, norepinephrine and dopamine (8). These substances are responsible for direct venom cardiotoxicity and several of the proteins and peptides are allergenic. The major allergen of honeybee venom is phospholipase A2. Other allergens include

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Table 1. Patient characteristics

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age, years	33	13	9	11	10	90
Sex	Male	Male	Female	Male	Male	Male
Allergic insult	AK (per os)	AK (per os)	Bee sting	AK (per os)	Wasp sting	CA (IM)
ST segment elevation	Anterior leads	Inferolateral leads	Inferolateral leads	Anterior leads	Inferolateral leads	Inferolateral leads
Symptoms	Chest pain	Pruritic skin rashes, chest pain	Erythematous rash, dyspnea	Chest pain, pruritus, palpitation	Erythematic rash, chest pain	Chest pain, pruritic skin rashes, dyspnea
Troponin I (ng/mL)	4.6	2.1	4.3	5	1.1	4
WMA	Anterior	Inferior	Inferior	Anterior	Inferolateral	Inferior
Total IgE* (IU/mL)	210	45	190	780	321	54
ASI	Positive	Negative	-	Positive	-	-
Tryptase* (µg/L)	43	31	45	42	33	43.5
Coronary angiography	Normal	Normal	Normal	Normal	Normal	Non-critical plaques in the LAD and Cx

AK- amoxicillin/clavulanic acid, ASI- amoxicillin spesific IgE, CA - cefuroxime-axetile, Cx - circumflex artery, Ig – immunoglobulin, IM – intramuscular, LAD- left anterior descending artery, WMA - left ventricular wall motion abnormality on admission
*Cut-off values for total IgE and serum tryptase are 0-100 IU/mL and 5.6–13.5 µg/L, respectively

melitin, hyaluronidase, and apanin (8). Although most severe reactions of hymenoptera stings occur with the first sting, patients who have previously experienced insect stings are at increased risk for severe allergic reactions from future stings. Our two patients admitted with hymenoptera sting were experiencing the first time of bee or wasp sting in their lives.

Two variants of KS has been described (5, 6). The type I variant includes patients with normal coronary arteries without predisposing factors for coronary artery disease, in whom the acute release of inflammatory mediators can induce either coronary artery spasm without increase of cardiac enzymes and troponins or coronary artery spasm progressing to acute myocardial infarction with raised cardiac enzymes and troponins. The type II variant includes patients with culprit but quiescent pre-existing atheromatous disease in whom the acute release of inflammatory mediators can induce either coronary artery spasm with normal cardiac enzymes and troponins or plaque erosion or rupture manifesting as acute myocardial infarction. All of our patients were diagnosed KS type I and were treated with oral antihistamines and prednisolone. They were discharged with complete recovery and regression of electrocardiographic and echocardiographic abnormalities within a few weeks. Although several reports (9) have shown mortality or malignant course of KS, our patients had an uneventful in-hospital course.

Although we have recently reported (10) one of these patients as an individual case report this is the first series of KS described in Turkish population and also in the literature. Our study highlights the fact that physicians (including pediatricians) should be aware of the allergic myocardial infarction. The diagnosis of KS should be entertained when acute-onset chest pain is accompanied by allergic symptoms, electrocardiographic changes and elevated cardiac enzymes. These patients should be interrogated for allergic insults.

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