

Letter to the Editor

Kounis syndrome associated with hypersensitivity to hymenoptera stings

John S. Kogias ^{*}, Skevos K. Sideris, Sotirios K. Anifadis

Department of Cardiology, Karditsa General Hospital, Karditsa, Thessalia, Greece

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Abstract

Hymenoptera stings can induce acute coronary syndromes by different pathogenetic mechanisms including direct action of the venom constituents on the coronary endothelium or allergic reaction with mediators acting on the coronary vasculature. Two patients were stung by wasps and honeybees and developed Kounis syndrome as a consequence of allergic reaction. Kounis syndrome is the concurrence of acute coronary syndromes with mast cell activation induced by allergic or hypersensitivity and anaphylactic or anaphylactoid reactions. It is caused via inflammatory mediators released through mast cell activation. The patients had pre-existing coronary artery disease (type II variant of Kounis syndrome) and the allergic reaction induced by hymenoptera stings seems to have triggered inflammatory mediator release. The pathophysiology and clinical implications of this association are discussed.

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1. Introduction

Hypersensitivity reactions, mediated through specific immunoglobulins, from hymenoptera stings range from urticaria and subcutaneous angioedema to severe anaphylaxis [1]. Coronary vasospasm and myocardial infarction, although rare, have been described and pose great risk to the patients. Kounis syndrome [2–4] is the concurrence of acute coronary syndromes with mast cell activation induced by allergic or hypersensitivity and anaphylactic or anaphylactoid reactions. Allergic angina and/or allergic myocardial infarction [5] might be the consequence of the above association.

Symptoms and signs of Kounis syndrome may include chest pain, with/without raised troponins and cardiac enzymes, dyspnoea, faintness, nausea, vomiting, syncope, pruritus, urticaria, diaphoresis, pallor, palpitations, hypotension and bradycardia [6]. There are several causes that have been reported as capable of inducing Kounis syndrome. These include several drugs, a number of conditions and a

variety of environmental exposures. The latter include stings by ants, bees, wasps, jellyfishes, as well as grass cutting, poison ivy, latex contact, limpet ingestion, millet allergy, shellfish eating and viper venom poisoning.

We describe two patients who developed acute anterior myocardial infarction following an allergic reaction after they were stung by flying hymenoptera and we present the pathophysiology and clinical implications of this syndrome.

2. Case 1

A 63-year old previously healthy male was stung on the head and neck several times by honeybees while working on his field. After stinging, he recalled a short-lasting period of dizziness, glossopharyngeal paresthesia, respiratory discomfort but not loss of consciousness. He was immediately transferred to the hospital by his relatives for further evaluation and treatment. On clinical evaluation in the emergency room, he had erythematous rash over the face, neck and thorax accompanied by periorbital edema and itching. He complained of chest discomfort but not chest pain.

On examination he was afebrile, his blood pressure was 130/80 mm Hg and the pulse 90 beats/min regular. He was

^{*} Corresponding author.

E-mail address: hippocratis@in.gr (J.S. Kogias).

no on regular medications. He was smoker but without previous history of allergy, rhinitis, bronchial asthma, dermatitis, eczema or diabetes. However, he recalled that he had been stung, in the past, by honeybees, without any sequelae. Examination of the heart, lungs, abdomen and central nervous system revealed no abnormality.

While he was in the treatment room, and before any medication given, he felt unwell, started sweating, became pale and complained of severe retrosternal pain radiating to both arms. An electrocardiogram (Fig. 1) performed immediately revealed sinus tachycardia with 102 beats/min and elevation of ST segment in V_2 – V_5 compatible with acute anterior myocardial infarction. He was given immediately intravenously the following medications: 1gr hydrocortisone sodium succinate, 5 mg morphine, 30 mg diphenhydramin and nitroglycerin infusion of 40 μ g/min. Blood samples were taken for cardiac enzymes, troponins, histamine, tryptase, immunoglobulins, complement proteins, and blood count estimation. He was transferred to the coronary care unit where thrombolysis with tenecteplase (bolus 7000 IV) was attempted within 2 h after the honeybee sting. Transthoracic echocardiography revealed diffused hypokinetic left ventricle involving the lateral wall and apex with ejection fraction of 45% and mild mitral regurgitation. The results of blood tests showed increased troponins and cardiac enzymes confirming the diagnosis of an acute myocardial infarction. Blood eosinophils were raised to 10% and the other measurements were increased as follows: IgE 250 IU/ml (normal values <110 IU/ml), tryptase 60 μ g/l (normal values 5.6–13.5 μ g/l).

However, blood histamine and complement proteins C_3 and C_4 were normal. A submaximal exercise treadmill test performed one week after admission was negative. Cardiac catheterization in a University hospital revealed 70% proximal left anterior descending artery lesion and he underwent successful angiography with stenting.

3. Case 2

A 70-year old overweight and hypertensive man was stung several times by wasps on his head and forearm while gardening. Within minutes local pain and urticarial swelling developed for which he self-administered an over the counter antihistaminic. Afterwards he was transferred by his relatives to the casualty department of our hospital where he was given 500 mg of hydrocortisone sodium succinate intravenously and was put under observation. He gave a history of previous ischemic heart disease but no rheumatic heart disease, allergy or diabetes. Clinical evaluation revealed periorbital edema, generalized urticarial rash and glossopharyngeal paresthesia without respiratory discomfort. Cardiac auscultation revealed normal heart sounds without murmurs.

While he was under observation in the emergency room he suddenly complained of severe retrosternal pain accompanied by nausea, diaphoresis and dizziness. His blood pressure dropped to 80/60 mm Hg. An electrocardiogram at this time (Fig. 2) revealed ST segment elevation V_2 – V_6 leads compatible with acute anterior myocardial infarction. Blood samples were taken for cardiac enzymes, troponins, immunoglobulins, tryptase, histamine, complement proteins and haematological and other biochemical screening. He was given 5 mg of morphine IV and a second bolus of 500 mg hydrocortisone sodium succinate IV. He was then transferred to the coronary artery care unit and was treated with thrombolysis. The following hours the patient became asymptomatic but the physical examination revealed bronchospasm and a 2/6 apical systolic murmur. Transthoracic echocardiography revealed mild mitral regurgitation and diffusely hypokinetic intraventricular septum and apex with ejection fraction of 35%.

The results of blood examination revealed increased troponins and cardiac enzymes confirming the diagnosis of an anterior wall myocardial infarction. Blood eosinophils,

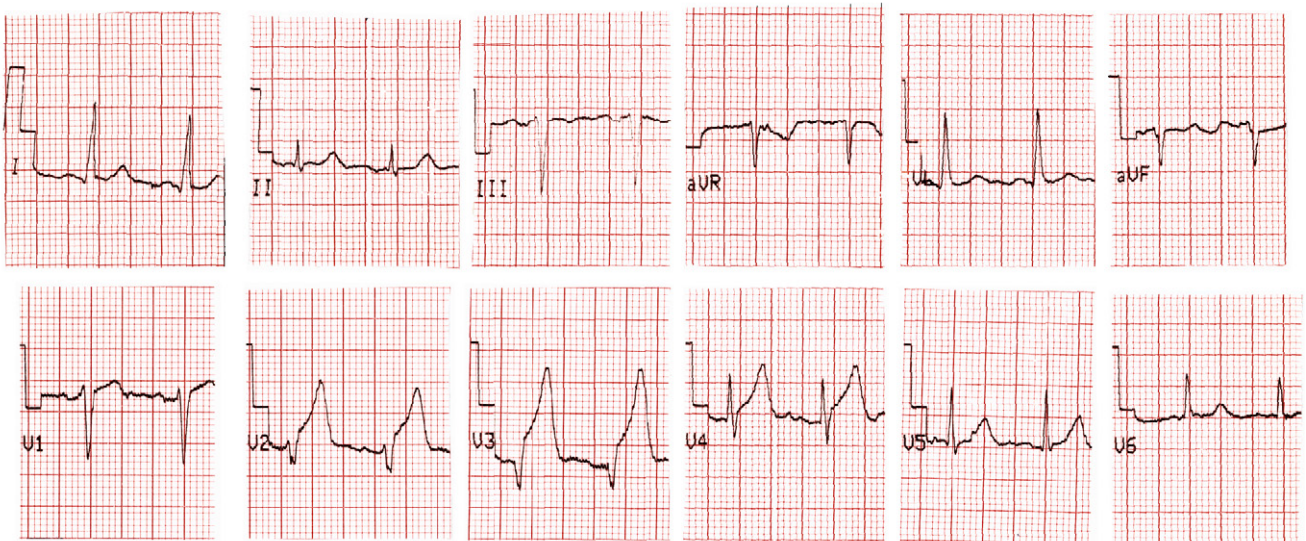


Fig. 1. Electrocardiogram showing ST elevation in V_2 – V_5 leads compatible with acute anterior myocardial infarction.

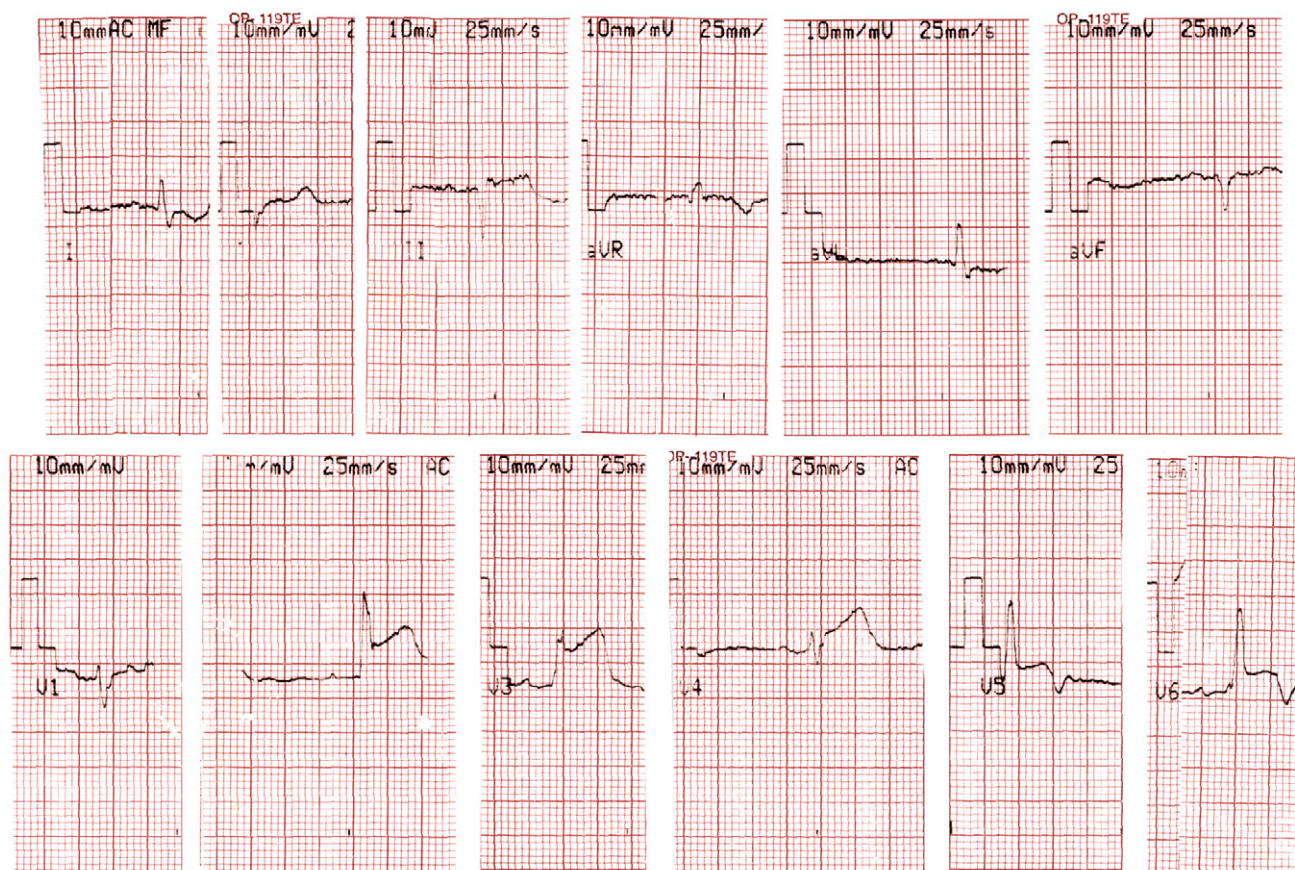


Fig. 2. Electrocardiogram showing ST elevation in V_2 – V_6 leads compatible with acute anterior myocardial infarction.

tryptase, histamine and immunoglobulins were also elevated. During the fourth day in the hospital the patient's condition was suddenly deteriorated and he died from cardiorespiratory arrest despite the efforts for resuscitation. Permission for post-mortem examination was not given by his relatives.

4. Discussion

The described patients developed periorbital oedema and generalized urticarial rash when they were stung by honeybees and wasps. This was followed by the symptoms and signs of acute myocardial infarction confirmed by the elevated cardiac enzymes and troponins. They were found to have concurrently raised levels of tryptase. Both patients were suffered from ischemic heart disease as it was shown by coronary angiography in the first patient and from the medical history in the second patient. This is a characteristic type II variant of Kounis syndrome as it has been described recently [6]. Type I variant includes patients with normal coronary arteries without predisposing factors for coronary artery disease in whom the acute allergic insult induces either coronary artery spasm with normal cardiac enzymes and troponins or coronary artery spasm progressing to acute myocardial with raised cardiac enzymes and troponins. This

variant might represent a manifestation of endothelial dysfunction or microvascular angina. Type II variant of Kounis syndrome includes patients with culprit but existing atheromatous disease in whom acute allergic episode can induce plaque erosion or rupture manifesting as an acute myocardial infarction.

Allergic reactions of any grading [7], to honeybee or wasp stings are seen in up to 5% of the total population in Europe and USA [8]. For reasons that are now under investigation these reactions vary greatly in severity with manifestations ranging from skin reactions such as rash and itching to respiratory, gastrointestinal or cardiovascular reactions as in our cases. In few patients, especially in those with severe anaphylactic reaction an association with mastocytosis has been reported [9].

There are three families of stinging insects in the order of hymenoptera: Apidae, Vespidae and Formicidae [10]. Honeybees and bumblebees belong to Apidae family (apids), wasps, yellow jackets and hornets belong to Vespidae family (vespids), and stinging ants belong to Formicidae family (formids). Flying hymenoptera venoms are mainly aqueous solutions that contain peptides, proteins, and vasoactive amines including histamine, acetylcholine, norepinephrine, dopamine and 5-hydroxy tryptamine [10]. These substances are responsible for direct venom cardiotoxicity and several of the proteins and peptides are

allergenic. Approximately 50 µg of protein is injected per sting. It has been estimated that about 1500 stings would be required to deliver a lethal dose of hymenoptera venom for an allergic adult who weighs 70 kg [11]. The major allergen of honeybee venom is phospholipase A₂. Other allergens include melitin, hyaluronidase, apanin and peptide 401 [10]. Apart from the direct toxic or allergenic action of hymenopter venom, sources of hymenoptera allergies include dried exudates, scales, hairs, fragment dead remains and metabolic products such as faeces and silks [11]. 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. Most fatalities occur in adults but children and adolescent experienced more insect sting reactions [10].

Several of the venom constituents such as histamine and phospholipase A₂ have physiologic effects that are the same or similar to the mediators released from mast cells during allergic reactions. These effects culminate to coronary vasospasm and/or atheromatous plaque erosion or rupture leading to acute myocardial infarction.

Cardiac histamine acts via four different histamine receptors all of which contribute to the severity of the allergic myocardial damage [12]. H₁-histamine receptors mediate coronary vasoconstriction while H₂-histamine receptors mediate a minor degree of coronary relaxation. The interaction of H₁ and H₂-receptor stimulation mediate decreased diastolic pressure and increased pulse pressure. H₃-histamine receptors inhibit endogenous norepinephrine release on the synaptic effector sympathetic terminals that innervate the heart and vessels and enhance the degree of shock observed during allergic reactions. H₄-histamine receptors control hemotaxis of mast cells, eosinophils and lymphocytes.

Phospholipase A₂ is a key enzyme for activation of the metabolism of the arachidonic acid. During the metabolism of the arachidonic acid an array of cytokines and chemokines are released. These include leukotrienes by the lipoxygenase pathway and prostaglandins such as thromboxane by cyclooxygenase pathway. These mediators have been incriminated in many clinical and laboratory studies to induce coronary artery spasm and/or acute myocardial infarction.

Both described patients presented with an allergic reaction followed by acute myocardial infarction and had raised blood levels of serum tryptase. Tryptase effectively activates the zymogen forms of metalloproteinases such as interstitial collagenase, gelatinase and stromelysin found in atheromatous plaques and plays an important role in plaque erosion or rupture. The described patients developed myocardial infarction while they did not developed severe hypotension during the allergic reaction and did not receive therapeutic adrenaline which can induce coronary spasm and myocardial damage. Therefore the myocardial damage was the result of the insect venom which induced mast cell mediator release and this seems to prove a causal association between venom allergy and the ensuing myocardial infarction.

Recent studies have shown that the same cells and the same substances are increased in both allergic coronary and non-allergic coronary syndrome. In example mast cells [13], histamine [14], tryptase [15] and arachidonic acid products [16] have been found present in acute coronary syndromes of non-allergic etiology. A common pathway seems to exist [5]. Is therefore Kounis syndrome the tip of the iceberg from a common pathway between allergic and non-allergic coronary syndromes that may implicate in cases of coronary spasm and plaque erosion or rupture? Studying therefore the responses to pharmacological agents at mast cells protection and stabilization may shed light on potential therapeutic strategies that may apply to the more generalized area of interference with plaque erosion or rupture and primary as well as secondary prevention of acute coronary syndromes.

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