



## Letter to the Editor

Hymenoptera sting-induced Kounis syndrome: Effects of aspirin and  $\beta$ -blocker administration

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## Abstract

Kounis syndrome is the concurrence of acute coronary syndromes with conditions associated with activation of interacting inflammatory cells including allergic or hypersensitivity and anaphylactic or anaphylactoid insults. It is caused via inflammatory mediators released during inflammatory cell activation. A variety of conditions, drugs, and environmental exposures can induce Kounis syndrome. A patient suffering from coronary artery disease and taking metoprolol and aspirin was stung by wasps and developed cutaneous allergic signs including rash, urticaria and orbital oedema. This was followed by retrosternal pain, chest discomfort and electrocardiographic changes compatible with acute myocardial ischemia. Cardiac enzymes, troponins and blood pressure remained normal but serum tryptase was raised. The clinical implications and pathophysiology of this rare association are discussed.

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## 1. Introduction

The Kounis syndrome [1] was firstly described in 1991 as “the allergic angina syndrome” which could progress to acute myocardial infarction which was named “allergic myocardial infarction”. There are several causes capable of inducing this syndrome including many drugs [2], various conditions [3], and a variety of environmental exposures [4] such as bee and wasp stings, ant stings, and jellyfish stings. Hymenoptera stings can induce Kounis syndrome because hymenoptera venom contains allergenic proteins and peptides. The following report is of a patient who was receiving metoprolol and aspirin for his coronary artery disease and who developed a generalized urticarial reaction associated

with coronary artery spasm and normal blood pressure after he was stung several times by wasps.

## 2. Case report

A 67 year old diabetic farmer was stung several times by wasps on his left arm while was working in his field. He had had already taken his daily medications which included aspirin 325 mg, metoprolol 25 mg tid and simvastatin 40 mg. He complained of a short lasting period of dizziness, headache, glossopharyngeal paraesthesia and was immediately transferred to the emergency room of our hospital.

On examination, he had generalized erythematous rash, but not chest pain. He had periorbital oedema with itching and complained of respiratory discomfort. He gave a history of previous cerebrovascular accident without residual impairment, diabetes on diet, and hyperlipidaemia. Eight months earlier he had a coronary artery bypass grafting for

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fixed atheromatous disease affecting the proximal left anterior descending artery. He did not recall any allergy, rhinitis, urticaria, but he could not exclude any previous hymenoptera sting. His relatives confirmed that under his present medication his systolic blood pressure and cardiac rhythm had remained normal.

On clinical evaluation, his BP was 100/80 mm Hg and the pulse 105 beats/min regular. The ECG taken 45 min after the sting showed (Fig 1) elevation of ST segment in II, III, AVF with reciprocal depression in I and AVL leads compatible with acute inferior myocardial ischaemia. At the same time the patient complained of mild chest discomfort. Pulse oximetry showed an oxygen saturation (SpO<sub>2</sub>) of 90%. Blood was sent for cardiac enzymes, troponins, histamine, tryptase, blood count and immunoglobulins. He was given a bolus of 500 mg of hydrocortizone sodium succinate and 50 mg ranitidine IV, and 50 mg of diphenhydramine hydrochloride per os. Afterwards, he was moved to the cardiac unit where he was given an infusion of nitroglycerin 40 µg/min. Thrombolysis was not attempted because troponins and cardiac enzymes were not elevated. During the following 24 h the patient's condition gradually improved and the ECG changes resolved. Serum tryptase was 35 µg/L (normal range 5.6–13.5) and serum IgE 180 IU/ml (normal >110). Sub-

sequent daily estimations of serum tryptase were within normal limits.

Stress test and hyperventilation tests were normal. Echocardiography revealed normal ejection fraction (60%) without wall motion abnormalities. Angiography was denied by the patient.

### 2.1. Allergology and aspirin provocation tests

Two weeks after discharge, the patient was referred to the area allergology center for diagnostic work up for hymenoptera allergy and aspirin provocation tests.

Intradermal skin tests with insect venoms (bee, wasp) were performed, in the volar side of the forearm, by injection of 0.02 ml of the relative venoms (Pharmacia, Uppsala, Sweden) in concentration of 10<sup>-4</sup> g/l and were paralleled with a negative (diluent) control. The tests, for both hymenoptera venoms, were considered positive because the longest wheal diameter was greater than 5 mm after 15 min. Skin test results were expressed as the mean value of the sum of the two diameters of the wheal according to the European Academy of Allergy and Immunology.

Bee and wasp venom – specific serum IgE antibodies were assessed by the commercially available CAP set

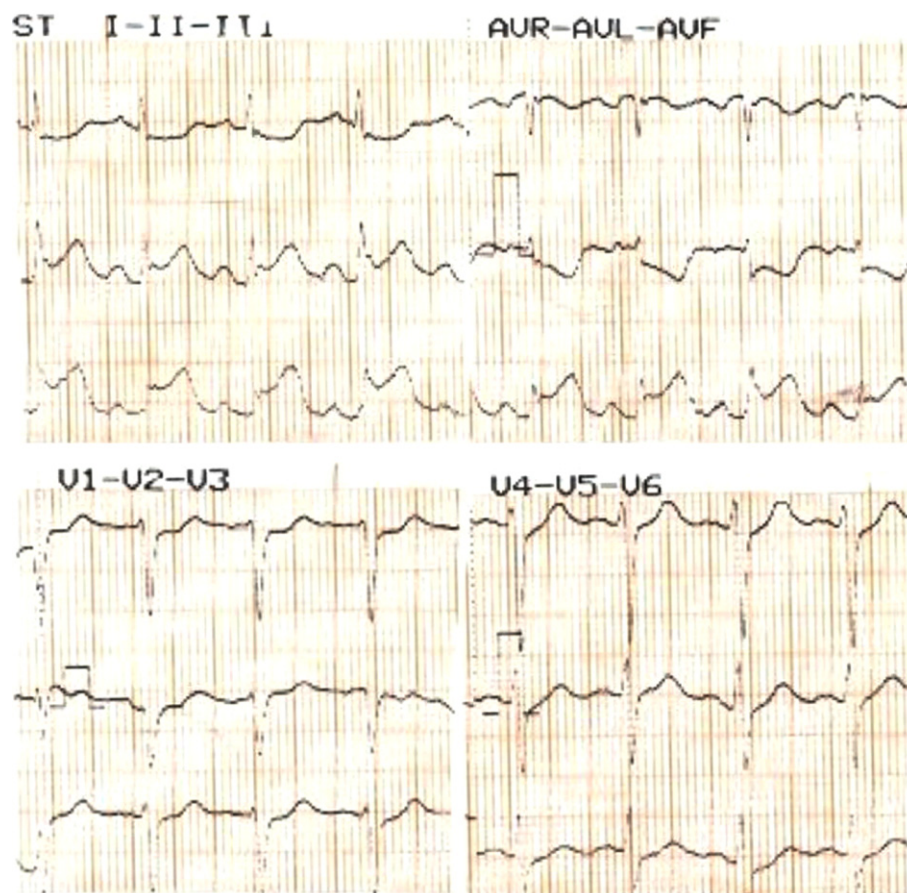


Fig. 1. Electrocardiogram showing ST elevation in II, III, AVF with reciprocal ST depression in I and AVL leads after the allergic reaction from the wasp sting.

(Pharmacia, Uppsala, Sweden). The test was performed according to the recommendations of the manufacturer. All tests were duplicated. The testing revealed only sensitization toward wasp venom (3.81 kUA/l). The patient had taken aspirin the same day before the actual wasp sting and in order to exclude aspirin-induced urticaria an oral aspirin provocation test was performed. This test consisted of oral administration of increasing doses of aspirin and placebo, according to a single-blind procedure with careful monitoring of clinical symptoms and skin the first 6 h following administration of the drug. Pulmonary function tests such as forced expiration volume measurements were also carried out, because some patients may develop bronchial obstruction beside urticaria. The cumulative dose of aspirin was 500 mg but did not evoke any positive reaction.

### 3. Discussion

The described patient was under treatment with metoprolol and aspirin for coronary artery disease and suffered an acute coronary event associated with allergic reaction after he was stung several times by wasps. The patient took both medications the same day and before the actual wasp sting. His blood pressure was normal during the period preceding the sting and did not change considerably during and after the allergic reaction. This is an unexpected event, because it is known that  $\beta$ -blockade inhibits the effect of both endogenously released and therapeutically administered epinephrine in patients suffering from anaphylaxis. Furthermore,  $\beta$ -blockers enhance the generation and release of mediators of anaphylaxis and enhance their effects on end organs [5]. During allergic reactions, the ensuing release of epinephrine might have varied effects. Some patients experience maximum peripheral vasoconstriction [6] but some others have decrease of systemic vascular resistance [7]. These variable effects of the internal compensatory mechanisms might explain why epinephrine injections sometimes fail to help acute and severe allergy. The endogenous epinephrine release which can be enhanced by therapeutic administration can have an adverse effect on the myocardium, including ischemic chest pain and electrocardiographic changes in the absence of diseased coronary arteries. Concomitant administration of  $\beta$ -blockade could have a protective effect on cardiac rhythm and blood pressure as in the described patient. It has been found that, a variety of subsets of T-lymphocytes, which are called T-regulatory cells can inhibit T-cell responses and prevent or ameliorate allergic reactions in several animal models of autoimmunity. Data obtained in beekeepers and in bee venom sensitive subjects have shown that T-regulatory cells can control allergic reactions [8]. The production of IL-10 from T-cells in response to allergens both in beekeepers who have become tolerant after repeated insect stings and in non atopic individuals supports the contention that IL-10 can regulate tolerance towards allergens [9].

Several reports of severe and fatal anaphylaxis among patients receiving  $\beta$ -blockers have raised concern about their

use in patients who are at risk for anaphylaxis [10]. Case series of fatal and non-fatal anaphylaxis have reported the use of  $\alpha$ -blockers in several instances but the number of patients at risk is uncertain [11–13]. However, one prospective study of patients receiving immunotherapy showed no increase of incidence of adverse reactions among patients receiving  $\beta$ -blockers compared with those not receiving  $\beta$ -blockers [14,15].

In a recent report [16], it was shown that more than 10% of patients with allergic reactions to hymenoptera stings have cardiovascular disease and about a third of them are receiving  $\beta$ -blockers. The authors of this study suggested that, in populations with high degree of exposure to hymenoptera stings such as beekeepers or gardeners who are suffering from coronary artery disease, heart failure or severe cardiac arrhythmias, immunotherapy should be applied under  $\beta$ -blockade but with special precautions. They concluded that the contraindications to  $\beta$ -blockade use during immunotherapy should not be considered as absolute but as relative.

In cases of anaphylaxis the usual dose of epinephrine for some patients might be inadequate when they receive  $\beta$ -blockers, but in other patients, due to unopposed  $\alpha$ -adrenergic effect may raise and promote coronary vasospasm [10]. It has been suggested that the use of glucagon may be more effective in the treatment of epinephrine resistant shock [17]. However, it should be remembered that rarely glucagon administration can induce itself severe anaphylactic shock [18]. Again, in a sulfite allergic patient epinephrine should be avoided, because every commercially available epinephrine preparation contains sodium metabisulfite. Sodium metabisulfite is a commonly used food and drug preservative. Methoxamine, a potent  $\alpha$  agonist should be an alternative.

The described patient was also taking aspirin. Aspirin can trigger or aggravate urticaria in up to 40% of patients [19]. Following aspirin ingestion, the reaction may occur in just 15 min or up to 24 h, but on average develops within 1–4 h [20]. Most cases of aspirin allergy settle in a few hours or within two days but sometimes may continue for two weeks. Ingestion of aspirin can induce the Kounis syndrome [21,22]. The urticarial reaction precipitated by aspirin appears to be familial [19] which has inherited the allele of leukotriene C4 synthase-444. However, in our patient, aspirin can be excluded as cause of the coronary event because the oral provocation test to aspirin was negative.

This patient developed allergic skin reaction and ECG changes compatible with acute inferior myocardial ischemia after he was stung by wasp. Myocardial injury did not follow because cardiac enzymes and troponins did not rise. Tryptase levels were elevated, but histamine was undetected. Histamine is short lived and circulates only for 8 min following the allergic insult, but tryptase has a half life of 90 min. The patient's blood pressure was normal during and following the allergic reaction suggesting that the ensued coronary artery ischemia was not the result of coronary hypoperfusion. It is anticipated that the allergic reaction has triggered coronary artery spasm, via the released mediators, as in type

I variant of Kounis syndrome. Hymenoptera venoms are allergenic because they contain peptides and proteins. Vasoactive substances such as histamine and acetylcholine are also some of the constituents of hymenoptera venoms. However, recent studies have shown [1] that the same inflammatory mediators have been found increased in patients with acute coronary syndromes of non-allergic etiology. Moreover, degranulated mast cells have been found abundant in areas of coronary plaque rupture of such patients with acute myocardial infarction [23].

A common pathway of allergic and non allergic coronary syndromes has been proposed [1]. If mast cells do contribute to non-allergic coronary events, there is scope for therapy with mast cell stabilizing drugs in order to prevent acute coronary and cerebrovascular events. This has been already achieved experimentally [24]. Is, therefore, Kounis syndrome nature's own experiment and magnificent natural paradigm implicated in cases of coronary artery spasm and plaque rupture?

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