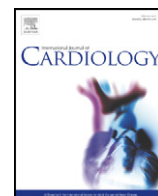




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Letter to the Editor

Non-ST segment elevation myocardial infarction after multiple bee stings. A case of “delayed” Kounis II syndrome?[☆]Marita Nittner-Marszalska, Agnieszka Kopeć, Marta Biegus, Magdalena Kosińska, Andrzej Obojski, Robert Pawłowicz^{*}, Małgorzata Gillert-Smutnicka, Bernard Panaszek

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The clinical manifestation of hypersensitivity from hymenoptera venoms range from mild to severe IgE-dependent anaphylactic reactions. Cardiac involvement, although rare, constitutes the most severe and life threatening scenario. Acute atrial flutter, atrial and ventricular fibrillation, Takotsubo type of cardiomyopathy and acute coronary syndrome in the form of STEMI and NSTEMI myocardial infarction have been described following single and multiple wasp/bee stings [1–10].

The concurrence of acute coronary syndromes with mastocyte activation induced by IgE or non IgE hypersensitivity agents is named Kounis syndrome [11–13]. Type I of Kounis syndrome refers to patients with normal coronary arteries without predisposing factors for coronary artery disease in whom the acute allergic insult induces a coronary artery spasm with normal cardiac enzymes and troponins or a coronary spasm progressing to acute myocardial infarction with raised cardiac enzymes and troponins [7,13]. Type II variant of Kounis syndrome includes patients with existing atheromatous coronary disease in whom an acute allergic episode can induce plaque erosion or rupture manifesting as an acute myocardial infarction [10,13].

We describe a patient who developed acute non-ST-segment elevation myocardial infarction following multiple bee stinging. We consider possible pathogenic scenarios of this event and their therapeutic consequences.

A 63-year old female, with a history of: ischemic strokes (1999, 2001, and 2004) resulting in residual impairment, inferior myocardial

infarction (1994), arterial hypertension, maturity-onset diabetes mellitus and dyslipidemia was admitted to our department after she had received 20–30 bee stings (*Apis mellifera*) on the head, neck and legs (she was stung by bees in her brother's garden where he keeps beehives). Immediately after the stinging she experienced respiratory discomfort, weakness, generalized pruritus, flushing and decrease of blood pressure (40/0) but neither loss of consciousness nor chest pain. She was treated by an ambulance intensive care unit physician with adrenalin (0.3 mg im), hydrocortisone hemisuccinate (300 mg iv), and clemastine (2 mg im). Intravenous infusion of colloids was also started. At the time of admission to our hospital she felt well and was clinically stable. She presented: multiple sting marks and erythematous rash over her face, thorax and extremities accompanied by itching and periorbital edema. Blood pressure was 110/80 mm Hg, HR 90 beats/min, regular. Examination of the heart, lungs, abdomen and CNS revealed no abnormalities (except residual right sided hemiparesis). 12-lead ECG revealed features of the significant Q waves in lead III, persistent ST segment elevation in leads III and aVF as a result of a past myocardial infarction and flattened negative T waves in lead I and aVL (comparable with the ECG performed in an outpatient clinic some time before the multiple sting incident) [Fig. 1A, B]. Laboratory test results including cardiac enzymes (troponin I level) were normal at 0.02 ng/ml (reference range below 0.04 ng/ml). Six hours later (9 h after stinging) the patient complained of severe chest pain. ECG revealed depression of ST segment in leads I and aVL, suggesting acute myocardial ischemia [Fig. 2A–D]. Cardiac enzymes showed evidence of MI; troponin level reached 1.8 ng/ml, CK-MB-MASS 6.9 ng/ml (reference range for women is <3.4 ng/ml). The patient was given aspirin of 300 mg, clopidogrel of 600 mg and NT. She was transferred to the cardiac intensive care unit where coronary angiography (ANG) was performed. ANG revealed 95% occlusion of proximal left anterior descending artery (LAD), 95% occlusion of Cx artery and critical stenosis of medial right coronary artery (RCA 99%) [Fig. 3A–D]. Cardiac surgical intervention was denied by the patient. CABG was successfully performed two months later. Three coronary artery bypass grafts were made; left internal mammary artery (LIMA) to LAD and two saphenous vein grafts: one to the RCA and one to the obtuse marginal (OM) artery.

Six months after discharge from the hospital, the patient was referred to our department for a follow-up visit. She was perfectly well. She remains in stable condition. An ECHO study confirmed depressed systolic cardiac function (LVEF was 55%) and showed regional dysfunction wall motion as well as hypokinesis of basal inferior and apical septal segments.

[☆] All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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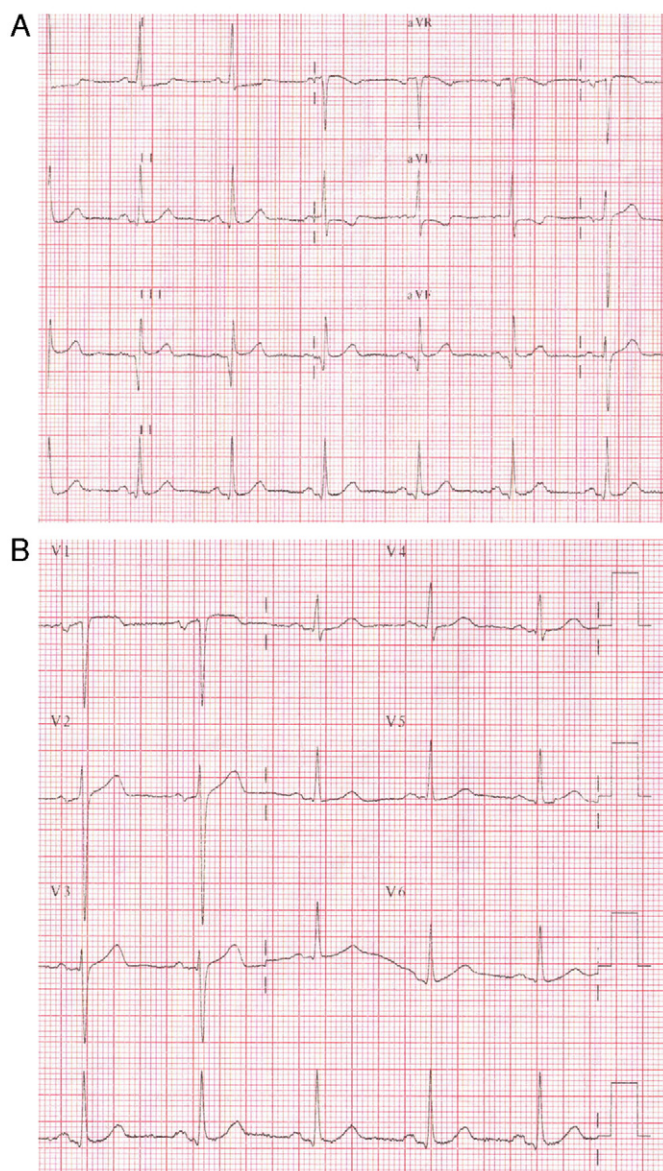


Fig. 1. A, B: ECG performed before the sting incident.

Intradermal skin tests with insect venom were performed, on the volar side of the forearm by injection of 0.02 ml of bee venom at the concentration of 10^{-6} g/l. The test with bee venom was positive at the concentration of 10^{-5} g/l – 10×12 mm. Bee venom sIgE level (specific serum IgE antibodies) was assessed by the commercially available test CAP. The bee venom sIgE level was 91.8 kU/l (class 5) and wasp venom sIgE level was 2.11 kU/l (class 2).

The described patient developed an anaphylactic reaction immediately after she had been stung by 20–30 bees. The incident was followed by an acute myocardial infarction after 9 h. She had had no previous history of a systemic manifestation of bee venom hypersensitivity but had developed a large local reaction after bee stings in the past; she presents sensitization to bee venom. Additionally, she presents significant cardiovascular risk factors: a history of ischemic strokes, a myocardial infarction in the past, hypertension, dyslipidemia and diabetes.

This case of an anaphylactic reaction followed by a myocardial infarction raises several questions about its possible pathogenic mechanism. (1) Was the myocardial infarction caused by an IgE-dependent hypersensitivity reaction to venom (a Kounis II syndrome)? (2) Was the myocardial infarction an outcome of the injection of toxic venom

components? (3) Was the myocardial infarction a consequence of adrenalin injection resulting in the decrease in coronary perfusion? A search for an answer to these questions is not meant to merely satisfy academic curiosity since important therapeutic decisions depend on it. If we hold the first possibility as true, then the patient should be qualified for venom immunotherapy in consideration of a high exposition risk, even despite the danger it might entail due to the existing comorbidities. Conversely, if we opt for positive answers to question 2, the patients should not be qualified for specific immunotherapy.

Scenario 1: The myocardial damage might have been a consequence of the experienced IgE-mediated allergic reaction and the cardiotoxic effect of mast cell mediators [12,13]. In venom sensitive patients insect venom allergens induce mast cell activation and mediator release. Some of them mediators (TxA₂, PGF₂, LTC₄, LTD₄ and PAF or chymase, which as a dipeptidase converts angiotensin I into angiotensin II) have a strong vasoconstrictive effect. It has been also reported recently that mastocytes are the only non-kidney source of renin that may indirectly contribute to the decrease in coronary perfusion during anaphylaxis [14–16]. Experiments conducted on animals proved renin to be released from heart mastocytes during IgE dependent anaphylactic reactions induced by specific allergen stimulation [15]. Renin activates local renin–angiotensin system, which results in: local increase in angiotensin II concentration, stimulation of noradrenaline release and consequent vasoconstriction [15,16].

During IgE dependent allergic reaction in patients with atheromatosis and ischemic heart disease, increased local mediator release because of increased mast cell density in the cardiac tissue is an additional risk factor. Mastocytes are localized in the coronary vessel perivascular area, between the myocardial fibers and also at the level of the endothelial intima of the coronary arteries. It is likely that an increased number of mastocytes increases the risk of acute cardiac ischemia [17–19].

Why the incident of the reported myocardial ischemia occurred several hours after stinging can be accounted for by the fact that mastocytes release their mediators not only immediately after allergen stimulation but also during the following few hours. Moreover, their mediators have a chemotactic effect and can induce influx of other effector cells, which characterizes the late phase allergic reaction.

Scenario 2: We cannot rule out the possibility that myocardial damage may be attributed to the cardiotoxic effects of multiple bee stings. Venom constituents like phospholipase A₂, hyaluronidase, melittin, apamin and peptides have physiological effects that are the same or similar to those of the mediators released from mast cells during allergic reaction [20]. Large amounts of venom and its cytotoxic components are capable of causing coronary vasospasm and/or atheromatous erosion or rupture leading to acute myocardial infarction. Studies on animals are available on this subject; one of these studies shows that intravenous inoculation of Africanized bee venom in rats causes an increase in enzyme levels and necrosis of the myocardium in light microscopy as well as in histochemistry [21]. This is the only available animal study which reports an acute necrosing cardiac lesions similar to human myocardial infarction.

In dismissal of this conception is the low total dose of venom injected during stinging. Although tolerance to multiple stings is variable, our patient got relatively a small number of stings. In most situations several hundred stings would be required to trigger a toxic reaction, and 1500 stings to deliver a lethal dose of venom for an adult who weighs 70 kg [22].

Scenario 3: The question is if adverse effects of therapeutic doses of epinephrine could be responsible for the reaction. There have been several reports of epinephrine induced coronary vasospasm and MI associated with therapeutic doses of epinephrine used for the treatment of anaphylaxis: 2 after sc injection, 1 after self-administration by way of an EpiPen and 2 after iv administration of a dose of 0.1 mg of a 1:10 000 solution (all of them in young people without risk factors for MI) [23–27]. Emergency treatment of anaphylaxis may induce complications in subjects with cardiovascular disease but in our patient

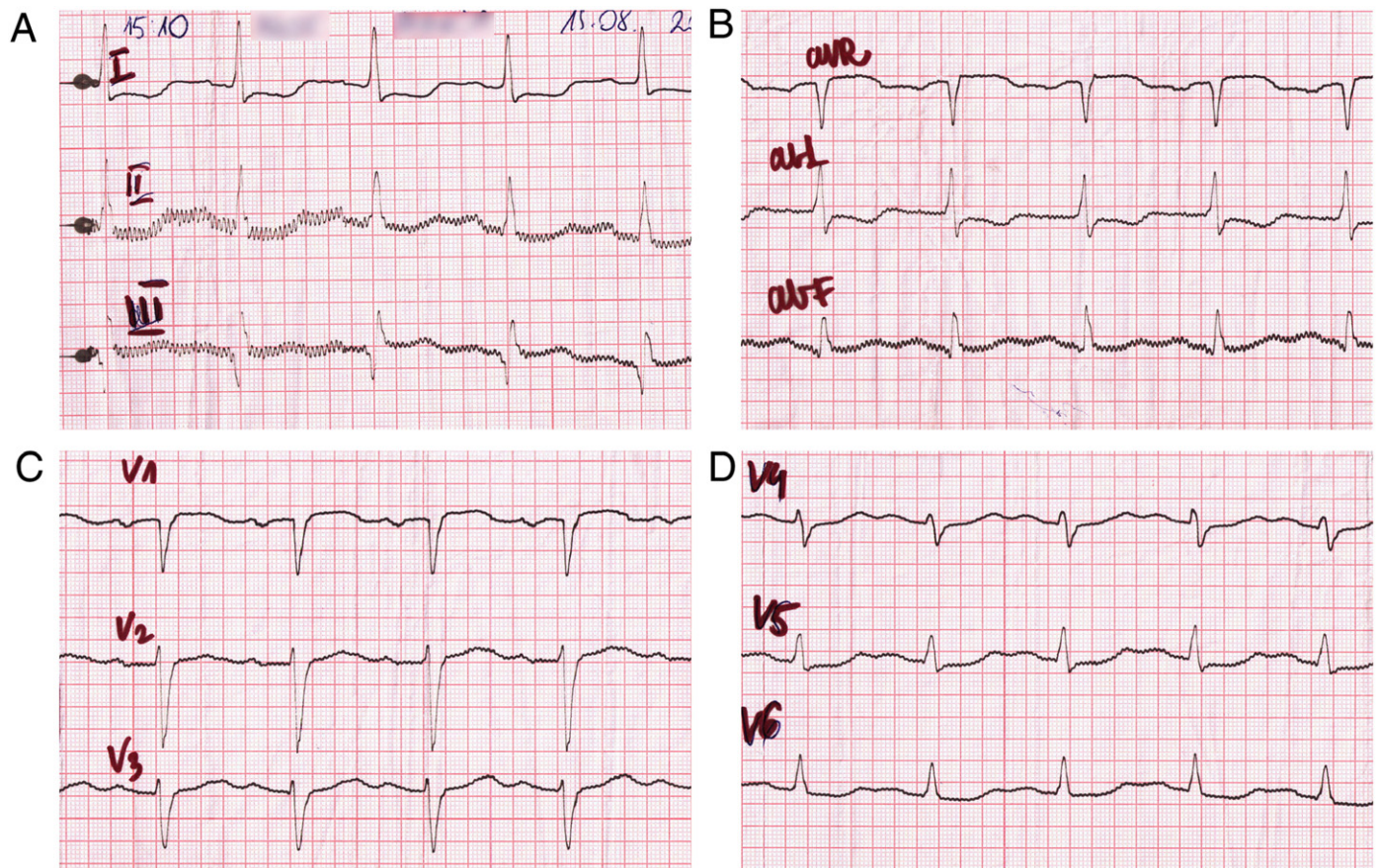


Fig. 2. A, B, C, D: ECG performed after the sting incident.

adrenaline could not have been the only factor responsible for MI because cardiac injury occurred 9 h after application of the drug.

In conclusion, we assumed that the reaction was IgE dependent and that the mediators released in its course were largely responsible for the myocardial infarction incident.

The case presented here and other similar cases reported in medical literature call for the following:

1. It is suggested that patients with systemic symptoms after hymenoptera stings should be observed closely for a prolonged period for delayed onset of cardiac reactions.
2. An important recommendation in the case of insect stings is to perform a standard ECG and a troponin evaluation test.

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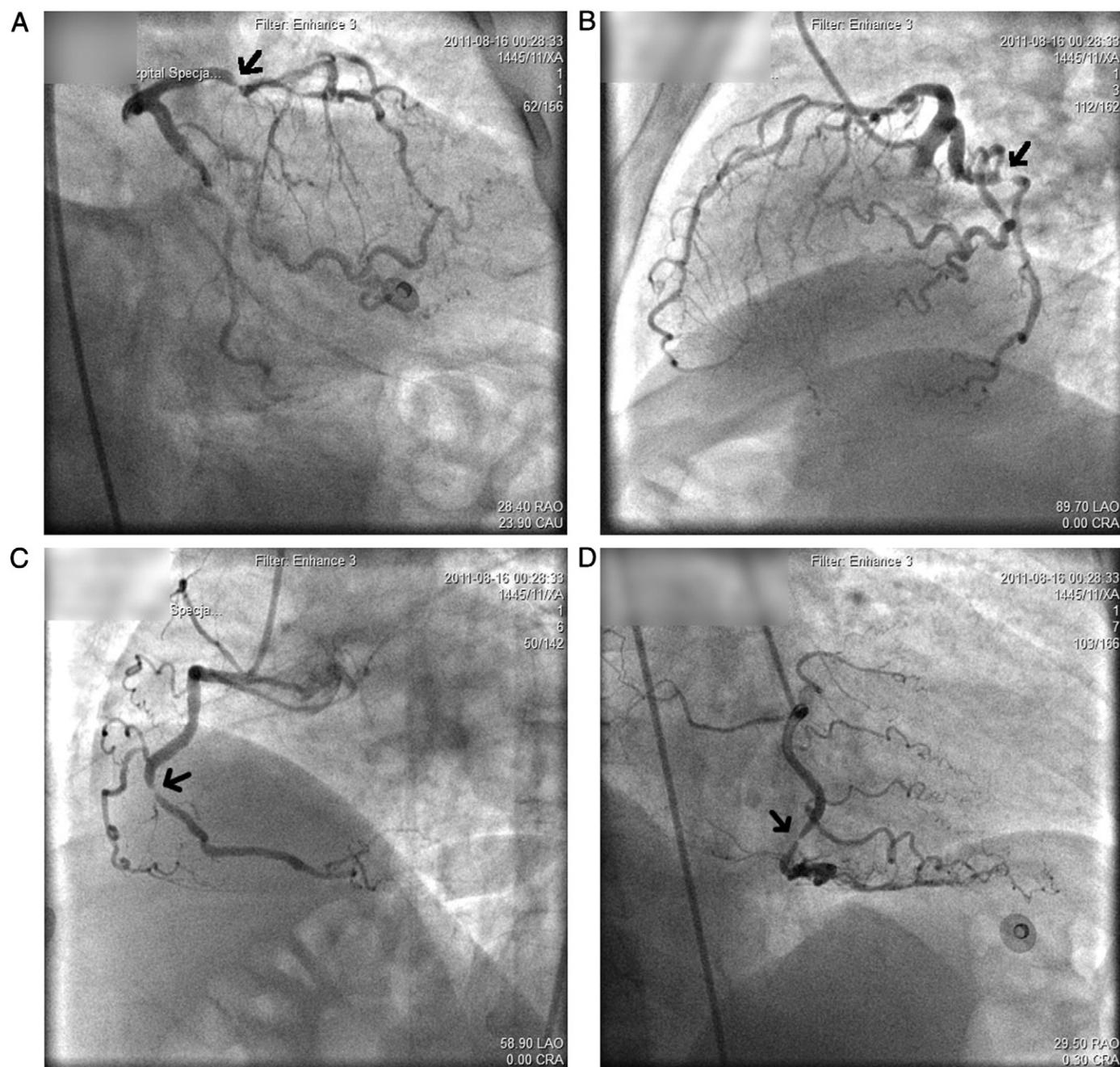


Fig. 3. A, B, C, D: Coronary angiography (ANG).