

## Case Report

# Kounis syndrome, two case reports from Kragujevac, Serbia

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**Abstract:** It is well-established that acute coronary syndromes occurs when thrombus formation from atheromatous plaques erode or rupture in the advanced stage of atherosclerotic process with severe reduction of coronary blood flow. Also, some conditions may trigger acute coronary syndrome even in the absence of prior cardiovascular disease, and with normal coronary vessels. One of the most important is Kounis syndrome, also known as “allergic angina” or “allergic myocardial infarction” in which the release of mediators during allergic insults has been incriminated to induce coronary artery spasm and/or atheromatous plaque erosion or rupture. The accurate incidence of Kounis syndrome is not known, but since it was described, many clinical cases have been reported, showing the occurrence due to various allergens. Here we present two cases of most probable Kounis syndrome, first in patients after multiple stings by non-venomous insect called “black-fly”.

**Keywords:** Kounis syndrome, anaphylactic reaction, myocardial ischemia, black fly

### Case I

A 30-year-old male without prior coronary heart disease and history of allergies was admitted to our emergency room after more than 100 bites in lower extremities, by unknown insect, while working on his field near Lake Gruža, Central Serbia, in June. Thirty minutes after the incident patient experienced dizziness, malaise, vomiting and prolonged chest pain.

On physical examination he had small papular, urticarial changes in lower extremities, accompanied by itching and local pain (**Figure 1**). Patient was hypotensive (70/40 mmHg), with signs of cardiovascular shock, heart beats were rhythmic with normal, audible tones. Normal respiratory sounds; no signs of lymphadenopathy and hemorrhage were present. An electrocardiogram on admission revealed sinus tachycardia and signs of inferolateral infarction (**Figure 2**). Blood samples were taken for cardiac enzymes, troponin, immunoglobulins and complete blood count estimation, and showed elevated white cell count with monocytosis ( $12.5 \times 10^3$  per ml), elevated troponin I (0.59), CK 301 U/L, CKMB 32 U/L and elevated

immunoglobulin fraction IgE-200 IU/ml (laboratory reference value up to 110 IU/ml), with normal hematocrit and hemoglobin. Patient was treated with: antihistamines, i.v. methylprednisolone 20 mg/daily, cloramine chloride i.v 10 mg twice daily, calcium chloride 10% with addition fluids (isotonic saline) and dual antiplatelet therapy, and referred to emergency angiography which revealed normal coronary arteries and TIMI III flow (**Figure 2**). At first we found fly bites to be circumstantial, but after normal coronary findings and no history of cardiovascular risks, or episodes of chest pain, allergic mediated ischemia was hypothesized so we stopped the antiplatelet therapy. Transthoracic echocardiography revealed referent systolic and diastolic dimensions, normal left ventricle wall motion and preserved ejection fraction (67%). In next few days, on continued antiallergic treatment patient fully recovered and was discharged with normal electrocardiographic finding and on prolonged therapy of loratadin 10 mg/daily, ranitidine 150 mg twice daily and local corticosteroid for next 10 days. At one month follow up patient was completely healthy and therapy was discontinued.



**Figure 1.** (A and B) Showing the *Simulium erythrocephalum*, order Diptera, commonly known as “blackfly” (A – female blackfly feeding; B – adult blackfly); local finding of urticarial, papular changes on lower extremities of the first (C) and the second (D) patient admitted after a multiple bites of blackfly.

## Case II

Day after the first patient was admitted in our hospital, another male, 52-year-old, bitten by the same type of insect, in the same area, near the Lake Gruža, was admitted to the emergency room. Ten minutes after he was bitten, he developed dizziness, local pain and urticarial swelling, and on admission he had acute episode of dyspnea, malaise and chest pain prolonged around 25 minutes before examination. In patient history we found diabetes type II (treated with oral antidiabetics), no other risk factors or previously established coronary disease.

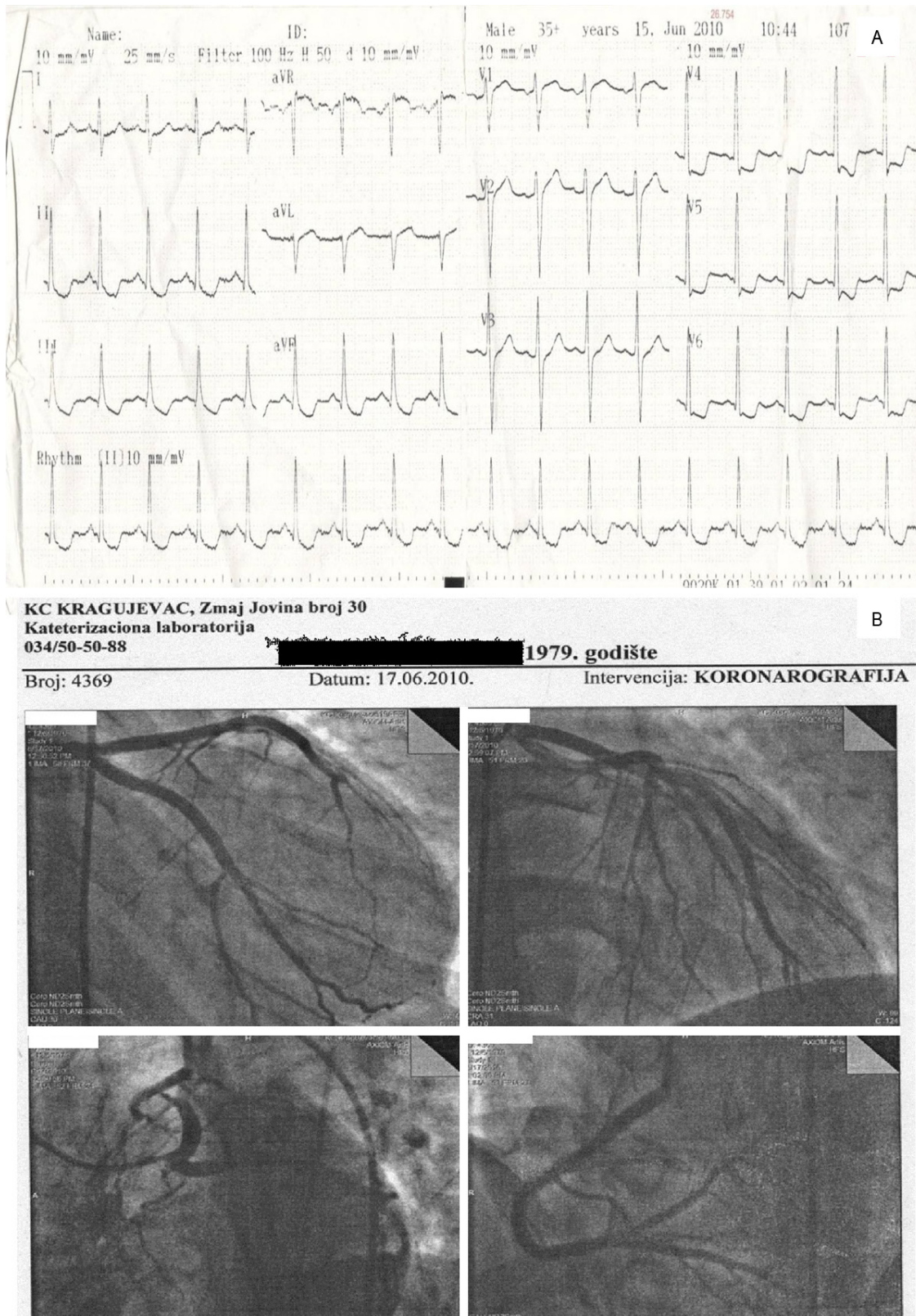
On physical examination: normal respiratory sound and arrhythmia with mild systolic murmur, patient was normotensive (140/75 mmHg). Insect bite marks, with a papular form were found at lower extremities, similar to previous patient (**Figure 1**). Electrocardiogram on admission showed atrial fibrillation with marked ST-segment depression in left precordial leads

and elevation in aVR lead (**Figure 3**). Blood tests results revealed eosinophilia (3% of total white blood cell count), elevated troponin I (0.79), CK 293 U/L and CKMB 28 U/L. Emergency angiography revealed diffuse, multi-vessel coronary disease corresponding to diabetes, but no proper culprit lesion (**Figure 3**). After angiography, we decided to apply only medical therapy. Echocardiography showed normal left ventricle wall motion and moderate mitral regurgitation (2+ by eyeballing) with enlarged left atrium. Patient was treated with dual antiplatelet therapy, statins, beta blockers and oxygen prior the intervention. Insulin therapy and ACE inhibitor were added to therapy after angiography. Local corticosteroids were used for skin lesion. Patient was discharged on the 8th day of hospitalization, completely stable, and he was also hemodynamically stable with persistent atrial fibrillation on follow up.

After both cases were analyzed, and no prior coronary heart disease was found, our aim remained to discover the culprit of these mani-

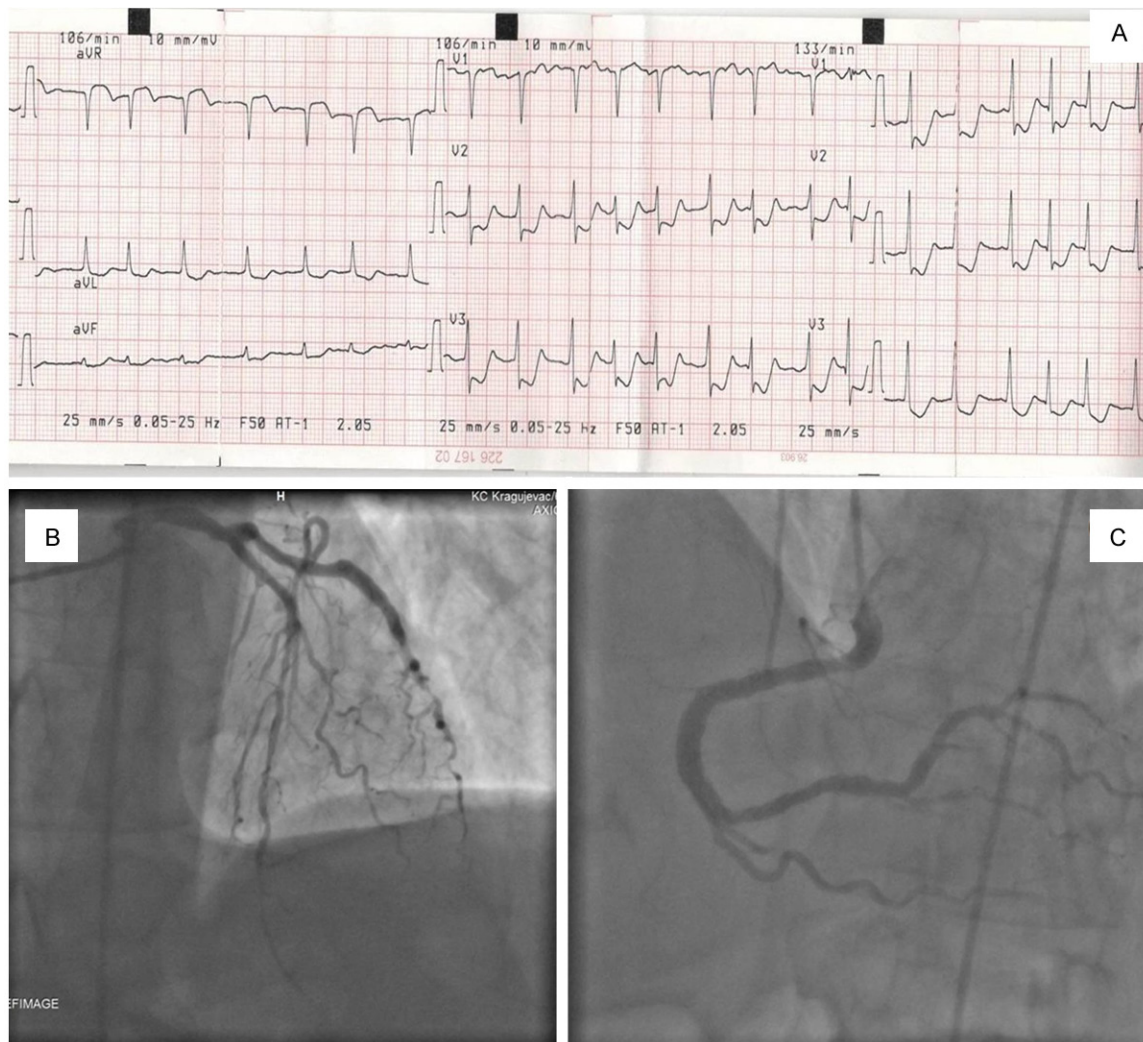


## Kounis syndrome



**Figure 2.** Electrocardiogram and coronarography findings of the first patient with suspected Kounis syndrome: A: Electrocardiogram showing sinus tachycardia, heart rate 107 beats/minute, and the signs of inferolateral myocardial infarction – 2 mm ST-segment depression in II, III, aVF and V4-V6 leads; B: Coronarography showing normal coronary arteries, without any sign of coronary disease.

## Kounis syndrome



**Figure 3.** Electrocardiogram and coronarography findings of the second patient with suspected Kounis syndrome: A: Electrocardiogram showing atrial fibrillation, tachyarrhythmia absoluta (heart rate 133 beats/minute) with marked, downward ST-segment depression, up to 5 mm, in V2-V6 leads and elevation in aVR lead (probably due to presence of multivessel coronary disease); B and C: Coronarography showing diffuse, multivessel coronary disease corresponding to diabetes mellitus, with TIMI 2 flow in distal segment of the LAD (left anterior descending artery) and D1 with important sub-occlusion; and changes along the LCx (left circumflex artery) and RCA (right coronary artery) diffuse disease (80% and 60% on PDA – posterior descending artery).

festations. The conclusion was that ischaemic changes developed due to allergic insult or hypersensitivity to a multiple insect bites. With the help of local biologist, we identified the insect as *Simulium erythrocephalum*, order Diptera, commonly known as blackfly (**Figure 2**). Bite of this species is known to cause intense local reaction, with periodical outbreaks common in our region.

### Discussion

Kounis syndrome was described for the first time in 1991 by Kounis and Zavras [1] as “the

coincidental occurrence of chest pain and allergic reactions accompanied by clinical and laboratory findings of classic angina pectoris caused by inflammatory mediators released during the allergic insult”. Later, in 1998, Braunwald [2] in his editorial noted that vasospastic angina can be induced by “allergic reactions with mediators such as histamine or leukotriens acting on coronary vascular smooth muscle”.

Today, Kounis syndrome is described as the occurrence of acute coronary syndrome with



mast cell activation induced by allergic or hypersensitivity and anaphylactoid reactions. It can manifest as unstable vasospastic or non-vasospastic angina, and even as acute myocardial infarction triggered by the release of inflammatory mediators [3]. There are two types of Kounis syndrome described so far with a proposition to include the third variant in a current classification. Type I refers to patients without cardiovascular risk factors and with healthy coronary arteries in whom allergic insult triggers coronary vasospasm that causes chest pain, ischaemic changes on electrocardiogram and normal/elevated markers of myocardial damage. This can be manifestation of endothelial dysfunction or microvascular angina. Type II occurs in patients with pre-existing coronary disease where mediators may induce coronary vasospasm with normal cardiac enzymes, or erosion/rupture of the atheromatous plaque, resulting in acute myocardial infarction [4, 5]. Type III, that has been proposed in recent years, refers to patients with drug-eluting stent thrombosis with the presence of mast cells and eosinophils revealed with Giemsa ad hematoxylin-eosin staining [6]. The first patient we presented could be classified as Type I considering his age, the fact that he had no prior coronary disease (normal coronary arteries) and no cardiovascular risk factors; while the second could be described as Type II because he had diabetes as risk factor and changes in 3 coronary vessels (left anterior descending, left circumflex and right coronary artery). Symptoms and signs may include chest pain, with/without raised troponins and cardiac enzymes, dyspnea, nausea, vomiting, syncope, pruritus, urticaria, diaphoresis, palpitations, hypotension and bradycardia [3]. Both patients had the most of above mentioned symptoms and signs, including signs of ischaemia on electrocardiogram.

Several causes have been reported as capable of inducing Kounis syndrome. These include some drugs, foods, a number of conditions and a variety of environmental exposures including insects stings. Most of the cases that have been reported, described anaphylaxis due to bites of the Apocrite (Hymenoptera) order like bees, wasps, ants, due to their proximity to humans. Other venomous insects like spiders and centipede are also shown to induce allergic and/or anaphylactic response in humans. In our cases, insect with similar behavior to other

hemophages was the principal suspect. We identified the insect as *Simulium erythrocephalum*, order Diptera, commonly known as black fly, which is very common in our region, especially during summer near the water surfaces. Adult insects are 1-5 mm in length, most frequently black but occasionally yellow or yellowish-brown. These flies have prominent eyes, short mouthparts, humped thorax, broad colorless wings with distinct venation and a pair of scissors. Only the adult females are blood-feeders and different species have different preferred feeding sites. Most species are particularly active during morning and evening in cloudy, warm weather [7]. Although black fly bites are known to cause anaphylaxis we haven't found any case report related to development of severe heart ischaemia.

Large blackfly populations and strong bite reactions can be life threatening, and the injection of saliva into the skin causes intense itching, local swelling and soreness, all present in our patients. The flies' bites are seriously painful with hypersensitivity induced due to the release of pharmacologically active substances from the flies' saliva [7]. Anaphylactic reactions after different insects sting may induce cardiovascular events, including acute myocardial infarction, even in patients with normal coronary arteries which was the case with our first patient.

The term "cardiac anaphylaxis" refers to the functional and metabolic changes in the heart caused by the release of inflammatory mediators following a serious allergic insult. The involvement of the heart in anaphylactic reactions may be described with several pathophysiologic mechanisms [8]. Mast cells that are derived from a distinct precursor in the bone marrow and mature under local tissue micro environmental factors can be found in most parts of the human body, including heart and vessels. These cells are involved in allergic and anaphylactic reactions throughout activation-degranulation process. Upon their activation they release the contents of granules by a rapid and slow process of degranulation which may operate individually or in parallel [3].

In the case of insect stings and bites, the venom or saliva contains proteins, peptides and vasoactive amines that can cause direct cardiotoxicity but also behave as allergens, with activation and degranulation of the mast

cells, resulting in the release into the systemic bloodstream of a number of vasoactive mediators and proteases [4]. The existence of mastocytes in heart tissue and their participation in the anaphylactic reaction that triggers tachycardia, coronary vasoconstriction, dysfunctional ventricular contractility and blockade of atrioventricular conduction was already demonstrated. These abnormalities are attributed to the release of mediators such as histamine, thromboxane, prostaglandins, leukotrienes, and platelet activation factor [8].

It is demonstrated that coronary vasospasm and plaque destabilizations are mediated by increased histamine concentrations and vice versa in episodes of acute coronary syndrome elevated histamine is found in concentrations similar to one in allergic reactions [9]. Cardiac histamine acts upon four types of receptors, each of which can contribute to the severity of allergic myocardial damage.

The H1 receptors act like potent coronary vasoconstrictor and increases vascular permeability, while the H2 receptors have minor effect to coronary vasodilatation and increase atrial rate and contractility of the heart muscle. Their interaction induces a drop in diastolic blood pressure and an increase in pulse pressure. Other histamine receptors promote vasodilatation by inhibiting norepinephrine (H3), and control chemotaxis of mast cell and eosinophil cell (H4). Also, histamine induces tissue factor expression and activity promoting coagulation cascade. Local proteases secreted in anaphylaxis via activated mast cells (chymase and triptase) can trigger degradation of collagen and induce plaque erosion or rupture, thus initiating an acute coronary event. Chymase convert angiotensin I to angiotensin II thus promoting vasospasm [4].

Several reports have shown that type I variant of Kounis syndrome has better prognosis than type II variant. In both types the prognosis depends on the magnitude of the initial allergic response, the patient's sensitivity which was lower in both cases we admitted, comorbidity, the site of antibody-allergen reaction, the allergen concentration and the route of allergen entrance. Patients with any grading of systemic allergic reactions associated with clinical, laboratory and electrocardiographic findings of acute myocardial ischemia should be diagnosed as having Kounis syndrome [3].

## Conclusion

Unfortunately we were unable to test triptase levels, as a marker of anaphylactic episode, but clinical setting and response to treatment seem to correlate to present definition of Kounis syndrome. Still we cannot explain mechanism of cardiac involvement due to local allergic reaction, but Kounis syndrome looks like most probable. To our best knowledge these are first reported cases of black fly bite related allergy/ischemia and in areas with high seasonal occurrence of the species, perhaps, more cases of unexplained concurrence of fly bite and myocardial ischemia might be recorded.

## Disclosure of conflict of interest

None.

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