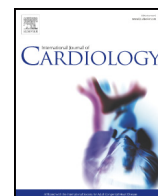




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Letter to the Editor

Kounis syndrome associated with brain injury after Hymenoptera sting: New presentation of an established entity

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Kounis syndrome is increasingly encountered in clinical practice, but it is rather underdiagnosed. It was defined by Kounis [1], as the occurrence of acute coronary events following release of allergic inflammatory mediators during an allergic reaction, mainly caused by Hymenoptera stings, drugs or foods. Several inflammatory mediators (including histamine, arachidonic acid derivatives and PAF) are locally released and also spread to systemic circulation, and they have been incriminated to induce vasospasm artery and to promote platelet activation. Neutral proteases, such as tryptase and chymase, are also released, and they can degrade collagen and elastine by activation of matrix-degrading metalloproteinases, transforming a pre-existing stable atheromatous plaque to a vulnerable plaque [2].

This syndrome has been categorized into three distinct types. Type I include patients who develop coronary artery spasm with normal coronary arteries. Type II is due to coronary spasm or plaque erosion in patients with pre-existing atherosclerotic disease [3]. Type III variant occurs with thrombosis in the setting of a pre-existing drug eluting-stent [4].

We present a 46-year-old man with heart valve disease secondary to rheumatic fever, replaced with mechanical prostheses and with a current treatment of acenocoumarol. He was bitten by a wasp, presenting immediately a mild local skin reaction. Then he developed

extreme dizziness and blurred vision without loss of consciousness, followed by difficulty pronouncing words and amnesia 10 min later. These neurologic symptoms subsided within hours. He also presented interscapular pain, nausea and vomiting.

He was treated in the emergency room. Physical examination did not reveal cutaneous rash and his blood pressure was normal, and therefore, epinephrine was not used. Blood chemistry evidenced cardiac enzymes within normal limits (CPK 133 U/l and troponin 0.06 ng/ml). An electrocardiogram (ECG) was carried out on arrival, without signs of myocardial ischemia (Fig. 1).

Because back pain persisted, a new ECG was performed revealing ST-segment depression in V1 to V6 leads (Fig. 2). Elevation of cardiac enzymes (CPK 202 U/l and troponin 1.9 ng/ml) was shown. Serial measurements were done, with increased level peaked 12 h after the bite (CPK 308 and troponin 7.7). Transthoracic echocardiography was made 14 h later, showing aneurysmal dilatation of the left atrium, mild mitral insufficiency and left ventricle systolic function preserved, which were previously described. A coronary angiography was carried out 18 h after the bite, disclosing unaltered coronary arteries.

Electrocardiographic changes and cardiac enzyme elevations were resolved four days later. Cardiac magnetic resonance, performed seven days after the bite, showed intramyocardial signal suggesting necrosis. Cardiology diagnosis was no q-wave myocardial infarction after wasp sting.

In subsequent weeks, the patient was evaluated in Neurology Unit, because he presented recurrent episodes of stiffness, memory loss, mental slowing, repetitive thoughts and mixed dysphasia with difficulty naming. Postictal electroencephalogram (EEG) showed diffusely slowed cerebral bioelectrical activity, suggesting moderate encephalopathy. Supra-aortic trunk echography was normal, and cerebral nuclear magnetic resonance showed small chronic infarcts in supratentorial white matter. Neurological diagnosis was epilepsy disorder with secondarily generalized partial seizures.

In allergy study, skin tests with Hymenoptera venom extract were performed. Intradermal-test with *Polistes* venom was positive at 0.1 µg/ml concentration. Serum specific IgE level was slightly positive to antigenic components of *Polistes*: Phospholipase A1 0.27 IU/ml by the ADVIA-Centaur® method (Siemens), and antigen 5 0.14 IU/ml by the CAP® method (Thermo-Fisher). Skin test and serum specific IgE tests were negative for other Hymenoptera venom (*Apis mellifera* and *Vespa* spp.). Thus, hypersensitivity to *Polistes* venom was diagnosed.

Because systemic reactions after Hymenoptera sting are more frequent in patients with mast cell activation disorders, tryptase levels

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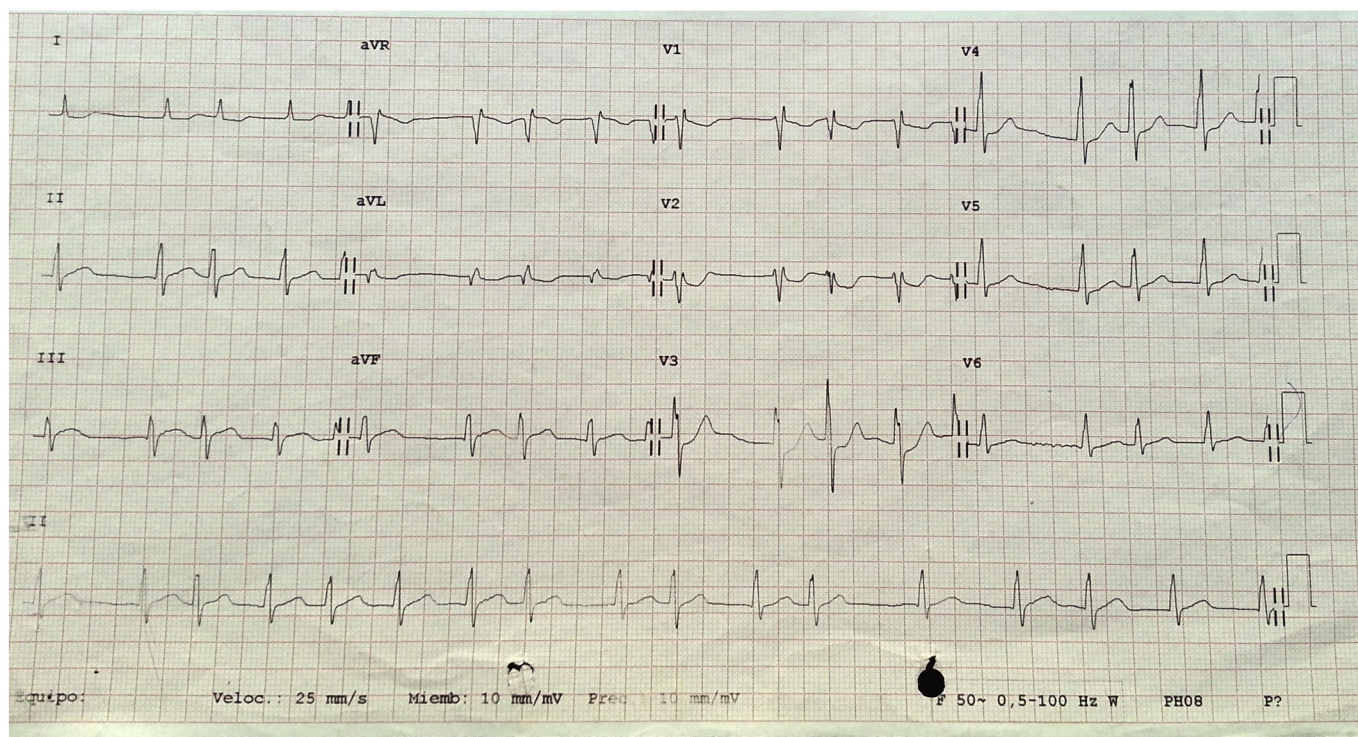


Fig. 1. Electrocardiogram on arrival to the emergency room.

were determined by the CAP method on several times, with results always below 6 $\mu\text{g/l}$ (low titres). REMA score [5] to calculate mast cell activity in this patient was 4 (positive when higher or equal to 2), suggesting a mast cell activation syndrome. Preventive treatment with oral cromolyn should be recommended, but it was not prescribed to avoid interference with gastrointestinal absorption of acenocoumarol.

Our final diagnosis was type I Kounis syndrome, associated with epileptic symptoms, due to hypersensitivity to wasp venom. The patient

is being currently treated with specific immunotherapy of *Polistes dominulus* with good tolerance.

The involvement of the coronary vessels in Kounis syndrome is explained by the vasospastic response and atherosclerotic plaque damage caused by mediator release. Similarly, vasospasm-related symptoms involving other organs might also occur. In this way, Kounis syndrome would be one of several expressions of a complex disorder, associated with pan-arterial hypersensitivity, and the entire arterial

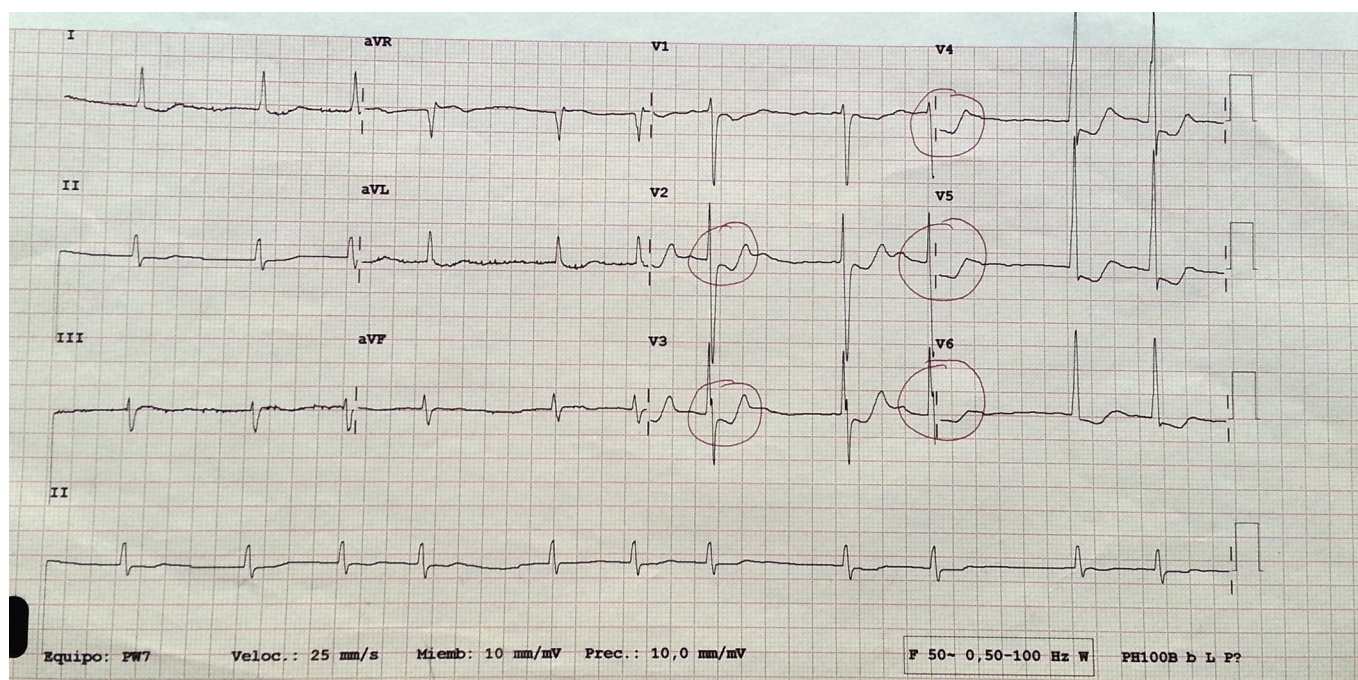


Fig. 2. Electrocardiogram performed 4 h later.

system could be vulnerable to mediators liberated in an allergic event [6], and in that regard, cerebral arteries affectation in Kounis-like syndrome have been described [7].

Mast cells are resident within the cerebral vasculature, and their vasoactive mediators could promote blood–brain barrier damage, brain oedema, prolonged extravasation and even haemorrhage [8]. Mediators, such as platelet-activating factor can reduce cerebral blood flow, and others, as histamine, chymase and leukotrienes can induce cerebral artery spasm [10].

It has been found that anaphylactic shock decreases cerebral blood flow more than what would be expected from severe arterial hypotension [9]. Therefore, in cases of massive release of mast cell mediators, brain injury should also be attributed to the early and direct action of these mediators on cerebral vessels, leading to post-ischemic hypoperfusion [10].

Our patient did not present at any time arterial hypotension, which could promote neurological symptoms by decreased cerebral blood flow. Therefore, brain injury following anaphylactic event should be due to direct action of mast cell mediators on the cerebral arterial system, triggering a pre-existing seizure focus.

In summary, we present an atypical case of type I Kounis syndrome induced by Hymenoptera hypersensitivity. Coronary artery disease was associated with the beginning of epileptic discharges, triggered by this acute allergic event. In this way, we propose a new variant of Kounis syndrome, in which acute coronary events are associated with symptoms induced by vascular changes in other territories, as the cerebral vasculature in our case. This new variant can be associated with any three classic types of Kounis syndrome described so far, making more complex the diagnosis and treatment of this kind of anaphylactic event.

Author's contribution

Francisco Vega conducted clinical history, participated in all stages of the study and wrote the article.

Tania Ramos and Paloma Las Heras contributed to skin-testing.

Carlos Blanco supervised the article writing.

All authors revised the article critically and gave their approval to the final version.

Conflicts of interest

The authors declare no conflicts of interest.

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