CASE PRESENTATION

Kounis syndrome. Allergic acute coronary syndrome after hornet stings (Vespa Crabro). A case report

Priscilla Pasc[1,2], Ioana Alexandra Cote[1], Mircea Ioachim Popescu[1,2]

Abstract: Kounis syndrome (also known as acute allergic coronary syndrome) is defined as an acute coronary syndrome caused by an allergic reaction or a strong immune reaction to a drug or other substance. It is a rare syndrome with authentic cases reported to 130 men and 45 women until 2017. Anaphylaxis is rarely seen as an acute vasospastic coronary syndrome, the main pathophysiological mechanism being the release of cytokines and other inflammatory mediators during a hypersensitivity reaction triggered by food, insect bites or drugs. In this article, we will present the case of an acute coronary syndrome occurring in the context of the anaphylactic reaction triggered by the sting of several hornets- Vespa crabro from the family of the Hymenoptera. The diagnosis of Kounis syndrome was supported by electrocardiographic appearance and biochemical markers associated with clinical manifestations of acute coronary syndrome in the context of anaphylactic shock.
Keywords: Kounis syndrome, acute allergic coronary syndrome, hornet stings

Rezumat: Sindromul Kounis (denumit și sindromul coronarian acut alergic) este definit ca sindromul coronarian acut cauzat de o reacție alergică sau o reacție imună puternică la un medicament sau altă substanță. Este un sindrom rar, cu cazuri autentice raportate la 130 de bărbați și 45 de femei, revizuite în 2017. Anafilaxia se manifestă foarte rar ca un sindrom coronarian acut vasospastic, mecanismul fiziopatologic principal fiind reprezentat de eliberarea citokinelor și a altor mediatori inflamatori în timpul unei reacții de hipersensibilitate declanșată de alimente, mușcături de insecte sau medicamente/droguri. În continuare, vom prezenta cazul unui sindrom coronarian acut apărut în contexul reacției anafilactice declanșată de întepătura mai multor viespi - Vespa crabro din familia himenopterelor. Diagnosticul sindromului Kounis a fost susținut de aspectul electrocardiografic și markerii biochimici asociați cu manifestări clinice ale sindromului coronarian acut în contextul șocului anafilactic.
Cuvinte cheie: sindromul Kounis, sindromul coronarian acut alergic, înțepătura de viespe

INTRODUCTION

Hymenoptera stings and subsequent allergic reactions, including fatal anaphylaxis, are common causes of medical emergencies. Data from the literature suggest that systemic venom reactions occur in less than 5% of the cases, with severe allergic reactions being more frequent in Hymenoptera insect bites than from any other arthropod and may be the number one cause of worldwide deaths caused by insect venom. The most important Hymenoptera groups are: Apoidea (bees), Vespoidea (wasps) and Formicidae (ants). Reactions downgraded by the bites of these insects range from small or large local reactions to anaphylaxis and even death. Also, studies suggest that they can lead to multisystemic damage, including intravascular haemolysis, rhabdomyolysis, thrombocytopenia, acute renal failure (ARF), liver failure, neuropsychiatric disorders and even cardiac arrest. Manifestations as myocardial infarction and myocarditis are uncommon.

Acute coronary syndrome that accompanies activation of mast cells from hypersensitivity or anaphylactoid allergic reactions was first described by Kounis and Zavras in 1991 and was referred to as „allergic angina" or „allergic myocardial infarction". The Kounis syndrome mechanism (KS) involves the release of inflammatory cytokines by activating mast cells, leading to vasospasm of the coronary artery and / or erosion or rupture of the atheromatous plaque. KS has been described in several situations, including exposures to a variety of natural or artificial allergens.

[1] Clinical County Emergency Hospital of Oradea, Romania
[2] Faculty of Medicine and Farmacy of Oradea, University of Oradea, Romania

Contact address:
Priscilla Pasc, MD
Clinical County Emergency Hospital of Oradea, Romania.
E-mail: priscilla_pasc@yahoo.com

Vespa crabro is part of the Vespidae family, the Hymenoptera order, and is the largest wasp in Europe and North America. Popular is called hornets or gooseberries. It can cause multiple stings, because, unlike bees, it does not lose its needle after stinging. Its venom contains a mixture of both toxic and allergenic substances responsible for triggering the hypersensitivity reaction. Reaction to the sting of this insect may be prolonged or severe in people with atopic predisposition, with manifestations such as urticaria, bronchospasm or circulatory collapse. Also, stings can precipitate an acute coronary syndrome by different pathophysiological mechanisms including direct action of venom constituents on coronary endothelium or allergic reaction with the release of mediators that act on coronary vascular muscles.It is requered to be taken into consideration a possible allergic acute coronary sindrom every time a patient has an anaphylactic reaction triggered by hymenoptera bites, especially if the pacient has chest pain and haemodynamic disorders, even if these conditions occur rarely because they require additional diagnosis and appropriate treatment.

CASE PRESENTATION

A 39-year-old patient, without a history of cardiovascular disease, shows up in the emergency department for systemic anaphylactic manifestations: respiratory (dyspnoea, polypnea, wheezing), subcutaneous and cutaneous (generalized erythema, pruritus, angioedema) and central nervous system reactions (the feeling of imminent death, irritability, restlessness). The patient reports that the symptoms appeared shortly after being stung simultaneously by several hornets from the Hymenoptera family, objectively, showing small erythematous papula at the bitten skin area. Also, the patient complains of precordial pain with epigastric irradiation, which have been occurred shortly after the occurrence of anaphylactic manifestations.

The general objective examination reveals an altered general condition, signs of cutaneous edema (face, extremities), three erythematous papules secondary to the sting, localized on the left laterally thorax, forearm and left arm. The targeted examination of the cardiovascular system detects rhythmic heartbeats, without any heart murmurs detected and a blood pressure of 80/60 mmHg.

Electrocardiogram performed on arrival in the emergency room does not reveal any significant changes, but the one performed one hour after arrival in the emergency service records normal sinus rhythm, 64 heartbeats/minute, QRS axis at -45 degrees and a 2 mm ST segment elevation in DII, DIII, AVF (Figure 1). Repeated ECGs at 3, 6 and 10 hours show progressive ST segment resolution and the appearance after several days of negative T-waves in DIII, AVF (Figure 2).

Laboratory tests. In terms of biochemical determinations, the enzymes of myocardial necrosis, namely troponin I, are fastly determined. Initially unreacted, its values progressively increase to subsequent serial determinations (at 2 hours, 6 hours and 10 hours) (Table 1), with maximum value determined at 1.7 pg / ml ten hours after presentation.

Additional laboratory tests shows neutrophilic leukocytosis, slightly increased level of C-reactive pro-

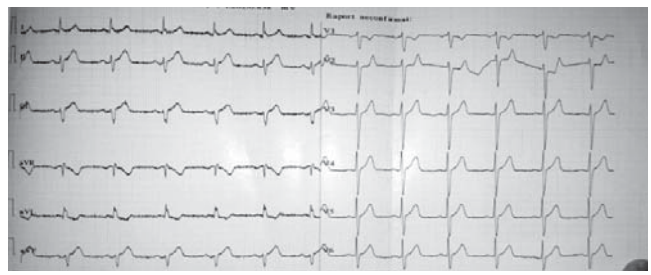

Figure 1. Electrocardiogram performed one hour after arrival in the emergency service.

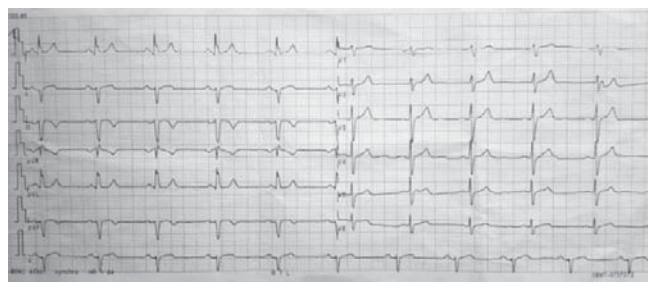

Figure 2. Electrocardiogram performed at discharge from hospital.

Table 1. The dynamics of myocardial enzymes

Time of troponin determination	Troponin I value	Normal range
At admission	0.003 ng/ml	0.020 ng/ml
After 2 hours	0.024 ng/ml	
After 6 hours	0.178 ng/ml	
After 10 hours	1.70 ng/ml	
Day 4	1.52 ng/ml	

Table 2. Laboratory tests

Parameter	Normal range	Case
White Blood Cell counts	23.050	4.0-10 *10 3 /uL
Neutrophils	20.490	2.4-6.5*10 3 /uL

tein (CRP), renal and hepatic samples within normal range (Table 2). The number of white blood cells decreases progressively over the next days.

The Echocardiography reveals left ventricular aneurysm, a LVEF of 56% and mild mitral regurgitation (Figure 3,4). In evolution, the echographic aspect is stationary.

Coronary angiography. Based on the highly suggestive clinical picture of an acute coronary syndrome, coronary angiography is performed urgently, revealing normal coronary angiography, without arterial plaques or other detectable anomalies (Figure 5,6).

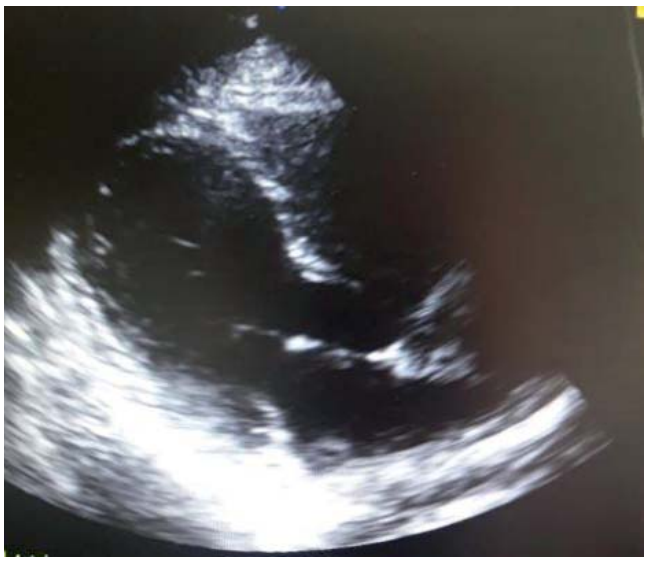

Figure 3. Echocardiography performed at the admission-parasternal long axis section.

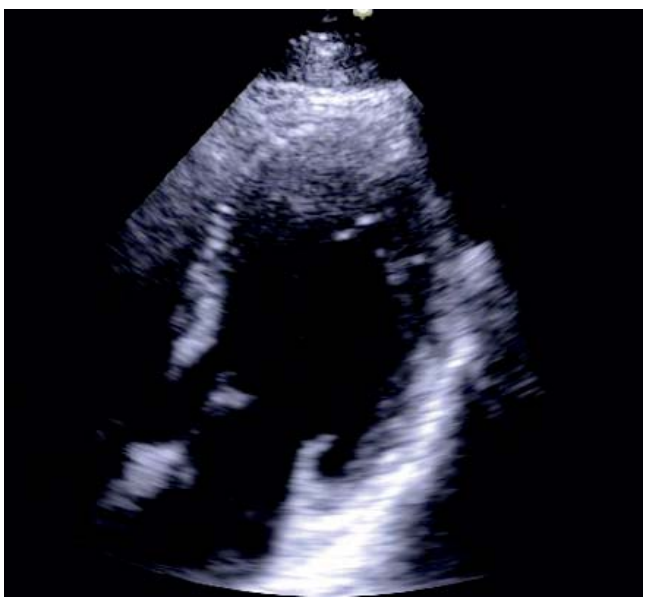

Figure 4. Echocardiography performed at the admission- apical section.

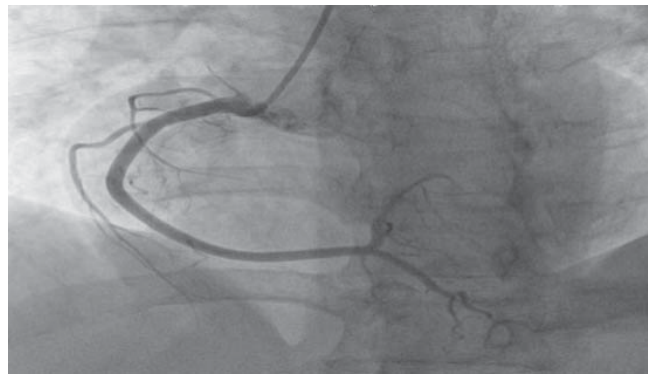

Figure 5. Right coronary artery.

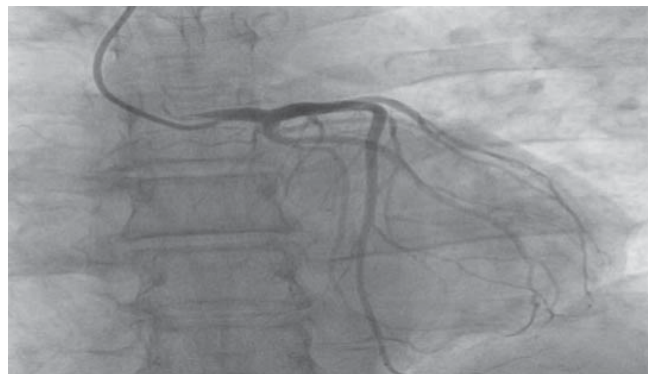

Figure 6. Left and circumflex coronary artery.

The medical treatment consisted in adrenaline 0.1 mg intramuscular injection (1: 1000 dilution), corticosteroids (methylprednisolone), intravenous fluids (Ringer lactate) and bronchodilators (ventolin). Also, platelet antiaggregants are administered in the context of suspicion of acute cardiac ischaemia.

Symptomatology resolved within a few hours without repeating the cardiovascular symptoms during the admission period. Repeated paraclinical examinations (laboratory tests, ECG, echocardiography) followed the course mentioned above, revealing a significant improvement over the course of a few days. The patient was discharged from the hospital on the 5th day of the disease fully recovered, with the review plan after two weeks when the repeated investigations were in the normal range.

DISCUSSIONS

Corroborating the clinical and paraclinical manifestations, the diagnosis of an acute coronary syndrome emerged in the context of an anaphylactic reaction caused by the sting of several hornets (Vespa crabro), from the Hymenoptera family. Precordial pain, electrocardiographic and enzymatic changes support the

diagnosis. Rare cases have been described in the literature, which is why the mechanism of myocardial involvement is unknown. Both the type I hypersensitivity pathway and the toxic direct effects of inoculated venom during the sting can be incriminated. The components of the hymenoptera venom are various, mostly allergenic, such as phospholipase A2, hyaluronidase and melitin. Of these, phospholipase is the most potent allergen, triggering an IgE mediated immune response, and melitin, responsible for pain and inflammation at the site of the sting, is an important component due to its ability to activate other poisonous proteins and its toxic potential. In addition, pharmacologically active constituents such as histamine, serotonin, dopamine, noradrenaline and a bradykinin-like substance that can induce histamine release have been isolated from the venom. The sequence of events in the triggered hypersensitivity reaction culminates with the release of serotonin and histamine with vasodilatory effect and formation of leukotrienes with a strong vasoconstrictor effect. At the cardiovascular level, these mediators can precipitate coronary artery spasm and accelerate the breakdown of coronary artery arterial plaques. In addition, all these substances can aggravate myocardial ischaemia either by the hypotension secondary to vasodilation or by increasing myocardial oxygen demand by direct ionotropic or chronotropic effect, in the presence of a compromised blood supply of the myocardium.

There are three variants of Kounis syndrome. The Type I variant includes patients with normal coronary arteries without predisposing factors for coronary artery disease, which evolves with coronary spasm but with normal myocardial necrosis enzymes, or with prolonged spasm that evolves to myocardial infarction. This variant could be a manifestation of endothelial dysfunction or microvascular angina. Type II includes patients with preexisting atheromatous disease, where the acute allergic episode may induce erosion or rupture of the plaque that manifests as an acute myocardial infarction. A type III variant was described as a coincidence of hypersensitivity reactions after implantation of drug-eluting stents, causing stent thrombosis. The case of the 39-year-old patien,t with no cardiovascular risk factors and no history of angina episodes, belongs to type I Kounis syndrome with electrocardiographic changes and elevated myocardial necrosis enzymes. The electrocardiographic aspect of ST segment elevation in inferior derivation with its progressive reduction to the isoelectric line and the subsequent development of negative T-waves are highly suggestive for myocardial ischemia. Also, the rise in troponin I dynamics to significant values for myocardial necrosis, supports the diagnosis. Emergency coronary angiography does not reveal significant lesions, but this does not rule out the possibility of transient myocardial ischaemia, most likely due to coronary spasm. Other investigations, such as perfusion myocardial scintigraphy or cardiac magnetic resonance imaging, would have been of great use to the case.

The case presented further supports for Kounis syndrome as a distinct phenomenon. Some authors have argued that the vasospastic process is the dominant pathophysiological explanation of Kounis syndrome, advocating systemic vasodilation and coronary hypoperfusion as the main mechanism in myocardial ischemia in the context of anaphylaxis. However, differentiation of primary myocardial injury from mast cell activation by global myocardial hypoperfusion may be challenging and remains a potential alternative explanation for acute coronary artery syndrome.

Another hypothesis of myocardial infarction in the anaphylactic reaction suggests that treatment with epinephrine frequently used in the emergency room for anaphylactic reactions may be responsible for myocardial injury. Epinephrine is considered the cornerstone in managing anaphylaxis. Intramuscular administration of adrenaline 1: 1000 at a maximum dose of 0.5 mg is recommended for the treatment of anaphylaxis. The mechanism of myocardial lesion would be coronary vasospasm secondary to administering epinephrine. The case described was also treated with adrenaline intramuscularly, but at a small and single dose of 0.1 mg. Knowing the pharmacokinetics and its very short half-life (5-10 minutes), coronary vasospasm is less likely to occur as a secondary to adrenaline administration, since angina symptoms occurred before adrenaline administration and electrocardiographic and enzymatic anomalies occurred two hours after administration. However, the possibility of worsening of coronary spasm after administration of epinephrine is not excluded.

CONCLUSIONS

Diagnosis and treatment of Kounis syndrome can be really challenging, requiring concomitant attention to both cardiac and anaphylactic pathophysiology. Although allergic episodes are common in everyday practice, early recognition of Kounis syndrome caused by the stings of the hymenoptera hornets is important

for the therapeutic conduct and choice of the optimal treatment. Further studies are needed in the future to understand the allergic mechanisms involved in acute coronary syndromes pathogenesis and to pave the way for effective therapeutic interventions.

Conflict of interest: none declared.

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