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Allergic acute coronary syndrome: a case report with a concise review

D. MARCHESINI, A. ESPERIDE, P. TILLI, L. SANTARELLI, M. COVINO, L. CARBONE, F. FRANCESCHI

Emergency Department, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Catholic University of the Sacred Heart, Rome, Italy

Abstract. – Occurrence of chest pain during an allergic reaction is a typical manifestation of the Kounis syndrome, defined in 1991 by Nicholas Kounis and George Zavras as an "allergic angina", whose clinical course can range from a simple coronary spasm without troponin elevation to an acute myocardial infarction with all the possible complications, including sudden cardiac death. The full pathogenetic mechanisms are still not fully understood, and this is one of the reasons why it is underestimated in the emergency practice; on the other hand, an immediate identification and an appropriate treatment could prevent the occurrence of the most serious consequences. In this article we report the case study of a patient with Kounis syndrome and we review the literature on this uncommon disease; it is fundamental to consider Kounis syndrome as a possible cause of chest pain in patients admitted in the emergency department with an ongoing allergic reaction

Key Words:
Kounis syndrome, Ischaemic heart disease, Allergic coronary vasospasm.

Introduction

Kounis syndrome is also known as "allergic angina"[1]: it is a clinical entity characterized by a coronary artery spasm following the action of inflammatory mediators, such as histamine, arachidonic acid, platelet activation factor and different cytokines[2] acting on endothelium and smooth muscle cells of the coronary artery tree. First considered mainly a cardiac disease, Kounis syndrome must be conceived as a part of the multi-systemic condition of allergic reactions that variously affects skin, respiratory function and the entire vascular system; the induced vasospasm, apart from coronary arteries, can also involve the brain and mesenteric vessels[3].

Kounis syndrome was first described in 1991 by the Greek cardiologist Nicholas Kounis and colleague George Zavras, who defined the concept of an acute coronary syndrome associated with the alterations of vascular vessels and platelets aggregation within the context of the biochemical allergic storm[4]: angina, dyspnea, nausea, vomiting, syncope, itching and urticarial reaction are the others well known manifestations. Frequently, these symptoms are associated with hypotension, diaphoresis, pallor, bradycardia and ischemic electrocardiographic findings[5].

The underlying mechanism of the cardiac symptomatology was not perfectly understood: the main hypothesis is that mast cells, platelet activation, cytokines cascade[6] and epinephrine may cause coronary vasospasm, plaque instability or intrastent thrombosis where present.

Kounis himself identified three different manifestations of the syndrome. The *type I variant* is identified by spasm of coronary arteries with normal coronary artery tree and without an increase of myocardial injury biomarkers or coronary artery spasm, which results in acute myocardial infarction with increase cardiac enzymes and troponins. The *type II variant* is characterized by erosion or rupture of pre-existing atherosclerotic plaque with normal of the cardiac injury markers or coronary artery spasm, which results in acute myocardial infarction with increase cardiac enzymes and troponins; *type III variant*, with thrombosis upon a medicated stent caused by hyperactivation of eosinophils and macrophages in the context of local inflammation[7].

Since Kounis syndrome is mostly under-diagnosed[8], its real prevalence is very difficult to be established; cases have been described in patients from 9 to 90 years of age[9], even though it seems to mainly affect patients between 40 and 70 years

Corresponding Author: Debora Marchesini, MD; e-mail: debora.marchesini90@gmail.com

old[10] with a history of atopy, diabetes mellitus, hypertension and smoking habit. A typical Kounis syndrome patient is a middle-aged man who shows allergic symptoms and myocardial ischemia after being exposed to an allergic trigger.

Despite of its recent awareness, the real number of cases of Kounis syndrome in the USA is still underestimated. Southern Europe, and especially Greece, Spain, Turkey and Italy, is considered the geographic area with the highest incidence of Kounis syndrome[3].

Potential triggers include a wide variety of environmental factors: consumption of particular foods (fish, shellfish, kiwifruit, mushroom, vegetables, tomato salad, canned food), use of selected drugs (antibiotics, analgesics, anesthetics, anticoagulants, antineoplastics, glucocorticoids, proton pump inhibitors, non-steroidal anti-inflammatory drugs, contrast media and skin disinfectants[5]), snakebites and Hymenoptera stings[11].

From the pathophysiological point of view, Kounis syndrome is the result of a combination between the action of different inflammatory mediators and the underlying condition of the artery wall, including endothelium: this interaction alternately causes muscle vasoconstriction or plaque instability and eventually rupture. Nevertheless, the reason why not all allergic patients may develop Kounis syndrome is still unclear; among different causes, Kounis[2] hypothesized that the occurrence of vasospasm may be related to mast cell degranulation threshold value, which may differ among subjects; moreover, other factors may be the area of exposure to the trigger, the quantity of mediators released and, most of all, the severity of the anaphylactic reaction.

Kounis syndrome and ischemic heart disease have in common high serum and urinary levels of histamine, leukotrienes, thromboxane and tryptase[12]. The trigger of the allergic reaction causes mast cell degranulation, which in turn promotes a massive release of the above mentioned vasoactive mediators; histamine and leukotrienes are the most powerful vasoconstrictors able to trigger type I Kounis syndrome. Similarly, in the presence of an underlying culprit lesion[5], metalloproteases activated by tryptase, would mainly determine erosion or rupture of the atherosclerotic plaque and subsequently cause myocardial ischemia. Interestingly, there are four histamine receptors located inside cardiac vessels, each one of them contributing to modulate the severity of an allergic reaction. H1 and H2 act in opposite way, one mediating the vasoconstriction, while the other one smooth muscle relaxation: this cause a drop in diastolic blood pressure that could worsen the diastolic coronary perfusion and increase the differential blood pressure. There are two additional histamine receptors: H3, which has been linked to the release of norepinephrine in an inhibitory way and H4, a recently identified receptor able to regulate chemotaxis of mast cells, eosinophils and lymphocytes[12]. On the other hand, histamine induces both coronary vasospasm and platelet activation. Metalloproteases, in the presence of an underlying plaque, cause collagen degradation leading to erosion plaque instability and rupture[2]; tryptases exert then a double action on the coagulation cascade showing both thrombotic and fibrinolytic properties. Similarly, thromboxane and PAF are powerful mediators of platelet aggregation and increase the release of leukotrienes, which are direct vasoconstrictors. Chimases and cathepsin D contribute to the same task, acting indirectly on cardiac function through the conversion of angiotensin I into angiotensin II[1].

Diagnosis of Kounis syndrome is mainly clinical and it is mostly based on the identification of signs and symptoms of an allergic reaction together with those of an acute coronary syndrome. Patients present chest pain associated with neurovegetative symptoms, such as nausea, vomiting and diaphoresis and all signs of an allergic reaction, such as erythema, edema, vasodilation, hypotension, bronchoconstriction and angioedema[5].

Post-allergic coronary syndrome, or cardiac anaphylaxis, can result in myocardial ischemia, conduction defects, arrhythmias, dysfunction of the cardiac muscle cell[13], frequently associated with electrocardiographic changes and/or increase in cardiac injury markers. Since there are no specific or pathognomonic findings of Kounis syndrome, it is essential to carefully investigate patient's clinical history to obtain a cause-effect temporal relationship between allergic trigger and acute coronary syndrome.

Troponins show a sharp rise in most of the cases. Recent scholars[3] have established a direct correlation between the severity of anaphylaxis and the increase in cardiac injury markers. This may be consistent with the severity of allergic reaction, extent of the vasoconstriction and myocardial damage. Serum tryptase show a sensitivity of 73% and a specificity of 98%[14] in the diagnosis

of anaphylaxis and, for a reliable dosage, a minimum of three determinations are recommended, distributed within few hours after the starting of drug treatment[15] but in emergency setting this is unlikely to usually be performed.

12-lead electrocardiogram (ECG) may commonly show ST elevation. Nevertheless, a depression or a perfectly normal ECG trace does not exclude the diagnosis. For unknown reasons, vasospasm affects mainly right coronary artery in almost all cases[12] of Kounis syndrome.

Cardiac ultrasound may be useful in order to exclude other similar conditions, such as Takotsubo[2], since there are no specific eco findings in patients with Kounis syndrome.

All patients with ST elevation will undergo coronary angiography; at this point it will be possible to distinguish type I Kounis syndrome from type II, thus allowing to establish an adequate management during hospitalization.

Finally, cardiac biopsy is not indicated, because indifferently can show mast cell infiltration or be normal[16].

Case Report

A previously healthy 72-year-old woman (Body Mass Index 26.7) got in emergency after four hours from the onset of precordial and epigastric pain associated with urticarial and itchy reaction on face and abdomen, which arose after the intake of pills of ketoprofen-lysine and amoxicillin-clavulanic acid salts. Patient had a clinical history of high blood pressure, dyslipidemia, Hashimoto's thyroiditis and nickel allergy, with no evidence of any significant previous cardiovascular event. She was under home treatment with bisoprolol, valsartan-hydrochlorothiazide, pantoprazole and levothyroxine. On arrival in the Emergency Department (ED) she was awake, alert and oriented; first clinical values showed hypotension (blood pressure 60/40 mmHg), tachycardia (heart rate 115 bpm) and tachypnea (RR 20/min). Oxygen saturation was 94% at pulse oximeter, with a FiO_2 of 21%.

ECG (Figure 1) showed ST elevation in the lower branches (DII, DIII, aVF), suggesting an acute myocardial infarction (STEMI) but with normal value of Troponin I at the first detection.

Blood cell count, including eosinophil levels, showed normal results. Patient was treated with a loading dose of clopidogrel, acetylsalicylic acid, fondaparinux, corticosteroids and antihistaminic drugs in standard dose. A further ECG (Figure 2) was then performed, when cardiac and allergic signs and symptoms improved, showing a complete remission of ST elevation previously observed.

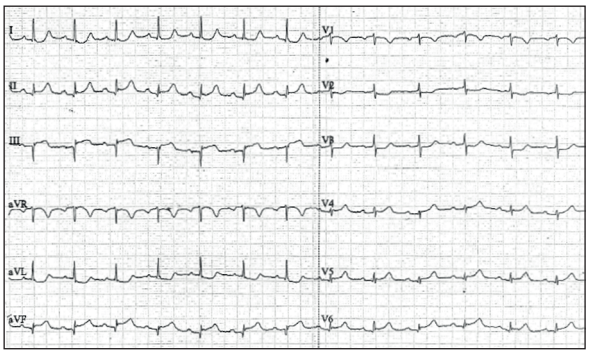

Figure 1. ST elevation in DII, DIII and aVF.

Parameters were normal. On physical examination there was a clear improvement in the urticarial reaction. Transthoracic cardiac ultrasound showed a preserved global systolic function and no significant alterations in regional kinetics and valve function. In the second and third determination, troponin I was once again found within the normal range.

Coronary angiography documented non-critical coronary artery disease, with an intermediate stenosis of mean anterior interventricular artery (IVA) at the bifurcation with D1 and right coronary artery. Both vessels were stimulated with adenosine, without evoking hemodynamically significant stenosis and had an adequate functional flow reserve. Based on the clinical history of allergy and drug intake together with the exclusion of any other possible causes of acute coronary syndrome, a final diagnosis of Kounis syndrome was then made. Our patient is classified as *type I variant*.

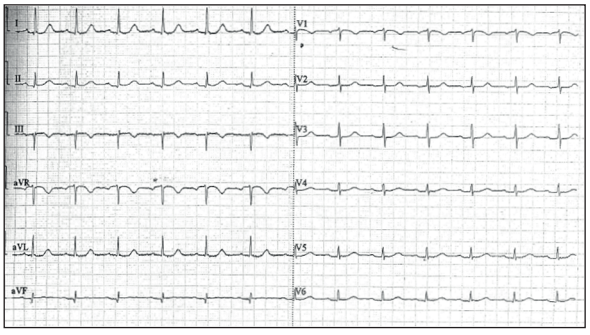

Figure 2. A second ECG shoed complete resolution of ST elevation.

Discussion

As a consequence of what abovementioned, we can split the therapy in immediate treatment (before PCI) and long-term treatment (after PCI). The PCI can identify the Kounis syndrome in the different types allowing a further specific management of the syndrome.

Immediate treatment include drugs to contain the allergic reaction and those commonly used for acute coronary syndrome: if the patient has no history of allergy to drugs, we usually use acetylsalicylic acid, morphine in case of pain, oxygen in case of dyspnea or hypoxia, fluid therapy in case of hypotension, corticosteroids and slow infusion of antihistaminic drugs for mild and local reaction, adrenaline in case a life-threatening systemic allergic reaction[10].

The main problem of the drugs administered to treat the allergic reaction is that they could potentially worsen the cardiac function, while those given to treat the acute coronary syndrome could aggravate anaphylaxis[2].

As for the immuno-allergic side, while the use of antihistamines and corticosteroids is still mandatory, the first line treatment remains adrenaline, even though it may aggravate the cardiac manifestation, through QT interval prolongation, induction of arrhythmias and further vasospasm. Antihistamines positively act on itching, rash and angioedema but can cause hypotension and worsening of hemodynamic flow; therefore they should only be used in hemodynamically stable patients. Concerning corticosteroids, different studies[17] have shown their efficacy on allergic symptoms few hours after their administration. In addition, it has been suggested[18] that atopic patients may also benefit from treatment with anti IL-4 receptor blockers or mast cell stabilizers.

Management of the cardiac is the same used in the international guidelines for the management of acute coronary syndrome, but extreme caution is needed for the use of beta-blockers, which could increase coronary artery spasm. Also, nitrates should be carefully used, due to their hypotensive and tachycardia effects, especially in patient with lower cardiac ischemia. Despite its possible and documented role in allergic vasospasm[19,20], the administration of aspirin is strongly recommended, being extremely beneficial. Elective drugs are also calcium channel blockers, due to their capability to reduce coronary vasospasm. Therefore, a perfect balance between risk and benefit is strictly required, which explains why it is so difficult to manage those patients in the short and long term.

Allergen-induced coronary artery spasm could begin after contact and/or intake of drugs, which represent the main trigger of anaphylaxis. Regardless of the cause, the resulting picture is acute coronary syndrome during a clinical manifestation of allergy. The case report described above is quite paradigmatic.

Kounis syndrome must always be considered for a differential diagnosis, especially if the patient took drugs or any other substance potentially triggering anaphylactic reactions. Bronchoconstriction, interstitial edema and cardiac involvement occur simultaneously in patients with Kounis syndrome, while making a prompt diagnosis and starting of an adequate treatment still represents a real challenge for physicians.

Conclusions

From what we have said, it is easy to understand how the condition can be confused with other disease that mimic a coronary syndrome; nerveless it is fundamental to identify it as soon as possible, already in the context of the emergency department, in order to start the correct therapy of the double aspects of this condition: the allergic side and the ischemic side.

In conclusion, increasing knowledge of all emergency medicine doctors on the clinical characteristics of Kounis syndrome appears to be mandatory; this will allow them to better recognize this syndrome from the beginning and to start an appropriate treatment, able to avoid even fatal complications.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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