Review

Kounis Syndrome - a Natural Paradigm

Luminiţa-Bianca GROSU[1], Ana Gabriela PRADA[1,2], Raluca Ioana DASCĂLU[1], Camelia Cristina DIACONU[1,2]

[1]*Department of Internal Medicine, Clinical Emergency Hospital of Bucharest, Bucharest, Romania*
[2]*"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*

Address for correspondence: Luminiţa-Bianca Grosu, Department of Internal Medicine, Clinical Emergency Hospital of Bucharest, Bucharest, Romania; e-mail: grosu_luminita@yahoo.com

Abstract

Kounis syndrome is a ubiquitous condition, representing a natural paradigm between coronary artery vasospasm, plaque rupture and anaphylactoid reactions. Kounis syndrome is underdiagnosed, as the inflammatory cells releases, in both allergic and non-allergic acute coronary syndrome, are the same. The syndrome is induced by various causes such as drugs, foods, environmental exposure, stents. There are three variants of Kounis syndrome: vasospastic allergic angina, allergic myocardial infarction, and stent thrombosis. All patients with systemic allergic manifestations correlated with clinical, laboratory and electrocardiography findings of acute myocardial infarction must be investigated for Kounis syndrome. The therapeutic management of Kounis syndrome represents a challenge, as it is necessary to treat both the cardiac and allergic events. After the acute event, a complete cardiological follow-up is mandatory, skin tests, verification of allergies to food, insect stings, drugs and environment agents. The awareness of etiology, epidemiology, pathogenesis, signs and symptoms is important for its diagnosis, treatment, prognosis and prevention.

Keywords: Kounis syndrome, anaphylaxis, angina.

INTRODUCTION

Kounis syndrome represents the presence of acute coronary syndrome associated with allergic events or anaphylactoid insults. It is determined by inflammatory mediators as histamine, platelet-activating factor, arachidonic acid products and other chemokines and cytokines. The mast cells play the dominant role in the inflammatory process and activate with the other cells a vicious cascade via multidirectional ways. Kounis syndrome was first described as concomitant occurrence of acute coronary event and anaphylaxis by Kounis in 1991 [1].

Until today, there is not detailed information about the background, evolution and consequences of Kounis syndrome, as there were reported only 300-400 cases in the literature [2]. The main causes described have been drugs, food, insect stings, different medical conditions. The syndrome is mainly found in Turkey, Greece, Italy and Spain, due to environmental conditions, overdose of certain drugs, inadequate preventive measures [3]. Also, it is important to take into consideration the genetic factor, as patients with Kounis syndrome seem to have a heterozygous E148Q mutation [4].

In the most known prospective study evaluating Kounis syndrome, that included 138,911 patients presented to emergency departments for one year, 793 complained of allergic events. The incidence of Kounis syndrome in that year was approximately 4% [5], [6].

Another large epidemiological study showed that the prevalence of Kounis syndrome was 1.1%, with a successive hospitalized patient all-cause mortality rate of 7%. In comparison to non-Kounis acute coronary syndrome, the Kounis syndrome group was older, with a predominance of males, more Caucasian patients, and higher duration of hospitalization. The number of cases of cerebrovascular, cardiac and thromboembolic events was higher in Kounis syndrome group [7].

Recent studies have described that Kounis syndrome can also affect the cerebral and mesenteric arteries [8],[9].

However, the real incidence of Kounis syndrome is not known and it is frequently underdiagnosed. This is the reason why more awareness of this condition is necessary along medical community and large population, for preventing severe complications or even fatal consequences.

ETIOLOGY

Kounis syndrome has been triggered by multiple causes. These include several drugs, food, environmental factors and severe conditions (Table 1).

When referring to drugs, losartan, corticosteroids, amoxicillin and propofol are the most incriminated in inducing Kounis syndrome. Treatment with losartan can lead to repeated episodes of angina pectoris and coronary artery spasm, progressing to acute myocardial infarction, with increased troponin and electrocardiographic changes [10],[11]. Corticosteroids are used for the treatment of different conditions, such as rheumatologic, cutaneous, respiratory, allergic, and even for refractory vasospastic angina, when the patient has an atopic condition. On the other hand, corticosteroids can cause allergic events, which can progress to anaphylaxis [12]. A report presented a case of Kounis syndrome in a young patient with normal coronary arteries after the ingestion of prednisolone for wasp sting anaphylaxis [13].

The most allergic types of food are fish, fruits, vegetables, and canned food. Most common examples of food-induced Kounis syndrome are scombroid syndrome, anisakiasis and kiwifruit allergy. The scombroid syndrome represents histamine toxicity resulting from intake of poisoned fish. The most mutual spoiled fish are Scombridae species, especially tuna, mackerel, and bonitos [14]. The clinical examination of these patients reveals rashes, flushing, palpitations, swelling of the face, vomiting, diarrhea, headaches, hypotension and shock [15]. Anisakiasis is associated with the intake of undercooked seafood infected with the nematode anisakis simplex, a mutual parasite in fish, which secretes allergenics [16]. The diagnosis of anisakiasis consists of the presence of allergic symptoms, positive serum-specific IgE levels and a positive skin prick test [17]. Kiwifruit is rich in vitamins, fibers, potassium, but allergies to this fruit have become frequent, as it can determine typical IgE-mediated allergic events [18].

Another important etiology of Kounis syndrome is related to the macromolecule gelofusin. There are cases of Kounis syndrome determined by gelofusin, associated with perioperative cardiac arrest [19]. Gelatin is the main component of a multitude of food-sweets, yogurt, plasma expanders, suppositories, heat stabilizers in vaccines [20]. Some gelatin antibodies have been found in patients who underwent vaccination, and this is the reason why the first route of sensitization is the vaccine [21].

Table 1. Etiology of Kounis syndrome

Drugs	Analgesics, anesthetics, anticoagulants, antibiotics, glucocorticoids, nonsteroidal anti-inflammatory drugs, proton pump inhibitors, thrombolytics, anti-neoplastics
Food	Fish, fruits, vegetables, tuna, mushroom poisoning
Conditions	Anisakiasis, scombroid syndrome, stents, asthma, skin itching, mastocytosis, Churg-Strauss syndrome, idiopathic anaphylaxis
Environment	Grass, latex, scorpion sting, viper venom, metals

CLASSIFICATION

Kounis syndrome has been classified in three types:

1. Type I (without coronary disease): chest pain in patients with normal coronary arteries, without risk factors; the allergic event is, probably, a representation of microvascular angina or endothelial dysfunction; the release of inflammatory mediators induces coronary artery spasm without the increase of cardiac enzymes, or coronary artery spasm which progresses to acute myocardial infarction, with the increase of troponins and other cardiac enzymes [22],[23].

2. Type II (with coronary disease): chest pain in patients with culprit, pre-existing atheroma disease; the release of inflammatory mediators induces coronary artery spasm with normal cardiac enzymes, or coronary artery spasm with plaque rupture, resulting in acute myocardial infarction [23],[24].

3. Type III: chest pain in patients with coronary artery stent thrombosis, where Giemsa and Hematoxylin-eosin staining shows the presence of mast cells and eosinophils [25],[26].

Diseases associated with Kounis syndrome:

- Hypersensitivity myocarditis: in both conditions, there is an allergic etiology affecting the coronaries (Kounis syndrome) and the heart muscle (myocardiopathy). Sometimes, these can be hardly distinguishable, requesting magnetic resonance imaging (MRI) and biopsy for differential diagnosis [27].
- Coronary artery disease in allogenic heart transplantation.
- Takotsubo myocardiopathy [28].

POSITIVE DIAGNOSIS

The diagnosis of Kounis syndrome is made based on clinical (symptoms, signs) and paraclinical criteria (electrocardiography, laboratory, echocardiography, angiography, cardiac magnetic resonance, scintigraphy). All patients with systemic allergic manifestations correlated with clinical, laboratory and electrocardiography findings of acute myocardial infarction must be investigated for Kounis syndrome.

CLINICAL DIAGNOSIS

The clinical diagnosis of Kounis syndrome is based on symptoms and signs of an acute coronary event and allergic reaction at the same time. Coronary events include unstable angina or acute myocardial infarction, associated with electrocardiographic alterations and/or increase of cardiac enzymes. The common symptoms of an anaphylactic reaction include hypotension, skin signs (rash, urticaria, angioedema), respiratory (dyspnea, wheezing, stridor) and digestive manifestations (nausea, vomiting, abdominal pain) [24].

For the assessment of an etiology-effect relationship, it is important to know the clinical history of the patient, especially the allergic antecedents (drugs, fruits, vegetables, insect stings).

The frequent symptoms and signs are presented in Table 2.

Table 2. Clinical symptoms and signs of Kounis syndrome

Symptoms	chest pain, weakness, dyspnea, nausea, vomiting, pruritus, urticaria, syncope
Signs	hypotension, palpitations, tachycardia, bradycardia, diaphoresis, cardiorespiratory arrest

PARACLINICAL DIAGNOSIS

- Electrocardiography (ECG): ST segment elevation in DII, DIII, aVF, V5-V6, compatible with acute inferior myocardial infarction, represents the most frequent ECG sign. The right coronary artery is frequently affected by vasospasm, the reason being unknown. Other ECG signs are arrhythmias, such as atrial/ventricular fibrillation, bigeminism, sinus bradycardia/tachycardia, extrasystoles, atrioventricular block, T-wave flattening/inversion, QT prolongation, wide QRS.
- Laboratory tests used are the ones for suspicion of acute myocardial infarction (cardiac enzymes, complete blood count, lipid profile, glucose, D-dimers) and the ones suggestive for allergic reactions (histamine, tryptase, arachidonic acid products, histamine, complement, eosinophilia, IgE, interleukins, tumor necrosis factor). Otherwise, normal values of these parameters don't eliminate the probability of an allergic reaction.

According to guidelines, tryptase represents the most beneficial indicator for diagnosing an allergic reaction, with a 98% specificity and 73% sensibility [29]. The main source of tryptase is the mast cells and it has a half-time of 90 minutes. Therefore, there are necessary three determinations of tryptase levels: the first one immediately after the reaction, the second one two hours after and the third one after 24 hours. The levels of tryptase normalize between 6 to 9 hours after the reaction [29], [30].

The main source of histamine are also the mast cells, but this inflammatory marker is less practical than the tryptase, as it has a half-time of 60 minutes, with 8 minutes peak after the beginning of the allergic reaction [29],[31].

It is mandatory to measure the cardiac troponin, CK, CK-MB levels in all patients with suggestive symptoms and signs, to diagnose and correctly manage a possible cardiac event manifesting as Kounis syndrome [24].

Some case reports highlighted the fact that, in patients with vasospastic angina, the number of eosinophils is significantly increased and can predict the severity of the disease. However, it can be observed an important decrease in eosinophils counts following treatment and improvement of clinical status [24].

Other inflammatory markers aren't always able to make a differential diagnosis between Kounis syndrome and acute myocardial infarction because they are significantly elevated in both cases.

- Echocardiography reveals contractility impairment and can help the differential diagnosis with other causes of chest pain [24].
- Angiography evaluates the coronary anatomy, treat vasospasm, and angioplasty must be performed when necessary [24].
- SPECT (thallium-201 single-photon emission computer tomography) and 125l-15-(p-iodophenyl)-3-(R,S) methylpentadecanoic acid (BMIPP) SPECT show severe myocardial ischemia with normal angiographic coronary arteries in type I Kounis syndrome [32].
- Cardiac magnetic resonance imaging helps differentiate between ischaemic and non-ischaemic cardiac diseases, by evaluating myocardial viability in the affected areas (sometimes after revascularization). It gives additive information about contrast enhancement patterns, area of myocardial lesion (epicardial, transmural, endocardial) and necrosis [33].

TREATMENT OF KOUNIS SYNDROME

The therapeutic management of Kounis syndrome represents a challenge, as it is necessary to treat both the cardiac and allergic events. The allergic manifestations should be treated early in the management of this syndrome. The problem is that some medications administered for cardiac symptoms can worsen allergies and medications administered for allergic

symptoms can worsen the cardiac function [34].

1. The therapeutic management of anaphylaxis uses adrenalin, H1 blockers, H2 blockers, corticosteroids, mast cell stabilizers, intravascular volume replacement [35].

- Adrenalin represents the treatment of choice in anaphylactoid events, and it must be administered early to ameliorate patient's survival and prevent cardiac failure and bronchospasm. The American College of Allergy, Asthma and Immunology guidelines recommend intramuscular administration, with the possibility to repeat the dose after 20 minutes, if necessary. In the case of an acute coronary syndrome, adrenalin can exacerbate ischemia, prolong the QT interval, and determine arrhythmias. Adrenalin is prohibited in patients allergic to sulfite, as it contains sodium metabisulfite [24],[36].
- H1 blockers are considered the second line of treatment and ameliorate pruritus, rash, and angioedema. They are recommended only in stable patients and must be administered slowly, because they can cause hypotension [24].
- H2 blockers are used in combination with H1 blockers, for better results.
- Corticosteroids are used in preventing biphasic and prolonged anaphylaxis [37]. Also, they are beneficial in patients with vasospastic angina and symptoms non-responsive to high doses of vasodilators [38].

2. The therapeutic management of acute coronary syndrome includes oxigenotherapy, vasodilators, aspirin, clopidogrel, nitroglycerin, beta-blockers, and calcium channel antagonists [39].

- Aspirin is administered to all patients with acute coronary syndrome for long time, in the absence of contraindications. However, aspirin may cause allergic reactions and its usefulness in Kounis syndrome is not well-known. Consequently, the decision of its administration is made by analyzing the risk-benefit balance [24].
- Nitroglycerin should be administered in all patients with acute coronary syndrome, to dilate the coronaries, lower the preload and increase the myocardial oxygen release [24].
- Beta-blockers are extremely useful in coronary syndrome, but they can alter the positive effects of adrenalin.
- Morphine has important analgesic and anxiolytic effects. However, morphine and codeine must be used cautiously, as they can exacerbate the mast cell degranulation and worsen the anaphylactoid events. The second option when opiates are necessary is fentanyl, because it leads to limited mast cell degranulation in comparison to other drugs [24].

Kounis syndrome is a complex acute coronary syndrome that needs immediate treatment. After the acute event, a complete cardiological follow-up is mandatory, and also skin tests, verification of allergies to food, insect stings, drugs and environmental agents.

CONCLUSIONS

In conclusion, Kounis syndrome or allergic angina syndrome represents a not so rare, but rarely diagnosed condition. Even nowadays, it is a challenge to early recognize and adequately treat this syndrome, which can progress to life-threating complications. More studies are needed to understand its epidemiology, signs and symptoms and to find and introduce efficient therapeutic methods. The medical community should be aware of this syndrome and exclude it in patients presenting to emergency departments with acute coronary syndrome, by making a thorough history for possible allergens exposure.

Author Contributions:

L.B.G. conceived the original draft preparation. L.B.G., A.G.P., R.I.D., C.C.D. were responsible for conception and design of the review. L.B.G., A.G.P., R.I.D. and C.C.D. were responsible for the data acquisition. L.B.G, was responsible for the collection and assembly of the articles/published data, and their inclusion and interpretation in this review. L.B.G, A.G.P.,

R.I.D., C.C.D. contributed equally to the present work. All authors contributed to the critical revision of the manuscript for valuable intellectual content. All authors have read and agreed with the final version of the manuscript.

Compliance with Ethics Requirements: "*The authors declare no conflict of interest regarding this article".*

Acknowledgements:
None

REFERENCES

[1] Kounis NG. Kounis syndrome: an update on epidemiology, pathogenesis,

diagnosis and therapeutic management. *Clin Chem Lab Med*. 2016;54(10):1545–59.

[2] Jing Li. Acute coronary syndrome secondary to allergic coronary vasospasm (Kounis syndrome): a case series, follow-up and literature review. *BMC Cardiovascular Disorders* 2018, 18:42.

[3] Kounis NG, Mazarakis A, Tsigkas G, Giannopoulos S, Goudevenos. J. Kounis syndrome: a new twist on an old disease. *Future Cardiol* 2011;7:805–24.

[4] Saylan B, Cevik A, Firat C. Kounis syndrome, a cause of chest pain to keep in mind, may be associated with E148Q mutation. *Hong Kong J Emerg Med* 2012;19:278–82.

[5] Akoz A, Tanboga HI, Emet M, et al. A prospective study of Kounis syndrome: clinical experience and cardiac magnetic resonance imaging findings for 21 patients. *Acta Med Mediterranea* 2013;9:811–6.

[6] Renda F, Landoni G, Trotta F, et al. Kounis syndrome: an analysis of spontaneous reports from international pharmacovigilance database. *Int J Cardiol* 2016;203:217–20.

[7] Desai R, Parekh T, Patel U, et al. Epidemiology of acute coronary syndrome co-existent with allergic/hypersensitivity/ anaphylactic reactions (Kounis syndrome) in the United States: a nationwide inpatient analysis. *Int J Cardiol.* 2019;292:35–8.

[8] Goto M, Matsuzaki M, Fuchinoue A, et al. Chronic atherosclerotic mesenteric ischemia that started to develop symptoms just after anaphylaxis. *Case Rep Gastroenterol* 2012;6:300–30.

[9] González-de-Olano D, Alvarez- Twose I, Matito A, Sánchez-Muñoz L, Kounis NG, Escribano L. Mast cell activation disorders presenting with cerebral vasospasm-related

symptoms: a "Kounis-like" syndrome? *Int J Cardiol* 2011;150: 210–11.

[10] Ahmad S. Losartan and angina pectoris. *Texas Heart Inst J* 1995;22:347–8.

[11] Josefsson J, Fröbert O. Losartan-induced coronary artery spasm. *BMJ Case Rep*; 2012. pii: bcr2012006252. doi: 10.1136/bcr-2012-006252.

[12] Takagi S, Goto Y, Hirose E, et al. Successful treatment of refractory vasospastic angina with corticosteroids-coronary arterial hyperreactivity caused by local inflammation? *Circ J* 2004;68:17–22.

[13] Arslan Z, Iyisoy A, Tavlasoglu M. Acute myocardial infarction after prednisolone administration for the treatment of anaphylaxis caused by a wasp sting. *Cardiovasc J Africa* 2013;24:e4–6.

[14] Coppola G, Caccamo G, Bacarella D, et al. Vasospastic angina and scombroid syndrome: a case report. *Acta Clin Belg* 2012;67:222–5.

[15] Kounis NG, Patsouras N, Grapsas N, Hahalis G. Histamine induced coronary artery spasm, fish consumption and Kounis syndrome. *Int J Cardiol* 2015;193:39–41.

[16] Pravettoni V, Primavesi L, Piantanida M. Anisakis simplex: current knowledge. *Eur Ann Allergy Clin Immunol* 2012;44: 150–6.

[17] Mejía-Rentería HD, Viana-Tejedor A, Sánchez-Enrique C, et al. Kounis syndrome after ingestion of undercooked fish: new role of intracoronary imaging techniques. *Int J Cardiol* 2014;177:e58–60.

[18] Fine AJ. Hypersensitivity reaction to kiwi fruit (Chinese gooseberry, Actinidia chinensis). *J All Clin Immunol* 1981;68:235–7.

[19] Shah G, Scadding G, Nguyen-Lu N, et al. Peri-operative cardiac arrest with ST elevation secondary to gelofusin anaphylaxis-Kounis syndrome in the anaesthetic room. *Int J Cardiol* 2013;164:e22–6.

[20] Bogdanovic J, Halsey NA, Robert A. Wood RA, Robert G. Hamilton RG. Bovine and porcine gelatin sensitivity in milk and meat-sensitized children. *J Allergy Clin Immunol* 2009;124:1108–10.

[21] Sakaguchi M, Nakayama T, Fujita H, Toda M, Inouye S. Minimum estimated incidence in Japan of anaphylaxis to live virus vaccines including gelatin. *Vaccine* 2001;19:431–6.

[22] Tsigkas G, Chouchoulis K, Kounis NG, Alexopoulos D. Allergic reaction reveals a non-lethal late stent thrombosis. A new subtype of Kounis syndrome? *Int J Cardiol* 2011;149:281–2.

[23] López PR, Peiris AN. Kounis syndrome. *South Med J.* 2010;103:1148-55.

[24] Cepeda PR, Herrejon EP, Aguirregabiria MMR. Kounis syndrome. *Med Intensiva*. 2012;36(5):358-364.

[25] Kounis NG, Filippatos GS. Takotsubo and Kounis syndrome: is there any association? *Circ J.* 2007;71:170.

[26] Chen JP, Hou D, Pendyala L, Goudevenos JA, Kounis NG. Drug-eluting stent thrombosis: the Kounis hypersensitivity-associated acute coronary syndrome revisited. *JACC Cardiovasc Interv*. 2009;2:583-93.

[27] Biteker M, Duran NE, Biteker FS, et al. Allergic myocardial infarction in childhood: Kounis syndrome. *Eur J Pediatr*. 2010;169:27-9.

[28] Yanagawa Y, Nishi K, Tomiharu N, Kawaguchi T. A case of Takotsubo cardiomyopathy associated with Kounis syndrome. *Int J Cardiol*. 2009;132:e65-7.

[29] Baldomà N, Cosmen CR, Galinski SF, García LM, Gracia LR, Villén FE. Serum tryptase levels in acute coronary syndromes with ST elevation. *Int J Cardiol*. 2009;131:403-4.

[30] Kounis NG. Serum tryptase levels and Kounis syndrome. *Int J Cardiol* 2007;114;407–8.

[31] Zavras GM, Papadaki PJ, Kokkinis CE, et al. Kounis syndrome secondary to allergic reaction following shellfish ingestion. *Int J Clin Pract* 2003;57:622–4.

[32] Goto K, Kasama S, Sato M, Kurabayashi M. Myocardial scintigraphic evidence of Kounis syndrome: what is the aetiology of acute coronary syndrome? *Eur Heart J* 2015. pii: ehv703.

[33] Matta A. Utility of enhanced cardiac magnetic resonance imaging in Kounis syndrome. *European Heart Journal-Case Reports* 2020; 4(4):1-5.

[34] Cevik C, Nugent K, Shome GP, Kounis NG. Treatment of Kounis syndrome. *Int J Cardiol* 2010;143:223–6.

[35] Lieberman P, Nicklas RA, Oppenheimer J, et al. The diagnosis and management of anaphylaxis: an updated practice parameter. *J Allergy Clin Immunol*. 2005;115 3 Suppl. 2:S483-523.

[36] Lin RY, Curry A, Pesola GR, et al. Improved outcomes in patients with acute allergic syndromes who are treated with combined H1 and H2 antagonist. *Ann Emerg Med.* 2000;36:462-8.

[37] Domínguez Franco AJ, Gómez Doblas JJ, Hernández García JM, et al. Treatment of refractory vasoespastic angina with

corticosteroids. A case report. *Int J Cardiol*. 2007;118:e51-3.

[38] Takagi S, Goto Y, Hirose E, et al. Successful treatment of refractory vasospastic angina with corticosteroids: coronary arterial hyperactivity caused by local inflammation. *Circ J.* 2004;68:17-22.

[39] Kushner FG, Hand M, Smith Jr SC, et al. 2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction and ACC/AHA/SCAI guidelines on percutaneous coronary intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2009;120: 2271-306.

[40] Kounis NG. Kounis syndrome: a monster for the atopic patient. *Cardiovasc Diagn and Ther.* 2013;3(1):1–4.