Kounis syndrome: a clinical entity penetrating from pediatrics to geriatrics

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1 Introduction

Kounis syndrome constitutes a coronary hypersensitivity disorder defined by the association of an anaphylactoid, anaphylactic, allergic or hypersensitivity reaction with an acute coronary syndrome, in a physiopathological context involving various interrelated and interacting inflammatory cells, such as mast-cells, eosinophils and platelets.[¹,²] Similar entities to Kounis syndrome might involve cerebral and mesenteric arteries.[³,⁴]

The scientific literature reports three variants of Kounis syndrome: type 1 or allergic vasospastic angina caused by endothelial dysfunction consisting one of MINOCA (myocardial infarction with non-obstructive coronary arteries) determinants;[⁵] type 2 or allergic myocardial infarction; type 3 also know as allergic stent thrombosis with an occluding thrombus (subtype A) or stent restenosis (subtype B).[¹,⁶]

A case of a 49-year-old man with myocardial infarction and urticaria after the treatment with penicillin was reported for the first time by Pfister, et al. in 1950.[⁷] In 1991, the complete notion of the physiopathology determining vasospastic angina and myocardial infarction associated to an allergic reaction was described by Kounis, et al.[⁸] Allergic angina was classified as a dynamic coronary occlusion condition, mediated by a vasospastic mechanism by Braunwald, et al.[⁹] Abdeghany, et al.[²] recently reviewed 175 Kounis syndrome published cases, highlighting type 1 as the most common variant (72.6%), followed by type 2 and 3 variants (22.3% and 5.1%, respectively).

2 Epidemiology

Currently, Kounis syndrome is established in the scientific literature, supported by an increasing number of clinical reports worldwide.[¹⁰,¹¹] A recent large epidemiological study in USA included 235,420 patient hospitalizations from the National Inpatient Sample database with allergic/hypersensitivity/anaphylactic reactions from 2007 to 2014, demonstrated a prevalence of Kounis syndrome of 1.1%, namely 2616 patients, with in-hospital mortality of 7.0% vs. 0.4% compared to the non-Kounis syndrome group. The patients with Kounis syndrome were older males, more often white, with prolonged hospitalization duration and higher hospitalization charges. The rates of cerebrovascular events (1.0% vs. 0.2%), arrhythmias (30.4% vs. 12.4%) and venous thromboembolisms (1.6% vs. 1.0%) were significantly higher in Kounis syndrome group compared to non-Kounis syndrome one.[¹²]

Data from a Turkish emergency department prospective study on adult patients demonstrated an estimated frequency of Kounis syndrome of 19.4 per 100,000 admitted patients.[¹³] Moreover, data from a Greek population-based epidemiological study evaluated a Kounis syndrome incidence of 3.33 cases/100,000 inhabitants per year.[¹⁴]

Even if Kounis syndrome can potentially affect patients of any age, the most vulnerable group is between 40 and 70 years old (68%).[²] However, there are few cases reported in pediatric age (9.1% under 20 years of age),[²] configuring such disease as a clinical entity penetrating from pediatrics to geriatrics. Interestingly, Kounis syndrome is reported more prominent in males than in females, 74.3% vs. 25.7%, respectively.[²]
This syndrome is associated with a significant morbidity and mortality, as it could be complicated with cardiac arrest (6.3%) or even with death (2.9%),[2] in case of widespread myocardial infarction or severe anaphylaxis manifestations.[1] Notably, a comparable mortality rate is recorded between males and females (3.0% vs. 2.2% respectively), with the majority of them triggered by drug (80%) or wasp sting (20%).[2] From an epidemiological point of view, the prognosis of this clinical condition is good, as Kounis syndrome type 1 represents the vast majority of cases, with a good response to the pharmacological therapy.[2]

3 Physiopathology

Mast cells are well-represented in the cardiac tissues, locating preferentially inside the coronary arteries, and further infiltrating coronary atherosclerotic plaques in case of erosion or rupture.[15–17] Regarding the pathophysiology of Kounis syndrome, pre-synthesized and newly produced mediators are released by mast-cells, platelets and other interconnected inflammatory cells into the systemic circulation during a hypersensitivity or allergic, anaphylactic or anaphylactoid reaction. Several cytokines and chemokines, histamine, arachidonic acid products, platelet-activating factor (PAF), neutral proteases, tryptase and cathepsin-D can be identified among the involved molecules.[18] These mediators can lead to coronary vasospasm or atheromatous plaque erosion, rupture or even coronary thrombosis, leading to myocardial infarction.[2,19] In particular, histamine can induce coronary artery constriction, peripheral artery dilation with decrease of the systemic blood pressure and platelet activation,[20–22] thromboxane can cause coronary artery vasoconstriction,[1] neutral proteases can lead to coronary atherosclerotic plaque erosion/rupture,[23] leukotrienes and cathepsin-D can determine coronary vasospasm,[24] whereas, tryptase is involved to the thrombotic pathway via fibrinogen-degradation.[25] A platelet subset of more than 20% with high-and low-affinity IgE surface receptors, histamine, thromboxane and PAF receptors is also involved in this cascade.[26]

4 Triggers

Several triggers have been associated with Kounis syndrome, such as foods, drugs, environmental elements, various conditions and coronary stents. Any substance, disease entity or environmental exposure that might induce IgE antibody production, could act as possible causes of Kounis syndrome. Potential nutritional triggers include fruits, vegetables, fish, shellfish, and mushroom. Pharmaceutical agents as analgesics, anti-inflammatory, anesthetics, antibiotics, antiviral, antifungal, glucocorticoids, antihistamines, proton-pump inhibitors, antiacids, anti hypertensives, antiplatelets, anticoagulants, thrombolytics, sympathomimetics, volume expanders, anesthetics, neuro-muscular blockers, skin antiseptics, contrast media, anti-neoplastics, and oral contraceptives can also serve as triggers. Moreover, environmental elements as grass, poison ivy, metals, latex, dialysate, nicotine, bites like viper or stings such as Hymenoptera, black widow spider, snake, scorpion or jellyfish can also induce Kounis syndrome. Various other conditions have been implicated with Kounis syndrome, such as idiopathic anaphylaxis, exercise-induced anaphylaxis, mastocytosis, serum sickness, Churg-Strauss syndrome, anuricemia, asthma, scumbord syndrome or Anisakiasis. Also, stent thrombosis can lead to Kounis syndrome type 3.[1,2]

Antibiotics and insects’ bites represent the most common triggers (27.4% and 23.4% respectively).[2] Contrast media,[27] carboplatin,[28] latex,[29] isotretinoin,[30] cobra bite[31] and fire ant bite[32] have also been identified recently as offenders.

5 Clinical manifestations

Kounis syndrome is characterized by the coexistence of cardiac signs and symptoms along with the clinical manifestations of hypersensitivity, allergic, anaphylactic or anaphylactoid reactions.[1,2] The cardiac clinical manifestations differ depending on the syndrome’s subtype: vasospastic angina due to endothelial dysfunction for the type 1, myocardial infarction for the type 2 and stent thrombosis or stent restenosis for the type 3. Cardiac clinical signs of the syndrome may include pallor, cold extremities, sweating, bradycardia, tachycardia, hypotension, vomiting, syncope or even cardiorespiratory arrest or sudden death. Cardiac symptoms such as chest discomfort, acute chest pain, malaise, palpitations, faintness, headache, nausea, and dyspnea, can accompanied Kounis syndrome as well.[1,2]

The clinical manifestations of a hypersensitivity or allergic reaction can range from mild and local reactions to life-threatening systemic reactions, as in case of anaphylaxis. The sign and symptoms can be variable, depending on the involved systems and organs, affecting skin or mucosal surface (e.g., hives, angioedema, itching), respiratory (e.g., wheeze, dyspnea, stridor), cardiovascular (e.g., hypotension), neurological (e.g., drowsiness, syncope) and gastrointestinal system (e.g., abdominal pain, diarrhea, vomiting).[33] Chest pain represents the most common cardiac manifestation of Kounis syndrome (86.8%), followed by the anaphylaxis symptoms (53.0%).[2]
In this clinical condition, several pathophysiological mechanisms could be identified, that act together leading to hypotension up to shock (2.3%) with joint cardiogenic and distributive mechanisms. The cardiac blood output decreases due to a cardiac contractility deficit and intravascular fluid redistribution occurs due to intravascular fluid leakage, linked to peripheral vessels’ vasodilation and increased vascular permeability. In some severe cases, acute pulmonary edema can be present.

6 Diagnosis

A good knowledge of Kounis syndrome along with increased clinical suspicion represented the cornerstone of its diagnosis, but however is still under-reported. An in-depth patient clinical history is mandatory for the diagnosis regarding the clinical manifestations, the suspected trigger, any previous past response, as well as the time interval between exposure and clinical signs and symptoms. Most commonly, the time span between the exposure to the trigger and the initiation of the clinical manifestations is under one hour (80%), but Kounis syndrome can also occur later as post 6 hours (9.2%). A thorough personal health and atopy history accompanied with meticulous examination are critical to assess the diagnosis of Kounis syndrome in those patients in which it is suspected. Hyperlipidemia, diabetes, smoking and hypertension were frequently identified among patients in which it is suspected. Hyperlipidemia, diabetes, smoking and hypertension were frequently identified among the patients who developed Kounis syndrome. They also had a history of previous allergic reactions (25.1%), and most commonly against a specific trigger is reported.

In addition, other diagnostic laboratory or imaging techniques, as ECG, chest X-ray, echocardiography and angiography are critical to confirm the diagnosis, in the presence of myocardial ischemia or infarction. Recent evidence supports new imaging techniques, such as dynamic contrast-enhanced cardiac magnetic resonance imaging (CE-CMRI), and myocardial single-photon emission computer tomography (SPECT) for diagnosis establishment.

Takotsubo or stress-induced cardiomyopathy should be taken into account in the Kounis syndrome differential diagnosis, even if these two clinical conditions can also co-exist. Hypersensitivity myocarditis represents another pathology to consider as a differential diagnosis of this syndrome.

6.1 Electrocardiography

Kounis syndrome is associated with various ischemia-related electrocardiographic alterations from ST segment changes such as depression or elevation, T wave changes such as flattening or inversion, to several arrhythmias such as heart block of any degree, atrial fibrillation, sinus bradycardia or tachycardia, ventricular ectopic beats or ventricular fibrillation. QRS complex or QT segment prolongation can be present as well. However, ST elevation represents the most common electrocardiographic alteration (76.0%), especially in the inferior leads (66.9% among the total ST elevation). Any type of electrocardiographic alterations resembling digitalis intoxication could be attributed to Kounis syndrome.

6.2 Echocardiography/Angiography

Echocardiography can be useful to evaluate heart contractility, indicating possible regional wall motion abnormalities corresponding to the specific coronary artery territory as well as any cardiac chamber dilatation. Angiography plays a crucial role to coronary, spasm, atherosclerotic stenosis or thrombosis evaluation and further interventional treatment.

6.3 Other imaging techniques

In severe cases, chest X-ray can show cardiomegaly. Dynamic CE-CMRI has been proven valuable in detecting cardiac involvement in Kounis syndrome type 1, highlighting lesions with a gadolinium defect at subendocardial level in early contrast phase and an intense signal in T2-weighted scans, with a regular wash-out in the delayed contrast phase. Myocardial SPECT, thallium-201 (TI) and 123I-15-(p-iodo-phenyl)-3-(R,S)-methylpentadecanoic acid (BMIPP) SPECT have significantly contributed to type 1 Kounis syndrome diagnosis demonstrating further myocardial ischemia, in case of a negative angiography result.

6.4 Laboratory tests

Kounis syndrome has been associated with positive myocardial damage markers such as cardiac enzymes e.g., creatine kinase-muscle/brain or troponin I, T and anaphylaxis markers such as tryptase. In Kounis syndrome type 1, myocardial damage markers can be negative in the case of coronary artery spasm due to endothelial dysfunction without a subsequent myocardial damage. Positive tryptase levels can be a useful biomarker in case of anaphylaxis but a negative tryptase cannot rule out anaphylaxis and Kounis syndrome.

7 Management

The management of Kounis syndrome is based on the simultaneous treatment of the cardiac and allergic manifestations. This can be particularly difficult as some medications used to resolve the cardiac clinical picture can im-
pair the allergic signs/symptoms and vice versa. Even if specific guidelines are lacking, an optimal clinical management of the Kounis syndrome should rely on a balanced approach, according to the syndrome subtype.\textsuperscript{[1]} After the management of the acute events, a joint cardiological and allergic full work-up is needed to assess the patient’s cardiovascular risk factors, cardiac structural and functional status and to investigate the potential triggers, in order to prevent further Kounis syndrome events.\textsuperscript{[1]}

7.1 Kounis syndrome type 1

In case of Kounis syndrome type 1 (allergic vasospastic angina due to endothelial dysfunction), the allergic reaction should be treated according to the clinical picture severity, with antihistamines and corticosteroids for mild and local reactions. As stated by current guidelines, among all the drugs indicated, intramuscular adrenaline represents the key treatment in case of anaphylaxis, a life-threatening systemic allergic reaction.\textsuperscript{[33]} The use of fluids is particularly important in case of anaphylaxis and even more in case of distributive cardiovascular shock. Current clinical practice guidelines regarding the anaphylaxis’ treatment suggest intravenous antihistamines’ administration with a slow infusion\textsuperscript{[33]} to avoid hypotension,\textsuperscript{[40]} and further coronary hypoperfusion. Interestingly, famotidine, an H2 histamine receptor blocker used for the treatment of Kounis syndrome, is associated with reduced risk of intubation or death in hospitalized patients suffering from COVID-19.\textsuperscript{[41]} Further research for a common patho-physiologic pathway between these 2 conditions is warranted. Corticosteroids demonstrate good impact on arterial inflammation and hyper-reactivity, preventing a biphasic anaphylactic reaction at the same time.\textsuperscript{[33,42]} During Kounis syndrome management, the use of adrenaline can lead to an increase of coronary vasospasm, worsening of the ischemia, QTc interval prolongation and arrhythmias induction. These consequences should be kept in mind facing this clinical condition, in order to perform an optimal approach based on the severity of both the allergic reaction and cardiac manifestations.\textsuperscript{[39]} The cardiac involvement manifesting as vasospasm can be approached with vasodilators such as nitrates or calcium channel blockers.\textsuperscript{[10]} However, their use has to be well balanced with the allergic reactions as they can lead to hypotension and anaphylaxis’ clinical manifestations worsening.

7.2 Kounis syndrome type 2

In the Kounis syndrome type 2 (allergic myocardial infarction), an acute coronary syndrome protocol should be followed based on the current guidelines.\textsuperscript{[43]} The allergic reaction can be treated as in type 1 syndrome, focusing on the treatments’ cardiac effects, that can be potentially dangerous. If the patient takes β-blockers chronically for cardiac conditions, the treatment of a potential acute anaphylaxis with adrenaline, an α-adrenergic agonist, might not be effective and glucagon may represent a valuable alternative.\textsuperscript{[44]} Moreover, the utilization of β-blockers for the treatment of the cardiac Kounis syndrome manifestations can lead to an increase of coronary vasospasm and ischemia progression due to a not counterbalanced α-adrenergic action.\textsuperscript{[39]} Opiates such as morphine represent key-players in the management of acute coronary syndrome pain, but they have to be used cautiously in patients with Kounis syndrome as they have been associated with mastocytes activation,\textsuperscript{[45]} and further potential deterioration of the allergic reaction.\textsuperscript{[1]}

7.3 Kounis syndrome type 3

In the Kounis syndrome type 3 (allergic stent thrombosis with occluding thrombus or stent restenosis), an acute coronary syndrome protocol should be followed and subsequent angiography with thrombus aspiration or a new stent deployment should be carried out.\textsuperscript{[1]} The allergic reaction should be treated as previously highlighted, with even more care on the treatments’ cardiac counter-effects, that can worsen the clinical condition.

8 Conclusions

In conclusion, Kounis syndrome is a clinical entity penetrating from pediatrics to geriatrics.\textsuperscript{[46–53]} Its management requires rapid diagnosis, appropriate decision-making and adequate treatment. A balanced approach needed for optimal management of allergic reaction and cardiac involvement seems not easy to reach. This could be attributed to limited published experiences on this topic (isolated case series), along with the lack of randomized clinical trials concerning appropriate management of Kounis syndrome. Thus, more research data are needed for the establishment of an evidence-based standard management approach. Moreover, for Kounis syndrome, it seems of critical importance to deepen the research on underlying physiopathological mechanisms as well as the proposal of novel specific diagnostic tests. Data regarding allergological work-up in patients with this syndrome are scarce and they should be expanded in the future. Moreover, in order to optimize the management of patients with Kounis syndrome as well as to push forward the research process in the area, it seems of critical importance to foster the collaboration between cardiologists and allergists.
Conflict of interests

The authors declare that they have no conflict of interests to disclose in relation to this paper.

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