

Allergic Acute Coronary Syndrome: A Case Report and Literature Review

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Abstract

Introduction: Kounis Syndrome was first described in 1991 by Kounis and Zavras as “the concurrence of chest pain during an allergic reaction, accompanied by clinical laboratory findings of classical angina pectoris caused by inflammatory mediators released during the allergic insult” [1].

The mechanism of Kounis Syndrome most likely involves the release of cytokines through mast-cell degranulation, which leads to coronary vasospasm and atheromatous plaque erosion or rupture following the allergic reaction to an allergen.[2]

The treatment is specific to acute coronary syndrome and anaphylaxis, with the added complication that the drugs used, while indicated in each of the two disorders separately, may present contradictions when administered jointly in one patient.[3]

The purpose of this review is to briefly revise the existing literature regarding its overlooked diagnosis and contradictory joint management of anaphylaxis and acute coronary syndrome.

We will conduct a brief review of the current literature on Kounis Syndrome while describing a suspected case of a female patient presented with both anaphylaxis symptoms and angina pectoris.

Conclusions: Kounis syndrome is defined as the co-incidental occurrence of an acute coronary syndrome with hypersensitivity reactions following an allergic reaction. Treatment of allergic reactions may be sufficient in type I KS. In contrast, coronary intervention is needed in the other two types, accompanied by vasodilator drugs, including nitrates and calcium antagonists, each of which may have contradictory effects.

Keywords: Kounis Syndrome, allergic angina, hypersensitivity reaction

Background

Anaphylactic shock is a severe allergic reaction as a response to an allergen, such as a particular food, drug, or insect bite, which can often be a life-threatening emergency. It can rarely

manifest with a vasospastic acute coronary syndrome, with or without the presence of an underlying coronary artery disease, the variability of which produces a broad clinical spectrum of this syndrome. [1] Acute coronary syndrome accompanying hypersensitivity, allergic or anaphylactic reactions, also called *Kounis Syndrome*, was first described in 1991 by *Kounis and Zavras* as “the concurrence of chest pain during an allergic reaction, accompanied by clinical laboratory findings of classical angina pectoris caused by inflammatory mediators released during the allergic insult” [2]. The mechanism of Kounis Syndrome is yet to be fully understood. However, it likely involves the release of cytokines through mast-cell degranulation, which leads to coronary vasospasm and atheromatous plaque erosion or rupture. [3] Kounis Syndrome has been related to

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multiple triggering factors, including a variety of health conditions, drugs, and environmental exposures. [4] A specific management guide for KS is yet to be established; the treatment is specific to acute coronary syndrome and anaphylaxis, with the added complication that the drugs used, while indicated in each of the two disorders separately, may present contradictions when administered jointly in one patient. [5]

Objective:

The purpose of this review is to briefly revise the existing literature on Kounis Syndrome, given the fact that its cases are recognized to be “not rare but underdiagnosed,” life-threatening and often overlooked by physicians and that the management of anaphylaxis and acute coronary syndrome, each on their own, sometimes contradict each other.

Methods:

We will conduct a brief review of the current literature on the etiology, epidemiology, pathophysiology, clinical appearance, and variance and discuss some of the controversies regarding the treatment of Kounis syndrome while describing a suspected case of a female patient presented with both anaphylaxis symptoms and angina pectoris.

Case Presentation

A 58-year-old female with previously diagnosed arterial hypertension presented with angina pectoris, severe pruritus of palms and feet, pruritic facial skin rash, labial, glossal, and periorbital angioedema, dyspnea, dysphonia, nausea, headache, vertigo, sweating, weakness and fatigue about an hour into her night sleep. The patient has previously undergone diagnostic testing for allergies, and her skin test has resulted in a positive for wheat allergen. She reports experiencing occasional dyspneic episodes, for which she has been medically recommended to use bronchodilator inhalators.

Her vital signs were a temperature of 36.6°C, respiration rate of 20 breaths/minute, pulse of 78 beats/minute, and SaO₂ of 97%. Examination disclosed facial angioedema, pruritic rash, shortness of breath, and scattered wheezing. The patient was treated with Dexamethasone 4 mg and Prednisolone 25 mg intravenously in the Emergency Department.

Her Complete Blood Count presented low levels of RBC (3.96 x 10⁶/uL), Hgb (10.9 g/dl), HCT (33.2%), and high levels of RDW (14.5 %).

Her basic chemistry panel presented high glycemic level (135 mg/dl), low creatinine level (0.49 mg/dl), high ALT/SPGT level (129 u/L), high AST/SGOT level (141 U/L), remarkably high level of NTproBNP (214,9 pg/mL),

CK (5776 U/L), CK-MB (70,5 ng/ml), troponin-I (0.024 ng/mL) Cl⁻ (110 mmol/L) and low levels of Calcium (8.3 mg/dL) and Potassium (3.3 mmol. L). The cardiac enzymes test was repeated two days later and demonstrated lower levels, yet still high, of CK (753 U/L), CK-MB (9,1 ng/mL), NTproBNP (214,9 pg/mL), and normal levels of troponin I (0,01 ng/mL).

The electrocardiogram featured normal sinus rhythm at a rate of 70/min. The patient was soon hospitalized in the Allergology Department, where she received her daily IV therapy with systemic corticosteroids and antihistamines.

Discussion

Kounis syndrome is defined as an acute coronary syndrome caused by an allergic reaction to a particular drug, food, or other precipitating factors. [6] Most cases of KS have been reported in Southern Europe (Greece et al.); they have been observed in a wide age range from 2 to 90, with the most vulnerable group being 40 to 70 years old (68%).[7]

Kounis Syndrome is often associated with comorbidities, such as arterial hypertension, hyperlipidemia, diabetes mellitus, smoking, and previous allergic reactions to a known or unknown allergen. Acute coronary syndrome secondary to allergic reaction is associated with cardiac arrest in 6.3% of the cases and even with death in 2.9% of widespread myocardial infarction or severe anaphylactic shock manifestation. [8]

Any factor that causes IgE antibody production can contribute to this syndrome, with the most common cause being druged, such as Allopurinol, Enalapril, Losartan, aspirin and dipyron, anesthetics, multiple antibiotics, anticoagulants such as heparin and Lepirudin, thrombolytics, anti-platelet therapy including Clopidogrel, glucocorticoids, NSAIDs, PPIs, antifungals, antivirals and oral contraceptives. [9] Other triggers include health conditions, such as bronchial asthma, Churg–Strauss syndrome, serum sickness, scombroid syndrome, angioedema, urticaria, and environmental exposure to insect bites, poison ivy, grass, latex, and nicotine.

The allergen induces mast cell degranulation, resulting in the local and systemic release of inflammatory substances such as histamine and leukotrienes (potent coronary vasoconstrictors) and proteases (tryptase, chymase), which induce collagen degradation and erosion of the other plaques, contributing to the coronary event. [10] The interaction of histamine receptors causes an increase in pulse pressure and a decrease in diastolic blood pressure by inducing coronary vasoconstriction (H₁) and reducing coronary relaxation (H₂). The H₃ receptors inhibit noradrenaline release, while the H₄ receptors regulate the chemotaxis of mast cells, eosinophils, and lymphocytes, which causes a change in eosinophil shape and favors molecular adhesion. Likewise, histamine can activate platelets, enhance the aggregation response of other agonists such as adrenalin or thrombin [11], and reduce tissue factor expression and activity— making this

enzyme a key factor in the coagulation cascade, favoring the final formation of thrombin.

The diagnosis of Kounis Syndrome is mainly based on clinical signs and symptoms of an acute allergic reaction, such as low blood pressure after exposure to the allergen, skin manifestations, including pruritic or non-pruritic rash, hay fever, angioedema, respiratory signs (shortness of breath, dysphonia, wheezing) and gastrointestinal alterations (abdominal pain, nausea, vomiting, diarrhea) and the concurrence of unstable chest pain, due to coronary vasospasm and myocardial ischemic event, accompanied by electrocardiographic changes and cardiac enzyme elevations (Table 1). The most frequent finding in ECG is ST-segment elevation in the four anterior and inferior leads. Although the tracing may sometimes be normal or show only nonspecific findings, as it happened to appear in our case, further studies are needed to explain the incoherent relation between a normal ECG and remarkably elevated cardiac enzymes and to define diagnostic criteria of Kounis Syndrome well.

Symptoms	Signs	Electrocardiogram
Angina	Hypotension	Negative or flat T-wave
Dyspnea	Bradycardia	ST-segment elevation/de-scent
Urticaria	Tachycardia	Wide QRS
Pruritus	Palpitations	Prolongation of the QT interval
Nausea	Diaphoresis	Sinus node tachycardia
Vomiting	Paleness	Sinus node bradycardia
Dysphagia	Cardiorespiratory arrest	Nodal rhythm
Syncope		Atrial fibrillation
Malaise		Extrasystoles
Fatigue		Bigeminism

Treatment of KS consists primarily of managing the allergic or anaphylactic reaction with adrenaline, corticosteroids, and antihistamines, followed by stabilization of the coronary vasculature with known medical/interventional techniques, according to each of the three KS variants. [12] Type I of Kounis Syndrome is defined as chest pain during an acute allergic reaction in patients without risk factors or coronary disease in which the allergic event induces coronary vasospasm secondary to ischemia. This type responds well to corticosteroids, antihistamines, and coronary vasodilators, such as nitrates and calcium channel blockers, if needed. Type II includes patients with preexisting atheromatous disease, symptomatic or not, in whom acute allergic reactions may induce plaque erosion or rupture, peaking in acute myocardial infarction. Type-III variant of Kounis syndrome includes patients with preexisting coronary disease and drug-eluting coronary stent thrombosis. Type II and III often require coronary interventions to manage acute plaque rupture and thrombus formation. [13]

Adrenalin is the treatment of choice in anaphylaxis, as it can prevent and revert bronchospasm and cardiovascular collapse. The recommended administration route is intramuscular at a dose of 0,3-0,5 ml of adrenalin 1:1000 in adults, which can be repeated after 20 minutes if needed. However, on the other hand, it can worsen the ischemia, prolong the QT interval, and induce coronary vasospasms and arrhythmias.

Likewise, drugs like nitrates increase myocardial oxygen release and dilate the coronary and peripheral vessels, reducing angina pectoris, but they can also cause hypotension and tachycardia, and even though it seems reasonable and safe to use them in non-hypotensive patients, they could complicate an anaphylactic reaction.

Acetylsalicylic acid is indicated in all patients with acute coronary syndrome as soon as possible. However, it is widely known for causing allergic and even anaphylactic reactions. As a result, its usefulness in KS is unclear, for it could quickly worsen anaphylaxis.

During anaphylaxis, more than 2/3 of the intravascular volume is displaced into the interstitial space, resulting in hypovolemia and hemoconcentration, making fluid replacement particularly important. However, patients with Kounis Syndrome can develop left ventricle dysfunction, and volume expansion may sometimes lead to acute pulmonary edema and even respiratory failure. Therefore, hemodynamic monitoring and echocardiographic assessment of cardiac function are of significant importance.

Regarding our patient, given the typical signs and symptoms of an allergic reaction, the presence of angina pectoris, and the specific elevation of cardiac enzymes (cardiac troponin-I, creatinine kinase/CK, CK-MB, NTproBNP), we suspected the occurrence of Kounis Syndrome type 1, with the primary mechanism being the coronary vasospasm, without underlying coronary disease, but with significant clinical and laboratory changes insinuating cardiac ischemia.

Conclusions:

Kounis syndrome is defined as the co-incidental occurrence of an acute coronary syndrome with hypersensitivity reactions following an allergic reaction. The three reported types of KS are caused by mast cell activation and the release of inflammatory mediators, leading to coronary vasospasms and plaque erosion or rupture. Treatment of allergic reactions may be sufficient in type I KS. In contrast, coronary intervention is needed in the other two types, accompanied by vasodilator drugs, including nitrates and calcium antagonists, each of which may have contradictory effects. Therefore, given that the risks may outweigh the benefits in these patients, further studies and evaluations of the risk-benefit ratio are needed before recommending these drugs. Kounis Syndrome is underdiagnosed and missed by emergency physicians, who tend to focus abundantly on anaphylaxis and sometimes overlook the possible

occurrence of myocardial dysfunction. Further reviews are needed to educate physicians on Kounis Syndrome's nosology, encourage them always to suspect its occurrence while dealing with a case of anaphylaxis, and investigate it mainly by its clinical appearance, ECG, and cardiac enzyme levels.

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