



Kounis Syndrome

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Abstract

Purpose of Review Severe allergic reactions, such as anaphylaxis, may trigger acute coronary events. This is known as the Kounis syndrome (KS). The aim of the article is to give an overview of the current knowledge on this syndrome.

Recent Findings An increasing number of cases of KS are reported in the literature. The involvement of cardiac mast cells seems to be critical in its development, through the release of mediators which may trigger acute events such as coronary vasoconstriction, arteriosclerotic plaque rupture, and coronary stent thrombosis.

Summary KS is a potentially severe condition resulting from the concurrent occurrence of a systemic allergic reaction and acute coronary events. Standardized epidemiological research is needed to determine the prevalence and risk factors of KS. Studies to further define the mechanisms underlying its development and to assess management issues are warranted.

Introduction

The cardiovascular system is one of the main organs which may be involved in systemic allergic reactions (anaphylaxis), rendering clinical manifestations such as hypotension, arrhythmias, or myocardial ischemia (1). But it was not until 1991 when the term “Kounis syndrome” (KS) was coined to describe the occurrence of

angina or myocardial infarction during acute allergic reactions due to coronary arterial spasm induced by mediators released during the allergic reaction (2). Currently, it is defined as “the concurrence of acute coronary syndromes including coronary spasm, acute myocardial infarction, and stent thrombosis, with conditions

associated with mast-cell and platelet activation and involving interrelated and interacting inflammatory cells, such as macrophages and T-lymphocytes, in the setting of allergic or hypersensitivity and anaphylactic or anaphylactoid insults" (3●●). The number of cases reported in PubMed has increased, especially in the last decade (Fig. 1).

Three variants of KS have been described. Type I is the most frequent and is characterized by coronary artery spasm (with or without myocardial enzyme elevation). Type II involves atherosclerotic plaque erosion or rupture producing an acute myocardial infarction. Finally, type III results in coronary artery stent thrombosis (3●●).

The use of epinephrine (adrenaline), used as a treatment of the anaphylactic reaction, may be a confounding factor in the development of this syndrome, since adrenergic drugs may intrinsically trigger cardiac adverse effects (4, 5). Also, in recent years, the recognition of cases of takotsubo syndrome (a form of acute and usually reversible heart failure syndrome, with transient regional systolic and diastolic dysfunction of the left ventricle), in the context of anaphylaxis and/or epinephrine use, has given rise to the description of a new disease complex termed ATAK (adrenaline, takotsubo, anaphylaxis, and Kounis syndrome) (6).

Epidemiology

Involvement of the cardiovascular system in anaphylaxis occurs in up to two thirds of cases (7). But the incidence of KS during acute allergic reactions has not been precisely established. In a prospective study performed at an emergency department, 27 out of 793 patients consulting for allergic reactions were diagnosed of KS, rendering an incidence of 3.4% (8). In another retrospective study reviewing 300 cases of anaphylaxis, myocardial injury detected by troponin elevation was diagnosed in 22 cases (7.3%) (9).

KS has been described to affect patients of both genders, all ages, races, and geographical areas. Two recent reviews of case reports searched through

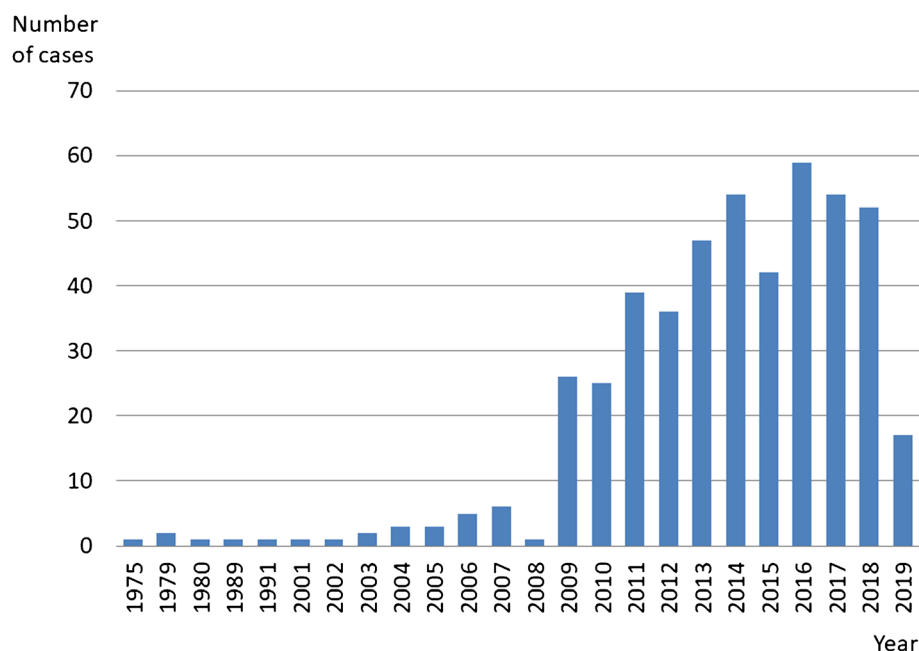


Fig. 1. Cases of Kounis syndrome reported in PubMed

Medline (10•) or through the WHO database for pharmacovigilance (11•) revealed a clear predominance in males and a peak incidence in patients over 50 years. Regarding triggering agents, drugs (27.4%) and insect venoms (23.4%) were the leading causes, although others, such as foods or latex, have also been described (10•). Because most publications correspond to case reports or small case series, there may be a bias to publish “rare cases.” An interesting analysis of the FDA Adverse Event Reporting System (2004–June 2016) showed 499 reports of KS caused by drugs, out of which, almost half were attributable to a single drug, where ibuprofen and amoxicillin (with/without clavulanate) were the most common, probably due to the frequent use of these drugs (12), which is in line with the results of the WHO database (11•).

Pathophysiology of Kounis Syndrome

KS can be classified into three different subtypes according to the previous risk factors for coronary artery disease of the patient and the myocardial damage as a result from mast cell/basophil degranulation during anaphylaxis. Mast cell/basophil mediators released in the reaction may induce myocardial injury both by direct and indirect myocardial effect leading to coronary vasospasm, atheromatous plaque rupture, or stent thrombosis that are the three outcomes defining the three subtypes of KS (Fig. 2) (3••, 13).

Rapidly after the initiation of an anaphylactic reaction, multiple mediators are released in tissues and circulation. Such mediators include histamine, mast cell proteases (tryptase, chymase), thrombin, arachidonic acid products

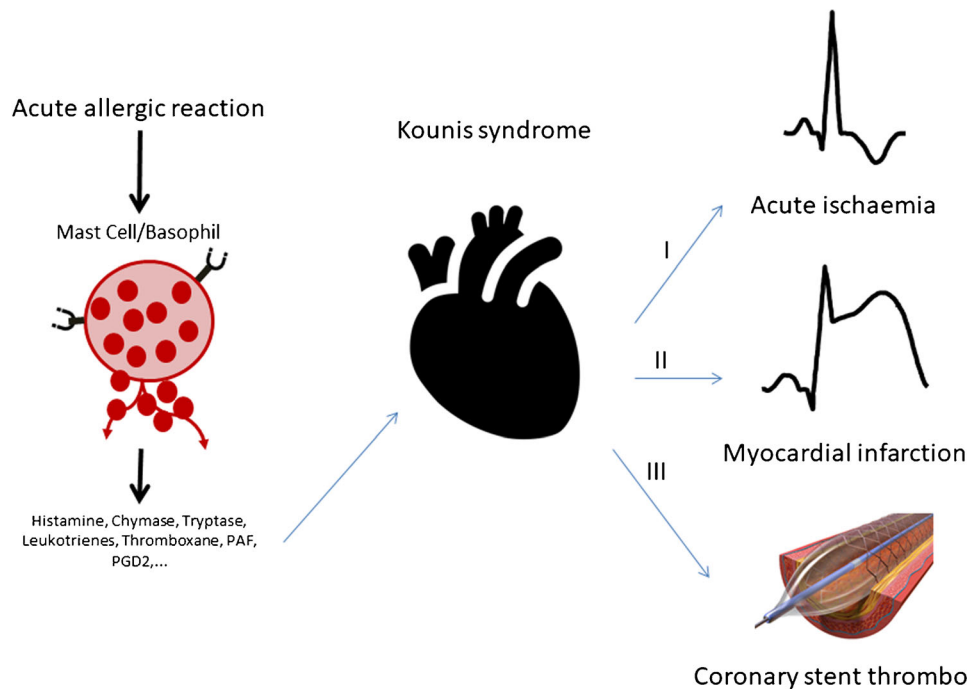


Fig. 2. Mechanisms underlying Kounis syndrome. *Coronary stent image by BruceBlaus—own work, CC BY-SA 4.0, <https://commons.wikimedia.org/w/index.php?curid=47113850>*

(prostaglandins and leukotrienes), platelet activation factor (PAF), and a variety of cytokines and chemokines (14) (Table 1). In the heart tissue, mast cells are abundant, accumulating at sites of coronary plaques. This fact is thought to be a crucial factor contributing to the development of coronary artery thrombosis events, typical of KS. The presence of mast cells in cardiac tissue is also thought to be critical in cases of anaphylaxis triggering coronary vasoconstriction, dysfunctional ventricular contractility, and blockade of atrioventricular conduction (3••, 10•).

Myocardial injury secondary to therapeutic doses of adrenaline used to treat anaphylaxis is a rare occurrence, and only a few cases have been reported in the literature. The mechanism underlying myocardial injury in these cases is considered to be to coronary vasospasm secondary to direct $\alpha 1$ and $\alpha 2$ adrenergic receptor activation by epinephrine, even with healthy coronaries (normal angiograms). Such reactions are much more frequent when epinephrine has been administered intravenously or when overdosed and very rarely when epinephrine has been injected intramuscularly. It is frequently associated with potential predisposing factors for epinephrine-induced vasospasm, such as beta blocker drug intake. However, the use of adrenaline in the setting of life-threatening anaphylaxis is life-saving, and the benefits far outweigh the risks of adverse effects (17).

Specific underlying mechanisms differ according to type of KS (11•). Type I KS is the most frequent (70–75%) and occurs due to coronary artery spasm with or without increase of cardiac enzymes and troponins. It affects patients without coronary artery disease and without risk factors for this disease. Type II KS (20–25%) occurs due to coronary artery spasm together with plaque erosion or rupture manifesting as acute myocardial infarction and requires that the patient presents

Table 1. Potential effects of mast cell/basophil mediators in Kounis syndrome

Mediator	Effect	Mechanism
Histamine	Coronary vasoconstriction, decreases diastolic blood pressure, increases intimal thickening, platelet activation	H1 receptor
Chymase	Vasoconstriction, plaque erosion, and rupture	Converts angiotensin I to angiotensin II
Cathepsin D	Vasoconstriction	
Tryptase	Promotes plaque disruption or rupture as well as induction of pericellular matrix degradation, destabilization, and maturation of thrombi	Activates the zymogen forms of metalloproteinases such as interstitial collagenase, gelatinase, and stromelysin, degradation of fibrinogen
Heparin	Plaque erosion and rupture, destabilization, and maturation of thrombi	Anticoagulation
Leukotrienes	Vasoconstriction	
Thromboxane	Platelet aggregation and vasoconstriction	
PAF	Arrhythmias, ST segment changes, and vasoconstriction	
PGD2	Vasoconstriction	

Adapted from (10, 15•, 16)

PAF platelet-activating factor, PGD2 prostaglandin D2

previous risk factors for coronary artery disease or stabilized coronary artery disease. Type III KS is the less frequent type (< 5%) and occurs by coronary artery stent thrombosis as a result of an allergic reaction. Obviously, it requires a previous coronary artery disease treated with a coronary stent implant. It occurs more often with drug-eluting stents, but it has also been reported with bare metal stents.

Diagnosis

The diagnosis of KS is based on clinical symptoms and on laboratory, electrocardiographic, echocardiographic, and/or angiographic evidence. KS is frequently underdiagnosed. Thus, clinical suspicion is crucial in patients with systemic acute allergic reactions. Patients presenting with anaphylaxis should be asked about acute chest pain and chest discomfort and should be accurately evaluated to rule out KS (10•, 18). Moreover, patients with preexisting atherosclerotic disease, either quiescent or symptomatic or with preexisting coronary disease and drug-eluting coronary stent presenting with an acute hypersensitivity event, should be carefully evaluated to exclude a KS. Evaluation for other causes of coronary syndromes, such as thrombophilic conditions, increased lipoprotein A, deficiency of protein C, protein S or antithrombin III, and dysfibrinogenemia, especially in younger patient, is advisable.

Laboratory workup should include tryptase level measurement and cardiac enzymes (19). Tryptase increases during the acute reaction will suggest an anaphylactic reaction. Elevated tryptase may be present in circulation for several hours and can be measured postmortem. Nevertheless, tryptase is not helpful to diagnose an anaphylaxis in situ, and it is known that it may not increase in up to one third of patients presenting in the ED with anaphylaxis (20). Histamine release from mast cells is rapid and short-lived. It circulates only for a few minutes; therefore, blood sample should be collected promptly after the onset of the allergic reaction and the chest pain. Thus, it is not a feasible marker for point-of-care diagnosis of KS.

Measuring cardiac enzymes (CK, CK-MB, and troponins) is mandatory when a KS

Table 2. Treatment strategy in Kounis syndrome

Symptoms	Therapeutic measures
Acute hypersensitivity reaction (anaphylaxis)	Remove allergic trigger Intramuscular adrenaline = 0.3–0.5 mg (repeat at 5–15 min if needed) Glucagon (beta blockers) = 1–2 mg intravenously in 5-min bolus Oxygen therapy Intravenous fluid (titrated according to ejection fraction) Glucocorticoids Antihistamines
Acute coronary syndrome	Nitroglycerin (sublingual or infusion) = 0.3–0.4 mg at 5-min intervals. IV: initiated at 5–10 mcg/min, increasing every 5 min of 10 mcg/min until improvement of symptoms or appearance of side effects Alternative: calcium channel blockers: in type I KS Avoid beta blockers Avoid opioids Type II KS: coronary event protocol Type III KS: coronary event protocol and urgent aspiration of intrastent thrombus

Adapted from (22••, 23)

is suspected. The systematic measurement of cardiac enzymes had been suggested in patients with anaphylaxis. Cardiac troponin was elevated in 7.3% of patients attending the Emergency Department in a single-center study, while electrocardiogram (ECG) and echocardiography alterations were detected in 4% and 2.3%, respectively (9). ST elevations in anterior and inferior leads have been the most reported findings in ECG in patients suffering KS. However, ECG may be normal or may show nonspecific ST-T wave changes (21).

Echocardiography and coronary angiography are useful to diagnose cardiac wall abnormalities and for delineating the coronary anatomy in cases of KS (3●●). Newer techniques such as SPECT (single-photon emission computer tomography) and 125I-15-3 BMIPP SPECT have been used in type I KS and revealed severe ischemia while coronary angiography showed normal coronary arteries. Dynamic cardiac magnetic resonance imaging (MRI) has also been suggested to assess cardiac involvement in KS (3●●).

Treatment

As KS is a complex acute coronary situation which requires rapid treatment decisions regarding myocardium injury and the concomitant allergic reaction, therefore, management should address both.

Treatment recommendations for KS are based on individual case reports or case series. Recently, a therapeutic algorithm has been proposed (22●●). Treatment of the allergic reaction should follow the anaphylaxis guideline recommendations (Table 2). Adrenaline can aggravate myocardial ischemia, prolong the QTc interval, and induce coronary vasospasm and arrhythmias that could further impair the heart function. If necessary, administer an intramuscular dose of 0.3–0.5 mg every 5–15 min (23, 24) until the resolution/improvement of anaphylaxis symptoms or the appearance of adrenaline side effects. While the use of fluids is crucial to treat the distributive shock in the context of an anaphylaxis, in the case of a KS or even when it is suspected, this intervention should be done cautiously (22●●). Ideally, fluid load needs to be titrated on the ejection fraction to avoid pulmonary edema.

Treatment of the allergic reaction can be sufficient in case of type I variant, while concomitant treatment of acute coronary syndrome is mandatory in type II variant (13). In type I KS, patients should be monitored and be checked for biphasic anaphylactic reactions. In patients with a type II KS, the rupture of a coronary plaque induced by the inflammatory mediators can occur and can lead to a myocardial infarction. Type II and type III KS will benefit of a dual antiplatelet therapy and percutaneous coronary intervention (22●●). Beta blockers are contraindicated in KS, due to a subsequent coronary spasm caused by unopposed activity of alpha adrenergic receptors (25). Glucagon may be used to treat anaphylaxis in patients under treatment with beta blockers, whereas patients with previous ischemic cardiac disease may benefit, as adrenaline could exacerbate the vasospasm due to the unopposed alpha adrenergic effect. Opioids are not recommended to treat acute chest pain because they can induce massive mast cell degranulation and aggravate the allergic reaction.

Conclusion

KS is a complex situation involving two severe circumstances: an acute allergic reaction and an acute coronary event. The involvement of cardiac mast cells

seems to be critical in its development, through the release of mediators which may trigger acute events such as coronary vasoconstriction, arteriosclerotic plaque rupture, and coronary stent thrombosis. Further studies to assess its prevalence, understand the underlying mechanisms, identify risk factors, and define the most appropriate management of KS are needed.

Compliance with Ethical Standards

Conflict of Interest

Mar Guilarte, Moises Labrador-Horrillo, and Victoria Cardona declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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