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Drug-Induced Kounis Syndrome: Latest Novelties

Paula Ollo-Morales, MD[1,2*,]
Marta Gutierrez-Niso, MD[1]
Elena De-la-Viuda-Camino, MD[1]
Marina Ruiz-de-Galarreta-Beristain, MD[1]
Ixone Osaba-Ruiz-de-Alegria, MD[3]
Carlota Martel-Martin, MD[1]

Address
[*,1]Department of Allergy, Hospital Universitario Araba, Vitoria, Spain
Email: paula.ollomorales@osakidetza.eus
[2]HUA Consultas Externas, Francisco Leandro de Viana Street, 01009 Vitoria, Spain
[3]Department of Cardiology, Hospital Universitario Araba, Vitoria, Spain

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Opinion statement

Kounis syndrome (KS) is defined by an acute coronary syndrome associated with hypersensitivity reactions, an under-diagnosed life-threatening medical emergency. Although multiple causes have been described, drugs constitute the most frequent cause. The purpose of this review is to update knowledge about drug-induced KS, to give guidelines on the correct diagnosis and treatment. This article reviews the literature on drug-induced KS from the last 5 years. Antibiotics and NSAIDs are the most frequently implicated drugs. In addition, data on pathophysiology, clinical presentation, diagnosis, and management are reviewed in detail. Highlight that there is a great deal of variability in the diagnosis and especially in the treatment of KS. This review provides a valuable selection of practical resources for all stakeholders to support effective care for KS, from a cardiologic and allergologic point of view. Future research should focus on developing validated, evidence-based, and patient-centered tools to improve the management of KS.

Introduction

Kounis syndrome (KS), also known as "allergic myocardial infarction," is defined by the appearance of an acute coronary syndrome (ACS) concomitant with hypersensitivity reactions triggered by an allergenic event, in which the allergic mediators can lead to vasospasm of the coronary arteries and subsequent myocardial ischemia [1••]. It usually appears in the context of anaphylaxis, in individuals with or without pre-existing coronary artery disease. The condition can manifest as angina, myocardial infarction, or even sudden death due to a hypersensitivity reaction [2, 3].

The first case of myocardial infarction associated with urticaria was described in 1950 in a patient who presented a reaction to penicillin [4]. Subsequently, in 1991, Kounis and Zavras described the pathophysiology of this condition and proposed it as a new clinical entity called "histamine-induced angina syndrome" [5]. Since it was first described, the syndrome has been increasingly recognized, and numerous cases have been reported in the literature [2]. Three variants of KS have been described, according to coronary involvement: type I, type II, and type III [1••].

Although the prevalence of KS is difficult to estimate, it is believed to be an underdiagnosed condition, and the incidence is increasing. In the USA, an annual prevalence of KS of 1.1% has been estimated after analyzing 253,420 patients who presented an allergic reaction in seven years [6, 7]. Healthcare professionals should be aware of this emerging condition and its potential to cause significant morbidity and mortality [8].

This review aims to update the knowledge about this little-known pathology and provide guidance on its proper diagnosis and specific treatment, focusing on drug allergy as the cause.

Etiology and epidemiology

Multiple causes of KS have been described: food, drugs, and different environmental exposures such as hymenoptera sting [1••]. The involvement of drugs stands out since they constitute the most frequent cause of KS [9]. According to a meta-analysis published by Raschi et al. in 2018, drugs were responsible for KS in 142 publication compared with other causes out of a total of 252 reviewed articles [10]. The most frequently implicated drugs are NSAIDs [11, 12], followed by antibiotics [13], antineoplastic drugs [14], contrast media [15], corticosteroids [16], and proton pump inhibitors [17], among others.

Paradoxically, medications used to treat anaphylaxis have been reported to cause KS, such as corticosteroids [1••, 18], ranitidine [19], and adrenaline itself [20, 21•]. In addition, drugs present in stents that prevent re-endothelialisation (everolimus, zotarolimus, or biolimus) or materials that make up cardiac stents (nickel, chromium, or titanium) have been reported to cause KS as well [1••, 22].

A typical KS patient is a middle-aged man who refers to allergic symptoms and myocardial ischemia after being exposed to an allergic trigger, usually a drug [3]. It occurs more often in males than in females [7]. KS has been reported in patients of every race and all ages (from 2 to 90 years old), but it is more common among the age group between 40 and 70 years [23]. Although this syndrome has been observed in all geographic locations, it has mostly been encountered in southern Europe, especially Turkey, Greece, Italy, and Spain [1••].

For this purpose, the authors searched resources in peer-reviewed journals by MEDLINE Pubmed for publications in English between 2018 and March

2023 using the terms "Kounis syndrome," "drug," and "allergy." Through this method, 68 publications were found but resources were only included if they were attributed to one drug, 23 articles in total (35%) (Table 1). Two publications were discarded because more than one drug was involved. The rest of the publications did not refer to KS or presented a non-pharmacological causative agent. It should be noted that outside of this search, we found more cases of pharmacological cause for KS, but those were not included for not containing the mentioned keywords.

Of the publications reviewed in Table 1, the most frequently implicated drugs were antibiotics (six cases, mainly beta-lactams), followed by NSAIDs (four cases), antineoplastic drugs (three cases), iodinated contrast media (two cases), and other different ones. A case secondary to the SARS-CoV2 ChAdOx1 vaccine (AstraZeneca®) stands out, vaccines with which numerous adverse reactions have been reported after the COVID-19 pandemic [24]. Regarding the sex of the patients, twelve were women (52,2%) and eleven were men (47,8%). The age ranges from 31 to 92 years, with the average age being 59 years. Among all the individuals included, sixteen presented KS type 1 (69.5%), five KS type 2 (21.7%), and two KS type 3 (8.7%), which agrees with the literature described so far. Among the data collected, only two individuals had a history of previous drug allergies (8,7%). Finally, we want to highlight that only four patients (17.4%) underwent a tryptase determination at the acute reaction and eight (34.8%), a posterior allergy study; however, most underwent a determination of troponins and a cardiology study.

Pathophysiology

KS can be classified as an acute coronary syndrome associated with an allergic reaction, usually anaphylaxis, in which various cells participate, including mast cells (MCs) and basophils. MCs are generally considered the most important cells responsible for the allergic reaction. They are located in the bone marrow, as well as in the skin, respiratory, genitourinary, gastrointestinal, and the cardiac system; in the proximity of blood and lymphatic vessels; and around peripheral nerves. It should be noted that the density of MCs at the cardiac system is increased in patients with coronary disease [15]. The anatomical location of MCs on the skin and mucosal surfaces places them in an ideal position for their involvement in allergic reactions, as they have the initial contact with antigens [25].

The classical mechanism of allergic reactions refers to the activation of MCs by the binding of antigen-specific IgE to the high-affinity IgE receptor found on their surface (FcεRI) [26]. However, other non-IgE-mediated mechanisms have recently been described that produce indistinguishable symptoms from IgE-mediated mechanism (Fig. 1) [26, 27]. The activation of the complement is among these non-IgE mediated mechanisms, being able to produce a reaction with the first exposure to the drug. It has been reported that these reactions can be prevented or reduced with pretreatment (antihistamines, corticosteroids, and NSAIDs) and by decreasing the involved drug infusion rate [26]. An IgG-mediated mechanism has also

Table 1. KS cases secondary to a drug from 2018 to March 2023

REFERENCE, YEAR	DRUG	AGE	SEX	CV RISK FACTORS	DRUG ALLERGY	KOUNIS TYPE	SYMPTOMS	TREATMENT	ECG	TROPONIN	ACUTE TRYPTASE	BASAL TRYPTASE	ALLERGY STUDY
Hangouche AJE, 2018	Aspirin	49	F	No	No	I	Chest pain Dyspnea	Aspirin clopidogrel angioplasty	Yes	elevated	NP	NP	NP
Absmaier M, 2018	Cefuroxime	60	M	Hypertension Tobacco	No	I	Chest pain Dyspnea Dizziness Flushing	prednisolone dimetindene aspirin stent	Yes	Normal	NP	normal	YES
Ozlek B, 2018	Insuline	57	F	Hypertension Dylipidemia Type 2 diabetes Obesirty	No	I	Chest pain Palpitation Urticaria	Aspirin, diphen-hydramine prednisolone	Yes	elevated	Elevated	NP	YES
Kounis NG, 2018	Triamcinolone	52	F	No	No	I	Chest pain	antihistaminic	Yes	elevated	NP	NP	NP
Mendoza Vasquez LE, 2018	Bupivacaine	31	F	No	No	I	Chest pain Dyspnea Dizziness Flushing	salbutamol dexamethasone adrenalin aspirin clopidogrel atorvastatin	Yes	elevated	NP	NP	NP
Dorniak k, 2019	Iopromide (ICM)	59	F	Hypertension Dylipidemia Tobacco	No	I	Chest pain Back pain Syncope	corticosteroids noradrenalin	Yes	elevated	NP	NP	YES
Moloney N, 2019	Amoxicillin—clavulanic	53	M	Not known	Not known	II	Chest pain Palpitation Urticaria Dizziness Nausea	adrenalin hydrocortisone ticagrelor aspirin, heparin fentanyl	Yes	NP	NP	NP	NP
Rajh f, 2019	Diclofenac	69	M	Hypertension Type 2 diabetes Previous ACS	NSAID induced asthma	II/III	Dyspnea	magnesium sul-fate methyl-prednisolone, ipratropio and albuterol	Yes	NP	Normal	NP	NP
Adachi H, 2019	Cefazoline	92	F	No	No	I	Dyspnea Nausea Syncope	atropine nicorandil noradrenalin heparin	Yes	Normal	Elevated	Normal	YES
Leibee C, 2019	Vancomicin	57	M	Hypertension Type 2 diabetes Tobacco	No	II	Chest pain Back pain Cefalea	Diphenhy-dramine Aspirin	Yes	Normal	NP	NP	NP
Shibuya K, 2019	Iopamidol (ICM)	60	M	Previous ACS	No	II	Dyspnea Syncope	adrenalin hydro-cortisone	Yes	elevated	NP	NP	NP

Table 1. (continued)

REFERENCE, YEAR	DRUG	AGE	SEX	CV RISK FACTORS	DRUG ALLERGY	KOUNIS TYPE	SYMPTOMS	TREATMENT	ECG	TROPONIN	ACUTE TRYPTASE	BASAL TRYPTASE	ALLERGY STUDY
Ozlek E, 2019	Gemifloxacin	46	F	No	No	I	Chest pain Palpitation Flushing	ranitidine diphenihydramine urbason adrenaline salbutamol	Yes	Normal	NP	Elevated	NP
Portero-Portaz JJ, 2020	Sonovue® (sulfur hexafluoride)	72	F	Previous ACS (stent)		III	Chest pain Dyspnea Dizziness Exanthema	Hydrocortisone angioplasty	Yes	NP	NP	NP	NP
Foruntzas M, 2020	Blue dye	58	F	Aortic Aneurysm	No	I	Palpitation Dyspnea Dizziness Urticaria	corticosteroids dimetindine norepinephrine clopidogrel aspirin	Yes	elevated	NP	NP	Yes
Narroway HG, 2020	Paclitaxel-coated balloon	79	F	Hypertension Dylipidemia Type 2 diabetes Tobacco	No	I	Palpitation Dyspnea Dizziness Urticaria Exanthema	Heparin Adrenalin antipatelet	Yes	elevated	Elevated	NP	YES
Lameiras C, 2021	Metamizole	62	M	Tobacco	Penicillin allergy	I	Chest pain Palpitation Urticaria	Hydrocortisone Clemastine Morphine clopidogrel aspirin	Yes	elevated	NP	NP	NP
Brili, S, 2021	Rituximab	80	M	Atrial fibrillation	No	I	Chest pain Palpitation Dizziness Dyspnea Flushing	nitrates amiodarone hydrocortisone	Yes	elevated	NP	NP	NP
Shrimanth YS, 2021	Nimesulide	45	F	Hypertension	No	II	Skin rush Flushing Angioedema Dizziness Dyspnea	Hydrocortisone diphenhydramine antiplatelet, statin Heparin, tirofiban, angioplasty	Yes	elevated	NP	NP	NP
Vu VH, 2021	Paracetamol	38	M	No	No	I	Chest pain Dyspnea	Not known	Yes	elevated	NP	NP	NP
Wang B, 2021	Paclitaxel	57	M	Tobacco	No	I	Chest pain Dyspnea Palpitation Flushing	salbutamol adrenalin nitrate hydrocortisone promethazine	Yes	normal	Normal	Normal	NP

Table 1. (continued)

REFERENCE, YEAR	DRUG	AGE	SEX	CV RISK FACTORS	DRUG ALLERGY	KOUNIS TYPE	SYMPTOMS	TREATMENT	ECG	TROPONIN	ACUTE TRYPTASE	BASAL TRYPTASE	ALLERGY STUDY
Herrera-Lasso, 2021	Urapidil	71	M	Atrial fibrillation Obesity	No	I	Dizziness	Vasoactive drugs	Yes	elevated	NP	Normal	YES
Gogos C, 2021	Azitromicine	52	F	Hypertension Aortic dilatation	No	I	Chest pain Dyspnea Eritema Cardiac arrest	adrenalin hydrocortisone, antiplatelet drugs, tinzaparin	Yes	elevated	NP	Normal	NP
Fialho I, 2022	ChAdOx1 (AstraZeneca SARS-CoV2 vaccine)	59	m	Atrial fibrillation Previous ACS Tobacco	No	III	Dizziness Skin rush	thrombus aspiration balloon dilation stent	Yes	elevated	NP	NP	YES

F, female; *M*, male; *ECG*, electrocardiogram; *ICM*, iodinated contrast media; *ACS*, acute coronary syndrome; *NP*, not performed

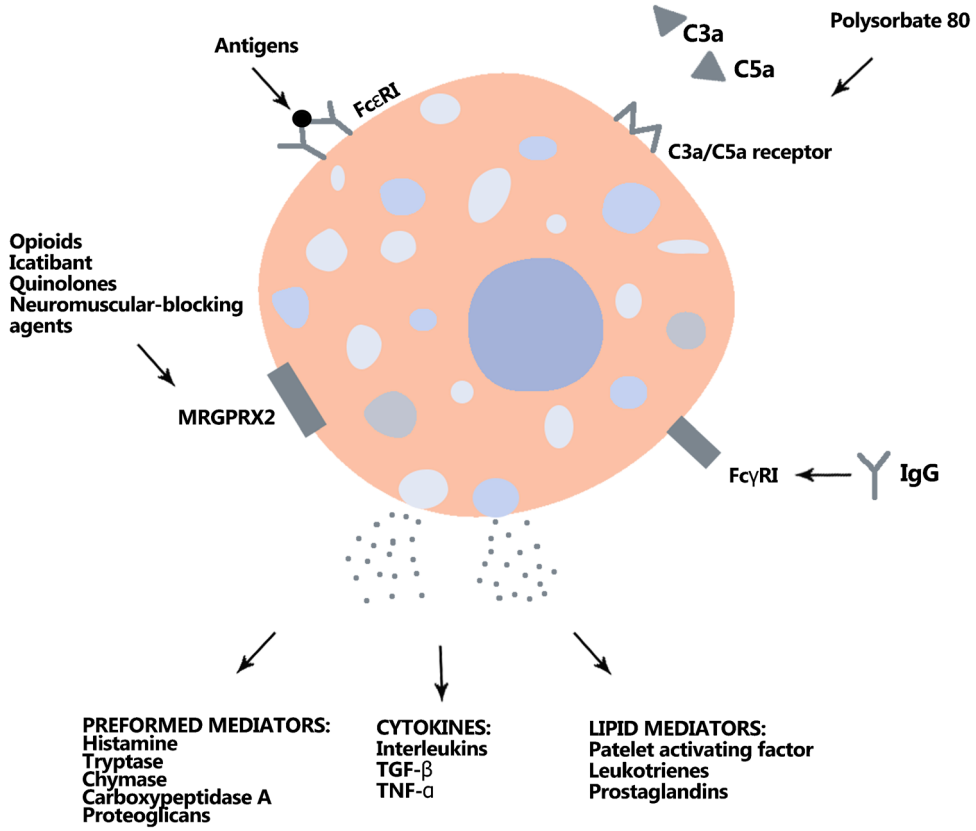

Fig. 1 Mast cell activation mechanisms and released mediators.

been described, which activates MCs and neutrophils through high-affinity receptors (FcγRI) found on their surface [28]. One of the most novel mechanisms is the activation of the MRGPRX2 receptor present in MCs, which is activated by peptide drugs such as opioids, icatibant, quinolones, and neuromuscular-blocking agents [29–31].

Once the MCs and the basophils are activated, multiple signaling cascades are produced precipitating biochemical reactions responsible for the degranulation and release of vasoactive mediators, enzymes, and cytokines contained inside the cells. These mediators are released locally and into the circulatory system, causing bronchoconstriction and increased vascular permeability leading to urticaria, angioedema, and hypotension, among other actions [32]. These mediators are classified as preformed mediators or de novo synthesized lipid mediators (Fig. 1).

In the cardiac system, preformed mediators can produce coronary vasoconstriction directly through histamine binding to coronary H1 and H2 receptors [1••] and by conversion of angiotensin I to II by chymase action [33]. Besides, histamine induces tissue factor expression and platelet activation [1••] and tryptase participates in the coagulation cascade producing both thrombosis and fibrinolysis [34]. Finally, tryptase and chymase can activate metalloproteinases triggering collagen degradation and inducing

erosion or rupture of a pre-existing atheromatous plaque, initiating the coronary event [1••, 35].

Lipid mediators also affect the cardiac system; specifically, leukotrienes can produce vasoconstriction, and their biosynthesis is enhanced in the acute phase of unstable angina [36]. Platelet-activating factor induces vascular permeability, decreases cardiac output, and contracts coronary artery smooth muscle causing circulatory failure [37].

In conclusion, due to all these mechanisms, during anaphylaxis systemic vasodilatation, decreased venous return, increased vascular permeability, and decreased cardiac output occur, contributing to coronary hypoperfusion with consequent vasoconstriction and myocardial damage.

Clinical presentation and classification

The most serious outcome of the entire spectrum of allergic reactions is anaphylaxis [38]. Different definitions of anaphylaxis have been proposed in recent years, one of the latest being that of the WHO in 2019: "Anaphylaxis is a severe, life-threatening systemic hypersensitivity reaction characterized by being rapid in onset with potentially life-threatening airway, breathing, or circulatory problems and is usually, although not always, associated with skin and mucosal changes" [38, 39].

In KS, the main clinical manifestations are characteristic of an acute, subacute, or chronic allergic reaction (usually anaphylaxis) accompanied simultaneously by cardiac symptoms. In 80% of cases, symptoms appear within an hour of exposure to the trigger [1••]. A recently published study concluded that the most common cardiac symptoms and signs were chest pain (60%) and hypotension (75%); on the other hand, dermatological, respiratory, and gastrointestinal symptoms appeared in 70%, 30%, and 20% of the patients, respectively [12].

Three types of KS have been described being important to distinguish them since they will determine different management regimens [2]. All three types have a common initial pathway, where an allergic response induces a mast cell-mediated inflammatory cascade leading to compromise of the coronary circulation. The differences between them lie in the following [40]:

- Type 1: A coronary obstruction occurs secondary to a vasospasm [1••, 40]. It represents the most common mechanism, around 72.6% of all variants [7, 41]. It is more typical in young patients, without cardiovascular risk factors or evidence of previous coronary disease [42]. It occurs due to endothelial dysfunction and/or microvascular angina and is characterized by a coronary spasm that produces electrocardiographic changes secondary to ischemia [1••]. Cardiac enzymes may be normal or reflect progression to an acute myocardial infarction.
- Type 2: Occurs in patients with a pre-existing atherosclerotic disease where the acute release of inflammatory mediators may cause isolated coronary vasospasm or plaque rupture/erosion leading to acute myocardial infarction [1••, 40]. It represents about 22.3% of KS cases [7].
- Type 3: It appears in patients with previous coronary stents (drug-eluting stents or bare metal stents), in which the allergic reaction can induce internal thrombosis by a thrombus rich in eosinophils, causing ischemia

secondary to platelet adhesion, activation, and aggregation triggered by inflammatory mediators [43]. It represents about 5.1% of KS cases [7]. Different clinical trials have shown an annual incidence of 0.2% to 0.5% of stent thrombosis from different causes, leading to a mortality rate of up to 40% [1••, 44]. A new subclassification in type 3 has recently been described [22, 45]: 3a in which a stent thrombosis occurs due to a systemic reaction (the most frequent) and 3b in which restenosis of the stent occurs due to a local reaction, probably to a component of the stent.

Lastly, an atypical clinical case of KS has been described, characterized by presenting an acute coronary event 48 h after the allergic reaction, proposing it as a new subtype of KS [46].

Diagnosis

KS is a more common disease than it seems, but it is infrequently recognized in clinical practice. It requires a high index of suspicion, and it should be considered in patients with an allergic reaction associated with clinical, electrographic, and laboratory findings of heart damage [1••, 47].

The diagnosis of KS due to drug allergy usually begins with the unexpected appearance of the characteristic clinical manifestations of anaphylaxis, leading to a medical emergency. Therefore, in the first place, a syndromic diagnosis must be made in the acute reaction to propose a correct therapeutic approach. Subsequently, once the acute event has been resolved, an outpatient etiological diagnosis must be made through a complete allergy study in order to give adequate recommendations and avoid new episodes.

In the acute reaction, clinical symptoms are unspecific, so when KS is suspected serum tryptase and myocardial damage enzymes such as troponins and creatine-kinase (CK) should be determined [48•], since they will be helpful later to define the event presented. It must be taken into account that the determination of tryptase should not be delayed because its half-life is about 90 min [49]. An electrocardiogram (ECG) should be performed, and if possible or available, an echocardiogram and coronary angiography, as they contribute to the complete initial diagnostic process [48•].

Regarding the ECG in KS, the most common finding is ST segment elevation in anterior and inferior leads, but it may show normal or nonspecific results. The right coronary artery is the most frequently affected by vasospasm, although the reason is unknown [7, 50]. In cases of vasospasm, ST elevation is characterized by being transient (Fig. 2) [51]. Based on the electrocardiogram, two groups of patients can be distinguished:

1 Those with persistent ST-segment elevation (>20 min) and chest pain, reflecting acute total or subtotal coronary occlusion to flow and who will require immediate reperfusion by the percutaneous coronary intervention (primary PCI).
2 Those without persistent elevation, including transient elevation (characteristic of vasospasm), transient or persistent ST-segment depression, T wave inversion, flat T waves, or pseudo-normalization of T waves. In these cases, the reperfusion may be delayed (deferred PCI).

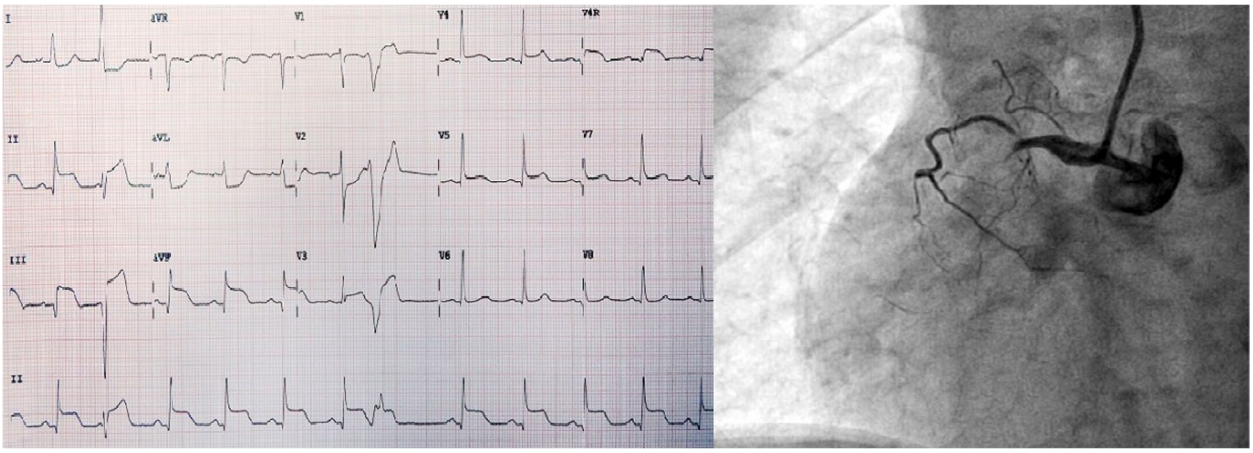

Fig. 2 ECG: right coronary artery vasospasm, inferior ST segment elevation. Angyography: complete occlusion of the proximal right coronary artery.

The echocardiogram, as in the rest of the coronary syndromes, will provide important information about cardiac function and anatomy. A regional movement abnormality corresponding to the territory of a coronary artery suggests obstruction of coronary flow, either due to vasospasm or thrombosis [52].

Once the acute event has been resolved, an outpatient allergy study should be carried out. In drug allergy study, in vitro test such as specific IgE and basophil activating test (BAT) and in vivo test such as skin tests (prick test and intradermal test) and drug provocation test (DPT) can be performed. Referring to the in vivo study in anaphylaxis, precautions should be taken as these can induce systemic reactions, especially DPT. Based on a EAACI position paper, in immediate reactions, patients should be classified as high-risk subjects when anaphylaxis, hypotension, laryngeal edema, bronchospasm, urticaria/angioedema, or generalized erythema occurred [53].

We have found a few articles in which skin tests and DPT have been carried out in patients who have suffered from KS. It has been described that intradermal tests can induce the development of a systemic reaction [54]. In fact, a case of KS has been described after performing an intradermal test with amoxicillin in a patient who suffered anaphylaxis three years earlier [55]. However, there are some studies in which skin tests have been carried out safely in patients who have suffered from KS [15]. On the other hand, in the case of DPT, despite being the gold standard in the study of drug allergy, in KS it is controversial due to the involved risks. No articles were found in which DPT was carried out in the KS study. It seems prudent to focus the topic of DPT on alternative drugs, taking into account the studies of cross-reactivity with respect to beta-lactams and NSAIDS, which are the most implicated drugs in KS [56].

In conclusion, in KS a careful selection of patients and adequate risk management must be carried out by qualified health professionals to guarantee patient safety during the allergy study.

Treatment

Currently, there are no established clinical guidelines for the treatment of KS, and the number of cases is too small to provide definitive recommendations in this regard. Most of the information on the management of this syndrome is derived from individual case reports or published case series.

An initial approximation should assess if allergy symptoms predominate with associated skin or respiratory involvement (for which the use of adrenaline cannot be delayed), or ACS symptoms with persistent chest pain (for which will prioritize the use of calcium antagonists). In addition, the presence or absence of coronary occlusion and the need for revascularization should be assessed based on the type of KS [1••, 57]. A series of indications based on current anaphylaxis and ACS guidelines are attached below:

Management of anaphylaxis

In the treatment of an anaphylactic reaction, success depends on several factors: the preparation of the personnel caring for the patient, early recognition of anaphylaxis, and prompt and aggressive treatment [38]. On many occasions, the diagnosis of anaphylaxis is not obvious, and therefore, the approach to the patient with anaphylaxis must be systematic. The first-line treatment in anaphylaxis is adrenalin or epinephrine, followed by second-line antihistamines [38]. If the patient takes beta-blockers, glucagon should be administered, since beta-blockers can create resistance to adrenaline. Glucagon is indicated because its inotropic and chronotropic action is not mediated by β adrenergic receptors, but by increasing the concentration of cyclic adenosine monophosphate in the myocardium, which can reverse refractory hypotension and bronchospasm associated with anaphylaxis [58, 59]. The most common side effects are nausea and vomiting, so airway protection will be important.

It should be noted that most anaphylactic reactions respond to initial treatment with a single dose of adrenalin; approximately 10% require two doses, and 2% require more than two [60]. Once stabilized, the patient should remain under observation for 6–8 h, because biphasic anaphylaxis can occur [59]. Biphasic anaphylaxis is a recurrent reaction or the appearance of new symptoms after the initial presentation without further exposure to the causative agent [61, 62]. It occurs in 4–4.5% of anaphylactic reactions between 1–72 h from the onset of the first symptoms. Until now, corticosteroids were expected to be useful in preventing biphasic and prolonged anaphylaxis, but a systematic review has found no evidence to recommend glucocorticoid treatment to prevent biphasic reaction [63].

Table 2. Beneficial and detrimental effects of drugs in anaphylaxis and acute coronary syndrome

ANAPHYLAXIS	DRUG	ACS
Improves pruritus, rash, urticaria and angioedema	H1 ANTIHISTAMINES	Hypotension and compromised coronary flow when administered very fast
Improves asthma associated with anaphylaxis	CORTICOSTEROIDS	Slow and impair healing causing thinning of the myocardial wall
		Decrease mortality in acute myocardial infarction
Peripheral vasoconstriction Decreases mucosal edema Positive inotropic and chronotropic effect Increases bronchodilation Decreases the release of mast cell and basophil mediators	ADRENALIN	Aggravates ischemia Prolongs QT interval Induces coronary vasospasm and arrhythmias
Reverses hypovolemia and hemoconcentration	INTRAVASCULAR VOLUME REPLACEMENT	Left ventricular dysfunction causing acute pulmonary edema and respiratory failure
Anaphylactoid events by inhibiting cyclooxygenase Aggravate pre-existing anaphylaxis by converting arachidonic acid to leukotrienes	ACETYLSALICYLIC ACID	Antiplatelet effect
Hypotension and tachycardia	NITRATES	Increases myocardial oxygen release Dilates coronary and peripheral vessels Decreases preload
Resistance to adrenalin	BETA BLOCKERS	Antihypertensive, antianginal and antiarrhythmic effect
	CALCIUM CHANNELS ANTAGONISTS	Vasodilation
Inotropic and chronotropic action	GLUCAGON	
Slightly reduce the bronchial inflammatory load	P2Y12 INHIBITORS	Antiplatelet effect
Nonspecific degranulation of mast cells	OPIOIDS	Analgesic and anxiolytic

Non-shaded, beneficial effect

Shaded, detrimental effect

Management of acute coronary syndrome

Regarding ACS, this syndrome should be managed like other types of ACS according to current ACS guidelines, including the need for immediate or deferrable reperfusion. An epicardial coronary thrombosis and coronary vasospasm cannot be differentiated with reasonable certainty based on symptomatology, so an invasive test such as coronary angiography is often unavoidable to rule out atherosclerotic coronary disease [64]. In fact, in most patients, KS will be a diagnosis of exclusion after performing an angiography, being necessary for the treatment of types II and III as well (since they are coronary arteries with lesions) [65].

Following the guidelines of the European Society of Cardiology [51], patients undergoing percutaneous coronary intervention (PCI) should receive dual antiplatelet therapy, a combination of aspirin (ASA) and an oral P2Y12 inhibitor (prasugrel or ticagrelor), and a parenteral anticoagulant (unfractionated heparin of choice) [66]. Cangrelor is a potent reversible intravenous inhibitor of P2Y12 with a very rapid onset and

discontinuation of action. The use of cangrelor can be considered at the time of PCI for patients who have not received pretreatment with oral P2Y12 inhibitors or who cannot take drugs by mouth such as in the case of an anaphylactic reaction with swallowing difficulties.

Management of Kounis syndrome

The management of the acute phase of KS is a challenge for the clinician, since peripheral vasodilation due to anaphylactic shock that requires vasopressors, together with coronary vasospasm that requires vasodilators, represent a complex balance. In addition, as a complication, some drugs used to treat cardiac manifestations can worsen the allergic reaction and vice versa, as detailed in Table 2 [67, 68].

Adrenaline is the treatment of choice in anaphylaxis, and it must also be administered early because it prolongs survival. However, in the presence of acute coronary syndrome, it can aggravate ischemia, prolong the QT interval, and induce coronary vasospasm and arrhythmias, especially in older and hypertensive patients [50]. As a further complication, an adrenaline-induced myocardial infarction can also occur [21•]. Adrenalin has been postulated to promote platelet aggregation secondary to increased thromboxane B2 production by platelets [69] and thrombin-induced increased platelet binding of fibrinogen [70]. Unlike KS, in adrenaline-induced myocardial infarction, the symptoms appear during the administration of adrenaline or in the first 15 min after administration [21•]. So, according to some authors, due to the worsening of vasospasm that its administration can cause in KS, adrenaline should be reserved for those cases with anaphylactic shock and laryngospasm [71].

On the other hand, in shock situations, systemic vasodilators such as nitrates can be harmful [13]. Although it is true that their use can be considered in patients who are not hypotensive, it should be reminded that they can aggravate hypotension and tachycardia [40]. Calcium channel antagonists are the anti-ischemic treatment of choice in KS, since their benefit is precisely linked to the pathophysiological process of vasospasm, which is common in KS [51].

ASA can cause allergic reactions including anaphylactoid symptoms, and can even aggravate pre-existing anaphylaxis. Its usefulness in KS is unknown, since on the one hand, it benefits acute coronary syndrome and on the other it could potentially worsen anaphylaxis [67].

In conclusion, in all three variants of KS, antiallergic treatment should be started as soon as possible, which may be sufficient to reverse the vasospasm in the type I variant [1••, 68] in addition to vasodilators including calcium channel antagonists [48•]. In addition, the intracoronary use of nitroglycerin can resolve vasospasm without having systemic vasodilator effects [13, 65]. In patients with the type II and III variants, in addition to the above treatments, the ACS protocol should be started. In the type III variant, moreover, the aspiration of the intra-stent thrombus should be

done, with its subsequent histological examination to verify the presence of eosinophils and mast cells [1••].

Once recovered, these patients should be referred to the cardiology and allergy departments in order to guarantee their follow-up and etiological study. Further studies are needed to develop a consensus treatment guideline.

Drug desensitization and Kounis syndrome

Rapid drug desensitization is a clinical procedure that allows the safe administration of a drug in patients with hypersensitivity to them. Using this procedure, first-line therapies can be maintained that lead to greater efficacy, fewer side effects, and greater life expectancy of patients compared to the use of second-line therapy [72]. Desensitization can be used as a therapeutic strategy for patients with type I and mild IV hypersensitivity reactions according to the Gell and Coombs classification and is absolutely contraindicated in type II and III reactions, as well as SCAR (severe cutaneous adverse reaction) in type IV hypersensitivity reactions [73].

It has not been found literature specifying that KS is a contraindication to carry out a drug desensitization, nor clinical cases of KS in which desensitization with the causative drug was performed. Cases of successful desensitization to aspirin have been described in KS, in previously sensitized patients, and without being the causative agent, as adjuvant therapy to the treatment of KS [74]. Castro Jimenez A et al. described the first documented case of a patient who presented KS type II after a wasp sting who was treated with specific immunotherapy with wasp venom without incident. Moreover, after completing the treatment, he tolerated new wasp stings without presenting anaphylaxis or cardiological involvement [75].

In conclusion, in KS desensitization could be considered when there are no alternative drugs to the causal drug, but more studies are needed to recommend it with certainty.

Conclusion

KS is an underdiagnosed pathology but, not for that reason, infrequent. Physicians must be aware to the clinical signs and symptoms described for the correct diagnosis of KS. Regarding the etiology, it should be noted that any drug can cause an allergic reaction and therefore KS. In particular, NSAIDs and beta-lactam antibiotics should be taken into account as the cause of KS, since they are the most frequently implicated drugs. Given the complexity of the management of KS and bearing in mind that the use of adrenaline is controversial, the use of glucagon as an alternative to adrenaline could be interesting due to its inotropic and chronotropic effect. More case series and, if possible, controlled clinical trials are needed, despite the fact that they are difficult to perform due to the limited number of cases, in order to issue solid

recommendations for the management of KS. Finally, rapid desensitization to drugs are increasing in the recent decades, especially with antineoplastic drugs, in which it is vital to maintain the first line of treatment. It would be interesting to investigate the safety of desensitization in KS, since if it is safe it could provide a solution in the treatment of pathologies for which there are no alternative drugs.

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Author contribution

Paula Ollo-Morales (the corresponding author) produced and designed the manuscript and did the final revision. All authors were involved in the acquisition of data, including the search, analysis, and interpretation of data and the critical revision of the manuscript for important intellectual content.

Compliance with Ethical Standards

Conflict of Interest
The authors declare no competing interests.

Human and Animal Rights and Informed Consent
This article does not contain any studies or animal subjects performed by any of the authors.

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