

Allergic Acute Coronary Syndrome—Kounis Syndrome



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KEYWORDS

- Vasospastic angina • Allergic reaction • Kounis syndrome
- Acute coronary syndrome

KEY POINTS

- Acute coronary syndrome in the setting of an immune reaction is known as Kounis syndrome.
- It is an underrecognized syndrome and easily missed clinically.
- Treatment should be aimed at both the allergic component as well as the coronary vasospasm, thrombus, or plaque rupture that occurs as a result of the immune reactions.

INTRODUCTION

Kounis syndrome (KS) is defined as the occurrence of an acute coronary syndrome (ACS) associated with mast cell and platelet activation in the setting of allergic or anaphylactic reactions.¹ For many decades the association between cardiac symptoms and acute allergic reactions has been suspected. In 1950, Pfister and Plice published a case report of a 49-year-old man who presented with an acute myocardial infarction associated with the development of an urticarial rash following administration of penicillin.² In 1991, Kounis and Zavras introduced the terms “allergic angina” and “allergic myocardial infarction,” which collectively are now better known as “Kounis Syndrome.”³ Multiple pharmacologic and environmental triggers have been identified. The proposed pathophysiological mechanism involves mast cell degranulation, resulting in inflammatory mediator release. These inflammatory mediators, including

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histamine, leukotriene, and prostaglandin, can induce a vasoconstrictive effect on the coronary smooth muscle cells leading to coronary vasospasm (KS type I), cause native plaque destabilization (KS type II), or lead to stent thrombosis (KS type III).^{4,5} Diagnosis is based on clinical presentation, electrocardiography, echocardiography, and angiography. The treatment of KS is challenging as there are limited data available on therapeutic options. Many physicians are not aware of KS; therefore, it is underrecognized and underreported. It is imperative for the emergency physician to be aware of this disease in order to promptly diagnose and manage patients who present with KS in the emergency department. This article discusses KS, its underlying pathophysiologic mechanism, diagnosis, and treatment.

DISCUSSION

Pathophysiology

The exact pathophysiologic mechanism of KS remains elusive, as most of the literature pertaining to KS consists of case reports or case series. The main proposed pathophysiological mechanism is thought to be vasospasm, plaque rupture, and thrombosis due to the rapid release of inflammatory mediators during a hypersensitivity reaction.

Mast cells play an essential role in the development of allergic reactions. During allergic reactions mast cells are activated through the cross-linking of immunoglobulin E (IgE) bound to antigen at high-affinity receptors, FcεR1s. Mast-cell activation can also occur in the presence of anaphylatoxins such as C3a and C5a, adenosine, or other stimuli.⁶ Activation leads to release of multiple preformed inflammatory mediators such as histamine, tryptase, and chymase, as well as de novo produced arachidonic acid-derived mediators, cytokines, and chemokines.⁷ Mast cells are omnipresent in cardiac tissue and are preferentially located at sites of coronary plaques.^{8–10} Mast cells can infiltrate areas of plaque erosion or rupture and act on the underlying smooth muscle cells. The cardiac mast cell load of patients with coronary plaques is up to 200-fold higher than in coronary arteries of healthy people.¹¹

Mast cell-induced release of mediators has many effects on the coronary arteries including vasospasm, plaque rupture, and thrombosis. Histamine release can lead to coronary vasoconstriction, decreased diastolic blood pressure, and increased intimal thickening; this may contribute to coronary plaque rupture and subsequent coronary artery thrombosis.^{3,12} Histamine can also initiate platelet activation and aggregation. The presence of mast cells in and around thrombi has been thought to lead to heparin- and tryptase-induced degradation of fibrinogen, which contributes to destabilization and maturation of thrombi.^{11,13} Leukotrienes are potent vasoconstrictors, and chymase and cathepsin-D might act to convert angiotensin I to angiotensin II, a potent vasoconstrictor.¹

Even in patients with nonallergic ACS, increased levels of serum inflammatory mediators are found, including tryptase, chymase, and arachidonic acid products such as thromboxane and leukotrienes.¹⁴ The mast cell activation in acute coronary syndrome has been thought to be a primary event, not the result from the coronary artery spasm, and this has been supported by evidence that tryptase levels in peripheral blood increases during spontaneous myocardial ischemia but not during pharmacologically induced coronary spasms.¹²

Multiple causes have been identified to trigger KS (**Table 1**). Among these are many well-known triggers of typical allergic reactions and anaphylaxis. In one review by Abdelghany and colleagues of 175 previously reported cases of KS, the most common triggers were antibiotics (27.4%) and insect bites (23.4%).¹³

Table 1
Known causes of Kounis syndrome

Drugs	Foods	Environmental Exposures
Analgesics (aspirin, dipyrrone, tramadol)	Canned food	Bee stings
Anesthetics (etomidate, isoflurane, midazolam, propofol, remifentanyl, rocuronium bromide, succinylcholine, suxamethonium, trimethaphan)	Fish	Black widow spider bite
Antibiotics (penicillins, cephalosporins, amikacin, cinoxacin, ciprofloxacin, clindamycin, lincomycin, metronidazole trimethoprim sulfamethoxazole, vancomycin)	Kiwi	Dialysate
Antifungals (fluconazole)	Mushrooms (<i>Coprinopsis atramentaria</i>)	Grass
Anticoagulants (heparin, lepirudin)	Shellfish	Hymenoptera stings
Antineoplastics (5-fluorouracil, capecitabine, carboplatin, denileukin, interferons, paclitaxel, vinca alkaloids)	Tomato	Jellyfish stings
Antivirals (brivudine, oseltamivir)	Vegetables	Latex
Contrast media (iohexol, ioxaglate, meglumine diatrizoate, sodium indigotindisulfonate)		Scorpion stings
Glucocorticoids (betamethasone, hydrocortisone)		
Nonsteroidal antiinflammatory drugs (alclofenac, diclofenac, naproxen)		Wasp stings
Proton pump inhibitors (lansoprazole)		
Skin disinfectants (chlorhexidine, povidone iodine)		
Thrombolytics (streptokinase, tissue plasminogen activator, urokinase)		
Others (allopurinol, bupropion, clopidogrel, dextran, enalapril, esmolol, fructose, gelofusine, insulin, iodine, iron, losartan, protamine, tetanus antitoxin, glafenine, mesalamine)		

Disease Presentation

Patients with KS will present with signs and symptoms of an acute coronary syndrome while simultaneously demonstrating evidence of an acute hypersensitivity reaction. Signs and symptoms can be waxing and waning. Cardiac symptoms may include chest pain, chest discomfort, palpitations, dyspnea, nausea, vomiting, lightheadedness, pallor, diaphoresis, and bradycardia.¹⁴ The signs and symptoms of an allergic reaction may include skin rash, pruritus, hives, nausea, vomiting, wheezing, and angioedema. Both cardiac and allergic components can lead to hypotension, shock, and cardiac arrest. Abdelghany and colleagues found that in 80% of cases, the cardiac symptoms will occur within the first hour of trigger exposure.¹³

Risk Factors

Risk factors for KS include a history of a previous allergy, hypertension, smoking, diabetes, and hyperlipidemia. Twenty five percent of patients with KS will have a known history of allergy. KS can occur at any age, but it is most commonly seen in patients aged 40 to 70 years.¹³

Definitions

Kounis and Zavras described the “allergic angina syndrome” that progresses to allergic acute myocardial infarction due to histamine-mediated vasospasm of the coronary arteries when triggered by certain antigens.³ It is defined as the “concurrency of acute coronary syndromes associated with mast cell and platelet activation in the setting of allergic or anaphylactic insults.”¹⁴ There are 3 known variants to KS based on the mechanism of coronary artery obstruction; however, they all have a common initial mechanism of an allergic response that induces mast cell-mediated inflammatory cascade that leads to compromise of the coronary circulation.^{4,14}

- Type I: this is the most common variant of KS, occurring in 72.6% of cases.¹⁴ This occurs in younger people without underlying native atherosclerotic artery disease who have ACS due to an allergic insult. The allergic reaction causes *coronary artery spasm* usually without an increase in troponin or other cardiac biomarkers. However, if this spasm results in myocardial infarction, troponin levels might be elevated. This variant is one of the causes of myocardial infarction with nonobstructive coronary arteries and represents microvascular angina or endothelial dysfunction.¹⁵
- Type II: occurs in 22.3% of cases. This variant occurs in those with preexisting atheromatous disease in whom the acute release of inflammatory mediators can cause coronary artery spasm, in addition to *plaque erosion or rupture*, thus presenting as acute myocardial infarction.¹⁴
- Type III: this is the least common variant, accounting for 5.1% of cases. This variant was further subdivided into *stent thrombosis* (subtype a) and *stent restenosis* (subtype b) that occur due to allergic inflammation.¹⁶ Coronary stents that contain nickel have been implicated as a trigger of KS.¹⁷ The aspirated thrombus, when stained with hematoxylin-eosin and Giemsa, demonstrates the presence of eosinophils and mast cells, respectively.¹⁸ Furthermore, both subtypes have been diagnosed post mortem in patients with stent implantation who died suddenly. The histologic examination of the coronary intima, media, and adventitia adjacent to stent deployment showed infiltration of eosinophils and mast cells.¹⁶

Diagnosis

KS is not a rare disease, but it is likely underdiagnosed in the clinical setting and can be easily overlooked or missed. It is important to keep this entity in mind when evaluating patients who come in with chest pain or even myocardial infarction in the setting of symptoms of an allergic reaction. It is important to focus on the duration of time between exposure to the trigger and the onset of symptoms. Most of the patients will have an interval of less than 1 hour but almost 10% were reported more than 6 hours after exposure.¹⁹

The diagnosis of KS is made based on clinical signs and symptoms, history of previous allergies, and the results of laboratory tests, electrocardiogram (ECG), echocardiogram, angiogram, and MRI.

- Clinical signs and symptoms
 - Cardiac component: 86.6% of patients will present with chest pain; it is the most common presentation. Similar to ACS pain, it is described as crushing or constrictive, and it may radiate to the neck, jaw, or arms. It may also be associated with diaphoresis, pallor, nausea, vomiting, palpitations, and shortness of breath.
 - Allergic manifestations: ranges from mild and localized to widespread and life-threatening. Some common findings include hives, rash, mucous membrane involvement, edema of the face or tongue, wheezing, hypotension, and shock.
- History
 - 25% of patients have a known history of allergies or have experienced an allergic reaction in the past. It is imperative to obtain a medication history in the patient and review medication allergies, including allergy to iodinated contrast media.
- Laboratory tests
 - There is no laboratory test that will definitely diagnose KS; however, obtaining a complete blood count, particularly looking at eosinophils, cardiac biomarkers (CK, CK-MB) and troponin I or T, C-reactive protein (high sensitivity), total and specific immunoglobulin E (IgE), histamine, chymase, and serum tryptase levels can all aid in the diagnosis of KS in the right clinical setting. Note that histamine has a very short half-life of approximately 8 minutes; therefore, a low level does not exclude the diagnosis. Other laboratories that might be helpful include levels of arachidonic acid products (thromboxane, leukotrienes, prostaglandins), tumor necrosis factor, interferon, and interleukin-6.¹³
- ECG
 - ECG changes are usually transient and occur during an episode of pain. ST elevation myocardial infarction (usually involving the inferior leads) is the most common ECG change seen with KS.¹⁹ There are no specific changes to distinguish KS from a nonallergic form of ACS. ST-T changes suggesting ischemia (ST segment depression and T wave inversion), sinus tachycardia or bradycardia, heart blocks, atrial fibrillation, ventricular fibrillation, ectopic beats, QRS and QT prolongation, and findings similar to digoxin toxicity have all been reported in KS.^{14,19}
- Echocardiogram
 - In KS, echocardiogram studies might reveal regional wall motion abnormality in the distribution of the affected artery.^{1,20} The subendocardial layer of the myocardium is affected in that coronary territory in contrast to acute myocarditis where heterogeneous and subepicardial involvement is detected.²¹

- Coronary artery angiogram may show coronary vasospasm or stenosis. The right coronary artery is the culprit lesion in more than half the cases.¹³
- Thallium-201 single-photon emission computed tomography (SPECT) and 125I-15-(p-iodophenyl)-3-(R,S) methyl pentadecanoic acid SPECT demonstrated severe myocardial ischemia in a 66-year-old who developed KS after local anesthetic infiltration for a dental procedure. The patient underwent coronary angiography, which demonstrated normal coronary arteries consistent with KS type I.²²
- Cardiac MRI has demonstrated normal washout in the subendocardial lesion area with delayed contrast-enhanced images.²³

Differential Diagnoses

- Obstructive coronary artery disease (CAD)
- Unstable angina
- Stress-induced cardiomyopathy (Takotsubo) is one of the major differential diagnoses to consider when diagnosing KS. Furthermore, those 2 entities can also coexist and present in the same patient.²⁴
- Hypersensitivity myocarditis
- Acute pericarditis
- Prinzmetal angina
- Eosinophilic coronary periarteritis
- Coronary allograft vasculopathy
- Esophageal spasm

Management

Revascularization of the myocardium while simultaneously managing the allergic reaction is the mainstay of treatment of KS. When patients present with acute coronary syndrome, they should be managed according to the ACS guidelines.¹² Unfortunately, these guidelines lack in specific details regarding the management of ACS due to KS. Most data come from case reports or case series. What complicates matters further is some drugs administered to treat cardiac manifestations of KS can worsen the allergic component, and other drugs given for the allergic symptoms can aggravate the cardiac dysfunction.¹⁶

Treating the allergic reaction in the type I variant usually resolves the cardiac manifestation:

- Corticosteroids (hydrocortisone 1–2 mg/kg/d) suppress the arterial hyperreactivity and relieves inflammation.²⁵ Prevention of biphasic reactions has not been demonstrated.²⁶
- H1 and H2 blockers (diphenhydramine 1–2 mg/kg and ranitidine 1 mg/kg) can also decrease the allergic manifestations.²⁷ These should be administered as a slow intravenous push because they may induce hypotension and worsen coronary perfusion.¹⁶
- Calcium channel blockers (CCB) and nitrates can help abolish the vasospasm induced by hypersensitivity and should be used if the blood pressure is satisfactory.^{16,28} However, caution must be taken with nitroglycerin because it may cause hypotension and tachycardia and further complicate the allergic reaction.¹
- Because epinephrine can worsen myocardial ischemia and induce coronary vasospasm and arrhythmias it should be used with caution in KS.¹¹ However, if the patient presents with anaphylaxis, the risks of untreated anaphylaxis outweighs the risk of possible worsening myocardial ischemia.²⁹

In patients with type II variant of KS, the management is similar to that of ACS with additional treatment with antihistamines and steroids.¹⁴ Vasodilators such as nitrates and CCBs may be used as necessary.¹⁶ Beware that using β -blockers can exaggerate coronary vasospasm due to unopposed α -adrenergic receptors action. Epinephrine can aggravate ischemia and worsen coronary vasospasm. Using a sulfite-free epinephrine is preferable (dose of 0.2–0.5 mg of the 1:1000 concentration intramuscularly [IM]).³⁰ Epinephrine may be ineffective in patients already on β -blockers. In those patients administer glucagon 1 to 5 mg intravenously (IV) followed by infusion at 0.05 to 0.1 mg/kg/h if needed.

Treatment in type III variant KS should also follow the ACS guidelines. Per guidelines, when indicated, aspiration of the in-stent thrombus is of crucial importance in histologic analysis and staining of the thrombus for eosinophils and mast cells. These can suggest an allergic reaction, which can alter management.¹⁴ In addition, if a patient develops an allergic reaction following coronary stent placement, steroids, antihistamines, and mast cell stabilizers (eg, sodium cromoglycate) can help relieve the allergic manifestations. Identifying the culprit cause via patch or skin test followed by desensitization might be indicated especially if these measures fail.¹⁴ If allergy to nickel-titanium alloy is confirmed by patch test, with failed desensitization, removal of the implanted stent might be necessary.³¹

Management of Kounis Syndrome in the Emergency Department

Diagnosing KS in the ED is challenging. The allergic component of the presentation can easily be missed (eg, if a patient has underlying asthma and presents with wheezing and chest pain).

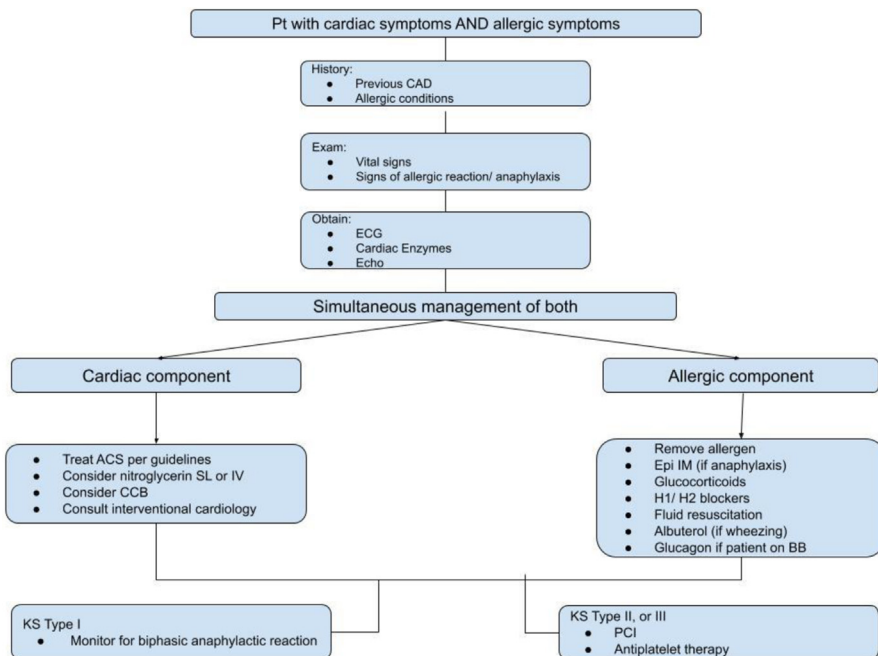


Fig. 1. Algorithm for management of patients suspected to have Kounis syndrome in the emergency department.

The following are steps that can you take to help manage a patient with suspected KS (**Fig. 1**):

- Ask about exposure to known allergens and when the exposure occurred. Most patients will present less than an hour postexposure.
- Ask about prior similar presentations, especially if they were previously evaluated with coronary angiography studies or MRI.
- Ask about previously diagnosed CAD:
 - No history of CAD: this presentation can be KS type I or new ACS.
 - History of CAD: this can be KS type II, III, or ACS—all of these are managed according to ACS guidelines.
- On examination, look for signs of allergic reaction.
- Manage the cardiac and allergic components of KS simultaneously.
 - Nitroglycerine (if BP acceptable)
 - Calcium channel blockers
 - IM epinephrine if anaphylaxis is present
 - Glucocorticoids, H1 and H2 blockers
 - Consult interventional cardiology if cardiac ischemia is suspected by ECG, elevated troponin level, or based on clinical picture.

Drugs to Avoid

- Nonselective β -blockers can exacerbate vasospasm.
- Opioids (eg, morphine, codeine and meperidine) may induce massive mast cell degranulation and aggravate allergic reaction.¹ Fentanyl and its derivatives are weak mast cell triggers and therefore are preferable.¹
- Acetaminophen (especially IV) has been associated with the development of severe hypotension due to a reduction in cardiac output.³²
- High-dose aspirin because it inhibits prostacyclin production.
- Oral sumatriptan can cause coronary vasospasm and myocardial infarction.
- 5-Fluorouracil has been reported to induce coronary artery spasm.

Prognosis

With appropriate treatment, KS generally has a good prognosis with complete recovery in most patients. Type I variant of KS is the most prevalent and most common of all variants. In this type, early identification and hence treatment is possible because of early appearance of allergic manifestations. The resultant coronary vasospasm can be reversed with vasodilators, and based on previous reports it also has good prognosis.³³

Overall, serious complications of KS are rare:

- Cardiogenic shock occurs in 2.3%.
- Cardiac arrest occurs in 6.3%.
- Mortality is 2.9%.

SUMMARY

ACS in the setting of an allergic/immunologic reaction is known as KS. It is an underdiagnosed and underrecognized disease entity. One must keep a high index of suspicions when managing a patient presenting with cardiac as well as allergic symptoms. There are 3 main variants to the syndrome. Treating the allergic reaction may alleviate the pain; however, ACS guidelines should be followed if cardiac ischemia is present.

CLINICS CARE POINTS

- Keep a high index of suspicion for the possibility of KS when treating patients with chest pain or ACS-like picture.
- When treating patients with anaphylaxis, obtain ECG and troponins to rule out KS.
- Treat the allergic as well as the cardiac components simultaneously.
- Epinephrine, although a life-saving necessity for anaphylaxis treatment, may worsen cardiac ischemia. The risk of untreated (true) anaphylaxis usually outweighs the risk of worsening ischemia.
- Avoid β -blockers, as they can worsen vasospasm.

DISCLOSURE

There are no commercial or financial conflicts of interest.

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