Acute Coronary Syndrome Treated with Antihistamines and Steroids: A Case Report of Kounis Syndrome

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Introduction: Kounis syndrome (KS) is described as the manifestation of acute coronary syndrome due to mast cell activation and resultant inflammatory mediator-induced coronary vasospasm or thrombosis. This can occur in both healthy and diseased coronary arteries, although the vasospastic response is significantly stronger in diseased vessels.

Case Report: A 70-year-old male with history of previous coronary artery bypass grafting presented to the emergency department with thoracic back pain, facial angioedema, hemodynamic instability, and a prehospital electrocardiogram (ECG) concerning for an inferior wall ST-segment elevation myocardial infarction. His troponin level increased, consistent with myocardial ischemia. However, his ischemic ECG changes and hemodynamic instability resolved following treatment of presumed anaphylaxis. Cardiac catheterization was performed and showed patency of his previous bypass grafts.

Conclusion: Some experts suggest that KS is significantly underdiagnosed due to a lack of awareness of this disease entity. Understanding the pathogenesis of KS is imperative as treatment is focused on the allergic response precipitating cardiac ischemia. Further, common resuscitative medications used in the treatment of acute coronary syndrome has the potential to exacerbate vasospasm, while epinephrine used in the treatment of anaphylaxis has the potential for worsening cardiac ischemia and should be used with caution. [Clin Pract Cases Emerg Med. XXXX;X(X)t:X-X.]

Keywords: Kounis syndrome; acute coronary syndrome; anaphylaxis; myocardial infarction; case report.

INTRODUCTION
Kounis syndrome (KS) is described as clinically apparent acute coronary syndrome (ACS) secondary to mast cell activation and subsequent release of various inflammatory mediators.1,2,3,4 These include histamine, tryptase, chymase, platelet-activating factor, arachidonic acid products, neutral proteases, cathepsin-D, and various inflammatory cytokines and chemokines.2,3,5 Mast cells are present in high concentrations in cardiac tissue, particularly in areas of coronary plaques, making these areas more susceptible to severe vasospastic response when exposed to histamine.3,4,6,7

Similar pathogenic features have also been noted to occur in mesenteric and cerebral arteries.5

Three clinical variants of KS have been described.2,6 In the type I variant, an allergic insult leads to coronary vasospasm in patients with normal coronary arteries and may or may not cause myocardial ischemia.2 The type II variant is due to coronary vasospasm or plaque instability in patients with otherwise stable underlying coronary artery disease (CAD).2 Finally, the type III variant occurs when an allergic insult...
leads to thrombosis of a known coronary stent with vessel wall infiltration by eosinophils and/or mast cells.2,5 Theoretically, exposure to virtually any allergenic insult could lead to KS.3,5 A summary of the most common causative agents is outlined in Figure 1. Coronary stents are commonly made of stainless steel or chromium and cobalt alloys, and studies have shown that 4% and 9% of individuals have local skin reactions to chromium and cobalt, respectively.2 The potential of these metals to act as allergens suggests that stent thrombosis may primarily be a manifestation of KS.3

The yearly incidence of KS in patients with anaphylaxis is estimated at 2% with a mortality of 2.9%, arguing that KS should be excluded in all patients presenting with anaphylaxis.6,7 The optimal treatment of patients presenting with KS relies on accurate diagnosis as standard treatments for ACS may be harmful.3,8,9

CASE REPORT

A 70-year-old male with past medical history of congestive heart failure, CAD with prior ED after falling while getting dressed at home. Family reported that he was complaining of difficulty breathing and diffuse pruritus at symptom onset and had been complaining of back pain for the prior three days. The prehospital electrocardiograph (ECG) was consistent with an inferior wall.

On arrival, the patient appeared flushed and diaphoretic with facial and lingual angioedema. He was awake but unable to respond to questions or follow commands and was immediately endotracheally intubated. Prescribed medications included lisinopril, metoprolol, atorvastatin, dutasteride, fenofibrate, glargine, metformin, and pregabalin. Initial vital signs were pertinent for temperature of 94.8˚F, heart rate of 76 beats per minute, pulse oximetry reading of 91% on room air, respiratory rate of 20 breaths per minute, and blood pressure of 66/48 millimeters of mercury. His initial ECG was concerning for inferior ST-elevation myocardial infarction (STEMI) (Image). The cardiologist evaluated the patient in the ED and concluded the ECG favored global ischemia. A point-of-care limited transthoracic two-dimensional (2D) echocardiogram done by the emergency physician showed normal cardiac wall motion throughout, and the consulted cardiologist recommended against emergent cardiac catheterization at that time.

The patient was administered norepinephrine for continued hypotension despite fluid resuscitation. Given his hypotension, reported history of back pain and ECG changes, CT angiography of the chest, abdomen, and pelvis was obtained to rule out aortic dissection, and was nonrevealing. Abnormal laboratory values included a lactate of 6.2 millimoles per liter (mmol/L) (reference range 0.5-1.6 mmol/L) and a high sensitivity troponin (hsTn) of 48 picograms per milliliter (pg/mL) (reference range less than 20 pg/mL).

With the patient’s combined history of pruritis, skin flushing, diaphoresis, angioedema, and hemodynamic instability, the diagnosis of anaphylaxis was considered. He was administered 125 milligrams (mg) intra-venous (IV) methylprednisolone, 50 mg of IV diphenhydramine, and 20 mg of IV famotidine. Within 60 minutes of receiving these medications, he became hemodynamically stable, and the norepinephrine was discontinued.

A complete 2D transthoracic echocardiogram read by the cardiologist showed a normal ejection fraction of 55-60% with a grade I diastolic dysfunction but was otherwise unremarkable. A repeat ECG done at 90 minutes showed significantly improved ST-segment elevation abnormalities (Image). A repeat hsTn at 90 minutes showed a significant delta change from 48 pg/mL to 715 pg/mL. Cardiac catheterization was deferred by the cardiologist given resolving ECG changes, and he was admitted on a heparin infusion for treatment of non-STEMI. Overnight, the patient’s hsTn peaked at 15,363 pg/ml; he developed a mild acute kidney injury and a low-grade fever.

The patient had an inpatient evaluation by an allergist 31 hours after initial presentation. At that time, an
immunological panel, histamine, and tryptase levels were drawn and read negative. Obtaining these levels during initial ED stabilization was not considered at the time of initial presentation. His renal function and mental status improved, and he was extubated on hospital day (HD) three. No infectious source of his fever was identified. Following extubation, the patient recalled taking naproxen approximately 15 minutes prior to his symptom onset but did not recall having chest pain at that time. Cardiac catheterization was performed on HD four and showed patency of his previous bypass grafts. There were no new lesions, and left ventricular systolic function was normal. The allergist suggested a diagnosis of Type II KS given the patient’s underlying CAD. Naproxen was considered to be the most probable etiology given symptom onset shortly after taking this medication. The patient was discharged home with instructions to avoid both lisinopril and naproxen indefinitely as both have been implicated to cause KS.

**DISCUSSION**

This case demonstrates KS in a patient with pre-existing CAD, but without preceding anginal symptoms and patent graft arteries. The most common presentation of KS is STEMI. As was seen in this patient, signs and symptoms of an allergic response or anaphylaxis are often present and accompanied by cardiac symptomatology. However, chest pain is only present in 86.6% of patients, and allergic manifestations in KS may be subclinical. Further, while symptoms of ACS may be apparent on presentation, ECG changes or elevated troponin may be the only indication of cardiac involvement.

The patient denied a history of known environmental or drug allergies. He reported a history of a cough as an adverse reaction to a medication. This is consistent with the presentation of KS, as coughing can be a symptom of an allergic reaction. Additionally, the patient had a history of aspirin allergy, which was not associated with KS in this case.

**Figure 1.** Allergic insults associated with Kounis syndrome.1,4,5,6

<table>
<thead>
<tr>
<th>Medications</th>
<th>Food</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antibiotics</strong> (penicillins, cephalosporins, metronidazole, clindamycin, clarithromycin, telithromycin, ciprofloxacin, trimethoprim-sulfamethoxazole and vancomycin)</td>
<td>- Shellfish</td>
</tr>
<tr>
<td><strong>Antivirals</strong> (brivudine, oseltamivir)</td>
<td>- Canned tuna</td>
</tr>
<tr>
<td><strong>Antifungals</strong> (fluconazole)</td>
<td>- Salt fish</td>
</tr>
<tr>
<td><strong>Anticancer</strong> (cispalatin, oxaliplatin, cyclophosphamide, 5-fluorouracil, rituximab, nafamostat, capcetibine, carboplatin, demileukin, interferons, paclitaxel, vinca alkaloids)</td>
<td>- Raw anchovies</td>
</tr>
<tr>
<td><strong>Anticoagulants</strong> (heparin, lepirudin)</td>
<td>- Blue crab</td>
</tr>
<tr>
<td><strong>Thrombolectes</strong> (streptokinase, tissue plasminogen activator, urokinase)</td>
<td>- Crucians</td>
</tr>
<tr>
<td><strong>NSAID</strong> (aspirin, ibuprofen, diclofenac, aclclofenac, naproxen, metimazole, propyphenzone)</td>
<td>- Kiwi (actinidia chinensis extract)</td>
</tr>
<tr>
<td><strong>Beta-blockers</strong> (esmolol)</td>
<td>- Mushroom (coprinus atramentaria)</td>
</tr>
<tr>
<td><strong>Angiotensin converting enzyme inhibitors</strong> (enalapril)</td>
<td>- Rice</td>
</tr>
<tr>
<td><strong>Angiotensin receptor blockers</strong> (losartan)</td>
<td>- Tomato salad</td>
</tr>
<tr>
<td><strong>Anesthesities</strong> (propofol, etomidate, isoflurane, midazolam)</td>
<td>- <strong>Environmental</strong></td>
</tr>
<tr>
<td><strong>Analgiesics</strong> (tramadol, remifentanil)</td>
<td>- Hymenoptera stings (bee, wasp)</td>
</tr>
<tr>
<td><strong>Neuromuscular blockers</strong> (sacculinylcholine, suxamethionine, rocurenium, atracurium)</td>
<td>- Scorpion sting</td>
</tr>
<tr>
<td><strong>Antiplatelets</strong> (clopidogrel)</td>
<td>- Viper venom</td>
</tr>
<tr>
<td><strong>Decongestants</strong> (pseudoephedrine)</td>
<td>- Jellyfish stings</td>
</tr>
<tr>
<td><strong>Oral contraceptives</strong></td>
<td>- Black widow spider</td>
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<tr>
<td><strong>Corticosteroids</strong> (hydrocortisone, betamethasone)</td>
<td>- Grass cutting</td>
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<tr>
<td><strong>Antihistamines</strong> (astemizole, ranitidine)</td>
<td>- Poison ivy</td>
</tr>
<tr>
<td><strong>Anticholinergers</strong> (hyoscine butylbromide, trimethaphan)</td>
<td>- Latex</td>
</tr>
<tr>
<td><strong>Antidepressants</strong> (bupropion)</td>
<td>- Iodine</td>
</tr>
<tr>
<td><strong>Antipsychotics</strong> (ziprasidone)</td>
<td>- Metals (and metal stents)</td>
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<tr>
<td><strong>Antiseptics</strong> (chlorhexidine, povidone-iodine)</td>
<td>- Nicotine</td>
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<td><strong>Proton pump inhibitors</strong> (lansoprazole)</td>
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<td><strong>Colloidal fluids</strong> (dextran, gelofusin)</td>
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<tr>
<td><strong>Intravenous contrast material</strong></td>
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<tr>
<td><strong>Dialysate</strong></td>
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<tr>
<td><strong>Others</strong> (atropine, allopurinol, mesalamine, insulin, sodium bicarbonate, iron, protamine, tetanus antitoxin, iron)</td>
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</tbody>
</table>

The diagnosis of KS is largely clinical but is supported by ECG changes, elevated cardiac markers, echocardiogram findings, and cardiac catheterization results. Takotsubo cardiomyopathy and type II non-STEMI (supply and demand mismatch) should be ruled out when considering KS, but it is also possible for these entities to occur in combination.

While increased serum histamine and tryptase levels may support the diagnosis, they are of little clinical utility in the ED due to their short half-life. Histamine, which causes coronary vasoconstriction through the histamine-1 (H1) receptors, has a half-life of eight minutes, while tryptase, which promotes plaque disruption, has a half-life of 90 minutes. While these markers may be elevated in ongoing allergic reaction, unless they are checked within two hours of symptom onset, they have minimal diagnostic utility.

Additionally, it has been shown that histamine and tryptase may be elevated in ACS in the absence of a hypersensitivity mechanism. The presence of urticaria, angioedema, dyspnea, and known exposure to an allergen are highly suggestive of a true hypersensitivity reaction.

Diagnosis and treatment of KS requires recognition of both anaphylactic and cardiac processes, with primary treatment focus toward the allergic insult. However, much of the treatment interplay between these two disease entities is not entirely known, and there are no established treatment guidelines. A proposed treatment diagram based on current evidence is outlined in Figure 2. Some authors express caution in the use of standard medications for ACS when KS is suspected.

Corticosteroids have historically played a primary role in the treatment of allergic reactions. Some authors suggest that the administration of an IV corticosteroid, an H1 antihistamine, and an H2 antihistamine may be adequate to control the allergic event. However, the use of corticosteroids and antihistamines for the general treatment of anaphylaxis has more recently been called into question. A systematic review published in 2020 by the Joint Task Force on Practice Parameters (JTFPP) highlighted a paucity of evidence for or against the use of corticosteroids and antihistamines in both the acute phase of anaphylactic reactions, as well as in the prevention of a biphasic anaphylactic response. In this practice parameter update, the JTFPP recommends that these supplemental therapies never delay the rapid administration of epinephrine as soon as anaphylaxis is recognized. This recommendation is based on the delayed onset of action of these medications coupled with the lack of randomized controlled trials assessing the ability of these medications to prevent biphasic anaphylaxis in patients adequately treated with epinephrine.

The benefit of corticosteroids and antihistamines in patients with vasospastic angina is primarily based on case reports and expert opinions noting benefit. While no specific outcome data has been established with the use of
Figure 2. Medication considerations in suspected Kounis syndrome.\textsuperscript{5,8,9}

\textit{H1}, histamine-1 receptor; \textit{H2}, histamine-2 receptor; \textit{mg}, milligrams; \textit{kg}, kilograms.

of these medications, it is reasonable to consider these medications as adjunctive therapies, particularly if Type I KS is suspected.\textsuperscript{5,6,8} While there is historical concern of potential for impaired wound healing and myocardial wall thinning with corticosteroid use in acute myocardial infarction, a 2003 meta-analysis of 186 articles showed no association with myocardial rupture and even suggested a 26\% decrease in mortality with corticosteroids (odds ratio 0.74, 95\% confidence interval: 0.59, 0.94; \textit{P} = 0.015).\textsuperscript{16}

Aspirin, which may lead to overproduction of leukotrienes, could theoretically aggravate ongoing anaphylactic reactions, although there is insufficient evidence to avoid its use given the apparent mortality benefit of aspirin in ACS.\textsuperscript{5,8,9} Beta-blockers can induce coronary vasospasm due to unopposed alpha-adrenergic response.\textsuperscript{5,8,9} Glucagon can be considered for patients on chronic beta-blockers for reversal in this situation.\textsuperscript{5} Calcium channel blockers and nitrates may reduce coronary vasospasm and can be considered the initial anti-ischemic drug of choice in the absence of hypotension.\textsuperscript{8,9}

Morphine has the potential to stimulate large amounts of mast cell-induced histamine release, leading to worsening coronary vasospasm and should be avoided.\textsuperscript{8,9} Synthetic opiates, such as fentanyl, have a much smaller degree of mast cell activation and resultant histamine release, and are therefore the preferable first-line agent if narcotic analgesia is needed.\textsuperscript{5,8,9} Epinephrine, which is the gold standard treatment of anaphylaxis, has the potential to worsen coronary vasospasm in KS.\textsuperscript{5,8,9} Further, most epinephrine concentrations contain sulfite, which has the potential to trigger anaphylaxis in certain individuals. While the exact incidence of sulfite additive-induced anaphylaxis is unknown and thought to be rare in most patients, currently available literature reports a sulfite-additive hypersensitivity prevalence of 3-10\% in asthmatics.\textsuperscript{17} When available, sulfite-free preparations of epinephrine are preferred.\textsuperscript{5}

Mast cell stabilizers may also play a role in relieving allergic manifestations, particularly in patients with type III variant KS.\textsuperscript{5} Patients should undergo allergy testing to assess for potential causative agents, and preventative guidance should be given in conjunction with an allergist.\textsuperscript{5}

CONCLUSION

Awareness of Kounis syndrome is important in the ED as it is thought to be a common disorder frequently overlooked. Any patient who presents with anaphylaxis should be concurrently evaluated for acute coronary syndrome as they can coexist. The primary goal in the treatment of KS should target the allergic insult, and ACS-specific treatments should be tailored based on current evidence, as there are no clinical guidelines to direct a standard model of care.

Documented patient informed consent and/or Institutional Review Board approval has been obtained and filed for publication of this case report.

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could be perceived as potential sources of bias. The authors disclosed none.

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