

CASE REPORT

BEGINNER

CLINICAL CASE

Kounis Syndrome Leading to Cardiac Arrest After Iodinated Contrast Exposure



Anthony R. Prisco, MD, PhD,^a Jason Allen, MD,^a Alejandra Gutierrez, MD,^a Alexander Zanutto, MD,^b Demetris Yannopoulos, MD,^a Jeremy Markowitz, MD,^a Jason A. Bartos, MD, PhD^a

ABSTRACT

Immune-mediated coronary spasm, called Kounis syndrome (KS), is not rare but is underdiagnosed. In this report, we present a case of KS induced by iodinated contrast resulting in cardiac arrest, requiring temporary mechanical circulatory support. We show angiographic evidence of KS and outline commonly associated clinical features that may predict KS. **(Level of Difficulty: Beginner.)** (J Am Coll Cardiol Case Rep 2020;2:626-9) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

HISTORY OF PRESENTATION

A 53-year-old woman was admitted for newly diagnosed cardiomyopathy (ejection fraction of 10% to 15%) with rapid atrial fibrillation. Physical examination findings were consistent with severe volume overload, including bilateral lower extremity edema, lung crackles, and distended neck veins. Over several days, she received diuretics and rate control agents, resulting in symptomatic improvement. Ischemic evaluation was performed via coronary angiogram;

initial images showed moderate coronary disease requiring assessment with fractional flow reserve (FFR). While preparing for FFR, the patient developed severe anxiety. Anxiolytics improved her symptoms, and FFR measurement began. During FFR evaluation of the left anterior descending artery, she developed progressive hypotension and acute hypoxemia. The coronary angiogram showed diffuse spasm of the left coronary arteries (**Figure 1, Video 1**). Despite injection of nitroglycerin, spasm persisted, and her blood pressure declined. Vasopressors were administered, but she developed pulseless electrical activity cardiac arrest. Advanced cardiac life support was initiated, and she was placed on venoarterial extracorporeal membrane oxygenation (VA-ECMO). Shortly after establishing VA-ECMO and respiratory support, the coronary spasm resolved. FFR showed nonobstructive lesions, and she was admitted to the cardiovascular intensive care unit. Within 24 h, she was weaned off inotropes and vasopressors and decannulated from VA-ECMO.

LEARNING OBJECTIVES

- To recognize the clinical presentation of immune-mediated coronary spasm, KS.
- To demonstrate the severity of KS, which can result in cardiac arrest.
- To compare and contrast anaphylaxis with KS and propose KS as an underdiagnosed etiology of cardiac arrest.

From the ^aDepartment of Medicine, Division of Cardiology, University of Minnesota, Minneapolis, Minnesota; and the ^bDepartment of Medicine, Division of General Internal Medicine, University of Minnesota, Minneapolis, Minnesota. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, or patient consent where appropriate. For more information, visit the *JACC: Case Reports* [author instructions page](#).

Manuscript received November 13, 2019; revised manuscript received December 13, 2019, accepted December 20, 2019.

PAST MEDICAL HISTORY

The patient had a history of type 2 diabetes.

DIFFERENTIAL DIAGNOSIS

Anaphylaxis, Prinzmetal angina, and immune-mediated acute coronary syndrome, otherwise known as Kounis syndrome (KS), were considered.

MANAGEMENT

At hospital discharge, the patient was started on lisinopril for heart failure and warfarin for atrial fibrillation. While she was an outpatient, warfarin was transitioned to rivaroxaban, and neurohormonal therapy for heart failure was slowly added and uptitrated as tolerated. Before her hospitalization, aside from seasonal allergies, she reported no allergies or adverse reactions to medications. Over the 6 weeks after hospital discharge, she had 3 emergency department (ED) visits for lip angioedema with concern for airway compromise, in addition to a visit to her primary care physician for a whole-body rash.

INVESTIGATIONS

Reactions all began shortly after starting new medications, including lisinopril, rivaroxaban, digoxin, and carvedilol. For further evaluation, the patient was referred to an allergist, who ruled out immunoglobulin (Ig) E-mediated allergy, and chronic idiopathic urticaria was diagnosed. Importantly, mast cell degranulation (anaphylaxis) is mediated via IgE. Therefore, re-initiation of lisinopril was attempted and failed due to another ED visit for angioedema.

DISCUSSION

The differential diagnosis in this case was narrow, requiring a mechanism that would explain coronary spasm leading to cardiogenic shock. Although an anaphylactic reaction to iodinated contrast might be the most plausible explanation, there was diffuse coronary spasm, which is unexpected in anaphylaxis. Spasm from a Prinzmetal mechanism or direct catheter stimulation are unlikely because the spasm was diffuse and refractory to administration of intracoronary nitroglycerin. Additionally, during allergic evaluation, the patient's tryptase level was found to be mildly elevated. Therefore, our working diagnosis is KS induced by intravenous contrast. In this situation, coronary spasm led to cardiac arrest due to the patient's underlying cardiomyopathy and minimal cardiac reserve.

KS is an immune-mediated acute coronary syndrome (ACS) in response to an environmental trigger. It is a relatively rare and understudied syndrome, with fewer than 200 reported cases, but many have hypothesized that it is much more common (1). A prospective cohort study was conducted to evaluate the incidence of KS and included 138,911 patients presenting to the ED with chest pain. Within this population, KS was suspected in 27 patients (0.02%). However, within the subset of patients who experienced allergy-related symptoms (793 total), KS was a relatively common occurrence (3.4%) (2). Another group conducted a retrospective analysis of patients admitted to the hospital who likely had KS by analyzing those admitted with allergy-related symptoms within the National Inpatient Sample database (2007 through 2014). Of the 235,420 patients admitted, 2,616 (1.1%) were thought to have KS due to a concomitant ACS-related diagnosis. Within this subpopulation, all-cause in-hospital mortality was 9.7-fold higher than in the allergic group (3). These data show the severity of KS and suggest that KS is under-recognized but not rare.

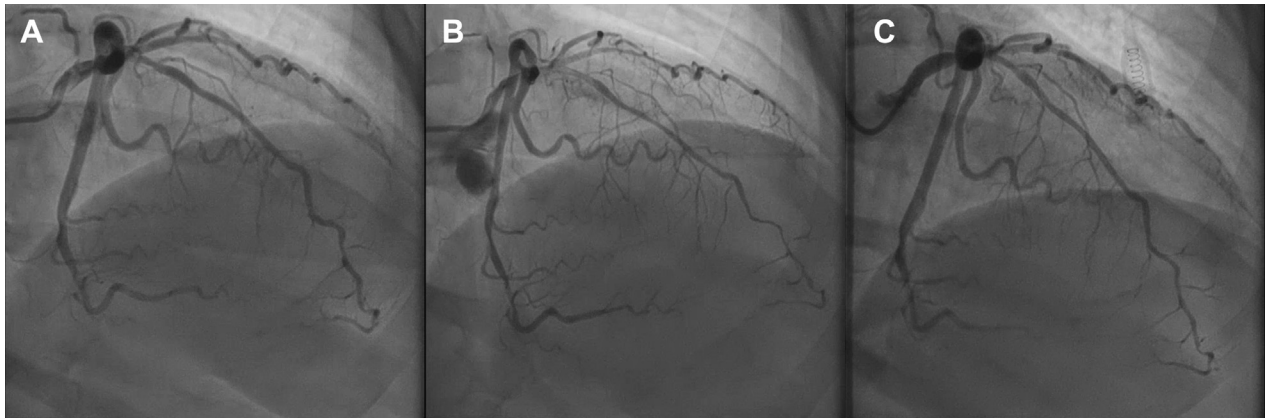
Three types of KS exist: type 1, ACS from coronary spasm in the absence of coronary artery disease; type 2, ACS from coronary spasm or plaque rupture in the presence of coronary artery disease; and type 3, coronary thrombosis that is found to contain mast cells/eosinophils (4). The differentiation of multiple types suggests that KS is a collection of pathologies rather than a single disease process. A recent review (5) called type 1 KS "anaphylactic cardiac collapse," pointing out that the complex phenotype seen when mast cells are activated might be masked because of impaired circulation impairing transport of inflammatory mediators to the skin and respiratory system.

Very little is known about the underlying molecular mechanisms of KS, but it is thought to be secondary to a poorly understood interaction of mast cells, macrophages, platelets, and T lymphocytes (6). In contrast to an allergic reaction, activation of mast cells in KS does not require degranulation, and the activation mechanism is thought to be IgE independent. Because type I KS can appear similar to anaphylaxis, multiple reports have described the importance of ruling out KS with an electrocardiogram before treating anaphylaxis, because epinephrine will worsen KS (7).

To compare KS to other inflammatory disorders, Ricciardi et al. (8) measured levels of advanced oxidation protein products (AOPPs) and advanced

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome
AOPP = advanced oxidation protein products
ED = emergency department
FFR = fraction flow reserve
KS = Kounis syndrome
VA-ECMO = venoarterial extracorporeal membrane oxygenation

FIGURE 1 Coronary Angiogram Images

Coronary angiogram images showing left anterior descending and left circumflex arteries both (A) before and (B) during spasm and (C) after spasm on venoarterial extracorporeal membrane oxygenation.

glycation end products in patients who had a diagnosis of KS (8). These serve as a surrogate for reactive oxygen species, which are difficult to measure directly in patients. In contrast to inflammatory disorders that are associated with an increase in both AOPPs and advanced glycation end products, it was found that only AOPPs were increased in patients with KS. This finding is also observed in mastocytosis, which involves the accumulation of dysfunctional mast cells within an organ system. If KS is a variant of mastocytosis, it would likely involve inappropriate proliferation of intracardiac mast cells that are activated in response to an environmental trigger.

Sulzgruber et al. (9) investigated the relationship between immune system dysfunction and cardiovascular disease. Patients with heart failure and atrial fibrillation were shown to have increased cytotoxic T cells. Furthermore, the number of cytotoxic T cells was found to be an independent predictor of both cardiovascular and all-cause mortality (9). Although this study did not specifically investigate KS, there may be a common molecular pathway, because our patient's presenting phenotype was also heart failure and atrial fibrillation.

FOLLOW-UP

It has been 2 years since the patient's initial presentation, and her systolic function has normalized with stable doses of metoprolol, spironolactone, hydralazine, and isosorbide dinitrate. She has not had further allergic-like reactions.

CONCLUSIONS

This case was important to report for 3 reasons. 1) KS is significantly under-recognized and could offer an explanation in patients with angina or cardiac arrest and a nondiagnostic follow-up investigation. Additionally, no etiology is discovered in 20% of pulseless electrical activity cardiac arrests (10). Post-arrest, KS should be considered after common diagnoses have been excluded. Those with type 1 KS would have unremarkable coronary angiograms but would show ischemic changes on electrocardiography before cardiac arrest. Unfortunately, those with type 2 or 3 KS would have coronary angiograms consistent with plaque rupture or coronary thrombosis, making a conclusive diagnosis difficult. 2) In patients with multiple true allergies to medications/agents, the potential for KS should be considered. In these patients, physicians should specifically inquire about chest pain-related symptoms, because patients with KS often report angina in the absence of ST-segment changes or biomarker elevation. If underlying KS is a likely comorbidity, the treating physician should consider the possibility of spasm in response to new agents/medications. If the patient has low cardiac reserve, further medical evaluation should be planned carefully. 3) The underlying mechanisms of KS are not well understood, making treatment of patients with KS difficult. It would seem reasonable to treat these patients similar to those with anaphylactic reactions to a medication: avoid the offending

agent(s). However, because patients with KS seem to have a tendency toward reaction to multiple medications, prevention of future episodes requires exercising caution when exposing the patient to any new medication/therapy while also avoiding offending agents. Finally, due to this heightened likelihood of reaction to medications, it is impor-

tant to develop an allergic action plan with the patient.

ADDRESS FOR CORRESPONDENCE: Dr. Jason A. Bartos, UMN-Cardiology Division, 420 Delaware Street SE, MMC 508, Minneapolis, Minnesota 55455. E-mail: jabartos@umn.edu.

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KEY WORDS allergic reaction, anaphylaxis, Kounis syndrome, PEA arrest

APPENDIX For a supplemental video, please see the online version of this paper.