Official Title: A Rare Presentation of Kounis Syndrome Induced by Echocardiography Contrast

Short Title: Kounis Syndrome Caused By Echo Contrast

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A Rare Presentation of Kounis Syndrome Induced by Echocardiography Contrast

Kounis syndrome is an inflammatory-mediated allergic response that manifests with clinical signs of acute coronary syndrome. This allergic reaction can be precipitated by common triggers in patients with atopy such as food, environmental allergens, and contrast agents (1). This uncommon phenomenon can be challenging to diagnose due to overlapping symptoms with coronary vasospasm. Early diagnosis is crucial to ensure the offending agent is quickly discontinued. We present a case of Kounis syndrome brought upon by the administration of sulfur hexafluoride lipid-type a microspheres (SHLTAM), a contrast agent used in certain echocardiographic studies during the workup of atypical cardiac symptoms.

Case Presentation

A 51-year-old man presented with chest pain, dyspnea, dizziness, chest heaviness, and diaphoresis that started after working outside for an extended period. His past medical history was notable for coronary artery disease, hypertension, active cocaine use, heart failure with reduced ejection fraction, and left ventricular (LV) thrombus on warfarin with subtherapeutic INR. There was no reported nor documented allergy history including sulfur products. His most recent left heath catheterization three months prior to admission showed patent stents in the obtuse marginal (OM), left anterior descending (LAD) and right coronary artery (RCA). On physical exam, he was afebrile, breathing comfortably on room air, and in no acute distress. Initial electrocardiogram (EKG) showed sinus rhythm with minimal anterolateral ST depressions and an intraventricular conduction delay (Supplementary Figure S1), consistent with findings on previous EKGs. Laboratory evaluation was significant for elevated high sensitivity troponin of 62 ng/L, creatinine of 3.3 mg/dL (baseline 0.9-1.1 mg/dL), BUN of 51 mg/dL, and CK of 120 U/L. Urine toxicology report was positive for cocaine. The patient was subsequently admitted for further cardiac work-up and treatment of acute kidney injury.

The patient’s troponins trended down over the next 16 hours, decreasing to 31.9 ng/L and 29.0 ng/L. On day two of admission, transthoracic echocardiography (TTE) with SHLTAM contrast was obtained for surveillance of the LV thrombus and compared to his baseline echo from four months prior to his hospitalization (Video 1a-1c). The study showed an ejection fraction of 40-45%. The LV thrombus was diagnosed on the echocardiogram four months before his admission. Shortly after the administration of echo contrast, a rapid response was called for tachypnea, hypotension, mouth swelling, 10/10 chest pain in the sternal area, and decreased responsiveness. Focused physical examination identified a diffuse confluent urticarial rash, edematous lips and tongue, and paradoxical breathing with wheezing heard on auscultation. EKG showed ST elevations in anterior leads and V2-V3 (Figure 1) and a troponin of 82.9 ng/L. Complete blood count with differential did not show elevated eosinophil counts before or after administration of contrast. Epinephrine, Solumedrol, and Benadryl were administered for suspected anaphylaxis and heparin drip was restarted. Repeat EKG obtained fifteen minutes later showed resolution of the acute ST changes (Supplementary Figure S2). A troponin obtained after the anaphylactic event trended down from 65.3 ng/L. Given the initial ST elevations on EKG, the patient was taken for urgent cardiac catheterization. Left heart catheterization revealed patent stents in the LAD, OM first branch, and RCA in addition to non- obstructive coronary disease (Supplementary Video S1a-
There weren’t any acute occlusions that could account for the ST changes during his anaphylactic episode. A follow-up TTE one day later showed an ejection fraction of 45-50%, mildly enlarged ventricular wall thickness, and resolution of the LV thrombus. (Supplementary Video S2).

Upon discharge, the patient’s antihypertensive was switched from lisinopril to losartan as a prophylactic measure against potential bradykinin reactions from ACE inhibitor usage. He followed up with cardiology four weeks after discharge and was reportedly doing well. No changes to patient care or medications were made at that visit and he was counselled on permanent cessation of cocaine.

**Discussion**

Anaphylactic symptoms and ST segment elevations on EKG following exposure to SHLTAM (Lumason®) during echocardiography is clinically consistent with a diagnosis of Kounis syndrome. This rare allergic-mediated disorder has been diagnosed clinically to the current date and has three different variants: vasospastic allergic angina, allergic myocardial infarction, and stent thrombosis (1). Antibiotics and insect bites were the most commonly reported triggers to induce Kounis syndrome across the literature with many other triggers reported including bean ingestion, anesthetic regimens, and vaccines (2). A review of our patient’s allergenic history did not reveal any incidence of allergic nor anaphylactic reactions to other sulfur-containing molecules. His lisinopril was started five years prior to admission and he was not initiated on any new medications within six months prior to his hospitalization. Furthermore, this was his third such exposure to SHALTAM echo contrast.

Contrast agents used in various imaging modalities were rarely reported as triggers to Kounis syndrome; in the literature review by Shibuya et al., ten cases of Kounis syndrome were associated with contrast media since 1991 (3). The offending contrast agents included iopromide, iohexol, gadoterate meglumine, and iopamidol. A single-center study in the Netherlands of adverse events from sulfur hexafluoride (SonoVue), a contrast agent widely used in Europe, identified an incidence of only 0.9% of anaphylaxis cases from 352 cardiac patients following during a four-year period (4). The paucity of cases may explain why early and accurate diagnosis of Kounis syndrome is incredibly challenging in the acute setting.

Despite the similar clinical symptoms and EKG changes seen in acute coronary syndrome, the main goal of treatment for Kounis syndrome is effectively terminating the anaphylactic reaction with antihistamines, corticosteroids, and epinephrine. Once control of the anaphylactic reaction has been achieved, standard treatment for acute coronary syndrome can be implemented. The decision to pursue cardiac catheterization and echocardiography is controversial in the setting of allergic symptoms; however, acute ST changes seen in Kounis syndrome often compel clinicians to definitively rule out acute coronary syndrome. Although the vast majority of cases are secondary to coronary vasospasm seen in subtype one of Kounis syndrome, evaluation with echocardiography may be required to exclude new wall motion changes. In a retrospective analysis evaluating 78,383 administered doses of perflutren, only four patients developed anaphylactic-like symptoms with perflutren (5). This is indicative of a very safe allergic profile and low risk for similar reactions.
Treatment of anaphylaxis in a patient with coronary disease and recent cocaine use as in our patient carries an elevated risk of provoking a fatal arrhythmia. Epinephrine’s activation of alpha-adrenoreceptors by way of its effect on hepatic calcium-dependent potassium channels can cause a sharp decrease in plasma potassium levels (6). Severe hypokalemia is a well-known cause of ventricular tachyarrhythmias, particularly ventricular tachycardia and ventricular fibrillation. The risk is further augmented in patients who use cocaine, a potent vasoconstrictor that can also lower potassium levels and predispose users to ventricular arrhythmias. Our patient tested positive for cocaine three days prior to receiving SHLTAM contrast; therefore, a vasospasm from the illicit substance was in the differential during the rapid response. However, cocaine’s metabolite half-life of approximately six hours confers a low probability that a significant amount of the substance was present in the patient’s body to cause the cardiac and allergic event. Per hospital policy, no admitted patients are permitted to leave the hospital before the discharge process is complete with exceptions only made for those under comfort care orders or patients who effectively leave against medical advice. This rule is stringently enforced in patients with documented history of illicit substance use. Therefore, it is highly unlikely our patient would have been able to obtain cocaine after he was hospitalized.

The use of echocardiography across various inpatient and outpatient settings has been steadily increasing over the past years given its broad spectrum in detecting myocardial-related pathologies. Contrast agents in echocardiography are occasionally used to enhance left ventricular opacification, especially during stress testing. However, given the infrequent use of such agents, awareness regarding their active ingredients and cross-reactivity may be absent among many clinicians. SHLTAM, as an example, contains sulfur in its active ingredient which can trigger an anaphylactic reaction among patients with sulfonamide allergies. Perflutren and SHLTAM have been implicated in anaphylactic and fatal reactions when used with polyethylene glycol (an ingredient commonly found in laxatives and colonoscopy bowel preparations) with eleven reported cases in the literature (7). As a result, the FDA has issued an official warning against the use of such agents with polyethylene glycol.

In the aftermath of our patient’s anaphylactic reaction following exposure to SHLTAM contrast, there was a change in protocol in our facility to ensure patient safety. All echocardiograms at our hospital are now performed with perflutren.

- Sulfur Hexafluoride Lipid-Type A Microspheres contrast may induce a coronary artery vasospasm
- Consider Kounis syndrome in a patient with anaphylaxis and ST elevations after exposure to contrast

**Conclusion**

Kounis syndrome is a rare allergic-mediated phenomenon that can be precipitated by sulfur hexafluoride lipid type-a microspheres contrast as reported in our case. While there are not many reported cases in the literature of similar adverse reactions to this contrast material, clinicians should consider the adverse profile of commonly used agents and if necessary, consider switching to different contrast agents with safer profiles.
References


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Patient Consent

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