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Case Report

A Rare Presentation of Kounis Syndrome Induced by an Echocardiography Contrast

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Kounis syndrome is an inflammation-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 its having symptoms overlapping with those of coronary vasospasm. Early diagnosis is crucial to ensure that the offending agent is quickly discontinued. We present a case of Kounis syndrome brought on 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 international normalized ratio (INR). The patient had no reported or documented allergy history, including to sulfur products. His most recent left heart catheterization 3 months prior to admission, showed patent stents in the obtuse marginal artery, the left anterior descending artery, and the right coronary artery (RCA). On physical examination, he was afebrile, breathing comfortably on room air, and in no acute distress. Initial electrocardiogram (ECG) showed sinus rhythm with minimal anterolateral ST depressions and an intraventricular conduction delay (Supplemental Fig. S1), consistent with findings on previous ECGs. Laboratory evaluation was significant for elevated high-sensitivity troponin level of 62 ng/L, creatinine level of 3.3 mg/dL (baseline 0.9-1.1 mg/dL), blood urea nitrogen level of 51 mg/dL, and creatinine kinase level of 120 U/L. The urine toxicology report was positive for cocaine. The patient was admitted subsequently for further cardiac workup and treatment of acute kidney injury.

The patient's troponin levels trended down over the next 16 hours, decreasing to 31.9 ng/L and 29.0 ng/L. On day 2 of admission, transthoracic echocardiography with SHLTAM contrast was obtained for surveillance of his LV thrombus and was compared to his baseline echo from 4 months prior to his hospitalization (Videos 1-3, view video online). The study showed an ejection fraction of 40%-45%. The LV thrombus was diagnosed on the echocardiogram 4 months before his admission. Shortly after the administration of the echo contrast agent, 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. An ECG showed ST elevations in the anterolateral leads (Fig. 1) and a troponin level of 82.9 ng/L. A complete blood count with differential did not show elevated eosinophil counts before or after administration of the contrast agent. Epinephrine, Solu-Medrol, and Benadryl were administered for suspected anaphylaxis, and heparin drip was restarted. A repeat ECG obtained 15 minutes later showed resolution of the acute ST changes (Supplemental Fig. S2). A troponin level obtained after the anaphylactic event trended down from 65.3 ng/L. Given the initial ST elevations on ECG, the patient was taken for urgent cardiac catheterization. Left heart catheterization revealed patent stents in the left anterior descending artery, obtuse marginal first branch, and right coronary artery in addition to nonobstructive coronary disease (Videos 4 and 5, view videos online). No acute occlusions were present that could account for the ST changes during his anaphylactic episode. Follow-up transthoracic echocardiography 1 day later showed an ejection fraction of 45%-50%, mildly enlarged ventricular wall thickness, and resolution of the LV thrombus (Video 6, view video online).

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Novel Teaching Points

- Sulfur hexafluoride lipid-type a microspheres contrast agent may induce a coronary artery vasospasm.
- Kounis syndrome should be considered in patients with anaphylaxis and ST elevations after exposure to a contrast agent.

Upon discharge, the patient's antihypertensive medication was switched from lisinopril to losartan as a prophylactic measure against potential bradykinin reactions from angiotensin-converting enzyme inhibitor usage. He followed up with cardiology 4 weeks after discharge and reportedly was doing well. No changes to patient care or medications were made at that visit, and he was counselled on permanent cessation of cocaine use.

Discussion

Anaphylactic symptoms and ST-segment elevations on ECG following exposure to SHLTAM (Lumason, Bracco Diagnostics Inc, Milan, Italy) during echocardiography are clinically consistent with a diagnosis of Kounis syndrome. This rare, allergy-mediated disorder has been diagnosed clinically to date and has 3 different variants—vasospastic allergic angina, allergic myocardial infarction, and stent thrombosis.[1] Antibiotics and insect bites were the most commonly reported triggers that induced Kounis syndrome, across the literature, with many other triggers reported, including bean ingestion, anaesthetic regimens, and vaccines.[2] A review of our patient's allergenic history did not reveal any incidence of allergic or anaphylactic reactions to other sulfur-containing molecules. His lisinopril was started 5 years prior to admission, and he was not initiated on any new medications within 6 months prior to his hospitalization. Furthermore, this exposure was his third to the SHLTAM echo contrast agent.

Contrast agents used in various imaging modalities rarely have been reported as triggers of Kounis syndrome; the literature review by Shibuya et al.indicates that 10 cases of Kounis syndrome associated with contrast media use have been reported since 1991.[3] The offending contrast agents include iopromide, iohexol, gadoterate meglumine, and iopamidol. A single-centre study in the Netherlands of adverse events from sulfur hexafluoride (SonoVue, Bracco Diagnostics Inc) exposure, a contrast agent widely used in Europe, identified an incidence of only 0.9% of anaphylaxis cases from 352 cardiac patients followed during a 4-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 ECG changes seen in acute coronary syndrome, for Kounis syndrome, the main goal of treatment 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 the coronary vasospasm seen in type 1 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 4 patients developed anaphylactic-like symptoms.[5] This result is indicative of a very safe allergic profile and a low level of risk for similar reactions.

Treatment of anaphylaxis in a patient with coronary disease and recent cocaine use, as in our patient, carries an elevated

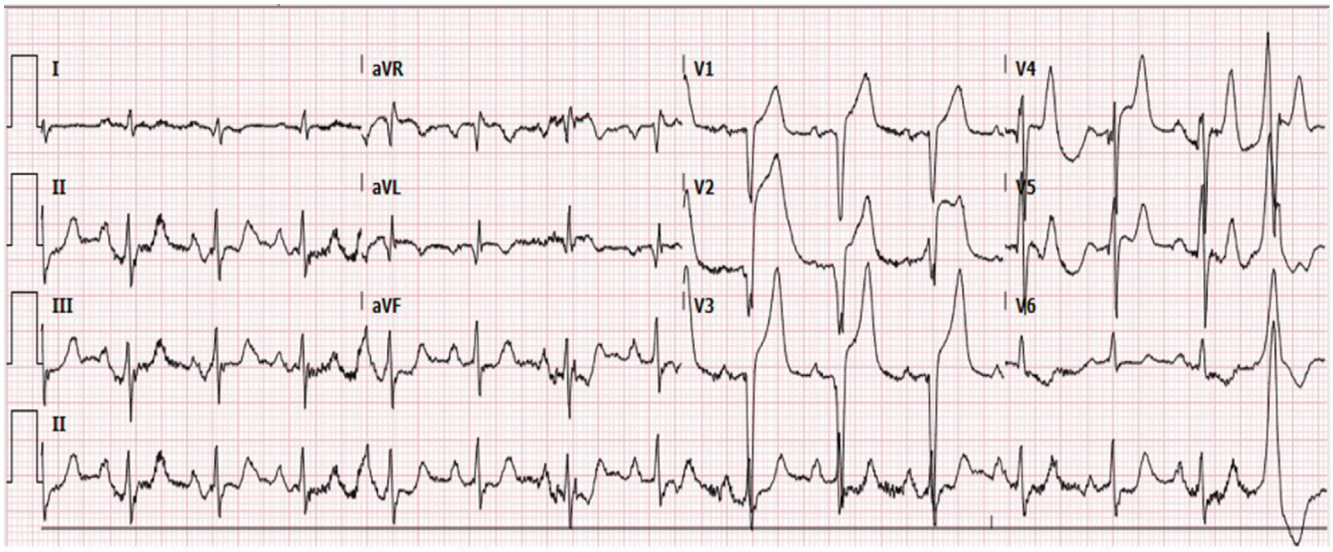

Figure 1. Initial electrocardiogram ordered due to decreased responsiveness and chest pain after echocardiogram with contrast. ST elevations are seen in the anterolateral leads.

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 3 days prior to receiving the SHLTAM contrast agent; therefore, a vasospasm from the illicit substance was in the differential during the rapid response. However, cocaine's metabolite half-life of approximately 6 hours confers a low probability that the amount of the substance present in the patient's body was significant enough to cause the cardiac and allergic event. Per hospital policy, no admitted patients are permitted to to leave the hospital before the discharge process is complete, with exceptions made only for those under comfort care orders or patients who effectively leave against medical advice. This rule is enforced stringently in patients with a documented history of illicit substance use. Therefore, our patient is highly unlikely to 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 several years, owing to its broad spectrum in detecting myocardial-related pathologies. Contrast agents in echocardiography occasionally are 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 they are used with polyethylene glycol (an ingredient commonly found in laxatives and colonoscopy bowel preparations), with 11 cases having been reported in the literature.[7] As a result, the US Food and Drug Administration has issued an official warning against the use of such agents with polyethylene glycol.

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

Conclusion

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

Ethics Statement

The research reported has adhered to the relevant ethical guidelines.

Patient Consent

The authors confirm that patient consent is not applicable to this article. This is a retrospective case report using deidentified data. Per our administration's research policy, institutional review board approval was not required in order to proceed with the writing and publication of this case report.

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Disclosures

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References

1. Kounis NG. Coronary hypersensitivity disorder: the Kounis syndrome. Clin Ther 2013;35:563-71.
2. Memon S, Chhabra L, Masrur S, Parker MW. Allergic acute coronary syndrome (Kounis syndrome). Proc (Bayl Univ Med Cent) 2015;28:358-62.
3. Shibuya K, Kasama S, Funada R, Katoh H, Tsushima Y. Kounis syndrome induced by contrast media: a case report and review of literature. Eur J Radiol Open 2019;6:91-6.
4. Geleijnse ML, Nemes A, Vletter WB, et al. Adverse reactions after the use of sulphur hexafluoride (SonoVue) echo contrast agent. J Cardiovasc Med (Hagerstown) 2009;10:75-7.
5. Wei K, Mulvagh SL, Carson L, et al. The safety of deFinity and Optison for ultrasound image enhancement: a retrospective analysis of 78,383 administered contrast doses. J Am Soc Echocardiogr 2008;21:1202-6.
6. Brown MJ, Brown DC, Murphy MB. Hypokalemia from beta2-receptor stimulation by circulating epinephrine. N Engl J Med 1983;309:1414-9.
7. American College of Radiology. FDA warns against some ultrasound contrast agents in patients with PEG allergy. Available at: https://www.acr.org/Advocacy-and-Economics/Advocacy-News/Advocacy-News-Issues/In-the-April-24-2021-Issue/FDA-Warns-Against-Some-Ultrasound-Contrast-Agents#:~:text=The%20federal%20Food%20and%20Drug. Accessed February 4, 2023.

Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at https://www.cjcopen.ca/ and at https://doi.org/10.1016/j.cjco.2023.07.009.