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A Vasospasm Conundrum: An Acute Myocardial Infarction in the setting of Anaphylaxis and Epinephrine administration. A Case Report

(Short title: Acute Myocardial Infarction Due to Anaphylaxis)

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Abstract

Background: *Acute myocardial infarction (AMI) and angina secondary to vasospasm are widely described in literature. The most common etiologies include administration vasoactive agents, allergic acute coronary syndrome, exposure to cold weather, and stress. We present a case of AMI secondary to intramuscular (IM) epinephrine used to treat anaphylaxis in a patient receiving IV contrast. We discuss diagnostic challenges, treatment considerations, and management of anaphylaxis and AMI in this patient.*

Case Report: *A 65-year-old female patient presented for elective computed-tomography urogram to evaluate microscopic hematuria. She was pre-medicated with prednisone and diphenhydramine due to a remote history of severe anaphylaxis to iodinated intravenous (IV) contrast. Soon after contrast was administered, she developed anaphylaxis and was transferred to the emergency department (ED). She was treated with epinephrine 0.3 mg IM, methylprednisolone 125 mg and diphenhydramine 50 mg intravenously. Shortly after treatment in the ED, she developed substernal chest pain, ST elevations, and troponin elevation consistent with AMI. After extensive work-up it was concluded the likely trigger for her AMI was vasospasm due to IM epinephrine use.*

Conclusion: *Our patient had at least two possible etiologies of her AMI, epinephrine and anaphylaxis (mast cell activation). Preventative measures against future events include avoiding vasoactive medications in the future. However, given the life-saving effect of epinephrine in the setting of anaphylaxis, shared decision making with the patient resulted in leaving epinephrine off the patient's allergy list but informing her of the risks in the future*

MeSH Keywords: *Acute myocardial infarction; vasospasm, acute myocardial infarction; anaphylaxis, acute myocardial infarction post- therapeutic dose of epinephrine, Kounis syndrome.*

Introduction

In 1959, Dr. Myron Prinzmetal published a preliminary report describing 32 cases of a variant form of angina occurring at rest. These patients had normal ECGs in the absence of pain, normal examinations, and normal stress tests. [1] Most patient's angina followed a circadian pattern, with attacks consisting of rhythmic bouts of pain occurring at night. Doctor Prinzmetal suggested coronary artery spasm might be the cause, a hypothesis confirmed years later. [1]

Since 1959, vasospasm as a cause of acute coronary syndrome (ACS) has been widely described and studied, and many triggers of vasospasm have been identified. A reversible, diffuse or focal vasoconstricution known as coronary artery spasm (CAS) is the most common diagnosis among patients presenting with myocardial ischemia without evidence of obstructive coronary artery disease. CAS accounts for up to 50% of patients presenting with angina and 57% of patients presenting with ACS. [2] The pathophysiology of CAS is complex and a variety of mechanisms have been proposed including endothelial dysfunction, oxidative stress, smooth muscle

hypercontractility, chronic inflammation, and autonomic dysfunction. [2] Matta et.al. postulated the following risk factors for CAS; age, smoking, hypercholesterolemia, diabetes mellitus, elevated Hs-CRP, stress, light morning exercise, cold exposure, hyperventilation, hypomagnesemia, Valsalva manoeuvre, alcohol and cocaine use, pharmacologic agents (sympathomimetic, parasympathomimetic, beta-blockers, anticholinergics), and platelet activation. [2]

In 1950, Pfister et.al proposed an association between AMI and allergic reactions, however it wasn't until 1991 that Kounis et. al. introduced the concept of allergic angina later to be known by Kounis Syndrome. [3], [4], [5], [6] Kounis syndrome consists of three major types; vasospastic allergic angina (Type I) characterized by pure vasospasm with normal angiogram, allergic myocardial infarction (Type II) characterized as spasm in the setting of coronary artery disease, and in-stent thrombosis with occluding thrombus (Type III). [7] Although most clinical presentations of Kounis syndrome relate to the coronary vasculature, there are recent reports of Kounis-like syndrome involving cerebral and/or mesenteric arteries raising concern for Kounis Syndrome being a systemic malady. [5], [6], [7]

Myocardial infarction (MI) in the setting of a severe, systemic allergic reaction such as anaphylaxis is likely fatal if untreated has been widely described in literature related to Kounis syndrome. Additionally, MI related to large doses of intravenous epinephrine due to its vasoconstrictive effects has been described. [8] There is a paucity of reports of MI in the setting of therapeutic or intramuscular (IM) administration of epinephrine. [9], [10], [11], [12], [13], [14].

We present a case of AMI in the setting of anaphylaxis after therapeutic IM epinephrine and discuss challenges treating and managing this patient.

Case Report

A 65-year-old female patient presented for elective computed-tomography urogram for evaluation of her persistent microscopic haematuria. She carried a remote history of severe anaphylaxis to IV contrast and was appropriately pre-medicated with standard doses of prednisone and diphenhydramine. Soon after contrast adminstration she developed significant chest and throat tightness, lip swelling, and dyspnea leading emergent transfer to the emergency department (ED) for concerns of anaphylaxis. In the ED she was treated with epinephrine 0.3 mg intramuscularly, methylprednisolone 125 mg and diphenhydramine 50 mg intravenously. After receiving treatment for her anaphylaxis, she developed chest pain and ST elevations in anterior/lateral leads of her electrocardiogram (ECG) raising concern for ACS.

Her medical history included: chronic dyspepsia with Barrett's oesophagus, hiatal hernia and remote Helicobacter pylori gastritis, microscopic haematuria, depression, hypovitaminosis D, remote history of anaphylaxis, and recent transient ischemic attack (TIA). Pertinent surgical history included appendectomy, partial hysterectomy and multiple orthopaedic surgeries. She endorsed a 40-pack year smoking history, quitting 15 years ago. She denied illicit drug use and endorsed social alcohol. She has a maternal family history of heart disease. Allergies included iodinated contrast, erythromycin, and shellfish. Home medications included aspirin 81 milligrams (mg) daily, atorvastatin 80 mg daily, cyclobenzaprine 5 mg every 8 hours as needed for pain, and over-the-counter laxatives.

On physical exam she was alert and in moderate to severe distress due to pain. Her vitals demonstrated blood pressure of 111/64 mmHg, heart rate of 90 bpm, respiratory rate of 20, a temperature of 36.9 degrees Celsius, and 96 % pulse oxymetry on ambient air. Her lungs were clear to auscultation, with intact distal pulses, warm skin, and good capillary refill. Her cardiovascular exam demonstrated regular rate, regular rhythm, without extra heart sounds. No evidence of lower extremity edema. Her abdomen was soft, non-tender, and non-distended. She had peri-oral angioedema and no skin rash.

ECG performed in the ED showed new anterolateral ST-elevations consistent with ACS (Figure 1). Laboratory results, including basic metabolic panel, complete blood count and international normalized ration (INR), were non-contributory. High-sensitivity (Hs)-Troponin level was 8 ng/L (reference range <54 ng/L), rising to 75 ng/L twenty minutes later, and 1,069 ng/L two hours later. SARS-CoV-2 Polymerase Chain Reaction (PCR) was negative. Urine toxicological screen negative for amphetamines, cocaine, benzodiazepines, methadone and opiates. Chest X-ray showed "low lung volumes with broncho-vascular crowding. No acute cardiopulmonary abnormality". Initial activation of cardiac catheterization laboratory was pursued, however due to patient's contrast allergy and ongoing anaphylaxis despite appropriate pre-treatment, clinical team decided to avoid further allergic insult and optimize medical therapy instead.

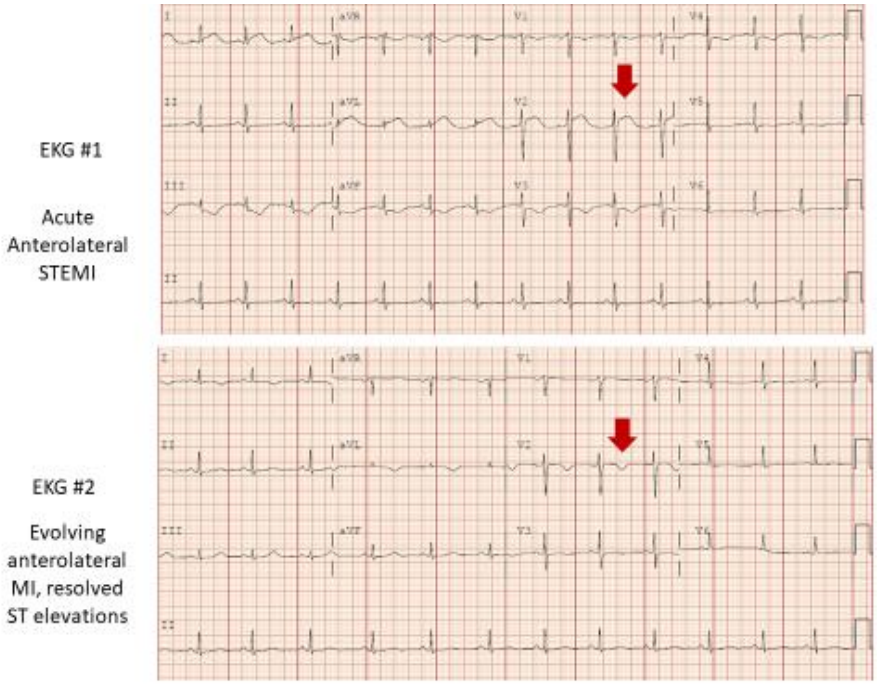

Figure 1. EKG #1: Red arrow demonstrating ST elevation seen primarly in lead V2. Additional elevations seen in lead I and aVL, with diffuse t-wave flattening and inversions in other leads. EKG #2: Red arrow demonstrating dynamic changes ST changes in lead V2, with additional ST and t-wave changes seen in leads I and aVL.

Cardiology physicians were consulted and she was admitted to the cardiac critical intensive unit (CCU). Hs-Troponin level peaked at 1,231 ng/L seven hours after presentation. In the CCU the patient was treated with a heparin drip, clopidogrel loading dose was given, and metoprolol was initiated. Metoprolol was soon discontinued thereafter due to hypotension. A transthoracic echo-cardiogram (TTE) was obtained hospital day 1 showing normal Left Ventricle (LV) function, no significant valve disease, and poor endocardial definition preventing definitive wall motion assessment. Subsequent nuclear myocardial perfusion study negative for AMI or stress-induced myocardial ischemia, LV with normal segmental wall motion and global systolic function consistent. Due to the aforementioned results and the high risk of anaphylaxis, a cardiac catheterization was not pursued with the consensus, among cardiologist and internists, that the likelihood of severe native coronary artery disease (CAD) was low. The patient remained stable and was transferred to a medicine floor for further management and stabilization. The remainder of her hospitalization was uneventful, metoprolol and clopidogrel were discontinued and aspirin and atorvastatin were initiated prior to discharge (see Figure 2 for hospital timeline).

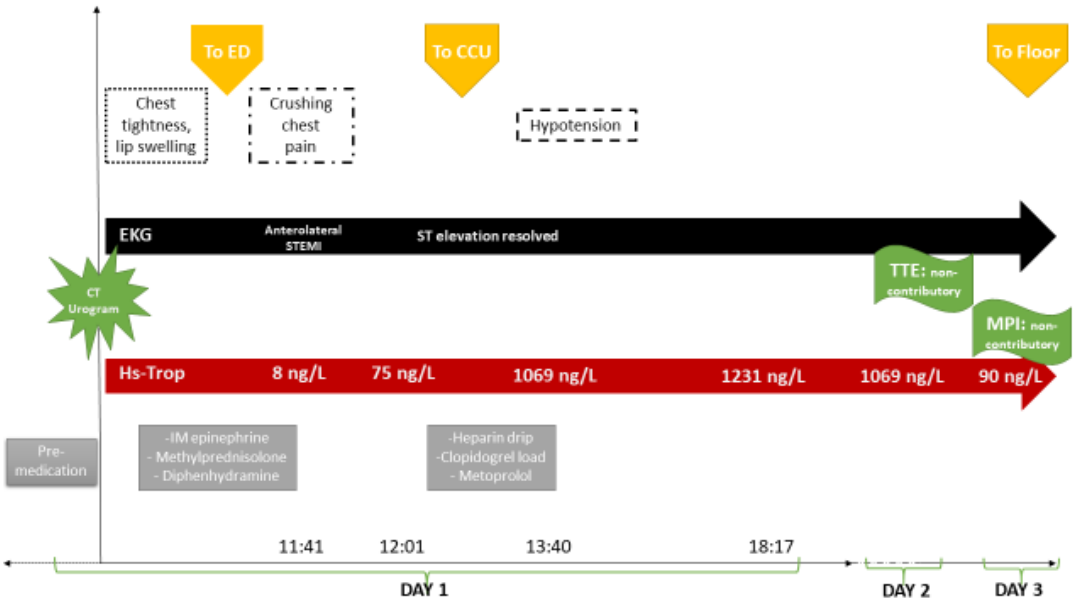

Figure 2: Demonstrates the clinical course of the patient from arrival to the ED through her transfer to the floor. She was discharged from the hospital two days after transfer to the floor.

Throughout her hospitalization, all involved provider teams engaged the patient on the conversation regarding her risk of developing vasospasm and myocardial infarction (MI) if she were to necessitate epinephrine for anaphylaxis in the future. It was determined the cause of her MI was likely secondary to CAS, either due to the therapeutic dose of epinephrine which was needed for the treatment of anaphylaxis versus a Kounis syndrome (likely Type I as there was low concern for coronary artery disease) in the setting of anaphylaxis. She verbalized her understanding and a note/ red-flag was added to chart to alert future providers that if she were to require epinephrine for her anaphylaxis to co-administer a low dose non-selective beta blocker and low dose IV diltiazem.

During her 1-month follow up visit at the cardiology clinic, cardiology recommended starting a low dose beta blocker for concern for another vasospasm. She deferred its initiation at the time of the visit and was referred to cardiac rehabilitation for persistent fatigue. She has yearly follow up with cardiology.

Discussion

The diagnosis of CAS in clinical practice is elusive. Provocation tests adjunctive to coronary angiography showing any luminal reduction associated to angina or ECG changes consistent with myocardial ischemia is widely understood as the most reliable method to diagnose CAS. [2], [15], [16] Intracoronary injection of ergonovine or acetylcholine are no longer used due to their multiple and serious side effects. Newer modalities such as intravascular ultrasound study (IVUS) and optical coherence tomography have been proposed for the diagnosis of CAS however these newer technologies are not widely available. [2], [17], [18] [19], [20] Cardiac magnetic resonance imaging (CMRI), a non-invasive testing methodology that is currently the gold standard for assessing ACS in patients with non-obstructive CAD, is controversial in use in diagnosing CAS. In summary, multiple testing modalities for the diagnosis of CAS can theoretically be used but their use is limited by their availability, all but CMRI are invasive procedures, and only IVUS and CMRI do not require intravenous contrast; hence making a definitive diagnosis of CAS elusive at best.

Shaker et.al. published 2020 updated guidelines for the management of anaphylaxis. [21] Anaphylaxis has a lifetime prevalence of 1.6 % -5.1%, with medications and stinging insects being the most common triggers in adults. Intramuscular administration of epinephrine (0.01 mg/kilogram (kg) of a 1:1000 solution, max dose 0.5 md in adults and 0.3 mg in children) into anterolateral thigh is the cornerstone of anaphylaxis management. Epinephrine is a non-selective adrenergic agonist that causes vasoconstriction, increases cardiac output, reverses bronchoconstriction and mucosal edema and stabilizes mast cells and basophils. Because of the vasoconstriction effects, it can lead to CAS and in certain patients to ACS but this complication is rare when administered intramuscularly. Antihistamines are second line treatment and there is no evidence supporting the use of glucocorticoids in anaphylaxis [21].

Kounis syndrome is a multisystem condition, most commonly attributed to coronary syndromes, of mast-cell associated disorders and inflammatory cell interactions inducing allergic, hypersensitivity, anaphylactic or anaphylactoid reactions. Its diagnosis is clinical and requires a high index of suspicion; even though not pathognomonic, measuring serum tryptase (30 minutes after initial episode), serum histamine (immediately after onset of event), Immunoglobulin E and cardiac troponins can help rule Kounis syndrome in. Evidence of severe myocardial ischemia in Thallium201 (Ta201) single-photon emission computed tomography (SPECT) in the setting of normal coronary angiogram can also be suggestive of Kounis syndrome. The recommended treatment of Kounis syndrome include intravenous corticosteroids and antihistamines. Calcium channel blockers and sublingual nitroglycerin can be administered to selected patients. [7]

Because it is not unusual that patients with Kounis syndrome present also with anaphylaxis, the management of these patients becomes a balancing act. Treating anaphylaxis can worsen CAS leading to ACS. Beta blockers, due to their unopposed action of alpha-adrenergic receptor, can also exaggerate CAS. In normotensive patients, adding calcium channel blockers and nitroglycerin can help minimize vasospasm. [6]

Our patient was admitted with an acute MI in the setting of anaphylaxis and post- IM epinephrine administration. Because of the lack of evidence of ischemia in TTE and MPI, as well as prompt resolution of symptoms and normalization of ECG and troponin, consensus was reached that the most likely cause of ACS was CAS, either secondary to Kounis syndrome versus vasoactive effect of epinephrine. More CAS sensitive cardiac imaging, such as CMRI are not available in our institution and imaging modalities requiring intravenous contrast were contraindicated in our patient; hence the diagnosis was based on clinical features. Alert was placed in the patient's medical record to suggest management approach in case of recurrence. All of these measures were discussed with and agreed upon with the patient and her family.

Conclusion

CAS is an under-recognized cause of ACS. There are multiple risk factors and precipitating factors for CAS; and definitive diagnosis of CAS as well as the definitive cause of CAS is challenging. Many patients presenting with ACS secondary to presumed CAS may have more than one risk or precipitating factors; so clinical management of these patients highlights the art of medicine and the primordial role that a multifaceted and multidisciplinary approach play for successful outcomes of patients with CAS.

Abbreviations

- Abbreviations are listed in alphabetical order.
- ACS: Acute Coronary Syndrome
- AMI: Acute Myocardial Infarction
- CAD: Coronary Artery Disease
- CAS: Coronary Artery Spasm

- CCU: Cardiac Critical intensive Unit
- CMRI: Cardiac Magnetic Resonance Imaging
- ECG: Electrocardiogram
- ED: Emergency Department
- Hs: High Sensitivity
- IM: Intra-muscular
- INR: International Normalized Ratio
- IV: Intravenous
- IVUS: Intravenous Ultrasound Study
- kg: Kilogram
- mg: milligram
- MI: Myocardial Infarction
- MPI: Myocardial Perfusion Imaging
- ng/L: nanogram/ Liter
- OCT: Optical Coherence Tomography
- PCR: Polymerase Chain Reaction
- SARS-CoV-2: severe acute respiratory syndrome-Coronavirus-2
- SPECT: Single Photon Emission Computed Tomography
- Ta: Thallium
- TIA: Transient Ischemic Attack
- TTE: Trans-Thoracic Echocardiogram

Declarations

- Ethical Approval and Consent to participate: Because case report is not considered Human Subject Research, Institutional Re-view Board (IRB) permission was not obtained. Patient provided both verbal and written consent for participation
- Consent for publication: Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.
- Availability of supporting data: CARE checklist and patient written consent available for editor's review
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