

Case Report

Kounis Syndrome With Samter–Beer Triad Treated With Intracoronary Adrenaline

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Kounis syndrome is a well-described clinical condition characterized by the simultaneous occurrence of chest pain and an allergic reaction accompanied by clinical and laboratory findings of angina caused by inflammatory mediators released during an allergic insult. We present the case of a 50-year-old male with the Samter–Beer triad of asthma, nasal polyps, and salicylate intolerance with an ST elevation myocardial infarction complicated with cardiac arrest due to multi-vessel coronary artery spasm secondary to aspirin anaphylaxis. Adrenaline is recommended during anaphylaxis but is controversial in Kounis syndrome as it may worsen coronary spasm. We report the use of intracoronary adrenaline in successfully reversing coronary artery spasm in this hemodynamically unstable patient. © 2015 Wiley Periodicals, Inc.

Key words: Kounis syndrome; coronary spasm; aspirin allergy; Samter–Beer triad; intracoronary adrenaline

INTRODUCTION

The association of an acute coronary syndrome (ACS) and an allergic reaction was first described in 1950 [1]. It was not until 1991 when Kounis and Zavras provided a detailed description of the allergic angina syndrome. It was described by the occurrence of chest pain and allergic reactions accompanied by clinical and laboratory findings of classical angina pectoris caused by inflammatory mediators released during the allergic insult [1]. The definition has been further expanded to encompass allergic myocardial infarction and stent thrombosis.

Kounis syndrome is divided into three subtypes. Type I is an allergic insult resulting in coronary vasospasm leading to angina pectoris with or without myocardial infarction in the patients with normal coronary arteries [2]. Type II occurs in patients with pre-existing atherosclerotic coronary artery disease in which the allergic insult and subsequent release of inflammatory mediators induce coronary artery spasm, in addition to plaque erosion or rupture, resulting in acute myocardial infarction [2]. Type III has been recently described as a variant in patients with coronary artery stent thrombosis in which the aspirated thrombus specimens stained with hematoxylin–eosin and Giemsa demonstrate the presence of eosinophils and mast cells [3].

CASE

A 50-year-old Caucasian male presented to the Emergency Department in active resuscitation for a pulseless electrical activity (PEA) cardiac arrest. The patient had a background of well-controlled asthma on regular inhalers, in addition to sinusitis with nasal polyps for which he had a polypectomy several years prior. His cardiovascular risk factors included well-controlled hypertension and hypercholesterolemia. His other medications included simvastatin and irbesartan. He had history of allergy with anaphylaxis requiring

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adrenaline secondary to a non-steroidal anti-inflammatory (NSAID) ibuprofen.

The patient developed chest pain soon after inadvertently ingesting a tablet of aspirin to treat a mild headache. While driving back from work he stopped by a service station to purchase paracetamol but accidentally purchased a box of aspirin. Within one hour of ingestion his symptoms worsened with severe central chest pain and shortness of breath associated with diarrhoea and vomiting. There was no urticarial rash or orofacial swelling. On arrival of the paramedics, the patient was in distress with a respiratory rate of 32 breaths per minute, sinus tachycardia at 112 beats per minute, blood pressure at 90/60 mm Hg, and saturating 91% on room air. A 3-lead electrocardiogram (ECG) showed ST-elevation in the inferior leads (II, III, AVF). The patient was given sub-lingual glyceryl trinitrate (GTN) and intravenous fentanyl. Soon after the patient became sinus bradycardic and went into a PEA arrest in the ambulance. The patient had immediate cardiopulmonary resuscitation (CPR) with four boluses of 1 mg of adrenaline. He had two episodes of ventricular tachycardia, which were successfully cardioverted into sinus rhythm and was eventually resuscitated after 30 min of downtime. During intubation it was noted the patient had laryngeal edema and was difficult to ventilate secondary to bronchospasm.

A 12-lead ECG in the emergency department showed significant ST-elevation in AVR and global ST-depression raising the suspicion of multi-vessel or left-main disease. The patient was urgently transferred for coronary angiography performed via the right femoral artery. This showed focal spasm in all three coronary arteries (Fig. 1). His left main artery was normal. His left anterior descending artery (LAD) had occlusive mid-vessel spasm and the left circumflex artery (LCx) had mid-vessel spasm in the first two obtuse marginal branches. His right coronary artery (RCA) showed spasm in the mid vessel, mid posterior descending artery (PDA) and proximal posterior left ventricular (PLV) artery. Initially, there was suspicion that there was a thrombotic occlusion of the LAD, hence the mid vessel was treated with aspiration thrombectomy with little improvement in the angiographic appearance. There was mild improvement in mid LAD caliber and flow following balloon angioplasty at 6 atmospheres using a 2.5 × 15 mm balloon. The patient was hemodynamically unstable with a systolic blood pressure at 80 mm Hg and was difficult to ventilate due to severe bronchospasm. Administration of systemic or intracoronary GTN was contra-indicated in the presence of hypotension. An intra-aortic balloon pump (IABP) was inserted and, an adrenaline infusion was commenced at 2 µg/min and uptitrated to a maximum dose of 8 µg/min.

Given the on-going hemodynamic instability from multi-vessel spasm, despite IABP support and intravenous adrenaline, the patient was given intracoronary adrenaline. Three boluses between 20 and 50 µg were administered. Within 10 min of administration there was complete resolution of spasm in all three coronary vessels with thrombolysis in myocardial infarction (TIMI) 3 flow and no evidence of underlying obstructive coronary artery disease. A left ventriculogram post relief of spasm showed normal systolic function.

Subsequent investigations showed an elevated white cell count at 21.2 with significant neutrophilia and a raised eosinophil count. His peak high-sensitivity troponin was 33,800 ng/L. A mast cell tryptase at the time of presentation was elevated at 17.7 µg/L, which normalized the next day to 6.8 µg/L.

The patient spent several days in ICU with the IABP removed within 48 hr. He remained on an adrenaline infusion for 5 days for severe bronchospasm and was also treated with regular nebulized salbutamol and intravenous corticosteroids. He was reviewed by the Immunology team, who prescribed an adrenaline auto injector and advised against all NSAIDs and aspirin in the future. He had made a full gross neurological recovery and was subsequently discharged home.

DISCUSSION

Kounis syndrome is mainly driven by the mediators of mast cell degranulation in addition to other inflammatory cells such as macrophages and T lymphocytes [4]. Mast cells are activated by exposure to an antigen, resulting in degranulation of stored and newly formed inflammatory mediators. Histamine activates platelets, the thrombotic pathway by inducing tissue factor and promotes coronary vasoconstriction [4]. Tryptase and chymase can activate matrix metalloproteinases, which can degrade collagen caps and induce plaque erosion and rupture [5]. In addition, tryptase can activate the thrombotic pathway and chymase facilitates conversion of angiotensin I into angiotensin II, a potent vasoconstrictor [4]. Leukotrienes, thromboxane, and platelet activating factor are also secreted, which all work by activating platelets, mediating platelet aggregation and vasoconstriction [4].

Mast cells have also been implicated in non-allergic myocardial infarction. Increased levels of mast cell mediators such as histamine, tryptase, chymase, thromboxane, leukotrienes, and interleukin-6 have been found in patients with non-allergic ACS and unstable angina [4]. This raises the question whether ACS precipitates mast cell degranulation or these mast cell mediators are involved in precipitating ACS. Increasing evidence suggests the latter with human autopsies

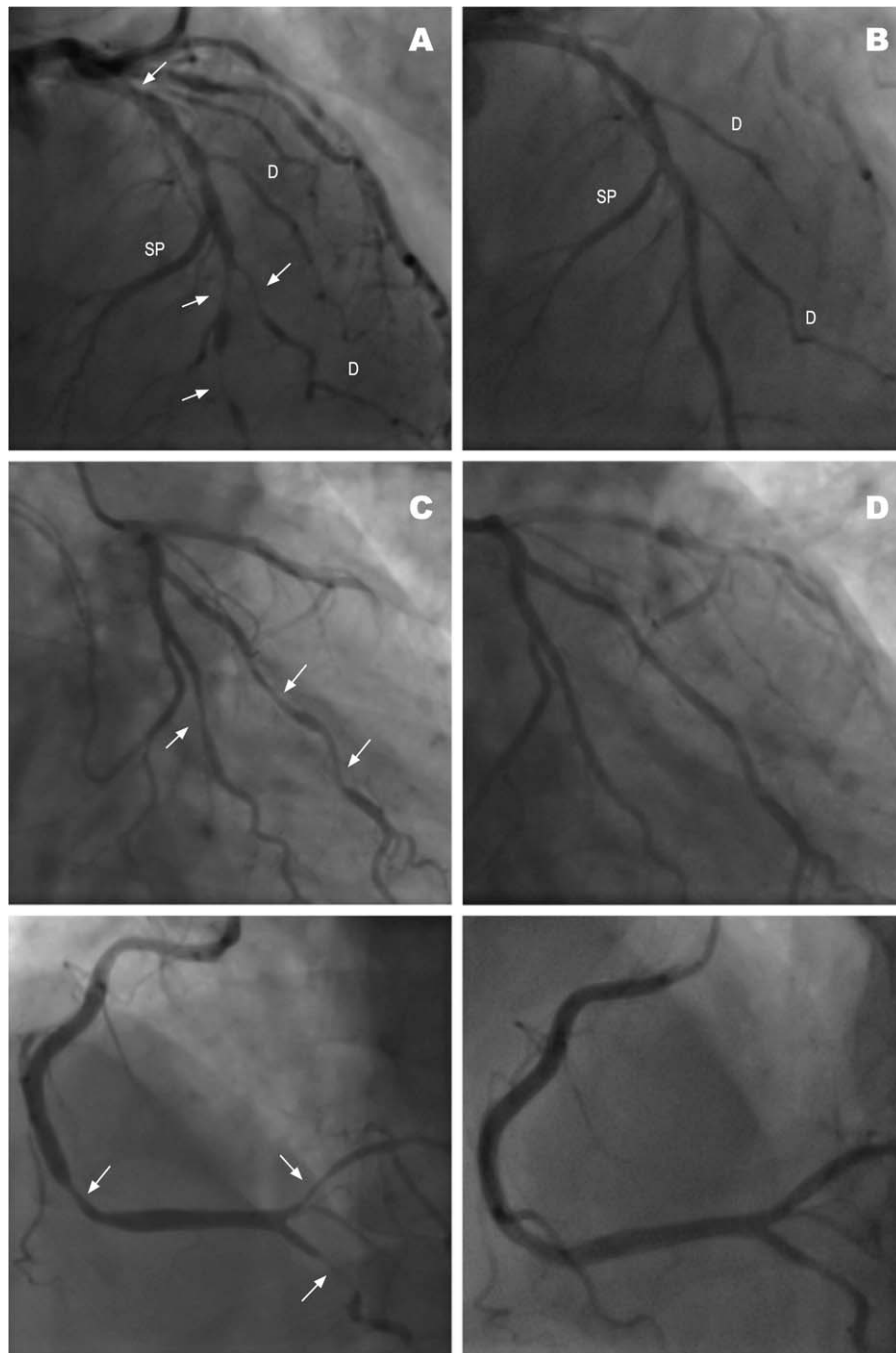


Fig. 1. Coronary angiogram before and after intracoronary adrenaline. **A:** LAD and diagonal artery spasm, **(B)** LAD after intracoronary adrenaline*, **(C)** Obtuse margin artery spasm*, **(D)** Obtuse marginal artery after intracoronary adrenaline*, **(E)** RCA, PDA, and PLV artery spasm, **(F)** RCA after intracoronary

adrenaline. **D:** diagonal artery; **SP:** septal perforator artery. *Inadequate contrast filling of LCx (Image B) and LAD (Image C, D) due to technical issues with short left main artery resulting in preferential engagement of Judkins left catheter into the LAD and LCx, respectively.

studies showing that the level of mast cells at plaque rupture are 200 times greater compared to normal endothelial segments [6]. In addition, a higher proportion of mast cells have been found at shoulder sites of susceptible plaque, indicating that mast cells invade the region

prior to the ACS [7]. This is also supported by evidence that circulating blood contains mast cell precursors, which require days to weeks to differentiate into mature cells, hence the presence of mature mast cells at the site of ruptured or vulnerable plaque suggests they must

have been there prior to ACS [4]. Given that mast cells and their mediators are capable of promoting arterial spasm, thrombosis, platelet activation, and plaque erosion, the inhibition of mast cell degranulation is a potential future target for the pharmacological primary and secondary prevention of ACS.

A broad range of drugs, foods, and environmental exposures have been associated with Kounis syndrome [4]. In theory, any exposure that can trigger an allergic reaction has the potential to cause Kounis syndrome. In our patient, aspirin was the culprit, which occurred in the context of the well-described Samter–Beer triad of asthma, nasal polyps, and aspirin sensitivity [8]. The triad usually begins with chronic sinusitis followed by nasal polyposis and then the development of salicylate intolerance and asthma over 1–5 years [9]. The intolerance to salicylates and NSAIDs is believed to be driven by a non-IgE mediated pathway, with inhibition of cyclooxygenase leading to overproduction of cysteinyl leukotrienes, which in turn promote the release of inflammatory mediators from mast cells [9].

The treatment for Kounis syndrome needs to address both cardiac and allergic symptoms. In patients with suspected allergic chest pain, coronary angiography is useful for both the diagnosis and treatment of coronary artery spasm and/or ACS. During angiography, intracoronary nitrates and calcium channel blockers can be used to treat coronary vasospasm [4]. These medications can cause hypotension and may not be ideal in hemodynamically unstable patients. In type I variant Kounis syndrome, intravenous corticosteroids and anti-histamines are recommended [4,10]. The type II variant should be treated as per ACS guidelines, in addition to corticosteroids and anti-histamines [4,10]. Beta-blockers are not recommended as they may worsen coronary spasm with unopposed alpha stimulation [10]. Type III variant should also be treated as per the ACS guidelines, in addition to aspiration of the instent thrombus. The diagnosis is confirmed by histological examination of aspirated material demonstrating positive staining for eosinophils and mast cells [4].

The use of adrenaline in Kounis Syndrome is controversial. Adrenaline is a mixed potent adrenergic agonist acting on both alpha and beta adrenergic receptors [11]. Adrenaline has long been used during anaphylaxis to treat systemic vasodilation and support systemic blood pressure by acting on alpha receptors causing vasoconstriction [12]. Adrenaline also has a chronotropic and inotropic effect via the activation of myocardial B1 receptors [11,12]. In patients with anaphylaxis, the recommended route of adrenaline administration is intramuscular, with studies in both children and adults demonstrating superior absorption, faster onset of action, and a higher peak concentration, compared to

subcutaneous administration [13]. Intravenous adrenaline is reserved as a last line for refractory anaphylaxis or cardiac arrest due to the risk of myocardial ischemia and arrhythmia. The use of adrenaline during Kounis syndrome has been cautioned due to the theoretical risk of worsening coronary vasospasm and myocardial ischemia, resulting from alpha receptor-mediated vasoconstriction [4,10]. This is of particular significance in patients already using beta-blockers who may have a diminished effect from adrenaline in addition to an increased risk of unopposed alpha-mediated vasoconstriction.

Adrenaline can produce coronary vasodilatation via a mechanism initially thought to be related to the metabolic effects of increased myocardial oxygen consumption as a result of its inotropic and vasoconstricting action [14]. More recently it has been shown that coronary B2 adrenoreceptors produce coronary vasodilatation in the presence of low dose adrenaline, while alpha receptors with a lower sensitivity, produce vasoconstriction at higher doses [11,14]. Intracoronary adrenaline proved to be particularly useful in our patient in the setting of profound hypotension, which precluded the use of intracoronary nitrates or a calcium channel blocker.

Intracoronary adrenaline has been used as a last resort for the treatment of refractory no-reflow following percutaneous coronary interventions [15,16]. The pathophysiology of no-reflow is complex, multifactorial, and is related to microvascular dysfunction. Retrospective reviews by Skelding et al. and Choi et al. have demonstrated that intracoronary adrenaline in refractory no-reflow was well tolerated and improved TIMI flow and hemodynamics in the majority of patients [15,16]. There is no consensus on the safe dosage of intracoronary adrenaline with documented doses ranging from 50 to 400 µg with no cases of acute dysrhythmia noted [15,16].

CONCLUSION

Kounis syndrome should be considered as a diagnosis in patients presenting with co-existing symptoms of acute coronary syndrome and allergic reaction. Patients with chronic sinusitis with nasal polyps are at risk of developing salicylate intolerance and allergic reaction with Kounis syndrome. The mediators of mast cell degranulation are involved in activating the thrombotic pathway, platelet aggregation, promoting vasoconstriction, and can precipitate plaque rupture. Increasing evidence suggests that mast cells play a causative role in non-allergic myocardial infarction, lending potential to the development of novel therapeutic agents for primary and secondary prevention of ACS. The treatment of Kounis syndrome focuses on both cardiac and allergic

symptoms. In particular, coronary artery spasm is traditionally treated with nitrates and calcium channel blockers. This case, however, highlights a novel use of intracoronary adrenaline for coronary artery spasm as a last resort in hemodynamically unstable patients.

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