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Case Series

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A Unique challenge in management in the Emergency department and Cardiac Cathlab: case review of two subjects with Kounis Syndrome complicated with ST Elevation Myocardial infarction and Ventricular tachycardia, following exposure to cutaneous or intravenous allergens.

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Abstract

Acute coronary syndromes, such as coronary spasm or acute myocardial infarction, have been reported following allergic reactions. These are known to affect patients of any age, and can have a variety of clinical manifestations, and are collectively referred to as Kounis syndrome [1]. We report 2 cases of acute myocardial infarction complicated by severe cardiac dysrhythmia, following an acute allergic reaction to cutaneous or intravenous allergens. To our knowledge, this is the first instance of a skin contact with caterpillar has been documented to provoke Kounis syndrome complicated by an acute STEMI with polymorphic VT. Management of such patients could be hazardous, particularly in emergency units and cardiac catheter labs, when decisions on drugs and urgent revascularization need to be made on a background of inflammation induced by severe allergic reactions. In theory, bare metal stents (when appropriate), Polymer free, Bio-absorbable scaffolds or rapid healing Drug Eluting Stents offer a better safety profile in emergency PCI, but according to our knowledge, duration of antiplatelet drugs and relative safety of various types of stents with variable drug and polymer combinations have not been formally evaluated in this condition in randomised control trials. The risk of early and late stent thrombosis and restenosis with chronic inflammation may be difficult to predict in the long term, without follow up data from trials. Such trials are very difficult to set up given the low volumes and emergency nature of events, hence review of clinical case series like ours will be invaluable to gain more insight into rapid decision making required in this interesting clinical syndrome. Reassuringly, both our patients who had emergency PCI with either Biolimus, Everolimus eluting or bare metal stents respectively in the acute setting, have not experienced repeat hospitalizations for ACS, arrhythmia or a repeat revascularization procedure at 7 and 5year follow-ups respectively.

Keywords: *Kounis Syndrome, Anaphylaxis, STEMI, Ventricular Tachycardia, Acute coronary plaque rupture, Primary PCI, Drug eluting stents, Bare metal stents, Stent thrombosis, Stent restenosis*

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CLINICAL PRESENTATIONS

CASE 1:

A 50-year-old man presented to the emergency department with, difficulty in breathing, tightness in the throat, abdominal cramps, vomiting, profuse sweating & generalized urticarial rash following contact 15 minutes prior to admission with a caterpillar. He was a heavy smoker, had hypertension and intermittent asthma. He had a previous documented episode of allergic reaction to contact with a caterpillar several years ago, requiring treatment in the emergency department. On examination, systolic blood pressure was 80mmHg, pulse 56 beats/minute, respiratory rate 16/min, Oxygen saturation 94% on air. He was diaphoretic, had inspiratory stridor & a generalised urticarial rash. Scattered rhonchi were heard in both lung fields.

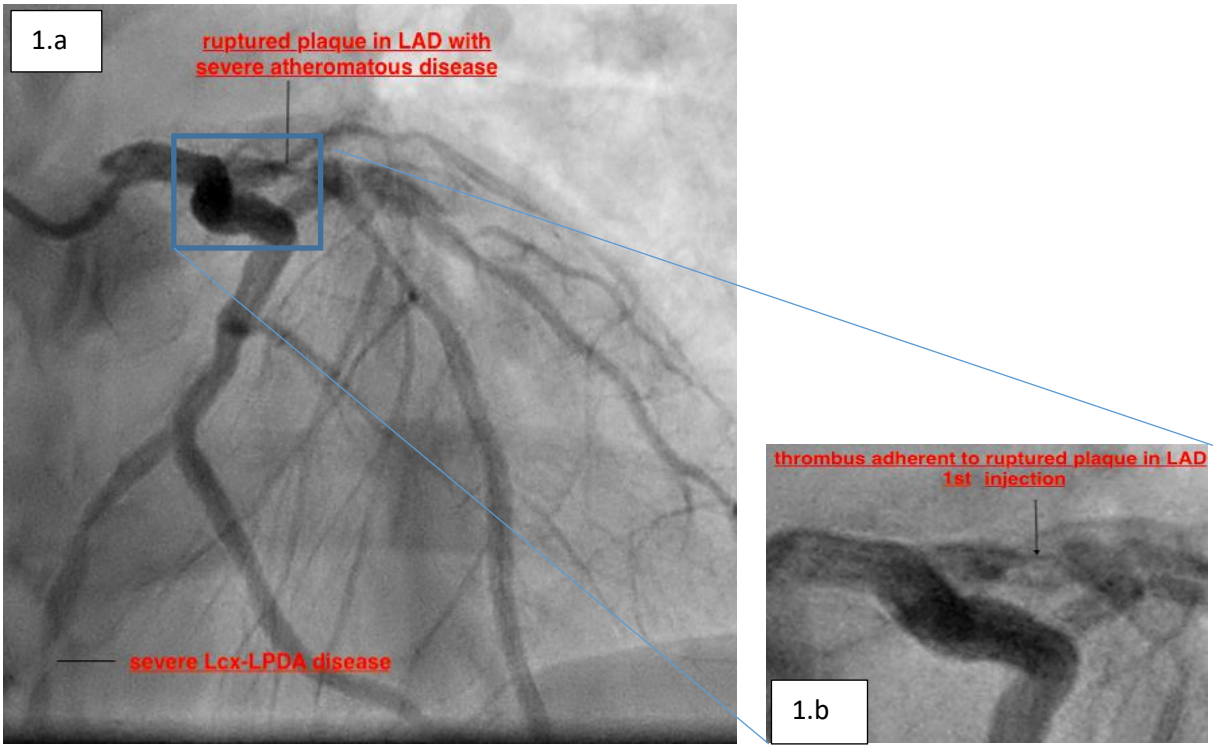
A diagnosis of anaphylaxis was made and he was treated based on standard treatment protocols. A 0.5 mg of 1:1000 Adrenaline was given intramuscularly. High flow oxygen was given nasally. Hydrocortisone 200mg and chlorpheniramine 10mg were administered intravenously. He was nebulized with salbutamol and 0.9% saline 500ml was administered over one hour. He responded well to treatment and haemodynamic stability was established.

However, one hour later, the patient complained of central chest discomfort radiating to the left arm. His blood pressure was 130/80 mmHg, pulse was 80/minute, respiratory rate was 16/minute and oxygen saturation was 99% on 2 litres of oxygen. He then suddenly developed polymorphic ventricular tachycardia (VT), which was cardioverted with a biphasic 100 J shock; he went on to develop two more episodes of polymorphic VT, and was successfully cardioverted. Magnesium sulphate 2g and potassium chloride 20mmol were administered by slow intravenous infusion. ECG now showed acute ST segment elevation in the anterior chest leads V1 to V4. A diagnosis of evolving STEMI was made, and he was given aspirin 300, clopidogrel 600mg, and intravenous heparin 2500 units.

Urgent coronary angiography was performed and showed the following (Figure 1. a,b,c) : Normal left main stem, severe >99% plaque disease (disrupted, with thrombus in situ- see images 1,2) in the proximal LAD, severe >99% LCx-LPDA plaque disease with further disease in the OM branch, normal non-dominant RCA. The LAD lesion was stented using a Biomatrix 3.5mm x 36mm drug eluting stent (DES) and post dilated to 4mm, covering the disrupted culprit lesion and the LCx-PDA lesion was also stented with a Xience Xpedition 2.75mm x 48mm DES and post dilated to 2.75mm. Post angiographic results were excellent. There were no immediate complications. The choice of two stents were based on lesion length and angiographic factors alone. Since there is no overlap of stents in two different arteries, we felt that the choice of any two different platforms could in theory be preferred in such cases; if there was an allergic response to one item of the two identical stents, it may be associated with acute stent thrombosis of both stents (with high mortality) if they were of the same platform, although with modern antiplatelet and anticoagulant therapy with good stent apposition makes this risk very low.

Initial pharmacological management included aspirin 100mg daily, clopidogrel 75mg daily, atorvastatin 40mg daily, bisoprolol 2.5mg twice daily, Enoxaparin 40 mg twice a day and ramipril 1.25mg twice daily with with regular antihistamines.

His blood investigation results on admission were as follows: Hb-18.2g/dL, packed cell volume 52.2%, total white cell count 20680/mm3, neutrophils 77%, lymphocytes 20%, platelets 232000/mm3; Random blood glucose 123mg/dL; troponin T on admission <0.01, rising to 0.17 six hours later; serum urea, creatinine, sodium, potassium, magnesium, calcium within normal range. Echocardiography was normal post PCI day 2 with good LVEF. The patient made an uneventful recovery after PCI with return to full physical activity and has been on long term antihistamines and dual antiplatelet drugs for 2 years, followed by single antiplatelet thereafter and remains well at 7-year follow-up.



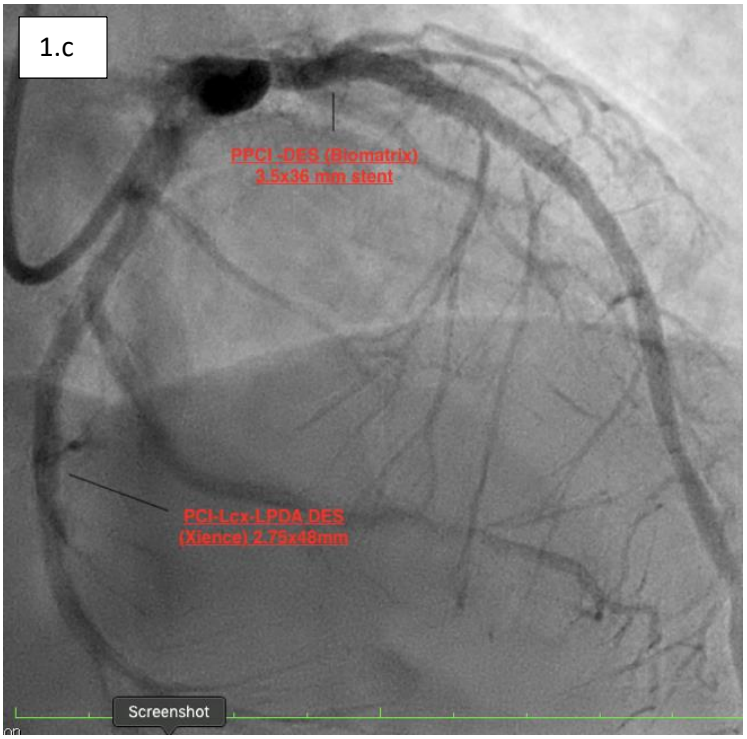


Figure 1:
a) Ruptured plaque in proximal LAD along with non-ruptured severe stenosis of Lcx.
b) Visible thrombus on first injection on the same plaque.
c) PTCA of LAD and Lcx with two Drug Eluting Stents.

CASE 2:

A 78yr old lady who had multiple substance allergies, had a fall and fractured neck of femur and was taken for urgent surgical repair. Perioperative intravenous administration of a Cephalosporin (Cefuroxime for which allergy status wasn't previously recorded) resulted in development of anaphylactic shock followed by chest pain, transient ST elevation and sudden ventricular tachycardia/ventricular fibrillation. She was defibrillated immediately, treated for anaphylaxis and loaded with 300 mg of Aspirin and 300 mg of Clopidogrel and heparin and then transferred for urgent cardiac evaluation.

Emergency coronary angiography showed that she had a critical ostial right coronary disease (a probable site of plaque disruption- see Figure 2), which upon wire crossing, resulted in ventricular tachyarrhythmia, requiring urgent cardioversion and prompt stenting with two bare metal stents (as she was pending hip surgery) and continued on dual antiplatelet therapy for one month and thereafter early DAPT discontinuation. Repair of fracture was undertaken at 6 weeks on a single antiplatelet drug. She made a good recovery and remains free of further events for 5 years on long term antihistamines.

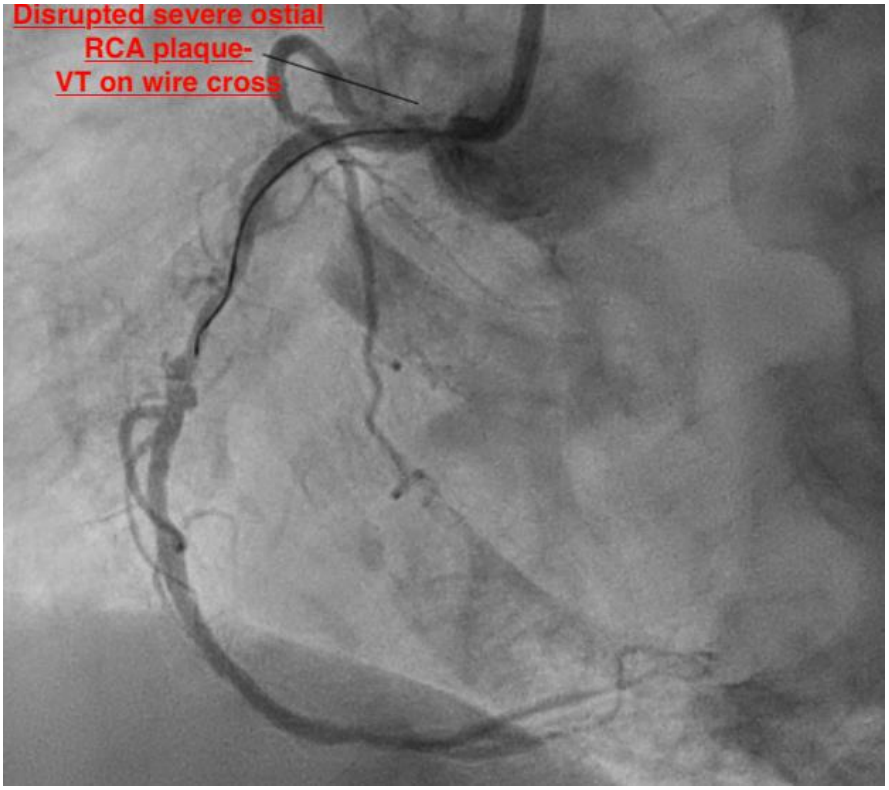


Figure 2: A probable site of plaque disruption

DISCUSSION

These two patients had developed acute coronary syndrome complicated by life threatening arrhythmia following an anaphylactic reaction to either skin contact (with a caterpillar) or intravenous administration of an antibiotic respectively. The differential diagnosis for acute coronary syndromes at the point of developing chest pain included coronary hypersensitivity disorder (Kounis Syndrome), acute ST elevation myocardial infarction (and arrhythmia) precipitated by hypotension caused by anaphylaxis, and Takotsubo cardiomyopathy, induced by either adrenaline or surgical stress respectively, but in the absence of the

characteristic wall motion abnormalities seen on echocardiography and the presence of subsequent coronary abnormalities[2] we felt it is unlikely to be Takotsubo cardiomyopathy. The time course of the first case rules out that hypotension was the trigger as he had been haemodynamically stable for an hour before sudden onset of chest pain, ECG changes and ventricular tachyarrhythmia. Following the clinical presentation with anaphylaxis, the presence of clear acutely disrupted plaques on coronary angiography, and easy provocation of VT on wire crossing of an unstable plaque in the second case, strongly point towards Kounis syndrome, although definitive proof of histamine mediated plaque fissuring will be difficult without post-mortem evidence. Intracoronary imaging with Optical Coherence Tomography(OCT) may prove certain features of plaque fissuring, but excess contrast or dextran use during OCT itself may not be appropriate in the context of anaphylaxis or VT.

Kounis syndrome or ACS post hypersensitivity and anaphylaxis is a well-recognized condition which was fully described in 1991 by Kounis et al [3]. This syndrome comprises a range of mast-cell activation disorders which result in coronary ischaemia and myocardial infarction. The condition can affect any age group, and follows hypersensitivity and anaphylaxis to a variety of triggers, including pharmacological agents (losartan [4], gelofusine [5]), latex [6], histamine fish poisoning (scombroid syndrome) [7], nonsteroidal anti-inflammatory drugs and omeprazole [8] and even common food items such as milk [9]. Whilst the pathophysiology of the condition is not fully understood, the condition is postulated to be primarily mast-cell mediated, with hypersensitivity resulting in mast-cell degranulation and release of histamine and other inflammatory mediators such as chemokines, enzymes such as the neutral proteases chymase, tryptase, cathepsin-D, peptides, proteoglycans, cytokines, growth factors and arachidonic-acid products such as leukotrienes, thromboxane, prostacyclin, PAF, and tumor necrosis factor[1]. Histamine causes coronary vasoconstriction and activates platelets. The neutral proteases chymase, tryptase and cathepsin-D activate matrix metalloproteinases, which can induce plaque rupture [10]. Many other chemokines released can play a role in causing coronary vasospasm and platelet aggregation.

Three variants of Kounis syndrome have been described [11]. In the type I variant, the coronary arteries are normal or near normal, with minimal or no risk factors for coronary artery disease. The type II variant occurs on pre-existing coronary plaques, with the inflammatory cascade resulting in coronary vasospasm or plaque rupture, or both. There is a third variant which results in stent thrombosis. The administration of adrenaline may provoke Kounis syndrome, by inducing coronary vasospasm. Other standard treatment for anaphylaxis may alleviate coronary artery spasm in type I Kounis syndrome, such as hydrocortisone, and antihistamines. There is a potential role for vasodilators such as calcium channel antagonists or glyceryl trinitrate both of which should be used with caution as it may result in severe hypotension. Coronary angiography or additional Intravascular Ultrasound (IVUS) imaging may sometimes help differentiate the types of Kounis syndrome.

It is difficult to determine what the correct strategy is when decision for emergency follow on PCI has to be undertaken. The complex pathophysiology of Kounis syndrome makes it likely that mast-cell mediated histamine and chemokine release may make placement of a coronary stent risky should overwhelming hypersensitivity to metal, drug or polymer develop soon afterwards. Indeed, Kounis syndrome has been reported with very late stent thrombosis in second-generation drug-eluting stents [12] and more recently, as a cause of recurrent acute stent thrombosis soon after implantation [13], which is uncommon but very worrying in a medical emergency. Theoretically, balloon angioplasty and anticoagulants with antiplatelet drugs to restore flow seems intuitive, but pre-existing severe coronary disease may not make this sufficient due to recoil and plaque fissuring. Metal free bio absorbable scaffolds (BVS) seems attractive, as the poly-glycoside (PGA), poly-lactides (PLA) are considered more bio compatible, but the time required for degradation of these polymers is long and may itself be hazardous, as per current US FDA guidance that highlights a higher risk of late scaffold thrombosis [14]. With regards to the drug elution systems, sirolimus is known to suppress eosinophil reaction in comparison to paclitaxel [14], but whether it is

clinically relevant is not known. Polymer free or rapidly degrading DES appear attractive, but again, whether the premature exposure of metal may be undesirable in Kounis is not known.

In addition to questions on stent designs, the perioperative pharmacological management in the emergency units, cardiac cathlab or intensive care may become tricky with Kounis syndrome. Morphine for pain relief, may need to be avoided due to risk of further histamine release from mast cells. Administration of Aspirin (possible anaphylactoid symptoms with a NSAID) could be a concern when no time is available for desensitization. If aspirin is not possible to administer, the adequacy of platelet inhibition with a single novel antiplatelet drug combined with heparin or bivalirudin may become questionable and with increased risk of acute stent thrombosis, that may be augmented further by the inflammatory component. How long to continue anticoagulants and antiplatelet drugs and whether pre-discharge aspirin desensitization is needed (or possible) post-PCI in Kounis syndrome, are all difficult clinical questions for which further evidence is required.

CONCLUSIONS

Allergy to contact with caterpillars is yet another of the numerous potential triggers for Kounis syndrome. Whatever the allergen precipitating it, Kounis syndrome complicated by ST elevation and ventricular tachycardia and requires a patient to undergo emergency cardiac procedures becomes a huge challenge for the emergency services. Both the patients described in our case series have survived the index episode without a complication and not required further revascularization 5 years to date. However, long term collective outcome data on cardiac interventions by type and pharmacological adjuncts best suited in these conditions is necessary.

Author declaration
Authors' contributions:
All 3 contributed to the publication equally.
[Clinical cases and emergency management, performance of procedures and long term follow up and final manuscript with images by PA.
Emergency unit initial management and 1st draft by NY, 1st revision by SR]

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