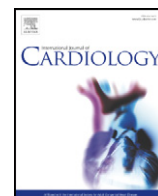




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Letter to the Editor

Peri-operative cardiac arrest with ST elevation secondary to gelofusin anaphylaxis – Kounis syndrome in the anaesthetic room

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Dear Editor,

The association between acute cardiac events and acute allergic reactions has been long recognized. In 1950, the first case was reported during an allergic reaction to penicillin [1]. Kounis and Zavras described the syndrome of allergic angina and allergic myocardial infarction in the 1990s, now known as Kounis syndrome [2–5]. We report an unusual case to highlight the possible mechanisms of ST elevation and cardiac arrest secondary to anaphylaxis in the context of non-obstructive coronary artery disease.

A 57 year old fit male patient was admitted for elective urological surgery. His medical history included treated hypertension and hypercholesterolaemia. He was previously investigated for atypical chest pain in 2008 including a normal exercise tolerance test. His preoperative 12 lead electrocardiogram (ECG) and resting transthoracic echocardiogram were normal. His surgical history included uncomplicated tonsillectomy and strabismus operations in childhood. He had a history of penicillin-induced fever and severe urticaria after anti-tetanus serum at a young age. Regular medications included atenolol 50 mg, cilazapril 5 mg, simvastatin 20 mg and tamsulosin 400 mcg. Prior to operation, cilazapril was withheld on the day of surgery and atenolol was continued. The patient had been well in the period prior to the elective operation.

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General anaesthesia was induced intravenously using propofol, atracurium and remifentanyl infusion, with intravenous gelofusin to maintain intravascular volume and in view of borderline low blood pressure. Hypotension developed within minutes of induction with an atrial tachycardia (max 220 beats per minute) (Fig. 1), associated with generalised erythema and decreased lung compliance with ventilation. Widespread ST elevation was witnessed on 3 lead ECG monitoring. Despite initial management with bolus doses of metaraminol and epinephrine (~0.1 mg) intravenously, hypotension worsened and cardiac output was lost for 3 min. The cardiac arrest rhythm was initially pulseless electrical activity, followed by P wave asystole. Cardiopulmonary resuscitation continued throughout this period, with a further 3 mg epinephrine and 3 mg atropine administered intravenously as per the local resuscitation protocol. There was a return of circulation with no residual cerebral deficit. Anaphylactic shock was the primary diagnosis, with gelofusin identified as the possible allergen. The gelofusin infusion was immediately stopped and intravenous antihistamines and steroids were administered. The patient stabilised with ongoing inotropic support (epinephrine and norepinephrine infusions) and initial portable bedside echocardiography demonstrated normal left and right ventricular dimensions and systolic function with no regional wall motion abnormalities.

The patient was transferred to a tertiary cardiac hospital for further cardiac investigations (Fig. 2).

Blood investigations revealed a normocytic anaemia, haemoglobin 11.7 g/dL (normal range: 13.4–16.6), mean cell volume 92 fL (84–98) with mildly elevated white blood cell count $11.9 \times 10^9/L$ (4.4–10.1) with a neutrophilia $10.1 \times 10^9/L$ (2.1–6.7). The alanine transaminase (ALT) was elevated at 100 IU/L (8–40) and C reactive protein was elevated at 60 mg/L (0–10). Troponin I measurement at 28 h was elevated at 1.32 µg/L (0–0.04). The serum brain natriuretic protein (BNP) level was also raised at 92 pmol/L (<4).

Mast cell tryptase levels at the time of the event peaked at 45.0 ng/ml (<11.4). Mast cell tryptase levels taken 3 h and 24 h post event were 35.1 ng/ml and 4.6 ng/ml respectively.

Post event 12 lead electrocardiogram (ECG) revealed sinus rhythm with non-specific repolarization abnormalities in leads V1–3 which resolved within 24 h (Fig. 2a). Departmental transthoracic echocardiography imaging confirmed normal left and right ventricular dimensions, wall thickness, ejection fraction and long axis function, with no detectable

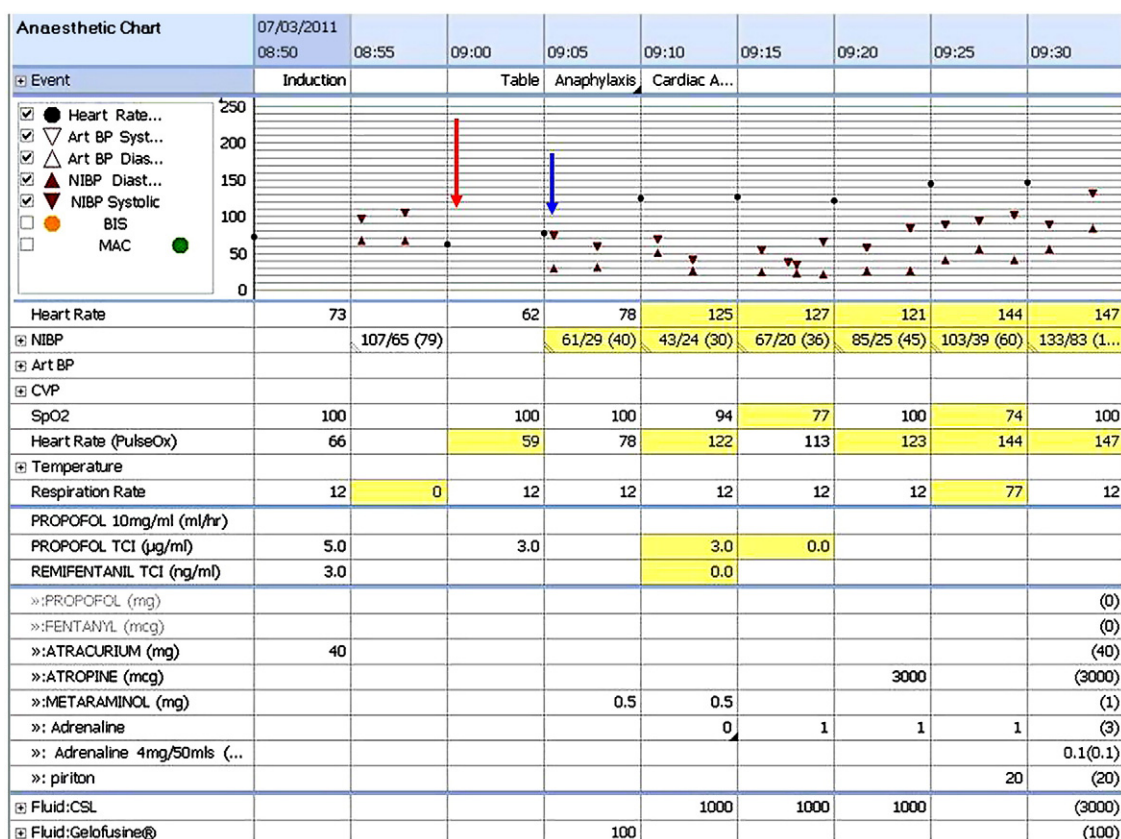


Fig. 1. Peri-arrest observation chart. Haemodynamic and vital signs plotted against time during induction of anaesthesia and administration of drugs. Red arrow denotes administration of gelofusin. Blue arrow indicates onset of haemodynamic instability with anaphylaxis, hypotension and then sinus tachycardia, followed by cardiac arrest. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

resting wall motion abnormalities. The left atrium was mildly dilated and there were no significant valvular or pericardial abnormalities. Cardiac magnetic resonance confirmed normal ventricular dimensions and function, with no regional abnormalities suggestive of infarction, and no evidence of acute myocardial inflammation was detected using T1STIR imaging. Late gadolinium enhancement imaging was not performed at the patient's request to minimize exposure to intravenous agents in light of recent anaphylaxis. Contrast-enhanced computerised tomography coronary angiography (CTCA) was selected as the initial coronary imaging modality (Fig. 2b). CTCA revealed eccentric calcified plaque in the left main stem and the proximal segment of the left anterior descending, but no significant luminal narrowing. The remaining arterial segments were normal and plaque free, confirming no evidence of flow limiting coronary disease. The coronary calcification score of 29 placed the patient below the 50th percentile for age and sex.

A physiological stress nuclear myocardial perfusion scan was chosen as the non-invasive modality using the least allergenic intravenous agent to confirm the non-obstructive nature of the coronary plaque lesions given their important locations (Fig. 2c). Tetrofosmin myocardial perfusion imaging was normal in the LAD and RCA territories. There was a suggestion of a possible small and mild inducible perfusion abnormality of the basal lateral wall, although artefact was most likely given the normal CTCA in that coronary territory, and it was deemed insufficient to cause

asystolic arrest. A provisional diagnosis of Kounis syndrome was suspected, with bystander non-flow limiting coronary artery disease.

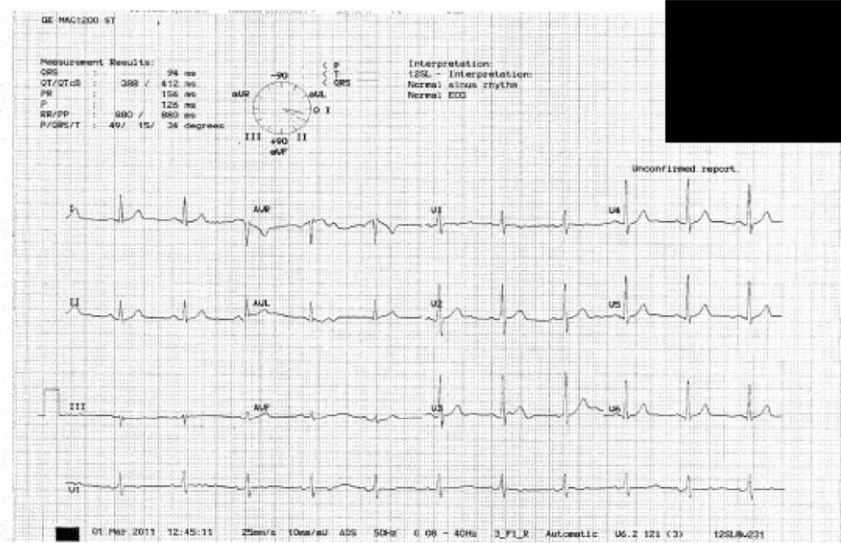
The patient was referred for assessment by the local Allergy Medicine team. Skin testing showed a strong positive response on intradermal testing to gelofusin at 1:30 dilution (Fig. 3); the same concentration tested negative on 3 control individuals. Tests to the other administered intravenous and topical agents (propofol, atracurium, remifentanyl, chlorhexidine and latex) were negative at skin prick testing and also at intradermal test level for propofol (1:100 dilution), atracurium (1:1000 dilution) and remifentanyl (1:10 dilution) (Fig. 3).

The clinical diagnosis of Kounis syndrome was confirmed, with the anaphylactic episode triggered by intravenous gelofusin with IgE-mediated hypersensitivity. The patient was advised to avoid gelofusin in the future and to wear a 'Medical Alert' bracelet stating his allergy. Gelofusin is a macromolecule made from succinylated bovine gelatin and therefore structurally different from most gelatins in foodstuffs. However gelatin is contained in various vaccines, and given the childhood reaction to tetanus vaccination, it is conceivable vaccination was the route of primary sensitization. There are previous case reports of gelatin sensitization following vaccination [6].

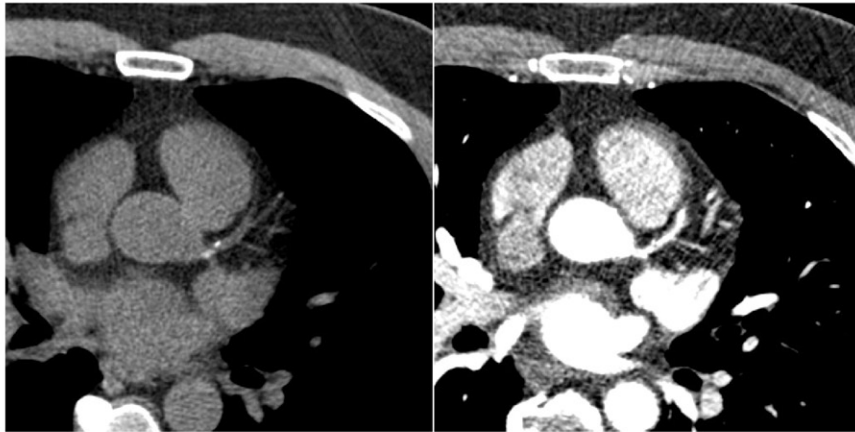
Cross reactivity has been reported between gelofusin and other colloid plasma expanders such as HemaCell (a urea-linked gelatin), and therefore it is recommended that all intravenous colloids should

Fig. 2. Cardiac Investigations. a. Twelve lead electrocardiograms recorded after anaphylaxis-induced cardiac arrest, resuscitation and return of cardiac output, demonstrating sinus rhythm with non-specific repolarisation abnormalities in leads V1–3. b. Cardiac computed tomography (CT) demonstrating calcified plaque in the left main stem and proximal left anterior descending coronary artery (left). Equivalent transverse slice from the contrast-enhanced CT coronary angiogram demonstrating the non-obstructive nature of the calcified plaques (right). c. Tetrofosmin myocardial perfusion imaging (MPI) demonstrating mild reversible stress-induced perfusion defect in the basal lateral wall evident on stress images (A), absent in resting images (B) and depicted in the bulls eye plot (right panel – stress above, resting below). Endsystolic left ventricular volume was reduced during stress, confirming the non-obstructive nature of the left main stem and LAD plaques. The basal lateral defect was judged to be artefact by two independent nuclear MPI experts.

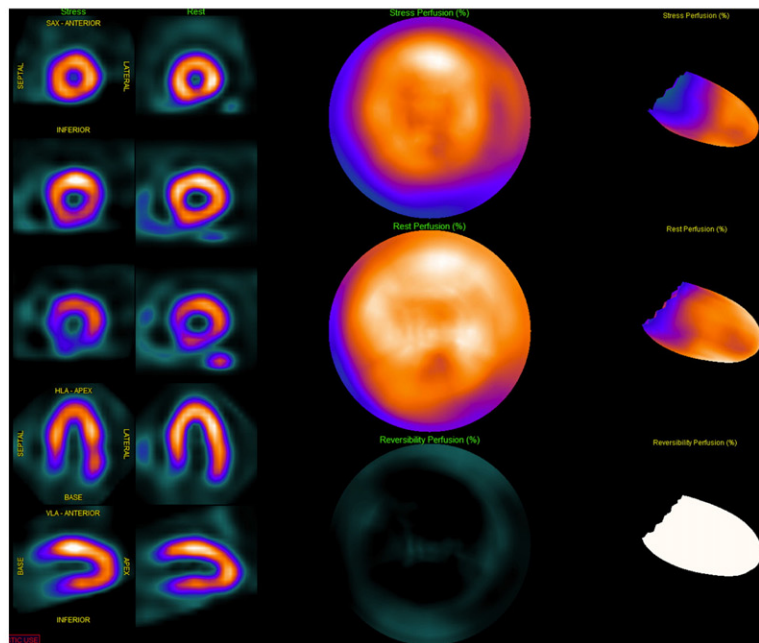
a



b



c



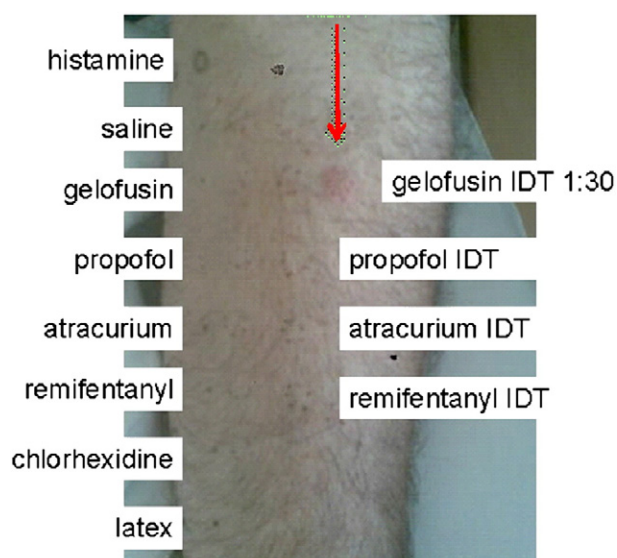


Fig. 3. Skin prick allergen testing. Left – skin prick tests with corresponding allergen – all negative; Right – intradermal tests, including the positive result (red arrow) to gelofusin at 1 in 30 dilution in normal saline. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

be avoided. As previously mentioned, gelatin is also present in certain vaccines and foodstuffs. The extent of cross reactivity between allergy to gelatin in the form of gelofusin (succinylated gelatin) and gelatin in these other forms is unclear. Whilst anaphylactic reactions have been described to both food gelatins and modified gelatins in intravenous colloids or medications, it is unclear whether or not cross reactivity exists. However, to be entirely safe the patient was advised to avoid exposure to all forms until skin testing and challenge testing to foods containing gelatin could be conducted to clarify this issue.

Kounis syndrome is characterized by the development of acute coronary or cardiac events triggered by the release of inflammatory mediators following an allergic or hypersensitivity reaction. In predisposed individuals allergic phenomenon can trigger angina or even acute myocardial infarction. This syndrome is becoming increasingly recognized [2].

Kounis syndrome has been divided into three types. The first is seen in patients with no predisposing factors for ischaemic heart disease with normal coronary arteries [7]. In this setting, inflammatory mediators released during the allergic insult may induce coronary vasospasm acting locally on coronary vascular smooth muscle. It is likely to be triggered by endothelial dysfunction resulting in an acute ischaemic insult. Alternatively the intense inflammatory and mast cell degranulation may directly impair cardiomyocyte function, causing a direct 'non-ischaemic' ventricular dysfunction [8–10].

The second type is seen in patients with pre-existing coronary artery disease in whom the release of inflammatory mediators triggers coronary vasospasm in the region of existing atherosclerotic plaque, and may cause erosion and plaque rupture manifesting as an acute coronary syndrome. Both manifest with typical cardiac symptoms, ECG changes and can be accompanied by elevated levels of cardiac enzymes, indicative of myocardial damage [2,11]. The third type is an allergic reaction to the presence of a coronary stent, and in particular the polymer or drug associated with drug-eluting stents [12]. This can trigger recurrent in-stent thrombosis.

Mast cells are found in most parts of the human body, including the heart and blood vessels [8,9,13], and are involved in allergic and anaphylactic reactions. These cells are derived from a distinct precursor in the bone marrow and mature under local tissue micro environmental factors. In a predisposed individual, the introduction of an allergen (food, insect venom, contrast agent or a drug) may induce mast cell degranulation, through IgE-allergen cross linking leading to the release of several

mediators, including histamine, thromboxane, prostaglandins, leukotrienes, proteases and platelet activation factor [14]. Cardiac mast cells also release renin, leading to local production of angiotensin [13]. Both angiotensin and these inflammatory mediators can directly trigger sinus tachycardia, coronary vasoconstriction, dysfunctional ventricular contractility, and blockade of atrioventricular conduction. Histamine and leukotrienes are strong coronary vasoconstrictors, whilst tryptase and chymase are metalloproteinase activators that can degrade collagen and induce plaque erosion or rupture, thus initiating an acute coronary event [2,3]. Indeed it has been proposed that serum tryptase may be used as a new marker of atherosclerotic plaque instability [15].

In the case of our patient, conceivably three simultaneous pathophysiological mechanisms may have been responsible for the involvement of the heart in the anaphylactic reaction. Firstly, systemic vasodilation secondary to inflammatory cytokines and metabolites of arachidonic acid released during the anaphylactic process, inducing profound arterial hypotension, the first abnormality on the haemodynamic chart (Fig. 1). Secondly, localised coronary artery vasospasm stimulated by inflammatory cytokines, given the locations of atherosclerotic plaque (left main stem and proximal LAD) may have caused significant global myocardial ischaemia, aggravated by reduced arterial perfusion pressure. Thirdly the direct toxic myocardial effect may also explain the ST changes and transient PEA and asystolic arrest in the absence of coronary vasospasm and ischaemia. The result is a 'perfect storm' causing myocardial hypoperfusion, myocardial ischaemia, myocardial dysfunction and cardiac arrest. Furthermore, the slow response to cardiopulmonary resuscitation and high doses of epinephrine may be related to the patient being well beta-blocked and ACE blocked (see low blood pressure and relative bradycardia at baseline). Identification of the anaphylactic syndrome, and gelofusin as the potential trigger, is critical to prevent ongoing fluid resuscitation using the primary allergen. This is relevant in all clinical scenarios where intravenous colloids are prescribed.

Kounis syndrome should be considered as a possible diagnosis when individuals present with an acute coronary syndrome, acute heart failure or other cardiac event in the context of acute anaphylaxis. The factors that determine which individuals develop Kounis syndrome during an anaphylactic episode are unknown, and conceivably there may be a threshold level of mast cell activation and inflammatory mediator release above which the coronary artery spasm, atheromatous plaque rupture and/or direct myocardial dysfunction occurs. The threshold may be determined by genetic factors, the extent and instability of the coronary atherosclerotic burden, the primary site of the antibody-antigen reaction and levels of inflammatory mediator release. Further research is required to determine the epidemiology and clinical features in order to establish suitable preventive and interventional measures, to achieve optimal management of patients with both acute allergic coronary and/or myocardial events.

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