Intraoperative myocardial infarction: Kounis syndrome provoked by latex allergy

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SUMMARY

We report the case of a 43-year-old man with anaphylactic shock and concurrent ST-elevation myocardial infarction during a planned inguinal hernia surgery. This event occurred shortly after introduction of latex into the surgical field. Coronary angiography revealed a 70% occlusive lesion in the right coronary artery. Further discussion with the patient revealed a potential latex allergy. Skin prick testing showed marked sensitisation to latex. The patient was subsequently diagnosed with the type II variant of Kounis syndrome.

BACKGROUND

Kounis syndrome (KS) was first described in 1950 by Pfister *et al*,¹ as a case of anteroseptal myocardial infarction and urticaria after treatment with penicillin. KS is now well recognised as a unique clinical scenario that describes the coincidental occurrence of allergic or hypersensitivity reactions with acute coronary syndrome (ACS).² KS has been classified into three subtypes. Type I is coronary vasospasm in the absence of coronary artery disease and presents with anginal chest pain. Type II is the occurrence of chest pain during an allergic reaction in those with angiographic evidence of coronary artery disease. Type III includes patients with stent thrombosis in whom aspirated thrombus stain positive for eosinophils and mast cells.^{3–4} We report a case of intraoperative KS induced by latex. KS poses therapeutic challenges since medications used in the treatment of anaphylaxis are often contraindicated in ACS. In the absence of published guidelines and recommendations, therapy should be tailored to suit individual patients and situations with prompt resuscitation directing management decisions.

CASE PRESENTATION

A 43-year-old Caucasian man presented for bilateral inguinal exploration and possible hernia repair. Medical history included multiple hernia repairs and orthopaedic surgeries. Cardiac risk profile included a 15-pack-year smoking history and an in-hospital diagnosis of diabetes mellitus type II. Medications included long-acting opioids for chronic pain. He denied any allergies preoperatively.

Anesthesia was achieved with intravenous midazolam, lidocaine, propofol, dexamethasone, cefazolin and remifentanyl. The airway was maintained with a laryngeal mask. His baseline haemodynamics were stable. All members of the operating team, with the exception of the attending surgeon, wore latex-free gloves. During inguinal nerve manipulation, sinus bradycardia and hypotension were noted with desaturation and wheezes.

Ephedrine and glycopyrrolate were administered. Third-degree AV-block and ST-elevations were observed on the monitor. Severe hypotension developed and intravenous epinephrine was administered in two doses of 100 µg. Sinus rhythm was restored, oxygen saturation improved and the ST segments normalised. Salbutamol was given via the endotracheal tube with further oxygen saturation improvement. The team elected to switch to mechanical ventilation and continued with the procedure. Within 10 min, significant ST-elevations recurred with haemodynamic compromise. Norepinephrine infusion and fluid resuscitation were initiated. A diagnosis of acute inferior wall myocardial infarction (IWM) with cardiogenic shock was strongly considered. The patient was transferred to the tertiary centre for left heart catheterisation-primary percutaneous coronary intervention (PCI). Physical examination in the coronary care unit revealed diffuse erythema with a congealing wheal pattern all over his body. After further probing, it was revealed that, in the past, the patient had noticed an itchy rash on his hands after wearing latex gloves.

INVESTIGATIONS

Twelve-lead ECG obtained shortly after the recurrent ST-elevations were observed on the monitor, revealed a pattern typical of an inferior ST-elevation myocardial infarction. ST-elevations were seen in leads II, III, AVF and V6 with reciprocal changes in leads V1 to V4, aVR and aVL (figure 1). Chest x-ray was showed mild bilateral pulmonary oedema. Coronary angiography revealed a single 70% occlusive lesion in the mid-right coronary artery with evidence of fresh plaque rupture, and a bare metal stent was deployed (figure 2). Subsequent cardiac biomarkers confirmed acute myocardial infarction. An ECG on day 2 revealed an ejection fraction of 57%, grade I diastolic dysfunction, normal valves and no regional wall abnormalities. Skin prick testing showed marked sensitisation to latex.

DIFFERENTIAL DIAGNOSIS

Patients with KS often present with transient acute left ventricular dysfunction which can mimic apical-ballooning syndrome. Left ventricular end-diastolic pressures may rise rapidly with overzealous fluid resuscitation, precipitating acute heart failure. Clinical presentation may also mimic that of hypersensitivity myocarditis with acute heart failure; however, the latter patients will have grossly abnormal myocardial biopsies in contrast to KS patients.

TREATMENT

Initial management of this patient focused on resuscitative measures. This decision was mainly based

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Figure 1 The ECG showed ST-elevation in leads II, III, aVF and V6 with reciprocal change in leads V1, V2, V3, V4, aVR and aVL.

on the initial working diagnosis of anaphylactic shock. Intravenous fluids and vasopressors, including epinephrine and norepinephrine, were administered. Salbutamol was also given because of wheezes and oxygen desaturations. After the recognition of a potential ACS, clopidogrel and acetylsalicylic acid (ASA) were given, and an unfractionated heparin infusion was started. The culprit lesion was angioplastied and a bare metal stent deployed with good results. The patient was started on solumedrol over a 2-day period and the rash resolved.

OUTCOME AND FOLLOW-UP

While in hospital, the patient had several symptomatic sinus pauses and eventually received a permanent pacemaker. The patient had recurrent visits to the emergency room over the following 4 months complaining of left-arm pain and dyspnoea on exertion. Repeat cardiac catheterisation revealed mild, stable in-stent re-stenosis and no intervention was performed.

DISCUSSION

KS describes the concurrence of ACS with allergic or hypersensitivity reactions. Three variants of KS have been described.⁴ Type I is coronary vasospasm in the absence of coronary artery disease and presents with anginal chest pain. Myocardial ischaemia is precipitated by an abnormal endothelial response to vasoactive amines released during an allergic reaction with resultant coronary vasospasm. Type II includes those with pre-existing coronary artery disease in whom the acute release of inflammatory mediators can induce either vasospasm alone or with plaque erosion or rupture. Type III includes patients with stent thrombosis in who aspirated thrombus from the culprit coronaries stain positive for mast cells and eosinophils, thus favouring hypersensitivity inflammation as a provoking agent for this feared and devastating complication.

The incidence of KS is currently unknown; however, Brown *et al*⁵ reported that 9.5% of healthy volunteers developed chest pain with ECG abnormalities consistent with ACS when

Figure 2 Cardiac catheterisation showed (A) a 70% occlusive lesion right coronary artery and (B) result after placement of bare metal stent.

challenged with an insect sting. Ridella *et al*⁶ have reviewed 17 cases of KS of varying severity induced by β -lactams, and claim that KS is under-reported. Intraoperative KS is even less well documented given the specifics of the operating room. Takenaka *et al*⁷ report a case of intraoperative KS, similar to ours, and underline the notion that once potential anaphylaxis is identified, the operating room should be converted to a latex-free environment.

Cardiac mast cells can respond to allergic stimuli by releasing endogenous mediators, including histamine, leucotrienes, thromboxane, platelet activation factor, tryptase, chymase and renin.² These biogenic compounds may precipitate ACS by acting on different receptors on the vessel wall and provoking plaque rupture, coronary spasm, platelet aggregation, arrhythmogenicity and left ventricular dysfunction. A wide variety of exposures have been identified in the literature through case reports as KS precipitants. These include environmental toxins, drugs such as antibiotics, contrast media, intravenous anaesthetics, analgesics, skin disinfectants, steroids, thrombolytics, anti-inflammatories and antineoplastics.²

In our case, the diagnosis of KS required identifying both anaphylactic and cardiogenic shock. In the setting of anaesthesia, the signs and symptoms become less well defined. Biteker⁸ has identified five clinical clues to the diagnosis of KS including (1) allergic symptoms, acute chest pain or dyspnoea after allergic insult; (2) ECG showing acute MI; (3) transient ventricular wall motion abnormalities; (4) absence of obstruction lesions on angiography for type I; (5) recovery of IV function within 1–4 weeks. With regard to anaphylaxis, the speed of the onset of symptoms directly correlates with severity and occurs more commonly after induction, although latex reactions can have a delayed and unpredictable response. Also, peripheral vasculature is more prone to vasoconstriction during haemodynamic instability and cutaneous signs may be absent or delayed. Bradycardia may be a result of the Bezold-Jarisch reflex secondary to extravasation of intravascular fluid during anaphylactic shock.⁹ Literature documents that inferior wall ischaemia and/or infarction with right coronary artery involvement is the most common presentation of KS.⁸ Supportive laboratory work for the diagnosis may also include an eosinophil count, histamine, chymase and tryptase serum levels; however, a negative result does not exclude the diagnosis.

Treatment of KS is controversial because treatment of anaphylactic shock may aggravate cardiogenic shock. Effective management should theoretically dilate coronary arteries as well as suppress the allergic reaction. We maintain that initial management of an unstable patient should be centred on maintaining adequate airway, ventilation and circulation, in particular optimising myocardial oxygen supply and demand. Large volumes of intravenous fluids are often required during anaphylaxis; however in KS, fluid resuscitation must be done with caution to prevent acute heart failure. According to international guidelines on the treatment of anaphylaxis, there is no absolute contraindication to the use of epinephrine and delayed administration results in poor outcomes.¹⁰ Four main issues arise with the use of epinephrine.¹¹ First, it may worsen ischaemia, induce coronary vasospasm, prolong the QTc interval and provoke arrhythmias. Second, the use of intravenous epinephrine is controversial, and should be mostly considered in severely unstable individuals. The IV route may precipitate elevated blood pressure and provoke intracranial bleeds, and so the

intramuscular route is recommended except in cases complicated by cardiac arrest. Third, patients on β -blockers may have diminished effect of the epinephrine and also experience unopposed α -adrenergic effects. Finally, most preparations contain sulphite preservatives that can exacerbate anaphylaxis. The published review of β -lactam-induced KS demonstrated that epinephrine was administered in only 23% of all cases.⁶ Systemic corticosteroids have been used successfully in the management of refractory vasospastic angina.¹¹ They are believed to suppress arterial hyper-reactivity and alleviate inflammation by stabilising the mast cell. Antihistamines, both H1 and H2, are recommended treatments after stabilisation of the patient and can provide symptom control.

Nitrates and calcium channel blockers as antispasm therapy should be considered first-line therapy in young, haemodynamically stable and previously healthy individuals in whom type I KS is suspected.¹¹ With the use of ASA, there is a potential risk of aggravating an ongoing anaphylactic reaction. ASA may shunt arachidonic acid towards the leukotriene pathway thus producing more inflammatory mediators.¹¹ Heparin is recommended; however, it has the potential to induce allergic reaction. Most allergic reactions involved heparin produced by the brand Baxter as well as using an initial bolus. It is recommended not to use the bolus option if the Baxter brand is used.¹¹ For perioperative pain control, opiates should be used with caution, especially those that are prone to induce mast cell degranulation; therefore, fentanyl should be the narcotic analgesic of choice.¹¹ ACS pathway should be followed in type II KS.

Type III KS may be prevented by the use of bioabsorbable allergy free poly-lactic acid self-expanding stents and nickel-free stainless steel components. Coating stents with nitric oxide donors and antibodies with endothelial progenitor cell capturing ability have also been proposed.⁴ Stents eluting anti-inflammatory and antiallergic agents may also prevent this potentially lethal complication.

The mast cell may be a potential target for therapy in KS. Mast cell stabilisers such as sodium cromoglycate, ketotifen and monoclonal antibody to IgE may be considered in patients who develop ACS after allergic reactions, though there is a paucity of supporting data.¹¹ It is reported that late thrombotic events have been abrogated experimentally by such therapy in hamsters.¹² Recent data on statins suggest they exhibit marked inhibitory effects on the function of immune cells. Krauth *et al*¹³ have shown that cerivastatin and atorvastatin inhibit stem cell factor-induced differentiation of mast cells. These therapeutic strategies may warrant further investigation.

KS is a unique clinical scenario that unites ACS and allergic syndromes through a common pathophysiological pathway. It encompasses a wide spectrum of clinical presentations, ranging from angina to cardiogenic shock in combination with allergic symptoms or anaphylactic shock. The diagnosis should be considered in younger patients presenting with ACS, particularly IWMI, in the absence of conventional risk factors, and who give a history of allergy. Management is challenging and should be tailored to the clinical presentation, with the haemodynamics and respiratory status guiding therapy. Epinephrine should be used judiciously. Our case reinforces the need for thorough history taking, particularly regarding potential allergens. Recognition of this syndrome by clinicians should lead to prompt diagnosis and appropriate management.

Learning points

- ▶ KS is the concurrence of an allergic event with an acute coronary syndrome (ACS), with the type III variant emerging as a potential novel mechanism of drug-eluting stent thrombosis.
- ▶ Several clinical clues aid in the diagnosis, including allergic symptoms and angina, diagnostic electrocardiogram changes, transient wall motion abnormalities, right coronary artery involvement, the absence of a lesion on angiography for type I KS and recovery of the left ventricular function within 4 weeks.
- ▶ The management of KS is multipronged and should be geared towards both the severity of the ACS and the allergic reaction, particularly being mindful of the potential deleterious effects of epinephrine and corticosteroids in these situations. Both should be used judiciously.
- ▶ Targeted therapy against the mast cell with mast-cell stabilisers, statins and monoclonal antibodies hold promise but warrant further investigation.

Competing interests None.

Patient consent Obtained.

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