

Coronary spasm secondary to cefuroxime injection, complicated with cardiogenic shock – a manifestation of Kounis syndrome: case report and literature review

European Heart Journal: Acute Cardiovascular Care
1–7

© The European Society of Cardiology 2017

Reprints and permissions:

sagepub.co.uk/journalsPermissions.nav

DOI: 10.1177/2048872617701885

journals.sagepub.com/home/acc



Andreas Mitsis¹, Evi Christodoulou² and Panayiota Georgiou³

Abstract

Kounis syndrome is defined as the coincidental occurrence of an acute coronary syndrome with hypersensitivity reactions following an allergic event. The three reported variants of Kounis syndrome are vasospastic allergic angina, allergic myocardial infarction and stent thrombosis with occluding thrombus. The syndrome is caused by various inflammatory mediators. The pathophysiological characteristics of Kounis syndrome involve coronary artery spasm and/or atheromatous plaque erosion or rupture during an allergic reaction. Several causes have been described to induce Kounis syndrome, and their number is increasing rapidly. The haemodynamic effect of the syndrome complicated by cardiogenic shock seems to combine allergic shock with extensive peripheral vasodilation and myocardial suppression with the characteristics of cardiogenic shock. Treatment of Kounis syndrome is challenging because it needs management of both cardiac and allergic manifestation simultaneously. We present a case report of type I Kounis syndrome, with coronary spasm secondary to cefuroxime injection complicated with cardiogenic shock. A brief review of the literature on the various facets of this condition is also provided.

Keywords

Kounis syndrome, allergic angina, allergic myocardial infarction, cardiogenic shock, distributive shock, inflammatory mediators

Date received: 18 June 2016; accepted: 17 January 2017

Introduction

Kounis syndrome or allergic angina is defined as the incidence of acute coronary syndrome (ACS) as a result of mast cell and platelet activation, following an allergic event or hypersensitivity and anaphylactic or anaphylactoid insult.¹ It was first described by Kounis and Zavras in 1991 with an allergic angina syndrome report¹ and has been currently expanded to multiple situations. The three reported variants are: vasospastic allergic angina, allergic myocardial infarction with or without pre-existing coronary artery disease and stent thrombosis with occluding thrombus. They are all caused by inflammatory mediators released by mast cells which may cause significant vasospasm and plaque ulceration, triggering angina or infarction.²

Beta-lactams are one of the most frequently used antibiotic groups in daily clinical practice. Allergy to this group

of drugs constitutes the first cause of pharmaceutical allergy worldwide.³ We report a patient with clinical presentation of type I Kounis syndrome, complicated with cardiogenic shock after the administration of cefuroxime-axetil as antibiotic perioperative prophylaxis for elective ENT surgery. There are already four cases published with a similar

¹Cardiology and Aortic Centre, Royal Brompton Hospital, UK

²AICU, Royal Brompton Hospital, UK

³Intensive Care Unit, Nicosia General Hospital, Cyprus

Corresponding author:

Andreas Mitsis, Cardiology and Aortic Centre, Royal Brompton Hospital, Royal Brompton and Harefield NHS Foundation Trust, Sydney Street, London SW3 6NP, UK.

Email: andymits7@gmail.com

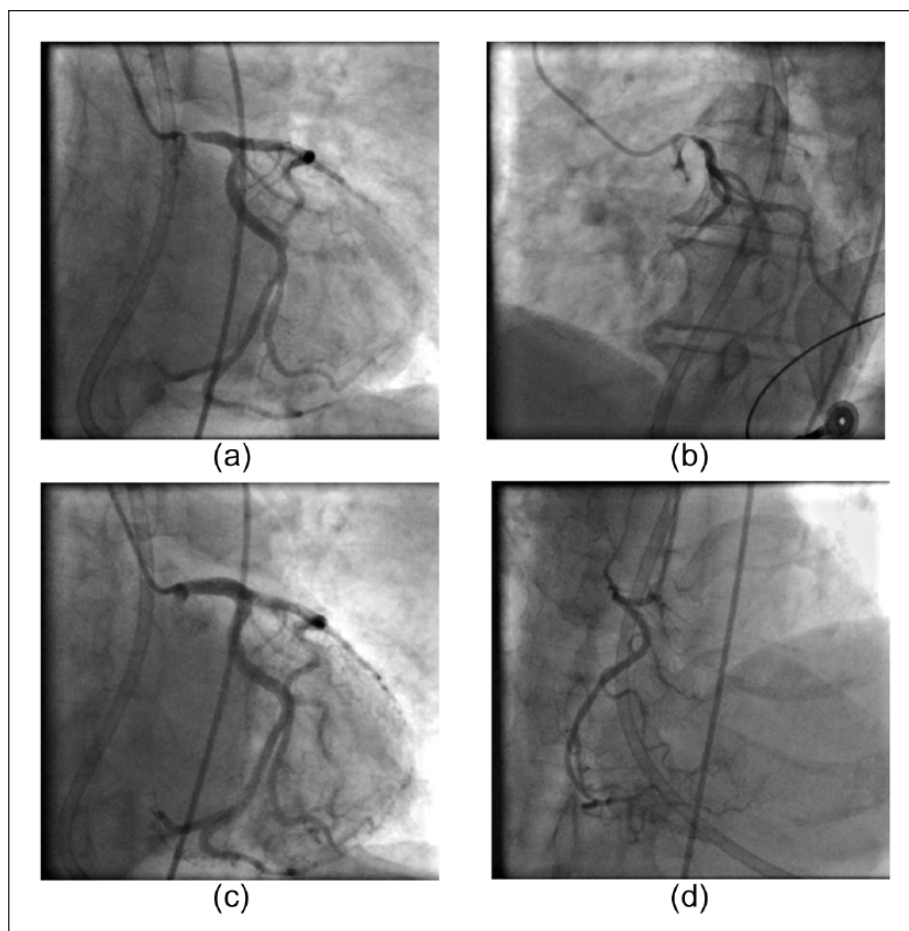


Figure 1. (a) Right anterior oblique (RAO) caudal view depicting the ostial spasm of the left main coronary artery (LMCA). (b) Left anterior oblique (LAO) cranial view depicting the LMCA spasm. (c) Same projection as in (a) after the intracoronary administration of nitrates. (d) RAO 30 view of the right coronary artery (RCA) showing no significant disease.

clinical picture of coronary artery spasm after cefuroxime administration.⁴⁻⁷ Our case is different in many ways and this is going to be discussed extensively below.

Case report

A 64-year-old man was admitted to our hospital for facial cranial operation after a fall down stairs. He presented with cheekbone fracture and surgery under general anaesthesia was planned 3 days later for bone reconstruction. The patient has a history of arterial hypertension, dyslipidaemia and was a heavy smoker (1 pp day for 30 years). On admission the electrocardiogram, chest x-ray and laboratory exams were within normal. Preoperatively, premedication with 5 mg of diazepam orally and 500 mg of cefuroxime IV as perioperative prophylactic treatment were administered.

During the 20 minutes following administration of drugs, the patient progressively developed acute bronchospasm, widespread erythema and generalised itching, periorbital oedema, general discomfort, dizziness and hypotension (blood pressure 80/50 mmHg). In addition to

severe allergic shock the patient developed retrosternal chest pain. An ECG revealed complete AV block and ST-segment elevation in inferior leads (II, III, aVF), with reciprocal ST depression changes in anterolateral leads (V4–V6, I, aVL). The anaesthetic team immediately administered epinephrine intramuscularly, prednisone intravenously, antihistamines and intravenous colloids in the operating theatre. Thirty minutes later the ECG returned to normal but the patient remained symptomatic and in critical condition with severe shock. The shock was persistent, so he was intubated. After intubation, he developed atrial fibrillation with rapid ventricular response and ECG signs of ischaemia reappeared, with extensive ST depression in inferolateral leads. Due to haemodynamic instability the arrhythmia was converted with 150 J of biphasic current. The patient was transferred to the cath lab for coronary angiography.

An emergency coronary angiogram was performed which revealed severe spasm of the left main coronary artery (LMCA) (Figure 1(a and b)). The spasm of the main stem was treated with intracoronary administration of

nitrates (Figure 1(c)) The right coronary artery (RCA) and the remaining major coronaries were free of significant disease (Figure 1(d)). Provocation test with ergonovine was not performed due to manifestation of ACS.

He was transferred to the intensive care unit (ICU) intubated and sedated with the diagnosis of severe allergic reaction and severe coronary spasm secondary to cefuroxime-axetil injection. Small doses of calcium antagonists and intravenous nitroglycerine were administered initially, despite the risk of further hypotension. The patient also received acetylsalicylic acid (ASA), clopidogrel, low molecular weight heparin and statin.

During the first hours in the ICU, the patient received sedation with propofol and remifentanyl. He was supported with mechanical ventilation, AC mode, FiO_2 : 35%, PEEP: 8. The patient manifested haemodynamic instability, with low blood pressure (70/40 mmHg) and signs of peripheral hypoperfusion (increased lactic acid and decreased urine output). The blood gas analysis revealed metabolic acidosis (pH 7.25, Lac 8). At first a central venous line (subclavian) was inserted, through which volume resuscitation was facilitated. Invasive monitoring of central venous pressure was allowed. An arterial line was also placed to provide continuous blood pressure monitoring.

A non-calibrating technique was used for continuous haemodynamic monitoring (Vigileo system). The stroke volume was markedly reduced (45 ml/beat, normal values 60–100 ml/beat) and systemic vascular resistances were within normal range (1300 dynes/sec/cm⁵, normal values 800–1200 dynes/sec/cm⁵) and were progressively increasing (up to 1800 dynes/sec/cm⁵) during his stay in the ICU. These haemodynamic parameters suggested a cardiogenic as well as a distributive component in the pathophysiology of shock. Echocardiography revealed severe hypokinesia of the intraventricular septum and the apex of the left ventricle, with an overall ejection fraction estimated at 40–45%. We supported the patient haemodynamically with titrated doses of intravenous dobutamine in combination with norepinephrine. Nitroglycerine was stopped. Intravenous fluids were also administered with a progressively decreased positive response, suggesting the progressive reversal of the distributive component. These therapeutic interventions reversed acidosis and the levels of lactic acid were reduced to normal less than 1.5, within the first three hours. Troponin levels were increased to 0.266 ng/mL six hours after the ischaemic event. Creatine kinase (CK) and CK myocardial type were also mildly elevated. Eosinophils appeared borderline elevated.

The patient's length of stay in the ICU was 4 days. A temporary pacemaker was implanted on the second day due to sinus pauses causing haemodynamic instability. The pauses were frequent and lasted up to 4 seconds. During his third day of stay he was stable haemodynamically, with only small needs in vasopressors. He was extubated easily after a short T-piece trial. During the fourth day he was

transferred to the cardiology care unit. A new echocardiographic assessment was performed on the sixth day of his hospital stay, with normal systolic function and absence of regional wall motion abnormalities. The previous findings of regional wall motion abnormalities were attributed to myocardial stunning. He was discharged on the sixth day with treatment for vasospastic ACS, with ASA, clopidogrel and calcium channel antagonist for at least one year. He was advised to avoid beta-lactamic medication life-long.

Discussion

Kounis syndrome is defined as the coincidental occurrence of ACS with hypersensitivity reactions following an allergenic exposure. It is associated with mast cell activation including allergic or hypersensitivity and anaphylactic or anaphylactoid attacks.¹

The syndrome is provoked by inflammatory mediators such as histamine, neutral proteases, arachidonic acid products, platelet activating factor and a variety of cytokines and chemokines released during the activation process.² It was first described by Kounis and Zavras in 1991 as a report of an allergic angina syndrome incidence.¹ Three different variants of Kounis syndrome have been defined.

Type I variant includes patients with normal or nearly normal coronary arteries without predisposing factors for coronary artery disease. In these patients the allergic event can induce either coronary artery spasm alone without raised cardiac enzymes and troponins but with electrocardiographic changes indicating ischaemia. They can also induce coronary artery spasm leading to plaque ulceration and acute myocardial infarction with raised cardiac enzymes and troponins. The probable pathophysiological mechanism for the explanation for this type would be endothelial dysfunction and/or microvascular angina.⁸

Type II variant includes patients with pre-existing silent coronary artery disease and atheromatous vessels in whom the acute allergic event can induce either coronary artery spasm, or plaque erosion or rupture manifesting as acute myocardial infarction. The rupture can be a result of neuro-hormonic activation during the allergic attack caused by inflammatory mediators.⁸

The type III variant of Kounis syndrome is a relatively new entity. It has been described in patients with pre-existing coronary artery disease and drug-eluting coronary stent thrombosis with occluding thrombus. In these patients, Giemsa and haematoxylin–eosin staining reveals the presence of mast cells and eosinophils, respectively.⁹ The activation of mast cells present at the stented and thrombotic areas might be the trigger of the phenomenon of drug-eluting stent thrombosis. The second generation drug-eluting stents are covered with polymer coatings that serve as drug carriers and permit controlled drug release. Allergic reactions to stent components (either nickel struts, polymer or ingrained drug) may play a role in this multifactorial

pathogenic condition. Finally, very late stent thrombosis could be another manifestation to be recognised as part of the Kounis syndrome.^{8,9}

Kounis syndrome seems to have geographical distribution. The syndrome has mostly been reported in southeastern Europe, especially in Greece and in Turkey. This geographical variation may be a result of an increased awareness of physicians of the existence of Kounis syndrome, climatic and environmental conditions, resulting in pollen cross-reactivities, hymenoptera exposure, overconsumption of medicine, and/or finally insufficient ways of prevention of genetic–environmental interactions.¹⁰

Causes

A variety of causes has been reported as capable of inducing Kounis syndrome and their number is increasing rapidly. These include several conditions, environmental exposures, poisons, venoms and a variety of drugs.

Drugs include analgesics (e.g. dipyrrone), anaesthetics (e.g. etomidate, rocuronium bromide, succinylcholine, suxamethonium, trimethaphan), antibiotics (e.g. ampicillin, amoxicillin, amikacin, cefazolin, cefuroxime, lincomycin, penicillin, vancomycin), thrombolytics and anticoagulants (e.g. streptokinase, urokinase, heparin, lepirudin), antineoplastics (e.g. 5-fluorouracil, capecitabine, carboplatin), contrast media (e.g. iohexole, loxaglate), corticosteroids (e.g. betamethasone, hydrocortisone), non-steroidal anti-inflammatory drugs (NSAIDs) (e.g. diclofenac, naproxen), skin disinfectants (e.g. chlorhexidine, povidone-iodine) and other drugs (allopurinol, enalapril, esmolol, dextran 40, fructose, insulin, iodine, protamine, tetanus antitoxin).

Conditions include angioedema, asthma, Churg–Strauss syndrome, exercise-induced anaphylaxis, intracoronary stenting, food allergy, hay fever, mastocytosis, nicotine exposure. Some environmental exposures include grass cutting, hymenoptera stings, jellyfish stings, latex contact, poison ivy, shellfish eating, viper venom.¹⁰ The most recently described offenders are scombroid syndrome (histamine fish poisoning) and exposure to gelatin succinylated/sodium chloride/sodium hydroxide (gelofusine), latex and the drug losartan.¹¹ Exposure to such allergens may occur directly or through the saliva of people or pets.¹¹

Pathophysiology

The suggested pathophysiology of allergic reactions include the following: (a) non-specific mast cell or basophil histamine release; (b) bradykinin accumulation; (c) complement activation; (d) possibly an alteration in arachidonate; and (e) the pharmacological action of certain substances inducing bronchospasm.¹²

The allergic reaction in the coronary tree can produce coronary vasospasm, platelet activation, aggregation and platelet-dependent arterial smooth cell hyperplasia.¹³ The

current hypothesis which explains the development of coronary spasm due to allergic reaction includes abnormalities in sympathetic and parasympathetic neural transmission, local arterial metabolic abnormalities, extensive responsiveness of the medium-sized arteries to circulatory vasoactive amines or combination of the above factors.¹⁴

The main inflammatory cells, mast cells, interact with macrophages and T-lymphocytes to cause Kounis syndrome. In acute coronary syndromes following allergic events, mast cells could be present in the culprit lesion before any plaque erosion or rupture. Kovanen et al. have demonstrated that the density of mast cells in the culprit atheroma of patients who died from acute myocardial infarction was 200 times higher than the density in normal coronary vessels from the same patients.¹⁵

The activation of mast cells, which are plenty in the coronary tree, leads to degranulation of several vasoactive mediators such as histamine, chemokine, enzymes as neutral proteases (tryptase, chymase, cathepsin-D), heparin, proteoglycans and cytokines. These mediators are released locally and in the peripheral circulation provoking vasoconstriction. Histamine induces coronary vasoconstriction, induces tissue factor expression, and activates platelets and intracoronary thrombosis.^{16–18} Degranulation of the mast cells also releases arachidonic acid products such as leukotrienes, thromboxane, prostacyclin, platelet activating factor and tumour necrosis factor. All the aforementioned metabolites in various degrees are implicated in the genesis of the syndrome.^{19–22}

The haemodynamic effect of the Kounis syndrome seems to be a combination of allergic–distributive shock with extensive peripheral vasodilation and myocardial suppression with the characteristics of cardiogenic shock. The indirect cardiac effect manifests as allergic shock with systemic vasodilation, which provokes a hypovolaemic state, reducing venous return and cardiac output. There are though, clinical case reports according to which patients with anaphylactic cardiac shock did not respond to fluid replacement but recovered with current protocol for myocardial infarction and anti-allergy treatment,^{23,24} thus denoting that the heart is directly involved, as in our patient.

The main direct cardiac effect constitutes coronary vasospasm, which provokes myocardial ischaemia. The acute myocardial ischaemia as a result of the prolonged coronary artery spasm led to myocardial stunning and acute heart failure. The heart can also be affected primarily by myocardial dysfunction because of the direct action of mediators such as tumour necrosis factor alpha, which reduce myocardial activity.²⁵

In experimental anaphylaxis with ovalbumin-sensitised guinea pigs²⁶ it was shown that within 3 minutes after the antigen administration there was a dramatic decrease of cardiac output by 90%, a significant increase of left ventricular end diastolic pressures by 35% indicating pump failure and finally the arterial blood pressure increased significantly by

35%. The above indicates that the human heart can be the primary target of anaphylaxis. This explains why patients with anaphylactic cardiac shock do not always respond to intravenous fluid administration and anti-allergic therapy but require myocardial infarction treatment and/or inotropic support.²⁷

The prognosis of patients with Kounis syndrome seems to be favourable beyond the acute phase, with left ventricular function normalising within 3 days to several weeks. A recent review on Kounis syndrome following beta-lactam antibiotic use supports that this syndrome seems to have a lower mortality and a better short-term prognosis than the usual ACS,²⁸ as no mortality has ever been reported, although the number of published cases is limited.

As mentioned above, there are four cases already published with a similar clinical picture of coronary artery spasm after cefuroxime administration.^{4–7} There are some crucial differences between these published cases and our case. First of all, the afore-mentioned four cases revealed normal coronaries during coronary angiography as the spasm was already resolved during basic treatment of systematic anaphylactoid response. In contrast, our patient was in sustained coronary spasm, which resolved only with intracoronary administration of nitrates. In the other four cases the coronaries were normal and/or with mild plaques during the angiography.

Second, it is remarkable that in our case the ST-T changes were initially in inferior leads but the coronary angiography revealed spasm of the LMCA. The finding of alternating vessels in spasm indicates the general tendency for coronary vasospasm during the syndrome's appearance.

Finally and more importantly, our patient's condition was complicated by cardiogenic shock. This altered the basic pathophysiological features of Kounis syndrome. Distributive shock with peripheral vasodilation was combined with an increase of peripheral resistances during cardiogenic shock as a result of a period of myocardial stunning. The haemodynamic parameters of our patient suggested a combination of cardiogenic shock and distributive shock. This shock was probably caused by direct myocardial suppression and by peripheral vasodilatation. It is an unusual case because myocardial stunning contributed significantly to the characteristics of shock, as a result of coronary spasm. The characteristics of cardiogenic shock were justified: (a) by the parameters of haemodynamic monitoring (reduced stroke volume, normal and not decreased systemic vascular resistances); (b) by the echocardiographic findings and their reversibility a few days after the episode; (c) by the fact that the patient was not responding to volume replacement but also required titrated doses of inotropes; (d) by the fact that the shock was sustained and required much more time to resolve than in allergic shock.

Treatment

Treatment of Kounis syndrome is challenging as it needs consideration of both the cardiac and allergic component simultaneously. The drugs administered may worsen allergy and aggravate heart function.¹¹ Problems that have to be taken into consideration are both the myocardium revascularisation and the concomitant allergic reaction. Guidelines for treatment are lacking and the majority of the evidence is based on individual case reports or case series following the principles of the treatment of ACS and anaphylaxis.²⁹ Therapeutic agents that inhibit mast cell degranulation may be efficient in preventing the acute coronary and cerebrovascular events of Kounis syndrome.

Patients with the type I variant may benefit from the treatment of the allergic reaction. The use of corticosteroids (hydrocortisone 1–2 mg/kg/day intravenously) and H1 and H2 antihistamines (diphenhydramine 1–2 mg/kg and ranitidine 1 mg/kg given slowly) is beneficial.^{10,11} The use of fluids is crucial in distributive shock due to anaphylactic reaction. In an adult, normal saline or lactated Ringer's solution rather than a colloid should be administered at a dose of 25–50 ml/kg initially, with caution because of the risk of pulmonary oedema and respiratory failure. Epinephrine is the drug of choice and can save lives in anaphylaxis, but in Kounis syndrome it can aggravate ischaemia and worsen coronary vasospasm. The recommended dose and route is 0.2–0.5 mg of aqueous epinephrine (1:1000) administered intramuscularly every 5–15 minutes.³⁰ In patients who receive beta-blockers, epinephrine may be ineffective and also induce more vasospasm, and the use of glucagon may be considered.¹⁰ The administration of vasodilators such as calcium channel blockers and nitrates may abolish hypersensitivity-induced vasospasm. However, nitroglycerine may cause hypotension and tachycardia, which may further complicate allergic reactions, therefore its use seems reasonable and safe if the blood pressure is satisfactory.²⁶ Beta-blockers are contraindicated in the Kounis syndrome, due to a subsequent coronary spasm caused by unopposed activity of adrenergic receptors.²⁹ Opioids (morphine, codeine and meperidine) should be used cautiously as they can induce mast cell degranulation and aggravate the allergic reaction. Fentanyl shows a slight activation of mast cells and may be the drug of choice if narcotic analgesia is necessary. Supplemental oxygen should be administered to patients with arterial saturation less than 90%, respiratory distress or other high risk features for hypoxaemia.³⁰

In patients with the type II variant, treatment should be initiated with an acute coronary event protocol together with corticosteroids and antihistamines.¹¹ Nitroglycerine and calcium channel blockers (diltiazem, verapamil) are the preferred vasodilators. A double antiplatelet therapy, ASA plus a P2Y₁₂ receptor inhibitor, is suggested irrespective of the pathogenesis of the ACS. ASA needs close monitoring as it can cause allergic reactions and induce anaphylaxis.

Anticoagulant therapy should be added, but considering the risk of anaphylactic reactions with heparin, it is suggested that low-molecular weight heparins or bivalirudin are used.³⁰

In patients with the type III variant, the acute myocardial infarction protocol with urgent aspiration of intrastent thrombus, and histological examination of aspirated material and staining for eosinophils and mast cells should be undertaken.^{10,11} In patients who develop allergic symptoms following stent implantation, desensitisation measures should be applied. Mast cell stabilisers such as cromoglycate (cromolyn) or flavonoids such as quercetin, together with corticosteroids and antihistamines could ameliorate the allergic symptoms.²⁹ If symptoms persist and the above-mentioned measures fail, stent extraction should be considered.¹¹

All patients should be followed in cardiology and allergy clinics after hospital discharge. The treatment of Kounis syndrome is challenging, due to the potential worsening of symptoms after treatment and the need to address both allergic and cardiac symptoms simultaneously. Promising preventive measures and a systematic approach may outstrip these issues.²⁹

Conclusion

Kounis syndrome is the coincidental occurrence of an ACS with hypersensitivity reaction following an allergenic event. Mast cells and their products are crucial for the pathogenesis of Kounis syndrome. The pathophysiological characteristics of Kounis syndrome involve coronary artery spasm and/or atheromatous plaque erosion or rupture during an allergic reaction. Kounis syndrome can be complicated by cardiogenic shock, as in our case by direct or indirect myocardial suppression. Treatment consists of myocardial revascularisation and solution of the concomitant allergic reaction. Treatment in cardiogenic shock attributed to Kounis syndrome is complicated as both distributive and cardiac components play an equally significant role.

Acknowledgements

The authors would like to thank all their colleagues of their clinic working on this case.

Conflict of interest

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

References

1. Kounis NG and Zavras GM. Histamine-induced coronary artery spasm: the concept of allergic angina. *Br J Clin Pract* 1991; 45: 121–128.
2. Kounis NG. Kounis syndrome (allergic angina and allergic myocardial infarction): a natural paradigm? *Int J Cardiol* 2006; 110: 7–14.
3. Rodriguez-Pena R, Antunez C, Martin E, et al. Allergic reactions to beta-lactams. *Expert Opin Drug Saf* 2006; 5: 31–48.
4. Murat SN, Karasu BB, Ornek E, et al. Cefuroxime-axetil induced allergic angina: an insight into classification management of Kounis syndrome. *Int J Cardiol* 2011; 151: e53–e55.
5. Ilhan E, Güvenç TS, Poyraz E, et al. Kounis syndrome secondary to cefuroxime axetil use in an asthmatic patient. *Int J Cardiol* 2009; 137: e67–e69.
6. Biteker M, Duran NE, Biteker FS, et al. Kounis syndrome secondary to cefuroxime-axetil use in an octogenarian. *J Am Geriatr Soc* 2008; 56: 1757–1758.
7. Mazarakis A, Koutsojannis CM, Kounis NG, et al. Cefuroxime-induced coronary artery spasm manifesting as Kounis syndrome. *Acta Cardiol* 2005; 60: 341–345.
8. Biteker M. A new classification of Kounis syndrome. *Int J Cardiol* 2010; 145: 553.
9. Akyel A, Murat SN, Cay S, et al. Late drug eluting stent thrombosis due to acemetacine: type III Kounis syndrome: Kounis syndrome due to acemetacine. *Int J Cardiol* 2012; 155: 461–462.
10. Kounis NG, Mazarakis A, Tsigkas G, et al. Kounis syndrome: a new twist on an old disease. *Future Cardiol* 2011; 7: 805–824.
11. Kounis NG. Coronary hypersensitivity disorder: the Kounis syndrome. *Clin Therapeut* 2013; 35: 563–568.
12. Demoly P, Adkinson NF, Brockow K, et al. International consensus on drug allergy. *Allergy* 2014; 69: 420–437.
13. Brown SGA, Kemp SF and Lieberman P. Anaphylaxis. In: Adkinson NF Jr, Bochner BS, Burks AW, et al. (eds) *Middleton's Allergy Principles and Practice*, 8th ed. Philadelphia, PA: Elsevier Mosby; 2013, chap 77.
14. Ginsburg R, Bristow MR, Kantrowitz N, et al. Histamine provocation of clinical coronary artery spasm: implications concerning pathogenesis of variant angina pectoris. *Am Heart J* 1981; 102: 819–822.
15. Kovanen PT, Kaartinen M and Paavonen T. Infiltrates of activated mast cells at the site of coronary atheromatous erosion or rupture in myocardial infarction. *Circulation* 1995; 92: 1084–1088.
16. Genovese A and Spadaro G. Highlights in cardiovascular effects of histamine and H1-receptor antagonists. *Allergy* 1997; 52(Suppl. 34): 67–78.
17. Steffel J, Akhmedov A, Greutert H, et al. Histamine induces tissue factor expression. Implications for acute coronary syndromes. *Circulation* 2005; 112: 341–349.
18. Shah BH, Lashari I, Rana S, et al. Synergistic interaction of adrenaline and histamine in human platelet aggregation is mediated through activation of phospholipase, nap kinase and cyclo-oxygenase pathways. *Pharmacol Res* 2000; 42: 479–483.
19. Kounis NG, Tsigkas G, Almpanis G, et al. Anaphylaxis-induced hyperfibrinogenolysis and the risk of Kounis syndrome: the dual action of tryptase. *Am J Emerg Med* 2011; 29: 1229–1230.
20. Gilfillan AM and Tkaczyk C. Integrated signalling pathways for mast-cell activation. *Nat Rev Immunol* 2006; 6: 218–230.

21. Frangogiannis NG, Lindsey ML, Michael LH, et al. Resident cardiac mast cells degranulate and release preformed TNF- α , initiating the cytokine cascade in experimental canine myocardial ischemia/reperfusion. *Circulation* 1998; 98: 699–710.
22. Zdravkovic V, Pantovic S, Rosic G, et al. Histamine blood concentration in ischemic heart disease patients. *J Biomed Biotechnol* 2011; 2011: 1–8.
23. Shah G, Scadding G, Nguyen-Lu N, et al. Peri-operative cardiac arrest with ST elevation secondary to Gelofusine anaphylaxis – Kounis syndrome in the anaesthetic room. *Int J Cardiol* 2013; 164(3): e22–6.
24. Kajander OA, Virtanen MP, Sclarovsky S, et al. Iatrogenic inverted takotsubo syndrome following intravenous adrenaline injections for an allergic reaction. *Int J Cardiol* 2013; 165(1): e3–5.
25. Fassio F and Almerigogna F. Kounis syndrome (allergic acute coronary syndrome): different views in allergologic and cardiologic literature. *Intern Emerg Med* 2012; 7: 489–495.
26. Felix SB, Baumann G and Berdel WE. Systemic anaphylaxis – separation of cardiac reactions from respiratory and peripheral vascular events. *Res Exp Med (Berl.)* 1990; 190: 239–252.
27. Kounis NG. Hymenoptera stings, anaphylactic shock and the Kounis syndrome. *N Am J Med Sci* 2013; 5: 159–160.
28. Ridella M, Bagdure S, Nugent K, et al. Kounis syndrome following beta-lactam antibiotic use: review of literature. *Inflamm Allerg Drug Targets* 2009; 8: 11–16.
29. Fassio F, Losappio L, Antolin-Amerigo D, et al. Kounis syndrome: a concise review with focus on management. *Eur J Intern Med* 2016; 30: 7–10.
30. Cevik C, Nugent K, Shome GP, et al. Treatment of Kounis syndrome. *Intl J Cardiol* 2010; 143: 223–226.