CASE REPORT

Vancomycin-induced coronary artery spasm: a case of Kounis syndrome

Eric Martinez,¹ Sonu Sahni,¹ Muhammad Al Cheema,² Asma Iftikhar²

¹Department of Primary Care, Touro College of Osteopathic Medicine, New York, USA

²Department of Pulmonary and Critical Care Medicine, New York Presbyterian Hospital Queens, New York, USA

Correspondence to
Dr Asma Iftikhar,
doctorasmi@gmail.com

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SUMMARY

Kounis syndrome defined as the appearance of acute coronary syndrome in the context of an allergic reaction is a relatively rare phenomenon. There are three variants of this syndrome in which the patient presents with symptoms of an acute chest. Herein, we describe a case of an 83-year-old woman who demonstrated type I variant of Kounis syndrome in response to vancomycin administration. After initialisation of vancomycin, she became unresponsive and an ECG demonstrated ST changes consistent with inferior-lateral myocardial infarction. Once allergic stimulus was removed, ECG normalised. Differential diagnosis includes, myocardial infarctions, angina as well as intravascular stent thrombosis, which must all be ruled out. The patient was monitored and discharged soon thereafter.

BACKGROUND

Kounis syndrome (KS) defined as the appearance of acute coronary syndrome (ACS) in the context of an allergic reaction was first described in 1991 by Kounis and Zavras.¹ It is thought that the pathomechanism of ACS in the setting of allergic reaction involves the effects of released histamine on cardiac function via H1 and H2 receptors, which are situated on the four cardiac chambers and coronary arteries.¹ This syndrome has been reported in response to many possible allergic entities: allergens such as endovascular implantations, insect stings and food ingestion.^{2,3} KS has also been observed in various cases with commonly used antibiotics such as amoxicillin and cephalosporins among others.⁴ However, to the best of our knowledge, KS has yet to be reported in the setting of vancomycin administration. Herein, we describe a case of an

83-year-old woman with presentation of ACS in response to vancomycin.

CASE PRESENTATION

An 83-year-old woman with a past medical history of bilateral total knee replacement, hypothyroidism, hypertension, aortic valve replacement and hyperlipidaemia was presented to the emergency department with a chief complaint of unbearable pain in her right knee, showing signs of possible infection. The patient had a history of several admissions due to complications such as cellulitis and infection of her right knee replacement. She complained of pain, swelling, warmth and redness of the right patellar area, which she said she had been experiencing for 1 week. She was seen in an orthopaedic clinic and was treated with cephalexin without any improvement, then referred to the hospital for intravenous antibiotics.

In the emergency department, the patient underwent right knee arthrocentesis, and a sample was taken for culture analysis. Due to lack of response to previous antibiotics, methicillin-resistant *Staphylococcus aureus* was suspected. The patient was started on intravenous vancomycin at a dose 15 mg/kg per 12 hours for suspected septic knee. After approximately 5 min of infusion, the patient became unresponsive with agonal respiration and a barely palpable thready pulse. The patient was placed on a non-rebreather mask to assist with ventilation until she became responsive again with strong pulses. On physical examination, there was no urticaria, rashes, facial oedema, tongue swelling or wheezing appreciated.

An immediate ECG was performed, which displayed normal sinus rhythm with an acute inferior-lateral myocardial ischaemia pattern, ST elevation in leads II, III and aVF with reciprocal minimal changes in the precordial leads (figure 1). A confirmatory ECG performed 4 min later displayed a normal sinus rhythm, surprisingly, without any ST elevation or depression (figure 2). Nitroglycerine was not administered due to lack of chest pain as a complaint as well as hypotensive status at that time.

After an immediate cardiology consultation, echocardiogram was done to evaluate structure and functionality. Echocardiography revealed a normal ejection fraction (60%–65%) without any valvular abnormalities. Mild tricuspid regurgitation and moderate aortic stenosis were observed as well. Cardiac catheterisation was recommended to

Figure 1 ECG displaying normal sinus rhythm with an acute inferior-lateral myocardial ischaemia pattern, ST elevation in leads II, III and aVF with reciprocal minimal changes in the precordial leads.

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Figure 2 ECG taken 4 min after initial ECG showing normalisation.

evaluate coronary artery disease due to observed ST changes; however, the patient denied it due to the invasive nature of the procedure.

After diagnostic testing and discussion with cardiologist, it was thought that her symptoms, respiratory failure and ECG were secondary to vancomycin infusion. The patient was given an intravenous push of intravenous diphenhydramine of 50mg, which improved her symptoms. Additionally, an ECG was repeated and her ST elevations was resolved. Her vital signs have been shown in [table 1](#). Laboratory results were all within normal range as well as cardiac enzymes. Results have been shown in [table 2](#). The patient followed up on an outpatient basis with at the cardiology clinic after 1 week. ECG after 1 week was normal sinus rhythm without any ST segment changes.

OUTCOME AND FOLLOW-UP

After normalisation of ECG and administration of antihistamines, the patient was monitored. Cardiac enzymes were monitored for any trends, echocardiography was performed and found to be unremarkable. Patient was administered other class of antibiotics for suspected septic joint and discharged soon thereafter.

DISCUSSION

Herein, we described a case of KS in an 83-year-old woman who suffered ACS after the administration of vancomycin. To the best of our knowledge, this is the first of such case. The exact pathophysiology of this syndrome is still uncertain. A proposed and most widely accepted pathomechanism involves the degranulation of mast cells in response to an allergen stimulus. Mast cell activation leads to the release of histamine, leucotrienes, proteases and other inflammatory mediators.¹ Another proposed mechanism involves the acute secretion of tryptase, which leads to the rupture of an atheroma plaque and formation of intravascular thrombus, which may cause an infarction.⁵ In the case of our patient, allergic response to vancomycin could be attributed to a histamine response, leading to her clinical presentation. Although various allergic stimuli have a similar end result in clinical presentation, there is variability in stimuli.

Table 1 Vital signs

Temperature	Pulse	Respiratory rate	BP	Pulse oximetry
99.7°C	108 bpm	24 per min	142/72 mm Hg	99% on 2 L/min nasal cannula

bpm, beats per min; BP, blood pressure.

Table 2 Laboratory results

Investigation	Results (normal values)
Total bilirubin	0.33 (0.0–1.2 mg/dL)
Direct bilirubin	0.10 (0.0–0.3 mg/dL)
Alkaline phosphatase	177 (40–130 U/L)
Albumin	2.6 (3.5–5.2 g/dL)
AST/SGOT	16 (5–41 U/L)
ALT/SGPT	8 (5–40 U/L)
Sodium level	139 (136–145 mmol/L)
Potassium level	4.3 (3.5–5.1 mmol/L)
Carbon dioxide level	22.8 (22–29 mmol/L)
Chloride level	106 (98–107 mmol/L)
Blood urea nitrogen	24.0 (8–23 mg/dL)
Creatinine	1.0 (0.70–1.20 mg/dL)
Calcium level	10.2 (8.6–10.4 mg/dL)
Random glucose	143 (74–99 mg/dL)
Total creatine kinase	14 (20–200 U/L)
Troponin I	<0.017 (0.010–0.030 ng/mL)
White blood count	2.2 (4.80–10.80 ×10 ⁹ /L)
Haematocrit	26.7 (40–50%)
Haemoglobin	7.8 (13.3–17.7 g/dL)
Platelet count	385 (150–400 ×10 ⁹ /L)
Mean corpuscular volume	80.2 (80–100fl)
Prothrombin time international ratio	1.09 (0.87–1.13)
Activated partial thromboplastin time	24.6 (25–35 s)
Prothrombin time	11.6 (10–13 s)

ALT, alanine amino transferase; AST, aspartate amino transferase; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase.

KS has traditionally been divided into two categories. However, in recent years new variants have been described: type I variant is seen in patients without the presence of coronary lesions caused by coronary vasospasm concurrent with definitive changes on ECG and normal cardiac enzymes. Type II variant occurs in patients with pre-existing atherosclerotic plaques that erode and rupture due to allergen-induced inflammatory response, leading to an ACS.⁶ Type III variant occurs with thrombosis of drug-eluting stents, also due to a chronic inflammatory response.⁷ Here, histopathological confirmation of the presence of eosinophils and mast cells in the thrombus is required. The patient in our case demonstrates the Type I variant of KS given that she presented a normal range of troponin levels with her coronary symptoms occurring after the administration of vancomycin, which was confirmed on ECG.

Since the initial description of KS, there have been numerous cases in which antibiotics had been given to the patient to treat a prior infection. Some of which are shown in [table 3](#). Our patient had a reaction to vancomycin, to the best of our knowledge the only case in recent times. The majority of antibiotic-induced KS cases are reportedly caused by the beta-lactam family of drugs. Analysis of a European pharmacovigilance database found that the most frequently reported suspected antibiotic was the combination amoxicillin/clavulanic acid.⁴

More specifically pertaining to our case is the implication of vancomycin. In a study by Valero *et al* who studied the adverse reactions of vancomycin prophylaxis in cardiac surgery, it was observed that slightly more than a quarter of all patients developed an allergic reaction, the most common of which was hypotension.⁸ Rapid infusion of vancomycin has been previously been implicated in 'red man's syndrome' or 'red neck syndrome' which is characterised by upper torso and neck erythema and pruritus.⁹ This is thought to

Table 3 Select cases of antibiotic-induced Kounis syndrome

Author (year)	Antibiotic
Mazarakis <i>et al</i> ¹⁴ (2005)	Cefuroxime
Soufras <i>et al</i> ¹⁵ (2005)	Penicillin
Tavil <i>et al</i> ¹⁶ (2008)	Amoxicillin/clavulanate
Biteker <i>et al</i> ¹⁷ (2008)	Cefuroxime/axetil
Biteker <i>et al</i> ¹⁸ (2009)	Amoxicillin/clavulanate
Kilic <i>et al</i> ¹⁹ (2009)	Sulbactam/ampicillin
Calogiuri <i>et al</i> ²⁰ (2012)	Piperacillin/tazobactam
Saleh ²¹ (2014)	Ceftriaxone
Bilgin <i>et al</i> ²² (2014)	Clarithromycin
Ralapanawa and Kularatne ²³ (2015)	Amoxicillin/clavulanate
Barbarroja-Escudero ²⁴ (2016)	Cefditoren pivoxil
Shim <i>et al</i> ²⁵ (2016)	Amoxicillin/clavulanic acid
Garcia-Núñez <i>et al</i> ²⁶ (2016)	Levofloxacin
Canpolat <i>et al</i> ²⁷ (2017)	Amoxicillin/clavulanate

be due to an infusion rate dependent increase in plasma histamine concentration.⁹ Other allergic reactions have also been noted such as spasm of chest and paraspinal muscles mimicking myocardial infarction as well as bullous skin disease.^{10 11}

Diagnosis of KS is usually made clinically. Oftentimes, signs of an acute allergic reaction are present with simultaneous ACS. There is no specific diagnostic test for this syndrome, so a detailed history is imperative. Due to often-serious presentation, a full diagnostic workup is performed including ECG, echocardiography and occasionally, catheterisation, depending on the variant of disease. In our patient, a stat ECG was performed due to her clinical picture. An expeditious cardiology consult aided in ruling out myocardial infarction. It is plausible to believe that this syndrome is underdiagnosed due to the variable manifestations of an allergic reaction.

Initial management of KS may be challenging. Drugs commonly used for chest pain such as morphine and beta-blockers should be avoided, as they may instigate the release of histamine, potentiate vasospasm, which would increase the symptoms of KS.¹² Once a diagnosis is made, epinephrine is preferred to counter any underlying allergic response. Further management depends on the variant of KS. In type I variant, a pure allergic response is most common and can be treated with intravenous steroids and antihistamine such as diphenhydramine and ranitidine. Vasodilators such as calcium channel blockers and nitrates may also assist in abolishing hypersensitivity induced vasospasm.¹³ A type II variant patient should be treated according to the acute coronary artery guidelines in conjunction with steroids, antihistamines, nitrates and calcium channel blockers. In type III variant, the use of mast cell stabilisers with steroids and an antihistamine are recommended. Further treatment may require desensitisation if the patient develops recurrent allergic reactions after stent placement.¹³

KS is defined as the appearance of ACS in the context of an allergic reaction. There exists three variants of KS, which may be due to a pure allergic reaction to a stimulus, a rupture of atherosclerotic plaque due to allergic stimulus leading to infarction or an allergic response to an intravascular stent in the coronary arteries presenting as a myocardial infarction. Herein, we described a case depicting the type I variant of KS. Management is mostly dependent on the variant of the disease; however, it must include an antiallergic regimen. Additionally, patients who present with acute chest syndrome symptoms without a clear aetiology should be ruled out for KS.

Learning points

- Kounis syndrome (KS) is defined as the appearance of acute coronary syndrome (ACS) in the context of an allergic reaction.
- There are three variants of KS: type I variant is seen in patients without presence of coronary lesions; type II variant occurs in patients with pre-existing atherosclerotic plaques that erode and rupture; type III variant occurs with thrombosis of drug-eluting stents.
- Opiates such as morphine, codeine and meperidine which are usually given to relieve acute chest pain should be avoided. Fentanyl and its derivatives show slight mast cell activation and should be the drugs of choice when narcotic analgesia is necessary.
- In patients who present with ACS soon thereafter, administration of new medication or possible allergic stimulus should be ruled out for KS. Once diagnosis is made, all efforts should be made to remove offending agent along with initialisation of antiallergy regimen.

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Competing interests None declared.

Patient consent Detail has been removed from this case description/these case descriptions to ensure anonymity. The editors and reviewers have seen the detailed information available and are satisfied that the information backs up the case the authors are making.

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