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Cefuroxime-associated Kounis syndrome with unique peculiarity in perioperative prophylaxis

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ABSTRACT

Cefuroxime is a broad spectrum antibacterial agent administered in cases of perioperative prophylaxis. Kounis syndrome is defined as the concurrence of anaphylactic events with acute coronary syndromes. Limited data is available for cefuroxime-associated Kounis syndrome in perioperative prophylaxis. We report the case of a 37-year-old woman undergoing bilateral sweat gland resection who presented with Kounis syndrome following cefuroxime infusion for perioperative prophylaxis. The patient had severe symptoms and unique manifestations that never been reported before: pink frothy sputum indicating heart failure, due to severe systolic dysfunction requiring invasive ventilation and intra-aortic balloon counter-pulsation. Cefuroxime-associated Kounis syndrome has several unique and life-threatening peculiarities which broaden our understanding of clinical and laboratory characteristics. It is important for physicians to be aware of possible cardiovascular complications in perioperative cefuroxime prophylaxis.

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Background

Perioperative antibiotic prevention is important because surgical site infections are associated with an adverse prognosis. According to the national drug policy in China, cefuroxime is recommended for antibiotic prophylaxis in operations with type I incision [1].

Kounis syndrome is defined as the concurrence of acute coronary syndromes with conditions associated with mast cell and platelet activation. It also involves interrelated and interacting inflammatory cells, such as macrophages and T-lymphocytes, in the setting of anaphylactic events such as pruritus, dyspnea, and vomiting [2]. The coronary arteries and the heart seem to be the primary target of anaphylaxis manifesting as Kounis syndrome [3]. Various factors have been found to trigger Kounis syndrome, such as drugs, food items or environmental factors [2].

To our knowledge, only a limited amount of data has been published with regard to cefuroxime-associated Kounis syndrome in perioperative antibiotic prophylaxis. This report represents the first

reported case of Kounis syndrome with systemic and rare manifestations associated with perioperative cefuroxime prophylaxis.

Case presentation

The patient was a 37-year-old woman admitted into our hospital for elective bilateral resection of the axillary sweat glands in order to treat bromhidrosis. Upon admission, the patient (height: 160 cm, weight: 56 kg) did not report any drug allergies, hypertension, diabetes mellitus, or dyslipidaemia. She had no history of cefuroxime infusion and did not mention a (family) history of coronary artery disease. She was a non-smoker. Vital signs were normal and her electrocardiogram (ECG) and physical examination were unremarkable.

On operation day (Day 1), she was administered cefuroxime (1500 mg) intravenously for perioperative prophylaxis. Twenty minutes later, she received lidocaine (200 mg) subcutaneously for local anaesthesia; 10 min later, an incision was made in her skin. Approximately 75 min after beginning the cefuroxime infusion, the patient developed nausea and vomiting, became pale, and experienced vertigo and headache. Blood pressure and heart rate fell to 60/40 mmHg and 40/min, respectively. The patient was given nasal oxygen, epinephrine (1 mg) and dexamethasone (5 mg) intravenously for anaphylactic shock. Thirty minutes later, the patient developed an erythematous rash and itching on both arms, prompting the administration of 25 mg of promethazine by intramuscular

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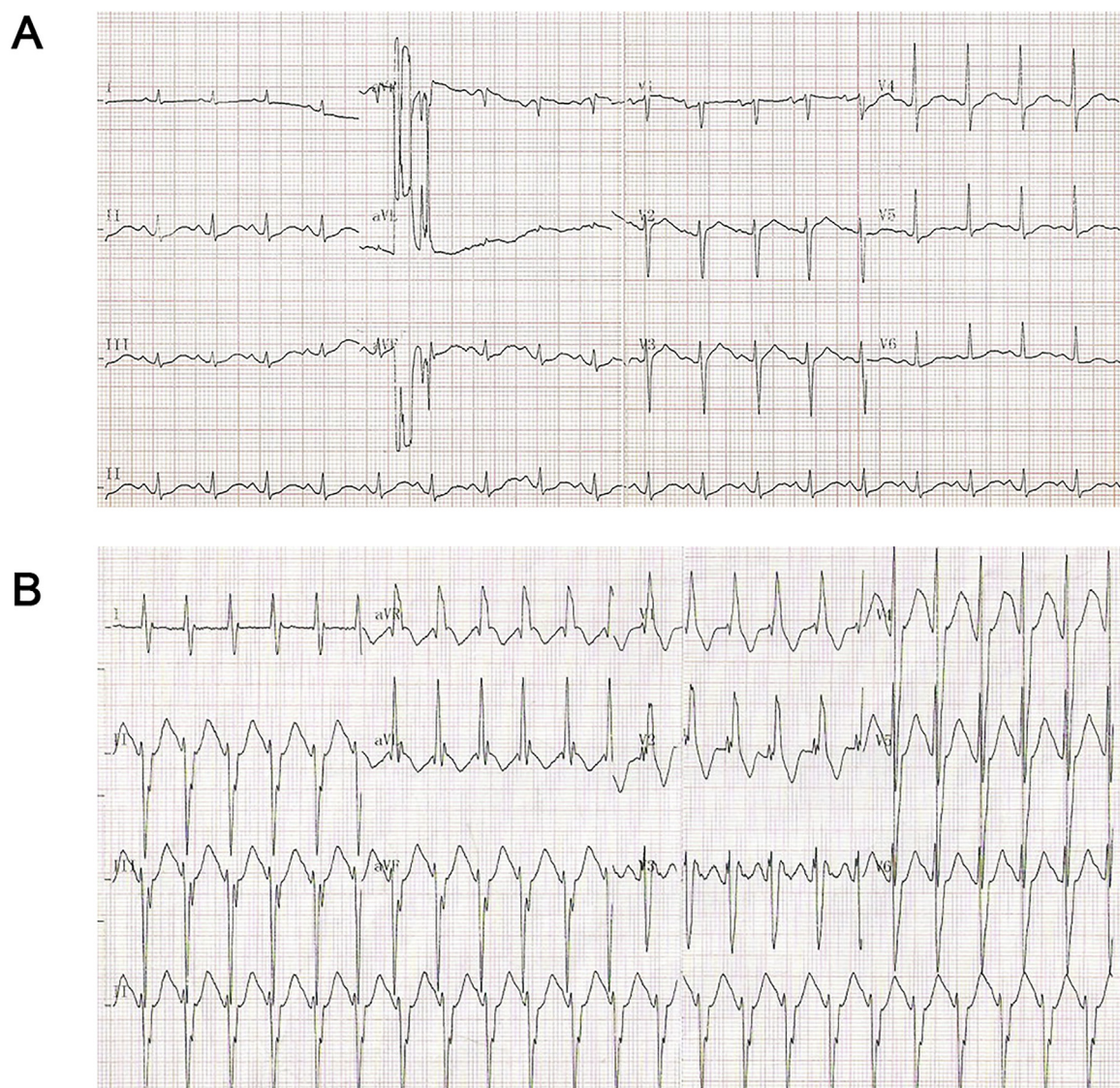


Fig. 1. Electrocardiogram of a 37-year-old woman with perioperative Kounis syndrome showing ST-segment depression in leads V5, V6 on day 1 (A) and ventricular tachycardia, ST-segment depression in leads I, V2, V3 on day 3 (B).

Table 1
Laboratory results relative to the patient's perioperative cefuroxime prophylaxis.

Subjects	D1	D2	D3	D4	D5	D6	D7	D11	D31
cTnI (ng/mL)	6.00	10.90	5.26	2.98	1.51	0.96	0.52	0.17	0.01
CK-MB (U/L)	52.84	74.02	89.52	24.18	16.38	16.96	22.96	17.17	4.09
LDH (U/L)	208.0	228.0	1046.4	1043.9	695.0	540.3	541.8	286.5	127.0
Myo (ng/mL)	257.0	214.4	97.7	239.9	183.1	252.2	251.2	303.4	NA
AST (U/L)	78.3	104	169.1	82	37.3	39.8	74.8	72.3	16.2
ALT (U/L)	NA	23	26	22	21	27	56	119	10
TBIL (μ mol/L)	NA	22.0	42.5	21.4	17.2	19.1	24.3	14.5	17.4
DBIL (μ mol/L)	NA	9.3	17.7	10.0	8.3	9.1	11.2	7.5	8.5
BUN (mmol/L)	NA	7.4	4.8	7.6	10.2	8.9	7.9	9.0	2.5
Cr (μ mol/L)	NA	125.0	66.0	56.0	61.0	52.0	48.0	45.0	46.0
Lac (mmol/L)	4.1	5.2	1.8	1.2	0.9	0.7	0.9	0.6	NA
Eosin ($10^9/L$)	0	0	0	0	0	0	0	0.04	NA

Normal ranges: cTnI (Troponin I) 0–0.08 ng/mL; CK-MB (Creatine kinase-MB) 0–16.0 U/L; LDH (Lactic dehydrogenase) 100.0–225.0 U/L; Myo (Myoglobin) 0–61.5 ng/mL; AST (Glutamic oxalacetic transaminase) 14.0–59.0 U/L; ALT (Glutamate pyruvate transaminase) 5.0–40.0 U/L; TBIL (Total bilirubin) 5.0–22.0 μ mol/L; DBIL (Direct bilirubin) 0–10.2 μ mol/L; BUN (Urea nitrogen) 2.5–7.5 mmol/L; Cr (Creatinine) 44.2–104.0 μ mol/L; Lac (Lactate) 0.5–2.2 mmol/L; Eosin (Eosinophil) 0.05–0.5 $10^9/L$.

injection. The patient expectorated pink frothy sputum and pulmonary moist rales were heard, particularly in the left lung. We suspected left heart failure and pulmonary oedema; the patient was transferred to the intensive care unit. We administrated dopamine,

norepinephrine, furosemide, deslanoside and dexamethasone and the patient was stabilized. However, 13 h after intravenous cefuroxime, the heart rate increased after positive inotropes; ECG showed non-specific ST-segment depression in leads V5 and V6 compati-

Table 2

Previous reports of cefuroxime induced Kounis syndrome [4–7].

	Case 1 [4]	Case 2 [5]	Case 3 [6]	Case 4 [7]
Age (year)	70	40	61	90
Sex	Female	Male	Female	Male
Reason for admission	Gynaecological operation	NA	NA	Urinary tract infection
Administration route	Intravenous infusion	Oral	Oral	Intramuscular injection
History of allergy	No	No	NA	NA
Dose (mg)	750	500	250	750
Latent period (min)	1	5	10	10
Length of stay (day)	4	4	7	5
Past medical history	Increased cholesterol levels	No	Mild asthma	No
Symptoms	Retrosternal pain, erythematous rash, periorbital oedema, itching, vomiting, pale	Chest pain	Chest pain, nausea, vomiting, vertigo, erythema, dyspnea, anaphylactic shock	Thoracic pain, pruritic skin rash
Cardiac biomarker	Normal	Normal	cTnI 0.06 ng/mL, CK-MB 59 U/L	cTnI 4–22 ng/mL, CK-MB 42–85 U/L
ECG	ST-segment elevation in leads II, III, aVF with depression in leads I, aVL, V2	ST-segment elevation in leads D2, D3, aVF	ST-segment elevation in leads II, III, aVF with depression in leads I, aVL, V1–V3	ST-segment elevation in leads II, III, aVF, V4–V6
CAG	Normal	Plaques in the circumflex and right coronary artery	Plaques without significant stenosis	Plaques in the left anterior descending and circumflex artery
TTE	NA	Normal wall motion	Minimal inferior wall hypokinesia	Inferior wall hypokinesia

NA: not available; ECG: electrocardiogram; CAG: coronary angiogram; TTE: transthoracic echocardiography.

ble with myocardial ischemia (Fig. 1A). Laboratory analysis showed elevation of cardiac biomarkers with troponin I (cTnI) at 6.00 ng/mL and creatine kinase-MB (CK-MB) at 52.84 U/L (Table 1).

On day 2, the patient's arterial oxygen saturation suddenly dropped to 81%; with a non-invasive ventilator, arterial oxygen saturation was 90%. One hour later, pink frothy sputum was expectorated again. A chest radiograph indicated pulmonary oedema. The arterial oxygen saturation and blood pressure were kept at 83% and 110/60 mmHg, respectively. Then, furosemide, deslanoside, and methylprednisolone were administered. The patient's arterial oxygen saturation was maintained between 90%–92% over the following 4 h. Suddenly, the patient developed dyspnoea with a respiratory rate of 47/min. Invasive ventilator-assisted ventilation was applied. One hour later, respiratory rate fell to 15/min; arterial oxygen saturation was 98%. Transthoracic echocardiography (TTE) revealed left ventricular inferior wall hypokinesia, with an ejection fraction (EF) of 26% (range: 50%–70%). cTnI and CK-MB were significantly elevated to 10.90 ng/mL and 74.02 U/L (Table 1). Intra-aortic balloon counter-pulsation support was provided to improve heart function.

On day 3, an episode of ventricular tachycardia occurred (Fig. 1B) which was returned to sinus rhythm after administration of intravenous amiodarone. TTE revealed left ventricular inferior wall hypokinesia with an EF of 31%. cTnI and CK-MB were 5.26 ng/mL and 89.52 U/L, respectively.

On day 4, blood pressure was maintained at 102/65 mmHg; intra-aortic balloon counter-pulsation support was discontinued. On day 9, ventilator support was discontinued. We suspected acute coronary syndrome and performed coronary angiography, which revealed atheroma-free coronary arteries.

The patient's recovery was uneventful; she was discharged on her 11th day at the hospital. And one month later, the patient's cTnI and CK-MB levels were within normal limits. Furthermore, both ECG and TTE had remained normal.

Discussion and conclusion

Administration of cefuroxime was the only factor that may have induced rapid development of allergic events in this patient. A PubMed search of “cefuroxime AND Kounis” yielded four previous reports of Kounis syndromes associated with cefuroxime (Table 2) [4–7]. This report represents the first case of Kounis syndrome

induced by cefuroxime with severe symptoms and unique manifestations which were never been reported before: pink frothy sputum indicating heart failure, due to severe systolic dysfunction requiring invasive ventilation and intra-aortic balloon counter-pulsation. The patient was accordant with type I variant of Kounis syndrome, with normal coronary arteries and inflammatory mediators induced coronary artery spasm progressing to acute myocardial infarction with raised cardiac enzymes and troponins [2]. Our experience with this patient significantly broadens our understanding of the clinical and laboratory characteristics of cefuroxime-associated Kounis syndrome.

The relationship between cefuroxime administration and Kounis syndrome was assessed by the Naranjo Adverse Drug Reaction Probability Scale score [8]; it was categorized as probable. The patient had received cefuroxime, lidocaine, epinephrine and dexamethasone from allergy start to culmination with skin manifestations. All these substances have been incriminated as inducing allergic reactions [9–12]. The initiation of allergic inflammation takes place when allergens cross-bridge IgE antibodies on the mast or basophil cell surface and IgE antibodies with different specificities can have additive effects. So they can join forces and trigger the cells to release their mediators, inducing easier and quicker an allergic reaction. This can happen when the patient is simultaneously exposed to the hypersensitive antigens [13].

Kounis syndrome patients are not rare, especially in allergic patients [14]. Being aware of cardiovascular involvements in perioperative cefuroxime prophylaxis and closely monitoring cardiac biomarkers, such as cTnI [15], can help manage Kounis syndrome patients and result in a favourable prognosis.

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Competing interests

None declared.

Ethics approval

Approved.

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