

## Case Report

# Kounis syndrome secondary to simultaneous oral amoxicillin and parenteral ampicillin use in a young man

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### Abstract

The concurrence of acute coronary syndrome with allergy or hypersensitivity as well as with anaphylactic or anaphylactoid reactions is increasingly encountered in daily clinical practice. There are several reports associating mast cell activation with acute cardiovascular events in adults. This was first described by Kounis as 'allergic angina syndrome', progressing to 'allergic myocardial infarction'. The main mechanism proposed is the vasospasm of coronary arteries. We present a case of a 28-year-old man who was admitted to our hospital with thoracic pain and dyspnoea. The symptoms recurred after simultaneous use of 1 g amoxicillin/clavulanic acid orally and 1 g ampicillin/sulbactam parenterally for tonsillitis the night before presentation and on the morning of admission.

**Keywords:** Kounis syndrome, allergic MI, penicilline-induced acute coronary syndrome

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Allergic angina and allergic myocardial infarction, referred as Kounis syndrome (KS), have gained acceptance as a cause of coronary artery spasm. Kounis and Zavras<sup>1</sup> described the 'syndrome of allergic angina' as the coincidental occurrence of chest pain and allergic reactions, accompanied by clinical and laboratory findings of classical angina pectoris caused by inflammatory mediators released during the allergic insult.

Causes of KS<sup>2</sup> include drugs (antibiotics, analgesics, antineoplastics, contrast media, corticosteroids, intravenous anesthetics, non-steroidal anti-inflammatory drugs, skin disinfectants, thrombolytics, anticoagulants), various conditions (angio-oedema, bronchial asthma, urticaria, food allergy, exercise-induced allergy, mastocytosis, serum sickness) and environmental exposure

(stings of ants, bees, wasps and jellyfish, grass cuttings, millet allergy, poison ivy, latex contact, eating shellfish, viper venom poisoning).

KS due to penicillin use is rare in adults. Its appearance, caused by the simultaneous use of these agents both parenterally and orally, may be even rarer, and it has not been reported before. Such was the case in a young man, to be described below.

### Case report

A 29-year-old male patient was admitted to the emergency department with symptoms of dyspnoea and severe squeezing chest pain. The symptoms had occurred the night before presentation and had recurred that morning. The patient had had an intramuscular injection of 1 g ampicillin sulbactam and 1 g oral amoxicillin clavulanate 30 min before each episode, for an upper respiratory tract infection.

His history was unremarkable for any allergic reaction, hypertension, diabetes mellitus or dyslipidaemia. He was a non-smoker. Lung sounds were clear, and no murmurs, rubs or extra sounds were found on cardiac auscultation.

The physical examination revealed blood pressure of 110/80 mmHg, a regular pulse of 81 beats/min, and oxygen saturation of 92%. He did not have pruritus or a rash. Initial and subsequent ECGs showed sinus rhythm and slight ST-segment elevation in the inferior leads (Fig. 1).

The patient's laboratory findings, taken in the emergency room, were as follows: haemoglobin 12.7 g/dl, leukocytes 11 700/μl, eosinophil count 0.04 (in the normal range), troponin I: 29 ng/ml, creatinine kinase (CK) 2 116 U/l, and CK-MB isoenzyme 101 U/l. Serum tryptase and IgE levels were not determined.

He was given 5 mg morphine sulfate, 25 mg prednisolone, 50 mg of diphenhydramine and 50 mg of ranitidine intravenously. On this treatment the retrosternal pain and dyspnoea started to improve. Transthoracic echocardiography revealed normal left ventricular systolic functions and no segmentary wall-motion abnormality. An emergency coronary angiogram was performed and showed normal coronary arteries (Fig. 2 A-B, Movie 1-2).

His recovery was uneventful and he was discharged on his third day of hospitalisation. On prick-skin testing for B-lactams, a strongly positive result to penicillin was noted after discharge.

### Discussion

Development of acute coronary syndrome after exposure to an allergic insult is an unexpected and rarely reported phenomenon.

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**Fig. 1. The electrocardiogram shows slight ST-segment elevation in the inferior leads.**

This concept of 'the coincidental occurrence of chest pain and allergic reactions accompanied by clinical and laboratory findings of angina pectoris' was first described in 1991 and is known as the Kounis syndrome.<sup>1</sup>

On recognition of this clinical entity, a number of hypotheses have been proposed to explain the causal relationship between allergic reactions and acute coronary syndromes. Of these, a mast cell-driven vasospastic and inflammatory response acting on the coronary endothelium has gained acceptance as the main causative mechanism.

Mast cells are present in numerous parts of the human body, including the heart and blood vessels. During an acute allergic reaction, activated mast cells degranulate and release large amounts of mediators, such as histamine, tryptase, platelet activating factor, leukotrienes and thromboxane. These have been experimentally shown to cause coronary artery spasm or plaque rupture.

Two types of KS have been described. The type I variant (coronary spasm), which may represent a manifestation of endothelial dysfunction or microvascular angina, includes

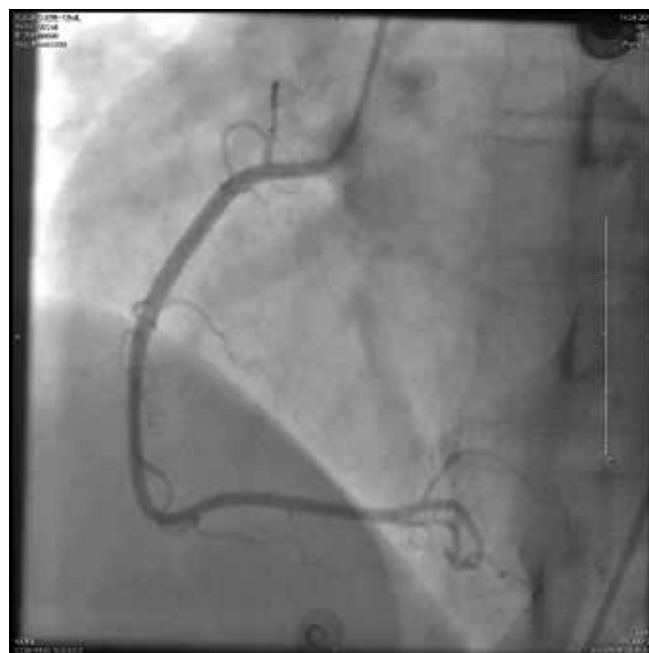


**Fig. 2. The patient's left (A) and right coronary arteries (B) were normal on coronary angiography.**

patients with normal coronary arteries without predisposing factors for coronary artery disease. In these patients, the acute release of inflammatory mediators can induce either coronary artery spasm without an increase in levels of cardiac enzymes and troponins, or coronary artery spasm progressing to acute myocardial infarction with raised cardiac enzymes and troponins.

The type II variant (coronary thrombosis) includes patients with culprit but quiescent pre-existing atheromatous disease. In these patients, the acute release of inflammatory mediators can induce coronary artery spasm with normal levels of cardiac enzymes and troponins, plaque erosion, or rupture, manifesting as acute myocardial infarction.<sup>2</sup>

Until now, KS was found to be related to poisons, venoms, drugs and contrast agents. Among these, antibiotic-related acute coronary syndrome is rare. It has been reported commonly only with penicillins in the course of an anaphylactic shock where coronary hypoperfusion and epinephrine-induced vasospasm were strongly proposed to explain the underlying mechanism of myocardial injury.<sup>3,4</sup>

However, allergy-induced acute coronary events in the absence of anaphylaxis are increasingly encountered in clinical practice, suggesting mast cell-based vasospasm as the principal mechanism.<sup>5</sup> It is also hypothesised that there is a threshold level of mast cell content above which it could provoke coronary artery spasm and plaque rupture. This threshold level is closely associated with the allergen concentration, the patient's sensitivity and the route of antigen entrance.<sup>3,6</sup>

There are studies reporting that IgE antibodies with different specificities can have an additive effect, and corresponding antigens can trigger mediator release when the patient is simultaneously exposed to them. This suggests that atopic individuals are more vulnerable to coronary artery spasm than normal people.<sup>3,5</sup>

The management of KS may be challenging for clinicians, and unfortunately guidelines have not been established yet. Patients with KS need treatment with steroids, antihistamines, fluid resuscitation, possibly epinephrine, oxygen and antithrombotics before transfer to the cardiac catheterisation laboratory.

The treatment should both dilate coronary vessels and suppress the allergic reaction. Vasodilator drugs, including nitrates and calcium channel blockers, should be considered as first-line therapy in young and previously healthy individuals, since vasospasm is the primary mechanism.

Acute coronary syndrome protocol should be followed in patients with the type II variant. These patients should be followed up in cardiology and allergy clinics following hospital discharge. A full cardiology work-up, including a 12-lead ECG, echocardiogram and cardiac risk-factor modification is necessary.<sup>7</sup>

In our patient, myocardial injury occurred in the absence of an anaphylactic reaction, strengthening the suspicion of mast cell-based pathophysiology. On the other hand, his chest pain developed suddenly without any apparent allergic reaction, suggesting a possible local effect of ampicillin and amoxicillin, individually or in combination, directly on the coronary mast cells. This sole cardiac involvement may represent another aspect of allergic reactions, ranging from urticaria to anaphylaxis.

Reasons for the variability in clinical manifestations of this syndrome are currently under research. The absence of coronary lesions on the angiogram and a positive skin-prick test for B-lactams indicated coronary spasm and type 1 variant of KS in our case.

To the best of our knowledge, this is the first case in the literature describing the association between this syndrome and penicillin simultaneously administered orally and parenterally. This report, as well as others,<sup>8</sup> show that this unique disease should be entertained when acute-onset chest pain is accompanied by allergic symptoms, electrocardiographic changes, and increased levels of markers of myocardial damage.

## Conclusion

All patients admitted to emergency departments with chest pain, ST-segment changes on electrocardiography and/or increased markers of myocardial necrosis should be investigated for allergic insults.

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