

Kounis syndrome: myocardial infarction secondary to an allergic insult – a rare clinical entity

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Abstract The association of an acute coronary syndrome with mast cell activation secondary to allergen exposure is known as the Kounis syndrome. We present two cases of the Kounis syndrome: (i) one was misdiagnosed as acute ST elevation myocardial infarction and treated with thrombolytics; (ii) the second diagnosis was made after a recurrence two months after the first incident.

Keywords Acute coronary syndrome – Kounis syndrome – myocardial infarction.

INTRODUCTION

Myocardial ischaemia in combination with allergic and anaphylactic reactions is known as the Kounis syndrome (KS)^{1,2}. The syndrome is considered as a trigger for coronary artery spasms^{3,4}. In 1991, Kounis and Zarvas reported the first case as ‘allergic angina syndrome’. Other reports followed: (i) 1995: Constantinides on allergic reactions provoking atherosclerotic plaque rupture; (ii) 1998: Braunwald about the role of histamine and leukotriene-like mediators⁵.

Well-defined KS cases are scarce. Several drugs, environmental factors and allergic triggers may cause the KS^{3,6}. So far, two types of KS have been defined⁶. Type 1 is seen in patients with normal coronary arteries. Mast cell activation and vasospasm lead to angina secondary to endothelial dysfunction and microvascular abnormalities. Type 2 occurs in patients with asymptomatic atheromatous plaques. Allergic triggers induce plaque

erosion or rupture. This condition may progress to myocardial infarction^{5,6}. The prognosis of type-1 KS is better than type-2 KS. Morbidity and mortality depend on: the severity of the allergic reaction, patient sensitivity, comorbidity factors, allergen concentration and the allergen's portal to the body⁵.

The most frequent symptoms are: substernal chest pain, dyspnoea, palpitations, weakness, nausea, urticaria, itching, sweating and hypotension⁵; briefly: symptoms of angina pectoris in addition to an allergic reaction.

We report KS in: (i) a young male with an initial diagnosis of atherothrombotic myocardial infarction (MI); (ii) another case of recurrent type-2 KS in an elderly lady. She was admitted to the hospital with the diagnosis of non-allergic MI. After 2 months, when she suffered a second episode, both events were considered as an allergic MI.

CASE 1

A 31-year-old male patient was admitted to the hospital with typical angina pectoris lasting for 30 minutes. The electrocardiogram (ECG) revealed 2-4 mm ST elevation on leads D2-D3-aVF-V5-V6-V7-V8-V9, ST depression and negative T waves on leads V1-V2-V3, and aVR. The blood chemistry showed elevated cardiac markers of creatine kinase (CK), CK-MB, and troponin T and I. The patient was transferred to the coronary care

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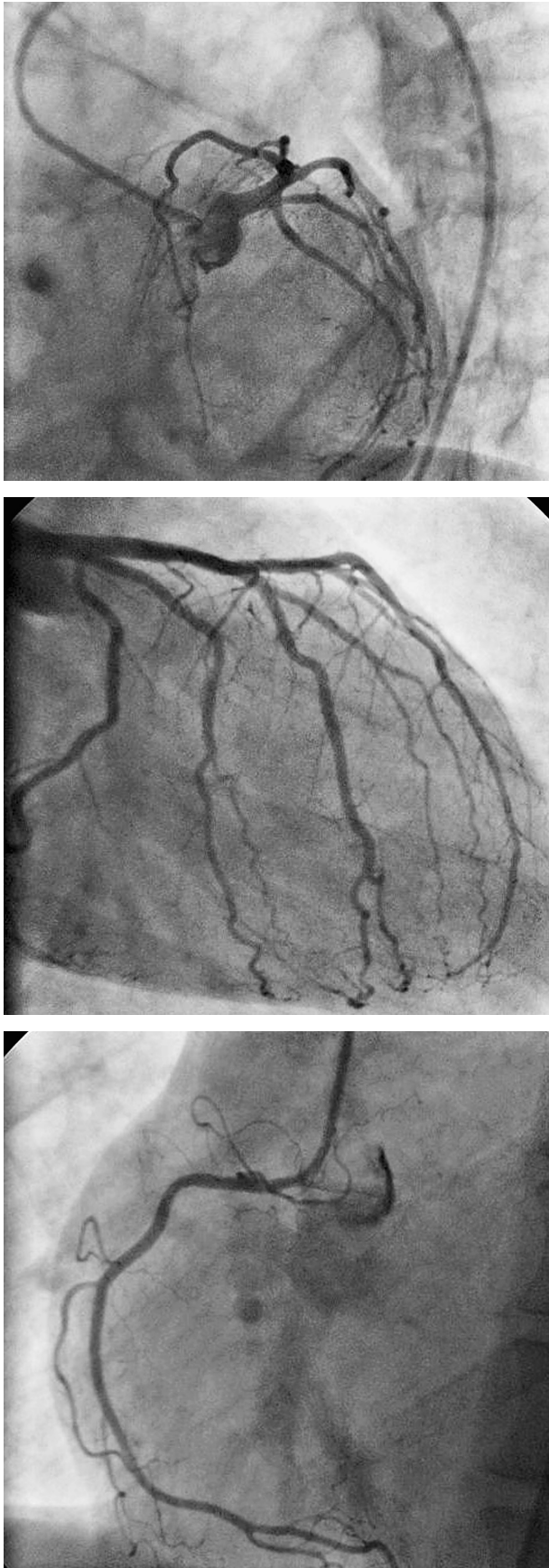


Fig. 1 a, b, c coronary angiography.

unit with the diagnosis of acute inferoposterolateral myocardial infarction. Physical examination was within normal limits. Thrombolytic therapy was started immediately. Two hours after tissue plasminogen activator (tPA) perfusion, ST elevations did not resolve and the patient had ongoing chest pain. A rescue percutaneous coronary intervention was planned. The patient's angiogram showed only a 30% stenosis at the distal region of the circumflex coronary artery and no further intervention was undertaken (figure 1 a, b, c). With supportive therapy, ST-segment elevations resolved within 22 hours. Echocardiography revealed a normal systolic function.

Upon these findings, medical history was checked more in detail. Actually, the patient had penicillin allergy and symptoms started 1 hour after taking amoxicillin-clavulanate because of a flu. A close look at the blood tests revealed leukocytosis with eosinophilia. These findings are compatible with an allergic myocardial infarction, i.e. Kounis syndrome.

CASE 2

An 85-year-old female patient complaining of chest pain and shortness of breath was admitted to our hospital. She was hypertensive and non-smoker. Physical examination, ECG and laboratory findings confirmed subacute anterior MI. Echocardiography revealed enlargement of the left atrium and the left ventricle, with left ventricular systolic dysfunction and an ejection fraction of 35%. The patient and her relatives did not give permission for coronary angiography; hence the patient was treated medically. After stabilization of the symptoms, the patient was discharged. Two months later, she was hospitalised again because of acute left heart failure. Four days later, seftriaxone therapy was started because of hospital-acquired pneumonia. Thirty minutes after administration of the first dose, the patient had complaints of itching and skin eruptions. Two hours after the skin lesions, she had chest pain, dyspnoea, and hypotension. The ECG showed ST elevation on the anterior precordial leads. After informed consent, a coronary angiography was negative: no acutely occluded coronary artery or severe stenosis (figure 2a, b). Blood tests revealed eosinophilia, elevation of cardiac markers and triptase levels. High-dose bolus systemic steroid therapy with 250 mg prednisolone was started and continued with a gradually decreasing dose. The dermatologic symptoms improved day by day. There were no further ischaemic symptoms and the patient was discharged from the hospital with medical treatment. History, laboratory and coronary findings were typical of the Kounis syndrome.

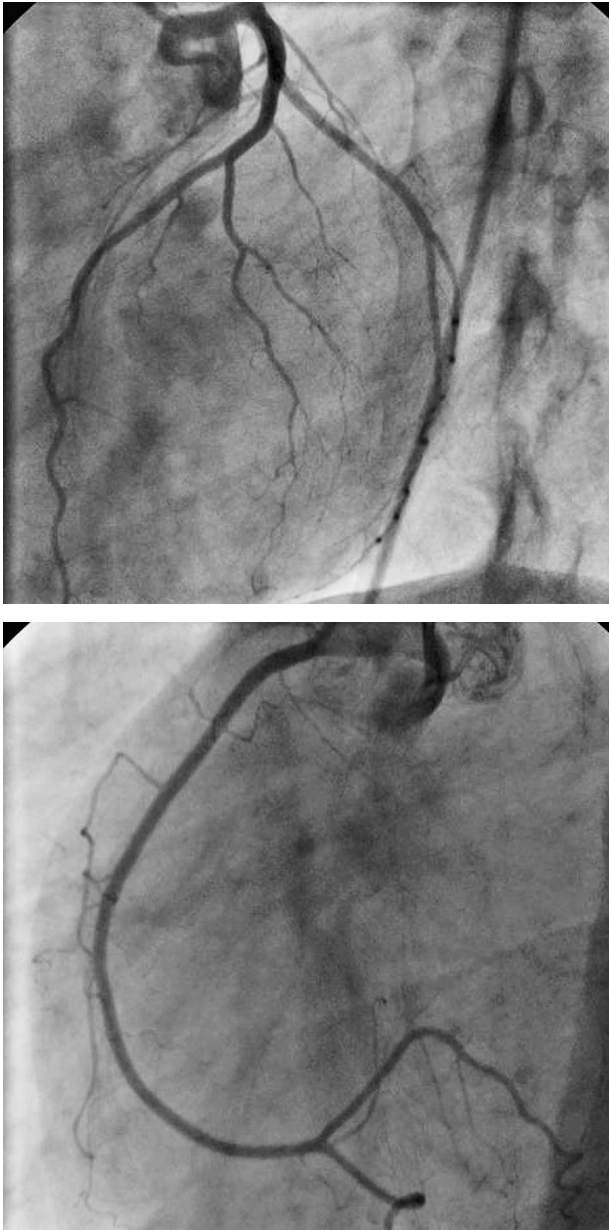


Fig. 2 a, b coronary angiography.

DISCUSSION

Myocardial infarction due to amoxicilline as an allergen was first described in 1950. Mast cells, the key elements of allergic reactions, are located between cardiomyocytes and coronary arteries in healthy people⁵. Larger amounts are present at atherosclerotic vessels. They play a major role in allergic and anaphylactoid reactions. After allergen exposure, antigen-antibody complexes or the allergen itself directly activate the mast cells^{3,5}. Mediators like histamine, leukotriens, neutral proteases, platelet-activating factor are released locally and to the systemic circulation by mast cell degranulation

with possible constriction of the coronary arteries. Other mediators like triptase and chymase activate metalloproteinase responsible for plaque erosion and rupture⁵. Whatever the factor that starts inflammation and plaque destabilization, the plaque rupture, thrombus formation and occlusion of the vessel are the common pathways for acute coronary syndromes. In the future, this patho-physiologic relation may also guide physicians to prevent non-allergic acute coronary syndromes with mast cell membrane stabilizers.

We postulate that, in clinical practice, KS occurs more frequently than anticipated^{3,4,6}. Also, in case of suspicion of an acute coronary syndrome, physicians should question the patients about allergen exposure. Our first case accounts as an example for this speculation. Many health care workers would most probably diagnose a 31-year-old male patient with typical chest pain, ST-segment elevations and elevated cardiac markers as suffering an acute MI. However, as in our first case, this may not be true for every case. Especially in hospitals where primary percutaneous coronary interventions are not available, physicians should be particularly careful not to delay diagnosis and treatment.

Usually, several type-2 KS cases are misdiagnosed because of predisposing risk factors for coronary artery disease. At the first admission to the hospital, our second patient's age, history of hypertension and clinical presentation were very typical of a non-allergic MI. Unfortunately, acute MI could not be definitely outruled because the patient refused any kind of invasive diagnostic workup. However, when the second episode suggested KS, a detailed anamnesis revealed that the first MI also occurred after antibiotic use. Moreover, at the time of the second admission, coronary angiography findings were suggestive of a type-2 KS case. To the best of our knowledge, this particular patient is the first case in literature in whom KS occurred twice.

In the differential diagnosis of KS, takotsubo cardiomyopathy, also known as transient apical ballooning syndrome (apical ballooning cardiomyopathy) or stress-induced cardiomyopathy, which is a type of non-ischaemic cardiomyopathy with a sudden temporary weakening of the myocardium, should be considered⁷. It is usually triggered by emotional stress, such as the death of a loved one, a break-up, or constant rejection. The insult provokes catecholamine release and increases cardiovascular activity, resulting in inflammatory cell activation, induction of adhesion molecules on the endothelial cells, endothelial injury, and myocardial damage. Such inflammation is characterized by the production of cytokines, macrophages and mast cell activation and release of inflammatory mediators, as in KS. However, so far, inflammatory mediators such as histamine, triptase, chymase, and arachidonic acid

products have not been measured in blood or tissues of patients diagnosed with takotsubo syndrome⁸.

CONCLUSION

In conclusion, for the appreciation of the clinical picture of myocardial infarction, allergic triggers should be kept in mind. Physicians should consider the possibility of Kounis syndrome.

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CONFLICT OF INTEREST: none declared.

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