

An Extraordinary Case Associated with an Allergic Reaction to Clopidogrel: Coronary Artery Spasm or Kounis Syndrome?



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Kounis syndrome is the concurrence of acute coronary syndrome with allergic reactions, such as anaphylaxis or anaphylactoid reactions. Here, we describe a unique case: CASs (coronary artery spasms) with both non-hypersensitivity and hypersensitivity aetiology (associated with clopidogrel hypersensitivity) were observed in a 61 year-old patient. Herein, the mechanism and clinical implications of this association are discussed.

Keywords

Allergic reaction • Clopidogrel • Kounis syndrome • Coronary artery spasm

Introduction

Kounis syndrome was described in 1991 by Kounis and Zavras as the coincidental occurrence of acute coronary syndromes (ACS) with allergic reactions (anaphylactic or anaphylactoid) [1]. Multiple causes of Kounis syndrome have been described, including drugs, insect stings, foods, environmental exposures and medical conditions, among others [2].

There are two variants of Kounis syndrome. Patients with the type I variant have normal or nearly normal coronary arteries without predisposing factors for coronary artery disease, and in those patients, acute allergic attacks can induce either CAS alone without raised cardiac enzymes and troponins or coronary artery spasm leading to acute myocardial infarction with raised cardiac enzymes and troponins. Patients with the type II variant have a quiescent pre-existing atheromatous disease that makes them susceptible to induction by acute allergic attacks of CAS or plaque erosion or rupture manifesting as acute myocardial infarction [3]. In recent years a third variant of Kounis syndrome

has been proposed in patients with drug-eluting stent thrombosis [4].

In the following report, we describe a case of Kounis syndrome associated with an allergic reaction to clopidogrel.

Case Report

A 61 year-old man was recently admitted to our hospital for worsening chest pain. He had a 10-year history of recurrent episodes of crushing chest pain at rest and during ordinary activity and ST changes on ECG. The patient's chest pain could be spontaneously relieved within 10 mins or within a few minutes after administration of sublingual nitro-glycerine. He was a heavy smoker who had smoked 20 cigarettes per day for nearly 30 years. Furthermore, he had a past history of hypertension and atopic eczema and allergic reactions.

On admission, his blood pressure was 130/70 mmHg, and his heart rate was 70 beats/min; electrocardiography and all other related tests were normal. Transthoracic echocardiography did not show any regional wall motion abnormality.

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Clopidogrel was administered in preparation for coronary angiography. He had not taken clopidogrel previously. After one hour, he complained of generalised itching and a widespread erythematous rash without any other discomfort. The patient's symptoms seemed to subside after he was treated with 10 mg of dexamethasone. However, after another hour, the patient suddenly fainted while on the toilet; this episode included a loss of consciousness and profuse sweating. The electrocardiogram revealed ST segment elevation in the inferior leads with complete atrioventricular block (Fig. 1). The patient was given 0.5 mg atropine, 3 mg dopamine, and 10 mg dexamethasone intravenously. The patient's cardiac rhythm reverted to a sinus rhythm, and his BP and HR were recovered at 90/60 mmHg and 80 beats/min, respectively. An emergency coronary angiography was immediately performed, and it initially showed approximately 80% stenosis of the midportion and 100% occlusion of the distal segments of the right coronary artery (Fig. 2A, arrow). The vasospasm was relieved after intracoronary administration of 200 µg isosorbide dinitrate, and the patient did not have significant lesions (Fig. 2B). The results of the blood examination revealed normal levels of cardiac enzymes, troponin, and blood eosinophils. However, total IgE was elevated to 245 IU/ml (normal value: 110 IU/ml), the tryptase level was elevated to 19.6 µg/l (normal range: 5.6–13.5 µg/l). The patient was diagnosed with type I Kounis syndrome secondary to an allergic reaction to clopidogrel. The patient was admitted to the coronary care unit and was orally administered 30 mg of altiazem every 8 h. Subsequently, nuclear myocardial imaging showed a small area of a partially reversible perfusion abnormality involving the apex. The patient's remaining

stay at the hospital was uneventful, and he was discharged on the fourth day of hospitalisation and advised to avoid taking clopidogrel.

Discussion

Kounis syndrome is defined as the concurrence of acute coronary syndromes with conditions associated with mast cell activation involving interrelated and interacting inflammatory cells and including allergic or hypersensitivity and anaphylactic or anaphylactoid attacks. It is caused by inflammatory mediators, such as histamine, neutral proteases, arachidonic acid products, platelet activating factors and a variety of cytokines and chemokines released during the activation process [2,5,6].

We believe this is an extraordinary case. The patient developed a generalised urticarial rash after taking clopidogrel. The patient then presented with symptoms and signs of CAS confirmed by ECG changes and coronary angiography; he had concurrently raised levels of tryptase and IgE but normal levels of cardiac enzymes and troponins. This is a characteristic case of type I Kounis syndrome. To our knowledge, this is the second case of clopidogrel-induced Kounis syndrome, and some unique clinical characteristics of this case are discussed here. The previous case of clopidogrel-induced Kounis syndrome was a patient who developed recurrent stent thrombosis following an allergic reaction to clopidogrel.

Previously, patients with type I Kounis syndrome were considered to lack predisposing factors for coronary artery disease. However, the current patient had a past history of

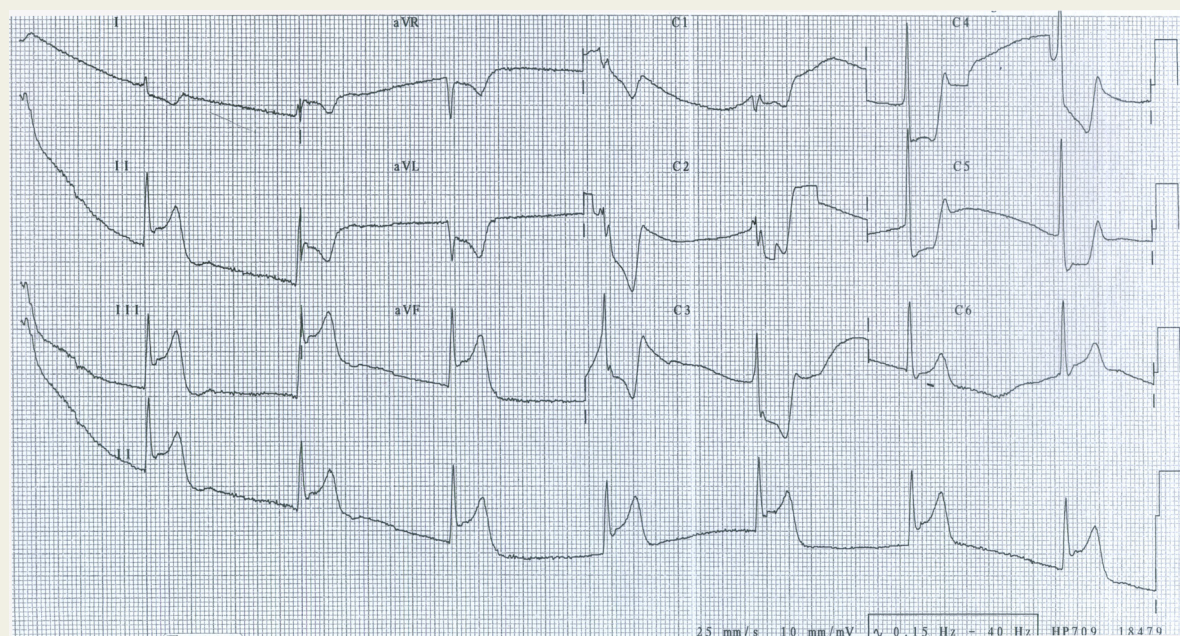


Figure 1 Electrocardiogram showing ST segment elevation in inferior leads with complete atrioventricular block.

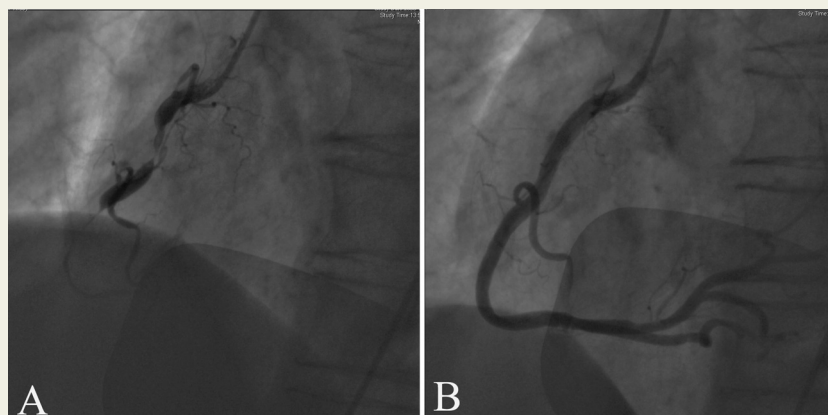


Figure 2 Coronary angiography showing approximately 80% stenosis of the midportion and 100% occlusion of the distal segments of the right coronary artery (2A), which returned to normal after the infusion of isosorbide dinitrate (2B).

smoking and hypertension. This suggests that type I Kounis syndrome may also be associated with traditional risk factors of ACS.

Additionally, the current patient had a previous history of recurrent atopic eczema and allergic reactions without any specific reactions, such as chest pain or allergic shock. Nevertheless, during this hospitalisation, he experienced a serious cardiac event. It appears that the concurrence of acute coronary syndromes and anaphylactoid reactions are selective and may be chance occurrences. However, what determines the occurrence of such events?

Clopidogrel is a well-known allergen, and the patient had also been taking aspirin for a long time (the last administration was the morning before hospital admission), which can also act as an allergen. It has been acknowledged that the more antigens a patient is exposed to, the easier and faster degranulation occurs [7]. Clopidogrel and aspirin may have had additive effects on multisensitised mast cells and/or basophils [8]. This suggests a certain level of activation of mast cells and of released mediators above which coronary spasm and/or plaque rupture occur. In addition, Yasue *et al.* [9] defined CAS as an abnormal contraction of an epicardial coronary artery resulting in myocardial ischaemia. By this definition, there is no limit to the degree of lumen reduction required to diagnose CAS. The American College of Cardiology/American Heart Association (ACC/AHA) guidelines for coronary angiography suggest that CAS is present when a reduction in lumen diameter of $> 50\%$ occurs during a provocative test [10]. Therefore, we infer that abnormal contraction of coronary arteries at different levels may be a common event during allergic reactions and that Kounis syndrome might only manifest as a result of quantitative changes to qualitative changes that result from lumen reduction. The absence of the clinical syndrome of myocardial ischaemia does not rule out the possibility of the development of an abnormal contraction of epicardial coronary arteries associated with an allergic reaction. The most likely explanation for this abnormal contraction of epicardial

coronary arteries in the absence of known myocardial ischaemia is that mild lumen reduction ($< 50\%$) always escapes detection.

Most importantly, in this case, the patient had recurrent episodes of spontaneous chest pain with ST changes on ECG for 10 years; however, immediate coronary angiography was necessary during the allergic shock associated with clopidogrel hypersensitivity. This indicates that the patient had CAS without atherosclerotic plaques and suggests that the most likely explanation for the patient's previous chest pain was CAS or coronary microvascular spasm. Coronary artery spasms of both non-hypersensitivity and hypersensitivity aetiology were observed in one individual. It is unclear whether the clinical diagnosis of this patient should be CAS or Kounis syndrome.

Kounis syndrome and CAS are currently considered two separate entities in the literature. However, just as many precipitating factors, such as physical and/or mental stress, magnesium deficiency, alcohol consumption, the cold pressor test, hyperventilation, the Valsalva manoeuvre, remnant lipoproteins *et al.* may contribute to the onset of CAS and act in the same patient to cause angina in different conditions, the release of inflammatory mediators during allergic reactions is likely a precipitating factor of the onset of CAS. Thus, it is difficult to define Kounis syndrome and CAS as two separate entities in one patient. To our knowledge, this is the first description of both CAS and Kounis syndrome in one individual, suggesting a large amount of overlap between CAS and Kounis syndrome.

In conclusion, in recent years, our understanding of Kounis syndrome has improved. However, even today, little is known about this syndrome. Coronary artery spasms with hypersensitivity aetiology may include a wide spectrum of mast cell activation disorders with wide clinical manifestations, and some of the unrecognised or undocumented signs and symptoms of those disorders may be discovered in the future. Further studies are needed to uncover the detailed mechanisms of Kounis syndrome.

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