



Case Report

Type 2 Kounis syndrome in an allergic woman: An uncommon presentation of acute coronary syndrome



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ABSTRACT

Acute coronary syndromes secondary to allergy-induced coronary vasospasm are known as “Kounis syndrome.” The main pathophysiological mechanism of coronary spasm in Kounis syndrome is the release of inflammatory mediators during a hypersensitivity reaction triggered by food, insect bites, or drugs. Here, we report a case of an acute coronary syndrome secondary to allergic reaction following levofloxacin administration in a 68-year-old female without a prior history of coronary artery disease. Our patient's coronary angiography revealed moderate lesions in the coronary vasculature and she was diagnosed as having a type II variant Kounis syndrome. Type II variant includes patients in whom the acute release of inflammatory mediators due to mast cell degranulation such as histamine, serotonin, and leukotrienes can induce either coronary artery spasm with normal cardiac enzymes and troponins or plaque erosion or rupture manifesting as acute myocardial infarction. According to our knowledge, this is the first case report of Kounis syndrome attributed to levofloxacin administration.

<Learning objective: Kounis syndrome is an established entity that describes the triggering of an acute coronary syndrome by an allergic reaction. This is the first case report of Kounis syndrome attributed to levofloxacin administration. We reviewed the literature and present the pathophysiologic mechanism of Kounis syndrome.>

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Introduction

Kounis syndrome is the coincidental occurrence of an acute coronary syndrome (ACS) with hypersensitivity reactions involving activation of interrelated and interacting inflammatory cells and including allergic or hypersensitivity and anaphylactic or anaphylactoid insults [1]. It is caused by inflammatory mediators such as histamine, neutral proteases, arachidonic acid products, platelet activating factor, and a variety of cytokines and chemokines released during the hypersensitivity insult [2–5]. Type II variant includes patients with culprit but quiescent pre-existing atherosclerotic disease in whom the acute release of inflammatory mediators can induce either coronary artery spasm with normal cardiac enzymes and troponins or plaque erosion or rupture manifesting as acute myocardial infarction. Here, we report a case of an ACS in a patient with systemic immediate hypersensitivity reaction which developed following oral administration of levofloxacin.

Case report

A 68-year-old woman, hypertensive, diabetic, and hyperlipidemic was admitted to our hospital with retrosternal chest pain, dyspnea, nausea, and vomiting of 1 h duration after taking a dose of levofloxacin due to erysipelas of the left lower limb. Her physical examination revealed a blood pressure and heart rate of 120/75 mmHg and 95 bpm, respectively, and generalized erythema and urticarial rashes. Heart and respiratory auscultation findings were normal. The electrocardiogram (ECG) showed ST depression in V3–V5 leads (Fig. 1a and b). The patient was treated with supplemental oxygen, intravenous methylprednisolone 40 mg along with nebulized albuterol and intravenous nitroglycerin infusion. Anti-ischemic treatment including aspirin, clopidogrel, beta-blocker, statin, as well as angiotensin-converting enzyme inhibitor were initiated. The patient showed prompt response to the therapy, and signs and symptoms of allergic reaction resolved in a couple of hours. Signs of ischemia and the ECG changes disappeared along with the signs of allergic reaction. Troponin I was elevated up to 1.3 ng/ml. Creatine phosphokinase and creatine kinase-MB values were elevated up to 550 U/l and 90 U/l, respectively. Blood tests showed moderate eosinophilia in her peripheral blood smear (10%) while the measurements of non-specific total immunoglobulin

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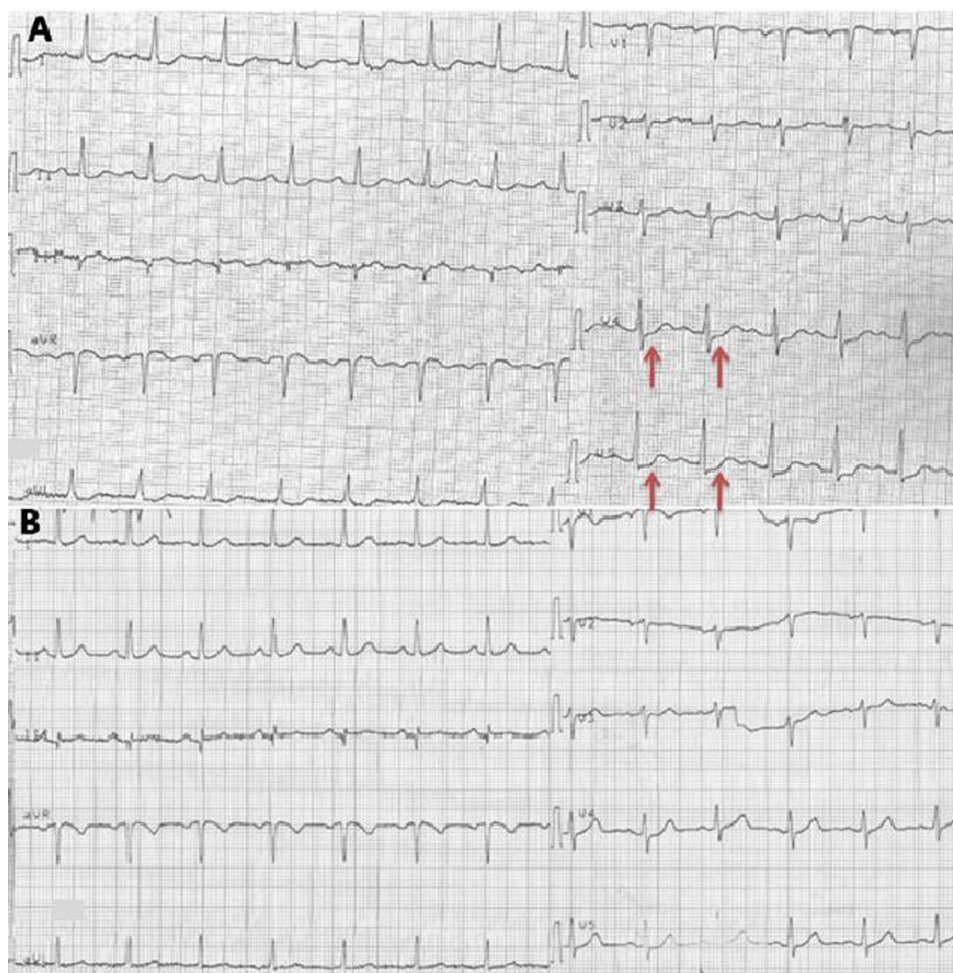


Fig. 1. Electrocardiogram traces during attack (panel a) and at convalescence (panel b). ST depression is indicated with red arrows.

E levels were increased up to 500 UI/ml. Coronary angiography which was performed 24 h later, revealed 50–60% stenosis of the mid left anterior descending artery (LAD), a 70% ostial lesion of the circumflex (LCx), as well as a 60% lesion in the mid right coronary artery (RCA) (Fig. 2a–c). A three-vessel fractional flow reserve (FFR) test was performed which revealed non-significant lesions in the LAD (FFR=0.83) and RCA (FFR=0.88) and a haemodynamically

significant lesion in the ostial LCx (FFR=0.74). On the basis of FFR measurements a percutaneous coronary intervention of the LCx was proposed which was refused by the patient. The echocardiographic study of the patient revealed left ventricular hypertrophy with preserved function without segmental motility abnormalities.

The rest of her hospitalization was without any complications. She was discharged on the 7th day of hospitalization.

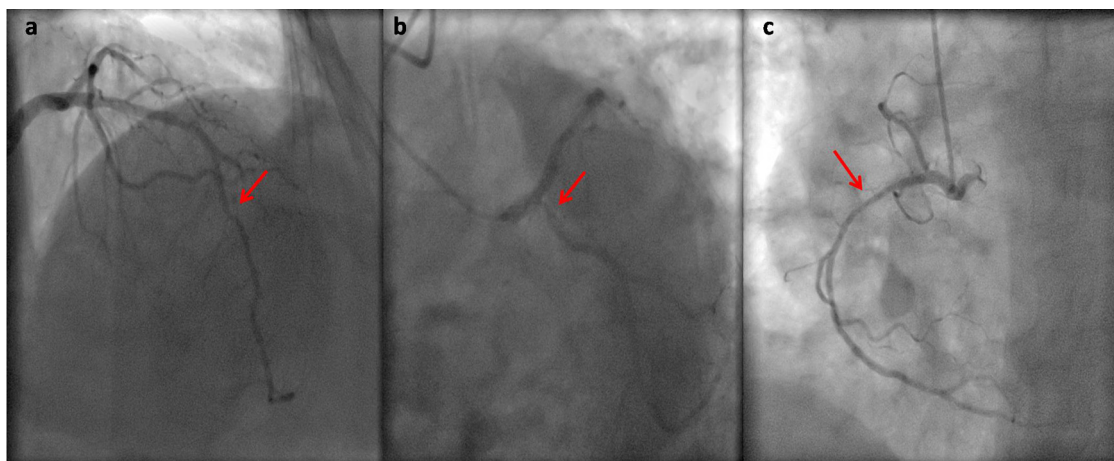


Fig. 2. Coronary angiography of the left coronary artery (panel a and b) and right coronary artery (panel c). Lesions are indicated with red arrows. (For interpretation of references to color in this figure legend, the reader is referred to the web version of this article.)

Discussion

Kounis syndrome has been defined as an ACS that manifests as vasospastic angina or ST-elevation myocardial infarction/non-ST-elevation myocardial infarction triggered by the release of inflammatory mediators following an allergic insult [2]. The mechanisms of this syndrome are characterized by coronary artery vasospasm due to mast cell degranulation and the subsequent release of vasoactive mediators [3]. The most important vasoactive mediators responsible for coronary artery spasm and consequences of Kounis syndrome are histamine, serotonin, and leukotrienes. There are two variants of Kounis syndrome [1–5]. The first is observed in patients with no cardiovascular risk factors and healthy coronary arteries in which the inflammatory cascade triggered by the allergic insult causes a coronary vasospasm accompanied by elevated or normal levels of cardiac enzymes. The second is observed in patients with pre-existing atherosclerotic disease (whether known or not) in whom the release of these mediators would also produce a coronary vasospasm, which occurs with normal cardiac enzymes or rupture of the atherosclerotic plaque, manifesting as an acute myocardial infarction [5–9]. Our patient's coronary angiography revealed moderate lesions in the coronary vasculature and was diagnosed with a type 2 variant. According to our knowledge, this is the first case report of Kounis syndrome attributed to levofloxacin administration.

Causes of Kounis syndrome include drugs (antibiotics, analgesics, antineoplastics, contrast media, corticosteroids, intravenous anesthetics, non-steroidal anti-inflammatory drugs, skin disinfectants, thrombolytics, anticoagulants), various conditions (angio-edema, bronchial asthma, urticaria, food allergy, exercise-induced allergy, mastocytosis, serum sickness), and environmental exposures (stings of ants, bees, wasps, jellyfish, grass cutting, millet allergy, poison ivy, latex contact, shellfish eating, viper venom poisoning) [9].

Although there are no definite diagnostic criteria to differentiate Prinzmetal angina from Kounis syndrome, a patient presenting with signs and symptoms of a systemic allergic reaction associated with clinical, laboratory and electrocardiographic findings of acute myocardial ischemia should be diagnosed as having Kounis syndrome [1,2].

The management of patients with Kounis syndrome differs from those for non-allergic common ACS [7]. These patients need treatment with steroids, antihistamines, fluid replacement, possibly epinephrine, oxygen, and antithrombotics before transfer to the cardiac catheterization laboratory. The treatment should be both treating coronary lesions and suppressing the allergic reaction. Vasodilator drugs, including nitrates and calcium-channel blockers, should be considered as a first-line therapy since vasospasm is the primary mechanism [7]. However the utilization of some

drugs is controversial due to the underlying anaphylactic reaction. Acetylsalicylic acid, a first-line drug for ACS, may itself cause allergic reactions and induce anaphylaxis [2]. Aspirin is among the most frequent causes of drug-associated anaphylactic reactions [2]. Therefore, the safety of aspirin in patients with Kounis syndrome is unknown regarding the potential risk of aggravating an ongoing anaphylactic reaction [2]. Both fractionated and low-molecular-weight heparins are derived from animals which are potentially antigenic and can cause allergic reactions. Beta-blockers may also offset some of the beneficial effects of epinephrine, which is the mainstay of treatment of anaphylaxis. Epinephrine is a life-saving medication in anaphylaxis, however it can aggravate the ischemia, and induce coronary vasospasm and arrhythmias. Therefore, given a narrow therapeutic window, the recommended dose is 0.2–0.5 mg of intramuscular injection [7].

Anti-ischemic treatment including aspirin, clopidogrel, beta-blocker, nitrates, statin, as well as angiotensin-converting enzyme inhibitor were initiated. Corticosteroids are agents playing a major role in the treatment of allergic reactions, but they are well known to impair wound healing and scar formation which may cause myocardial wall thinning, cardiac aneurysms, and wall rupture [10,11]. Successful use of corticosteroids in allergic ACS has been reported, and is thus probably safe and appropriate.

The Kounis syndrome is probably not an uncommon disease but, rather, an underdiagnosed one. Regarding the complex course of ACS associated with allergic reactions, high awareness, rapid diagnosis, and appropriate treatment are of utmost importance.

References

- [1] Kounis NG, Kourelis T, Hahalis G, Manola A, Kourelis T, Theoharides T. Kounis syndrome (allergic angina and allergic myocardial infarction). In: Gallo AP, Jones ML, editors. *Angina pectoris etiology, pathogenesis and treatment*. New York: Nova Biomedical Books; 2008.
- [2] Kounis NG, Kouni SN, Koutsojannis CM. Myocardial infarction after aspirin, and Kounis syndrome. *J R Soc Med* 2005;98:296.
- [3] Cheng TO, Kounis NG. Takotsubo cardiomyopathy, mental stress and the Kounis syndrome. *Int J Cardiol* 2012;161:65–7.
- [4] Kounis NG, Zavras GM. Histamine-induced coronary artery spasm: the concept of allergic angina. *Br J Clin Pract* 1991;45:121–8.
- [5] Kounis NG, Zavras GM. Allergic angina and allergic myocardial infarction. *Circulation* 1996;94:1789.
- [6] Kounis NG, Grapsas GM, Goudevenos JA. Unstable angina, allergic angina and allergic myocardial infarction. *Circulation* 1999;100:e156.
- [7] Cevik C, Nugent K, Shome GP, Kounis NG. Treatment of Kounis syndrome. *Int J Cardiol* 2010;143:223–6.
- [8] Ridella M, Bagdure S, Nugent K, Cevik C. Kounis syndrome following beta-lactam antibiotic use: review of literature. *Inflamm Allergy Drug Targets* 2009;8:11–6.
- [9] Gázquez V, Dalmau G, Gaig P, Gómez C, Navarro S, Mercé J. Kounis syndrome: report of 5 cases. *J Invest Allergol Clin Immunol* 2010;20:162–5.
- [10] Koutsojannis CM, Malliouris CN, Corticosteroids Kounis NG. Kounis syndrome and the treatment of refractory vasospastic angina. *Circ J* 2004;68:806–7.
- [11] Mazarakis A, Koutsojannis CM, Kounis NG, Alexopoulos D. Cefuroxime induced coronary artery spasm manifesting as Kounis syndrome. *Acta Cardiol* 2005;60:341–5.