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Letter to the Editor

Kounis syndrome secondary to amoxicillin use in an asthmatic patient

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ABSTRACT

A sixty-four year old man with a past history of hypercholesterolemia, asthma, food allergy, epilepsy and myocardial infarction was admitted to the emergency department because of a generalized erythema, nausea, vomiting, and chest pain after taking an oral dose of amoxicillin. Electrocardiography showed ST segment elevation in anterior leads. After coronary angiography, type 2 variant of Kounis syndrome was diagnosed. We present the first case of oral amoxicillin induced Kounis syndrome in an asthmatic patient with severe anaphylactic shock. The present report also shows that atopic people expressing an amplified mast cell degranulation may have more serious hemodynamic decompensation during hypersensitivity reactions. Case selective mast cell surface membrane stabilization should be considered a potential therapeutic strategy for people with food induced allergy, for atopic patients and for patients who have already experienced a first Kounis syndrome.

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1. Introduction

Despite the fact that they are not that frequently reported, signs and symptoms of coronary artery involvement during allergic reactions have been noticed by the patients. A special type of vasospastic myocardial ischemia or infarction, which is called Kounis syndrome, is increasingly being encountered in clinical practice.

The main pathophysiological mechanism is vasospasm of epicardial coronary arteries due to increased inflammatory mediators that are released during a hypersensitivity reaction. Possible triggers include drugs, animal or insect bites, and even drug-eluting stents or endovascular devices.

Anaphylactic or anaphylactoid reactions can make a clinical situation even more serious. We present first case of oral amoxicillin induced Kounis syndrome in an asthmatic patient with anaphylactic shock.

2. Case report

A sixty-four year old man with a past history of hypercholesterolemia, asthma, food allergy, epilepsy and myocardial infarction was admitted to the emergency department because of a generalized erythema, nausea, vomiting and chest pain after taking an oral dose of amoxicillin.

Five years prior to this admission, he suffered an acute myocardial infarction treated with two drug-eluting stents in the left anterior descending (LAD) artery. The rest of coronary arteries had no significant lesions and left ventricle ejection fraction was preserved at discharge. He was under treatment with aspirin, a statin and fenitoin, free from angina and with a I/IV NYHA functional class.

The afternoon prior to admission, he sought care from his primary doctor complaining of shortness of breath. He was treated with bronchodilators and amoxicillin. After taking amoxicillin at home, the patient immediately started with severe dyspnea, rash and generalized urticaria. He arrived to the emergency department of our hospital, where he was diagnosed with anaphylactic shock. He also complained of oppressive chest pain, radiating to the left arm, nausea and vomiting, similar to his prior infarction. Electrocardiogram showed peaked T waves and ST segment elevation in leads V2–V5, I & aVL and ST depression with negative T waves in leads III & aVF (Fig. 1). He was admitted to the Coronary Care Unit. He had no fever, his arterial blood pressure was 115/75, and he was tachypneic, with generalized hypoventilation and expiratory wheezing.

Chest pain resolved after administration of nitroglycerin and chlorpheniramine and EKG changes normalized, so we did not perform an urgent coronary angiography. Instead, a catheterization was performed after 7 h, under prophylaxis for iodinated contrast media reactions with chlorpheniramine, corticoids and ranitidine. Coronary angiography showed a thrombotic lesion in the origin of the first left anterior descending (LAD) diagonal branch, distal to the prior stent, that was permeable and without significant restenosis (Fig. 2). Two drug-eluting stents were implanted in the first LAD diagonal branch and in the LAD, with *kissing stent* technique. The outcome was excellent. Right coronary and circumflex had no significant lesions. There was a mild elevation of myocardial necrosis markers (Troponin

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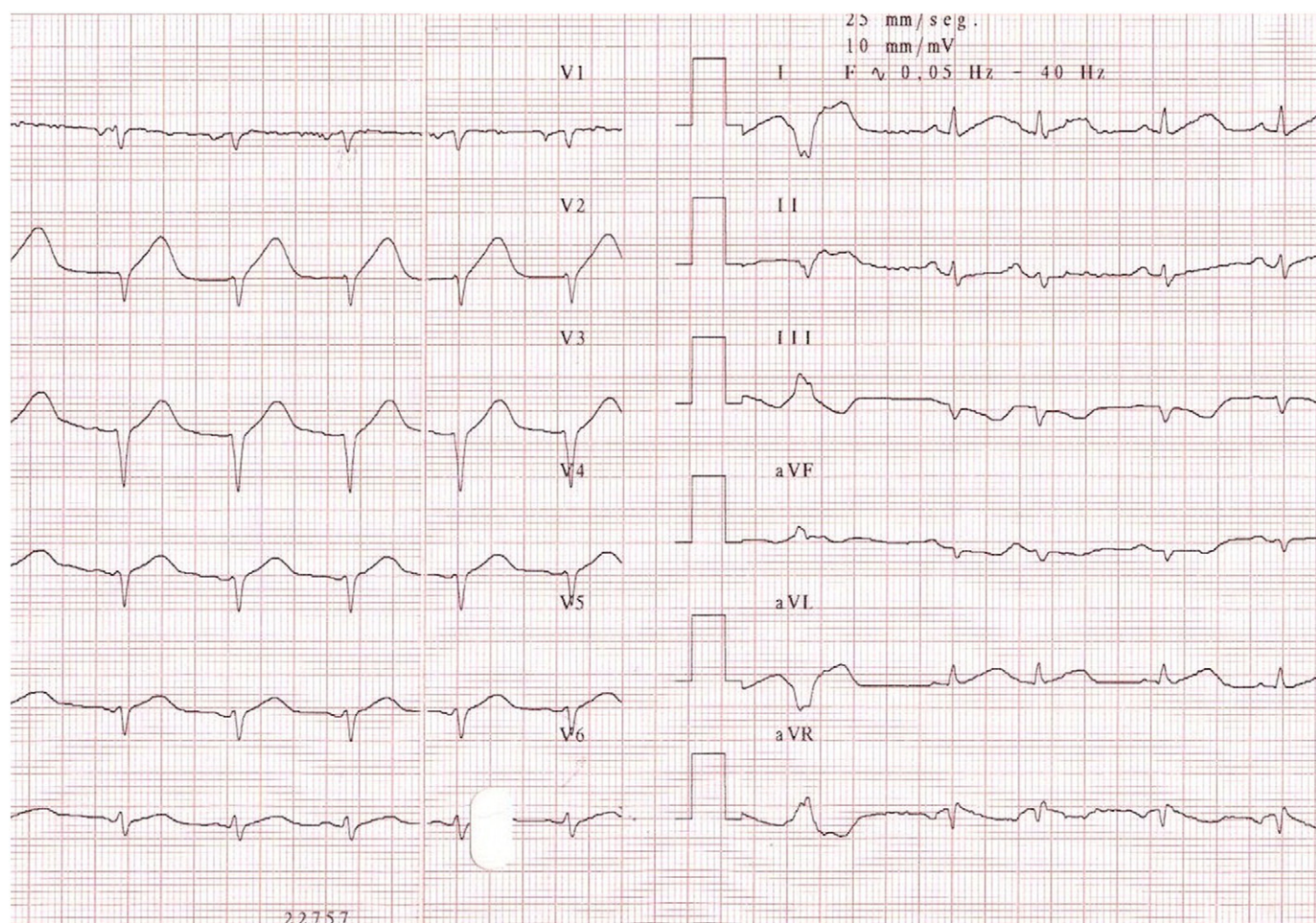


Fig. 1. Electrocardiogram showing peaked T waves and ST segment elevation in leads V2–V5, I & aVL and ST depression with negative T waves in leads III & aVF.

T was 4.48 ng/ml and CPK 1640 ng/ml). Echocardiogram at discharge showed akinesia of apical and mid-septum segments with a preserved global left ventricle ejection fraction.

He was discharged after three days with the diagnosis of variant 2 of Kounis syndrome. The Allergy department facilitated him a list of drugs and other allergens to avoid.

3. Discussion

The first report of myocardial infarction during an allergic reaction (to penicillin) was published in 1950 [1]. Kounis and Zarvas [2] introduced the concept and nomenclature of the “syndrome of allergic angina” in 1991, and five years later [3] they described the “syndrome



Fig. 2. A. Coronary angiography showing a thrombotic lesion in the origin of the first left anterior descending (LAD) diagonal branch, distal to the prior stent, that was permeable and without significant restenosis. B. Excellent outcome after angioplasty with implantation of two drug-eluting stents in the first LAD diagonal branch and in the LAD, with kissing stent technique.

of allergic myocardial infarction". Today, Kounis syndrome is a recognized cause of acute coronary syndrome and cases are being reported with allergic reactions to various drugs, chemicals, foreign bodies, environmental exposures or some other conditions that give rise to inflammatory mediator release [4–7]. Many experts believe that Kounis syndrome is not an uncommon disease but, rather, an under-diagnosed disease.

The concurrence of acute coronary syndromes with conditions associated with mast cell activation, including allergic or hypersensitivity and anaphylactic insults, constitutes the Kounis syndrome. Two types of Kounis syndrome have been defined. In type 1, myocardial ischemia or infarction occurs in patients with normal coronary arteries due to coronary spasm. Our patient was diagnosed with a type 2 variant, in which myocardial spasm or thrombosis occurs in atherosclerotic coronary arteries.

Coronary involvement in hypersensitivity reactions is probably secondary to increased circulatory inflammatory mediators mainly histamine, proteases such as tryptase and chymase or products of arachidonic acid metabolism [8]. Mast cell degranulation and anaphylaxis or anaphylactoid reactions can occur after drug exposure.

In allergic reactions an allergen interacts with and cross-links surface IgE antibodies on mast cells and basophils. Once the mast cell–antibody–antigen complex is formed, a complex series of events occurs that eventually leads to cell degranulation and the release of histamine (and other chemical mediators) from the mast cell or basophil.

Experimental and clinical evidence indicates that the human heart can be the site and the primary target of anaphylaxis [9]. It is known that histamine acts via four different histamine receptors all of which contribute to the severity of the allergic myocardial damage. Once released, histamine can react with local or widespread tissues through histamine receptors. The recruitment of these specific inflammatory cells at the sites of the allergic response correlates with the severity of the allergic reaction.

Histamine, acting on H1-receptors, produces pruritis, vasodilatation, hypotension, flushing, headache, tachycardia, and bronchoconstriction. Histamine also increases vascular permeability and potentiates pain. A novel action of histamine is the induction of tissue factor expression and activity. Tissue factor is a key enzyme in the activation of coagulation. It binds activated factor VII, which in turn activates factor X, leading to thrombin formation. Elevated tissue factor antigen and activity have been detected in plasma and in atherectomy specimens of patients with unstable angina, denoting that tissue factor is involved in the initiation and propagation of acute coronary syndromes. This effect of histamine is completely abolished by H1 receptor antagonists. Our patient experimented relief of his chest pain after the administration of nitroglycerin and chlorpheniramine, which is a histamine H1 antagonist (or more correctly, an inverse histamine agonist) of the alkylamine class.

It seems likely that atopic individuals are at higher risk of acute coronary syndromes than normal people. In a population based study, men with increased levels of IgE had significantly increased incidence of myocardial infarction, stroke and peripheral arterial disease. In the same study women had both significantly lower IgE levels and lower rates of cardiovascular disease. The authors of this study concluded that a causal role of IgE in the development of cardiovascular disease should not be excluded [10]. It has been shown that in platelets isolated from atopic

patients, the immunological stimulation with anti-IgE antibodies produced platelet aggregation and release of histamine. The exposure of platelets from healthy donors to increasing concentrations of thrombin produced a progressive aggregation of platelets which was parallel to the release of histamine. Both effects were significantly enhanced in platelets isolated from atopic donors [11,12].

It has been stated that in atopic patients, inhibition of mast cell degranulation could prevent acute thrombotic events. This has already been achieved experimentally by Nemmar et al. [13]. These investigators managed to abrogate late thrombotic events by stabilizing mast cell membrane with sodium cromoglycate and reducing inflammation with dexamethasone.

Kounis syndrome is increasingly encountered in clinical practice. Myocardial ischemia or infarction may be more common than suspected in hypersensitivity, anaphylactic or anaphylactoid reactions and can explain some unexpected cardiac arrests or mortalities in these situations [14]. Case selective mast cell surface membrane protection and stabilization should be considered a potential therapeutic strategy for patients prone to food induced allergy, for atopic patients and for patients who have already experienced a first Kounis syndrome.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [15].

References

- [1] Pfister CW, Pllice SG. Acute myocardial infarction during a prolonged allergic reaction to penicillin. *Am Heart J* 1950;40:945–7.
- [2] Kounis NG, Zavras GM. Histamine-induced coronary artery spasm: the concept of allergic angina. *Br J Clin Pract Summer* 1991;45(2):121–8.
- [3] Kounis NG, Zavras GM. Allergic angina and allergic myocardial infarction. *Circulation* 1996;94:1789.
- [4] Zavras GM, Papadaki PJ, Kokkinis CE, et al. Kounis syndrome secondary to allergic reaction following shellfish ingestion. *Int J Clin Pract Sep* 2003;57(7):622–4.
- [5] Frangides C, Kouni S, Niarchos C, Koutsojannis C. Hypersensitivity and Kounis syndrome due to a viper bite. *Eur J Intern Med May* 2006;17(3):215–6.
- [6] Mytas DZ, Stougiannos PN, Zairis MN, et al. Acute anterior myocardial infarction after multiple bee stings. A case of Kounis syndrome. *Int J Cardiol Jun* 11 2008.
- [7] Taggar JS, Watson T, Musarrat K, Millane T. Kounis syndrome presenting as ST segment elevation myocardial infarction following a hymenoptera (bee) sting. *Int J Cardiol Jul* 21 2008.
- [8] Kounis NG. Kounis syndrome (allergic angina and allergic myocardial infarction): a natural paradigm? *Int J Cardiol* 2006;110:7–14.
- [9] Bristow MR, Ginsburg R, Harrison DC. Histamine and the human heart: the other receptor system. *Am J Cardiol* 1982;49:249–51.
- [10] Criqui MH, Lee ER, Hamburger RN, Klauber MR, Coughli SS. IgE and cardiovascular disease. Results from a population-based study. *Am J Med* 1987;82:964–8.
- [11] Masini E, Di Bello MG, Raspanti S, Bani Sacchi T, Maggi E, Mannaioni PF. Platelet aggregation and histamine release by immunological stimuli. *Immunopharmacology* 1994;28:19–29.
- [12] Masini E, Di Bello MG, Cappugi P, Berni L, Mirabella C, Mannaioni PF. Platelet aggregation and platelet histamine release by immunological stimulation in atopic patients: modulation by nitric oxide. *Inflamm Res* 1997;46(Suppl 1):S81–2.
- [13] Nemmar A, Hoet PHM, Vermeylen J, Nemery B, Hoylaerts MF. Pharmacological stabilization of mast cells abrogates late thrombotic events induced by diesel exhaust particles in hamsters. *Circulation* 2004;110:1670–7.
- [14] İlhan Erkan, Güvenç TolgaSinan, Poyraz Esra, Ayhan Erkan, Soyulu Özer. Kounis syndrome secondary to cefuroxime axetil use in an asthmatic patient. *Int J Cardiol* 2009;137:67–9.
- [15] Coats AJ. Ethical authorship and publishing. *Int J Cardiol* 2009;131:149–50.