

Acute coronary syndrome in diclofenac sodium-induced type I hypersensitivity reaction: Kounis syndrome

Zoran M Gluovic, Biljana Putnikovic, Milos Panic, Aleksandra Stojkovic, Zorica Rasic-Milutinovic, Jelena Jankovic-Gavrilovic

Abstract

Drug-induced type I hypersensitivity reactions are frequent. Sometimes, acute coronary syndrome (ACS) can be registered in such patients, which may have a serious impact on the course and management of the allergic reaction. Because of potentially atypical ACS clinical presentations, the ECG is an obligatory diagnostic tool in any allergic reaction. Coronary artery spasm is the pathophysiological basis of ACS, triggered by the action of potent vasoactive mediators (histamine, neutral proteases, arachidonic acid products) released from the cells involved in type I hypersensitivity. Allergic angina and allergic myocardial infarction are referred to as Kounis Syndrome.

We describe herein a case of ACS in a patient with registered systemic immediate hypersensitivity reaction which developed following the muscular administration of diclofenac sodium.

Key words

Hypersensitivity, anti-inflammatory agents, non-steroidal mast cells, inflammatory mediators, coronary vasospasm

Zoran M. Gluovic* MD, MS

Department of Medicine, Division of Endocrinology, Diabetes and Metabolism Disorders,
Zemun Clinical Hospital, Zemun-Belgrade, Serbia
Email: gluovic@beotel.yu; zorangluovic@hotmail.com

Biljana Putnikovic MD, PhD

Division of Cardiology, Department of Medicine,
Zemun Clinical Hospital, Zemun-Belgrade, Serbia

Milos Panic MD

Department of Medicine, Division of Cardiology,
Zemun Clinical Hospital, Zemun-Belgrade, Serbia

Aleksandra Stojkovic MD

Department of Medicine, Division of Cardiology,
Zemun Clinical Hospital, Zemun-Belgrade, Serbia

Zorica Rasic-Milutinovic MD, PhD

Clinical Endocrinology Section, Department of Medicine,
Division of Endocrinology, Diabetes and Metabolism Disorders,
Zemun Clinical Hospital, Zemun-Belgrade, Serbia

Jelena Jankovic-Gavrilovic MD

Barts & London School of Medicine, Queen Mary,
Department of Psychiatry, University of London, London, UK

* corresponding author

Introduction

Diclofenac sodium (DS) is a frequently used non-steroidal anti-inflammatory drug (NSAID). Gastrointestinal, haematological, hepatic and renal side effects, as well as allergic reactions are registered frequently. The hypersensitivity reactions with the symptoms and signs of coronary arteries involvement (Kounis Syndrome) are not rare, despite the fact that they are not frequently documented in the medical literature^{1,6} Therefore, the report of Mori *et al.*¹ on the first two cases of vasospastic angina presented after NSAID administration is debatable. Kounis Syndrome is the concurrence of ACS with mast cell activation induced by allergic or hypersensitivity and anaphylactic or anaphylactoid reactions.^{2,6} In our discussion we review a case of ACS in a patient who suffered an anaphylactic reaction after the administration of DS.

Case report

A 66-year-old man was admitted to the CCU of Zemun Clinical Hospital after CPR had been performed on him in the Casualty Medicine Cubicle. His medical history evidenced the parenteral administration of DS in the Casualty Surgical Cubicle as he complained of pain in his left toe caused by foot injury he had sustained a few days before. He had no medical record of drug allergies, nor did he provide any drug allergy data to medical staff prior to DS administration. Several minutes after the parenteral administration of DS, he suddenly experienced cardio-respiratory arrest, and was immediately transferred to the Casualty Medicine Cubicle for resuscitation. The ECG recording showed up to 5mm ST segment elevation in inferior and entire precordial leads (Figure 1). He was transferred to CCU after CPR had been successfully performed (airway intubation, oxygen therapy, establishing IV access, precordial thump, crystalloid administration). Later on, we received his health insurance card only to discover that it contained a written warning of DS hypersensitivity. The patient's family said that similar episodes had occurred after the application of DS two or three years before, except that he then experienced no cardio-respiratory arrest and had no ECG pathological findings. The patient had always refused to undergo the recommended allergy testing.

At admission to the CCU, the patient was unconscious, intubated, with irregular spontaneous respirations, centrally and peripherally cyanosed, afebrile. Clinical: raised JVP (1-2+), apparent pathological venous pulsations. Chest: weak

pulmonary sound on auscultation with prolonged expiration, diffuse polyphonic wheezing and inspiratory crackles at the lung bases. Heart: quiet heart sounds, regular action, PR 110bpm, and BP 10.5/6.5kPa (80/50mmHg). With the exception of the swelling and bruising of the left toe, other physical examination of extremities was regular.

Laboratory findings. Complete blood count (CBC) showed eosinophilia (8%) and neutrophilia (82%), but no abnormalities in the count of other blood cells. Biochemical analyses showed mild hyperglycemia (7.4mmol/L), whereas hepatic, electrolyte, creatin-kinase, BUN and creatine findings were normal. Blood gases showed partial respiratory acidosis (pH 7.2, pCO₂ 60mmHg, pO₂ 90mmHg, and haemoglobin-oxygen saturation 94%). The urinalysis showed haematuria (a urinary catheter inserted). Findings on the chest X-ray showed air trapping (pulmonary emphysema), presumably due to the excessive smoking habit.

The patient was managed by oxygen, methylprednisolone, theophylline, IV nitrates (Nirmin®) and carefully monitored for ST elevations. A few hours later, spontaneous respirations were restored and the patient gradually regained consciousness. He had an almost regressed chest auscultation finding showing inspiratory crackles at the lung bases. Four hours after admission to the CCU, he was extubated and showed stabilized haemodynamic parameters - PR 96bpm, BP 17/11kPa (125/80 mmHg). On the second day, control laboratory tests revealed hyperglycemia (10.1mmol/L), elevated creatine kinase (468 U/l) and overall serum IgE levels (356 U/l). The measurements of serum specific IgE directed to NSAID, serum histamine and tryptase levels were not performed (due to the lack of funds and equipment for such measurement). Other haematological (eosinophils) and biochemical parameters, including Troponin I (<0.2ng/ml) were within the reference range. Repeated ECG recordings (Figure 2) showed a regular heart rhythm and a rate of 84 bpm, with no specific ST-T changes. Echocardiography revealed no motility disorders of the heart muscle (EF 53%, trace mitral and tricuspid regurgitation). The patient was discharged at his own request and refused to undergo the recommended exercise stress testing and coronary arteries angiography. Four weeks later, the repeated overall serum IgE level showed a significant decrease (69 U/l).

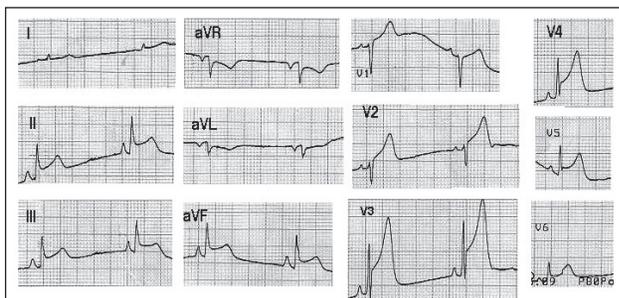


Figure 1: ECG report at admission

Discussion

The occurrence of ACS is a serious clinical problem, despite its being seldom reported in patients with anaphylactic responses to drug administration. The mechanism of its onset is characterized by coronary arteries spasm due to mast cells degranulation and the subsequent release of vasoactive mediators.² Mast cells are recruited to heart tissue and adventitia of coronary arteries.³ Released mediators can be preformed (histamine, neutral proteases - chymase and tryptase, platelet activating factor) or newly synthesized (cytokines, chemokines, arachidonic acid products - leukotrienes, prostaglandins). They can act either locally and/or systemically, and have important roles in the activation and interaction between other cells involved in allergic reactions (macrophages, T-lymphocytes, endothelial cells).⁶⁻⁸ The most important among the various mediators are histamine, serotonin, and leukotrienes, the exogenous application of which provoked coronary spasm in patients who suffered from vasospastic angina.^{4,5} Likewise, one cannot disregard the inhibition of vasodilative prostaglandin production, such as PGI₂, caused by the NSAIDs influence on the enzyme involved in prostaglandin synthesis (cyclooxygenase).¹

Nikolaidis *et al.*⁶ described two variants of Kounis syndrome. The type I variant, includes patients with normal coronary arteries and represents a manifestation of endothelial dysfunction. Type II variant of Kounis syndrome includes patients with preexisting atheromatous coronary arteries disease. Causes of Kounis syndrome include drugs (antibiotics, analgesics, antineoplastics, contrast media, corticosteroids, intravenous anesthetics, NSAIDs, 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).^{6,7}

To conduct provocative NSAIDs testing in the course of a coronary angiography study is not recommended as it may lead to potentially fatal anaphylaxis, as well as for ethical reasons. Assured of "normal coronary arteries" on angiography, Mori *et al.*¹ administered acetylcholine and ergonovine to two patients, which provoked coronary arteries spasm, chest pain, and specific ECG changes. Our patient was unwilling to undergo

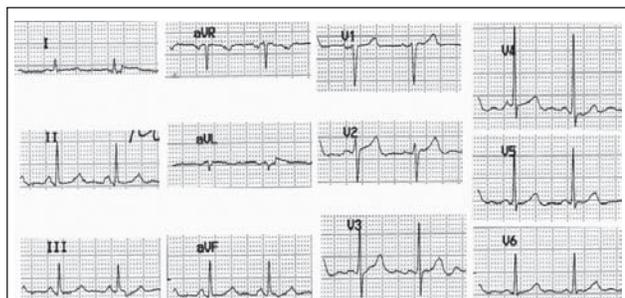


Figure 2: ECG report at discharge

coronary angiography. Furthermore, he resolutely rejected both angiography and exercise stress testing. For this reason, the clinical, ECG and serological findings of a significant IgE level decrease were taken into account to confirm ACS.

Conclusion

The manifestations of ACS in drug-induced hypersensitivity reactions could be completely atypical and therefore cause diagnostic confusions. It is of great importance to ask the patient if he is aware of any allergies, and not only drug-related. Before any drug administration, it would be prudent to check whether there are any medical records of drug hypersensitivities or intolerances. Likewise, health authorities must provide allergy alert cards. Because of potentially fatal anaphylaxis, drug allergy testing is of limited and cautious use. Therefore, even a suspicion about drug allergy must be treated seriously. In cases where hypersensitivity reactions are developed, ECG must unavoidably be recorded. When one encounters poor patient compliance, as we did in this case, diagnosis may be established if only some, rather than all diagnostic criteria for ACS in hypersensitivity reactions, are fulfilled. It is noteworthy that administration of mast cell membrane stabilization drugs should be used as a therapeutic strategy for patients prone to food induced allergy, for atopic patients and such who have already experienced allergic angina and/or infarction.^{9,10}

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