

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Kounis syndrome as a cause of acute coronary syndrome

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Introduction Kounis syndrome (KS) represents an acute coronary syndrome (ACS) induced by a hypersensitivity reaction. First described by Kounis and Zavras in 1991, KS today represents an infrequently diagnosed clinical syndrome. Three different KS variants have been defined: type I vasospastic allergic angina, type II allergic myocardial infarction, and type III stent thrombosis.

Outlines of cases This paper presents three cases of type II KS causing anaphylactic ACS. In the first case, a 66-year-old female presented with dyspnea, dizziness, and electrocardiography findings suggesting ACS after she was stung by a bee. In the second case, we present a 64-year-old female admitted to the Emergency Department with chest pain after an anaphylactic reaction due to an iodine contrast injection used for a thoracic computed tomography scan. In the third case, an 80-year-old female presented with chest pain, palpitation, and skin rash shortly after administration of the intravenous anesthetic propofol during elective malignant colon tumor surgical intervention. All patients were treated at the Cardiology Clinic, University Clinical Center of Serbia.

Conclusion The primary mechanism of KS corresponds to the release of inflammatory mediators during a hypersensitivity reaction triggered by different sources. Although well known, constant reminders of this cause of ACS are needed.

Keywords: acute coronary syndrome; hypersensitivity reaction; anaphylaxis; Kounis syndrome

INTRODUCTION

Kounis syndrome (KS) is defined as simultaneously arising acute coronary syndrome (ACS), myocardial infarction, or stent thrombosis in allergic hypersensitivity, anaphylactic, or anaphylactoid reaction settings. The first descriptions of allergic reactions associated with cardiovascular symptoms and signs appeared more than seven decades ago [1]. However, in 1991, Kounis and Zavras [2] first described “allergic myocardial infarction” caused by mast cell activation following allergic reactions. The lifetime prevalence of allergy and anaphylaxis is increasing, with an estimated lifetime risk of 0.02–2%, with more KS reports in the literature. Most data are sparse and based on isolated clinical cases and series, while exact pathophysiological mechanisms remain unclear [3–7].

Many inflammatory cells are activated during the allergic reaction, releasing their subsequent preformed mediators in circulation, leading to an inflammatory vicious cycle [8]. The entire arterial system seems vulnerable, and besides the coronary arteries, there have been reports of mesenteric and cerebral arteries being affected [6–8].

Since its first description, three different variants of KS have been defined: type I vasospastic allergic angina (without coronary disease), type II allergic myocardial infarction (with prior coronary disease), and type III stent

thrombosis (after percutaneous intervention) [3]. It was reported in every age group, race, and diverse geographic location. The treatment strategy for this syndrome may be particularly challenging due to simultaneous cardiac dysfunction and allergic reactions.

We present three cases of anaphylactic ACS treated at the University Clinical Center of Serbia 2019–2021.

REPORTS OF CASES**Case No. 1**

A 66-year-old female presented to the Emergency Department (ED) after being stung by a bee while sitting in her yard. Shortly after the sting, she developed dyspnea, palpitation, and dizziness. Her medical history included hypertension, type II diabetes mellitus, hyperlipidemia, and sideropenic anemia.

Emergency medical services found her in hemodynamic compromise. She was administered intravenous epinephrine, methylprednisolone, and chlorpyramine, which led to clinical improvement, and sent to the Emergency Department (ED) for further evaluation. Serum tryptase level three hours after the event was 19.8 ng/mL (normal value < 11 ng/ml).

The initial electrocardiogram (ECG) demonstrated ST-elevations in the aVR, and V1

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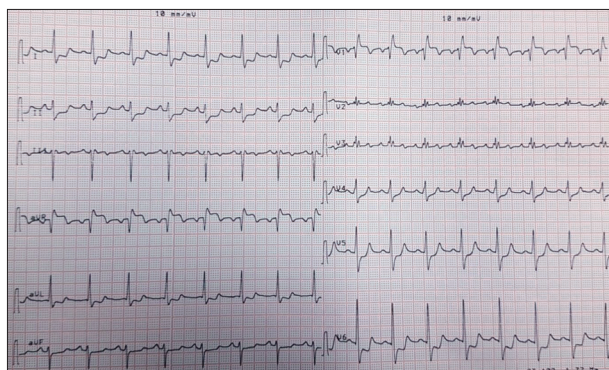


Figure 1. Electrocardiogram at the Emergency Department

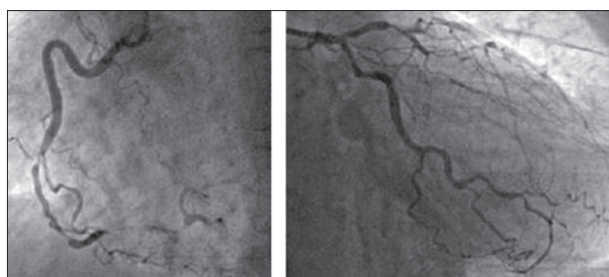


Figure 2. Coronary angiography: triple-vessel disease

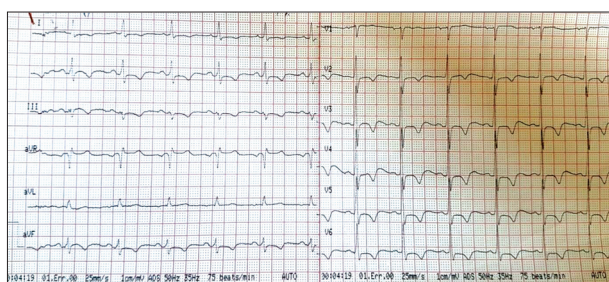


Figure 3. The patient's initial electrocardiogram showed negative T wave in the anterior and inferior wall with ST depression in aVR

leads with ST-depression in D1, D2, aVL, aVF, and V4–V6 leads with right bundle branch block pattern (Figure 1). The patient was admitted to the Coronary Care Unit (CCU), where she was hemodynamically stable with a slightly lower level of arterial pressure (100/60 mmHg). Her high-sensitivity troponin T (hsTnT) was elevated at 289 ng/L (normal value < 14 ng/L). The patient was treated with corticosteroids, antihistamines, and protocol for ACS with dual antiplatelet therapy, acetylsalicylic acid 100 mg and clopidogrel 75 mg, with a beta-blocking agent (bisoprolol 2.5 mg). During the first days of treatment, she did not experience chest pain or heart failure. Transthoracic echocardiography showed mild aortic stenosis with hypokinesis of the inferobasal septum and inferior wall, altered left ventricular systolic function [ejection fraction (EF) 45%], and mild ischemic mitral insufficiency.

Coronary angiography showed triple-vessel disease with left main stenosis of 50–70%, proximal left anterior descending artery (LAD) stenosis of 50–70% and medial LAD stenosis of 50–70%, ostial circumflex artery stenosis of 50–70%, medial right coronary artery (RCA) stenosis of 50–70% with distal occlusion (Figure 2). After initial cardiology treatment and recovery, she was transferred

to the Clinic for Cardiac Surgery, where she underwent myocardial revascularization.

Case No. 2

A 64-year-old female presented to the ED with chest pain after an anaphylactic reaction due to an iodine contrast injection used for a thoracic multislice computed tomography. She was regularly followed up after breast cancer, treated surgically and with chemotherapy nine years previously. Her personal history included hypothyroidism. Her medication included capecitabine and acetylsalicylic acid. She was a smoker and had a family history of cardiovascular disease.

Immediately after the intravenous application of the iopromide contrast injection, she experienced dizziness, skin rash, and chest pain. The operating radiologist and emergency medical services administered adrenaline, methylprednisolone, and chloropyramine without improving symptoms. She was transferred to ED with ongoing dizziness, generalized urticaria, chest pain, and hypotension 90/60 mmHg.

An ECG showed sinus rhythm and signs of myocardial injury with a negative T wave in an anterior and inferior wall with ST-segment elevation of 1 mm in aVF with typical angina chest pain (Figure 3). Due to clinical deterioration with hypotension and electrical findings of ACS, she was admitted to the CCU.

Laboratory tests showed the following: serum hsTnT 381 ng/L (normal value < 14 ng/L); creatine kinase 137 U/L; serum glucose 29 mmol/L and no abnormalities in electrolytes, renal function, and routine blood tests. At the time of hospitalization, analysis of blood tryptase was not available. Methylprednisolone, chloropyramine, and dual antiplatelet treatment (acetylsalicylic acid 100 mg, clopidogrel 75 mg with enoxaparin 2 × 0.6 ml subcutaneously) were given. During the next hospital day, our patient's symptoms gradually improved with the maintenance of ECG changes.

Transthoracic echocardiography showed hypokinesis of the medial and apical septum and anterior wall with reduced left ventricular systolic function (EF 40%) and minor ischemic mitral insufficiency. Coronary angiography was postponed due to a hypersensitivity reaction to iodine contrast, withdrawal of symptoms, and stabilization of vital signs. During the further hospital stay, the patient did not have chest pain nor signs and symptoms of heart failure, with normalization of the troponin level. She was discharged stable after seven days.

After four weeks, at the Allergy and Immunology Clinic, drug provocation tests with alternative iodine contrast (ioversol) were performed and were negative. The patient was allowed to use the tested iodine contrast with a corresponding premedication. Following an allergological examination, elective coronary angiography was scheduled. Due to the COVID-19 pandemic, an invasive examination was postponed due to the patient's stable status. A year after the event, selective coronary angiography was scheduled. An angiogram showed a two-vessel disease with

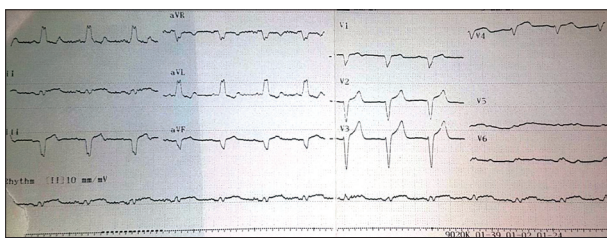


Figure 4. Electrocardiogram after administration of the anesthetic showing left bundle branch block pattern

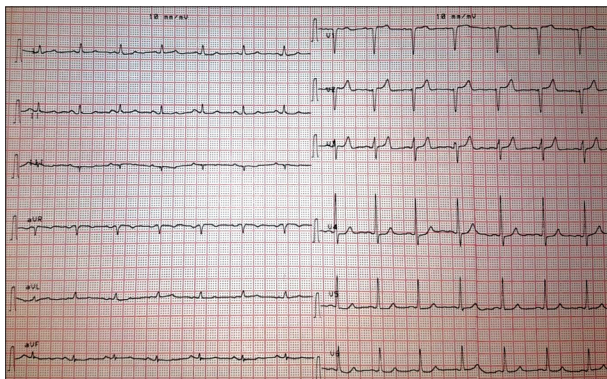


Figure 5. Electrocardiogram on the second hospital day, the same as the preoperative findings

stenosis of the proximal LAD of 80–90% and medial RCA of 70–90%. The percutaneous coronary intervention of the proximal LAD and medial RCA with implantation of two drug-eluting stents was performed.

Case No. 3

An 80-year-old female with known hypertension, type II diabetes mellitus, hyperlipidemia, and chronic obstructive pulmonary disease presented to ED with chest pain, palpitation, and skin rash, which developed shortly after administration of intravenous anesthetic propofol during the elective surgical intervention of malignant colon tumor. Shortly after administration of the drug, the patient was hypotensive (90/60 mmHg). The anesthesiologist administered her methylprednisolone and chloropyramine. The ECG demonstrated a new left bundle branch pattern (Figure 4). The intervention was canceled, and the patient was transferred to ED and further to the CCU with normal arterial pressure without ACS symptoms. Her hsTnT was elevated at 96 ng/l, and the patient received dual antiplatelet therapy with low-molecular-weight heparin, an antihistaminic, and corticosteroids. At the time of hospitalization, the analysis of blood tryptase was not available. On the second day of hospitalization, her ECG returned to the prior normal recorded level (Figure 5).

Transthoracic echocardiography showed a standard dimension of the left ventricle without regional wall motion abnormalities and with borderline systolic function (EF 50%) and minor mitral insufficiency. The patient had no previous history of allergy reactions. Furthermore, until this operation, she had no interventions under total anesthesia.

Coronary angiography was performed. One-vessel disease with the proximal LAD stenosis of 50% and medial sub-occlusion of the LAD of 90–99% was found. After multidisciplinary team consultation, she was transferred to the Clinic for Cardiac Surgery and underwent myocardial revascularization with the left internal mammary artery on the LAD. Previously, allergologic testing for sensitivity to other anesthetics was made. After a short recovery period, she underwent a successful operation on a colon tumor.

We confirm that we have read the journal's position on issues involving ethical publication and affirm that this work is consistent with those guidelines. Written consent to publish all shown material was obtained from the patients.

DISCUSSION

KS is induced by the activation of mast cells and platelets, interacting with inflammatory cells, such as macrophages and T-lymphocytes, leading to a discharge of inflammatory mediators, like histamine, platelet-activating factor, arachidonic acid products, and various cytokines and chemokines during the allergic activation course [8].

Our cases support KS as a recognizable phenomenon by showing three forms of type II KS with myocardial infarction after exposure to different allergens. Iodine contrast, bee sting, and intravenous anesthetic led to the development of allergic myocardial infarction. Our patients had different ECG changes, all with elevated hsTnT levels at the initial presentation.

Furthermore, in Case 1, the patient had no chest pain or typical skin rash known to be an allergic reaction following a bee sting. Without knowing of insect bites, KS would not have been considered. In Case 2, multiple exposures to iodine contrast led to the development of KS with consequent obstacles in further cardiovascular diagnosis and treatment. Also, in Case 3, there were only transient ECG changes and a few symptoms.

This unique disease should be thought of when allergic symptoms, electrocardiographic changes, and elevated cardiac enzymes accompany an acute onset chest pain. All patients referred to ED with chest pain and ST-elevation on ECG should be examined for allergic events. Also, every patient with an allergic reaction in the ED should have an ECG recording.

Dealing with both cardiac and allergic symptoms simultaneously makes treating KS challenging. Treatment with corticosteroids and antihistamines alleviates symptoms in patients with type I KS. For hypersensitivity-induced vasospasm, drugs of choice are vasodilators, such as calcium-channel blockers [9]. Along with type II and type III KS, all standard protocols for ACS should be applied [10,11]. In contrast, the use of morphine and other drugs known to have histamine-liberating properties should be avoided due to the potential of aggravating histamine-induced vasospasm, while epinephrine use must be done with caution due to its potentially vasospastic effect on coronary arteries [11].

Mast cells in allergic reactions interact with macrophages and T-lymphocytes. These cells produce and store secretory granules, released when specific antigens react with IgE antibodies attached to them, inducing degranulation (releasing histamine, leukotrienes, proteases, chymases, and many more mediators) [10]. This process occurs only in around 10% of atopic individuals. All these preformed and newly synthesized inflammatory mediators released locally and running into systemic circulation can cause either coronary artery spasm, which could progress to acute myocardial damage, or coronary plaque erosion or thrombosis, which establishes the main clinical manifestations of KS [11, 12, 13].

KS is doubtlessly a common disease. So far, many case reports support its presence, but knowledge about the pathophysiology still needs to be improved. More studies are required to enhance proper diagnostics and treatment

strategies. Correct and prompt treatment is necessary to improve patient prognosis and outcome. In addition to cardiological evaluation and treatment, it is essential to conduct an adequate allergological examination to identify potential disease triggers. We emphasize the importance of ECG in allergic reactions and vice versa, consideration of allergic episodes in patients with ACS.

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Conflicts of interest: None declared.

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Кунисов синдром као узрочник акутног коронарног синдрома

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САЖЕТАК

Увод Кунисов синдром представља акутни коронарни синдром изазван реакцијом преосетљивости. Описан први пут 1991. год. од стране Куниса и Завраса, данас представља ретко дијагностикован клинички синдром. Описне су три различите варијанте Кунисовог синдрома: тип I – вазоспастична алергијска ангина, тип II – алергијски инфаркт миокарда и тип III – тромбоза коронарног стента.

Прикази болесника У овом раду приказана су три различита случаја Кунисовог синдрома типа II која су довела до анафилактичког акутног коронарног синдрома. У првом приказу, 66-годишња жена је добила симптоме у виду диспнеје, несвестице и бола у грудима, после уједа пчеле, уз електрокардиографске промене карактеристичне за акутни коронарни синдром. У другом приказу, 64-годишња жена је добила болове у грудима после анафилактичке реакци-

је током употребе једног контрастног средства у склопу дијагностичке процедуре (компјутеризована томографија грудног коша). У трећем приказу, 80-годишња жена је добила болове у грудима, палпитације и осип по кожи руку и трупа после апликације интравенског анестетика пропофола током елективног хирушког лечења малигне болести дебелог црева. Све болеснице су лечене у Клиници за кардиологију Универзитетског клиничког центра Србије.

Закључак Основа механизма Кунисовог синдрома јесте ослобађање медијатора запаљења током хиперсензитивне реакције изазване различитим узрочницима. Иако је овај синдром прихваћен као узрочник акутног коронарног синдрома, неопходно је константно подсећање да треба мислити и на овај узрок настанка исхемије миокарда.

Кључне речи: акутни коронарни синдром; хиперсензитивна реакција; анафилакса; Кунисов синдром