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СИНДРОМ КОУНИСА: ИНФАРКТ МИОКАРДА ПОСЛЕ УКУСОВ ОС

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Kounis Syndrome: Myocardial Infarction After Wasp Bites

Резюме

В представленном клиническом случае описывается довольно редко встречающийся синдром Коуниса (СК) II типа, возникший у мужчины 69 лет с факторами риска ишемической болезни сердца (ИБС) после укусов ос и сопровождающийся развитием острого инфаркта миокарда (ОИМ) вследствие тромбоза коронарной артерии (КА). Диагноз ОИМ был подтверждён на основании лабораторно-инструментальных данных: повышения уровня тропонина (>10000 пг/мл), изменений на электрокардиограмме (ЭКГ) (элевация сегмента ST в отведениях II, III, aVF), выявленных нарушений сократимости левого желудочка (ЛЖ) по данным эхокардиографии (зона акинезии базального нижнего сегмента ЛЖ, гипокинезия срединных нижнего и переднебокового сегментов ЛЖ, апикального бокового сегмента ЛЖ), результатов коронароангиографии (острая окклюзия с признаками пристеночного тромбоза в правой коронарной артерии). Причиной тромбоза КА могла послужить как выраженная иммунно-воспалительная реакция, так и введение адреналина для купирования анафилактической реакции. У СК в настоящее время нет четких критериев для верификации заболевания, диагноз подтверждается на основании комплексной оценки пациента с острым коронарным синдромом (ОКС) и наличием выраженной аллергической/анафилактической реакции. Дополнительно для подтверждения СК предлагается оценивать уровень гистамина и триптазы в крови, однако данные биомаркеры довольно быстро метаболизируются, и в большинстве случаев выявить их повышенный уровень не удается.

Представленный клинический случай в очередной раз подчеркивает важность информирования клиницистов о риске развития ОКС на фоне выраженной аллергической реакции, а также необходимость дальнейшего изучения СК с целью разработки тактики лечения и профилактики для данной группы пациентов.

Ключевые слова: *аллергическая реакция, острый коронарный синдром, инфаркт миокарда, синдром Коуниса*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

The presented clinical case describes a rather rare type II Kunis syndrome (SC) that occurred in a 69-year-old man with risk factors for coronary heart disease (CHD) after wasp bites and was accompanied by the development of acute myocardial infarction (MI) due to coronary artery thrombosis (CA). The diagnosis of MI was confirmed on the basis of laboratory and instrumental data: an increase in troponin levels (>10000 pg/ml), changes in the electrocardiogram (ECG) (elevation of the ST segment in II, III leads, aVF), revealed violations of the contractility of the left ventricle (LV) according to echocardiography (zone of akinesia of the basal lower segment LV, hypokinesia of the median inferior and anterolateral segments of the LV, the apical-lateral segment of the LV), the results of coronary angiography (acute occlusion with signs of parietal thrombosis in the right coronary artery).

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The cause of CA thrombosis could be either a pronounced immuno-inflammatory reaction or the administration of adrenaline to stop anaphylactic reaction. Currently, there are no clear criteria for the verification of SC, the diagnosis is confirmed on the basis of a comprehensive examination of a patient with acute coronary syndrome (ACS) and the presence of a pronounced allergic/anaphylactic reaction. Additionally, to confirm the SC, it is proposed to assess the level of histamine and tryptase in the blood, however, these markers are metabolized quite quickly and, in most cases, it is not possible to identify their elevated levels.

This case once again underlines the importance of informing doctors about the risk of developing ACS against the background of a pronounced allergic reaction, as well as the need for further study of SC in order to develop tactics for the treatment and prevention of this group of patients.

Key words: *allergic reaction, acute coronary syndrome, myocardial infarction, Kounis syndrome*

Conflict of interests

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AH — arterial hypertension, BP — blood pressure, ASA — acetylsalicylic acid, BB — beta blocker, GCS — glucocorticosteroids, IHD — ischemic heart disease, MI — myocardial infarction, ACEi — angiotensin converting enzyme inhibitors, CA — coronary artery, CAG — coronary angiography, LV — left ventricle, ACVE — acute cerebrovascular event, ACS — acute coronary syndrome, CxA — circumflex artery, RCA — right coronary artery, PGD — prostaglandin, DM — diabetes mellitus, KS — Kounis syndrome, COX — cyclooxygenase, AF — atrial fibrillation, ECG — electrocardiogram

Introduction

Kounis syndrome (KS) is a medical emergency, which comprises marked allergic reaction and acute coronary syndrome, the pathogenic cause of which is immune-mediated reaction of mast cell activation and degranulation [1].

The incidence of KS is approximately 0.02 % of all ICU admissions and 3.4 % of all patients hospitalised with allergies; therefore, this disease is considered rare [1]. There are three types of this syndrome: type I (72.6 %) develops as a result of a vasospasm in patients without ischaemic heart disease (IHD); type II (22.3 %) is typical for patients with a history of IHD, where release of inflammatory mediators causes not only coronary artery spasm, but also atherosclerosis plaque erosion or rupture; type III (5.1 %) includes patients with thrombosis of a coronary artery stent [2].

KS is triggered mainly by antibiotics (27.4 %) and insect stings (23.4 %) [2]. This paper describes a clinical case of KS in a patient who was stung by wasps.

Clinical Study

The patient signed an informed consent for the publication of the clinical case.

Patient A., 69 years old, on June 22, 2023 was urgently hospitalised with an allergic reaction (acute anaphylaxis) and newly diagnosed paroxysmal atrial fibrillation (AF) to the city inpatient unit (St. Petersburg).

The patient had a history of arterial hypertension (AH) for 5 years; the highest blood pressure (BP) was up to 160/100 mm Hg, normal blood pressure: 120/85 mm Hg. He did not take any regular antihypertensive medications; in case of high BP values, he took a half of a tablet of a combined drug (amlodipine 10 mg + indapamide 2.5 mg + perindopril 8 mg). The patient had shortness of breath when climbing the fourth floor (for three years). He did not have any other cardiovascular complaints (rhythm irregularities, anginal pain, etc.) and denies diabetes mellitus (DM), history of MI and acute cerebrovascular events. The patient has a family history of AH, MI, acute cerebrovascular events (ACVE) (mother). From the age of 22 years old, the patient has been smoking 20 cigarettes/day. Comorbidities: chronic haemorrhoids with frequent exacerbations; chronic gastroduodenitis. He did not sustain any traumas and surgeries in his life. History of allergies: previously, wasp stings were associated with swelling in the area of stinging and shortness of breath, which the patient managed to eliminate with antihistamines. The patient denies food and drug allergies.

His condition aggravated on June 22, 2023, at 01.00 pm, when he was stung by wasps two times in his garage. A couple of minutes after the stings, he felt short of breath, fear of death, and sudden weakness. The patient called his friend, who transported him to the security point, where the patient collapsed. In 35 minutes, an emergency team arrived. At the prehospital phase, the patient received epinephrin 0.5 mg IM, prednisolone 90 mg IV bolus, chloropyramine 20 mg IV. The electrocardiogram (ECG) showed paroxysmal atrial fibrillation (AF) with a ventricular contraction rate of 110 bpm; there were no focal changes in ventricle repolarisation. Acute anaphylaxis, syncope and newly diagnosed paroxysmal AF were the reason for urgent hospitalisation to the city inpatient unit (St. Petersburg) (Figure 1).

Upon admission, the patient was lucid and was complaining of general weakness, feeling short of breath and arrhythmia. He denied having anginal pain. His objective condition was moderately severe. The skin was

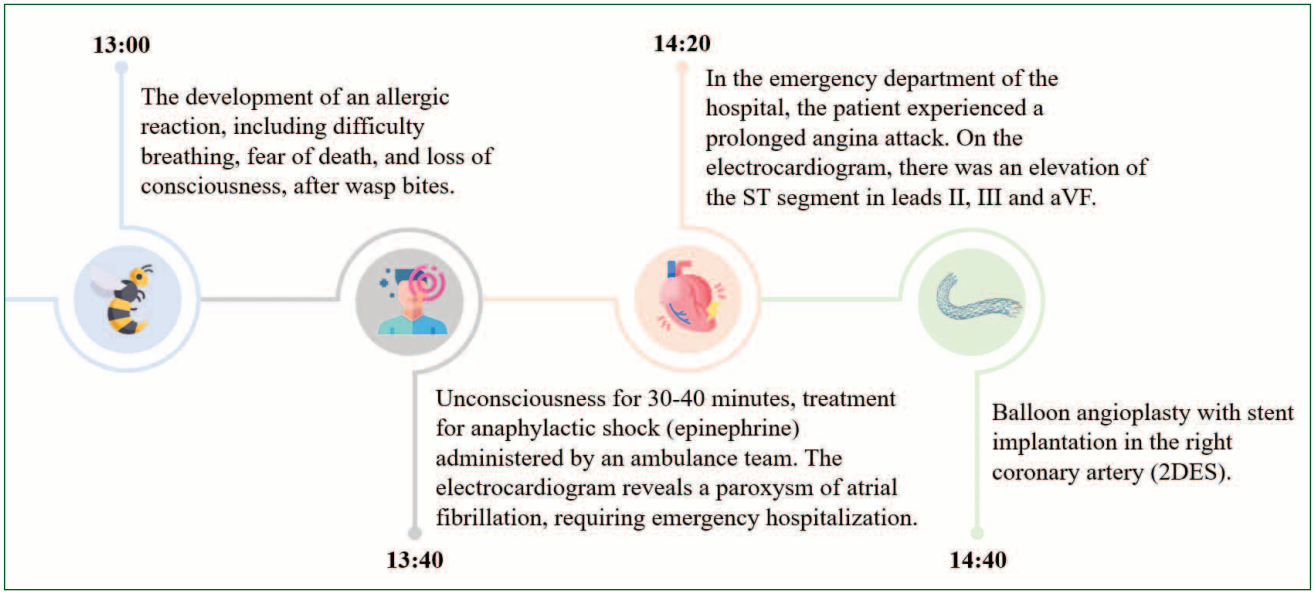

Figure 1. *Timeline of disease progression*
Note: EMS — emergency medical care, ECG — electrocardiogram, AF — atrial fibrillation, RCA — right coronary artery, PCA — posterolateral branch

pale, without acrocyanosis, oedema and eruptions; local hyperaemia and swelling are seen at the area of stinging (right arm, neck). Visible mucosa: unremarkable. BP: 100/55 mm Hg on both arms. Pulse: 98 bpm, arrhythmical. Respiratory rate: 20/minute. Auscultatory cardiac sounds were muffled, without cardiac murmur. Upper and middle sections of lungs: harsh respiration; lower sections: weaker respiration with crepitation. The abdomen was soft and non-tender on palpation.

ECG in the Admission unit showed spontaneous sinus rhythm restoration; myocardium repolarisation processes were not recorded. Upon admission, troponin T level was 24.73 pg/mL (N < 50 pg/mL). Clinical blood assay was remarkable for mild normochromal anaemia (Hb 120 g/L); blood biochemistry was remarkable for low total protein levels (53 g/L), higher creatinine (129 μmol/L) and glucose (9.07 mmol/L) values. High creatinine levels (up to 115–130 μmol/L) during standard medical examinations and self-referral were observed for over 1.5 years, therefore, chronic kidney disease was verified. Lipid profile: total cholesterol — 6.31 mmol/L, low-density lipoproteins — 4.53 mmol/L, triglycerides — 0.89 mmol/L. Blood electrolytes were normal. Urinalysis: glucosuria: 14 mmol/L (N < 1.7 mmol/L), protein: 1 g/L (N < 0.1 g/L). Coagulation profile: within reference ranges. Chest X-ray dated June 22, 2023: no new focal and infiltrative changes in lungs; moderate pulmonary vascular congestion. Abdomen and kidney ultrasound examination dated June 22, 2023: diffuse changes in liver and pancreas; right kidney cysts of up to 2 cm.

30 minutes after admission to the inpatient unit, the patient experienced sudden acute, severe constricting/gripping retrosternal pain, irradiating to the interscapular region, with suffocating feeling, excessive sweating and lightheadedness. ECG: sinus rhythm, elevated ST segment in leads II, III, aVF (Figure 2). Based on these observations, the patient was urgently transferred to the X-ray Surgery Diagnosis and Therapy Unit for coronary angiography (CAG). Before the intervention, the patient was given clopidogrel 600 mg per os, acetylsalicylic acid (ASA) 300 mg and heparin 5,000 units IV.

CAG dated June 22, 2023 (Figure 3): stenosis of the middle third of the anterior interventricular artery up to 50 %, more distally — a muscular bridge, stenosing the systolic orifice; the first diagonal artery is stenotic in the proximal third up to 85 %, the second diagonal artery is stenotic in the proximal third up to 85 %; the circumflex artery (CxA) is sub-occluded; the right coronary artery is stenotic in the middle third up to 70 %; the distal third is acutely occluded with signs of mural thrombosis. Balloon angioplasty of the right coronary artery (RCA) and its posterior lateral branch (2 DES) was performed. Revascularisation: without complications. Scheduled CxA stenting was recommended.

After surgery, the patient's condition was stable; he was transferred to ICU for follow-up.

Echocardiography was performed on day 2 of hospitalisation: LV end-diastolic volume — 120 mL; end-systolic volume: 60 mL; interventricular septum thickness: 12 mm; Simpson's ejection fraction: 50 %; left atrium volume: 60 mL; an area of akinesia of the LV basal lower segment; hypokinesia of LV middle lower and anteriolateral segments, LV apical lateral segment; the aorta is moderately dilated in its ascendant section (to 41 mm); the valvular heart apparatus: without any remarkable haemodynamic changes; estimated pulmonary arterial pressure: normal; pericardium: unremarkable. Changes in T: > 10,000 pg/mL. Clinical blood assay: persistently low Hb levels (105–115 g/L); higher WBC levels

on day 3 of hospitalisation (to 16.15×10^9/L), gradually lowering by day 5 of hospitalisation to 6.9×10^9/L; otherwise unremarkable. Blood biochemistry: persistent hyperglycaemia with the highest value of 15.4 mmol/L on day 2 of hospitalisation; the patient was consulted by an endocrinologist.

Endocrinologist consultation dated June 23, 2023: newly diagnosed type 2 diabetes mellitus; glycaemia-dependant insulin therapy is recommended.

By the end of day 2 of hospitalisation, the patient's condition was stable, and he was transferred to the Cardiology unit for further examinations and treatment. Due to the therapy (disaggregants, anticoagulants, beta-blockers (BB), angiotensin converting enzyme inhibitors (ACEi), statins, proton pump inhibitor, diuretics), the patient's condition improved; his haemodynamics was stable; cardiac and pulmonary insufficiency were compensated; anginal pain disappeared.

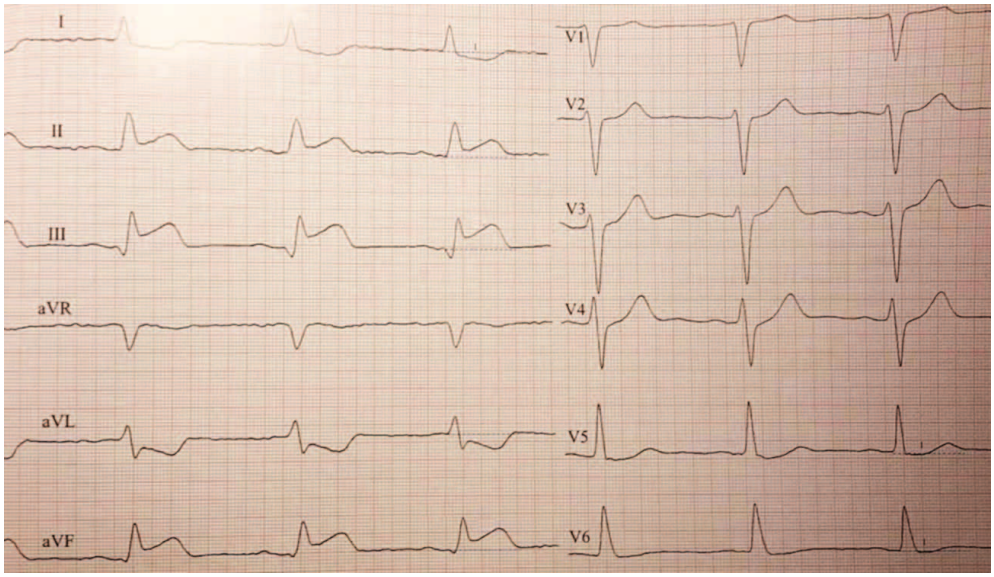

Figure 2. *Electrocardiogram taken in the emergency room — sinus rhythm with a heart rate of 75 beats per minute, normal electrical axis of the heart, ST segment elevation in leads II, III, aVF*

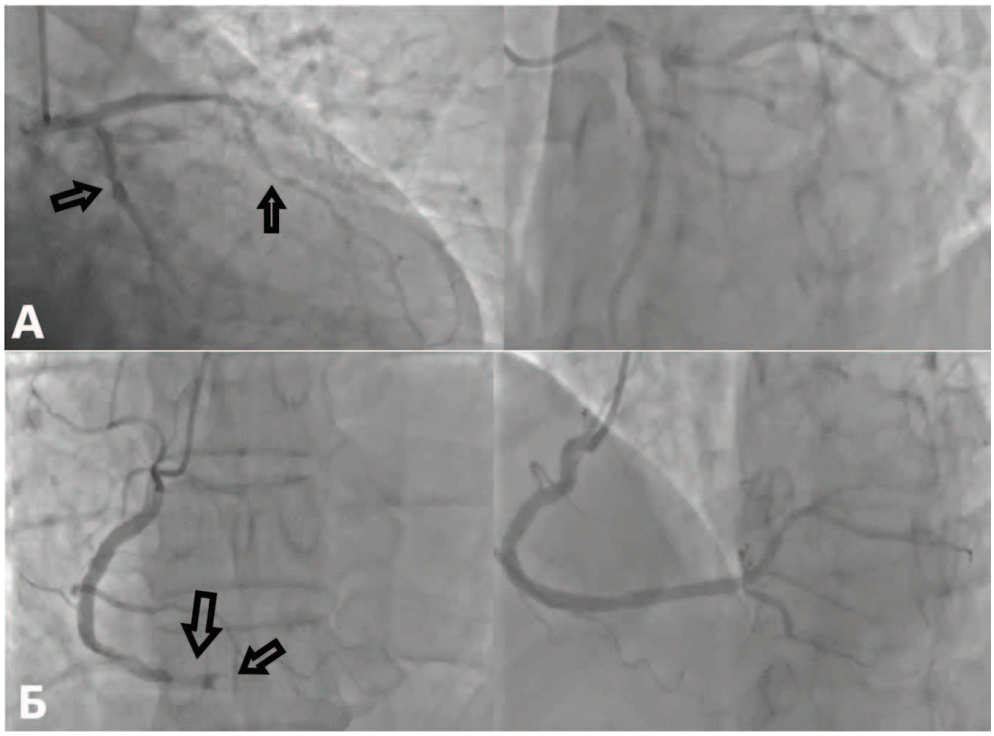

Figure 3. *Results of percutaneous coronary intervention: A — left coronary artery in two projections (the left arrow indicates subocclusion in the OA, and the right arrow indicates stenosis in the LAD), B — the right coronary artery before and after stenting (arrows indicate stenosis and occlusion of the artery lumen)*

Diagnosis

Primary: ischaemic heart disease. Acute transmural myocardial infarction of the lower LV wall on June 22, 2023. Balloon angioplasty of RCA and posterior lateral RCA branch (2DES) on June 22, 2023.

Stage III hypertensive disease. Uncontrolled AH. LV hypertrophy. Hyperlipidemia. Type 2 diabetes mellitus; target HbA1c value: ≤ 7.5 %. Chronic kidney disease C3a (eGFR (CKD EPI 2021) — 52 mL/min/1.73m2). A1? Risk grade 4 (very high). Target BP: < 130/80 mm Hg.

Complications: acute cardiac insufficiency Killip II → chronic cardiac insufficiency with preserved ejection fraction (50 %), stage IIa, functional class 2.

Newly diagnosed paroxysmal atrial fibrillation (June 22, 2023); spontaneous sinus rhythm restoration on June 22, 2023. EHRA I, CHA_2DS_2-VASc 3 points, HAS-BLED 2 points.

Secondary: allergic reaction (acute anaphylaxis) to wasp sting; arrested on June 22, 2023.

Mild normochromic, normocytic anemia.

Chronic haemorrhoids, moderate exacerbation.

Chronic gastroduodenitis, not in exacerbation.

After discharge from the inpatient unit, the patient was recommended to take rivaroxaban 15 mg/day; clopidogrel 75 mg/day; atorvastatin 40 mg/day; bisoprolol 5 mg/day; perindopril 6 mg/day; indapamide 1.5 mg/day; omeprazole 20 mg/day in outpatient settings. It was recommended to have another outpatient consultation with an endocrinologist to select therapy.

Later, when the patient came for an outpatient visit to the cardiologist 6 and 12 months after hospitalisation, the patient still had shortness of breath when climbing the third floor; otherwise, no complaints. Taking into account the history of allergies, the patient was recommended to see an allergy specialist; but the patient refused.

Discussion

The pathogenesis of KS is still unclear. It is assumed that the onset of KS is associated with the release of inflammatory mediators (histamine, platelet-activating factor, arachidonic acid metabolites, neutral protease) during an allergic reaction, as well as various cytokines and chemokines [3].

There are no specific diagnostic tests for KS verification [4]. In addition to clinical characteristics, ECG results and values of myocardial damage biomarker, histamine, tryptase and IgE levels should be taken into account as well. However, additional diagnostic tests are challenging, since, due to its short half-life, histamine levels are useful only within 10 minutes after onset of anaphylaxis, whereas tryptase levels elevate 30 minutes after allergy manifestation and reduce as soon as in 120 minutes [5].

In this case, a systemic anaphylaxis reaction, which preceded an acute MI, in a patient with a risk factor for IHD (family history, male sex, age, smoking, AH, diabetes mellitus, and dyslipidemia) allowed suspecting type II Kounis syndrome [1]. The cause of atherosclerosis plaque rupture and coronary artery (CA) thrombosis is still unclear: whether this event was a direct result of vasospasm and/or inflammatory mediator release as a response to allergy, or whether it was caused by exogenous adrenaline injection, which, according to literature, can be an independent trigger of MI [6].

Currently, there are no therapeutic guidelines for KS, and all available information is based on description of clinical cases. At the same time, management of KS patient is challenging, because it requires the use of several medicinal products to arrest an allergic reaction and agents, which help to prevent or reduce an area of myocardial ischaemia [7].

In particular, adrenoceptor agonists, used to treat acute anaphylaxis, can negatively impact the course of ACS. For instance, adrenaline, which is essential for the management of allergic reaction, can contribute to CA spasm and extend an area of myocardial ischaemia [8]. However, there are no reports on deaths among KS patients after IM adrenaline injections [9].

According to literature, use of H1-receptor blockers, such as diphenhydramine and chlorpheniramine, has no harm in KS; however, if administered too fast, they can cause hypotension and reduced tissue perfusion [9].

As for glucocorticosteroids (GCS), there is no consensus among experts. Marked anti-inflammatory effect of GCSs can increase the risk of cardiac aneurysm in MI and cause arrhythmias [10]; however, Clemen B. et al. (2021) believe that the use of GCSs in patients with KS is safe, efficient and useful in prevention of recurrent anaphylaxis [9].

Once the condition is stable and the allergic reaction in KS is arrested, further management of the patient should focus on ACS therapy in accordance with current clinical guidelines; however, there are fine points [9]. Morphine, which is often used in ACS for pain treatment and pulmonary oedema prevention, causes mast cell degranulation, which can aggravate anaphylaxis and vasospasm [9]. Therefore, fentanyl is a preferred choice if anaesthesia is required [11].

If possible, it is advisable to avoid using beta-blockers (BB) and ASA in KS patients. BBs are believed to cause uncontrolled alpha-adrenergic effect and worsening of CA spasm [12]. ASA mechanism of action is based on inhibition of activity of cyclooxygenases (COX-1 and COX-2), which take part in synthesis of prostacyclins, thromboxane and prostaglandin (PGD), particularly PGD2. Since PGD causes coronary angiospasm, reduction in their levels with the use of ASA has positive effect on ACS. However, impaired PGD2 synthesis contributes to higher production of leukotriene by non-inhibited lipoxygenase, which can support an allergic reaction [9].

In their 2022 overview , Gopinath B. et al. propose a treatment strategy for a patient with type II KS [13].

Management of patients with type II KS should be based on the ACS management protocol, with concurrent use of GSC and antihistamines. If necessary, vasodilating agents (nitrates, calcium channel blocking agents) can be prescribed. In patients with type II KS, who were previously treated with BB, adrenaline can be inefficient and at the same time can cause or boost the coronary angiospasm due to unpredictable and uncontrolled α-adrenergic effect. Therefore, patients, who were treated with BB before the onset of type II KS or during ACS therapy, are advised to have intravenous glucagon (1–5 mg within 5 minutes, with subsequent infusion of 5–15 μg/min) for anaphylaxis reaction [14]. Also, if a patient with type II SK does not respond to adrenaline, they can be prescribed a potent alfa-agonist — methoxamine [14].

In this clinical case, the patient did not have confirmed IHD, so it was quite impossible to predict type II KS; therefore, the management approach could not follow the algorithm proposed by Gopinath B. et al. (2022). Probably, a more precise management approach in such patients requires development of prognostic scores to assess the risk of KS; still, more clinical data are required for this purpose [15].

Conclusion

Kounis syndrome is an unsolved challenge in cardiology, which requires a multidisciplinary approach. Currently, there are a number of questions on the diagnostic algorithm of this disease, management during the acute period, as well as methods of primary and secondary prevention, especially in patients, who are susceptible to frequent allergic reactions and have risk factors of cardiovascular diseases.

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