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Case Report

Kounis Syndrome Caused by Hornet Sting: A Case Report and Literature Review

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Abstract

Kounis syndrome (KS) is defined as an acute coronary syndrome, secondary to an anaphylactic or hypersensitivity reaction. In literature, it is also called "allergic myocardial infarction". KS is divided into three clinical types: I- caused by coronary spasm, II- plaque erosion or rupture, III- coronary artery stent thrombosis. KS's pathophysiology is based on the immune pathways related to the activation of mast cells and subsequent activation of platelets, macrophages and T lymphocytes, followed by the release of inflammatory mediators including histamine, platelet-activating factor, neutral proteases, arachidonic acid metabolism products as well as multiple cytokines and chemokines. The most common causative factors include drugs and Hymenoptera stings (wasps dominating). Kounis syndrome is rarely diagnosed, which is most likely due to low awareness rather than low incidence of this condition, which leads to the underestimation of epidemiologic data. In this paper, we present a case of an acute coronary syndrome associated with hornet sting in a patient with no previous history of coronary artery disease, which meets the criteria for Kounis syndrome type I diagnosis.

Keywords: Kounis Syndrome; Anaphylactic Shock; Anaphylaxis; Hornet Sting; Acute Coronary Syndrome.

Case Report

A 70-year-old woman with hypertension and type 2 diabetes, without any further comorbidities, including coronary heart disease and allergies, was stung by a hornet on her right hand while resting in the garden. She fainted and lost consciousness immediately after the incident. The patient's family called the Emergency Medical Service, who, upon arrival at the scene, found the patient had low blood pressure. Antihistamines and parenteral steroids were immediately administered (no data regarding the administration of adrenaline), fluids were transfused, and the patient was transported to the hospital emergency department for further observation.

In the Emergency Department, about two hours after the sting, she suddenly complained of shortness of breath, chest pain, and abdominal pain accompanied by nausea (without vomiting). During a physical examination, urticarial wheals were visible on the skin of the back, as well as edema of the lips, blood oxygen saturation level was 90%, and no other abnormalities were found. The electrocardiogram (ECG) showed normal sinus rhythm 90 bpm and nonspecific ST segment changes. Transthoracic echocardiography (TTE) revealed hypokinesis of the basal segment of the inferior wall with preserved left ventricular

ejection fraction; no significant valvular defects were detected. The results of laboratory blood tests revealed increased values myocardial necrosis markers: high-sensitivity troponin (0.28 ng/ml with normal values up to 0.014 ng/ml) and creatine kinase MB (88.3 U/L with normal values up to 24 U/L), as well as markers of inflammation: CRP (0.88 mg/dl with a norm of up to 0.5 mg/dl) and procalcitonin (5.7 ng/ml with a norm of up to 0.5 ng/ml) with no clinical symptoms of infection. Blood and urine cultures did not show the growth of pathogenic microorganisms. Total eosinophil count was within the normal range.

On the same day, the patient was transferred to the Cardiology Department as an emergency admission. Coronary angiography was performed, which revealed no significant changes in coronary arteries (changes narrowing the lumen by up to 40% in the left anterior descending artery (LAD) and right coronary artery (RCA) were described, otherwise without any significant changes). The troponin dynamics followed a pattern typical for myocardial infarction with a rise up on admission and normalization within Taking into account the overall clinical picture, acute coronary syndrome (caused by coronary vasospasm) as a result of an anaphylactic reaction was diagnosed. The patient was qualified for conservative treatment, so antihistamines, systemic steroids, and antiplatelet drugs were used, and the existing antihypertensive treatment was modified due to high blood pressure. After nine days of hospitalization, the patient was discharged home with a recommendation to take antiplatelet therapy (acetylsalicylic acid), rosuvastatin to stabilize atherosclerotic plaques, as well as ramipril, amlodipine, and metformin. On follow-up, she did not experience other episodes of chest pain.

More than a year after the event described above, the patient was admitted on an elective basis to the Department of Allergology, Pulmonary, and Internal Diseases in order to further investigate the diagnosis of hypersensitivity to Hymenoptera venom and possible qualification for venom-specific immunotherapy (VIT). Laboratory and imaging tests were performed during hospitalization. The results of blood tests showed no significant deviations from the norm, the basal serum tryptase level was within the norm (4.2 ug/l). The electrocardiogram showed a regular sinus rhythm of 70 bpm, left axis deviation, and no changes in the ST segment. The chest radiograph revealed no abnormalities. Echocardiography of the heart did not reveal contractility disorders (LVEF 65%) or significant valvular defects and the size of the heart chambers were normal, but a small, well-saturated echo of the non-coronary aortic valve leaflet was visible. Cardiac magnetic resonance imaging (CMRI) revealed no foci of edema or late contrast enhancement, segmental akinesia or hypokinesia of the muscle, local thickening or additional structure was visible in the noncoronary leaflet of the aortic valve (Figure 1).

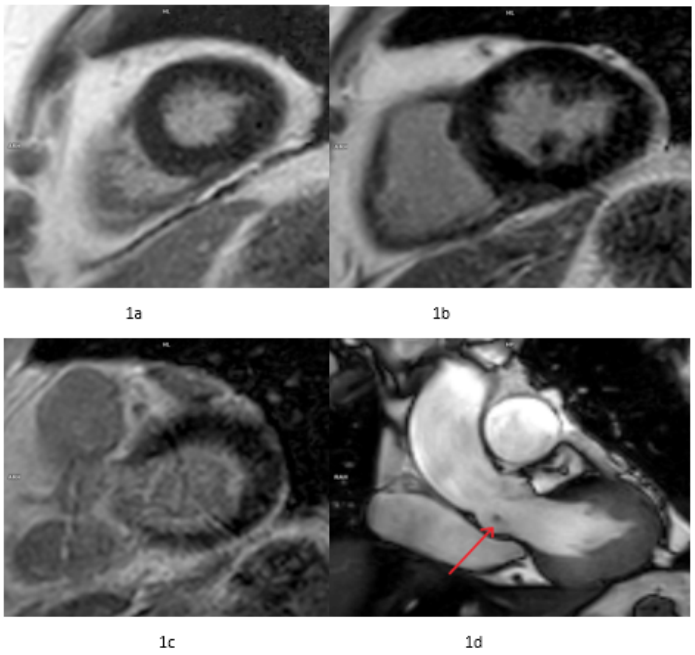

Figure 1: Cardiac MR, delayed enhancement images of apical (a), middle (b), and basal (c) segments of the left ventricle and cine image (d) of the aortic valve. There is no delayed enhancement within the myocardium of the left ventricle that indicates no post-ischemic changes (a, b, c). MR reveals local thickening (up to 3mm) of the non-coronary leaflet of the aortic valve (d); in the differential diagnosis, fibroeleastoma should be considered.

Due to the above, the patient was consulted for cardiac surgery, and no urgent indications for surgical intervention were found, and she was referred for further diagnostics at the Cardiothoracic Clinic.

Under hospital conditions and intensive medical supervision, skin prick tests (SPT) with wasp and bee venom were performed, which were negative, and intracutaneous tests (ICT) were performed - positive for both venoms. Additionally, IgE antibodies specific to European hornet venom in class II and common wasp venom in class IV were found. Testing of allergen components for wasp venom showed class IV titers for the 5-rVes v5 antigen in wasp venom. Moreover, the presence of IgE antibodies specific to bee venom in class I was found, and the examination of allergen components did not show the presence of phospholipase A2 - rApi m1, hyaluronidase - rApi m2 or icarapine - rApi m10. Moreover, the patient had been stung by wasps and bees in the past, without any significant reactions, and she denied being stung by a hornet.

Therefore, the patient met both the clinical and immunological criteria for VIT implementation. Based on the entire clinical

picture, the results of additional tests, and the correct identification of the insect species, the patient was qualified for wasp venom immunotherapy. Throughout the next hospitalization, vaccination with wasp venom was started using the ultra-rush protocol. During direct observation, an erythema with a diameter of approximately 5 cm was visible at the site of administration, otherwise, no adverse reactions were observed during hospitalization. Over the following weeks, the planned dose of 100 μg of wasp venom was achieved, with no complications observed. The patient is currently undergoing immunotherapy with maintenance doses and tolerates it well.

Discussion

BBroadly understood cardiovascular diseases have been the leading cause of death in the world for many years. According to a 2019 report by the World Health Organization (WHO), they are responsible for over 17 million premature deaths worldwide, which is 32 % of all deaths [1].

Kounis syndrome (KS), first described in 1991 by Nicholas G. Kounis [2], remains a rarely diagnosed disease, most likely because the causative factor is easily missed. So far, about 400 cases have been described worldwide, including about 100 cases involving insect stings, therefore publishing data on the etiology, pathogenesis, and on characteristic sequence of clinical symptoms seems important to increase the percentage of correct diagnoses and appropriate treatments. There is no data on the estimated incidence of KS in the world in the available scientific literature. In 2019, epidemiological data for the USA was published [3]. KS was diagnosed in 1.1% of patients hospitalized due to allergies, hypersensitivity or anaphylaxis, and the hospital mortality rate was 7%. Importantly, in the group of patients diagnosed with acute coronary syndrome, patients who were also diagnosed with KS had a higher mortality rate than those without the diagnosis (7 vs. 0.4%). Kounis syndrome occurs more often in men than in women (74.3% vs. 25.7%) [4], and most cases have been observed in people in their 50s and 60s, although recent reports suggest that it may occur in any age group (from 2 to 90 years old) [5].

The most common inducing factors include antibiotics (27.4%, including cephalosporins and penicillins) [4,5], and hymenoptera insect venoms (23.4%, wasp, bee, and other species).

Drugs	Environmental factors	Food	Chronic diseases
Antibiotics (ampicillin, amoxicillin, amikacin, cefazolin, cefuroxime, lincomycin, penicillin, cefoperazone with sulbactam, piperacillin with tazobactam, trimethoprim and sulfamethoxazole, vancomycin)	Venoms of insects from the order Hymenoptera	Seafood	Angioedema
Nonsteroidal anti-inflammatory drugs (ex. acetylsalicylic acid, diclofenac, naproxen)	Venoms of spiders and ants	Fish	Allergic rhinitis
Proton pump inhibitors	Viper venoms	Fruit and vegetables	Asthma
Anticoagulants (heparin, lepirudin)	Scorpion venom	Mushrooms (common ink cap)	Eosinophilic granulomatosis with polyangiitis (EGPA)
Thrombolytics (streptokinase, tissue plasminogen activator, urokinase)	Jellyfish stings		Mastocytosis
Glucocorticoids (hydrocortisone, betamethasone)	Latex		Parasitic diseases
Anticancer drugs (5-fluorouracil, carboplatin, paclitaxel, interferons)	Metals		Serum sickness
Contrast agents			Nicotine addiction
Disinfectants (chlorhexidine, iodopovidone)			Previous coronary stenting
Other (allopurinol, bupropion, clopidogrel, ACE inhibitors, sartans, esmolol, insulin, iron preparations, tetanus toxin)			

Table 1: Factors potentially inducing Kounis syndrome, according to Kounis Nicholas G. [5]

So far, three types of Kounis syndrome have been differentiated [4,5]. In type I (the most common, 72.6%), the release of inflammatory mediators leads to coronary artery spasm with or without the release of markers of myocardial necrosis. It should be emphasized that type I only affects people without previously diagnosed coronary heart disease. It is worth noting that this variant clinically resembles vasospastic angina (Prinzmetal's angina). Both conditions are caused by a coronary vasospasm, and coronary angiography does not reveal any significant abnormalities. Type II (22.3%) includes patients with previously diagnosed coronary artery disease in whom the release of inflammatory mediators causes coronary artery spasm along with erosion or rupture of the atherosclerotic plaque, which manifests itself as a typical acute coronary syndrome. Type III is the rarest form of the syndrome (5.1%), the cause of which is stent thrombosis leading to complete occlusion of the artery. A definite diagnosis can be made based on histopathological examination of the aspirated thrombus, in which, after staining with hematoxylin-eosin and Giemsa, eosinophil and mast cell infiltrates are visible (Figure 2).

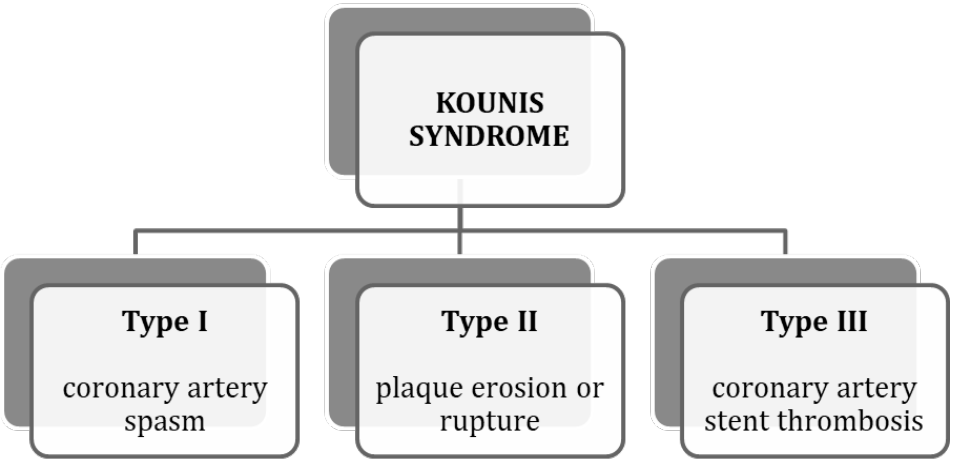

Figure 2: Types of Kounis Syndrome

Due to the growing interest in this syndrome, resulting in an increasing number of studies and published cases, there is an ongoing discussion about introducing a new clinical division and expanding the definition of KS.

The most common clinical manifestations of KS are chest pain (86.8%), anaphylaxis (53%), skin rash and urticaria (47%), shortness of breath and wheezing (14%), and pulmonary edema (5.1%) [4]. However, the most important element that can often lead to the correct diagnosis is not how frequently certain symptoms occur, but the order in which they appear. Attention should be paid to the presence of any symptoms that suggest an anaphylactic reaction. Cardiovascular symptoms appear earlier and later dominate the clinical picture, which is why this element is often overlooked. Even though KS seems to be easy to miss due to its specificity, failure to combine both of its components may result in an incorrect diagnosis. Physical examination (changes on the skin and mucous membranes) and an allergy medical history both play a special role in the diagnostics.

An increase in the concentration of markers of myocardial necrosis, i.e. high-sensitivity troponin, and creatine kinase MB, should be expected in the laboratory test results. In terms of pathogenesis of the syndrome, it is also worth determining the serum baseline tryptase concentration (sBT), which should be elevated. However, it should be noted that sBT results are not always reliable due to its relatively short half-life (about 90 minutes) [6]. The best time to collect a blood sample is within the first 30 minutes of the onset of symptoms.

The most characteristic features of the electrocardiogram are: ST segment elevation (76%) in leads II, III, and aVF (inferior wall), less frequently in V1-V4 (anterior wall) and I, aVL and V5-V6 (lateral wall and apex of the heart), or ST depression in the above-mentioned leads (17.1%) [4]. Abnormalities in echocardiography in the form of segmental contractility disorders are detected in more than half of patients (57.7%) [4], although this examination does not allow to distinguish between fresh and existing changes. Magnetic resonance imaging is a relatively new

method that is helpful in establishing the diagnosis, as it allows for the differentiation between acute coronary syndrome, myocarditis, and cardiomyopathies (e.g. Takotsubo cardiomyopathy). In currently published studies on the usefulness of CMRI in the diagnosis of Kounis syndrome [7], late contrast enhancement images showed normal contrast washout from the subendocardial areas in type I KS.

Therapeutic management of Kounis syndrome is complex because both of its components, i.e. anaphylactic reaction and coexisting acute coronary syndrome, must be considered. So far, no guidelines for the management of KS have been published, and the current treatment is based largely on available review articles and case reports [5,8,9]. Drugs typically used to treat ACS may worsen allergic symptoms, and vice versa - allergy treatment may worsen heart function. Adrenaline is the perfect example – the first line of treatment in anaphylaxis, which in the case of Kounis syndrome may intensify coronary vasospasm and lead to life-threatening arrhythmias, for example by prolonging the QT interval. It is worth noting that epinephrine should be administered at a dose of 0.3-0.5 mg, intramuscularly, into the anterolateral surface of the thigh. If there is no improvement, the dose can be repeated every 5-15 minutes until the symptoms disappear [10].

In type I, considering the predominance of coronary artery spasm resulting from the mediator-induced mast cell reaction, improvement may only be brought with the use of glucocorticosteroids and antihistamines. It is recommended to administer parenteral steroids (e.g. hydrocortisone at a dose of 1-2 mg/kg/day) and both H1 and H2 receptor antagonists (diphenhydramine and ranitidine), as their combination gives better results than the administration of an H1 antagonist on its own. Vasodilators such as nitrates (nitroglycerin) should be used depending on the initial values of blood pressure and heart rate, as they may worsen hypotension. It is worth noting that in type I, calcium channel blockers (verapamil, diltiazem) are preferred. Beta-blockers, especially non-selective ones, are contraindicated, as they may contribute to the intensification of coronary vasospasm. In type II, it is recommended to treat it as an acute coronary syndrome with simultaneous administration of steroids and antihistamines (using the same doses as mentioned above). Treatment of ACS should be based on current guidelines [11, 12]. For patients presenting with ST-segment elevation due to STEMI, immediate reperfusion therapy remains the immediate priority. Opiates such as morphine, given to relieve chest pain should be used very carefully as they may induce massive mast cell degranulation and intensify allergic reactions. Antiplatelet therapy (including acetylsalicylic acid) is a key element of treatment in the acute phase of ACS, as well as in secondary prevention after stabilization. In type III, the priority is to immediately unblock the thrombosed stent with simultaneous administration of steroids and antihistamines, as in other types.

It should be noted that every patient diagnosed with KS (or suspected of having KS) should be referred for further elective allergy diagnostics.

Conclusion

The presented case of KS draws attention to the need for an even broader approach to patients with ACS or anaphylaxis because data indicates that their co-occurrence in the form of KS is much more frequent than current statistics demonstrate. Early detection of KS influences further therapy, and given that ACS in KS is more severe and has a worse prognosis than in the general population, a quick diagnosis of the syndrome may be a factor that significantly improves the prognosis. In the diagnosis of the causes of acute coronary syndrome, Kounis syndrome should, in our opinion, be treated as a separate disease entity, which has its therapeutic implications (for example in terms of adrenaline use) and prognostic ones.

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