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Allergic myocardial infarction

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Abstract

In the literature there are very few well-documented cases of myocardial ischemia with pathomechanism accompanying allergic reaction. It is defined as Kounis syndrome, i.e. angina pectoris or infarction with allergic etiology. It is suggested, that few few cases of myocardial ischemia after a Hymenoptera *sting reported thus far represent only a minute percentage of the total number of allergic reactions which occur in the circulatory system. It is difficult to make a credible decision whether allergic mechanisms are responsible for a greater number of deaths than we suspect.*

In the light of the literature, this review deals with current views regarding pathomechanisms of myocardial ischemia in the course of anaphylactic reaction and presents the clinical manifestation of myocardial ischemia with an allergic background, pointing out that allergic reactions involving cardiac muscle are not limited to the development of ischemia. The term organ anaphylaxis, *in relation to the heart, also comprises rhythm and contractility disturbances which are present after exposure to the allergen.*

At the same time, the authors touch upon therapeutic aspects of immunotherapy in patients with significant cardiovascular risk and draw attention to the possibility of an alternative treatment for patients with allergic history, not only during desensitization but also for long-term outpatient treatment. (Cardiol J 2008; 15: 220–225)

Key words: allergic myocardial infarction, anaphylactic shock, immunotherapy

Introduction

Symptoms of myocardial ischemia accompanying allergic reactions are defined in the literature as Kounis syndrome or allergic angina/myocardial infarction [1]. In 1998 Braunwald [2] noted that vasospastic angina can be induced by "allergic reactions with mediators such as histamine or leukotrienes acting on coronary vascular smooth muscle". It has been nearly 15 years since the announcement made by Kounis about the contraction of coronary arteries which was induced by histamine in the course of allergic reaction, but in the literature one can find very few well-documented cases of myocardial ischemia of such pathogenesis [3, 4].

Allergic reactions following a *Hymenoptera* sting have three main clinical manifestations: excessive local reaction, systemic reaction and delayed type of reaction. These types of reactions can occur even following minimal doses of venom. After stinging by a higher number of insects (from tens to hundreds of stings), one can observe toxic symptoms resulting from the direct cytotoxic effect of venom components (i.e., melittin, apamine) [5].

The anaphylactic reaction can develop after a sting to any part of the body, but the most predisposed areas are the head, neck and throat. If cardiac ischemia develops, an angina type chest pain occurs within several tens of minutes after stinging [6]. Myocardial ischemia, in the course of anaphylactic

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reaction, can result from circulatory system instability (drop in coronary perfusion pressure) and pathophysiologically it does not differ from disturbances which are seen in shock, regardless of its etiology [3, 7]. However, allergic reactions can lead to myocardial ischemia as a result of coronary vessel contraction. This form of ischemia is defined as allergic angina (Kounis syndrome). Its most common symptoms, beside typical stenocardial pain, are the following: dyspnoe, palpitation, serious weakness, nausea, vomiting, fainting, urticaria, itching, profuse sweating, paleness, hypotonia and sometimes bradycardia.

Acute coronary syndromes with allergic etiology

Two types of Kounis syndrome are recognized: type I occurs in patients with angiographically normal coronary vessels, whereas in type II concomitant atheromatic lesions are found. Vasospasm develops in both types. However, in type I, the only cause responsible for ischemia and the probable mechanism leading to vasospasm is the dysfunction of endothelium [8].

Under such conditions, substances released during allergic reaction, among them histamine, lead to vasospasm, whereas in normal vessels vasodilatation occurs [9].

Usually, at least 30 min elapse from the exposure to the allergen to the development of anginal pain [3, 8], while the half-life of the histamine in circulation is estimated at about eight minutes. Therefore, it seems that the pathomechanism of myocardial infarction is more complicated and cannot be considered exclusively as a vasospasm evoked by histamine [8]. In type II Kounis syndrome, the constriction of vascular walls leads to the rupture of atheromatic plaque, mostly at its margin. Additional factors predisposing atheromatic plaque to rupture are proteolytic enzymes such as chymase and tryptase, which, when released by activated mast cells, degrade the collagen cover of the lipid core of the plaque. As a result of the plaque lesion, thrombogenic material is exposed and the process of coagulation starts. The coronary vessel is then closed in a mechanism typical for classic acute coronary syndrome. Moreover, exposure to allergen enhances platelet aggregation with the help of serotonin, adrenalin, bradykinin, leukotrienes and thromboxane [4].

Considering the scarcity of descriptions of myocardial infarction with proven allergic etiology, credible data regarding the relative frequency of both types of syndrome is hard to obtain. In the period of two years, one intensive cardiac care centre treated eight patients with acute coronary syndrome who had been stung by *Hymenoptera* insects in the preceding 48 hours. In all patients who underwent coronarography, the presence of at least one narrowing > 70% in coronary vessels (type II Kounis syndrome) was found [10]. On the basis of the aforesaid data, one can assume that type II of the syndrome occurs more often. The authors suggest that atopic patients, having higher proneness to degranulation of mast cells, are more exposed to the destabilization of atheromatic plaque in the course of allergic reaction, compared with non-atopic patients [10].

Mechanisms of allergic coronary syndromes

Acute coronary events in the course of allergic reaction were described after exposure to *Hymenoptera* venom [11], food allergens (e.g. shellfish) [8, 12], intravenous [11] and even oral drugs [13]. Acute vascular neurological events were also reported after insect stings [14]. It could be hypothesized that similar changes (vessel contraction and/or lesion of pre-existing atheromatic plaque) can also take place in cerebral circulation. There are a lot of factors and diseases which may evoke Kounis syndrome (Table 1).

Few cases of myocardial ischemia have been proven to have an etiological connection with *Hymenoptera* stings. They are probably only a small proportion of the allergic reactions occurring in real

Table 1. Kounis syndrome — possible etiologic factors [8, 13, 15, 16].

Diseases	Drugs	Venoms and toxins
Angioneurotic oedema	Antibiotics	Viper venom
Bronchial asthma	Bupropion	Wasp venom
Exercise induced anaphylaxis	Contrast media	Bee venom
Food allergy	Glucocorticoids	
Idiopathic anaphylaxis	Dextran	
Serum sickness	Heparin	
Urticaria	Intravenous anesthetics	
	NSAID	
	Protamine	
	Skin disinfectants	
	Streptokinase	

NSAID — non-steroids anti-inflammatory drugs

life in the cardiovascular system. It is possible that coronary vasospasm during coronarography may have an allergic origin as well. In this case it would be a form of organ restricted allergy. Moreover, sudden deaths caused by allergic mechanisms are probably underestimated as well. In statistical data from England, on average only four deaths a year are caused by *Hymenoptera* stings. However, it is suggested that the majority of acute deaths caused by stings remain undiagnosed [17]. Steady growth in the prevalence of atopic diseases would suggest an increase in the number of cardiologic cases of allergic etiology is to be expected.

The key elements of organ allergic reaction are mast cells located in the heart. They are present between cardiomyocytes, in the internal layer of arteries and around coronary vessels [18–20]. They are found in the hearts of healthy humans, but at the same time occur in considerably higher amounts in the intima and adventitia of vessels with preexisting atheromatic lesions, particularly in marginal regions of atherosclerotic plaques. Cardiac mast cells possess specific immunohistochemical features distinguishing them from mast cells of other organs. Probably the activation of mast cells accumulated around atheromatic foci is one of the key steps leading to their destabilization. In place of plaque rupture, about 200 times more mast cells are found compared with surrounding vascular segments without atheromatic changes, in patients with non-allergic acute myocardial infarction [8, 19, 21]. The majority of mast cells in coronary vessels, especially in marginal regions of atheromatic plaques, contain both tryptase and chymase [22]. Mast cells can be activated by T lymphocytes and macrophages [23]. The classic example of mast cell stimulation is its activation trough immunoglobulin IgE (IgE). During IgE dependent mast cell degranulation, a specific antigen reacts with one or more IgE particles bounded with mast cells through the high affinity receptor FceRI.

In the course of anaphylactic reaction, a complement is activated with the anaphylotoxin generation. The specific receptors for them are present on the surface of cardiac mast cells [24]. The final step of this processes is mast cell degranulation, resulting in histamine, tryptase and chymase release, as well as in prostaglandin and leukotriene synthesis. The histamine concentration is elevated in arterial walls containing atheromatic changes [25]. Similarly, the number of mast cells in vascular adventitia increases proportionally with the extent of atherosclerosis. A higher number of mast cells is found in coronary vessels containing acute atherothrombotic changes, whereas in already organized thrombi the number is low [26]. Peptidases released form stimulated mast cells activate metalloproteinases (MMP: MMP-1, MMP-3 and MMP-9) which degrade connective tissue covering the atheromatic plaque. The plaque becomes vulnerable i.e. more prone to rupture. If the fibrous cap covering the lipid core splits, acute coronary syndrome evolves. Moreover, prostaglandin D2, leukotrienes and angiotensin II formed under chymase influence contract coronary vessels [27]. They may trigger vulnerable plaque rupture and facilitate vessel closure. The next factor playing an important role in atherothrombosis is the tumour necrosis factor α (TNF-α), a strong pro-inflammatory cytokine, which, if released from mast cells, activates inflammation and transforms stable plaque into vulnerable plaque [28].

It was shown that activated mast cells were present around the rupture in the atherosclerotic plaque. If it is possible to prove the role of mast cells in plaque destabilization even in acute coronary syndromes not of allergic origin, a common final pathway could be discovered. The well-known mechanisms leading to plaque destabilization — oxidized LDL or allergic processes — also stimulate inflammation [19, 21, 29–32]. Rupture of the atheromatic plaque and thrombus formation with subsequent vessel closure would be the final step of any mechanism stimulating inflammation and therefore destabilizing plaque, regardless of the initiating factors.

If this hypothesis were proven, knowledge about the common final pathway leading to plaque destabilization could widen the range of available therapeutic methods in the prophylaxis of acute coronary syndromes. In light of this, drugs which inhibit the degranulation of mast cells could become the successive tool for atheromatic plaque stabilisation. Initial experiments investigating the prevention of acute coronary syndromes with drugs originally used in patients with asthma have already started. If mast cell activation proves to be a universal phenomenon leading to plaque destabilization, the efficiency of drugs which stabilize mast cell membranes in the prevention of acute coronary syndromes can be expected [15].

Type I Kounis syndrome and Prinzmetal angina

Many similarities between type I Kounis syndrome and Prinzmetal angina have been observed. In both cases, the key element resulting in myocardial ischemia is the contraction of vessels. It often

develops in places angiographically unchanged. However, intravascular ultrasonography reveals, at least in some cases, the presence of minimal atheromatic lesions in such places [33]. Stimuli which cause vasospasm in Prinzmetal angina are similar to factors released during allergic reactions; among others: catecholamines, thromboxane A2, serotonin, endothelin, vasopressin [34] and histamine [35]. In blood taken from the coronary sinus of variant angina patients, elevated concentrations of histamine were seen [15, 19, 35]. Cuculo and co. observed transient serum tryptase concentrations several times higher in patients with unstable angina after chest pain episodes. This suggests that mast cells are activated during unstable angina, but the stimulus remains unrecognized [27].

Substances indicating mast cell activation are present in the circulation in both allergic and non-allergic episodes of acute myocardial ischemia [8]. It was also shown that some patients with Prinzmetal angina, with normal coronary angiography, evolve typical chest pain with accompanying ST elevation after intravenous histamine administration (dose ranges 0.5–1 mcg/kg b.w./min) [36]. This observation is important not only in the diagnostic aspect of variant angina, but, probably more importantly, it proves that the administration of histamine releasing drugs (e.g. opiates and some relaxants) can cause coronary vessels spasm in susceptible patients [36]. *In vitro* studies have revealed that human coronary arteries afflicted with atherosclerosis were more susceptible to vasoconstriction caused by catecholamines, 5-hydroxytryptamine and histamine, compared to vessels without atheromatic lesions. The biggest difference was observed for histamine, which contracts atherosclerotic vessels about 1000-times stronger than the unchanged ones. Moreover, coronary segments with atheromatic lesions contain nearly two times more histamine than adjacent unchanged segments. Similar differences in histamine content were found by postmortem study between coronary arteries taken from patients with ischemic heart disease and from people who died due to other reasons. No such differences were found for 5-hyroxytryptamine and catecholamines. In people with coronary artery disease, mast cells are present in adventitia in amounts proportional to the intensity of atherosclerotic changes. Increased content of histamine and mast cells in walls of diseased coronaries proves that the mediator can be released in high amounts in response to various stimuli. This might result in strong coronary artery contraction leading to flow decrease, chest pain and rhythm disturbances [37].

In literature attempts were described to counteract the actions of inflammatory mediators by using, experimentally, mediator antagonists, inhibitors of mediator biosynthesis and mediator receptor blockers. Leung et al. [38], in a recent study, applied anti-IgE therapy with humanized IgG1 monoclonal antibodies to mask the region of mast cell surface responsible for IgE binding thus offering protection against mast cell degranulation. It has also been suggested that in atopic patients treatment with anti-IL-4Rα antibodies might inhibit acute allergic episodes [39]. All these agents capable of stabilizing and protecting mast cell membrane could also prevent acute thrombotic events [7].

Clinical manifestation of myocardial ischemia with allergic etiology

Allergic reactions relating to cardiac muscle are by no means limited to the development of ischemia. The term organ anaphylaxis, regarding the heart, also includes disturbances of rhythm and contractility which occur after exposure to allergens.

In the beginning, it was reckoned that lesions relating to the heart are only the result of systemic disturbances, such as drop in arterial pressure, growth of resistance in airways and disturbances of ventilation. However, changes resembling those symptoms developing in the heart *in vivo* were also observed in isolated organs (*in vitro*) of guinea pigs, in response to allergens after previous passive allergisation [40, 41]. In *in vitro* experiments, antigen administration into coronary circulation triggers histamine release. Similar changes occur after parenteral application of antigen *in vivo*. Exposure to the allergen evokes a transient, profound drop in contractility and rhythm disturbances as sinus tachycardia, atrio-ventricular blocks, ventricular tachycardia or idioventricular rhythm. Intensity of the described reaction is in proportion to the amount of released histamine, but this relationship is not linear. This proves the co-participation of other mediators in the development of disturbances [41]. In the ECG in the course of anaphylactic reaction, as well as rhythm disturbances, one can observe flattening or inversion of T waves and ST segment displacement (depression or elevation) [42]. The ectopic and sinoatrial node automatism stimulation is H2 receptor dependent, whereas conductance disturbances are H1 receptor mediated [41].

Therapeutic problems related to immunotherapy

Specific immunotherapy of patients with severe life-threatening allergic reactions in anamnesis is associated with a risk of adverse events. The risk is particularly high during the administration of higher concentrations of allergen and in cases of desensitization with venom of *Hymenoptera* insects. The risk of systemic reactions during the immunotherapy is estimated at about 10% [17]. Despite the fear of adverse events related to the specific immunotherapy in such patients, the prevailing opinion is that desensitization is the only form of treatment that significantly decreases the risk of life-threatening allergic reaction in the case of another sting [6]. There is no data from controlled trials concerning the role of specific immunotherapy in allergic myocardial infarction survivors. Repeated uncontrolled allergen exposition after past infarction is probably associated with the threat of another infarction. However, do we know enough to qualify the patient after allergic myocardial infarction to specific immunotherapy? Sometimes the significant left ventricle systolic dysfunction results from acute coronary events. Advanced heart failure is a commonly accepted contraindication to immunotherapy. For patients with compromised left ventricular function, after an allergic event, another episode may be fatal. It is estimated that the risk of serious systemic reaction in the case of another sting is 50%. Having taken into account the relative contraindications, the authors attempted to administer specific immunotherapy to the patient with post-myocardial ventricular systolic dysfunction, without any undesirable circulatory side effects [43]. Violent local reactions do not announce systemic reactions and therefore are not an indication for desensitization.

According to current recommendations, the prevalence of local reactions during immunotherapy, found in up to 25% of desensitized patients, does not increase the risk of treatment-related serious systemic reactions and is not an indication for a change in dosage regimen [37, 44]. In patients with different forms of ischemic heart disease (especially after myocardial infarction), the use of beta-blockers and angiotensin converting enzyme inhibitors (ACEI) is standard. Unfortunately, treatment with these drugs is related to a higher risk of serious anaphylactic reactions which are, moreover, difficult to treat [45–48]. Similar unfavourable effects of these drugs can be expected after exposure to an allergen (e.g. *Hymenoptera* sting) in real life. As much as possible, it is worth considering switching the patient to alternative treatment (for example with angiotensin II receptor blockers instead of ACEI) in patients with allergic history during desensitization and probably in long-term treatment on an outpatient basis [49].

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