Kounis Syndrome: Allergic Angina and Allergic Myocardial Infarction: Review

Kounis Sendromu: Allerjik Anjina ve Allerjik Miyokard İnfarktüsü

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ABSTRACT Allergy and immunology are mostly investigating and fundamental provinces of science. Besides their classical presentations, allergic diseases are contributing to pathophysiology of several disorders. One of them is allergic angina and/or allergic myocardial infarction, which is called as the Kounis Syndrome. Kounis syndrome divided into two subgroups: Type 1 and type 2. Type 1 patients have normal coronary arteries and lacking of risk factors for ischemic heart disease and present two different clinical courses: Some of them experience with coronary spasm and angina without elevated levels of cardiac enzymes and troponine. And others, have a more severe course with elevation in cardiac enzymes which may progress to acute myocardial infarction. In patients with Kounis syndrome type 2, there is an underlying coronary disease. Allergic reactions may facilitate plaque erosion and rupture, which is consequence with myocardial infarction. Collaboration with an allergy specialist in the treatment and management of patients with Kounis syndrome is essential. Not only cardiologist also by allergist should follow the patients with diagnosed allergic disease and coronary heart disease, especially in those patients have allergy to foods or bee venoms, namely carrying increased risk for anaphylaxis. Awareness of Kounis syndrome between physicians, who are dealing with cardiovasculary diseases in their daily practice, is important to attain new visions in diagnosis and treatment.

Key Words: Drug hypersensitivity; myocardial ischemia; anaphylaxis; mast cells

ÖZET Allerji ve immünoloji en fazla araştırma yapılan önemli bilim alanlarıdır. Allerjik hastalıklar klasik klinik seyirleri dışında birçok hastalığın fizyopatolojisi içinde de yer almaktadır. Bunlardan birisi de Kounis sendromu olarak adlandırılan allerjik anjina ve/veya allerjik miyokard infarktüsüdür. Kounis sendromu tip 1 ve tip 2 olarak iki alt grupta incelenir. Tip 1 hastalar normal koroner arterlere sahiptir ve iskemik kalp hastalığı yönünden risk faktörleri taşımazlar. Bu hastalarda iki farklı klinik seyir söz konusudur. Bir kısmında koroner vazospazm ve anjina olur ama beraberinde kardiyak enzim ve troponin yükselmesi gözlenmez. Diğerlerinde ise, seyir daha ciddi olup, enzim yüksekliği ile birlikte miyokard infarktüsüne doğru ilerleme görülebilir. Tip 2 Kounis sendromunda ise altta yatan koroner kalp hastalığı vardır. Allerjik reaksiyon, miyokard infarktüsü ile sonuçlanacak plak erozyonu ve rüptüre olaylarını kolaylaştırmaktadır. Kounis sendromu düşünülen hastaların tedavi ve izleminde allerji uzmanı ile işbirliği yapılması önemlidir. Tanı konulmuş bir allerjik hastalığı ve koroner hastalığı olan hastalar sadece kardiyoloji uzmanı değil, aynı zamanda allerji uzmanı tarafından da takip edilmelidir. Bu durum özellikle gıda allerjisi ya da arı venom allerjisi olup, anafilaksi riski yüksek olan hastalarda önemlidir. Günlük pratikte kardiyovasküler hastalıklarla uğraşan hekimlerin, Kounis sendromu hakkında bilgilerinin olması, tanı ve tedavide yeni yaklaşımların kazanımı açısından önemli olacaktır.

Anahtar Kelimeler: İlaç aşırı duyarlığı; miyokard iskemisi; anafilaksi; mast hücreleri

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The most extensive field of research in the last few years are allergy and immunology, and each passing day continues to bring more revelations to these scientific fields. Aside from their classical clinical appearance, they are also invaluable in a number of illness pathogenesis. One of these is acute coronary disease. Articles with supporting evidence that mast cell activation and acute coronary related states are increasing.

HISTORY

In 1991, Kounis and Zavras first defined a relationship between inflammatory mediators caused by allergic reactions and classic angina pectoris,[1] where chest pains and allergic reactions were dual symptoms, and this was called "allergic angina syndrome". Then when case results were myocardial infarction of the angina, this was called "allergic myocardial syndrome".[2] Later on, in 1995 Constantinides put forward a physiopathologic argument stating that the mediators released during allergic reactions can cause defects in the atheroma plaques.[3] In 1998, Braunwald defined a mechanism that histamine and the leukotriene caused vasospastic angina by the effects on the coronary arteries.[4]

CLASSIFICATIONS

Today, this syndrome is classed under two sub-groups, "type 1" and "type 2".[5] Patients in the "type 1" sub- group have normal coronary arteries; in addition to this they carry no risk of coronary artery diseases. These patients' clinical courses are divided into two. First, the patient experiences coronary vasospasms and angina but their cardiac enzyme and troponin levels follow a normal range. The second clinical course is of a more serious nature, coronary vasospasms not only cause angina but they lead to the possibility of acute myocardial infarction by the increase of cardiac enzymes and troponin levels.

Patients in the "type 2" sub- group show findings of atheromatous coronary illness. In relation to the allergic reactions these patients suffer, plaque erosions and ruptures cause acute myocardial infarctions.

PHYSIOPATHOLOGY

CARDIAC MAST CELLS

Type 1 mast cells, which can be found in a number of tissues and organs of the organism, play an important role in hypersensitivity reactions and allergic inflammations. The heart muscle and the vascular wall are among the tissues where mast cells are localized. The interstitial areas within myocytes, coronary vessels and nerve peripheries are the main areas of localization for mast cells within the heart.[6] The close vicinity of mast cells to vessels and nerves are important in the development of various heart diseases (this will be further discussed in detail).

Mast cells can also be found within the heart tissue of healthy people, however, in pathological circumstances, especially around atherosclerotic plaques, with the rich granules from chymase and tryptase they localize in the adventitia.[7] Cardiac mast cells, with their synthesized and released mediators are not much different from other tissue mast cells.[6] The number of cardiac mast cells decreases with heart failure and cardiomyopathy.[8]

Other than their classical function, cardiac mast cells are also important in their role as part of the kidney renin-angiotensin system. Within the mast cell cytoplasm, angiotensin that is ready to be released angiotensin II and "renin angiotensin system gene" expressions have been used.[9]

THE EFFECTS OF CARDIAC MAST CELLS IN THE CARDIOVASCULAR SYSTEM

Alongside other inflammatory cells, mast cells also play a role in the emergence and development of atherosclerosis. A histopathologic study has shown that mast cells are found in abundance within the coronary arteries adventitia layer where there are ruptured atheroma plaques.[10] Damage or ruptures to the atheroma plaques usually occur in areas where there are a high number of inflammatory cells such as mast cells, T lymphocytes and macrophages. High numbers of mast cells are especi-

ally found around areas where there are unstable atheroma plaques.[10]

During anaphylaxis mast cells release neutral proteinases like histamine, tryptase, and chymase, pre-synthesized mediators like platelet activating factors (PAF) and a variety of arachidonic acid products like cytokines and chemokines. These damage the collagen tissue surrounding the lipid nucleus and, especially in Type 2 patients, cause the way for ruptures on the plaques sides.

Anaphylactic reactions, with the increase of anahphylatoxins (C3a, C5a) create a complementary activation. Receptors belonging to these are found on the surface of cardiac mast cells.[11] The degranulation of cardiac mast cells continues in the process. When the mediators that are released by mast cells are individually analysed, their role in hyperacute coronary events can be seen.

HISTAMINE

Since mast cells neighbour the sensory nerves in the coronary arteries, mast cell derived histamine causes an increase in the sensitivity of the nerve fibres and coronary artery spasms.[12] Alongside its coronary vasoconstrictor characteristic, histamine also causes platelet activation and thrombin, 5-hydroxytryptamine, and it potentiates also coagulation response by increasing adrenaline effects.[13] Histamine regulates both inflammatory cell activities like neutrophil, monocyte and eosinophils, and stimulate proinflammatory cytokine secretions of endothelial cells.[14] In acute stress situations the histamine and interleukin 6 (IL-6) caused by the cardiac mast cells activate the inflammatory mechanism in the coronary arteries.[15]

A newly discovered effect of histamine is that it stimulates the aortic endothelial cells and the vessels of the smooth muscle activations and tissue factor expression.[16] As it is known, tissue factor being the key enzyme in coagulation activation, it binds to activated factor VII during coagulation and causes factor X activation and thrombin formation. Tissue antigens levels and their activations are found high in plasma and atherectomy samples of patients with unstable angina.[17] This result indicates that tissue factor is effective in the activation and progression of acute coronary syndrome.

TRIPTASE/CHYMASE

Tryptase and chymase, by activating the metalloproteins like interstistial collagenase, gelatinase and stromelysin in the form of zymogens found in the atheroma plaques, play a role in plaque activation and rupture.[18]

Angiotensin II receptors are found in the coronary artery muscle cells. Chymase converts angiotensin I into angiotensin II. Hence, chymase, synergistically alongside histamine increases the force of local vasospasm in damaged coronary arteries.[19]

TUMOUR NECROSIS FACTOR-α

Another cytokine derived from mast cells is the tumour necrosis factor-α (TNF-α) which is a strong pro-inflammatory cytokine. It activates the inflammation period and enables the stable plaque to be easily damaged.[20] It also stimulates other pro-inflammatory cytokines (such as IL-6) release.

LEUKOTRIENES

They have strong vasoconstrictor characteristics. During the acute phase of unstable angina pectoris, an increase in the biosynthesis of leukotrienes can be observed.[21] In patients with acute coronary syndromes, the positive effects of administration of aspirin in the early phases of treatment can be explained like this.

THROMBOXANE

Just as it is a strong mediator in platelet aggregation, it also has vasoconstrictor effects.[22]

PLATELET ACTIVATING FACTOR

PAF, being it as a proadhesive molecule or as a cause of increasing the release of platelet and leukocyte mediators, causes acute ischemia.[23] In an experimental study PAF caused changes in S-T segments in favour of arrhythmia and myocardial ischemia.[23]

KNOWN FACTS ABOUT ALLERGIC AND ACUTE CORONARY EVENTS

Various mediators released in the course of allergic reactions can be found in high count in blood and urine samples from patients with non-atopic structured acute coronary syndrome. In these types of patients, histamine levels in blood samples were found to be twice as high as in normal cases.[24]

In comparison to healthy cases, patients with non-allergic myocardial infarctions blood sample have showed a higher level of thromboxane and leukotrienes.[25] In a study with similar patients, higher levels of IL-6 were found in coronary plaques and myocardial necrosis areas.[26]

Tryptase levels were also high in patients with ST segment depression in course with acute myocardial damage.[27] According to this data tryptase, it can be conceived that chronic inflammation activity due to atherosclerotic plaques can be a diagnostic identifier of asymptomatic coronary artery patients and help deduce unstable plaque characteristics.

There is evidence that indicates that mast cells not only immigrate to the lesion areas before the plaque is damaged or ruptures, they also degranulate before the coronary event.[28] This circumstance is not only limited to mast cells, but also includes other inflammatory cells such as macrophages and T lymphocytes.

In a patient who died two days after a coronary event, the mast cell count that infiltrated the atheromatous area was 200 times higher than the normal endothelial area samples taken from the same patient.[29] If it is thought that days, in fact weeks, are necessary to fill the mast cells with cytoplasmic secretion granules, active mast cells found in the atheroma plaque areas, as stated above, must settle in the lesion areas long before plaque rupture occurs.

In eight out of 11 patients with variant angina, blood samples taken from the heart during the time of chest pains showed significantly higher levels of histamine in comparison to healthy cases.[30]

In another study, arachidonic acid derivatives like leukotrien and thromboxane in patients, who were not allergic and with unstable angina pectoris, were determined at significantly higher levels than those in patients with stable angina pectoris.[31]

THE TARGET ORGAN OF ANAPHYLAXIS: THE HEART

It is known that one of the target organs of anaphylaxis is the heart. During an anaphylactic attack, systemic vasodilatation, decrease in the venous return, intravascular volume loss due to elevated vessel permeability and a decrease in coronary perfusion resulted from increased heart rate in turn result in myocardial ischemia or necrosis.[32]

In an experimental study supporting this notion, cardiac pulsation volume three minutes after the allergen injection decreased by 90% while arterial blood pressure levels showed an increase of 33% and the electrocardiogram taken at this time showed changes leaning towards myocardial ischemia.[33]

During severe allergic reactions, the circulating blood volume showed a decrease of 35% in the first ten minutes and severe vasodilatation resistant to epinephrine.[34] In answer to this reaction, the release of epinephrine-norepinephrine increases and the angiotensin system is activated.

Myocardial injury due to histamine materializes with four different histamine receptors: H 1 histamine receptors increase vessel permeability and coronary vasoconstriction. H 2 histamine receptors enable very low levels of expansion in the coronary arteries causing increased arterial beat pace and arterial and ventricular contractility. During the course of anaphylaxis, histamine attaches itself to the H 1 receptors and the L- arginine found in the endothelium cells is converted into nitric oxide (NO) which is a powerful vasodilator.[35] The increased production of NO causes the decrease in

the venous turn which in turn causes the expansion of vessels during anaphylaxis. Histamine shows efficacy on heart and systemic circulation by way of the H 3 receptors found in the sympathetic effecter nerves presynaptic end areas.[36] Additionally, the activation of these receptors suppresses the endogen norepinephrine increase expected with anaphylactic shock. The more recently discovered H 4 receptors, helps control the eosinophil chemotaxis of the mast cells and the release of IL-I6 from the lymphocytes.[37]

CLINICAL FINDINGS

"Kounis syndrome" as a new cause of coronary artery spasms, comes under classic data to explain allergic myocardial infarction and allergic anginas.[38] Other than chest pain, this syndrome also shows signs of dyspnea, palpitations, severe fatigue, hypotonia and in some cases bradycardia.

CLINICAL ASSOCIATION

The first case to be reported was the myocardial infarction during anaphylaxis due to an allergic reaction to penicillin in 1950.[39] The numbers of cases of acute coronary syndrome caused by sudden allergic reactions being reported are increasing.

However, as it is still a fairly new and different mechanism the frequency of this unity cannot be realistically assessed. In a study of 21 healthy voluntary patients, it was observed that within 60 seconds of the allergen being introduced 2 cases complained of chest pains and the analysis of the electrocardiographic findings showed changes leaning toward myocardial ischemia.[40] In a study conducted in Switzerland, throughout a time period of three years, 226 anaphylaxis cases were first presented with problems in the circulation system.[41]

A number of agents and clinical situations cause to Kounis syndrome have been identified. This data is summarised in Table 1. Drugs and bee stings are the most detected reasons. Onset acute allergic reactions caused by different reasons cause atheroma plaque damage or coronary artery spasms in patients with coronary artery disease or endothelium dysfunctions.

TABLE 1: Capable agents and clinical situations that causes of Kounis syndrome.

A. Allergic patients
Angioedema
Bronchial asthma
Urticaria
Food allergies
Serum disease
B. Drug reactions
Antibiotics
Anaesthetics
Radio contrast substances
Non-steroid anti-inflammatory drugs
Corticosteroids
C. Environmental exposure
Bee stings
Ant bites (fire ants)
Latex contact (natural rubber)

According to the results of the studies that take place in the literature, allergic patients with coronary syndrome are seen at more risk than non-atopic patients. When anti-Ig E antibodies are compared with platelets isolated from the blood of atopic patients, it shows that there is an increase and cluster of released histamine.[42] In healthy volunteers, the increase in thrombin concentrations parallels the increase and aggregation in the release of histamines in the platelets. The same result was found in cases with the isolated platelets.[43]

OUR EXPERIENCE (UNPUBLISHED CLINICAL DATA)

A 21-year-old patient was hospitalized to investigate the cause of intractable chronic urticaria. During the time of hospitalization, cefuroxim was prescribed with indication of a gingival infection. A half hour after the first dose of Cefuroxim given per orally, the patient experienced with severe chest pain and palpitation. Initial electrocardiographic examination was revealed acute inferior myocardial ischemia. He was immediately transferred to co-

ronary angiography unit to perform rescuer Percutaneous transluminal coronary angioplasty (PTCA). There was a thrombus lesion in left anterior descending coronary artery (LAD), which diminishing the lumen in 99%. After the thrombus aspired intravascular ultrasonographic examination was performed to expose the cause of thrombosis. A ruptured atherosclerotic plaque was determined at the site of thrombus in LAD. Operation completed without complication and medical treatment was started.

Angiography was repeated at fourth week, the only finding was irregularity at vessel wall in the site of previous lesion. The patient referred again to allergy clinic to resume etiological investigations which was considered for chronic urticaria. Allergy to house dust mite was determined by epidermal skin tests. The peripheral eosinophil count was 900 per mm^3. Other tests including serum biochemistry and autoantibody screenings were in normal ranges. The final diagnoses were chronic idiopathic urticaria and atopy (mite allergy). Antihistamine treatment and regular control visits were suggested.

CASES IN OUR COUNTRY

Some cases of Kounis syndrome have been reported in our country, one in 2007, a case who a 21 year old showed cardiogenic shock after being treated with intravenous penicillin.[44] Due to this picture an angiography was performed on this patient and all coronary arteries were found to be a normal.

A case report presented from Turkey shows that, 30 minutes into the treatment of amoxycilline/ clavulanic acid tablets, the 13 year old patient developed a condition of itchy and peeling skin, chest pains. Electrocardiographic evaluation during this period showed traces of myocardial ischemia and the transthoracic echocardiography showed hypokinesia in the inferior wall. The coronary angiograph of a patient similar to the one described above showed that the coronary arteries were normal.[45] In addition to the fact that amoxicillin specific IgE was found to be negative, the increasing level of serum tryptase supports the allergic etiology.

Another Kounis syndrome in Turkey reported a patient, 15 minutes after using sulbactam-ampicilline tablets suffered from a syncope attack and stated that myocardial ischemia indications were followed by the analysis of the electrocardiography, the coronary angiography showed multiple vessel disease.[46] Analysis in order to present allergic etiology, showed average and slightly positive degrees of ampicilline, penicilloyl V, cefaclor and amoxicillin specific IgE values.

Where these cases have been observed, in light of the symptoms discussed before, the first and the second cases can be classified as type 1, whereas the last case presented lesions in the coronary arteries so can be classified as type 2.

Six Kounis syndrome cases, those had previously been diagnosed within the last two years, were reported in 2009.[47] In this first Turkish case serial, age- range of patients ranged from 9 to 90, and coronary angiographies were performed; other than findings of non-critical atheromatic plaques in the 90 year old patient, all other cases were within normal limits.

One possible Kounis syndrome case is in Turkey is due to bee sting. Authors describe the acute myocardial infarction with ST- segment elevation after a bee sting case. However authors didn't exam any for allergic etiology of this case.[48]

TREATMENT AND PROGNOSIS

Acute period treatment does not change for patients with Kounis syndrome. They go through the same standard treatment protocol in the coronary intensive care units. There is no special or effective treatment for allergic angina but some drugs are preferred.

Recently, there has been evidence that apart from known mast cell stabilizers, such as sodium nedocromil and sodium chromoglycate, lodoxamide, flavanoids also suppress the release of basophilic and mast cell mediators.[49] Ig E, which is a

monoclonal antibody with Ig G1 structure, suppresses the degranulization of mast cells.[50] Again, in a similar study it has been shown that anti-IL-4R α antibodies suppress acute and severe allergic reactions.[51]

Mast cell induced thrombotic cases can be prevented by the above list of suppressors, a study showed that mast cell membranes were stabilized with dexamethasone and sodium chromoglycates, thus suppressing the inflammation and preventing future thrombotic events.[52] To prevent damage to the structure of atheroma plaques in the coronary arteries and rupture risks, mast cell degranulization can be alternatively treated.

Not only are the prognosis of patients in the type 1 group generally better than those of the type 2 group, both groups are changeable due to a number of different factors such as; severity of the allergic reaction at the start of the prognosis, the patients level of allergic sensitivity, other illnesses and the concentration and entry route of the allergen.

CONCLUSION AND SUGGESTIONS

In patients who are considered to have Kounis syndrome, follow up and long term treatment by allergist is important. Where patients have a known allergic illness, it is essential that both cardiologists and allergist should collaboratively work, especially during the follow up of cases pertaining to food and bee allergies, where the patient carries the risk of sudden severe allergic reactions (anaphylaxis).

Even though there are a limited number of diagnosed patients in a number of cases of myocardial ischemia due to decreased coronary blood flow, allergic etiology can be considered. Coronary vasospasm during a coronary angiography can occur because of an allergic reaction, limited to the organ, or unexplained sudden deaths can occur due to an allergic mechanism.

The circulatory blood defects that occur during severe allergic reactions can increase mortality. These kinds of severe reactions are generally developed due to drugs, food and venoms. Therefore, all patients with ischemic heart disease and atopic medical histories or allergic illnesses need to be accessed via *in vivo* or *in vitro* diagnostic methods. If allergy is defined to have a role in the etiology, it can lead to a successful treatment in ischemic heart disease and positive contributions on the prognosis.

It is important that physicians, who encounter patients with a variety of cardiovascular diseases, have knowledge and information about Kounis syndrome in their daily clinical practices, so that this knowledge will add a new vision into the physicians' choices in the diagnosis and treatment of ischemic heart disease and cerebrovascular diseases.

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