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Kounis Syndrome; An Allergic Blow Up The Coronaries; A Review on Pathogenesis, Diagnosis and Therapeutic Management

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ABSTRACT

Kounis syndrome is a hypersensitivity reaction that is caused by various allergic reactions induced by certain drugs, foods, environmental factors, and also the coincidental occurrence of acute allergic coronary syndrome including coronary spasm, myocardial infarction, and stent thrombosis. The first case of myocardial infarction with hypersensitivity allergic reaction was described 60years ago. Then, in 1991, Kounis and Zavras coined the term "syndrome of allergic angina" to define the illness, which includes chest pain and an allergic reaction, as well as clinical and laboratory findings of inflammatory mediators generated during acute allergic reactions. The main mechanism proposed by them was the vasospasm on coronary arteries. Allergic angina can develop into allergic myocardial infarction both together referred to as "Kounis Syndrome". That may include the activation of mast cells thereby the release of inflammatory mediators like histamine platelet-activating factors, proteases, and certain cytokines which may lead to a hypersensitivity reaction. This syndrome is associated with anaphylactic, anaphylactoid, hypersensitivity reactions. which mainly occur in males rather than females.

INTRODUCTION:

Kounis syndrome is a hypersensitivity reaction that is caused by various allergic reactions induced by certain drugs, foods, environmental factors, and also the coincidental occurrence of the acute allergic coronary syndrome including coronary spasm, myocardial infarction and stent thrombosis. Allergic angina can develop into allergic myocardial infarction both together referred to as "Kounis Syndrome ". That may include the activation of mast cells thereby the release of inflammatory mediators like histamine platelet-activating factors, proteases, and certain cytokines which may lead to hypersensitivity reaction [1-4]. This syndrome is associated with anaphylactic, anaphylactoid, hypersensitivity reactions [1]. It may also involve cerebral and mesenteric arteries [5-6]. Kounis syndrome can affect any age group but it is most vulnerable to age groups between 40 to 70[7]. There are three variants of Kounis syndrome, Kounis syndrome type 1 or allergic vasospastic angina, Kounis syndrome type 2 or allergic myocardial infarction, Kounis syndrome type 3 or allergic stent thrombosis [2].

It's a hypersensitivity reaction that occurs due to the activation of mast cells which are mainly present in the cardiac tissues which are mainly located in the coronary arteries [8,9]. The mechanism involved in the activation and deregulation involves immunoglobulin E, macrophages, T-lymphocytes [10-11]. Mast cells are activated by the inducible macrophage protein 1a, CD8 T activated by $CD169^{+}$ and activation and proliferation of mast cells by T cells. Activation of mast cells results in the release of pre-synthesized and newly produced inflammatory mediators like histamine, chemokines, platelet-activating factors, proteases and certain cytokines, prostacyclin, arachidonic acid products, tryptase, cathepsin D and these mediators have important cardiovascular activity and may lead to hypersensitivity reactions where the mediators are released into the systemic circulation by mast cells [12]. These mediators can cause coronary vasospasm, plaque formation, erosion, and rupture that may lead to myocardial infarction[7,13], and histamine that can induce constriction to the coronary arteries and dilation to the peripheral arteries results in a decrease in systemic blood pressure and platelet activation[14-16], thromboxane that can cause vasoconstriction to the coronary arteries[17], proteases can cause coronary atherosclerotic plaque erosion/rupture, tryptase cause fibrinogen degradation, cathepsin D can determine the coronary vasospasm and enhance the conversion of angiotensin 1 to angiotensin 2 which is major vasoconstricting agents[1]. In the case of myocardial ischemia, platelet-activating factors act as signaling units to activate the platelets and leukocytes to release leukotrienes or act as a direct vasoconstrictor [1].

TABLE 1: ACTIONS OF HISTAMINE

1. Potentiate the aggregatory response of agonist by activating platelets
2. Induce intimal thickening
3. Regulate the activity of monocytes, neutrophils, eosinophils
4. Tissue factor expression and activity
5. Generate P-selectin upregulation
6. Vasoconstriction

TRIGGERING FACTORS:

Kounis syndrome can be triggered by several factors like foods, drugs, environmental factors, coronary stents, and other potential factors include fruits, vegetables, shells, fish, and mushrooms. Any disease condition or any other substance or any factors that can produce IgE antibodies that can cause Kounis syndrome. Environmental factors like grass, metal, latex, poisons, nicotine dialysate, and bites of viper snakes and stings of Hymenoptera, black widow spider can cause Kounis syndrome. Drugs include analgesics, anti-inflammatory agents, antibiotics, antivirals, anesthetics, antifungal, glucocorticoids, antihistamines, proton pump inhibitors, antacids, antiplatelets, anti-neoplastic, oral contraceptives, neuromuscular blocker, thrombolytics, sympathomimetics, anticoagulants. Other conditions include idiopathic anaphylaxis, angioedema, exercise-induced anaphylaxis, eosinophilic granulomatosis with polyangiitis, asthma, scombroid syndrome, mastocytosis, and stent thrombosis can lead to Kounis syndrome. The most common triggering factors include antibiotics and insect bites approximately about 27.5% and 24% respectively [7,17].

CLASSIFICATION:

Kounis syndrome type 1 or hypersensitive vasospastic angina caused because of endothelial dysfunction where the coronary arteries are normal and clear and without any predisposing factors for coronary artery disease result in the release of acute inflammatory mediators that can cause coronary artery spasm without any increase in cardiac enzymes or the coronary artery spasm progressing to myocardial infarction with increase in the cardiac enzymes and troponins [2].

Kounis syndrome type 2or hypersensitive myocardial infarction, the coronary arteries are not normal and clear with inactive pre-disposing atheromatous disease results in the release of

acute inflammatory mediators that can either cause coronary artery spasm without any increase in the cardiac enzymes and troponins or along with plaque rupture and erosion expressed as acute myocardial infarction [2].

Kounis syndrome type 3 or allergic stent thrombosis occurs in patients with coronary artery stent thrombosis and also their aspirated thrombus specimens stained with hematoxylin-eosin and Giemsa shows the presence of eosinophils and mast cells. In this variant, the stents act as an allergen because they are metals made of nickel, chromium, titanium, manganese, and molybdenum that may cause allergic reactions [2].

TABLE 2: KOUNIS SYNDROME SUBTYPES

Variants	Pathophysiology
Type 1 variant	Patients had a clear and almost normal coronary artery and no risk factors for plaque formation (atherosclerosis) and coronary spasms can be caused by an acute release of inflammatory mediators either by an increase in the cardiac enzymes or without any increase in the cardiac enzyme.
Type 2 variant	In these, coronary arteries are not normal and clear and the patient with atherosclerosis and the inflammatory mediators can either induce coronary spasm with plaque rupture or erosion results in allergic myocardial infarction.
Type 3 variant	Components of the stent can cause hypersensitive reaction can induce thrombosis

Signs and symptoms:

Kounis syndrome is distinguished by the presence of coexisting signs and symptoms of cardiac disease and shows hypersensitivity, allergic reactions, anaphylactic reactions [7,17]. The signs and symptoms of cardiac issues differ depending upon the type of Kounis syndrome subtype: vasospastic angina/coronary artery spasm by type I variant, myocardial infarction by type 2 variant, stent thrombosis/restenosis by type 3 variant. Signs of Kounis syndrome include pallor, cold extremities, bradycardia, tachycardia, hypotension, vomiting, even cardiorespiratory arrest, and symptoms include chest discomfort, malaise, acute chest pain, palpitation, headache, nausea and difficulty in breathing. In the case of anaphylaxis, the hypersensitivity and allergic reactions range from mild to life-threatening reactions [7,17]. The

signs and symptoms vary depending on the type of the organs and sys involved: skin: -itching angioedema, respiratory: -wheeze, difficulty in breathing, cardiovascular: -hypotension, gastrointestinal: -vomiting, diarrhea, abdominal pain, neurological: -drowsiness, syncope [18]. Chest pain is the most common indication of Kounis syndrome (87%). Certain pathophysiological actions leading to hypotension up to shock result in the decreased cardiac blood output due to cardiac contractility deficit, and in severe cases, acute pulmonary edema can occur [17].

TABLE 3: SEVERITY SCORE SCALE WHEN SUDDEN HYPERSENSITIVE REACTION OCCURS.

Score	Clinical signs and symptoms
I	Mucocutaneous signs, angioedema, urticaria, erythema
II	Mucocutaneous signs, tachycardia, difficulty in breathing, gastrointestinal disturbance
II	Life-threatening visceral signs, cardiac collapse, tachycardia, bradycardia, arrhythmia, bronchospasm, gastrointestinal disturbance
IV	Heart attack/cardiac arrest

Diagnosis:

Kounis syndrome can be diagnosed by identifying the clinical manifestation, laboratory values, electrocardiographic, echocardiographic, and angiographic findings. It is mandatory to understand the clinical history of patients, triggering factors, past response, the time interval between the exposure, and signs and symptoms. It is identified that the patients with diabetes mellitus, smoking, hyperlipidemia, hypertension, and a history of allergic reaction developed Kounis syndrome [7].

❖ **Electrocardiography**: In the case of kounis syndrome electrocardiography shows alternation in the ST segments as elevation or depression, changes in T wave include flattening or inversion to a certain condition like heart block, atrial fibrillation, bradycardia and tachycardia and ventricular fibrillation [17], Prolongation in QT segment or QRS complex can also occur [17]. ST-segment elevation indicates the most common alternation in

electrocardiography findings [7]. Any electrocardiography changes show any digitalis intoxication may be attributed to Kounis syndrome [19].

❖ **Echocardiography**: It's used to evaluate the heart contractility, cardiac chamber dilation, also indicating the artery wall motion abnormalities [7,17].

❖ **Chest X-ray**: Shows cardiomegaly (enlarged heart) [20].

❖ **Dynamic (CE-CMRI)**: Finds the involvement of cardiac in Kounis syndrome type 1[20].

❖ **Myocardial (SPECT)**: Mainly shows type 1 Kounis syndrome and showing myocardial ischemia if the angiography results are negative [20,21].

❖ **Laboratory tests**: Measurement of inflammatory mediators like histamine, cardiac enzymes, troponins, tryptase helps in estimation [7,17]. The mast cell is the main source of tryptase which is found in a negligible amount in basophils (0.04pg/basophil) these mediators are short-lived and have a half-life of about 90 minutes [22]. Histamines are also mainly released from mast cells and the specimen should be collected immediately because they are rapid and short-lived for about 8 min after an allergic reaction, so the blood sample should be collected after the onset of chest pain and before the intake of analgesics, especially morphine. All patients with acute hypersensitivity reactions should have their troponin levels checked [23].

TABLE 4: LABORATORY FINDINGS/SIGNS

Electrocardiographic	**Laboratory findings**
– Flattening/inversion of T wave – ST-segment elevation/depression – OT segment prolongation – Atrial fibrillation – Ventricular fibrillation – Atrioventricular block – Sinus tachycardia/bradycardia	– Troponin level increased – Increased cardiac enzymes mainly creatinine phosphokinase-MB – Eosinophilia – Change in heart size/shape – Subendocardial gadolinium concentration – Single Photon Emission Computed Tomography (detects ischemia)

MANAGEMENT:

Treatments of Kounis syndrome include management of both cardiac issues and allergic reactions. Management is based on the type of Kounis syndrome subtype. Treatment should be assigned based on the patient's cardiovascular risk factors, cardiac structure, and functional status and also based on the suspected triggering factors and the patient's clinical history and time between the exposure and cardiac signs and symptoms.

In the case of type 1 variant, the treatment of allergic reaction may reduce the symptoms. By administration of hydrocortisone (1-2 mg/kg/IV) and antihistamines such as diphenhydramine (1-2 mg/kg) and ranitidine (1 mg/kg) are adequate, administration of vasodilators such as calcium channel blockers and nitrates that reduce the vasospasm induced by hypersensitivity reactions, use of nitroglycerine may induce tachycardia and hypotension which will further complicate the allergic reactions and more uncommon allergic reaction to nitroglycerine like contact dermatitis and urticaria can occur while taking transdermal and oral nitroglycerine so to avoid these condition administration of nitroglycerine through intravenous or sublingual will be safer. Administration of antihistamines can induce hypotension so these drugs should be given very slowly [24].

In the case of type 2 variant, the patient should start with an acute coronary protocol, along with corticosteroids and antihistamines, vasodilators and calcium channel blockers can also be considered. Due to the unopposed activity of α-adrenergic receptors, the β blockers can inflate the coronary spasm. Epinephrine can be used for anaphylaxis but it can irritate the ischemia thereby worsening the coronary spasm, in severe conditions sulfur-free epinephrine is intravenously given as it has a faster onset of action. Epinephrine is ineffective in patients who have a history of ischemic heart disease who receive β-blockers, in this condition glucagon infusion can be given (1-5mg iv over 5 min). Methoxamine can be given to patients who are not responding to epinephrine. Patients with kounis syndrome opioids like morphine, codeine, should be well aware that they can cause mast cell degranulation and may provoke an allergic reaction. Paracetamol is not recommended because it decreases the cardiac output and results in hypotension [25].

In case of type 3 variant treatment begin with current myocardial infarction along with the sudden aspiration of in stent thrombosis also conduct the histologic examination of the aspirated materials and staining of eosinophils should be done. After the stent implantation, the patient may develop allergic reactions, and receiving antihistamines together with

corticosteroids and mast cell stabilizers can reduce the symptoms, if these symptoms prolong then identify the main cause by patch or prick skin test should find out and desensitization measures should be applied if these measures fail then stent extraction are unavoidable [26].

Understanding of Kounis syndrome:

The first case of myocardial infarction with hypersensitivity allergic reaction was described 60years ago [27]. In 1950 the first case reported was a 49year old male patient diagnosed with myocardial infarction and urticaria treated with 300,000unit of penicillin in oil for 4 days then the patient was treated with dicumarol, papaverine, morphine later it is identified that the patient had prolonged allergic to penicillin. Then, in 1991, Kounis and Zavras coined the term "syndrome of allergic angina" to define the illness, which includes chest pain and an allergic reaction, as well as clinical and laboratory findings of inflammatory mediators generated during acute allergic reactions. The main mechanism proposed by them was the vasospasm on coronary arteries. In 1995, Kovanen et al experimented with 20 patients who died with myocardial infarction, and they found that the degree of mast cell degranulation is higher at the site of erosion and rupture when compared with the unaffected areas. In 1998, Braunwald found that coronary vasospasm can be caused by an allergic reaction due to inflammatory mediators like histamine and leukotrienes acting on the coronary vascular smooth muscles. After the acceptance of Kounis syndrome as a cause of acute coronary artery spasm and acute coronary syndrome, many case reports are published. In 2005 Nicholas G Kounis reported the first review about the disease, and in 2006 it was found the relationship between the drug provoking coronary stent thrombosis and Kounis syndrome. In 2009 the first report of literature about Kounis syndrome in children was published. Nearly about 300 cases of Kounis syndrome have been reported in the literature, often the true number of cases is unknown and many of them are misdiagnosed.

Challenges in treatment:

Management for Kounis syndrome is very challenging because it needs to consider both the allergic reactions, and cardiac symptoms at the same time, and the drugs given for these conditions may provoke the allergic reaction and the heart functions and may worsen the patient's condition and may often lead to death. Consideration in the management include[s] [28].

❖ Administration of Aspirin in patients with Kounis syndrome is unknown because it has the potential risk of provoking the ongoing anaphylaxis reaction as it may provide arachidonic acid into the leukotriene pathway leading to increased production of leukotrienes.

❖ Intake of nitroglycerine can cause hypotension and tachycardia which may worsen the allergic reaction so it is safe to administer intravenously and sublingually.

❖ β-blockers can cause vasospasm because of their α-adrenergic effects that may affect the effects of epinephrine.

❖ Calcium channel blockers, the initial anti-ischemic drug for the patient with Kounis syndrome.

❖ Opioids such as morphine and meperidine should be used with caution since they can trigger mast cell degranulation and exacerbate allergic reactions.

❖ Corticosteroids are mainly used for the management of allergic reactions and a study stated that the use of corticosteroids in patients with myocardial infraction (MI) are safe.

❖ Although epinephrine preparations include sulfite, which can cause allergies in sensitive persons, administration of epinephrine is not safe. It is used to treat anaphylaxis; however, it can cause coronary vasospasm and arrhythmias in people with kounis syndrome. In people using -blockers, it can also cause cardiac vasospasm.

❖ Mast cell stabilizers can be given to patients with kounis syndrome.

❖ Administration of non-steroidal anti-inflammatory drugs in Kounis syndrome is not considered as there is evidence of drug-induced anaphylaxis reactions.

❖ Rocuronium and Cisatracurium are used along with general anesthesia, as they can induce severe anaphylactic reactions and it may cause Kounis syndrome in patients with cardiac symptoms [29].

Mast cell mediators in coronary circulation:

Histamine has an important effect on the cardiac tissues, acts on H_1 receptors on the vascular smooth muscles thereby dilates the coronary arteries, it decreases the aortic pressure that leads to baroreceptor mediated tachycardia, also causes arrhythmias. Vasospastic angina reduces coronary blood flow and causes significant coronary spasms in people with cardiac symptoms. Formation of thrombus by histamine results in increased tissue factor expression in endothelial cells and smooth muscles [30-32].

Platelet-activating factors can cause a decrease in coronary blood flow, and direct effect on arrhythmias [33]. It may also involve the instability of atherosclerotic plaques and plaque

rupture by inducing platelet aggregation and release of lytic enzymes by macrophages [34]. Causes peripheral vasodilation as well [35].

Cysteinyl leukotrienes (leukotrienes D4) via intravenous/intra-coronary may lead to a sudden increase in coronary vascular resistance and a decrease in the coronary blood flow [36]. Thromboxane and prostaglandin D2 can cause vasoconstriction [37].

Anaphylaxis:

The world allergy organization had developed and published anaphylactic guidelines based on the cases from 2010-2014, contains the number of protocols for operative anaphylaxis, and recommended following any one of these [38].

The first-line treatment for anaphylaxis is a prompt injection of adrenaline, which has a beneficial effect on the cardiovascular and respiratory system, it also suppresses the further release of mast cell mediators and basophils during the anaphylaxis reaction via β_2 adrenergic receptors [39,40]. IV fluids/crystalloids can be used to compensate for the intravascular loss of up to 35% of the volume that leaks into the extravascular space within minutes [41].Antihistamines (diphenhydramine 1-2 mg/kg & ranitidine 1 mg/kg) and hydrocortisone 1-2 mg/kg are effective treatments for people with moderate anaphylaxis and type 1 variation [40,42].Continuous infusion of vasopressors is used for the management of refractory anaphylaxis, and in addition vasopressin, glucagon, atropine, methylene blue can also be used for refractory cases [43].

ACUTE CORONARY SYNDROME:

Kounis syndrome is a hypersensitivity reaction with a coincidental occurrence of acute allergic coronary syndrome. The treatment for the acute coronary syndrome should be based on the guidelines.

Patients with ST-elevation myocardial infarction mainly focus on conducting an angiogram, providing further management based on the findings. fibrinolytic streptokinase is a major risk for Kounis syndrome. Anaphylaxis guidelines recommend the use of 100% oxygen, but regular use of oxygen in myocardial infarctions shows an increased mortality rate, oxygen should be titrated to normoxia [44]. Nitroglycerine is used for ischemic conditions but it may worsen the hypotension so should be given with care [28]. The use of β-blockers reduces the beneficial effect of adrenaline (epinephrine) so extreme care should be given while

administering these agents, glucagon can be used for anaphylaxis with those who are taking β-blockers [28,45]. Calcium channel blockers and nitrates are considered as the beneficial treatment for the patient with hypersensitivity induced coronary spasm [17]. Aspirin and Non-Steroidal Anti Inflammatory drugs should be avoided because they can influence the pathogenesis of anaphylaxis through inhibition of cyclooxygenase and also by releasing arachidonic acid into the leukotriene pathway producing more inflammatory mediators [17].In the case of type 3 variant treatment involves Intra stent thrombus aspiration along with the treatment of Acute Coronary syndrome.

CONCLUSION:

Kounis syndrome is a hypersensitivity reaction and is associated with acute allergic coronary syndrome including coronary spasm, myocardial infarction, and stent thrombosis. which mainly affects the age group between 40-70 and mainly occurs in male than females. In this condition, the patients have to face both symptoms of an anaphylactic reaction and cardiac symptom, so immediate diagnosis should be done to decide the management for the condition more often the treatment for Kounis syndrome is challenging because the treatment for both the anaphylactic reaction and cardiac symptoms may lead to worsening other condition, therefore, the treatment should be given with caution and exactly it means that optimal treatment for Kounis syndrome is unknown. Treatment should be given only after the close evaluation of signs and symptoms, laboratory findings, patient's cardiac and allergic history. The agents that stop the mast cell degranulation may be beneficial for Kounis syndrome.

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