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A review on Kounis syndrome in Pathophysiology, allergens, advanced diagnosis and treatment protocol

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ABSTRACT: Following an allergic reaction, the fast onset of chest discomfort and other cardiovascular symptoms is known as Kounis syndrome, a distinct medical illness. It's also known as allergic myocardial infarction or allergic angina. The inflammatory process that initiates this condition involves mast cell activation and the subsequent release of several mediators, which may result in a coronary artery spasm or plaque rupture. Numerous allergens, such as foods, medicines, insect stings, and environmental exposure, can cause Kounis syndrome. This presentation provides an overview of the pathophysiology, clinical presentation, diagnostic criteria, of Kounis syndrome. Diagnosing the condition is challenging due to its wide range of clinical symptoms and high index of suspicion. Management requires early identification and treatment of the underlying allergic trigger in addition to conventional cardiac care techniques. The goal of this study is to increase the understanding of Kounis syndrome among medical professionals so that early diagnosis and efficient treatment may be provided, ultimately leading to better patient outcomes. Further research is needed to better understand this unique and possibly lethal illness, as well as to develop diagnostic standards, treatment strategies, and potential prevention measures.

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INTRODUCTION:

A set of symptoms known as unstable vasospastic or non-vasospastic angina resulting from an allergic reaction characterizes Kounis syndrome [1]. It was initially defined as a combination of an allergic reaction, an anaphylactic or anaphylactoid reaction, coronary artery spasm, or even myocardial infarction by Kounis and Zavras in 1991 [2]. It has been demonstrated that patients' plasma exhibiting acute coronary syndromes has higher levels of inflammatory mediators, including neutrophil and monocyte adhesion molecules [3]. An acute, systemic hypersensitivity reaction known as anaphylaxis is brought on by the quick release of mediators from mast cells and basophils via IgE. The accidental connection of these two separate diseases, coupled with clinical and biochemical evidence of

angina pectoris resulting from inflammatory mediators released after an allergic assault, is known as Kounis syndrome. The condition known as "allergic myocardial infarction" can develop from allergic angina to acute myocardial infarction. It has been noted that Kounis syndrome can be caused by a number of factors. It has been determined to be a hypersensitive coronary disorder brought on by a number of illnesses, medications, foods, exposure to the environment, and coronary stents. This syndrome is linked to allergic, hypersensitive, anaphylactic, and anaphylactoid reactions [4]. The three documented forms of this illness to date are vasospastic allergic angina, allergic myocardial infarction, and stent thrombosis with an obstructing thrombus infiltrated by eosinophils and/or mast cells. It affects the cerebral and mesenteric arteries in addition to the coronary arteries. Its etiology continues to develop, as do its manifestations [5]. Kounis syndrome is a common illness that serves as a great example of a natural paradigm and a natural experiment in the final trigger pathway linked to instances of plaque rupture and coronary artery spasm [6]. Kounis syndrome appears to be a clinical entity that is rarely detected rather than an uncommon disease. Research has shown that the same mediators secreted from the same inflammatory cells are also present in acute coronary events that do not have an allergic cause [7]. These cells not only reside in the area of the plaque that is causing erosion or rupture, but they also secrete their contents shortly before a coronary event occurs [8]. When allergic symptoms appear suddenly, along with chest pain, one should be suspicious about Kounis syndrome [9]. Since the evaluation and treatment must take into account both cardiac and allergy disorders at the same time, this is not an easy scenario, and both diagnosis and management may be challenging [10].

PATHOPHYSIOLOGY:

The primary inflammatory cells implicated in the development of Kounis syndrome are mast cells, which engage in multidirectional stimulation interactions with T-lymphocytes and macrophages. The activation cascade also involves a fraction of platelets that have FCγRI, FCγTII, FCεRI, and FCεRII receptors [11]. Mast cells originate as mononuclear cell precursors from the bone marrow and circulate as mast cell precursors with stem cell factor-binding KIT receptors on their surface. One important cytokine that is necessary for mast cell formation, proliferation, adhesion, growth, and migration is stem cell factor. All human tissues, including the brain, are penetrated by mast cells; this is because IgE antibodies are unable to pass through the blood-brain barrier, protecting brain tissue from allergic reactions. They develop and differentiate inside the tissues. It takes days, or maybe weeks, to complete this. Conversely, basophils develop from granulocyte precursors in the bone marrow into mature cells that reach the circulation. They only penetrate the tissues in the latter stages of an allergic reaction. Approximately 500 secretory granules are formed and stored by mast cells. Many more, which are produced de novo, are released both locally and systemically when particular antigens react with IgE antibodies bound to mast cells, causing mast cell degranulation. This degranulation, which only happens in around 10 % of allergic people, is like a bag of corn "popping" until the contents spill out. Numerous human organs and systems, such as the heart and coronary arteries, have been connected to mast cells. When allergens crossing their comparison trigger receptor-bound immunoglobulin E (IgE) antibodies on the surface of mast cells or basophils, an allergic, hypersensitive, or anaphylactic reaction is initiated [12]. When the necessary number of bridging IgE antibodies hits the order of 2000 out of the maximal number of around 500,000 to 1,000,000 IgE antibodies on the cell surface, these cells degranulate and release their mediators [13]. It takes about 1000 bridges in total to cause mast cell degranulation. Recent research, however, shows that mast cells can be selectively triggered by nonallergic stimuli, frequently without degranulation and with the production of strong vasoactive substances [14]. Mast cells degranulate in response to allergy, hypersensitivity, or anaphylaxis, releasing a range of immediately created and stored inflammatory mediators both locally and throughout the body [15]. These comprise: growth factors, peptides, proteoglycanes, neutral proteases (chymase, tryptase, cathepsin-D), chemokines, biogenic amines (like histamine), arachidonic acid products (like leukotrienes, thromboxane, prostacyclin, PAF, and tumor necrosis factor-α) (TNF-α). These mediators mostly have significant effects on the cardiovascular system. In addition to inducing tissue factor expression and platelet activation, histamine also causes coronary vasoconstriction [16]. The three neutral proteases have the ability to trigger matrix metalloproteinases, which in turn can cause erosion and rupture of plaque and break down the collagen cap [17]. Thromboxane is a powerful

mediator of platelet aggregation with vasoconstricting capabilities [18], and PAF functions as a direct vasoconstrictor or a proadhesive signaling molecule in myocardial ischemia by activating leukocytes and platelets to generate leukotrienes [19]. The primary clinical manifestations of Kounis syndrome are either coronary artery spasm, which may lead to acute myocardial damage, or immediate coronary thrombosis, which is brought on by all of these pre-formed and immediately synthesized inflammatory mediators that are released locally and transfer into the systemic circulation.

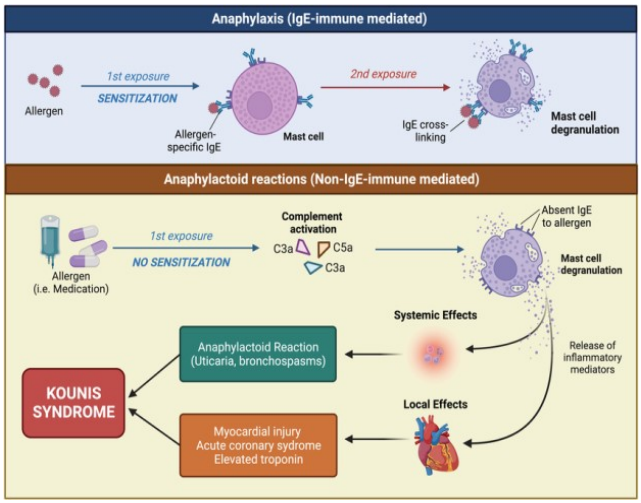

Fig 1. Pathophysiology of Anaphylaxis (IgE-Immune Mediated) and Anaphylactoid Reactions (Non-IgE-Immune Mediated).

Fig 1 shows how allergic reactions might result in heart-related conditions like Kounis syndrome. Upon first encountering an allergen, the body generates antibodies that attach to mast cells, resulting in IgE-mediated anaphylaxis. When the allergen is exposed again, it attaches itself to these antibodies and causes mast cells to release inflammatory chemicals. Certain allergens, such as chemicals, can directly stimulate the immune system in non-IgE-mediated reactions, resulting in the rapid release of these medications from mast cells. Both pathways can impact the heart, causing symptoms including bronchospasms and hives, as well as high cardiac enzyme levels, heart attacks, and chest pain - all of which are hallmarks of Kounis syndrome.

ALLERGENS:

An evaluation of additional food, insect, and environmental allergies should be included in an allergy work-up. To find the culprit, meal challenges and skin testing could be helpful.

FOOD ALLERGY:

An accurate past is essential. The prick test for food allergies has a 50 % false-positive rate. At almost 95 %, sensitivity is fairly high. A positive skin prick test for suspected food almost validates the etiologic diagnosis of anaphylaxis in the presence of a required history [20]. When a food is tested on the skin and comes back negative, it is ruled out as the cause of anaphylaxis. Radioallergosorbent testing (RAST) can identify allergen-specific IgE if a skin test is unsatisfactory or unclear. Skin tests are typically more sensitive than blood tests. A single-blind or double-blind food challenge administered by a qualified clinician may be necessary for ultimate confirmation; this method is still the gold standard for diagnosing food allergies.

DRUG ALLERGY:

Numerous medications, biological agents, hormones, and dyes can cause systemic symptoms mediated by IgE that result in anaphylaxis. Tetracycline, NSAIDs, sulfa, and penicillin are the most commonly used medications. Once more, historical evidence is crucial in linking a medication to anaphylaxis. With the exception of penicillin, the majority of medications lack a standardized skin test or blood test (RAST). It is possible for specific IgE to react with main and/or minor penicillin metabolite determinants. IgE antibodies specific to key determinants can only be detected by blood tests (RAST testing). The most dangerous penicillin-related anaphylactic reaction, however, is secondary to IgE, which targets the minute determinants that RAST testing is unable to identify. The diagnosis is typically clinical [21].

STINGING INSECT HYPERSENSITIVITY:

A skin test should be performed to confirm the diagnosis if the clinical history is significant. RAST testing for stinging insect hypersensitivity is offered if the skin test is negative but the clinical history is consistent with this diagnosis [22]. Anaphylaxis caused by stinging insects should always be diagnosed with certainty since desensitization is highly effective (approximately 98 %) and highly recommended.

DIAGNOSIS:

Kounis syndrome should be identified in patients with systemic allergic reactions linked to clinical, laboratory, and electrocardiographic findings of acute myocardial ischemia. Thus far, Kounis syndrome has been documented in three different forms [23].

Type 1 variant includes individuals who do not have a history of coronary artery disease and who have normal coronary arteries. In these patients, an acute release of inflammatory mediators may cause either an acute myocardial infarction with elevated cardiac enzymes and troponins or an acute coronary spasm without these abnormalities [1].

Type 2 variant comprises individuals who have pre-existing atheromatous lesions that are quiescent but are the culprit; in some patients, the sudden release of inflammatory mediators can cause either plaque erosion or rupture that manifests as an acute myocardial infarction or coronary artery spasm with normal cardiac enzymes and troponins [1].

Type 3 variants include individuals with coronary thrombosis (including stent thrombosis), where mast cells and eosinophils are seen in aspirated thrombus specimens stained with Giemsa and hematoxylin-eosin, respectively [1].

Actions taken when the syndrome is suspected:

***Clinical and Electrocardiographic features*:**

All of the signs and symptoms of an allergy and myocardial infarction, such as pallor, diaphoresis, hypotension, bradycardia or tachycardia, shortness of breath, nausea, difficulty swallowing, abdominal pain, numbness, vomiting, syncope, pruritus, urticaria, and chest pain, can also be signs of Kounis syndrome. The diagnosis of Kounis syndrome relies heavily on electrocardiography, clinical history, and biochemical markers. The most frequently observed electrocardiographic results are ST elevations in the anterior or inferior leads; however, an ECG may also be normal or just exhibit some general ST-T wave abnormalities. Individuals with Kounis syndrome frequently have angiographically normal coronary arteries and typically present with inferior wall myocardial ischemia or infarction. For unknown reasons, the most common location of coronary vasospasm is the right coronary artery.

Laboratory tests:

These tests - cardiac enzymes, blood count, cholesterol levels, and D-dimer—are used to evaluate cardiac damage and are typically ordered for patients with ACS. On the other hand, they are used to demonstrate a potential allergic reaction and include measures for tryptase, histamine, arachidonic acid products, interleukins, tumor necrosis factor (TNF), complement, eosinophilia, total IgE, and specific IgE. The guidelines include measuring total IgE, complement, histamine, tryptase, and eosinophils. The likelihood of a previous allergic reaction is not completely eliminated by these measures. Tryptase concentration, with a sensitivity of 73 % and a specificity of 98 %, is the most helpful criteria for diagnosing anaphylaxis, according to the Spanish Galaxia guide. Furthermore, if the parameter is assessed repeatedly, these percentages rise. It is advised to make at least three decisions: when to begin medication therapy right away following the reaction; two hours after symptoms appear; and once more 24 h later. After the reaction, tryptase levels often return to normal six to nine hours later. Compared to plasma histamine, serum tryptase is a more useful indicator of mast cell activity [24]. This is due to the fact that tryptase has a 90 min half-life, which makes it easier to utilize, but histamine has a half-life of 60 minutes with a maximal peak that occurs 5 to 10 min after the reaction begins. It is also possible to measure the amount of methylhistamine in 24 h urine. Mast cell degranulation is not eliminated by the lack of particular IgE antibodies or by a general elevation in IgE since, in hypothesis, degranulation happens when IgE mediates the allergic response—which is not always the case. Other inflammatory markers that exhibit large elevations in acute myocardial infarction of non-allergic origin, such as leukotrienes and thromboxanes, are not able to distinguish such a condition from a conventional ischemic event.

Arteriography:

This method might be used to assess the coronary anatomy, administer intracoronary medication for vasospasm, or carry out angioplasty when necessary. Intracoronary ultrasonography should be used to detect occult coronary disease in patients in whom type II KS is suspected.

Vascular biopsy:

This method shows mast cell infiltration in the spasm site, the ruptured plaque, and the atheromatosis-prone areas [25]. Still, the results of the cardiac biopsy are usually normal

Kounis syndrome and Hypersensitivity myocarditis: a differential diagnosis:

It may be challenging to distinguish between hypersensitivity myocarditis and hypersensitivity coronary syndrome (also known as Kounis syndrome), despite the clinical and laboratory findings that have

Table 1. Treatment and follow up of acute coronary events [29].

Aspects	Details
Basis of Care (Acute Stage)	Supportive Measures: Ensuring the patient receives necessary support to stabilize their condition. This includes monitoring vital signs, providing medications, and other interventions as needed.
Oxygen	Additional Oxygen: Every patient experiencing acute coronary syndrome should receive supplemental oxygen to ensure adequate oxygenation of tissues and to help relieve cardiac workload.
Main Cause of Acute Coronary Syndrome	Vasospasm: The primary cause of acute coronary syndrome in Kounis syndrome is vasospasm, which is the sudden constriction of the blood vessels, reducing blood flow to the heart.
Treatment Regimens for Vasospasm	Calcium Channel Blockers: Medications that help relax and widen blood vessels by inhibiting calcium from entering the cells of the heart and blood vessel walls. Nitrates: Vasospasmolytic drugs that help dilate blood vessels, increasing blood flow and oxygen to the heart muscle.
Guidelines for Acute Coronary Syndrome	Current Guidelines: Adhere to the guidelines set forth by the American College of Cardiology Foundation and the American Heart Association for the management of acute coronary syndrome. These guidelines provide evidence-based recommendations for treatment protocols.
Usefulness of Common Drugs	Uncertain Effectiveness in Kounis Syndrome: The utility of common drugs such as β-blockers, heparin, aspirin, clopidogrel, and nitroglycerin is not well established in patients with Kounis syndrome due to the potential for exacerbating anaphylactic reactions.
Patient Assessment	Individual Assessment: Each patient should be evaluated on a case-by-case basis to determine the appropriate treatment regimen, considering their specific condition and response to medications.
Medication Administration	ICU Setting: If clinical evidence supports the use of common acute coronary syndrome medications, they should be administered in an intensive care unit (ICU) setting where the patient can be closely monitored for adverse reactions and effectiveness of the treatment.
Observation Period	Close Monitoring: Patients should be observed closely for at least 8 to 10 hours after medication administration to monitor for worsening symptoms or adverse reactions. Continuous monitoring allows for timely intervention if the patient's condition deteriorates.
Severe Left Ventricular Dysfunction Management	Diuretics: Medications that help reduce fluid overload in the body by promoting urine production, thereby decreasing the workload on the heart. Inotropic Drugs: Medications that strengthen heart contractions and improve cardiac output. Hemodynamic Support: In cases of severe left ventricular dysfunction, mechanical support such as intra-aortic balloon-pump counter pulsation may be necessary to assist the heart in pumping blood more effectively.

been reported. The etiology and symptomatology of these two clinical entities are identical; the first is an inflammatory disease that affects the cardiac conduction system and myocardium, and the second is the connection of acute coronary syndromes with conditions linked to mast cell activation [26]. Electrocardiographic, laboratory, and cardiac signs and symptoms may be identical. The presence of eosinophils, atypical lymphocytes, and large cells in cardiac biopsy in hypersensitivity myocarditis, as opposed to the normality of biopsy in Kounis syndrome, is the only distinction between these two hypersensitivity diseases. When hypersensitive myocarditis and the type I variation of Kounis syndrome are present, coronary angiography reveals a normal coronary angiogram; however, in the case of the type II variant of Kounis syndrome, the angiogram reveals coronary artery disease. The management of Kounis syndrome and hypersensitivity myocarditis involves the same medications, such as corticosteroids and histamine H1 and H2 blockers [27].

THERAPEUTIC MANAGEMENT:

For those who are hypersensitive, acute coronary syndromes resulting from allergic reactions are linked to notable morbidity and mortality rates. Early in the

patient's care, the inflammatory mediator-induced systemic allergic reaction has to be under control. However, because both cardiac and allergy symptoms must be treated at the same time, therapeutic management of Kounis syndrome is a difficult process. Medication used to treat allergic symptoms can exacerbate cardiac function, while medication used to treat cardiac signs can exacerbate allergies [28].

TREATMENT FOR ANAPHYLAXIS:

For the treatment of allergic responses, current anaphylaxis management guidelines should be followed to [30] Assessing the patient's respiration, circulation, airway, and degree of awareness right away is important. Lower extremities should be lifted and patients should be placed in the supine position. All anaphylactic patients with ongoing reactions, pre-existing hypoxemia, or cardiac dysfunction should get oxygen.

DISCUSSION:

As of right now, there are no clear treatment guidelines for patients with Kounis syndrome, and the majority of knowledge regarding this disease's management comes from individual case reports or case series. A recent assessment of the literature on cases of Kounis syndrome after beta-lactam antibiotic therapy was conducted by Ridella et al. According to this review, the majority of patients were treated with steroids (76 %), nitroglycerin (4 7%), H1 blockers (70 %), and H2 blockers (35 %). Only 23 % of the cases involved the use of epinephrine. About 18 % of the instances involved the use of aspirin. Overall, there were no recorded fatalities and a very acceptable response rate. Although there aren't enough examples to draw firm recommendations about the management of Kounis syndrome, the majority of medical professionals seem to steer clear of using both aspirin and adrenaline [39].

In hypersensitive individuals, acute coronary syndromes resulting from allergic reactions are linked to notable morbidity and mortality rates. Early in the patient's care, the inflammatory mediator-induced systemic allergic reaction has to be under control [40].

Before starting therapy with a medication that may cause allergies, like a beta-lactam antibiotic, all patients should have a thorough allergy profile examination. When a potentially allergenic drug is administered to young, healthy patients who do not have atherosclerotic risk factors and develop acute coronary syndrome (particularly inferior myocardial infarction), Kounis syndrome should be taken into consideration. When these patients are transferred to the cardiac catheterization laboratory, they require treatment with steroids, antihistamines, fluid resuscitation, oxygen, and antithrombotics [41]. Both coronary artery dilatation and allergic response suppression should be goals of treatment. Since vasospasm is the major mechanism, vasodilator medications, such as nitrates and calcium channel blockers, should be regarded as first-line therapy in young and previously healthy individuals. Patients with a type II variation should adhere to the Acute Coronary Syndrome regimen. After being released from the hospital, these individuals should follow up at cardiology and allergy clinics [41]. It is required to perform a complete cardiologic work-up, which includes an echocardiography, 12-lead ECG, and cardiac risk factor modification.

CONCLUSION:

Finally, a thorough summary of Kounis syndrome's pathogenesis, allergens, sophisticated diagnostic techniques, and management approaches has been given in this review. It is now clear that Kounis syndrome poses a serious challenge to clinical practice due to the complex interactions between allergic reactions and cardiovascular problems. The discovery of several triggers, from medications to external circumstances, emphasizes how crucial a comprehensive patient history and allergy testing are to the diagnosis process. Furthermore, the development of sophisticated diagnostic tools, such as imaging methods and cardiac biomarkers, has improved our capacity to identify and distinguish Kounis syndrome from other acute coronary syndromes, enabling timely and precise treatment. A multidisciplinary strategy combining emergency physicians, cardiologists, and allergists is crucial for care. Despite traditional cardiovascular therapies, the immediate use of anti-allergic drugs, such as corticosteroids and antihistamines, can attenuate allergic reactions and prevent future cardiac problems. Preventing recurring episodes also requires educating patients about allergy avoidance and possible hazards related to identifying triggers. Finding new allergens and creating focused treatments are two of the many obstacles that still need to be overcome in order to fully comprehend and treat Kounis syndrome. To improve outcomes and raise the standard of care for individuals with this complicated condition, further research is needed to clarify the underlying mechanisms and improve diagnostic and treatment approaches.

Table 2. Assessment and Initial Management.

Aspect	Details
Assessment and Initial Management	➢ Assess respiration, circulation, airway, and awareness. ➢ Place patient in supine position with legs elevated. ➢ Administer oxygen to patients with ongoing reactions, hypoxemia, or cardiac dysfunction
Intravenous Fluids [31]	➢ Adults: 1-2 liters normal saline at 5–10 ml/kg in the first 5 min ➢ Children: up to 30 ml/kg in the first hour ➢ Monitor closely in patients with chronic renal disease or congestive heart failure to avoid fluid overload
Antihistamines[32,33]	➢ H1 and H2 receptor blockers for symptoms of urticaria, angioedema, and itching. ➢ Use as second-line treatment after epinephrine Diphenhydramine: 25-50 mg (adults) or 1-2 mg/kg (children) parenterally Ranitidine: 50 mg diluted in 20 ml 5% dextrose (adults) or 12.5-50 mg (1 mg/kg for children) over 5 minutes IV. Cimetidine: 4 mg/kg IV (adults), no pediatric dose established.
Glucocorticosteroids [34-36]	➢ For severe or prolonged anaphylaxis, asthma history, or idiopathic anaphylaxis. ➢ May prevent recurrent/prolonged anaphylaxis ➢ IV Dose: 1.0-2.0 mg/kg/day every 6 h. ➢ Oral Dose: Prednisone 0.5 mg/kg for less severe cases
Epinephrine [37]	➢ Life-saving in anaphylaxis, but caution in acute coronary syndrome ➢ Preferred route: Intramuscular injection ➢ Dose: 0.2-0.5 mg (1:1000) IM into the thigh every 5-15 min ➢ IV epinephrine (1:10,000 to 1:100,000) in severe cases (e.g., cardiac arrest) ➢ Consider glucagon infusion for patients on β-blockers
Mast Cell Stabilizers [38]	➢ Stabilizers (e.g., sodium cromoglycate, ketotifen) may help reduce thrombotic events and allergic reactions. ➢ Use is based on case-specific considerations.

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