

Kounis Syndrome: A Comprehensive Review of Pathophysiology, Clinical Manifestations, Diagnostic Challenges, and Therapeutic Strategies

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ABSTRACT

Kounis syndrome, also known as allergic angina or allergic myocardial infarction, is a rare but potentially life-threatening condition characterized by the acute onset of chest pain, myocardial infarction, or sudden cardiac death in the setting of allergic or hypersensitivity reactions. The syndrome encompasses a spectrum of acute coronary syndromes triggered by various allergic insults, including medications, insect stings, food allergens, and environmental exposures. The pathophysiology involves the activation of mast cells and platelets, leading to coronary artery spasm, atheromatous plaque erosion or rupture, and subsequent myocardial ischemia or infarction. Diagnosis can be challenging due to the diverse clinical presentations and the need for a high index of suspicion. Management includes the identification and avoidance of triggers, along with the use of standard therapies for acute coronary syndromes. This review aims to provide a comprehensive overview of Kounis syndrome, focusing on its pathophysiology, clinical manifestations, diagnostic considerations, and therapeutic strategies.

KEYWORDS: angina, myocardial, infarction, allergy

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INTRODUCTION

Kounis syndrome, first described by Kounis and Zavras in 1991, represents a unique clinical entity that bridges the fields of allergy and cardiology. It is characterized by the development of acute coronary syndromes, including angina, myocardial infarction, or sudden cardiac death, in the setting of allergic or hypersensitivity reactions. The syndrome has gained recognition over the past few decades, reflecting an increased awareness of the complex interplay between allergic responses and cardiovascular pathology. The underlying pathophysiology involves the release of inflammatory mediators, such as histamine, tryptase, and leukotrienes, from activated mast cells and platelets, leading to coronary vasospasm, plaque destabilization, and thrombosis. The clinical presentation of Kounis syndrome can vary widely, ranging from mild chest discomfort to fulminant myocardial infarction, depending on the severity of the allergic reaction and the extent of coronary involvement. Diagnosis is challenging and often requires a high degree of

clinical suspicion, especially in patients without a history of coronary artery disease. 1,2,3

Management strategies include the identification and avoidance of triggers, along with the use of standard therapies for acute coronary syndromes, such as antiplatelet agents, anticoagulants, and coronary revascularization procedures. This review aims to provide a comprehensive overview of Kounis syndrome, focusing on its pathophysiology, clinical manifestations, diagnostic challenges, and therapeutic approaches, to enhance the understanding and management of this intriguing clinical entity.4,5

EPIDEMIOLOGY

Kounis syndrome, an increasingly recognized clinical entity, represents a unique intersection between allergic reactions and cardiovascular pathology. While exact epidemiological data on Kounis syndrome remain limited due to its relatively rare occurrence, several key aspects of its epidemiology have been elucidated through case reports, case series, and retrospective studies.6

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Incidence and Prevalence:

The exact incidence and prevalence of Kounis syndrome are challenging to determine due to its underdiagnosis and underreporting. However, the syndrome has been reported worldwide, with cases documented across various age groups and populations. The incidence may be higher in individuals with a history of allergic conditions, such as asthma, allergic rhinitis, or atopic dermatitis, as well as in those with a predisposition to cardiovascular disease.⁶

Age and Gender Distribution:

Kounis syndrome can occur at any age, from infants to the elderly, although it appears to be more common in adults. The mean age of presentation varies across studies but generally ranges from the fourth to sixth decade of life. There does not appear to be a significant gender predilection, with cases reported in both males and females.⁶

Seasonal Variation:

Some studies suggest a potential seasonal variation in the incidence of Kounis syndrome, with a higher number of cases reported during certain times of the year, particularly in association with seasonal allergens such as pollen. This observation highlights the role of environmental factors in triggering allergic reactions that can lead to Kounis syndrome.⁶

Underlying Allergic Triggers:

Various allergic triggers have been implicated in the development of Kounis syndrome, including medications (e.g., antibiotics, nonsteroidal anti-inflammatory drugs, contrast media), insect stings (e.g., bee venom, wasp venom), food allergens (e.g., nuts, shellfish, fruits), and environmental exposures (e.g., pollen, latex). The prevalence of specific triggers may vary based on geographical location, individual susceptibilities, and local allergen profiles.⁶

Association with Cardiovascular Risk Factors:

While Kounis syndrome can occur in individuals without significant cardiovascular risk factors, there is some evidence to suggest that certain risk factors, such as hypertension, diabetes, hyperlipidemia, and smoking, may predispose individuals to more severe manifestations of the syndrome. However, further research is needed to fully elucidate the relationship between cardiovascular risk factors and the development of Kounis syndrome.⁶

While Kounis syndrome remains a relatively rare and underrecognized condition, its epidemiology is characterized by a wide age range of presentation, potential seasonal variation, and association with various allergic triggers. Continued research efforts are needed to better understand the epidemiological patterns of Kounis syndrome and to improve its diagnosis, management, and outcomes.⁶

CLINICAL MANIFESTATIONS

Kounis syndrome, also known as allergic angina or allergic myocardial infarction, is a unique clinical entity characterized by the acute onset of chest pain, myocardial infarction, or

sudden cardiac death in the setting of allergic or hypersensitivity reactions. The syndrome encompasses a spectrum of acute coronary syndromes triggered by various allergic insults, including medications, insect stings, food allergens, and environmental exposures. The clinical manifestations of Kounis syndrome can vary widely depending on the severity of the allergic reaction, the underlying coronary artery disease, and individual patient factors.^{7,8}

Chest Pain:

The hallmark symptom of Kounis syndrome is chest pain, which can range from mild discomfort to severe, crushing pain typical of myocardial infarction. The chest pain is often described as retrosternal or precordial and may radiate to the neck, jaw, arms, or back. The onset of chest pain is typically sudden and may be accompanied by other symptoms such as shortness of breath, diaphoresis, and nausea.^{7,8}

Cardiovascular Symptoms:

In addition to chest pain, patients with Kounis syndrome may experience a variety of cardiovascular symptoms, including palpitations, dizziness, syncope, and signs of hemodynamic instability such as hypotension or shock. These symptoms are suggestive of acute myocardial ischemia or infarction and should prompt immediate medical evaluation and intervention.^{7,8}

Cutaneous Manifestations:

Allergic reactions associated with Kounis syndrome can often manifest with cutaneous symptoms, such as urticaria (hives), angioedema (swelling), erythema (redness), and pruritus (itching). These skin findings may precede or accompany the onset of cardiovascular symptoms and can provide important clues to the underlying allergic trigger.^{7,8}

Respiratory Symptoms:

In some cases, allergic reactions in Kounis syndrome can involve the respiratory system, leading to symptoms such as wheezing, dyspnea (shortness of breath), coughing, and bronchospasm. These respiratory symptoms may be indicative of underlying airway inflammation and should be promptly evaluated, especially in patients with a history of asthma or other respiratory conditions.^{7,8}

Gastrointestinal Symptoms:

Allergic reactions associated with Kounis syndrome can also affect the gastrointestinal system, leading to symptoms such as nausea, vomiting, abdominal pain, and diarrhea. These symptoms may be nonspecific but should be considered in the context of other allergic symptoms and cardiovascular manifestations.^{7,8}

Other Systemic Symptoms:

In severe cases of Kounis syndrome, systemic allergic reactions can lead to a cascade of inflammatory mediators and cytokines, resulting in a systemic inflammatory response known as anaphylaxis. Anaphylaxis is characterized by a constellation of symptoms, including hypotension, tachycardia, respiratory distress, and multisystem organ

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dysfunction, and represents a medical emergency requiring immediate intervention.^{7,8}

Kounis syndrome is characterized by a wide range of clinical manifestations, including chest pain, cardiovascular symptoms, cutaneous manifestations, respiratory symptoms, gastrointestinal symptoms, and systemic symptoms. Recognition of these diverse manifestations is critical for the timely diagnosis and management of Kounis syndrome, which requires a high index of suspicion, especially in patients with a history of allergic reactions or cardiovascular disease.^{9,10,11}

DIAGNOSIS

Kounis syndrome, also known as allergic angina or allergic myocardial infarction, presents a diagnostic challenge due to its variable clinical manifestations and the need for a high index of suspicion. The diagnosis of Kounis syndrome is primarily based on clinical findings, supported by laboratory tests, imaging studies, and cardiac investigations. A multidisciplinary approach involving allergists, cardiologists, and emergency physicians is crucial for accurate and timely diagnosis.^{11,12}

Clinical Evaluation:

The initial evaluation of patients suspected of having Kounis syndrome includes a detailed medical history, focusing on the presence of allergic reactions, cardiovascular risk factors, and prior cardiac events. A thorough physical examination is performed to assess for signs of allergic reactions, cardiovascular abnormalities, and systemic involvement.¹³

Electrocardiography (ECG):

An ECG is a crucial tool in the diagnosis of Kounis syndrome, as it can reveal characteristic changes indicative of myocardial ischemia or infarction. These changes may include ST-segment elevation, ST-segment depression, T-wave inversion, and arrhythmias. However, it is important to note that ECG findings may be normal or nonspecific in some cases of Kounis syndrome.¹⁴

Cardiac Biomarkers:

Cardiac biomarkers, such as troponins and creatine kinase-MB (CK-MB), are essential for the diagnosis of myocardial infarction in Kounis syndrome. Elevated levels of these biomarkers indicate myocardial injury and support the diagnosis of acute coronary syndrome. However, it is important to interpret these biomarkers in the context of the clinical presentation, as they can also be elevated in the setting of systemic allergic reactions.¹⁴

Allergy Testing:

Allergy testing, including skin prick tests and serum-specific IgE testing, can help identify the allergic trigger responsible for Kounis syndrome. However, the timing of allergy testing is crucial, as acute allergic reactions can transiently suppress the results. In some cases, a detailed history of allergic exposures may be sufficient to establish the diagnosis.¹⁴

Imaging Studies:

Imaging studies, such as echocardiography and coronary angiography, play a valuable role in the diagnosis and management of Kounis syndrome. Echocardiography can assess for structural abnormalities, ventricular function, and the presence of pericardial effusion. Coronary angiography is essential for evaluating the coronary arteries for vasospasm, thrombus formation, or atheromatous plaque rupture.¹⁵

Provocation Tests:

Provocation tests, such as the acetylcholine provocation test and the drug provocation test, can be used to induce coronary vasospasm in patients suspected of having Kounis syndrome. These tests are typically performed in a controlled setting under the supervision of an experienced physician and can help confirm the diagnosis of coronary artery spasm.¹⁶

The diagnosis of Kounis syndrome requires a comprehensive approach that integrates clinical findings, laboratory tests, imaging studies, and cardiac investigations. A high index of suspicion is crucial, especially in patients with a history of allergic reactions or cardiovascular disease, to ensure prompt diagnosis and appropriate management. Collaborative efforts between allergists, cardiologists, and emergency physicians are essential for the accurate diagnosis and optimal management of Kounis syndrome.¹⁴

TREATMENT

Kounis syndrome, characterized by allergic angina or allergic myocardial infarction, requires a multidisciplinary approach for optimal management. Treatment strategies aim to alleviate allergic symptoms, stabilize cardiovascular status, and prevent future episodes of Kounis syndrome. The management of Kounis syndrome includes pharmacological interventions, supportive care, and identification and avoidance of allergic triggers.¹⁶

Pharmacological Interventions:

1. **Antihistamines:** Histamine antagonists, such as cetirizine or diphenhydramine, can help relieve allergic symptoms and reduce the release of inflammatory mediators.¹⁶
2. **Corticosteroids:** Systemic corticosteroids, such as prednisone or methylprednisolone, may be used to suppress the inflammatory response and prevent further allergic reactions.¹⁶
3. **Bronchodilators:** In patients with respiratory symptoms, bronchodilators such as albuterol may be used to relieve bronchospasm and improve respiratory function.¹⁶
4. **Antiplatelet Agents:** Aspirin is commonly used in the acute management of Kounis syndrome to inhibit platelet aggregation and prevent thrombus formation.
5. **Nitroglycerin:** Nitroglycerin is a vasodilator that can help relieve chest pain and improve coronary blood flow in patients with Kounis syndrome.¹⁶

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6. Beta-Blockers: Beta-blockers may be used cautiously in patients with Kounis syndrome to reduce myocardial oxygen demand and prevent arrhythmias.¹⁶

Supportive Care:

1. Oxygen Therapy: Supplemental oxygen may be administered to patients with hypoxemia or respiratory distress to improve oxygenation and reduce myocardial ischemia.¹⁶
2. Fluid Resuscitation: In patients with hypotension or shock, intravenous fluids may be administered to maintain hemodynamic stability and improve tissue perfusion.¹⁶
3. Cardiac Monitoring: Continuous cardiac monitoring is essential to assess for arrhythmias, ST-segment changes, and other signs of myocardial ischemia or infarction.¹⁶

Identification and Avoidance of Allergic Triggers:

1. Allergen Avoidance: Identification and avoidance of allergic triggers, such as medications, insect stings, food allergens, and environmental exposures, are crucial to prevent future episodes of Kounis syndrome.¹⁶
2. Patient Education: Educating patients about their allergic triggers and how to avoid them can help reduce the risk of recurrent episodes of Kounis syndrome.¹⁶

Conclusion:

The management of Kounis syndrome involves a multidisciplinary approach that includes pharmacological interventions, supportive care, and identification and avoidance of allergic triggers. Early recognition and prompt treatment are essential to improve outcomes and prevent recurrent episodes of Kounis syndrome. Collaboration between allergists, cardiologists, and emergency physicians is crucial for the optimal management of this complex clinical entity.¹⁷

CONCLUSIONS

Kounis syndrome, characterized by allergic angina or allergic myocardial infarction, represents a unique clinical entity that highlights the complex interplay between allergic reactions and cardiovascular pathology. While Kounis syndrome remains a relatively rare and underrecognized condition, its incidence may be underestimated due to underdiagnosis and underreporting. The syndrome can occur in individuals of all ages and is triggered by a variety of allergic insults, including medications, insect stings, food allergens, and environmental exposures.

The clinical presentation of Kounis syndrome can vary widely, ranging from mild chest discomfort to fulminant myocardial infarction, and may involve a constellation of symptoms affecting the cardiovascular, cutaneous, respiratory, gastrointestinal, and systemic systems. The

diagnosis of Kounis syndrome requires a high index of suspicion and is based on clinical findings supported by laboratory tests, imaging studies, and cardiac investigations.

Management strategies for Kounis syndrome focus on alleviating allergic symptoms, stabilizing cardiovascular status, and preventing future episodes. Pharmacological interventions, including antihistamines, corticosteroids, antiplatelet agents, and nitroglycerin, are used to manage acute allergic reactions and improve coronary blood flow. Supportive care, including oxygen therapy, fluid resuscitation, and cardiac monitoring, is essential to maintain hemodynamic stability and prevent complications.

Identification and avoidance of allergic triggers are paramount in the management of Kounis syndrome to prevent recurrent episodes. Patient education plays a crucial role in empowering individuals to recognize and avoid their allergic triggers, thereby reducing the risk of future episodes.

In conclusion, Kounis syndrome is a complex and potentially life-threatening condition that requires a multidisciplinary approach for optimal management. Continued research efforts are needed to further elucidate the pathophysiology, epidemiology, and management of Kounis syndrome, with the ultimate goal of improving outcomes and quality of life for affected individuals.

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