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Allergic Myocardial Infarction: A Clinical Perspective on Kounis Syndrome

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ABSTRACT

Background: Kounis syndrome is defined as an acute coronary syndrome occurring in the setting of a hypersensitivity, allergenic, anaphylactic, or anaphylactoid reaction. The syndrome involves mast cell activation and the release of inflammatory mediators, leading to coronary vasospasm, plaque rupture, or thrombosis during allergic or anaphylactic reactions. It is an underdiagnosed life-threatening medical emergency. As a wide array of drugs, foods, environmental conditions such as Hymenoptera sting, and disease states may be associated with Kounis Syndrome, it is essential for clinicians to maintain a thorough understanding of its pathophysiology, clinical presentation, and associated risks. This article reviews the pathophysiology, classification, clinical presentation, diagnostic approach, and management strategies of Kounis syndrome, with reference to recent guidelines and case studies.

Keywords: acute coronary syndrome; coronary vasospasm; hypersensitivity; Kounis syndrome.

INTRODUCTION

Kounis syndrome (KS) is defined as the concurrence of acute coronary syndromes such as coronary vasospasm, acute myocardial infarction, and stent thrombosis, with conditions associated with mast-cell and platelet activation in the context of a hypersensitivity reaction, triggered by an allergic, anaphylactic, or anaphylactoid event.[1] Kounis and Zavras first described "an allergic angina syndrome" in 1991, today better known as "Kounis syndrome".[2] Three different variants of KS have been defined.[3] They have a common underlying pathophysiological mechanism and similar outcomes but differ in the extent of coronary involvement and comorbidities of the patient. Type I (Allergic Vasospastic Angina): most common variant, characterized by coronary vasospasm in patients without risk factors or coronary disease. Type II (Allergic Myocardial Infarction): Patients with pre-existing atherosclerotic disease in whom acute hypersensitive reactions induce coronary vasospasm or plaque erosion/rupture resulting in Acute myocardial Infarction. Type III (Allergic Stent Thrombosis): Coronary Stent thrombosis (subtype a) or stent restenosis (subtype b) in patients with pre-existing coronary disease and coronary stents.

Pathophysiology

Mast cells are abundantly present in cardiac tissues, particularly within coronary arteries, and tend to infiltrate atherosclerotic plaques during erosion or rupture. Mast cells are activated either by IgE-bound antigen cross-linking or non-IgE mediated mechanisms like complement activation (C3a and C5a) or direct mast cell degranulation. In KS, hypersensitivity or allergic reactions trigger the release of various preformed and newly synthesized vasoactive and proinflammatory mediators from

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mast cells/ platelets, and other inflammatory cells. These include histamine, tryptase, chymase, cathepsin-D, platelet activating factor, thromboxane, leukotrienes, and cytokines. These mediators can cause coronary artery vasoconstriction, plaque disruption, or even thrombosis, potentially leading to myocardial infarction.

Especially, histamine is responsible for coronary artery vasoconstriction and peripheral artery dilation with decrease of the systemic blood pressure and platelet activation whereas thromboxane can cause coronary artery vasoconstriction. Neutral proteases can lead to coronary atherosclerotic plaque erosion/ rupture whereas tryptase is involved to the thrombotic pathway via fibrinogen-degradation. Leukotrienes and Cathepsin-D can determine coronary vasospasm. Platelet activating factor prompts the activation of thrombotic cascades, directly alters the heart rate, and can result in coronary artery vasoconstriction. All these reactions can lead to the appearance of KS.[4]

Clinical Presentation

Kounis Syndrome involves the concurrent occurrence of cardiac manifestations and symptoms of hypersensitivity or allergic reactions. The cardiac signs vary based on the subtype. Chest discomfort, acute chest pain, palpitations, headache, nausea, and dyspnea are the common cardiac symptoms seen in KS whereas clinical signs may include pallor, cold extremities, sweating, bradycardia, tachycardia, hypotension, vomiting, syncope or even cardiorespiratory arrest or sudden death. The clinical manifestations of a hypersensitivity or allergic reaction can range from mild and local reactions to life-threatening systemic reactions, as in case of anaphylaxis. The sign and symptoms can be variable, depending on the involved systems and organs, affecting skin or mucosal surface (e.g., hives, angioedema, itching), respiratory (e.g., wheeze, dyspnea, stridor), cardiovascular (e.g., hypotension), neurological (e.g., drowsiness, syncope) and gastrointestinal system (e.g., abdominal pain, diarrhea, vomiting).[5] Chest pain represents the most common cardiac manifestation of KS, followed by anaphylaxis symptoms.

Anesthesia and Kounis Syndrome

Diagnosing anaphylaxis during anesthesia is challenging as cutaneous manifestations, such as flushing, urticaria, and angioedema, may not appear. Multiple agents used in the perioperative period can trigger anaphylactic reactions and Kounis syndrome. These include neuromuscular blocking drugs, antibiotics, latex exposure, contrast media, sedative agents, opioids, colloids, apronitin, protamine, chlorhexidine, dyes, local anesthetics, blood transfusion, and even allergens transferred through donor blood products.

Several grading systems have been introduced for the classification of anaphylaxis during anesthesia. The Ring and Messmer grading system, a widely used classification for assessing the severity of anaphylactic reactions, especially in perioperative and anesthesia settings. This includes:

Grade I: cutaneous and mucus signs. Grade II: mild muco-cutaneous signs with cardiorespiratory signs. Grade III: muco-cutaneous signs and/or bronchospasm with cardiovascular collapse. Grade IV: cardiac arrest. The grades III and IV may correlate with Kounis syndrome symptomatology.

Diagnostic Approach

KS is more prevalent than it seems, yet it often goes undiagnosed in clinical settings. Diagnosis requires a high index of suspicion. Clinical history regarding clinical manifestations, the suspected trigger, any previous past response are required for the diagnosis along with laboratory findings, ECG, echocardiographic results, and evidence from coronary angiography. In acute phase of reaction, serum tryptase and cardiac enzymes such as troponins and Creatinine (CK) should be determined. Serum tryptase should not be delayed because of its short half-life (about 90 min).

A 12-lead electrocardiogram (ECG) and if possible or available, an echocardiogram and coronary angiography should be performed. Common ECG

finding of KS include ST segment changes such as depression or elevation, T wave changes such as flattening or inversion, to several arrhythmias such as heart block of any degree, but it may also show normal or nonspecific results. However, ST segment elevation is the most common finding especially in inferior leads and right coronary artery, the most frequently affected by vasospasm.

Outpatient allergy study should be conducted once the acute event is resolved. This includes drug allergy study such as skin tests (prick test and intradermal test) and drug provocation test (DPT). Other tests like elevated serum histamine, immunoglobulins (IgE) and complement proteins (C4 and C1 esterase inhibitor levels) and eosinophil counts are helpful to confirm the diagnosis. Newer techniques such as thallium-201 single-photon emission computer tomography (SPECT) and 125I-15-(p-iodophenyl)-3- (R, S) methyl pentadecanoic acid (BMIPP) SPECT have revealed severe myocardial ischemia, while coronary angiography showed normal coronary arteries.

Management

Kounis syndrome is a complex form of acute coronary syndrome that requires prompt treatment decisions, addressing both myocardial revascularization and the simultaneous management of the allergic reaction that triggered the event. Currently, there are no established guidelines for the treatment of KS and optimal management of KS should be guided by a carefully balanced strategy, tailored to the specific subtype involved. The initial assessment should determine whether allergic symptoms such as cutaneous or respiratory symptoms are predominant, which requires immediate administration of adrenaline, or if acute coronary syndrome symptoms like ongoing chest pain, in which case calcium channel blockers should be prioritized. In addition, the presence or absence of coronary occlusion and the need for revascularization should be identified.[6]

Type I (Allergic Vasospastic Angina): Allergic reaction can be managed with the use of intravenous corticosteroids such as hydrocortisone at a dose of 1–2 mg/kg/day and H1 and H2 antihistamines such as diphenhydramine at a dose of 1–2 mg/kg and ranitidine at a dose of 1 mg/kg according to clinical severity Cardiac manifestations such as coronary vasospasm can be managed with coronary vasodilators nitrates and calcium channel blockers. However, their administration must be carefully balanced, as they may exacerbate hypotension and worsen the clinical picture of anaphylaxis.[7]

Type II (Allergic Myocardial Infarction): Treatment is initiated with an acute coronary syndrome protocol based on the current guidelines.[8] The allergic reaction can be treated as in type I syndrome.

Type III (Allergic Stent Thrombosis): Current acute coronary syndrome protocol should be followed together with urgent aspiration of intrastent thrombus, or a new stent deployment should be done. The allergic reaction should be treated as previously mentioned.

B-blockers should be avoided due to coronary vasospasm that can occur due to unopposed alpha-adrenergic activation. Epinephrine, which is the drug of choice and can save lives in anaphylaxis, but in Kounis syndrome can aggravate ischemia and worsen coronary vasospasm. Thus, Epinephrine is preferable to be given intramuscularly at doses 0.2-0.5 mg (1:1000) only in cases of severe anaphylaxis whereas it is avoided in patients already on beta-blockers. Glucagon (1–5 mg, intravenously over 5 min, followed by infusion 5–15 µg/min) should be preferred in such cases.[9] Morphine, codeine and meperidine should not be used, since these can also induce mast cell degranulation.[10] Fentanyl shows slight mast cell activation and are preferable. Acetaminophen (paracetamol) is not recommended, particularly when administered intravenously, might cause severe hypotension by decreasing cardiac output.

DISCUSSION

Kounis syndrome (KS) represents a unique intersection between allergic reactions and acute coronary syndromes (ACS), posing significant diagnostic and therapeutic challenges. Although

traditionally considered rare, increasing case reports suggest that KS is underdiagnosed, particularly in emergency settings where it mimics classic ACS.[11] The pathophysiology of KS is primarily driven by mast cell activation, leading to the release of histamine, leukotrienes, and other inflammatory mediators. These substances can cause coronary artery spasm, platelet aggregation, and even thrombus formation resulting in myocardial infarction. This mechanism underscores the importance of distinguishing KS from other forms of ACS, as the treatment strategies differ significantly. Management of KS requires a dual approach:

1. Cardiac care, including myocardial revascularization when necessary.
2. Allergy management, involving the use of antihistamines, corticosteroids, and withdrawal of the triggering agent. However, the use of epinephrine must be carefully considered, as it may exacerbate coronary vasospasm in some patients.

Recent case series have highlighted the importance of early recognition and tailored treatment. In a 2025 study, patients with KS were successfully managed with a combination of percutaneous coronary intervention and anti-allergic therapy, resulting in favorable outcomes despite initial diagnostic delays.[11] As the spectrum of triggers continues to expand, including common medications like cephalosporins, atropine,[12] clinicians must maintain a high index of suspicion, especially in patients presenting with chest pain following an allergic reaction. Despite growing awareness, KS remains a diagnostic challenge due to its variable presentation and the lack of standardized guidelines. Effective management of Kounis Syndrome requires a dual approach: addressing both the allergic trigger and the cardiac event.

CONCLUSIONS

Although Kounis syndrome is often overlooked and underdiagnosed, it is not actually a rare condition. Increased clinical suspicion, especially in patients presenting with chest pain following an allergic reaction, is essential for timely diagnosis and appropriate management. Further research and standardized diagnostic protocols are essential to improve detection, guide treatment, and prevent recurrence. Kounis Syndrome serves as a reminder of the importance of interdisciplinary collaboration in managing complex clinical scenarios.

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