

Current understanding of Kounis syndrome

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Murat Biteker

Department of Cardiology, Haydarpaşa
Numune Education and Research
Hospital, Istanbul, Turkey
Tel.: +90 216 414 4502
Fax: +90 216 459 6321
murbt2@yahoo.com

Inflammatory mediators, adhesion molecules of neutrophils and monocytes, have been shown to be increased in the plasma of patients presenting with acute coronary syndromes. Anaphylaxis is a systemic, immediate hypersensitivity reaction caused by rapid IgE-mediated release of mediators from mast cells and basophils. Kounis syndrome is the coincidental occurrence of these two distinct conditions accompanied by clinical and laboratory findings of angina pectoris caused by inflammatory mediators released during an allergic insult. Allergic angina can progress to acute myocardial infarction, which is termed 'allergic myocardial infarction'. There are several causes reported to be capable of inducing Kounis syndrome. These include a number of conditions, several drugs, foods and insect stings, among others. In this article, the clinical aspects, diagnosis, pathogenesis, incidence and epidemiology, related conditions and therapeutic management of this important syndrome are discussed.

KEYWORDS: acute coronary syndromes • allergic angina • allergic myocardial infarction • Kounis syndrome • mast cell activation

Six decades ago, Pfister reported a 49-year-old man who developed antero-septal myocardial infarction and urticaria after 4 days of treatment with 300,000 units/day penicillin in oil [1]. The patient was treated with dicumarol, papaverine, morphine and diphenhydramine hydrochloride. In 1991, 41 years after the first report of acute myocardial infarction during a prolonged allergic reaction to penicillin, Kounis and Zavras [2] described the 'syndrome of allergic angina' as the coincidental occurrence of chest pain and allergic reactions accompanied by clinical and laboratory findings of classical angina pectoris caused by inflammatory mediators released during the allergic insult. The main mechanism proposed was the vasospasm of coronary arteries. Kounis syndrome now refers to the clinical spectrum of angina pectoris to acute myocardial infarction after an allergic reaction to food, drugs, insect stings and so on. Since the first report of allergic myocardial infarction, nearly 300 cases of Kounis syndrome have been reported in the literature.

Historical perspective of Kounis syndrome

Although myocardial infarction due to an allergic insult was first described 60 years ago [1], the first definition of allergic angina and allergic myocardial infarction as a different clinical entity was made 41 years after the first report

(FIGURE 1) [2]. In 1995, Kovanen *et al.* analyzed specimens of coronary arteries from 20 patients who had died of acute myocardial infarction and found that the degree of mast cell degranulation was much higher at the sites of erosion or rupture than in adjacent areas or in the more distant unaffected areas [3]. In 1998, Braunwald noted that vasospastic angina can be induced by "allergic reactions with mediators such as histamine or leukotrienes acting on coronary vascular smooth muscle" [4]. Since the acceptance of Kounis syndrome as a cause of coronary artery spasm and acute coronary syndrome, many case reports have been published. In 2005, Nicholas G Kounis reported the first comprehensive review concerning this unique disease [5] and, in 2006, he drew attention to a potential relationship between drug-eluting coronary stent thrombosis and Kounis syndrome [6]. Finally in 2009, the first reports in the literature of children with Kounis syndrome were published [7,8]. Nearly 300 cases of Kounis syndrome have been reported in the literature; however, the true number of cases is unknown as many are probably misdiagnosed or go unreported.

Pathogenesis

Mast cells are necessary for the development of allergic reactions. They are granulocytes found in peripheral tissues that play a central role in

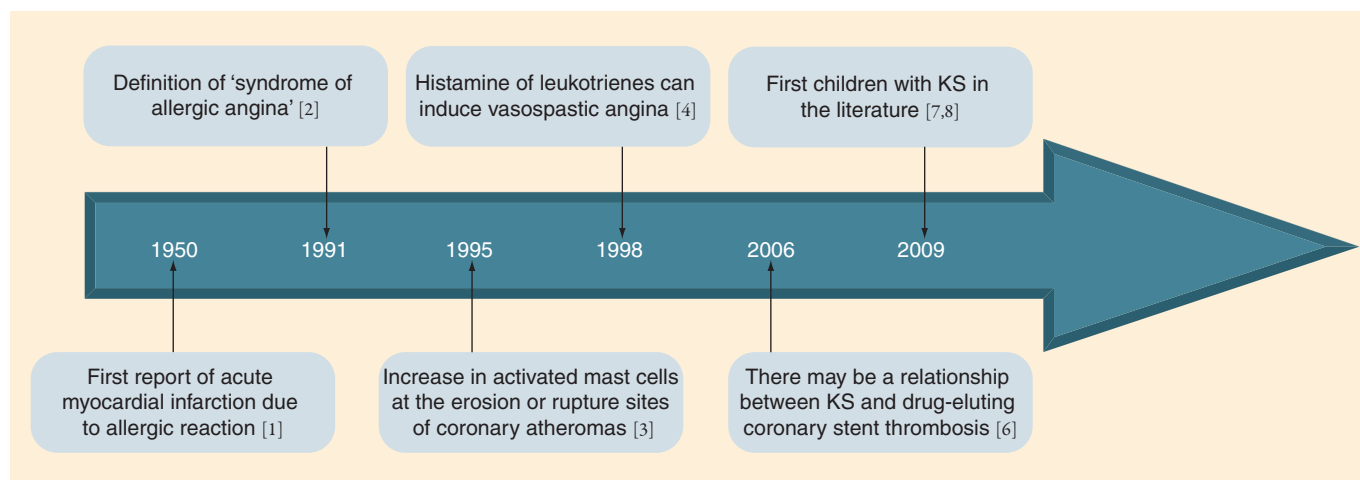


Figure 1. Historical perspective of Kounis syndrome.

KS: Kounis syndrome.

acute hypersensitivity reactions [9]. Derived from CD34⁺ bone marrow precursor cells, they circulate in the blood as precursors before being recruited into peripheral tissues such as the dermis of the skin, the lungs, and the mucosa and submucosa of the intestines [10]. They then differentiate and mature under the influence of mast cell growth factor and play a central role in inflammatory and immediate allergic reactions initiated by IgE [9,10]. Mast cells are activated by either multivalent antigens cross-linking surface-bound IgE molecules or by anaphylatoxins (C3a and C5a), leading to degranulation and the release of preformed and newly generated vasoactive and proinflammatory mediators that include histamine, inflammatory cytokines, proteolytic enzymes and hematopoietic factors (Box 1) [11]. They have a pivotal role in allergic reactions and take part in other pathophysiological conditions, such as innate and acquired immunity, wound healing, fibrosis, tumors and autoimmune diseases [12,13]. Several chemical mediators are generated and released by mast cells after allergen exposure in sensitized hosts through IgE-dependent mechanisms. These mediators provoke plasma extravasation, tissue edema, bronchoconstriction, mucus secretion, leukocyte recruitment and inflammation [14]. The release of these mediators may be induced by physical destruction (mechanical trauma and high temperature), bacteria, free radicals, emotional stress, radiation, viruses, the contrast media used in radiology, chemical substances (toxins and venoms), endogenous mediators (proteins and tissue proteases) and immune mechanisms, including IgE-dependent and IgE-independent mechanisms.

The mammalian heart contains a significant number of resident mast cells predominantly located in close proximity to vessels [15]. Cardiac mast cells have been also demonstrated to be present in the coronary artery intimal layer and atherosclerotic plaques [16]. In addition to their well-known participation in inflammatory allergic reactions, there is increasing evidence that mast cells might play a role in the pathogenesis of atherosclerosis and that their products, such as histamine, may contribute to the initiation and progression of the atherosclerotic plaque [17]. Mast cells play a role in the genesis of a vulnerable plaque; with progressive maturation of an atheromatous lesion, the density of mast cells decreases in

the center of the lesion and increases mainly at the shoulder region of fully formed atheromas [16,17]. Several mediators released from mast cells (such as histamine and tryptase) are suggested to contribute to fatty streak formation and to the generation of unstable plaques susceptible to rupture [17,18]. Kovanen and coworkers found increased numbers of mast cells at the site of atheromatous rupture in patients who had died of acute myocardial infarction, and also found that mast cell degranulation was significantly higher at the site of rupture than in adjacent, unaffected intima [3,17]. Mast cells are also found extensively in and around thrombi, and could contribute to the destabilization and maturation of thrombi by the anticoagulant effect of heparin- and tryptase-induced degradation of fibrinogen [17]. An association may also exist between increased levels of biogenic amines and atherosclerosis.

Kalsner and Richards found significantly higher concentrations of histamine in coronary arteries from patients who died of coronary heart disease compared with controls [18]. Gill *et al.* reported higher leukocyte, platelet and plasma histamine levels in patients with peripheral vascular disease compared with controls [19,20]. All these findings suggest that mast cells appear to provide a novel link between inflammation and atherogenesis.

Kounis syndrome is caused by the release of inflammatory mediators during mast cell degranulation. However, inflammatory mediators have also been reported to be increased in blood samples of patients with acute coronary syndromes of nonallergic etiology [21,22]. Histamine, prostaglandin D₂, serotonin and leukotrienes, which are present in mast cells, may contribute to abnormal vascular responsiveness; increased numbers of mast cells have been found to be associated with coronary vasospasm [23]. Clejan *et al.* showed increased levels of histamine in patients with stable coronary artery disease and acute coronary syndrome [24]. In another study, plasma histamine was found to be elevated in the great cardiac vein in eight out of 11 patients with variant angina but in none of eight control patients [25]. Deliargyris *et al.* measured tryptase levels in 102 patients without acute coronary syndromes undergoing catheterization and compared levels in patients with and without obstructive coronary artery disease [26].

They found that patients in the highest quartile of tryptase levels had a 4.3-fold risk for coronary artery disease. They concluded that tryptase measurements may emerge as a novel way of identifying asymptomatic patients with coronary artery disease, and represent a new biomarker of therapeutic efficacy in patients with coronary artery disease.

These findings suggest that the same mediators from the same cells are present in both acute allergic and acute nonallergic coronary events, indicating a final common pathway for allergic and nonallergic coronary syndromes. If mast cells do contribute to nonallergic coronary events, a new possibility emerges for the prevention of the progression of coronary plaques to unstable lesions, that is, the potential to stabilize mast cell membrane with drugs such as sodium cromoglicate or ketotifen or with monoclonal antibody to IgE. Anti-IgE acts as a mast cell-stabilizing agent owing to its ability to downregulate FcεRI and IgE-FcεRI on basophils and mast cells. Omalizumab was approved in 2003 and is the first monoclonal antibody developed for use in asthma and allergic diseases; however, it has serious side effects and, as with most bioengineered drugs, it is very expensive.

Statins are inhibitors of hydroxymethylglutaryl coenzyme A reductase, and recent data suggest that statins exhibit profound inhibitory effects on the growth and function of various immune cells. Krauth *et al.* showed that cerivastatin and atorvastatin and, to a lesser degree, lovastatin, were found to inhibit the stem cell factor-induced differentiation of mast cells [27]. In another study in a rat mast cell line, lovastatin induced impaired tyrosine phosphorylation and inhibition of IgE-mediated degranulation [28].

Inhibition of mast cell differentiation and degranulation with statins, and prevention of the progression of coronary plaques to unstable lesions with mast cell stabilizers and statins should be investigated in further studies.

Incidence & epidemiology

The epidemiology of allergic reactions in the general population remains uncertain. Yocum *et al.* investigated the epidemiology of anaphylaxis among residents in Olmstead County (MN, USA) and reviewed the medical records of 1255 residents [29]. During the 5-year study, 133 residents experienced 154 anaphylactic reactions. The annual occurrence rate of anaphylaxis was 30 per 100,000 person-years, and the annual incidence rate was 21 per 100,000 person-years. The observed case–fatality rate was low at 0.65%.

The prevalence of allergic reactions and anaphylaxis also remains uncertain. The prevalence of systemic reactions to hymenoptera stings, which is one of the most common allergic reactions, ranges from 0.15 to 3.9% [30]. The prevalence of anaphylaxis among emergency department patients ranged from 0.09% in one single-center study [31] to 2.1% in a large national database [32].

Cardiovascular symptoms are rarely seen during an allergic insult. Helbling *et al.* assessed the incidence of anaphylaxis with circulatory symptoms during a 3-year period [33]. During the study period, 226 individuals suffered 246 episodes of severe life-threatening anaphylaxis with cardiovascular symptoms, with an incidence of 7.9–9.6 per 100,000 inhabitants per year. The case–fatality rate was 0.0001%.

Box 1. Mediators expressed by human mast cells.

Preformed mediators

- Tryptase
- Histamine
- Heparin proteoglycan
- Chondroitin sulfate proteoglycan
- Chymase
- Carboxypeptidase
- Cathepsin G

Newly generated mediators

- Prostaglandin D₂, prostaglandin E₂
- Leukotriene B₄, leukotriene C₄
- Platelet-activating factor
- Thromboxanes

Cytokines and chemokines

- Inflammatory cytokines (IL-4, IL-5, IL-6, IL-13, TNF-α)
- Chemokines (MCP-1, IL-8, RANTES)
- Hematopoietic factors (IL-3, GM-CSF)
- Growth factors (bFGF, VEGF, TGF-β, PDGF)

GM-CSF: Granulocyte-macrophage colony-stimulating factor; MCP: Monocyte chemotactic protein.

Acute coronary syndromes associated with allergic reactions have been reported all over the world. Epidemiological studies of Kounis syndrome are difficult as many physicians are unaware of the diagnosis or may miss the syndrome owing to its variable manifestations. Owing to missed and/or undiagnosed cases and a lack of prospective trials, determining the prevalence and true incidence of Kounis syndrome is impossible with our current state of knowledge. Although considered to be an uncommon disorder, it is increasingly reported in the literature and recognized in clinical practice. Recent reports have shown that Kounis syndrome has been observed in every race, age group (from 9 to 90-year-olds) and geographic location [7,34].

In Kosuyolu Heart Center, which is a tertiary hospital in Istanbul, Turkey, a total of 3876 patients underwent urgent coronary angiography for suspected acute myocardial infarction during a 3-year period (2006–2009) and eight patients were diagnosed with Kounis syndrome. Thus, the catheterization laboratory prevalence of Kounis syndrome is estimated to be 0.002%.

Etiology

There are several factors and diseases that may induce Kounis syndrome (Box 2). These include hymenoptera and viper venom [35–37], food allergens (e.g., shellfish) [38,39], oral and parenteral drugs [40–60], stings by ants and jellyfishes, various conditions (angioedema, bronchial asthma, urticaria, exercise-induced allergy, mastocytosis and serum sickness) and a variety of environmental exposures (e.g., grass cutting, poison ivy, latex contact, limpet ingestion and millet allergy). In recent years, an association between Kounis syndrome, Takotsubo cardiomyopathy (also called stress-induced cardiomyopathy, transient left ventricular apical ballooning or broken heart syndrome) [61,62] and drug-eluting coronary stent thrombosis [63–75] has been argued.

Box 2. Possible etiologic and related conditions of Kounis syndrome.

Drugs

- Antibiotics (ampicillin, ampicillin/sulactam, amoxicillin, amikacin, cefazolin, cefoxitin, cerufoxime, cephradine, cinoxacin, lincomycin, penicillin, sulbactam/cefoperazone, trimethoprim-sulfamethoxazole, sulperazon, vancomycin)
- Contrast media (Iohexone, Ioxaglate, meglumine diatrizoate, sodium indigotindisulfonate)
- Glucocorticoids (betamethasone, hydrocortisone)
- Anti-neoplastics (5-fluorouracil, capecitabine, carboplatin, denileukin, interferons, paclitaxel, vinca alkaloids)
- Anesthetics (etomidate, rocuronium bromide, suxamethonium, trimethaphan)
- Analgesics (dipyrone)
- Nonsteroidal anti-inflammatory drugs (diclofenac, naproxen)
- Skin disinfectants (chlorhexidine, povidone-iodine)
- Thrombolytics (streptokinase, urokinase)
- Anticoagulants (heparin, lepirudin)
- Proton pump inhibitors (lansoprazole)
- Others (allopurinol, enalapril, esmolol, dextran, bupropion, fructose, insulin, iodine, protamine, tetanus antitoxin, glaphenine, mesalamine etc.)

Diseases and several conditions

- Angioedema
- Bronchial asthma
- Exercise-induced anaphylaxis
- Food allergy
- Idiopathic anaphylaxis
- Serum sickness
- Urticaria
- Nicotine skin patches
- Takotsubo cardiomyopathy
- Coronary allograft vasculopathy
- Churg–Strauss syndrome
- Mastocytosis
- Drug-eluting coronary-stent thrombosis

Environmental exposures

- Ant/bee/wasp/jellyfish sting
- Latex contact
- Millet allergy
- Shellfish consumption
- Viper venom
- Poison ivy
- Grass cutting

Metal-induced allergic reactions and Kounis syndrome secondary to intracardiac metal devices is also a matter of debate [76].

Drug-eluting coronary stent thrombosis & Kounis syndrome

The use of drug-eluting coronary stents in cardiology practice has increased. As a result, drug-eluting coronary stent thrombosis is a major problem in the current drug-eluting stent era [77].

Coincidence of hypersensitivity reactions following implantation of drug-eluting stents and stent thrombosis is considered to be a manifestation of Kounis syndrome [63–75].

The development of stent has been a major advance in the treatment of obstructive coronary artery disease since the introduction of balloon angioplasty. However, neointimal hyperplasia occurring within the stent leading to in-stent restenosis is a main obstacle in the long-term success of percutaneous coronary intervention [78]. The recent introduction of drug-eluting stents contributes a major breakthrough to interventional cardiology. Randomized clinical trials using drug-eluting stents have shown a remarkable reduction in angiographic restenosis when compared with bare-metal stents [79]. Despite reduced rates of restenosis, drug-eluting stents have not reduced the incidence of stent thrombosis as compared with bare-metal stents [79]. Coronary stent thrombosis is a rare complication following stent implantation; however, if it occurs, it is associated with a high morbidity and mortality. Stent thrombosis is considered acute when it occurs between 0 and 24 h after stent implantation; subacute, between 24 h and 30 days; late, between 30 days and 1 year; and very late, after 1 year. Many predictors have been identified for stent thrombosis after drug-eluting stent implantation. These include acute coronary syndrome at index presentation, left ventricular ejection fraction, diabetes mellitus, renal failure, total stent length, number of stents used, bifurcation lesions, side branch occlusion, stent underexpansion and/or malposition, and cessation of antiplatelet therapy [79].

Although the pathophysiology of drug-eluting stent thrombosis is multifactorial and has not been fully elucidated, allergic reactions to stent components may be one of the potential causes of this catastrophic entity. The use of bare-metal stent is not associated with allergic reactions. However, all the components of the drug-eluting stent (nickel strut, polymer and impregnated drug) can induce allergy either separately or synergistically [72].

Concomitant drugs such as clopidogrel and aspirin may also act as potential antigens [70]. Although allergic reactions are now recognized as key components of stent thrombosis, the incidence, especially of subclinical cases, is probably under-reported. Before consideration for drug-eluting stent implantation, a thorough atopic history should be sought, with specific attention paid to previous Kounis syndrome or other allergic reactions. In atopic patients, bare-metal stents should be the first choice. However, when drug-eluting stents are indicated, skin tests to stent components and desensitization strategies should be performed.

Diagnosis

Patients with systemic allergic reactions associated with clinical, laboratory and electrocardiographic findings of acute myocardial ischemia should be diagnosed as having Kounis syndrome. Two variants of Kounis syndrome have been described so far [80]. The type I variant (coronary spasm), which might represent a manifestation of endothelial dysfunction or microvascular angina, includes patients with normal coronary arteries without predisposing factors for coronary artery disease in whom the acute release of inflammatory mediators can induce either coronary artery spasm without increase of cardiac enzymes and troponins

or coronary artery spasm progressing to acute myocardial infarction with raised cardiac enzymes and troponins. The type II variant (coronary thrombosis) includes patients with culprit but quiescent pre-existing atheromatous disease in whom the acute release of inflammatory mediators can induce either coronary artery spasm with normal cardiac enzymes and troponins, plaque erosion or rupture manifesting as acute myocardial infarction.

We would like to propose herewith a type III variant (stent thrombosis), which would include patients with stent thrombosis in whom thrombus harvesting and staining with hematoxylin-eosin and Giemsa shows the presence of eosinophils and mast cells, respectively, in the pathology specimens.

Chest pain during an allergic insult with electrocardiographic ischemic changes but with normal cardiac enzymes, negative troponins, normal coronary angiogram and positive tryptase or histamine test are in favor of the type I variant of the syndrome. Acute allergic reactions associated with acute myocardial infarction with angiographic evidence of coronary artery disease constitute the type II variant of Kounis syndrome.

Some clinical, electrocardiographic, echocardiographic and laboratory findings may help the differential diagnosis of Kounis syndrome (Box 3).

Clinical & electrocardiographic features

Signs and symptoms of Kounis syndrome may include all features of allergy and myocardial infarction, such as chest pain, faintness, nausea, malaise, shortness of breath, difficulty in swallowing, abdominal pain, numbness, vomiting, syncope, pruritus, urticaria, diaphoresis, pallor, hypotension, bradycardia or tachycardia, and cardiorespiratory arrest (Box 4).

Electrocardiography is a mainstay in the diagnosis of Kounis syndrome, along with clinical history and biochemical markers. Although ST elevations in the anterior or inferior leads have been the most commonly recorded electrocardiographic findings, ECG may be normal or just show some nonspecific ST-T wave changes. Patients with Kounis syndrome usually present with inferior wall myocardial ischemia/infarction and often have angiographically normal coronary arteries. The right coronary artery is the most frequent site of coronary vasospasm for uncertain reasons.

Laboratory findings

Acute-onset chest pain accompanied by allergic symptoms should raise suspicion of Kounis syndrome. In addition to the routine work-up of patients with acute coronary syndromes (ECG, cardiac enzymes and troponin, complete blood count, D-dimer, brain natriuretic peptide and serum cholesterol levels), serum histamine, tryptase, specific IgE antibody and eosinophil levels can help in the identification of this syndrome.

The biologic effects of complement include the promotion of chemotaxis and anaphylaxis, opsonization and phagocytosis of microorganisms, and the removal of immune complexes from the

circulation. C4a, C3a and C5a are anaphylatoxins and bind to mast cells, triggering the release of histamine and other mediators, leading to vasodilation, erythema and swelling [9,10,81,82]. C5a is a major stimulus for the influx of neutrophils, basophils, monocytes and eosinophils. Because of these reasons, complement protein levels may also be helpful.

Exclusion of any other cause of acute coronary syndromes such as thrombophilia, collagen disease (lupus anticoagulant antibodies), polycythemia, increased lipoprotein A levels, congenital dysfibrinogenemia, reduced tissue plasminogen activator activity, increased tissue plasminogen activator inhibitor, and deficiencies in protein S, protein C and antithrombin III may be necessary, especially in younger patients. The serologic tests for viral etiology may also be studied to exclude myopericarditis.

Box 3. Diagnosis of Kounis syndrome.

- Presentation of allergic symptoms, acute chest pain or dyspnea after allergic insult
- Electrocardiographic abnormalities that mimic an acute myocardial infarction
- Transient left ventricular wall motion abnormalities
- Absence of obstructive coronary lesions on coronary angiography (only for type I variants)
- Recovery of left ventricular function within 1–4 weeks of presentation

Box 4. Clinical and electrocardiographic features of Kounis syndrome.

Symptoms

- Chest discomfort and acute chest pain
- Dyspnea
- Faintness
- Malaise
- Nausea
- Difficulty in swallowing
- Vomiting
- Syncope
- Pruritus
- Urticaria

Clinical signs

- Hypotension
- Diaphoresis
- Pallor
- Palpitations
- Bradycardia or tachycardia
- Cardiorespiratory arrest

Electrocardiographic signs

- T-wave flattening and/or inversion
- ST segment depression or elevation
- QRS complex prolongation
- QT segment prolongation
- Sinus tachycardia or bradycardia
- Nodal rhythm
- Atrial fibrillation
- Ventricular ectopics
- Bigeminal rhythm

As discussed, mast cells can release a variety of mediators. Pre-formed mediators (such as histamine, heparin, chondroitin sulfates and tryptase) are stored in secretory granules, and are released upon mast cell activation. Newly generated mediators (leukotrienes, prostaglandins, TNF and interleukins [IL-4, IL-5 and IL-6]) are not present in the resting mast cell, but are produced during IgE-mediated activation [82]. Mediators released by activated mast cells are involved in atherogenesis and coronary artery disease [83–86]. Histamine, the biogenic amine released by mast cells, endothelial cells and aggregating platelets can induce coronary vasospasm, leading to variant angina and acute myocardial infarction [83–86]. Once released into the circulation, histamine is metabolized by histamine *N*-methyl transferase after one pass through the system. Plasma histamine is not frequently measured during anaphylactoid reactions owing to its short half-life of less than 30 min [83].

Mast cell tryptase, which is a potent growth factor for epithelial cells, airway smooth muscle cells and fibroblasts, is a neutral serine protease (molecular weight 134 kDa) [87,88]. It can induce type I collagen synthesis and cell chemotaxis, stimulates the release of granulocyte chemoattractant IL-8 and upregulates expression of ICAM-1 on H292 epithelial cells [89,90]. Owing to activated neighboring mast cells, tryptase release amplifies the activation process in allergic reactions. Thus, tryptase plays a key role in allergic diseases by amplifying the responses of mast cells to allergens. Serum tryptase levels are elevated in most subjects with systemic anaphylaxis. Histamine levels peak at 5 min and decline to baseline within 15–30 min, whereas tryptase levels peak 1–1.5 h after the onset of anaphylaxis and can persist for as long as 5 h after the onset of symptoms. The best time to measure serum tryptase levels is between 1 and 2 h but no longer than 6 h after the onset of symptoms, whereas the best time to measure plasma histamine levels is between 10 min and 1 h after the onset of symptoms. There can be a disconnection between histamine and tryptase levels, with some patients exhibiting increase of only one of these mediators [91,92].

Although elevated serum histamine and tryptase level strongly support the possibility of an ongoing allergic reaction, their short half-lives make them relatively inconvenient for routine use, and a negative tryptase or histamine test does not exclude this possibility.

Allergy tests, such as skin prick and serum-specific IgE testing, detect sensitization to an allergen. Mast cell degranulation follows after antibody-mediated antigen recognition. However, sometimes direct action against the mast cell can occur [93,94], especially with drugs. Therefore the absence of IgE antibodies does not exclude mast cell degranulation.

All cases of coronary vasospasm due to an allergic insult require additional work-up to identify the offending agent and to avoid future reactions. This work-up would include serum tryptase and specific IgE measurements, patch testing, skin prick and intradermal skin testing.

Skin tests or *in vitro* tests that determine the presence of specific IgE antibodies can identify specific causes of anaphylaxis. Causes of anaphylaxis that can be defined in this way include foods, medications (e.g., penicillin and insulin) and stinging insects.

Echocardiography & coronary angiography

Transthoracic echocardiography may help to differentiate Kounis syndrome from other causes of chest pain such as pericarditis or aortic dissection. Echocardiography reveals segmental wall motion abnormality in most patients, which usually regresses in a few days or weeks without any complications after the acute phase of the disease.

Coronary angiography is usually needed for patients with suspected Kounis syndrome to assess the coronary anatomy and to make a differential diagnosis.

Differential diagnosis of hypersensitivity myocarditis & Kounis syndrome

Despite the clinical and laboratory findings described, differentiation between hypersensitivity myocarditis and hypersensitivity coronary syndrome (Kounis syndrome) may be difficult. These two clinical entities share the same etiology and symptomatology, one of which is an inflammatory disease affecting the myocardium and the cardiac conduction system and the second is the concurrence of acute coronary syndromes with conditions associated with mast cell activation. Cardiac signs and symptoms, and electrocardiographic and laboratory signs may be similar. However, the only differences between these two hypersensitivity conditions are the presence of eosinophils, atypical lymphocytes and giant cells in myocardial biopsy in hypersensitivity myocarditis; whereas biopsy in Kounis syndrome is typically normal. Coronary angiography reveals normal coronary angiogram in hypersensitivity myocarditis and the type I variant of Kounis syndrome; whereas angiogram in Kounis syndrome type II variant shows coronary artery disease. The treatment of hypersensitivity myocarditis and Kounis syndrome is the same, including corticosteroids, histamine (H)1 and H2 blockers.

Prognosis

Although several reports have shown that the type I variant of Kounis syndrome has a better prognosis than the type II variant [95], in both types the prognosis depends on the magnitude of the initial allergic response, the patient's sensitivity, the patient's comorbidity, the site of antibody–antigen reaction, the allergen concentration and the route of allergen entrance.

The prognosis of patients with Kounis syndrome is very good beyond the acute phase, with the left ventricle function normalizing over 3 days to several weeks. Although death is very rare [35], during the acute phase patients may develop pulmonary edema, arrhythmias and, very rarely, thrombus. In these cases, management should usually be active as complete recovery of left ventricle function is to be expected. Long-term follow-up confirms good prognosis with a low incidence of heart failure. Follow-up should include echocardiography at approximately 4 weeks after discharge to document normalization of left ventricular function. Complete resolution of contractile abnormalities within weeks is characteristic of this syndrome, so another diagnosis should be considered for patients with persistent contractile abnormalities. Although recurrence of Kounis syndrome has not been reported, repeated uncontrolled allergen exposition may cause similar allergic reactions and allergic myocardial infarction.

Treatment

No consensus exists regarding appropriate therapy for Kounis syndrome because the number of reported cases is low and the disorder is possibly underdiagnosed. Most data regarding treatment have been derived from case reports. Kounis syndrome has two aspects that need to be treated: acute coronary syndrome and allergic reaction (Box 5). Treatment of allergic reaction can abolish the type I variant alone, but concomitant treatment of acute coronary syndrome is mandatory in the type II variant of Kounis syndrome.

Treatment of acute coronary events

Supportive measures are the mainstay of management during the acute phase. Supplemental oxygen should be administered to all patients. Since vasospasm is the primary mechanism of acute coronary syndrome in Kounis syndrome, treatment protocols should include vasospasmolytic agents such as nitrates and calcium channel blockers. Current American College of Cardiology Foundation/American Heart Association guidelines on acute coronary syndromes should be followed for the treatment of acute coronary syndrome [96]. However, the utility of common medications used in acute coronary syndromes, such as aspirin, clopidogrel, heparin, nitroglycerin and β -blockers in patients with Kounis syndrome is unknown given the potential risk of aggravating an ongoing anaphylactic reaction. All patients should be evaluated individually. If the clinical judgment favors the use of these drugs, it is reasonable to administer them in an intensive care unit setting, and the patients should be monitored more closely for at least 8–10 h for the development of increased symptoms [97].

Severe left ventricular dysfunction may warrant diuretics, inotropic agents and/or hemodynamic support with intra-aortic balloon-pump counterpulsation.

Treatment of anaphylaxis

Current guidelines for the management of anaphylaxis should be followed for the treatment of allergic reactions [98]. Airway, breathing, circulation and level of consciousness should be immediately assessed. Patients should be placed in the recumbent position and the lower extremities should be elevated. Oxygen should be administered to all patients with anaphylaxis who have prolonged reactions, pre-existing hypoxemia or myocardial dysfunction.

Increased vascular permeability in anaphylaxis might permit transfer of 50% of the intravascular fluid into the extravascular space within 10 min. Between 1 and 2 l of normal saline should be administered to adults at a rate of 5–10 ml/kg in the first 5 min. Children should receive up to 30 ml/kg in the first hour. However, patients with congestive heart failure or chronic renal disease should be observed cautiously to prevent volume overload. Extreme amounts of fluid replacement could cause pulmonary edema and respiratory failure in patients with Kounis syndrome owing to left ventricular dysfunction.

Antihistamines (H1 and H2 receptor blockers) provide symptomatic control of itching, urticaria and angioedema. However,

Box 5. Treatment of Kounis syndrome.

Treatment of an allergic event

- Oxygen
- Antihistamines
- Steroids
- Epinephrine (?)
- Fluid resuscitation

Treatment of an acute coronary event

- Acute coronary syndrome protocol

they are considered a second-line treatment after administration of epinephrine and should never be administered alone in the treatment of anaphylaxis. Diphenhydramine, 1–2 mg/kg or 25–50 mg per dose, may be given parenterally. Ranitidine, 50 mg in adults and 12.5–50 mg (1 mg/kg) in children, can be diluted in 5% dextrose to a total volume of 20 ml and injected intravenously over 5 min. Cimetidine (4 mg/kg) can be administered intravenously to adults, but no pediatric dosage in anaphylaxis has been established [98]. Combination of a H2 antagonist with a H1 antagonist has better results than H1 treatment alone in acute allergic syndromes [99].

Systemic glucocorticosteroids are recommended for patients with a history of idiopathic anaphylaxis or asthma and patients who experience severe or prolonged anaphylaxis. Glucocorticosteroids are not usually helpful immediately but might potentially prevent recurrent or protracted anaphylaxis. Corticosteroids have also been used successfully in the treatment of refractory vasospastic angina, particularly when a patient has an allergic diathesis [100]. If given, intravenous glucocorticosteroids should be administered every 6 h at a dosage equivalent to 1.0–2.0 mg/kg/day. Oral administration of glucocorticosteroids (e.g., prednisone 0.5 mg/kg) might be sufficient for less critical anaphylactic episodes.

Glucocorticoids and several nonsteroidal anti-inflammatory drugs, when administered early after coronary occlusion, may interfere with myocardial scar formation. Corticosteroids impair wound healing and scar formation, which could cause myocardial wall thinning, cardiac aneurysms and cardiac wall rupture [101]. However, a meta-analysis of the studies of corticosteroid treatment in acute myocardial infarction reported no harm and possible mortality benefit with these drugs in acute myocardial infarction [102]. Use of corticosteroids in the treatment of Kounis syndrome needs more investigation but is probably safe and appropriate.

Anaphylaxis may be triggered by nonimmunologic mechanisms. For example, mast cells may be activated directly by constituents of insect venoms, or by radiocontrast media, opiates or nonsteroidal anti-inflammatory drugs [103]. Opiate medications, such as morphine, codeine and meperidine, should be used cautiously in this group of patients because they can induce mast cell degranulation and aggravate the allergic reaction. Fentanyl and its derivatives show only a slight activation of mast cells and should be the drugs of choice when narcotic analgesia is necessary.

Although their efficacy and potency is questionable, mast cell membrane stabilizers (e.g., sodium cromoglycate and ketotifen) may be considered in patients who develop acute coronary syndromes after drug reaction.

Guidelines recommend epinephrine for anaphylaxis as soon as anaphylactic symptoms occur [98]. Aqueous epinephrine in 1:1000 dilution (1 mg/ml), 0.2–0.5 ml (0.01 mg/kg in children, maximum 0.3 mg dosage) should be administered intramuscularly or subcutaneously every 5 min, as necessary, and should be used to control symptoms and increase blood pressure. In patients with cardiac arrest, intravenous epinephrine (1:10,000–1:100,000) can be considered.

Although epinephrine is a life-saving medication in anaphylaxis, it has a narrow therapeutic window and, in cases of allergic reaction and acute coronary syndrome, its risks may outweigh the benefits. There are three main reasons why epinephrine use is challenging in acute coronary syndromes secondary to an allergic reaction:

- Every commercially available preparation of epinephrine contains sulfite as a preservative and antioxidant. In addition to reports of bronchospasm, urticaria, angioedema, nausea, abdominal pain, diarrhea, seizures and death, anaphylactic and anaphylactoid reactions to sulfites have been documented [104–106];
- Epinephrine can induce coronary vasospasm, cardiac ischemia and arrhythmias, and prolong the corrected QT interval. Uncontrolled increase in blood pressure may cause intracerebral hemorrhage;
- Some patients may have received β -blockers in the initial management of the acute coronary syndrome, and the usual dose of epinephrine may be ineffective. It may also promote more vasospasm secondary to unopposed α -adrenergic effects in patients who have received β -blocking agents. Glucagon may be considered for patients who are already receiving β -blockers or who received them during the management of the acute coronary syndrome. Methoxamine, a potent α -agonist, can also be considered in patients who do not respond to epinephrine.

Because most of the information about Kounis syndrome comes from case reports or small case series and owing to a lack of controlled trials, more case studies are needed to establish the appropriate use of epinephrine in patients with Kounis syndrome.

Recently, Ridella *et al.* reviewed the literature on Kounis syndrome cases following β -lactam antibiotic administration and demonstrated that most cases have been treated with steroids (76%), H1 blockers (70%), nitroglycerin (47%) and H2 blockers (35%) [47]. Epinephrine was used in only 23% of the cases and aspirin was used in 18% of the cases. In general, the overall response rate was excellent, and no mortality was reported secondary to β -lactam antibiotics. We have very recently reported six Turkish patients with Kounis syndrome who were treated with oral antihistamines and prednisolone [107]. Although the number of cases is too limited to reach definitive conclusions about the treatment of Kounis syndrome, most clinicians appear to avoid the use of both aspirin and epinephrine.

Expert commentary & five-year view

Kounis syndrome (allergic angina or allergic myocardial infarction) is the coincidental occurrence of chest pain and allergic reactions accompanied by clinical and laboratory findings of classical angina pectoris caused by inflammatory mediators released during an allergic insult. Kounis syndrome is still a relatively unknown disease. Much of the general public has no knowledge about Kounis syndrome and there are still a great number of physicians who are unaware of this disease. The diagnosis of this unique disease should be considered when acute-onset chest pain is accompanied by allergic symptoms, electrocardiographic changes and elevated cardiac enzymes. All adults and children admitted to the emergency departments with allergic symptoms, chest pain and ST elevation on electrocardiography should be investigated for allergic insults. Kounis syndrome is not a very rare disease but it is a very rarely diagnosed disease.

Although the pathogenesis of Kounis syndrome is not fully understood, there are no studies using animal models of this disease. Future preclinical and clinical studies, especially those using animals, may lead to improved understanding of the pathogenesis and the development of specific treatment modalities.

Kounis syndrome, as a possible manifestation of hypersensitivity to stent components or antiplatelet agents, might play a key role in the mechanism of drug-eluting coronary stent thrombosis. A third variant of Kounis syndrome should be considered in patients with drug-eluting coronary stent thrombosis accompanied by allergic symptoms. Further studies using corticosteroids and mast cell stabilizers in patients with drug-eluting stents implantation and concomitant allergic reactions seem to be necessary to prevent stent thrombosis.

Inflammatory mediators released from mast cells have been found to be increased in the blood or urine of patients suffering from acute coronary syndromes of allergic and nonallergic etiology. These mediators have been implicated in many clinical and experimental studies as inducing coronary artery spasm and/or acute myocardial infarction. Stabilizing mast cells and preventing the release of such mediators could emerge as novel therapeutic modalities capable of preventing acute coronary and cerebrovascular events. An observational study in order to measure the effects of mast cell-blocking agents on the risk of serious coronary and cerebrovascular events seems to be worthwhile.

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Key issues

- The exact cause of Kounis syndrome is unknown.
- Kounis syndrome may remain undiagnosed since many doctors are unaware of this syndrome.
- Patients often undergo unnecessary, expensive and invasive tests.
- The key to diagnosis is a thorough patient history.
- Drug-eluting coronary stent thrombosis may be a manifestation of Kounis syndrome and it should be added as a third group to the classification of Kounis syndrome.
- There are no set guidelines for the treatment of Kounis syndrome.
- Antihistamines and steroids are necessary in addition to anti-ischemic therapy. Epinephrine therapy should be considered in hypotensive patients secondary to anaphylaxis. Coronary vasospasm should be treated with nitrates and/or calcium channel blockers.
- Clinicians should be aware that various mediators of mast cells can cause coronary spasm and even plaque rupture, thereby having a serious impact on the course, prognosis and management of the allergic reaction.

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