

Review

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Kounis syndrome: an update on epidemiology, pathogenesis, diagnosis and therapeutic management

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Abstract: Kounis syndrome has been established as a hypersensitivity coronary disorder induced by various conditions, drugs, environmental exposures, foods and coronary stents. Allergic, hypersensitivity, anaphylactic and anaphylactoid reactions are associated with this syndrome. Vasospastic allergic angina, allergic myocardial infarction and stent thrombosis with occluding thrombus infiltrated by eosinophils and/or mast cells constitute the three reported, so far, variants of this syndrome. Apart from coronary arteries, it affects the cerebral and mesenteric arteries. Its manifestations are broadening and its etiology is continuously increasing. Kounis syndrome is a ubiquitous disease which represents a magnificent natural paradigm and nature's own experiment in a final trigger pathway implicated in cases of coronary artery spasm and plaque rupture. Kounis syndrome seems to be not a rare disease but an infrequently diagnosed clinical entity which has revealed that the same mediators released from the same inflammatory cells are also present and in acute coronary events of non allergic etiology. These cells are not only present in the culprit region before plaque erosion or rupture but they release their contents just before an actual coronary event. Therefore, awareness of etiology, epidemiology, pathogenesis and clinical manifestations seems to be important for its prognosis, diagnosis, treatment, prevention.

Keywords: allergy; anaphylaxis; coronary spasm; coronary thrombosis; Kounis syndrome; stent thrombosis.

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Historical background

Cardiovascular symptoms and signs associated with allergic, hypersensitivity, anaphylactic or anaphylactoid reactions started to appear in the English, German and Austrian medical literature >7 decades ago [1–6]. Such reactions were mainly due to serum sickness and tetanus antitoxin and were characterized as “morphologic cardiac reactions”, “acute carditis” or “lesions with basic characteristics of rheumatic carditis”. The first report of true acute myocardial infarction associated with urticaria [4] was of a 49-year-old man who was under treatment with 300,000 units/day penicillin in oil. This patient was treated with dicumarol, papaverine, morphine and diphenhydramine hydrochloride with favorable results.

However, the detailed description of the “allergic angina syndrome” as coronary spasm, which represents a manifestation of endothelial dysfunction or microvascular angina and progresses to allergic acute myocardial infarction, was not described until 1991 [7].

In 1995, Kovanen et al. examined specimens of coronary arteries from 20 patients who did not suffer from any kind of allergic disease but they had died of acute myocardial infarction and found that the degree of mast cell degranulation was much higher (200:1) at the sites of plaque erosion or rupture than in adjacent areas or in the more distant unaffected areas [8]. The conclusion was that collagen-degrading proteases, from mast cells, could induce plaque erosion and/or rupture.

In 1995, Paris Constantinides raised the possibility that “even ordinary allergic reactions could promote plaque disruption” [9]. This was based on Constantinides's findings that circulating mast cell precursors could penetrate the open junctions between endothelial cells that line human atheromatous plaques in contrast to closed junctions over the normal arterial intima [10].

In 1998, Braunwald categorized allergic angina in a subgroup of dynamic coronary occlusion lesions by stating that “allergic reactions with mediators such as

histamine or leukotrienes acting on coronary vascular smooth muscle” can induce vasospastic angina [11].

In 2002, Theoharides found that mast cell’s role is versatile [12] and compels a more appropriate name to indicate its polydimensional potential, perhaps ‘pleiotropocyte’ (multifaceted cell in Hellenic).

In 2006, the first comprehensive report, concerning this unique association, was published [13] and characterized as “magnificent nature’s own experiment”. In the same year attention was drawn to a potential relationship between drug-eluting coronary stent thrombosis and hypersensitivity to coronary stent components [14].

In 2009, the first reports of children with allergic myocardial infarction were published by Biteker [15].

Finally, in 2015, Lippi and his colleagues [16] found that in patients who were admitted to the emergency department and suffering from anaphylaxis, angioedema, urticaria and urticaria-angioedema, the troponin I levels, that are specific for diagnosing acute myocardial injury, are significantly increased in comparison with healthy controls. This denotes that the heart and especially the coronary arteries constitute primary targets in anaphylaxis.

Today, allergic angina and allergic myocardial infarction are coronary artery disorders that have become ubiquitous diseases [17] affecting patients of any age, involving numerous and continuously increasing causes with broadening clinical manifestations and cover a wide spectrum of mast cell-activation disorders that are referred to as Kounis syndrome.

Definition of Kounis syndrome

Kounis syndrome is defined as the concurrence of acute coronary syndromes including coronary spasm, acute myocardial infarction, and stent thrombosis, with conditions associated with mast-cell and platelet activation and involving interrelated and interacting inflammatory cells, such as macrophages and T-lymphocytes, in the setting of allergic or hypersensitivity and anaphylactic or anaphylactoid insults. This syndrome is caused by inflammatory mediators such as histamine, platelet-activating factor, arachidonic acid products, neutral proteases and a variety of cytokines and chemokines released during the allergic activation process [18]. In this activation cascade, a subset of platelets is also taking place via Fc γ RI, Fc γ RII, Fc ϵ RI, and Fc ϵ RII receptors situated on the platelet surface [19]. Although mast cells are numerically a minority in this inflammatory cascade, they influence decisively the inflammatory process. All of these inflammatory cells

participate in an inflammatory vicious cycle in which can activate each other via multidirectional signals and be co-activated. For example, mast cells can activate macrophages [20] and may enhance T-cell activation [21]. Inducible macrophage protein 1a may activate mast cells [22], while CD169-macrophages activate CD8 T cells [23]. T cells may mediate mast-cell activation and proliferation [24] and regulate macrophage activity [25].

Recent research has shown that Kounis like syndromes can affect the mesenteric [26] and cerebral arteries [27]. The coronary arteries, the heart and the entire arterial system seem to be vulnerable to allergic, hypersensitivity, anaphylactic, and/or anaphylactoid events and physicians should be alert for its consequences.

Etiology

Various causes have been found to trigger Kounis syndrome and their number is increasing rapidly (Table 1). These include several kinds of food, a variety of drugs, environmental exposures and several conditions. The most recent offenders for food-induced Kounis syndrome are fish, shellfish, fruits, vegetables and canned food. The scombroid syndrome [28] which is called also histamine fish poisoning, the anisakiasis caused by nematode parasite [29], the Kiwifruit (*actinidia chinensis*) allergy [30] are some characteristic examples of food-induced Kounis syndrome. Scombroid syndrome or histamine fish poisoning is a histamine toxicity condition resulting from the consumption of spoiled fish. Fish flesh contains the aminoacid histidine and when fish is infected by gram negative bacteria that contain the enzyme histidine decarboxylase, then this enzyme converts histidine to histamine which induces Kounis syndrome. The most commonly spoiled fish causing histamine poisoning include the Scombridae species, such as tuna, mackerel and bonitos, and less commonly the Clupeidae species, such as sardines, anchovies and herring [31]. Common allergic symptoms associated with scombroid syndrome have been reported to include flushing, rashes, swelling of the tongue and face, sweating, palpitations, vomiting, diarrhea, headaches and, in severe cases, bronchospasms, hypotension and shock. Several cases of scombroid syndrome associated with Kounis syndrome have been reported [32]. Scombroid syndrome cases have been often encountered in Mediterranean territory due to existence of several fish species and abundant fish consumption.

Anisakiasis is another condition associated with ingesting raw or undercooked fish or seafood infested

Table 1: Causes incriminated of inducing Kounis syndrome.

Drugs	Conditions	Food consumption	Environmental exposures
– Analgesics (aspirin, dipyron)	– Angioedema	– Actinidia chinensis	– Grass cutting
– Anesthetics (etomidate, isoflurane, midazolam, propofol, remifentanyl, rocuronium bromide, succinylcholine, suxamethonium, trimethaphan)	– Anisakiasis	– Canned food (tuna)	– Hymenoptera stings
– Antibiotics (ampicillin, ampicillin/sulfactam, amoxicillin, amikacin, cefazolin, ceftiofime, cerufoxime, cephradine, cinoxacin, lincomycin, penicillin, sulbactam/cefoperazone, piperacillin/tazobactam, trimethoprim-sulfamethoxazole, sulperazon, vancomycin)	– Bronchial asthma	– Fish	– Jellyfish stings
– Anticoagulants (heparin, lepirudin)	– Churg-Strauss syndrome	– Fruits	– Latex contact
– Anti-neoplastics (5-fluorouracil, capecitabine, carboplatin, denileukin, interferons, paclitaxel, vinca alkaloids)	– Exercise-induced anaphylaxis	– Mushroom poisoning (Coprinosopsis atramentaria)	– Millet allergy
– Contrast media (iohexone, loxaglate, meglumine diatrizoate, sodium indigotindisulfonate)	– Food allergy	– Shellfish	– Poison ivy
– Glucocorticoids (betamethasone, hydrocortisone)	– Hay fever	– Vegetables	– Scorpion sting
– Nonsteroidal anti-inflammatory drugs (alclufenac, diclofenac, naproxen)	– Idiopathic anaphylaxis	– Tomato salad	– Viper venom
– Proton pump inhibitors (lansoprazole)	– Intracoronary stenting		– Metals
– Skin disinfectants (chlorhexidine, povidone-iodine)	– Mastocytosis		
– Thrombolytics (streptokinase, tissue plasminogen activator, urokinase)	– Nicotine		
– Others (allopurinol, bupropion, clopidogrel, dextran, enalapril, esmolol, fructose, gelofusin, insulin, iodine, iron, losartan, protamine, tetanus antitoxin, glaphenine, mesalamine)	– Scombroid syndrome		
	– Serum sickness		
	– Skin itching		
	– Stents (bare metal, drug eluting)		

with anisakis simplex [33] that is a common nematode parasitizing in fish that secretes allergenic substances. In anisakiasis and scombroid syndrome, humans are sensitized via the alimentary system (Figure 1). Cardiovascular involvement and Kounis syndrome are occasionally additional serious manifestations [34, 35]. Allergic symptoms, compatible history, positive serum-specific IgE levels, and positive skin prick test constitute the basis for diagnosis of anisakiasis. The latter is a confirmatory test for allergy to anisakis simplex. Therefore, contrary to scombroid syndrome, anisakiasis is an IgE-mediated food allergy and future abstention from eating raw or undercooked fish or seafood fish is always required.

Kiwifruit or *Actinidia chinensis* is a fruit rich in vitamins A, C, K, E, copper, fibers, folate, potassium, iron and manganese and has become popular for consumption in many parts of the world. However, allergies to kiwifruit are becoming increasingly common, and severe reactions have occasionally been reported, especially in children. Several publications have shown that eating or peeling green-fleshed kiwifruit may elicit typical IgE-mediated allergic reactions in both children and adults [30, 36, 37].

Birch and grass pollinosis as well as latex allergies are often associated with kiwifruit allergy. Eleven green kiwifruit allergens recognized to date, termed Act d 1 through Act d 11. Bet v 1 homologue (Act d 8) and profilin (Act d 9), are important allergens in polysensitized subjects, whereas actinidin (Act d 1) is important in kiwifruit monosensitized subjects.

Gelofusin is a macromolecule made from succinylated bovine gelatin and is used intravenously as plasma substitute or expander that modifies fluid gelatins. Kounis syndrome associated with perioperative cardiac arrest due to Gelofusin anaphylaxis confirmed with skin prick test has been [38]. Gelatins are proteins derived from collagen obtained from cow and pig bones and the hides and skin of fish that are used in lunch meats and as clarifying agents in wine, juices and other beverages. Gelatins are common ingredients in foods such as jellies, sweets, yogurt and frozen desserts [39]. There are also drug capsules, suppositories, plasma expanders and stabilizers in vaccines, including diphtheria-tetanus-pertussis, measles, mumps, rubella, varicella, yellow fever, rabies, and some influenza vaccines that contain bovine and

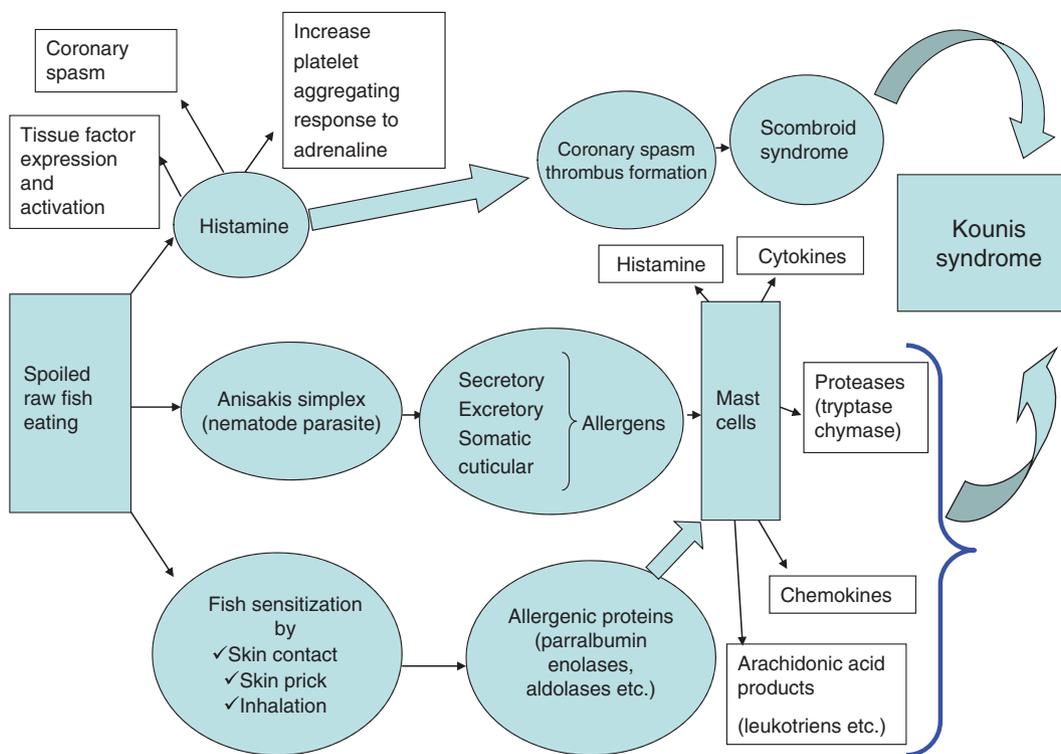


Figure 1: The mechanism by which fish eating can induce Kounis syndrome.

porcine gelatins. Gelatins are added to these vaccines as heat stabilizers. Specific gelatin antibodies have been detected in patients following vaccination, and type I hypersensitivity reactions to gelatin have been reported in patients with specific IgE levels as low as 0.8 kUa/L [40]. Since gelatin is an ingredient of various vaccines given in children, vaccination is thought to be the primary route of sensitization. They can induce severe allergic reactions, including anaphylaxis and Kounis syndrome (Figure 2). Recently, anaphylaxis with cardiovascular symptoms, such as profound hypotension, tachycardia and elevated airway pressure, has been reported following intraosseous gelatin administration [41].

Commonly used drugs such as losartan and corticosteroids are also incriminated to induce Kounis syndrome. Losartan is a nonpeptide imidazole derivative and constitutes the first angiotensin II receptor antagonist that has been approved for treatment of hypertension since 1995. Despite its extensive use, allergic reactions rarely have been reported [42]. Cardiovascular events affecting the coronary arteries are also very uncommon but reports associating the use of losartan with repeated attacks of angina pectoris and coronary artery spasm progressing to acute myocardial infarction with electrocardiographic changes and raised troponin resembling Kounis syndrome have been published [43, 44].

Corticosteroids are widely used today for the treatment of allergic, cutaneous, respiratory, rheumatologic, renal diseases as well as in transplant recipients. Even for the treatment of refractory vasospastic angina, particularly when the patient has an allergic tendency, such as bronchial asthma, corticosteroids are beneficial [45]. Paradoxically, corticosteroids may themselves cause allergic reactions and even anaphylaxis. Prednisolone given for the treatment of wasp sting anaphylaxis in a young patient with normal coronary arteries was complicated by acute myocardial infarction resembling Kounis syndrome [46].

It should be always remembered that environmental exposure to various substances can occur through the “kiss of death” [47] and “dog licking” [48]. “The kiss of death” occurs when a person after consumption of shellfish or peanuts kisses passionately his or her friend who happens to be allergic to these substances. Furthermore a dog, who receives antibiotic such as penicillin for any infection, can be very dangerous when he licks his penicillin allergic master.

In the folk literature the Superman Christopher Reeves, who died from acute myocardial infarction following an allergic reaction to amoxicillin and the pop singer Michael Jackson who died after having consumed repeated doses of the anesthetic propofol which is a known antigenic substance, had suffered Kounis syndrome.

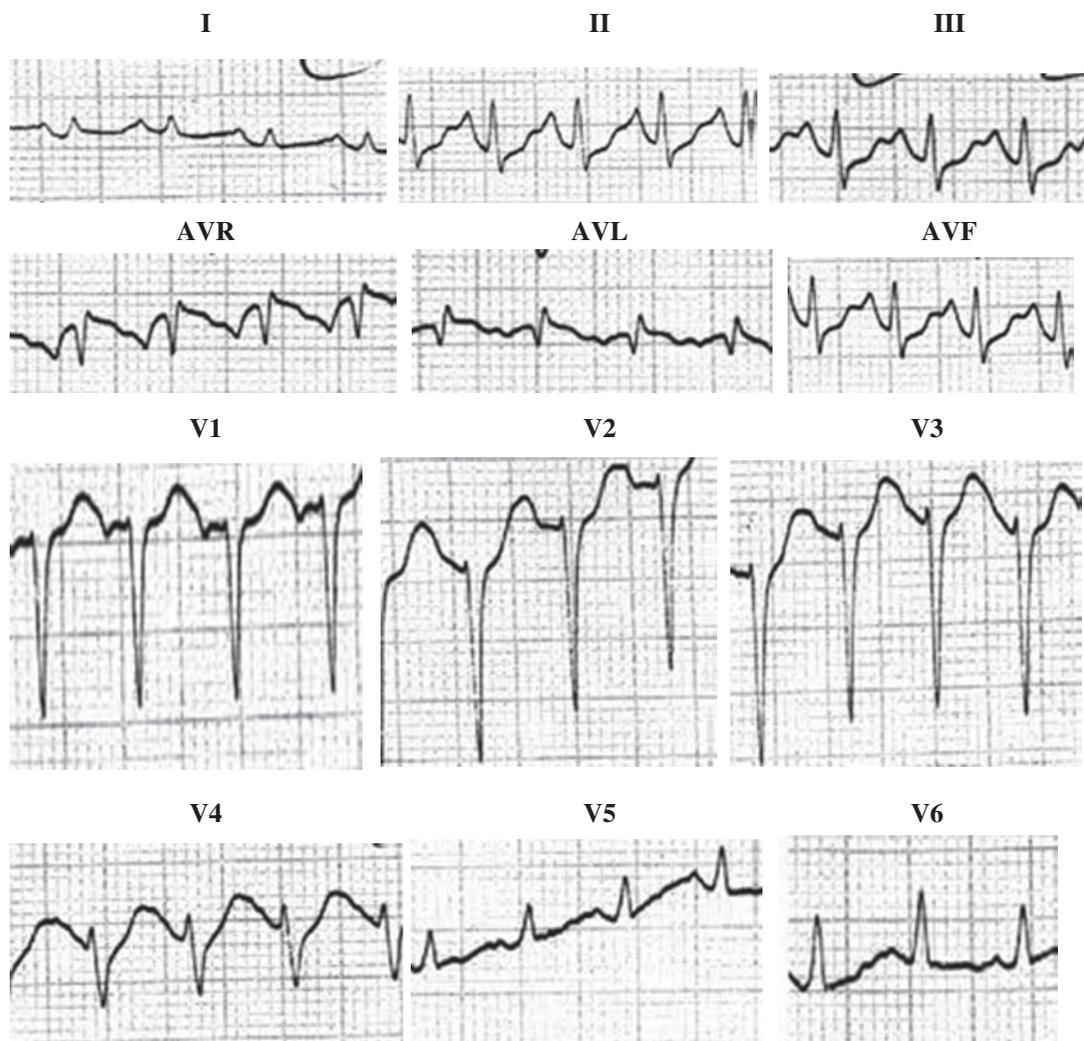


Figure 2: Electrocardiogram of Kounis syndrome following rubella vaccination (unpublished data).

Sinus tachycardia, low voltage, ST elevation in I and AVL, T inversion in V5–V6 with diminished R wave in V1–V4 leads, minutes after an allergic reaction to rubella vaccination and 2 h before sudden death. Coronary histology showed infiltration of coronary intima, media and adventitia by numerous eosinophils and mast cells.

Incidence and epidemiology

The incidence of anaphylaxis with circulatory symptoms during a 3-year period has been estimated in a retrospective study [49]. In this study, 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. Death due to anaphylaxis had occurred in three subjects making the case–fatality rate to be 0.0001%.

As far as Kounis syndrome is concerned, recent reports have shown that this syndrome has been observed in every race, age group (from 2 to 90 year olds) and geographic location. Kounis syndrome seems to be not a rare disease, but it is infrequently reported in the literature

and recognized in clinical practice. This is due to missed, unrecognized and/or undiagnosed cases. Furthermore, there is paucity of large prospective trials, determining its prevalence and exact incidence.

However, in the only prospective study undertaken so far [50], it was found that between of 138,911 patients who were admitted to the hospital's emergency department during 1 year, 793 presented with complaints of allergy. Between them, 769 were admitted with urticaria and 24 with angioneurotic edema. The incidence of allergy admissions during 1 year was 5.7 per 1000 patients. The incidence of Kounis syndrome at the emergency department in that year among all admissions and allergy patients was 19.4 per 100 000 (27/138,911) and 3.4% (27/793), respectively.

Between 51 cases of Kounis syndrome reported to International Pharmacovigilance Agency (VigiBase™) in the period 2010–2014 almost half cases (22 reports) belonged to the year 2014. Most cases occurred in the USA and non-steroidal anti-inflammatory drugs were the most frequent trigger drugs [51].

In the district of Achaia, Greece with a population of 300,000 inhabitants, and with increased awareness for the existence of Kounis syndrome, 52 cases of this syndrome have been encountered in the last 4 years caused by environmental exposures, drug allergies and stent implantation. The annual incidence of Kounis syndrome in this district was estimated of 4.33 cases/100,000 inhabitants [52].

The catheterization laboratory prevalence of Kounis syndrome it was estimated to be 0.002% in a tertiary hospital in Istanbul, Turkey [53]. In this hospital, 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.

In the recent important study [16], of 31 patients admitted to the emergency department and suffering from anaphylaxis, angioedema, urticaria and urticaria-angioedema it was found these patients had significantly increased troponin I serum levels in comparison with 125 healthy controls. In the subgroup of anaphylaxis, troponin I levels were higher than those of patients with milder allergic reactions. The authors suggested systematic troponin measurement in patients with acute allergic reactions in order to detect and treat potential myocardial injury.

In another important study [54] measuring troponin I levels and using, for the first time echocardiographic techniques in the emergency department, it was found that, between 300 anaphylaxis cases, myocardial injury was present in 7.3% of patients. Various cardiomyopathy, including Kounis syndrome and Takotsubo cardiomyopathy, was also observed in patients with myocardial injury.

These two recent studies might have profound clinical, therapeutic and pathophysiologic implications as far as anaphylaxis, myocardial injury and the incidence of Kounis allergy-associated acute coronary syndrome is concerned. The above studies come to support our view that in allergic and anaphylactic reactions, the heart and especially the coronary arteries are the primary target of the released mediators that induce myocardial injury manifesting as Kounis syndrome resulting in troponin raising and physicians should focused their attention on this matter. Furthermore, there is previous laboratory and clinical evidence that inflammatory mediators released

locally and in the systemic circulation during allergic and anaphylactic reactions are causing myocardial damage implicated in anaphylactic cardiac shock and cerebral hypoperfusion. This denotes that the incidence of Kounis syndrome is higher that it has estimated so far.

Kounis syndrome has mostly been encountered in southern Europe, especially Turkey, Greece, Italy and Spain. This geographical variation could be attributed to the increased awareness of physicians of the existence of Kounis syndrome, climate and environmental conditions, resulting in pollen cross reactivities and hymenoptera exposures, overconsumption of medicines, or inadequacy of preventative measures.

Gene–environment interactions starting in early life using the epigenetic approach should be also explored too. Indeed, a patient who had been admitted with chest pain to the emergency department, hospitalized for coronary vasospasm and diagnosed to have Kounis syndrome, had also heterozygous E148Q mutation [55].

It is anticipated that with increased awareness about the existence of Kounis syndrome and conduction of large prospective trials the true estimation of its incidence will be achieved.

Pathogenesis

The main inflammatory cells that are involved in the development of Kounis syndrome are mast cells that interact with macrophages and T-lymphocytes via multidirectional stimuli. A subset of platelets bearing FC γ RI, FC γ TII, FCeRI and FCeRII receptors are also involved in the activation cascade [19, 56]. Mast cells enter the circulation from bone marrow as mononuclear cell precursors and circulate as mast cell precursors bearing in their surface KIT receptors for stem cell factor. Stem cell factor is a major cytokine which is essential for mast cell growth, differentiation, development, proliferation, survival, adhesion, and homing. Mast cells go to all human tissues even to the brain tissue which does not suffer from allergic reactions because IgE antibodies could not cross the blood-brain barrier. In the tissues, they differentiate and mature. This takes several days, even weeks to accomplish. On the contrary, basophils mature in bone marrow from granulocyte precursors and enter the circulation as mature cells and they do not go into the tissues, going there only during the late stage of an allergic reaction. Mast cells preform and store approximately 500 secretory granules and many others which are made de novo and are released locally and in systemic circulation when specific antigens react

with IgE antibodies attached to mast cells and induce mast cell degranulation. This degranulation resembles a bag of popcorn ‘popping’ until the contents overflow and occurs only in approximately 10% of atopic individuals. Mast cells have been linked to many human organs and systems including the heart and the coronary arteries.

The initiation of an allergic, hypersensitivity or anaphylactic reaction takes place when allergens cross-bridge their corresponding, receptor-bound immunoglobulin E (IgE) antibodies, on the mast cell or basophil cell surface. These cells degranulate and release their mediators when the critical number of bridged IgE antibodies reaches the order of 2000 out of maximal number of some 500,000–1,000,000 IgE antibodies on the cell surface [57]. A total of approximately 1000 bridges are necessary to induced mast cell degranulation. However, recent findings indicate that mast cells can be activated by nonallergic triggers often without degranulation, but with selective release of potent and vasoactive compounds [58]. During allergy, hypersensitivity, or anaphylaxis degranulation of mast cells takes place and a variety of stored and newly formed inflammatory mediators are released locally and in the systemic circulation. These include: biogenic amines such as histamine, chemokines, enzymes such as the neutral proteases chymase, tryptase, cathepsin-D, peptides, proteoglycans, cytokines, growth factors and arachidonic acid products such as leukotrienes, thromboxane, prostacyclin, PAF and tumor necrosis factor- α (TNF- α). Most of these mediators have important cardiovascular actions. Histamine induces coronary vasoconstriction, induces tissue factor expression and activates platelets (Table 2). All three neutral proteases (Table 3) can activate matrix metalloproteinases, which can degrade the collagen cap and induce plaque erosion and rupture [59]. Tryptase exerts a dual action on the coagulation cascade with both thrombotic and fibrinolytic properties [60]. Furthermore, chymase and cathepsin-D can act as converting enzymes and convert angiotensin I to angiotensin II, which is a

Table 2: Cardiac actions of histamine.

1. Induces coronary vasoconstriction (histamine test)
2. Induces tissue factor expression and activity
3. Activates platelets and potentiates the aggregatory response of agonists, e.g. adrenaline, 5-hydroxytryptamine, and thrombin
4. Induces intimal thickening
5. Induces inflammatory cell modulation
6. Modulates the activity of neutrophils, monocytes, and eosinophils
7. Causes proinflammatory cytokine production
8. Causes P-selectine upregulation
9. Sensitizes nerve endings in coronary plaques

Table 3: Main actions of neutral proteases.

Tryptase

1. Activates the zymogen forms of metalloproteinases such as interstitial collagenase, gelatinase, and stromelysin and can promote plaque disruption or rupture
2. Degrades the pericellular matrix components fibronectin and vitronectin and neuropeptides, such as vasoactive intestinal peptide (VIP) and calcitonin gene related peptide (CGRP)
3. Can degrade HDL
4. Activates neighboring cells by cleaving and activating protease-activated receptor (PAR) 2, and thrombin receptors

Chymase

1. Converts angiotensin I to angiotensin II and angiotensin II receptors are found in the medial muscle cells of human coronary arteries. Thus, angiotensin II generated by chymase could act synergistically with histamine and aggravate the local spasm of the infarcted coronary artery. Chymase also can remove cholesterol from HDL
2. Activates MMP-1,-2,-9 and plays a major role in the physiologic degradation of fibronectin and thrombin

Cathepsin D

1. Is angiotensin II-forming protease
2. Degrades both fibronectin and VE-cadherin which are necessary for adhesion of endothelial cells to their basement membrane and to each other

major vasoconstricting substance [61]. Leukotrienes are also powerful vasoconstrictors and their biosynthesis is enhanced in the acute phase of unstable angina [62, 63]. Thromboxane is a potent mediator of platelet aggregation with vasoconstricting properties [64, 65] and PAF, in myocardial ischemia, acts as proadhesive signaling molecule via activation of leukocytes and platelets to release leukotrienes or as a direct vasoconstrictor [66]. All these pre-formed and newly synthesized inflammatory mediators released locally and pouring into systemic circulation can cause either coronary artery spasm which could progress to acute myocardial damage or immediate coronary thrombosis which constitute the main clinical manifestations of Kounis syndrome.

Clinical presentation

The main clinical symptoms and signs of Kounis syndrome are always associated with subclinical, clinical, acute or chronic allergic reactions accompanied by cardiac symptomatology. A variety of electrocardiographic changes ranging from ST segment elevation or depression to any degree of heart block and cardiac arrhythmias resembling digitalis intoxication are always associated with the cardiac symptoms and signs (Table 4). A high index of

Table 4: Clinical and laboratory findings in Kounis syndrome.

Clinical symptoms	Clinical signs	Electrocardiographic signs	Laboratory signs
– Acute chest pain	– Bradycardia	– Atrial fibrillation	– Coronary angiography (spasm, thrombosis)
– Chest discomfort	– Cardiorespiratory arrest	– Bigeminal rhythm	– Eosinophilia
– In swallowing	– Cold extremities	– Heart block	– Increased cardiac enzymes and especially CPK-MB
– Dyspnea	– Diaphoresis	– Nodal rhythm	– Increased troponins
– Faintness	– Hypotension	– Sinus bradycardia	– Cardiomegaly in the chest X-ray
– Headache	– Pallor	– Sinus tachycardia	– Dilated cardiac chambers in echogram
– Malaise	– Palpitations	– ST segment depression or elevation	– Eosinophils, and/or mast cells in coronary biopsy
– Nausea	– Skin rash	– T-wave flattening and/or inversion	– MRI: subendocardial gadolinium concentration
– Pruritus	– Sudden death	– QRS complex prolongation	– SPECT: detects ischemia
– Skin itching	– Sweating	– QT segment prolongation	
– Syncope	– Tachycardia	– Ventricular ectopics	
– Vomiting		– Ventricular fibrillation	

suspicion regarding this syndrome is of paramount importance. Although it is not a rare disease is infrequently diagnosed and easily overlooked [67]. Kounis syndrome cases, although under reported, are more often encountered in clinical practice and it is anticipated that many more causative factors will be implicated in the future.

Three variants of Kounis syndrome have been described [68]: The type I variant (coronary spasm), which seems to represent a manifestation of endothelial dysfunction or microvascular angina, includes patients with normal or nearly 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 that includes patients with culprit but quiescent pre-existing atherosclerotic disease in whom the acute release of inflammatory mediators can induce either coronary artery spasm with normal cardiac enzymes and troponins or coronary artery spasm together with plaque erosion or rupture manifesting as acute myocardial infarction. The type III variant that includes patients with coronary artery stent thrombosis in whom aspirated thrombus specimens stained with hematoxylin-eosin and Giemsa demonstrate the presence of eosinophils and mast cells, respectively. This variant is also diagnosed in patients with stent implantation who died suddenly and histological examination of coronary intima or media and/or adventitia adjacent to stent is infiltrated by eosinophils and/or mast cells.

The life saving implantation of coronary stents has become the most frequent performed therapeutic procedure in medicine [69]. There are three kinds of stents used today. The bare metal stents with platform made of stainless steel which contains nickel, chromium,

titanium, manganese, and molybdenum. The first and the second generation drug eluting stents and the bio-absorbable stents. The second generation drug eluting stents that carry the misleading term cobalt-chromium and platinum-chromium stents and have platforms which contain also nickel and other metals. These stents are covered with polymer coatings which serve as drug carriers and permit controlled drug release. The released drugs have antiproliferative properties and include the everolimus, zotarolimus or biolimus substances that inhibit the mammalian target of rapamycin and prevent re-endothelialization thus avoiding stent restenosis. The bio-absorbable stents are usually made from highly biocompatible poly (D, L-lactic-co-glycolic) acid that is considered to be hypo-allergic. However, in recent reports, it was shown that, although rarely, bio-absorbable scaffold components can induce local foreign body reactions and hypersensitivity reactions [70]. All these types of stents are complicated with the rare but so much feared stent thrombosis. Randomized clinical trials [71] have shown a 0.2%–0.5% incidence of stent thrombosis yearly with death rate up to 40%. As it is not known whether stent thrombosis is a time limited phenomenon, the problem might increase, if events continue to accrue over the years. Despite that stent thrombosis is thought to be multifactorial, so far, clinical reports and reported pathology findings in patients died from coronary stent thrombosis as well as animal studies and experiments, point towards a hypersensitivity inflammation.

Metals constitute an important class of substances that can act as allergens. It is known that metals are constituents in consumer products such as jewelers, cosmetics, paints, dental and body implants as well as endovascular and intracardiac devices. Apart from the well known significance of nickel, chromium, and cobalt in inducing skin hypersensitivity other metals such as

aluminum, beryllium, copper, gold, iridium, mercury, palladium, platinum, rhodium, and titanium are emerging human body sensitizers. In the US nickel, chromium and cobalt induce allergic skin reactions in about 14%, 4%, and 9% while in Europe in about 20%, 4%, and 7%, respectively [72]. Stented regions constitute, therefore, an ideal surrounding for endothelial damage and dysfunction, together with hemorheologic changes and turbulence as well as platelet dysfunction, coagulation and fibrinolytic disturbances. All stent components, namely, stent platforms with their metals, polymer coatings and the released drugs are strong allergens which apply continuous, repetitive, persistent and chronic allergic irritation to the coronary intima. Consequently, the stented and thrombotic areas are infiltrated by inflammatory cells including eosinophils, macrophages, T-cells and mast cells [73]. That is why we have insisted that stent thrombosis is mainly a manifestation of Kounis syndrome [74].

One should be always bear in mind that allergic inflammation goes through three phases [75], the early phase which lasts minutes, the late phase which lasts from 2 h to 2 days and the chronic phase which follows a continuous, persistent, and repetitive allergen exposure and lasts as long as the allergen is present. It seems likely that early (acute <24 h and sub acute 1–30 days), late (>30 days) and very late (>12 months) stent thrombosis correspond temporally with the early, late and chronic allergic inflammation [76] independently of level of documentation as definite or confirmed (symptoms suggestive of an acute coronary syndrome and angiographic or pathologic confirmation), probable (unexplained death within 30 days or target vessel myocardial infarction without angiographic confirmation) and possible (any unexplained death after 30 days).

Innate release of pro-inflammatory molecules: common pathway between allergic and non allergic coronary syndromes?

The discovery of Kounis hypersensitivity-associated acute coronary syndrome has paved the way to discover that the same pro-inflammatory molecules released during acute allergic episodes are also present in blood or urine of patients suffering from acute coronary events of non allergic etiology. Therefore, it seems likely that a common pathway between allergic and nonallergic coronary syndromes exists. The presence of similar pro-inflammatory

molecules found in Kounis syndrome that are also found in other similar cases suggests that this is a more general problem. The following reports support this view:

Increased histamine levels were found in the great cardiac vein in patients suffering from attacks of variant angina without any correlation with an allergic event [77]. Blood concentration of histamine, more than twice than age- and sex-matched controls, associated with enhanced oxidative stress was found in patients with acute coronary syndromes of non allergic etiology [78]. Histamine blood levels were significantly higher in patients with various types of non allergic etiology ischemic heart disease such as unstable angina and acute myocardial infarction when compared with control normal subjects [79]. Persistent tryptase elevation was detected in patients with non allergic acute coronary syndromes with higher concentration in the ST segment depression group in the acute phase and at follow up [80].

In non allergic patients with acute myocardial infarction and unstable angina pectoris, serum tryptase and chymase levels were higher than in patients without substantial coronary disease [81]. Raised tryptase levels were observed in non allergic patients with significant chronic coronary artery disease as a result of chronic low-grade inflammatory activity present in the atherosclerotic plaques [82]. Tryptase levels were found fivefold increased after 5 min, tenfold increased after 15 and 60 min and twice as low in the free-symptom period in patients with unstable angina immediately after the onset of chest pain with electrocardiographic signs of ischemia [83].

Arachidonic acid products including thromboxane and leukotrienes were found to be significantly higher in nonallergic patients with unstable angina than in patients with stable angina and in patients with nonischemic chest pain [84]. The same mediators have been found at significantly higher levels in the systemic arterial circulation in the acute stage of nonallergic myocardial infarction than in circulation of normal controls [85]. Interleukin-6 levels, derived from inflamed coronary plaques and areas of myocardial necrosis, are elevated in patients with nonallergic acute coronary syndromes [86, 87].

Since the medical literature abounds with the above reports which show that the same mediators, deriving from the same cells and being capable to induce arterial spasm and atheromatous plaque erosion and rupture, are found to be present in both acute allergic and in acute coronary events of non allergic etiology, then a new possibility emerges for prevention of the coronary plaque to become unstable. This can be done by inhibition of mast cell degranulation which has been already achieved experimentally [88, 89]. Therefore is Kounis syndrome a

magnificent natural paradigm in a final trigger pathway implicated for coronary spasm and plaque erosion or rupture leading to acute myocardial infarction? Is Kounis syndrome Nature's own experiment which shows to us how to prevent acute cardiac and cerebrovascular events? Future trials towards this direction seem to be justifiable.

Kounis syndrome: Nature's own experiment?

Mother Nature continuously offers natural paradigms and performs natural experiments pointing towards discovering therapeutic and scientific modalities in order to alleviate human diseases. The following additional findings suggest the existence and emphasize the significance of Kounis syndrome:

Allergic rhinoconjunctivitis and wheezing, that are common allergic symptoms, were found to be significantly associated with an increased risk of coronary heart disease according to National Health and Nutrition Survey III on non-institutionalized civilian population in the US from 1988 through 1994 [90]. Eosinophil counts were found significantly increased in patients with vasospastic angina pectoris and could predict the severity of the disease. Following medical treatment and relief of chest symptoms the eosinophil count decreased significantly to the same level as those of the control group [91]. Clinical reports have shown that the absolute number of eosinophils and the eosinophil/leukocyte ratio, in the peripheral blood, are significantly elevated in patients with coronary artery disease [92]. Coronary vasospasm associated with eosinophilia responds poorly to conventional vasodilator treatment and while the risk of recurrent coronary events is high, the majority of patients respond to treatment which suppresses eosinophilia such as corticosteroids [93]. Subcutaneous allergen-specific immunotherapy used for treatment of IgE-mediated allergic diseases was found to be associated with lower risk of acute myocardial infarction and autoimmune disease [94]. Pollen is a well known trigger of allergies and daily variations of air pollution was found to be associated with increased incidence of deaths from cardiovascular disease [95] and Kounis syndrome [96]. Inhaled corticosteroids were found able to reduce the risk of myocardial infarction in patients suffering from asthma and in particular in those with more severe disease [97]. Several experiments have also shown that diesel exhaust particles can trigger mast cell degranulation and histamine release [96]. Anti-inflammatory pretreatment with sodium cromoglycate and dexamethasone

can abrogate late thrombotic events by preventing histamine release from mast cells [88]. Furthermore, mast cell stabilization with cromolyn was found to prevent all pathophysiological events such as intraplaque hemorrhage, macrophage apoptosis and vascular leakage in atheromatous plaques leading to plaque rupture and the development of acute coronary events [98].

All above paradigms and experiments that associate allergic manifestations with cardiac events together with the fact that anti allergic therapy with mast cell stabilizing agents can prevent late thrombotic events and atheromatous plaque erosion or rupture provide new potential therapeutic targets. It seems likely that once again Mother Nature is performing her duties!

Diagnosis

The diagnosis of Kounis syndrome is based on clinical symptoms and signs as well as on laboratory, electrocardiographic, echocardiographic and angiographic evidence. A variety of these findings might accompany allergic symptomatology that helps in putting the correct diagnosis. Recently, modern tools such as cardiac magnetic resonance imaging and myocardial scintigraphy have helped to confirm the diagnosis. A high index of suspicion is of paramount importance. Therefore, patients with systemic allergic reactions associated with clinical, electrocardiographic and laboratory findings of acute myocardial ischemia should be suspected as having Kounis syndrome (Table 4).

Measuring serum tryptase, histamine, cardiac enzymes and cardiac troponins are particularly helpful estimations. The sole source of tryptase is the mast cells, although negligible amounts of tryptase are found in human basophils (0.04 pg per basophil). Tryptase, like other inflammatory mediators, is short lived and has a half-life of about 90 min [99]. The best time for the first specimen seems to be half an hour after the initial symptoms and 30 min thereafter during the following 2 h [100]. It must be pointed out that elevated levels of tryptase may be present in the circulation for several hours. Aortic post-mortem tryptase measurements can be of value as soon as possible after death in cases where Kounis syndrome is suspected [101]. Histamine release from mast cells is rapid and short lived and circulates for only about 8 min after an allergic event, therefore blood samples should be collected immediately after the onset of chest pain and before any analgesic, especially morphine, administration [102]. Cardiac enzymes such as CK and in particular

CK-MB are of value in diagnosing cardiac damage associated with allergic or anaphylactic insults. The systematic measurement of cardiac troponins in all patients admitted to the emergency department with acute allergic reactions in order to timely diagnose and appropriately manage a potential cardiac injury manifesting as Kounis syndrome [16] or as takotsubo cardiomyopathy [54] has been already suggested. Echocardiography and coronary angiography are necessary in diagnosing cardiac wall abnormalities including takotsubo cardiomyopathy and delineating the coronary anatomy in cases of Kounis syndrome. It must be pointed out that these two clinical entities could be co-existed [103]. Newer techniques such as thallium-201 single-photon emission computer tomography (SPECT) and 125I-15-(p-iodophenyl)-3-(R,S) methylpentadecanoic acid (BMIPP) SPECT have been already used, recently, in type I variant of Kounis syndrome and revealed severe myocardial ischemia while coronary angiography showed normal coronary arteries [104]. Dynamic cardiac magnetic resonance imaging (MRI) is also a reliable tool for assessing cardiac involvement in Kounis syndrome. Delayed contrast-enhanced images show normal washout in the subendocardial lesion area in patients with Kounis syndrome type I variant [105].

Therapeutic management

Acute coronary syndromes, secondary to allergic reactions, are associated with significant morbidity and mortality in sensitized individuals. The systemic allergic response caused by inflammatory mediators should be controlled early in the management of these patients. However, therapeutic management of Kounis syndrome is a challenging procedure because it needs to treat both cardiac and allergic symptoms simultaneously. Drugs administered to treat the cardiac manifestations can worsen allergy and drugs given to treat the allergic symptoms can aggravate the cardiac function [106].

In patients with type I variant, treatment of the allergic event alone can abolish symptoms. 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 are adequate. The administration of vasodilators such as calcium channel blockers and nitrates can abolish hypersensitivity induced vasospasm. Calcium channel blockers can induce minor skin rash and angioedema is extremely uncommon. However, nitroglycerin can cause hypotension and tachycardia

that may further complicate anaphylactic reaction. In addition, although uncommon, allergic reactions to nitroglycerin such as urticaria and contact dermatitis can occur especially with the transdermal use of nitroglycerin. Most patients with these reactions have tolerated oral and sublingual nitroglycerin [107]. Therefore, the use of intravenous or sublingual nitroglycerin seems reasonable and safe in patients with Kounis syndrome if the blood pressure is satisfactory. Bolus administration of antihistamines can precipitate hypotension and compromise coronary flow; therefore, these drugs should be given slowly.

In patients with type II variant, treatment should be initiated with an acute coronary event protocol together with corticosteroids and antihistamines. Vasodilators such as nitrates and calcium blockers are given when these are necessary. The use of β -blockers can exaggerate coronary spasm due to unopposed action of α -adrenergic receptors. Epinephrine which is the drug of choice and can save lives in anaphylaxis, but in Kounis syndrome can aggravate ischemia and worsen coronary vasospasm. In severe cases sulfite free epinephrine is preferable to be given intramuscularly because it has faster onset of action and more sustained levels as compared with the subcutaneous route (recommended intramuscular doses 0.2–0.5 mg [1:1000]). Aqueous solution is preferable. In patients with previous history of coronary heart disease, who receive β -blockers, epinephrine may be ineffective. It may also induce more vasospasm due to unopposed α -adrenergic effect. In this case glucagon infusion (1–5 mg, intravenously over 5 min, followed by infusion 5–15 μ g/min) can be used for patients who are already on β -blockers or received them during the management of the acute coronary syndrome [106]. Methoxamine, a potent α agonist, can also be considered in patients who do not respond to epinephrine [106]. Opiates such as morphine, codeine and meperidine given to relieve acute chest pain should be administered with extreme caution in patients with Kounis syndrome, since they can induce massive mast cell degranulation and aggravate allergic reaction. Acetaminophen (paracetamol) is not recommended, especially its intravenous administration, because it might cause severe hypotension due to reduction of cardiac output. Fentanyl and its derivatives show slight mast cell activation and are preferable.

In patients with type III variant the current acute myocardial infarction protocol together with urgent aspiration of intrastent thrombus followed by histological examination of aspirated material and staining for eosinophils (hematoxylin and eosin) and mast cells (Giemsa) should be undertaken. In patients who develop allergic

symptoms following stent implantation administration of antihistamines together with corticosteroids and mast cell stabilizers may relieve the symptoms. When symptoms persist, identification of the culprit cause by patch and/or prick skin tests should be ascertained and desensitization measures should be applied. If these measures fail, stent extraction seems unavoidable [108].

Kounis syndrome is a complex acute coronary syndrome that requires rapid treatment and decisions. Following the relieve of the acute event a full cardiologic work-up, including a 12-lead ECG, echocardiogram and cardiac risk factor modification, is necessary. An allergy work-up should follow to include the assessment of other allergies to food, insect stings, drugs and other environmental agents. Skin tests and food challenges may be useful in identifying the culprit agent.

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