Foods, Drugs and Environmental Factors: Novel Kounis Syndrome Offenders

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Abstract

Kounis syndrome is hypersensitivity coronary disorder induced by various types of environmental exposures, drugs, conditions and stents. Allergic, hypersensitivity, anaphylactic and anaphylactoid reactions are associated with this syndrome. The disorder manifests as coronary spasms, acute myocardial infarction and stent thrombosis and affects the cerebral and mesenteric as well as coronary arteries. Importantly, its manifestations are broad and its etiology is continuously increasing. Recently, a variety of unusual etiologies have been reported including Anisakis simplex, scombroid syndrome, the use of Gelofusin or ultrasound contrast agents, kiwifruit, fly bites, and bee stings. Furthermore, losartan and the paradox of corticosteroid allergy have been implicated as possible causes. Although not rare, Kounis syndrome is infrequently diagnosed. Therefore, awareness of its etiology, manifestations and pathophysiology is important for providing the proper diagnosis and treatment and determining prognosis.

Key words: Anisakis simplex, drugs, Gelofusin, kiwifruit, Kounis syndrome, scombroid syndrome


Introduction

Kounis syndrome, a coronary hypersensitivity disorder, has become ubiquitous and can affect patients of any age, from 2 to 80 years (1, 2). It involves numerous and continuously increasing causes with broadening clinical manifestations (3), and covers a wide spectrum of mast cell-activation disorders (4). Kounis-like syndromes have been reported to affect the cerebral (5) and mesenteric (6) arteries and the heart and entire arterial system are thought to be vulnerable to allergic, hypersensitivity, anaphylactic and/or anaphylactoid events. This syndrome may also complicate mast cell activation disorders (7) and affected areas appear to be the primary sites and targets of anaphylaxis (8).

Kounis syndrome is encountered in patients with stent thrombosis (9), is believed to constitute the main cause of anaphylactic cardiovascular collapse (10) and is regarded as Nature’s own experiment and a magnificent natural paradigm (11) paving the way for treatment to prevent acute coronary and cerebrovascular events. This syndrome is the result of the actions of inflammatory mediators released locally or in the systemic circulation following mast cell degranulation. The released mediators induce either coronary artery spasm that may progress to acute myocardial infarction or atheromatous plaque erosion and/or rupture culminating in coronary thrombosis. Vasospastic angina (type I), acute coronary thrombosis (type II) and stent thrombosis with thrombi infiltrated by mast cells and eosinophils (type III) are the three variants of this syndrome described today. The allergic thrombotic process may also occur following the activation by mast cell mediators of high-and low-affinity FCγRI, FCγRII, FCERI and FCERII receptors situated on the platelet surface (12). It has been demonstrated that mast cells degranulate when 2,000 nearby antibodies attached to the cell surface are bridged by corresponding antigens to form the critical number of 1,000 bridges. This process can be achieved by antibodies of different specifici-

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ties, and the combination of several exposures within a given time is related to the disease severity, especially in children (13).

Several novel offenders have recently been reported to induce Kounis syndrome, including Anisakis simplex, scombroid syndrome, Gelofusin, ultrasound contrast agents, kiwi-fruit, bites from various flies, such as warble flies and bumblebees, losartan and the corticosteroid paradox.

**Anisakis Simplex**

Anisakis simplex is a common nematode parasite in fish that subsequently sensitizes humans via the alimentary system. It parasitizes many commercially important fish species and can cause, although rarely, anisakiasis in humans when accidentally ingested in raw or undercooked infested fish or seafood. Acute IgE-mediated urticaria, angioedema and anaphylaxis are the main manifestations of Anisakis allergy (14). Common immediate hosts include codfish, hake, sardines, anchovy, salmon, tuna, mackerel and squid. Four principal clinical syndromes associated with anisakiasis have been described: gastric, intestinal, ectopic or extra-gastrointestinal and allergic (15). Gastric anisakiasis manifests with severe epigastric pain, vomiting, diarrhea and mild fever one or two hours after the parasite reaches the human stomach. Intestinal anisakiasis characterized by the presence of intermittent or constant abdominal pain starting five to seven days after larva ingestion. Ectopic anisakiasis occurs when the larva penetrates the gastric or gut mucosa and migrates into the peritoneal or pleural cavity, mesentry, liver, pancreas and/or ovaries. Leukocytosis and eosinophilia accompany these clinical syndromes. Allergic anisakiasis is an IgE-mediated allergic syndrome caused by the production of proteases and protease inhibitors secreted during larva penetration, namely excretory/secretory allergens, somatic allergens obtained from the whole body of the parasite and cuticular allergens secreted to protect the parasites from digestive juices (15). The diagnosis is based on a compatible history, such as typical allergic symptoms, particularly urticaria and anaphylactic reactions, a positive skin prick test and positive serum-specific IgE levels. The first report of Kounis syndrome associated with anisakiasis was reported recently (16). The case concerned a 59-year-old mechanic who received treatment with corticosteroids and antihistamines, but not adrenaline, which subsequently induced echocardiographic changes similar to those encountered in patients with Takotsubo cardiomyopathy. Since anaphylactic reactions can induce stress cardiomyopathy, stress may stimulate mast cell and other interrelated inflammatory cell activation, and Kounis syndrome is induced via anaphylactic mechanisms. Therefore, measuring the levels of inflammatory mediators, such as histamine, neutral proteases and arachidonic acid products, and the use of mast cell stabilizers or corticosteroids for the treatment and/or prevention of stress-induced cardiomyopathy may shed further light on the etiology, pathophysiology and treatment of Takotsubo cardiomyopathy (18). Adrenaline is considered to be the drug of choice for anaphylaxis, although an excessive dose may result in coronary spasms and transient Takotsubo syndrome due to direct myocardial stunning. Adrenaline, Takotsubo, anaphylaxis and Kounis syndrome (ATAK) constitutes a challenging contemporary complex (19). The research community should “attack” Takotsubo cardiomyopathy in order to elucidate the etiology and pathophysiology of this disease and develop proper preventive and therapeutic measures. Taken together, these observations show that Kounis syndrome induces Takotsubo cardiomyopathy via the effects of inflammatory mediators. In the described anisakiasis case, the patient was a male mechanic who received treatment with corticosteroids and antihistamines, but not adrenaline, which supports the view that his condition was in fact Kounis syndrome, which subsequently induced echocardiographic changes similar to those encountered in patients with Takotsubo cardiomyopathy. Indeed, an allergy to Anisakis simplex was confirmed on skin-prick testing (16).

**Scombroid Syndrome**

Scombroid syndrome or histamine fish poisoning is a histamine toxicity condition resulting from the consumption of spoiled fish. 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 (20). Fish flesh contains the aminoacid histidine, and when the fish is infected with Gram-negative bacteria containing the enzyme histidine decarboxylase, the enzyme converts histidine to histamine, which consequently causes Kounis syndrome. To date, 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. Recently, a report of scombroid syndrome associated with vasospastic angina progressing to acute myocardial infarction compatible with the type II variant of Kounis syndrome was published (21).
This report concerned a 56-year-old woman who developed a facial rash, parageusia, headache, sweating and hypotension after eating cooked tuna. Simultaneously, she developed retrosternal constrictive pain with bradycardia and electrocardiographic changes compatible with inferior-lateral myocardial ischemia. Coronary angiography revealed critical left anterior coronary artery stenosis necessitating treatment with angioplasty and stenting. Since scombroid syndrome is not an IgE-mediated food allergy, but rather a form of histamine intoxication, future abstinence from eating fish is not required, although caution is necessary to avoid consuming spoiled fish.

**Gelofusin Substance**

Gelatins are proteins derived from collagen obtained from cow and pig bones and the hides and skin of fish. These components are found in lunch meats and are used extensively as clarifying agents in wine, juices and other beverages. They are also common ingredients in foods such as jellies, sweets, yogurt and frozen desserts. Drug capsules, suppositories, plasma expanders and stabilizers in vaccines, including diphtheria-tetanus-pertussis, measles, mumps, rubella, varicella, yellow fever, rabies, and some influenza vaccines contain bovine and porcine gelatins. Gelatins are added to these vaccines as heat stabilizers. However, they can induce severe allergic reactions, including anaphylaxis, when used intravenously as modified fluid gelatins and plasma substitutes or expanders. 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. Gelofusin is a macromolecule made from succinylated bovine gelatin and is therefore structurally different from the gelatins present in foodstuffs. Since gelatin is an ingredient of various vaccines given in children, vaccination is thought to be the primary route of sensitization. Recently, anaphylaxis with cardiovascular symptoms, such as profound hypotension, tachycardia and elevated airway pressure, has been reported following intraosseous gelatin administration. In another recent report, a case of Kounis syndrome associated with perioperative cardiac arrest due to Gelofusin anaphylaxis on confirmed skin prick tests was published. That case involved a 57-year-old patient who developed anaphylactic shock while under anesthesia and developed worsening hypotension and lost cardiac output despite initial management with bolus doses of metaraminol and epinephrine administered intravenously. The patient gradually recovered after receiving intravenous antihistamines, steroids and inotropic support. The details of this case support our view that anaphylactic shock maybe a manifestation of Kounis syndrome.

**Ultrasound Contrast Agents**

Severe anaphylactic reactions with reversible ST segment elevation resembling type I variant Kounis syndrome have previously been reported with microbubbles of sulfur hexafluoride used as the ultrasound contrast agent. Such second-generation ultrasound contrast agents are currently commercially available as suspensions of phospholipid-stabilized sulfur hexafluoride microbubbles in several countries and are used for scanning the heart chambers, large blood vessels and lesions in the breast and liver. They are exclusively used when the results of imaging tests performed without a contrast agent are inconclusive. Hypersensitivity reactions, including anaphylactic shock, have been reported during post-marketing surveillance. In a study of 274 patients assessed over a 4-year period, seven subjects (2.0%) experienced allergic reactions, among whom four individuals (1.1%) developed mild allergic reactions, such as skin erythema and mild sinus tachycardia, and three patients (0.9%) developed severe allergic reactions, such as nonfatal shock. In a recent report concerning a 60-year-old man with two drug-eluting stents subjected to contrast-enhanced dobutamine stress echocardiography to detect myocardial ischemia, a severe allergic reaction developed one minute after the administration of a 1-mL bolus of the agent (SonoVue, Bracco, Milan, Italy). The patient’s symptoms consisted of nausea, sweating, hypotension and severe chest pain with electrocardiographic signs of acute inferior myocardial ischemia. Coronary angiography revealed good stent patency, albeit with 50% stenosis of the proximal to stented segment area compatible with coronary spasms and Kounis syndrome, type II variant. This observation supports our view that stents attract like magnet mast cells that subsequently degranulate and induce coronary spasms and/or plaque erosion or rupture.

**Kiwifruit (Actinidia Chinensis)**

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. The first report of IgE-mediated kiwifruit allergy was published in 1981, and, since 1995, several publications have shown that eating or peeling green-fleshed kiwifruit may elicit typical IgE-mediated allergic reactions in both children and adults. 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.

Recently, an extremely rare trigger of Kounis syndrome, type I variant due to Actinidia chinensis was published. That case concerned a young 23-year-old man with a previous history of oral allergy syndrome to kiwifruit who devel-
oped acute myocardial infarction after ingesting a piece of kiwifruit. This is the second report of kiwifruit-induced Kounis syndrome since the first report in 2010 (35).

**Warble Fly Bites and Bumblebee Stings**

Wasp, bee and fly bites or stings are serious events responsible for more deaths than those from all other poisonous creatures. These bites can cause systemic symptoms, such as hypotension, dyspnea, anaphylactic shock and angioedema (36). Atopic and non-atopic individuals are vulnerable to such stings or bites, and cardiovascular events and Kounis syndrome have been reported on several occasions (37). Two recent reports have documented unusual etiologies of Kounis syndrome. The first report (38) involved the onset of warble fly bite-induced type II variant Kounis syndrome in a 59-year-old patient who subsequently developed dyspnea, nausea and chest pain. An electrocardiogram showed ST segment elevation in the anterior leads compatible with acute anterior myocardial infarction, and coronary arteriography revealed critical lesions in the left anterior descending artery. The second report (39) concerned bumblebee sting-induced type II variant Kounis syndrome in a 60-year-old hypertensive man who presented with an erythematous rash all over his body in addition to chest discomfort, hypotension and bradycardia after the sting. An electrocardiogram showed atrioventricular block and ST segment elevation compatible with a diagnosis of inferior myocardial infarction. Cardiac catheterization revealed severe proximal and medial right coronary artery stenosis.

**Angiotensin II Receptor-α Antagonist Losartan**

Losartan is a non-peptide imidazole derivative and the first angiotensin II receptor antagonist approved for the treatment of hypertension since 1995. Despite its extensive use, allergic reactions to this drug are rarely reported. Only one recent case describing losartan-induced anaphylaxis and angioneurotic edema has been published (40). Cardiovascular events affecting the coronary arteries are also very uncommon, with only one case of repeated attacks of angina pectoris associated with the use of losartan in a patient with a history of coronary revascularization having been reported (41). The patient had not undergone any cardiology or allergology assessments, and the mechanism of the angina attacks remained unclear.

However, a report describing a 55-year-old woman with the skin disease prurigo nodularis (42) who developed coronary artery spasms 15 minutes after receiving the first 50 mg of losartan was recently published. An electrocardiogram revealed ST segment elevation in the lateral leads and a coronary angiogram showed severe migrating stenosis of the left main coronary artery suggesting coronary spasms, while the remainder of the arteries were normal. Due to the persistent symptomatology and falling blood pressure, the patient received anti-allergic treatment, inotropic support and later intra-aortic balloon pump placement. Finally, plasmapheresis was initiated, as losartan becomes highly bound to plasma proteins, with a good response. The authors of this report wondered whether their case involved allergic angina and Kounis syndrome, type I variant due to the presence of migrating coronary spasms, severe elevation of the troponin level and skin disease (prurigo nodularis), which are known to be associated with higher than normal levels of mast cells (43).

**Corticosteroid Paradox: Can Corticosteroids Induce Kounis Syndrome?**

Corticosteroids are currently widely used for the treatment of allergic, cutaneous, respiratory, rheumatologic and renal diseases as well as in transplant recipients. Corticosteroids are beneficial for treating refractory vasospastic angina, particularly when the patient has an allergic tendency, such as bronchial asthma (44). Paradoxically, corticosteroids may themselves cause allergic reactions and even anaphylaxis. Although, immediate-type, anaphylactic reactions to systemic corticosteroids are very uncommon, they can prove fatal (45). The first case of a steroid-induced anaphylactic reaction and contact hypersensitivity was described in the 1950’s (46). We subsequently reported unusual and untoward allergic reactions to corticosteroids, particularly with the use of hydrocortisone sodium phosphate during the treatment of status asthmaticus (47, 48). To date, allergic reactions have been reported following intramuscular, intra-articular, periartricular, intralesional, oral, inhalation and intravenous corticosteroid administration. The frequency of Type 1 or immediate allergic reactions to systemic corticosteroids has been estimated to range from 0.1 to 0.3% (25). On the other hand, the incidence of Type 4 or delayed allergic reactions to topically applied glucocorticoids is estimated to be between 0.2% and 5% (49, 50). The most commonly reported corticosteroids causing anaphylaxis-like reactions are hydrocortisone, prednisone and methylprednisolone. Recently, acute ST-elevation myocardial infarction following intravenous administration of methylprednisolone for anaphylaxis caused by a wasp sting was published (51). In that case, prednisolone was given for the treatment of wasp sting anaphylaxis in a young patient with normal coronary arteries. Although no allergology investigations were conducted, the authors attributed the development of acute myocardial infarction to wasp sting anaphylaxis or the corticosteroids used for its treatment. Indeed, six to seven minutes after methylprednisolone administration, the patient developed acute myocardial infarction and his blood pressure dropped to 80/60 mmHg. Although the administration of prednisolone could have treated the coronary spasms within the subsequent few minutes, it was associated with deterioration of chest pain and electrocardiographic changes. In this case, both wasp sting anaphylaxis and prednisolone treatment, acting as mast cell activators, may have acted synergistically to increase the release.
of mast cell contents above the threshold required to induce coronary artery spasms and/or plaque erosion or rupture (11). Furthermore, three cases of vasospastic angina following the initiation of prednisolone therapy were recently reported in Internal Medicine (52). These patients had remitting seronegative symmetrical synovitis with pitting edema syndrome, pemphigus erythematosus and idiopathic interstitial pneumonia. Although they did not exhibit any characteristic symptoms of an allergic reaction, the authors suggested that further investigations are needed to clarify the exact mechanisms involved in the onset of corticosteroid-induced vasospastic angina.

Conclusion

New etiologies of Kounis syndrome are being detected each year, and physicians should be aware of their existence in order to obtain an early and correct diagnosis and apply appropriate therapeutic measures.

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References