

Kounis Syndrome

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Abstract: The association between acute coronary events and acute allergic reactions has been recognized for several years. The first reported case occurred in 1950, during an allergic reaction to penicillin. In 1991, Kounis and Zavras described the syndrome of allergic angina and allergic myocardial infarction, currently known as Kounis syndrome. Two subtypes have been described: type I, which occurs in patients without predisposing factors for coronary artery disease and is caused by coronary artery spasm, and type II, which occurs in patients with angiographic evidence of coronary disease when the allergic events induce plaque erosion or rupture. This syndrome has been reported in association with a variety of medical conditions, environmental exposures, and medication exposures. Entities such as Takotsubo cardiomyopathy, drug-eluted stent thrombosis, and coronary allograft vasculopathy appear to be associated with this syndrome. In this review, we discuss the pathobiology, clinical features, associated entities, and management of Kounis syndrome.

Key Words: allergic acute coronary syndrome, allergic angina and allergic myocardial infarction, allergic coronary spasm, Kounis syndrome

Allergic phenomena in predisposed subjects can trigger not only anginal episodes, but also acute myocardial infarction.¹ This was first reported in the *American Heart Journal* in 1950 with a case of a prolonged allergic reaction to penicillin.² In 1991, Kounis and Zavras initially described a syndrome of allergic angina as the coincidental occurrence of chest pain associated with an allergic insult. The chest pain would present as classical angina pectoris, and if severe enough, this allergic angina could progress to an allergic myocardial infarction.³⁻⁷ In 1995, Constantinides raised the possibility that even ordinary allergic reactions

could promote atheromatous plaque disruption, and in an editorial in 1998 Braunwald noted that vasospastic angina can be induced by allergic reactions, with mediators such as histamine and leukotrienes acting on coronary vascular smooth muscle.^{8,9} Thus, allergic angina and allergic myocardial infarction have become recognized as the Kounis syndrome.^{6,7}

Kounis syndrome (KS), or the concurrence of acute coronary events with allergic or hypersensitivity reactions, has increasingly been reported in the medical literature. The true frequency of KS is unknown. However, during a diagnostic insect sting challenge study Brown et al reported that 9.5% of healthy volunteers developed chest pain with electrocardiographic abnormalities consistent with acute myocardial ischemia.¹⁰

Classification and Clinical Presentation

KS has been divided into two subtypes:

- **Type I** is the occurrence of chest pain during an acute allergic reaction in patients without predisposing factors for coronary artery disease. An acute allergic event induces coronary artery spasm, resulting in chest pain

Key Points

- Kounis syndrome is the concurrence of acute coronary syndrome with acute allergic reaction.
- Coronary vasospasm or plaque erosion and rupture can be triggered by vasoactive, collagen-degrading compounds that are released from activated mast cells during an allergic reaction.
- Several medical conditions, environmental exposures, and medications have increasingly been reported in association with cases of Kounis syndrome. Kounis syndrome has also been reported in pediatric populations.
- Entities such as Takotsubo cardiomyopathy, drug-eluted stent thrombosis, and coronary allograft vasculopathy of transplant seem to have an association with Kounis syndrome.
- Additional research, including randomized trials, is needed to better characterize the epidemiology, clinical characteristics, and diagnosis, and to define appropriate preventive and interventional measures for this interesting syndrome.

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and ischemic electrocardiographic changes, and the cardiac enzymes can either be normal or reflect progression to an acute myocardial infarction.^{6,11} These cases have a normal myocardial perfusion scan, normal coronary angiogram, and positive ergonovine test.¹¹ The explanation for this type would be endothelial dysfunction or microvascular angina.¹²

- **Type II** is the occurrence of chest pain in patients with angiographic evidence of coronary artery disease during an acute allergic reaction.^{6,11} This type includes patients with quiescent pre-existing atheromatous disease, in whom an acute allergic episode can induce plaque erosion or rupture manifesting as an acute myocardial infarction.^{1,6,12}

The clinical presentation of KS includes a mixture of symptoms and signs of an allergic reaction and acute coronary syndrome, with chest pain, dyspnea, faintness, nausea, vomiting, syncope, pruritus, urticaria, diaphoresis, pallor, palpitations, hypotension, bradycardia, etc.¹³

Though this syndrome has been mostly reported in adults, Biteker et al recently published an interesting review of children presenting with KS.¹⁴ The ages of the patients were between nine and thirteen years old; two of them developed an allergic reaction to amoxicillin/clavulanic acid, one after a honeybee sting, and one after a wasp sting. All four children developed chest pain associated with ST segment elevation and positive cardiac enzymes. Serum tryptase level was elevated in all of the children, and the specific immunoglobulin E (IgE) was elevated in one of the two patients exposed to amoxicillin/clavulanic. The patients were successfully treated with oral antihistamines, prednisolone, and mast cell stabilizers.

Pathophysiology

The pathophysiologic characteristics of KS involve coronary artery spasm and/or atheromatous plaque erosion or rupture during an allergic reaction. Coronary spasm is the result of local hyperreactivity of a coronary segment to a vasoconstrictor stimulus.¹ The exact mechanisms resulting in vasospastic angina have not been fully established. It has been postulated that endothelial injury and hypercontractility of vascular smooth muscle may be the result of vasoconstrictor mitogens, leukotrienes, serotonin, endothelin, angiotensin II, histamine, and higher local concentration of blood-borne vasoconstrictors in areas adjacent to neovascularized atherosclerotic plaque.¹⁵

Mast cells are derived from a distinct precursor in the bone marrow and mature under local tissue microenvironmental factors; these cells are found in most parts of the human body, including the heart and blood vessels, and are involved in allergic and anaphylactic reactions.⁶ In a capable individual, the introduction of an allergen such as food, insect venom, a contrast agent, or a drug may induce mast cell

degranulation and liberation of several mediators, including histamine, leukotrienes, and proteases.¹

Mast cell degranulation is triggered by stimuli such as histamine-releasing factors, complement system (C3a, C5a), and/or the cross-bridging of culprit antigens with corresponding receptor-bound IgE antibodies located on the basophil or mast cell surface.⁶ Of the total 500,000 to 1,000,000 IgE antibodies present on the mast cell surface, only a threshold number of about 2,000 bridged IgE antibodies are required for degranulation and mediator release.^{16,17} This number of bridges might be possible to accumulate by more than one non-cross-reactive antigen and its corresponding IgE antibody; therefore, patients simultaneously exposed to several antigens experience more symptoms than monosensitized patients.¹⁷ Likewise, IgE antibodies with different specificities can elicit an additive effect, and simultaneous exposure to subthreshold quantities of multiple antigens can synergistically trigger the release of mediators.^{16,17}

In coronary artery events occurring during allergic reactions, mast cells would be present in the culprit lesion before any plaque erosion or rupture. Forman et al describe a case of severe allergic vasospastic angina and sudden death, where the autopsy showed mast cell infiltration at the site of coronary artery spasm.¹⁸

During mast cell degranulation several vasoactive mediators (histamine, leukotrienes, serotonin) and collagen-degrading compounds like neutral proteases (tryptase, chymase) are released locally and in the peripheral circulation.¹² A complete list of the preformed and newly synthesized mast cell mediators released during an allergic reaction is presented in Table 1.

Histamine and leukotrienes are powerful coronary vasoconstrictors, while tryptase and chymase are metalloproteinase activators that can trigger degradation of collagen and induce plaque erosion or rupture, thus initiating an acute coronary event.^{12,19}

Histamine not only constricts the coronary arteries, but also sensitizes the nerve endings adjacent to adventitial mast cells in atherosclerotic coronary arteries.²⁰ Cardiac histamine acts via four different histamine receptors, and each receptor can contribute to the severity of the allergic myocardial damage. The H1 receptor mediates coronary vasoconstriction, while the H2 receptor mediates a minor degree of coronary relaxation. The interaction between H1 and H2 causes a decrease in diastolic blood pressure and an increased pulse pressure. H3 inhibits the endogenous norepinephrine release (enhancing the degree of shock observed during allergic reactions), and finally the H4 receptor regulates the chemotaxis of mast cells, eosinophils, and lymphocytes, causing change in the shape of eosinophils and upregulating adhesion molecules.^{6,13,20}

Moreover, histamine causes proinflammatory cytokine production from endothelial cells, upregulates P-selectin on the endothelial surface, and induces intimal thickening

Table 1. Preformed and newly synthesized mast cell mediators released during an allergic reaction^{47a}

Preformed/stored mediators	
Biogenic amines	Histamine 5-Hydroxytryptamine
Chemokines	Interleukin 8 Monocyte chemotactic protein-1, -3, -4
Enzymes	Arylsulfatases Carboxypeptidase A Chymase Kinogenases Metalloproteinases Phospholipases Trypsin
Peptides/proteins	Corticotropin-releasing hormone Endorphins Endothelin Kinins (bradykinin) Neurotensin Renin (connective tissue) Somatostatin Substance P Vasoactive intestinal peptide Urocortin Vascular endothelial growth factor
Proteoglycans	Chondroitin sulfate Heparin Hyaluronic acid
Angiogenic factors	Adrenomedullin Angiogenin/angiopoietin Endothelial growth factor Fibroblast growth factor α and basic Interleukin 8 Neuropilin Transforming growth factor β Vascular endothelial growth factor
De novo synthesized mediators	
Cytokines	Interleukins-1, -2, -3, -4, -5, -6, -8, -10, -13, -16, -17, -32 Interferon γ Macrophage inflammatory factor Tumor necrosis factor α Transforming growth factor β
Growth factors	Stem cell factor GM colony stimulating factor Fibroblast growth factor Nerve growth factor Vascular endothelial growth factor
Phospholipid metabolites	Leukotriene B4 Leukotriene C4 Platelet activating factor Prostaglandin D2
Other	Nitric oxide Reactive oxygen species

^aGM, granulocyte-macrophage.

in a mouse model of thrombosis.⁶ Histamine also activates platelets and potentiates the aggregatory response of other agonists, including adrenaline, 5-hydroxytryptamine, and thrombin.^{6,12}

Another novel action of histamine is the induction of tissue factor expression and activity. Tissue factor is a key

enzyme in the activation of coagulation. It binds activated factor VII, which in turn activates factor X, leading to thrombin formation. Elevated tissue factor antigen and activity have been detected in plasma and atherectomy specimens from patients with unstable angina.²¹

Chymase converts angiotensin I to angiotensin II, which acts through receptors found in the medial muscle cells of coronary arteries, working synergistically with histamine to aggravate coronary artery spasm.⁶ Trypsin effectively activates the zymogen forms of metalloproteinase, such as interstitial collagenase, gelatinase, and stromelysin found in atheromatous plaques, playing an important potential role in plaque erosion and/or rupture.^{13,22}

Not all patients suffering from an allergic reaction develop an acute coronary event. What determines the development of KS remains unclear; however, it has been suggested that there is a threshold level of mast cell activation and mediator release above which the coronary artery spasm and plaque erosion or rupture occurs. This threshold level would be closely linked to the body site where the antibody-antigen reaction occurs, the area of exposure, mediator release, and, of course, the severity of the allergic reaction.^{19,23}

Kounis syndrome may represent the tip of the iceberg in terms of a final pathway leading to acute coronary events. There may be some commonality in the mechanisms contributing to both acute allergic episodes and acute coronary syndromes.²³ In patients with acute myocardial infarction of non-allergic origin, activated mast cells abound at the plaque rupture site in a ratio of 200:1 compared with normal endothelial segments.¹⁹ Indeed, mast cell infiltrates and other inflammatory cells such as macrophages and T lymphocytes have been found not only at the sites of plaque rupture but also at sites of susceptible coronary plaques. Cell infiltrates therefore may not only be part of an acute inflammatory response to the plaque rupture, but may precede the event.⁶

Etiology

As shown in Table 2, multiple agents may result in KS. In some cases such as hymenoptera (honeybee, wasp, etc) stings, the venom itself contains peptides, proteins, and vasoactive amines, including histamine, acetylcholine, norepinephrine, dopamine, and 5-hydroxytryptamine. These may be responsible for direct cardiotoxicity, and several of the proteins are also allergenic, causing mast cell activation.¹³

Several antibiotics have been associated with generalized allergic reactions and KS. Vivas et al reported the occurrence of an acute coronary syndrome with ST segment elevation after exposure to amoxicillin and recurrence after a new exposure to the same agent; the patient was later confirmed to be allergic to penicillin and beta-lactam agents.¹ Likewise, Tavi et al reported the case of a patient without residual significant coronary lesions post-angioplasty, who developed a new acute coronary event during an allergic reaction to

Table 2. Etiology of Kounis Syndrome^a

Various medical conditions	Angioedema ⁶
	Bronchial asthma ⁶
	Urticaria ⁶
	Food allergy ⁶
	Exercise-induced anaphylaxis ⁶
	Mastocytosis ⁶
	Serum sickness ⁶
Environmental exposures	Intracoronary stents ¹⁶
	Intracardiac prosthetic devices used for patent foramen ovale closure ¹⁶
	Ant, bee, wasp, jellyfish stings ⁶
	Grass cutting ⁶
	Millet allergy ⁶
	Poison ivy ⁶
	Latex contact ⁶
	Shellfish eating ^{6,19}
	Viper venom ⁴⁸
	Limpet ingestion ⁶
	Poisoning ^{6,7}
	Diesel fumes ⁴⁹
	Sarin poisoning ¹⁹
	Fly carvaria sting ²⁹
Medications	
Analgesics	Dipyrone ²³
Anesthetics	Etomidate ²³
Antibiotics	Beta-lactams in general, ⁵⁰ ampicillin, ampicillin/sulbactam, amoxicillin, amikacin, cefazolin, cefuroxime, cephadrine, cinoxacin, lincomycin, penicillins, sulbactam/cefoperazone, vancomycin, ²³ ciprofloxacin ²⁴
Anticholinergics	Trimethaphan ²³
NSAIDs	Diclofenac, ⁵¹ naproxen sodium, ^{23,52} ibuprofen ⁵³
Antineoplastic drugs	5-Fluorouracil, capecitabine, carboplatin, ²³ cisplatin, cyclophosphamide ⁵⁴
Contrast media	Iohexol, loxaglate, meglumine diatrizoate, sodium indigotindisulfonate ²³
Corticosteroids	Betamethasone, hydrocortisone ²³
Muscle relaxants	Suxamethonium, ²³ cisatracurium, ⁵⁵ rocuronium ⁵⁶
Proton pump inhibitors	Lanzoprazole ⁵⁷
Skin disinfectants	Chlorhexidine, povidone-iodine ²³
Thrombolytics and anticoagulants	Heparin, ¹⁹ streptokinase, ¹⁹ urokinase, ²³ lepirudin, ⁵⁸ hirudin, ³⁰ bivalirudin ²¹
Others	Allopurinol, enalapril, esmolol, dextran 40, fructose, insulin, iodine, protamine, tetanus antitoxin and glaphenide, ^{23,48} nicotine patch, ²⁴ mesalamine ³¹

^aNSAIDs, nonsteroidal anti-inflammatory drugs.

amoxicillin/clavulanic acid.¹² The first case of ciprofloxacin-associated KS was reported recently by Almpanis et al in a female patient after intravenous administration of the antibiotic.²⁴ Mazarakis et al reported a case of cefuroxime-induced type I KS during antibiotic prophylaxis for a gynecological procedure in a patient without history of allergies or coronary artery disease.²³

The report of a patient who developed coronary artery spasm during the induction of general anesthesia (involving use of propofol, midazolam, remifentanyl, succinylcholine, and isoflurane), raised the possibility of KS as an etiology. This case also reinforces the concept that simultaneous exposures to multiple antigens can trigger or aggravate the mast cell mediator release.¹⁷ Foreign bodies can also cause allergic reactions and KS. Patients with coronary artery disease undergoing stent implantation are exposed to multiple substances, each of which is a potential antigen that can have an additive effect. The metal is made from 316L stainless steel containing nickel, chromium, manganese, titanium, and molybdenum.²⁵ Nickel hypersensitivity by itself occurs in up to 17.2% of the general population, and is the most frequent cause of allergic contact dermatitis.¹⁶ Patane et al reported the case of a 73-year-old female who underwent coronary stent placement and was readmitted four days later because of a severe allergic reaction to flavoxate-propyphenazone. She developed ischemic electrocardiogram (EKG) changes and troponin elevation with a new coronary angiography confirming intra-stent thrombosis, probably related to the allergic insult.²⁶

In the case of a drug-eluting stent (DES), the antigen's substances include not only the metal itself, but also the polymer coating and impregnated drugs such as the antimicrotubule, antineoplastic agent paclitaxel (TAXUS® Liberté® Paclitaxel-Eluting Coronary Stent System, Boston Scientific Corporation, Natick, MA) or the anti-inflammatory, immunosuppressive, and antiproliferative agent rapamycin (CYPHER® Stent, Cordis Corporation, Bridgewater, NJ).^{25,27,28} In a recent review, Chen et al interestingly described KS as a contributing factor to drug-eluting stent thrombosis.¹⁶ Patients with allergic patch test reactions to the metallic strut components (nickel and molybdenum) seem to have increased rates of stent thrombosis.¹⁶ In the review, data from the United States Food and Drug Administration's Manufacturer and User Device Experience Center and Adverse Drug/Device Events and Reports Project indicate several hundred registered cases of hypersensitivity reactions in conjunction with DES implantations. Seventeen of the cases were probably or definitely associated with the DES, and four of them developed fatal intra-stent thrombosis. The reactions included rash, itching, hives, dyspnea, fever, atypical chest pain, hypertension, hypotension, arthralgia, joint swelling, and anaphylaxis.^{16,28}

New coronary events after DES implantation may represent not only a local phenomenon, but a more generalized hypersensitivity reaction involving circulating mediators that enable or induce thrombotic events and/or vasoconstriction. Cases of severe diffuse and simultaneous spasm involving multiple coronary vessels after DES implantation have been reported. The induction of coronary artery vasospasm in a different artery than the stented artery, as well as multiple artery thromboses involving not only the stented coronaries but also peripheral arteries after DES implantation support this assumption.²⁸

Although the precise mechanism of DES thrombosis appears to be multifactorial, including procedural and technical

variables, the lesion characteristics and histopathological data have implicated an allergic or hypersensitivity factor in the process. Autopsies have revealed inflammatory cells in all three vascular wall layers, with similar characteristics to those observed in KS.¹⁶ Histological examination of patients who died due to stent thrombosis have demonstrated eosinophilic infiltrates and poor intimal healing, and extracted thrombus revealed infiltrates of neutrophils and eosinophils consistent with an allergic hypersensitivity reaction—findings similar to those of KS.²⁹

Patients undergoing DES implantation are also exposed to antiplatelet therapy with aspirin and clopidogrel, two well-known antigenic substances.^{16,25} Patane et al reported a case of recurrent myocardial infarction and KS associated with the ingestion of clopidogrel.³⁰ The salicylic hypersensitivity is explained by overproduction of leukotriene metabolites through the lipoxygenase pathway after the exposure to salicylates. Leukotrienes are powerful coronary arterial vasoconstrictors, and their biosynthesis is enhanced in the acute phase of unstable angina.³¹ In patients undergoing percutaneous atrial septal defect and patent foramen ovale closure, nickel allergy can cause systemic symptomatology, including chest discomfort and palpitations. Type I KS has also been reported during these procedures. Interestingly, patients without nickel allergy have not developed those post-closure symptoms.²⁵ Allergic reaction to the implanted device could elicit platelet adhesion and activation, resulting in coronary or cerebrovascular thromboembolism.¹⁶

Even nicotine patches have been implicated in the development of KS. A recent report describes a patient without cardiovascular or allergic disease who developed an allergic reaction to a nicotine patch; this was partially relieved with antihistamine treatment, but the patient experienced recurrence of symptoms after a fish bone puncture (additive effect) and associated acute coronary syndrome.²⁴ Nicotine patches could also facilitate the development of subsequent allergic or anaphylactoid reactions from other causes.²⁴

Associated Entities

Takotsubo, or stress-induced cardiomyopathy, is a transient left ventricular hyperkinesis at the cardiac base with a severe hypokinesis throughout the mid ventricle and apex.^{32,33} A variety of stress mechanisms (excess cortisol, norepinephrine, and epinephrine release, as well as activation of the renin-angiotensin system) seem to lead to heightened cardiovascular activity, resulting in myocardial damage and endothelial injury. An inflammatory process characterized by cytokine production, macrophage and mast cell activation, and release of inflammatory mediators appears present, as in KS.^{32–34} Yanagawa et al recently reported the case of a 65-year-old female who developed variant angina, transient left ventricular dysfunction, and life-threatening arrhythmia triggered by an asthma exacerbation. The asthma, angina, and

arrhythmia resolved after the eosinophilia was corrected with steroids, and, as would be expected in Takotsubo, the left ventricular akinesis progressively improved.³²

Coronary allograft vasculopathy affects 50% of heart transplant recipients during the first five years after transplant and is the primary cause of death following transplantation. This entity has also been linked to KS.³⁵ It is speculated that a hypersensitivity process with release of inflammatory mediators resulting in smooth cell proliferation, vasospasm, and thrombosis may be responsible.³⁵ Several years ago, histological examination of the 193 explanted hearts of heart transplant recipients revealed hypersensitivity myocarditis in 15 (7%). None of those cases were detected clinically, but all manifested eosinophilia at some point during the two weeks before the transplantation. The authors suggest that the vigorous drug treatment, particularly with antibiotics, could have triggered the allergic myocarditis.^{35,36}

Hypersensitivity myocarditis and KS are two cardiac entities of allergic etiology affecting the myocardium and coronary arteries, respectively. Hypersensitivity myocarditis is an inflammatory condition that affects the myocardium and the cardiac conduction system as an allergic complication of drug therapy.¹¹ These two entities can mimic each other and be clinically indistinguishable.³⁷ The presence of eosinophils, atypical lymphocytes, and giant cells on myocardial biopsy suggests hypersensitivity myocarditis, whereas the biopsy is typically normal in KS.¹¹ Interestingly, a case of simultaneous occurrence of both entities was recently reported in a patient who developed type I KS after exposure to amoxicillin, and was also found by cardiac magnetic resonance imaging to have changes compatible with hypersensitivity myocarditis.³⁷

Diagnosis

Careful review of clinical history, including medications and allergies, is always imperative. The potential diagnostic laboratory work-up in suspected KS patients is shown in Table 3.

Although some studies have found elevation of histamine and other markers of mast cell activation during acute coronary

Table 3. Potential diagnostic laboratory work-up in suspected Kounis Syndrome²¹

Complete blood count (CBC): eosinophils
Histamine, chymase, tryptase serum levels
Cardiac enzymes and troponin
Total immunoglobulin E (IgE)
Specific IgE
Arachidonic acid products: thromboxane, leukotrienes, prostaglandins
C-reactive protein (CRP, high sensitivity)
Tissue factor
Tumor necrosis factor (TNF), interferon (INF), interleukin-6 (IL6)

events, none have demonstrated a causal temporal relationship between the allergic reaction and the acute coronary event.¹ Histamine is short-lived and circulates for approximately 8 minutes after an allergic insult; as such, negative levels do not exclude the diagnosis of KS.^{7,14} On the other hand, serum tryptase has a half-life of 90 minutes, making it more conducive for diagnostic testing in patients who may have KS.⁷ Tryptase level is a marker of mast cell activity and is useful in demonstrating that an allergic reaction has happened.³⁸ It has a sensitivity of 73% and specificity of 98% in detecting anaphylactic reactions, and serial measurements may further increase the sensitivity and specificity of the test.¹⁴

Since mast cells invade coronary plaque before the rupture or erosion has occurred, and mast cell activity has also been elevated during ischemic episodes of non-allergic etiology, tryptase levels are being investigated in acute coronary syndromes of non-allergic etiology.^{23,38} The use of IgE levels in the diagnosis of allergic reactions or KS remains unclear. Mast cell degranulation follows an antibody antigen reaction. However, sometimes direct action against the mast cells can occur. This applies particularly to drugs, and the absence of IgE antibodies does not exclude the occurrence of mast cell degranulation.¹⁴ Other inflammation markers such as leukotrienes and thromboxane would not be helpful in differentiating KS from a regular ischemic event, because these have been found to be significantly elevated in acute myocardial infarction of non-allergic etiology. In fact, urinary leukotriene and thromboxane A₂ have been found to be significantly higher in patients with unstable angina than in patients with stable angina or non-ischemic chest pain.²³ Vascular biopsies have shown mast cell infiltration at the site of coronary artery spasm, at the plaque rupture, and also at sites of susceptible coronary plaques. Other inflammatory cells such as macrophages and T lymphocytes may also play a role.^{6,39} The myocardial biopsy, though, is typically normal in Kounis syndrome.^{11,31}

Treatment

The use of corticosteroids in patients with vasospastic angina with evidence of allergy or the presence of symptoms refractory to high-dose vasodilators has been reported to resolve symptoms.³⁹ Dominguez et al reported the case of a male patient with history of Raynaud phenomenon, refractory vasospastic angina, and eosinophilia who had resolution of symptoms completely after a low dose of methylprednisolone.⁴⁰ Okada et al also reported that corticosteroid therapy effectively alleviated the symptoms of refractory coronary vasospasm in a patient with chronic thyroiditis and eosinophilia.⁴¹

A series of four cases of refractory vasospastic angina that were completely controlled after administration of corticosteroids was reported by Takagi et al.⁴² Although none of the patients were found to have eosinophilia, three of them had bronchial asthma and one had chronic thyroiditis. In some cases,

the patients were steroid dose-dependent and required slow tapering to avoid recurrence of the vasospastic angina episodes. Another patient required chronic oral steroid therapy to avoid recurrences. In one case the steroids were completely discontinued and the patient developed recurrence of coronary spasm six months later, complicated with ventricular fibrillation, and died due to complications during hospitalization.⁴²

The mechanism attributed to corticosteroid treatment is the suppression of arterial hyperreactivity and alleviation of inflammation.⁴² It is postulated that corticosteroids would inhibit phospholipase A₂ and the release of arachidonic acid from cell membranes, thus inhibiting eicosanoid biosynthesis, especially from mast cells. Corticosteroids may also reduce inflammation by inducing cell apoptosis via an autocrine or paracrine pathway involving the upregulation of the death receptors CD95 and CD95L on cell membranes.⁴³ Other drugs suggested in the management of KS are sodium nedocromil, sodium cromoglycate, ketotifen, lodoxamide, acadesine, and ribavirin, which can stabilize the mast cells and prevent the degranulation process.⁶

In many of the reported cases the initial approach has been intravenous morphine, hydrocortisone sodium succinate, diphenhydramine, and ranitidine, followed in some cases by nifedipine, aspirin, nitroglycerine, and prednisolone.^{22-24,29} Medications like epinephrine should be avoided in patients with a history of sulfite allergy, since every commercially available epinephrine contains sodium metabisulfite as a preservative.^{44,45} Furthermore, epinephrine administration per se has also been shown to induce mast cell degranulation, causing false positive results.¹⁷

Patients under the effect of beta blockers have a decreased response to both the endogenously released and therapeutically administered epinephrine. As such, the usual dose of epinephrine in these patients may be inadequate, and in other cases coronary vasospasm may be promoted due to the unopposed alpha adrenergic effect of epinephrine.^{45,46} Furthermore, beta blockers may enhance the generation and release of anaphylaxis mediators and their effects on end organs.⁴⁵ Morphine, a commonly used drug in the management of acute coronary syndromes, stimulates the release of histamine from mast cells and could contribute to a false positive result.¹⁹

It is important to take a careful history in order to avoid implantation of DES in atopic individuals. When DES is indicated, skin testing for DES components and desensitization strategies should be performed, as well as therapy with mast cell stabilizers in association with steroids.²⁹ Immunosuppressants may be advisable in specific cases.³⁵ In patients undergoing DES implantation, impregnation of the stent polymer with mast cell stabilizers has been proposed.²¹

Conclusion

Kounis syndrome is likely an underdiagnosed entity. Knowledge of this syndrome will enable optimal manage-

ment of patients with both acute allergic and/or myocardial events. Additional research, including randomized trials, is needed to better characterize the epidemiology, clinical characteristics, and diagnosis of KS, and to better define appropriate preventive and interventional measures.

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