

# Kounis syndrome: a monster for the atopic patient

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Submitted Jan 25, 2013. Accepted for publication Feb 20, 2013.

doi: 10.3978/j.issn.2223-3652.2013.02.05

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When anaphylactic or anaphylactoid and allergic or hypersensitivity reactions from causes such as insect stings, drugs and other environmental exposures combine with cardiovascular signs and symptoms, acute coronary events and stent thrombosis with thrombus infiltrated by eosinophils and/or mast cells, the result is the Kounis hypersensitivity associated syndrome (1). Kounis syndrome is caused by preformed and newly synthesized inflammatory mediators released from mast and other interacting inflammatory cells during the anaphylactic activation and manifests as vasospastic angina, acute myocardial infarction and stent thrombosis. A subset of platelets bearing, in their surface, FC $\gamma$ RI, FC $\gamma$ TII, FC $\epsilon$ RI and FC $\epsilon$ RII receptors are also involved in this activation cascade.

In 1902, French physiologists Paul Portier and Michael Richet described a dog that developed cardiorespiratory arrest and died after injection of a jellyfish toxin called actinotoxin, although 14 days earlier the dog had well tolerated the same injection (2). These scientists introduced the term 'anaphylaxis' (from Greek *aphylaxis* = *no phylaxis*) meaning without protection, whereas prophylaxis means protection) and were awarded the Nobel Prize in Medicine and Physiology in 1913. In 1906, the Viennese pediatrician and immunologist Clements von Piquet, recognized that antigens can induce changes in reactivity in both protective immunity and hypersensitivity reactions and introduced the term 'allergy' (from Greek *allergia* = *allo ergo*, meaning altered capacity to react) (3). 'Atopy' (from the Greek *atopos* = *no topos*, meaning out of place) is a term used today to describe IgE-mediated diseases and denotes a genetic predisposition to produce significant amounts of antibodies (4). These entities cover the whole spectrum of modern immunology and constitute the basis for the development the of Kounis syndrome (5).

In the important report published in the current issue of Cardiovasc Diagn Therapy (6) a patient suffering from hypertension, dyslipidemia, diabetes, tobacco abuse coronary artery disease with a percutaneous coronary intervention and drug eluting stent placement, developed an acute myocardial infarction following anaphylaxis from bee sting. The condition was complicated with anaphylactic-cardiogenic shock necessitating intra-aortic balloon pump assistance. Furthermore, the patient developed gastrointestinal bleeding, right upper lobe pulmonary embolism and heparin induced thrombocytopenia (HIT) confirmed with positive HIT-antibody test, which was treated with an inferior vena cava filter and intravenous argatroban. Coronary angiography revealed acute thrombotic occlusion of the proximal right coronary and proximal left anterior descending coronary arteries.

This report raises important issues concerning coronary thrombosis following stent implantation, allergic-cardiogenic shock, HIT, pulmonary embolism and gastrointestinal bleeding as consequences of an allergic reaction.

## Coronary stents seem to attract, like magnet, IgE antibodies in order to create stent thrombosis

The described patient had a drug eluting stent implanted in the right coronary artery and following the allergic reaction, from the bee sting, developed acute coronary thrombosis in 2 main coronary arteries including the previously stented right coronary artery. Drug eluting stent components include the metal platform which contain nickel and other metals, the polymer coating and the impregnated antiproliferative drugs which constitute an antigenic complex that applies continuous, persistent, repetitive

and chronic inflammatory irritation on the arterial intima lasting as long as the antigens stay present. That is why some unexpected, peculiar, bizarre, strange, surprising, extraordinary and astonishing reports are appearing in the medical literature, according to which patients with implanted stents who accidentally developed an allergic reaction elsewhere in the human body from various different causes are prone to develop, contemporarily intrastent thrombosis. The same has happened to the described 51 year old patient as a result of an allergic reaction to bee sting. Indeed, stent thrombosis has been associated with allergic symptoms such as glottis edema, cold sweat, and tongue enlargement following a flavonate-propyphenasone administration a week after stent implantation (7). Acute myocardial infarction, in the stented area, coincided with allergic reaction following intravenous administration of the non-anionic contrast material iopromide during a routine excretory urography (8). Late drug eluting stent thrombosis defined as type III variant of Kounis syndrome (9) has occurred following an allergic reaction to non steroidal anti-inflammatory agent acemetacine (10). Intrastent thrombosis has also been reported following insect and larvae sting-induced allergic reactions (11). Even the astonishing event that allergy to clopidogrel (12), the drug given to prevent stent thrombosis, has induced itself stent thrombosis!

### **The heart seems to be the primary site and the target of anaphylaxis resulting in the development of Kounis syndrome**

The described patient developed anaphylactic-cardiogenic shock necessitating intra-aortic balloon pump assistance in order to recover. So far, it is generally believed, that anaphylactic shock is the result of systemic vasodilation, reduced venous return, leakage of plasma and volume loss due to increased vascular permeability ensuing to depression of cardiac output that contributes to coronary hypoperfusion with subsequent myocardial damage. However, experimental and clinical studies indicate that the human heart can be the primary site and the target of anaphylaxis resulting in the development of Kounis syndrome. In experimental anaphylaxis with ovalbumin sensitized guinea pigs (13) it was shown that within 3 min after the antigen administration cardiac indices were changed as follows: (I) cardiac output decreased by 90%; (II) left ventricular end diastolic pressure increased significantly by 35% indicating pump failure; (III) arterial blood pressure increased significantly by 35%. The blood pressure started declining steadily after

4 min; (IV) Concurrently, electrocardiographic changes showed signs of acute myocardial ischemia. The authors of these experiments concluded that “the idea that the registered anaphylactic damage might be due to peripheral vasodilation can be definitely excluded. In addition, the rapid increase in left ventricular end diastolic pressure suggests that decreased venous return and volume loss due to an increase of vascular permeability are unlikely to be the primary causes of the documented depression of cardiac output and blood pressure”. In another experiment (14) the anaphylactic cardiac damage was dissociated temporarily into two sets of events: an initial primary cardiac reaction caused by intracardiac release of histamine and a subsequent cardiovascular reaction secondary to systemic release of mediators. Other studies (15) with isolated guinea pig hearts undergoing anaphylaxis following intra-aortic injection of antigen, showed an abrupt heart rate increase reaching the peak within 2 min, a transient increase in ventricular contractile force followed by prolonged decrease, and a prompt and prolonged decrease in coronary blood flow. In the clinical setting, there are current reports (16,17) according to which patients with anaphylactic cardiac shock do not respond to fluid replacement but recover with current myocardial infarction protocol and anti-allergic treatment thus denoting that the heart is primarily affected. The same has happened to the described patient who did not receive any anti-allergic treatment but recovered with intra-aortic balloon assistance and acute myocardial infarction treatment.

### **Heparin-induced thrombocytopenia seems to be a new manifestation of Kounis syndrome**

During the course of Kounis syndrome, the described patient developed HIT which was confirmed by positive HIT-antibody test, and was treated with an inferior vena cava filter and intravenous argatroban. Heparin induced thrombocytopenia is the result of antibody formation against heparin, leading to platelet and monocyte activation with consequent thrombin production (18). Heparin-induced thrombocytopenia can lead to stent thrombosis (19) through specific antigen that is the 3- component immune complex, composed of platelet factor 4 (PF4), heparin and IgG which serves as the primary antigen in order to activate platelets via the FcγR2 and induce thrombosis. Following heparin exposure, a highly positive protein present in the α-granules of platelets, the PF4, quickly binds and neutralizes heparin. The PF4-heparin complex then serves as the primary antigen to create antibodies, normally of IgG class. These antibodies

recognize and bind (20) to exposed epitopes on PF4 making a 3- component antigen-antibody immune complex, composed of IgG, PF4 and heparin. This immune complex activates platelets via the FC $\gamma$ RII receptors situated on platelet surface which aggregate and result in thrombosis

The clinical paradox is that physicians are cautious and alerted for any bleeding side effect of heparins while heparins themselves can induce thrombocytopenia which is expected to worsen bleeding but leads to unexpected serious thrombosis. Thrombocytopenia is the result of removal of platelet aggregates by the reticuloendothelial system. The ensuing extensive thrombosis increases platelet consumption and worsens thrombocytopenia. The 3- component antigen-antibody immune induces endothelial injury by binding to FC $\gamma$ RII receptors on monocytes (21), leading to tissue factor and thrombin production. That is why the described patient received the direct thrombin inhibitor argatroban with good result.

### **Kounis syndrome a pan-arterial monster**

Recent reports have shown that Kounis syndrome can affect not only the coronary arteries but the mesenteric and cerebral arteries. Indeed, mast cells are found in most organs of the human body including the brain, the cerebral arteries and the mesenteric arterial system. There are reports of mast cell activation disorders manifesting with cerebral vasospasm symptoms similar to Kounis syndrome (22). In another report anaphylactic reaction to diclofenac triggered the development of abdominal pain syndrome resembling Kounis syndrome in a patient with chronic atherosclerotic mesenteric artery disease (23). The described patient, following anaphylaxis, developed gastrointestinal bleeding and this could be associated with anaphylaxis. The released inflammatory mediators can induce both thrombotic and fibrinolytic events (24). For example tryptase can degrade fibrinogen and can activate pro-urokinase. Chymase can inactivate thrombin. Mast cells are a unique and important source of heparin which does not exhibit fibrinolytic activity but prevents coagulation by acting as a co-factor of antithrombin III. Heparin has been described as tissue-type plasminogen activator. Mast cells themselves are another important source of tissue plasminogen activator (24).

### **Can we predict Kounis syndrome?**

The described patient suffered an allergic reaction and developed Kounis syndrome with all its consequences

following a bee sting. It has been found, recently, that patients with serum baseline tryptase greater than normal have clonal mast cell disorder, either systemic mastocytosis or monoclonal mast cell activation syndrome and are prone to developed immediate and severe hypersensitivity reaction to hymenoptera sting (25). Furthermore, raised salivary levels of mast cell carboxypeptidase may be helpful in confirming that an allergic reaction to drugs has occurred and baseline levels in serum and saliva may be predictive of the severity of future allergic reactions. In patients with raised baseline serum tryptase, bone marrow aspiration showed mast cell granulomas and spindle shaped mast cells. Flow cytometric analysis of mast cells revealed mast cells expressing CD2 or CD25 on their surface and KIT mutation analysis showed KIT mutation at codon 816. KIT is the mast receptor for the stem cell factor that is essential for mast cell development, proliferation, survival, adhesion and homing. Therefore, patients with increased serum baseline tryptase might have KIT mutations that lower the stimulus threshold for anaphylaxis, and have hyper responsive mast cell phenotype resulting in the development of Kounis syndrome (26).

All of the above show that Kounis syndrome has broadening clinical manifestations, covers a wide spectrum of mast cell activation disorders and involves numerous and continuously increasing causes. It is not a rare disease but it is no commonly diagnosed disease.

### **Acknowledgements**

*Disclosure:* The author declares no conflict of interest.

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**Cite this article as:** Kounis NG. Kounis syndrome: a monster for the atopic patient. *Cardiovasc Diagn Ther* 2013;3(1):1-4. doi: 10.3978/j.issn.2223-3652.2013.02.05