



## Editorial

## Editorial: Kounis syndrome (allergic angina and allergic myocardial infarction) for cardiologists




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**Keywords:**

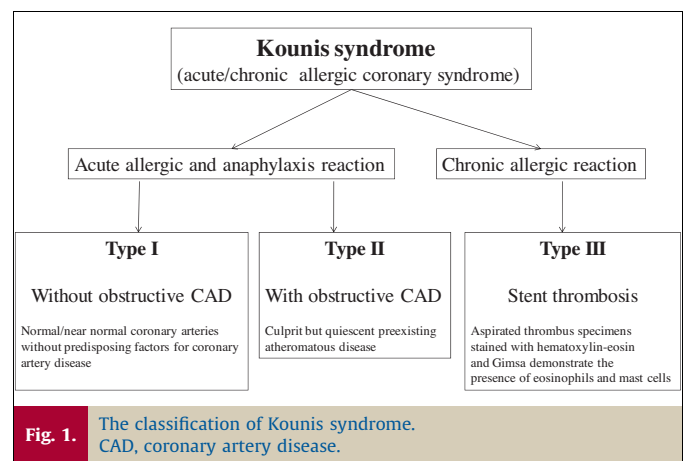
Allergy  
Anaphylaxis  
Acute coronary syndrome  
Coronary artery spasm  
Histamine  
Late stent thrombosis

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In 1965, cases of allergic, anaphylactic, and anaphylactoid reactions with acute myocardial infarction were first published [1]. A quarter century ago, Kounis and Zavras reported allergic angina due to histamine-induced coronary artery spasm in 1991 [2]. Allergic angina can progress to acute myocardial infarction which was named “allergic myocardial infarction”. In 1995, Constantinides reported the potential that ordinary allergic reactions could induce coronary plaque disruptions [3]. Braunwald noted that coronary artery spasm can be provoked by allergic reactions with mediators such as histamine or leukotrienes acting on coronary vascular smooth muscle in 1998 [4]. Allergic angina and allergic myocardial infarction are referred to as “Kounis syndrome” and cardiologists sometimes may encounter this syndrome in the cardiac catheterization laboratory. Three variants of Kounis syndrome have been described, as shown in Fig. 1. Type I variant includes patients with normal or near 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. Type II variant includes patients with culprit but quiescent preexisting atheromatous 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. Type III variant 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 [5,6].

Anaphylaxis is a systemic, immediate hypersensitivity reaction caused by rapid IgE-mediated release of mediators from mast cells and basophils. Kounis syndrome is defined as the occurrence of acute coronary syndromes with conditions associated with mast

cell degranulation, involving interrelated and interacting inflammatory cells, and including allergic or hypersensitivity and anaphylactic or anaphylactoid insults. It is caused by inflammatory mediators such as histamine, neutral protease, arachidonic acid products, platelet activating factors, and a variety of cytokines and chemokines released during the activation process. It is well known that histamine acts through four different histamine receptors all of which contribute to the severity of the allergic myocardial damage. H1-histamine receptors mediate coronary vasoconstriction and increase vascular permeability. H2-histamine receptors mediate a minor degree of relaxation of the coronary arteries and increase atrial rate and atrial and ventricular contractility. The interaction of H1- and H2-receptor stimulation mediates decreased diastolic pressure and increased pulse pressure. Histamine binding to H1-receptors during anaphylaxis stimulates endothelial cells to convert the amino acid L-arginine into nitric oxide, a potent autocoid vasodilator. Enhanced nitric oxide production decreases venous return, thus contributing to the



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vasodilation that occurs during anaphylaxis. H3-histamine receptors have been identified on presynaptic terminals of the sympathetic effector nerves that innervate the heart and the systemic vasculature. These receptors have been found to inhibit endogenous norepinephrine release which would be expected to enhance the degree of shock during anaphylaxis events. H4-histamine receptors control chemotaxis of murine mast cells and human eosinophils and the release of interleukin-16 from human lymphocytes. The recruitment of these specific inflammatory cells at the sites of the allergic response correlates with the severity of the allergic reaction [7].

In their paper, Kounis and Zavras reported the histamine-induced coronary artery spasm [2]. Allergic angina is caused by several chemical substances released during any immunologically mediated reaction. Histamine is the most important of these substances and has strong vasoconstrictive action mediated by H1-receptors. Histamine induces coronary artery spasm with impaired coronary perfusion and various electrocardiographic appearances. In contrast, according to the report by Okumura et al., coronary spasm was induced in 6 patients with histamine, in 18 with acetylcholine and 1 with ergonovine in 21 patients with variant angina [8]. Okumura et al. concluded that histamine induced coronary spasm in some patients with variant angina by stimulation of the H1 receptor of the coronary artery and it caused coronary vasodilatation in the majority of patients, especially those without advanced coronary artery disease, presumably through release of the endothelium-derived relaxing factor. Sakata et al. also reported that whereas histamine concentration was elevated in the great cardiac vein in 8 of 11 patients suffering from attacks of variant angina, they did not observe any histamine elevation during or after acetylcholine-induced coronary artery spasm. While elevation of plasma histamine levels was antecedent to angina attacks in 3 patients, high levels of histamine were observed even in the absence of ST segment elevation in the same group of patients [9]. Considering these issues, allergic angina probably induced by histamine may be a different state from variant angina. Although the phenomenon of coronary vasoconstriction is the same response, Kounis syndrome may be a different disease from variant angina.

In this case report, a 79-year-old man without allergic history presented with an anaphylactic reaction complicated with showing ST elevation in inferior leads when he had received transcatheter arterial chemoembolization for treatment of hepatocellular carcinoma at the sixth time. Emergency coronary angiography did not reveal any organic stenosis nor occluded lesions of the coronary arteries. Therefore, the author made diagnosis of Kounis syndrome (Type I). Although Kounis syndrome is a rare disease, physicians in the clinic should be aware of this disease [10]. It is helpful for cardiologists to realize the presence of Kounis syndrome in the real world. Cardiologists should treat both anaphylactic shock and coronary artery spasm. In this report, all three cases demonstrated ST elevation in inferior leads and the author suggests that right coronary artery may be prone to be affected by acute allergic insults more than left coronary artery. In fact, Kounis syndrome should be considered in young, healthy patients with no atherosclerotic risk factors when they develop acute coronary syndrome, especially inferior myocardial infarction, after administration of potentially allergic agents [11]. Cardiologists should suspect Kounis syndrome in young patients with anaphylactic shock and inferior ST elevation.

Kounis syndrome is a category of coronary artery disease. Many chemical mediators may concern the occurrence of Kounis syndrome. Histamine may be the most important chemical mediator but other factors, such as coronary atherosclerotic state and general condition, may also contribute to the occurrence of this syndrome. However, we cannot know the occurrence of

anaphylactic shock and coronary artery spasm before clinical use. Just after the occurrence of Kounis syndrome, we realize this phenomenon.

In the future, we may understand the relationship between coronary spastic angina and Kounis syndrome (allergic angina and allergic myocardial infarction) if we performed the spasm provocation tests in some patients with Kounis syndrome [12]. However, it may be difficult to perform the spasm provocation tests in these Kounis syndrome patients due to the point of procedures or ethical problems. Patients with Kounis syndrome have a good prognosis and a rare reoccurrence. Coronary spastic angina also has a good prognosis under the optimal medications including long-acting calcium channel antagonists. However, Kounis syndrome (type I and type II) is a coronary artery disease which may be remarkably different from coronary spastic angina.

Kounis et al. described a series of eight patients (0.67–0.8%) who had both allergic or anaphylactic reactions and acute coronary syndromes as type II of Kounis syndrome in approximately 1000–1200 patients with coronary care unit admissions [13]. They performed six percutaneous coronary interventions and one coronary aorta bypass graft surgery in 7 out of 8 all patients. They noted that atherosclerotic plaques might rupture as a result of the humoral effects of an allergic insult. In these patients, allergic or anaphylactic reactions may be one of the triggers of occurrence of acute coronary syndrome. However, it is controversial whether all eight patients had plaque ruptures at the atherosclerotic portions or not. They also mentioned that their study could not constitute the sole proof of evidence for a cause and effect relationship.

Kounis syndrome is classified into three types. While type I and type II are acute allergic reactions, type III is considered as chronic allergic reaction [14,15]. Kounis syndrome is well recognized as acute allergic angina and acute allergic myocardial infarction. Although chronic inflammation after the implantation of coronary stents may lead to the occurrence of acute coronary syndrome, the majority of cardiologists may have some reservations about the definition of Kounis syndrome type III. Because original Kounis syndrome was defined as histamine-induced coronary spasm in 1991, physicians may have some difficulty to understand that Kounis type III syndrome is related to late stent thrombosis after the implantation of coronary stents. General cardiologists in the real world may understand that Kounis syndrome is acute allergic angina and acute allergic myocardial infarction.

As a therapy in patients with Kounis syndrome type I and type II, it is necessary to manage acute coronary syndrome and anaphylaxis. Most cases have been treated with steroids, H1-blockers, nitroglycerin, H2-blockers, and epinephrine. The Kounis syndrome type III, as a possible manifestation of hypersensitivity to stent components or anti-platelet agents, might play a key role in the mechanism of drug-eluting stent thrombosis. Recently, some experimental studies have reported attenuation of allergic and thrombotic events through treatment with corticosteroids and other mast cell stabilizing agents. Although Kounis syndrome is a rare phenomenon, cardiologists should investigate the relationship between allergic reactions and coronary artery diseases in the clinic in the future.

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#### Conflict of interest

The authors state that there are no conflicts of interest.

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Shozo Sueda (MD, FJCC)\*

Yasuhiro Sasaki (MD)

Hirokazu Habara (MD)

Hiroaki Kohno (MD)

*Department of Cardiology, Ehime Prefectural Niihama Hospital,  
Ehime, Japan*

\*Corresponding author at: The Department of Cardiology,  
Ehime Niihama Prefectural Hospital, Hongou 3 chome 1-1,  
Niihama City, Ehime 792-0042, Japan. Tel.: +81 897 43 6161;  
fax: +81 897 41 2900

*E-mail address: EZF03146@nifty.com (S. Sueda).*

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