Review Article

Coronary Hypersensitivity Disorder: The Kounis Syndrome

Nicholas G. Kounis, MD, PhD

Department of Medical Sciences, Patras Highest Institute of Education and Technology, Patras, Greece

ABSTRACT

Background: When allergy or hypersensitivity and anaphylactic or anaphylactoid insults lead to cardiovascular symptoms and signs, including acute coronary events, the result might be the recently defined nosologic entity *Kounis syndrome*. Vasospastic allergic angina, allergic myocardial infarction, and stent thrombosis with occluding thrombus infiltrated by eosinophils and/or mast cells are the 3 reported variants of this syndrome.

Objective: The purpose of this review was to highlight and consolidate the recent literature on allergic angina and allergic myocardial infarction and to propose new therapeutic modalities for stabilizing mast cells.

Methods: A search for current literature on the pathophysiology, causality, clinical appearance, variance, prevention, and treatment of Kounis syndrome was conducted.

Results: Kounis syndrome is caused by inflammatory mediators such as histamine; neutral proteases, including tryptase, chymase, and cathepsin-D; arachidonic acid products; platelet-activating factor; and a variety of cytokines and chemokines released during the mast-cell activation. Platelets with Fc γ receptor (FcγR) I, FcγRII, FcεRI, and FcεRII also have a role in the activation cascade. The same mediators released from the similar inflammatory cells are involved in acute coronary events of nonallergic etiology. These cells are not only present in the involved region before plaque erosion or rupture but also release their contents just before an acute coronary event. Pro-inflammatory mediators similar to those found in Kounis syndrome are found in some cases with nonallergic etiology, suggesting that this is a more general problem. The acute coronary and cerebrovascular events in Kounis syndrome may be prevented by the inhibition of mast-cell degranulation. Substances and natural molecules that protect the mast-cell surface and stabilize the mast-cell membrane are emerging as novel agents in the prevention of acute coronary and other arterial events.

Conclusions: The 3 reported variants of Kounis syndrome—vasospastic allergic angina, allergic myocardial infarction, and stent thrombosis with occluding thrombus—are caused by inflammatory mediators. Agents that inhibit mast-cell degranulation may be efficacious in preventing the acute coronary and cerebrovascular events of Kounis syndrome. (*Clin Ther*. 2013; 35:563–571)

Key words: acute coronary events, inflammatory mediators, Kounis syndrome, mast-cell stabilizers.

INTRODUCTION

The first reports associating cardiovascular symptoms and signs with hypersensitivity and anaphylactic insults were published >6 decades ago.[1–3] However, a detailed description of the allergic angina syndrome, which could progress to acute allergic myocardial infarction, was not described until 1991.[4] Today, allergic angina and allergic myocardial infarction are ubiquitous diseases that affect patients of any age, involve 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*.[5–8]

DEFINITION

Kounis syndrome is defined as the concurrence of acute coronary syndromes such as coronary spasm, acute myocardial infarction, and stent thrombosis, with conditions associated with mast-cell and platelet activation involving interrelated and interacting inflammatory cells in the setting of allergic or hypersensitivity and anaphylactic or anaphylactoid insults. It is caused by inflammatory mediators such as histamine, neutral

Accepted for publication February 25, 2013.
http://dx.doi.org/10.1016/j.clinthera.2013.02.022
0149-2918/$ - see front matter

proteases, arachidonic acid products, platelet-activating factor (PAF), and a variety of cytokines and chemokines released during the activation process.[6,8–10] A subset of platelets bearing Fc γ receptor (FcγR) I, FcγRII, FcεRI, and FcεRII are also involved in the activation cascade.[11] All of these inflammatory cells participate in an inflammatory cycle and activate each other via multidirectional signals. Recently, Kounis-like syndromes that affect the cerebral[12] and mesenteric arteries[13] have been described. It is anticipated that the heart and the entire arterial system is vulnerable to allergic, hypersensitivity, anaphylactic, and/or anaphylactoid events.

PATHOPHYSIOLOGY

The main inflammatory cells—the mast cells—interact with other macrophages and T lymphocytes to cause Kounis syndrome.

Mast cells can activate macrophages[14,15] and may enhance T-cell activation.[16,17] Inducible macrophage protein 1a may activate mast cells,[18] while $CD169^+$ macrophages activate CD8 T cells.[19] T cells may mediate mast-cell activation and proliferation[20,21] and regulate macrophage activity.[22] Although mast cells are numerically a minority in this inflammatory cascade, they influence decisively the inflammatory process.

During hypersensitivity, degranulation of mast cells takes place and a variety of stored and newly formed inflammatory mediators are released locally and into the systemic circulation. These mediators 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. Most of these mediators have important cardiovascular activity. Histamine induces coronary vasoconstriction, induces tissue factor expression, and activates platelets. All 3 neutral proteases can activate matrix metalloproteinases, which can degrade the collagen cap and induce plaque erosion and rupture.[23] Tryptase exerts a dual action on the coagulation cascade with both thrombotic and fibrinolytic properties.[24]

Furthermore, chymase and cathepsin-D might act as enzymes to convert angiotensin I into angiotensin II, a major vasoconstricting substance.[25] Leukotrienes are also powerful vasoconstrictors, and their biosynthesis is enhanced in the acute phase of unstable angina.[26,27] Thromboxane is a potent mediator of platelet aggregation and has vasoconstricting properties,[28,29] and PAF, in myocardial ischemia, acts as a proadhesive signaling molecule via the activation of leukocytes and platelets to release leukotrienes or as a direct vasoconstrictor.[30]

CAUSALITY

Several causes have been described to induce Kounis syndrome, and their number is increasing rapidly. These causes include various drugs, environmental exposures, and several conditions. The most recently described offenders are the scombroid syndrome[31] (also called *histamine fish poisoning*) and exposure to gelatin succinylated/sodium chloride/sodium hydroxide (Gelofusine),[32] latex,[33] or the drug losartan[34] in those who are hypersensitive or allergic. Fish flesh contains the amino acid histidine, and when fish infected with gram-negative bacteria containing the enzyme histidine decarboxylase is ingested, then this enzyme converts histidine into histamine, which may induce Kounis syndrome. Gelofusine is a bovine gelatin administered to maintain intravascular volume. Gelofusine is a component of various vaccines for children and constitutes the main cause of sensitization in children. Exposure to such allergens may occur directly or through the saliva of people (eg, kissing)[35] or pets (eg, licking by dogs).[36]

CLINICAL MANIFESTATIONS

The main clinical symptoms and signs of Kounis syndrome are associated with subclinical, clinical, acute, or chronic allergic reactions accompanied by cardiac symptomatology. A variety of ECG changes, ranging from ST-segment elevation or depression to any degree of heart block and cardiac arrhythmias, may be observed resembling digitalis intoxication. A high index of suspicion regarding this syndrome is of paramount importance. Although it is not a rare disease, its diagnosis is spare and easily overlooked.[37] Kounis syndrome is becoming increasingly encountered in clinical practice, and it is anticipated that many more causative factors will be implicated in the future. Kounis syndrome has mostly been reported in southern Europe, especially in Spain, Italy, Greece, and Turkey. This geographic variation could be attributed to increased awareness of physicians of the existence of Kounis syndrome; climate and environmental conditions resulting in pollen cross-reactivity; and hymenoptera exposures, overconsumption of medicines, and/or inadequacy of preventative measures.[8] Kounis syndrome has been re-