The Allergic Angina Syndrome in Naproxen Sodium Induced Type 1 Hypersensitivity Reaction in an Allergic Asthmatic Young Woman: Kounis Syndrome

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A twenty-year old female with a history of allergic asthma and Raynaud's phenomenon was admitted to our emergency department with retrosternal chest pain of one hour duration accompanied by generalized erythema, urticarial rashes, moderate dyspnea, nausea and vomiting. Her symptoms developed after taking a dose of naproxen sodium for dysmenorrhea. ECG showed ST segment elevation in leads I and aVL and ST segment depression in leads III and aVF. The patient's chest pain relieved and ST elevations resolved during her transport to the catheterization laboratory. Immediate angiography revealed normal coronary arteries.

This coronary syndrome was thought to be secondary to allergy-induced coronary vasospasm known as "Kounis syndrome". The main pathophysiological mechanism of coronary spasm in Kounis syndrome is the inflammatory mediators released during a hypersensitivity reaction triggered by food, insect bites or drugs. Here, we report a case of coronary spasm secondary to allergic reaction following naproxen sodium intake.

Key Words: Allergic angina • Coronary vasospasm • Hypersensitivity • Kounis syndrome

INTRODUCTION

Coronary vasospasm can be induced by allergic reactions, and this special type of vasospastic myocardial ischemia or infarction is called Kounis syndrome. Kounis syndrome should be considered in young, healthy patients with no atherosclerotic risk factors presenting with acute coronary syndrome after administration of a potentially allergic agent.[1] The main pathophysiological mechanism is vasospasm of epicardial coronary arteries due to increased vasoactive mediators such as catecholamines, thromboxane A2, serotonin, endothelin, vasopressin and histamine, which are released during a hypersensitivity reaction. Release of cardiac mast cell-derived histamine is believed to play a pivotal role in coronary spasm.[1]

There are several etiologies that have been reported as capable of triggering Kounis syndrome. These include a number of drugs (antibiotics, analgesics, anti-neoplastics, contrast media, corticosteroids, intravenous anesthetics, non-steroidal anti-inflammatory drugs, etc.), various conditions (angio-edema, bronchial asthma, urticaria, food allergy, exercise-induced allergy), and environmental exposures (stings of ants, bees, wasps, jellyfish, poison ivy, latex contact, shellfish ingestion, viper venom poisoning).[1,2]

The most common manifestations of this clinical syndrome are retrosternal chest pain and chest discomfort, dyspnea, palpitation, nausea, vomiting, fainting,

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urticaria, itching, sweating, paleness, hypotonia and sometimes cardiogenic shock.

Here, we report a case of vasospastic angina in a patient with systemic immediate hypersensitivity reaction which developed following oral administration of naproxen sodium.

CASE REPORT

A twenty-year old female with a known history of allergic asthma and Raynaud's phenomenon was admitted to our emergency department with retrosternal chest pain, dyspnea, nausea and vomiting of one hour duration after taking a dose of naproxen sodium for dysmenorrhea. Her physical examination revealed a blood pressure and heart rate of 120/75 mmHg and 81 bpm, respectively, and generalized erythema and urticarial rashes. Heart and respiratory auscultation findings were normal except bilateral prolonged expiration and expiratory wheezing in all lung fields. The patient had a past history of smoking, allergic asthma and Raynaud's phenomenon. ECG at admission showed ST segment elevation in leads I and aVL and reciprocal ST segment depression in leads III and aVF (Figure 1). The patient's chest pain spontaneously relieved and ST elevations resolved during her transport to the catheterization laboratory. Immediate angiography revealed normal coronary arteries and normal ventricular function (Figure 2). Supplemental oxygen along with nebulized albuterol was administered, intravenous metilprednisolone 40 mg was given and intravenous nitroglycerin infusion was started. The patient showed prompt response to the therapy, and signs and symptoms of allergic reaction resolved in a couple of hours. Echocardiographic examination was normal. Cardiac markers including troponin I and creatinin kinase-MB revealed no pathologic elevations. The patient revealed a moderate eosinophilia (10%) in her peripheral blood smear. The measurements of serum-specific IgE directed to non-steroid anti-inflammatory drug (NSAID), and serum tryptase levels which were performed on the day of admission were elevated (total IgE, 205 IU/mL and tryptase, 42 μg/L). However, subsequent daily measurements of serum tryptase and histamines were within normal ranges. This patient pre-

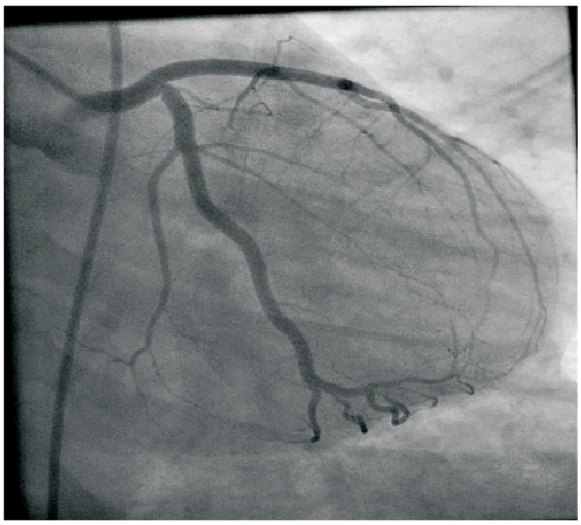

Figure 2. *The coronary angiography, which was performed at the time of chest pain, revealed normal coronary arteries.*

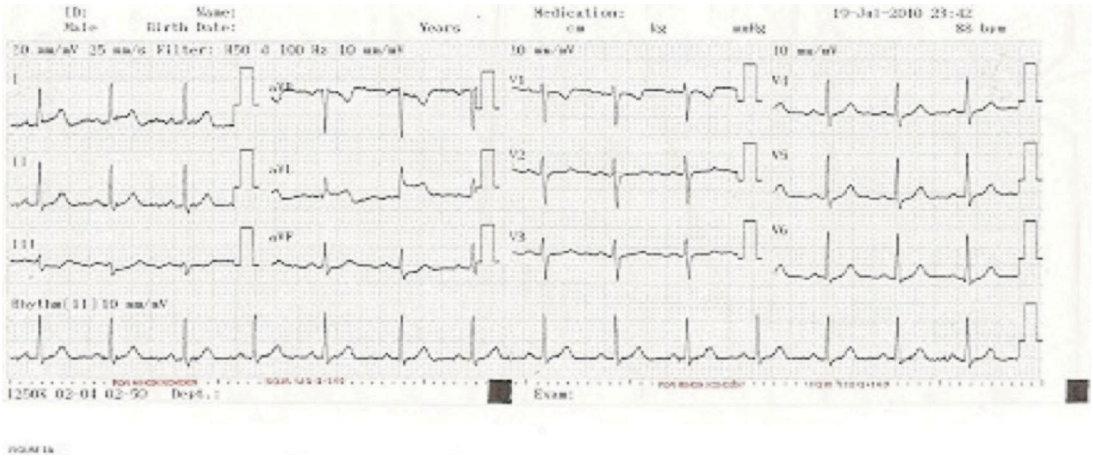

Figure 1. *Twelve-lead electrocardiography during chest pain showing ST segment elevation in leads I and aVL and reciprocal ST segment depression in leads III and aVF.*

senting with signs and symptoms of systemic allergic reaction associated with clinical and electrocardiographic findings of acute myocardial ischemia was diagnosed as having Kounis syndrome (type 1 variant). After an uneventful hospital stay of 7 days, she was discharged with a prescription of long acting nifedipine, nitrate and antiasthma drugs.

DISCUSSION

Kounis syndrome has been defined as an acute coronary syndrome that manifests as vasospastic angina or acute coronary syndrome triggered by the release of inflammatory mediators following an allergic insult. The mechanisms of this syndrome are characterized by coronary artery vasospasm due to mast cell degranulation and the subsequent release of vasoactive mediators. Mast cells are found specifically in heart tissue and adventitia of coronary arteries.[3] Released mediators can be preformed (histamine, neutral proteases-chymase and tryptase, platelet activating factor) or newly synthesized (cytokines, chemokines, arachidonic acid products-leucotrienes, prostaglandins). The most important vasoactive mediators responsible for coronary artery spasm and consequences of Kounis syndrome are histamine, serotonin, and leukotrienes, Kounis syndrome consist of two variants. The first is observed in patients with no cardiovascular risk factors and healthy coronary arteries in which the inflammatory cascade triggered by the allergic insult causes a coronary vasospasm accompanied by elevated or normal levels of cardiac enzymes. The second is observed in patients with pre-existing atheromatous disease (whether known or not) in whom the release of these mediators would also produce a coronary vasospasm, which occurs with normal cardiac enzymes or rupture of the atheromatous plaque, manifesting as an acute myocardial infarction. Our patient was diagnosed with a type 1 variant, in which myocardial ischemia or infarction occurs in normal coronary arteries due to coronary artery vasospasm.

It may be challenging to make a differential diagnosis between Prinzmetal angina (pure variant angina) and Kounis syndrome. Many similarities between type I Kounis syndrome and Prinzmetal angina have been observed.[1] In both cases, the key element resulting in myocardial ischemia is the contraction of vessels. It often develops in angiographic disease free segments of coronaries. ECG and angiographic findings may be identical in both clinical situations. Furthermore there is considerable evidence suggesting that both conditions have similar underlying pathophysiology. Stimuli which cause vasospasm in Prinzmetal angina are similar to factors released during allergic reactions such as cathecholamines, thromboxane A2, serotonin, endothelin, vasopressin and histamine. Although there are no definite diagnostic criteria to differentiate Prinzmetal angina from Kounis syndrome, a patient presenting with signs and symptoms of systemic allergic reaction associated with clinical, laboratory and electrocardiographic findings of acute myocardial ischemia should be diagnosed as having Kounis syndrome. Chest pain, during an allergic insult, with electrocardiographic ischemic changes but with normal cardiac markers, normal perfusion scan, normal coronary angiogram and positive ergonovine or histamine test are in favor of type I variant of the Kounis syndrome. Ergometrine maleat also shown to be related to coronary spasm in allergic acute coronary events, therefore not helpful in differentiating two situations.[4] A positive cold pressor test or hyperventilation induced coronary spasm may be considered as findings favoring Prinzmetal angina. Intravascular ultrasonography may be a tool for documenting the presence of minimal atherosclerotic lesions which are usually found in patients with Prinzmetal angina. Inflammatory mediators such as tryptase and histamine blood levels are shown to be elevated not only in allergic acute coronary syndromes but also in patients with non-allergic acute coronary syndromes.[5] Moreover, degranulated mast cells have been found abundant in the coronary plaque rupture areas of such patients with recent myocardial infarction.[3] For these reasons, some authors have suggested the existence of a final common pathway for allergic and non-allergic coronary syndromes. Therefore, it was postulated that these vasoactive mediators may be potential new markers characterizing an unstable plaque. Elevated serum histamine and tryptase levels strongly support the possibility of an ongoing allergic reaction, but these molecules have short half lives (less than 10 minutes for histamine and 90 minutes for tryptase) that makes especially histamine relatively impractical for routine use.[6] Therefore, a normal tryptase level does not exclude

the possibility of allergic cardiac event. However, very marked elevations of these molecules could possibly be considered as a finding favoring an allergy-related event, like Kounis syndrome, rather than Prinzmetal angina. Additional allergy work-up including skin prick tests may also be helpful for diagnosis.

Increasing evidence also indicates that mental or psychological stress is associated with cardiac events, especially in patients with coronary artery disease.[7] Acute psychological stress can lead to cardiac mast cell degranulation through corticotropin releasing hormone (CRH) acting directly or through the neuropeptide neurotensin. Neurotensin is present in the heart and known to trigger mast cell degranulation. Acute stress can result in local CRH and nonpeptide neurotensin release, which can contribute to myocardial pathophysiology through direct or indirect release of cardiac mast cell mediators.[8] Mast cell mediators with vasoactive and neurosensitizing properties, such as histamine, can then contribute to myocardial ischemia and/or arrhythmias. Differentiation of Kounis syndrome from stress-related Takotsubo cardiomyopathy may also be required. Takotsubo cardiomyopathy is a stress-related acute cardiac disorder characterized by reversible systolic ballooning and hypokinesia of the distal part of the left ventricle, cardiac symptoms, and ECG-changes, but no coronary artery stenosis and no other causative disease. Our patient showed no preceding emotional stress or development of apical left ventricle ballooning, excluding the possibility of psychological stress-induced acute coronary events.

The management of patients with Kounis syndrome differs from those for non-allergic common acute coronary syndromes.[6] These patients need treatment with steroids, antihistamines, fluid replacement, possibly epinephrine, oxygen and antithrombotics before transfer to the cardiac catheterization laboratory. The treatment should both dilate coronary vessels and suppress the allergic reaction. Vasodilator drugs, including nitrates and calcium channel blockers, should be considered first-line therapy since vasospasm is the primary mechanism. However the utilization of some drugs is controversial due to the underlying anaphylactic reaction. Acetylsalicylic acid, a first-line drug for acute coronary syndromes, may itself cause allergic reactions and induce anaphylaxis. Aspirin and NSAIDs (as shown in our case) are among the most frequent causes of drug-associated anaphylactic reactions. Therefore, the safety of aspirin in patients with Kounis syndrome is unknown regarding the potential risk of aggrevating an ongoing anaphylactic reaction. Both fractionated and low-molecular-weight heparins are derived from animals which are potentially antigenic and can cause allergic reactions. Beta-blockers may also offset some of the beneficial effects of epinephrine, which is the mainstay of treatment of anaphylaxis. Epinephrine is life-saving medication in anaphylaxis, however it can aggrevate the ischemia, induce coronary vasospasm and arrhythmias. Therefore, given a narrow therapeutic window, the recommended dose is 0.2-0.5 mg of intramuscular injection. Although there is extensive escape of intravascular volume into interstitial space causing hypovolemia in anaphylaxis, in patients with Kounis syndrome, large amounts of fluid replacement may cause pulmonary edema due to development of left ventricular dysfunction. Nitroglycerine and calcium channel blockers are first-line drugs to relieve coronary artery spasm, but they should be used with caution in patients with hypotension. Corticosteroids are agents playing a major role in treatment of allergic reactions, but they are well known to impair wound healing and scar formation which may cause myocardial wall thinning, cardiac aneurysms and wall rupture. Successful use of corticosteroids in allergic acute coronary syndromes has been reported, and is thus probably safe and appropriate. Finally, the administration of mast cell membrane stabilization drugs such as sodium cromoglycate, nedocromil sodium or ketotifen can be used as a therapeutic strategy for atopic patients and ones who have already experienced allergic angina and/or infarction.[9,10] Moreover, since mast cell activation and degranulation are proposed to be the common pathway leading to plaque destabilization in both allergic and non-allergic coronary syndromes, the efficiency of drugs which stabilize mast cell membranes in the prevention of both allergic and non-allergic acute coronary syndromes can be expected. Routine acute coronary syndrome protocol should be followed in patients with a type II variant. These patients should be followed up in cardiology and allergy clinics after hospital discharge. A full cardiologic work-up including invasive and non-invasive examinations and management of cardiac risk factors are also necessary.

The Kounis syndrome is probably not an uncommon disease but, rather, an underdiagnosed one. Regarding the complex and complicated course of acute coronary syndromes associated with allergic reactions, high awareness, rapid diagnosis and appropriate treatment has utmost importance.

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